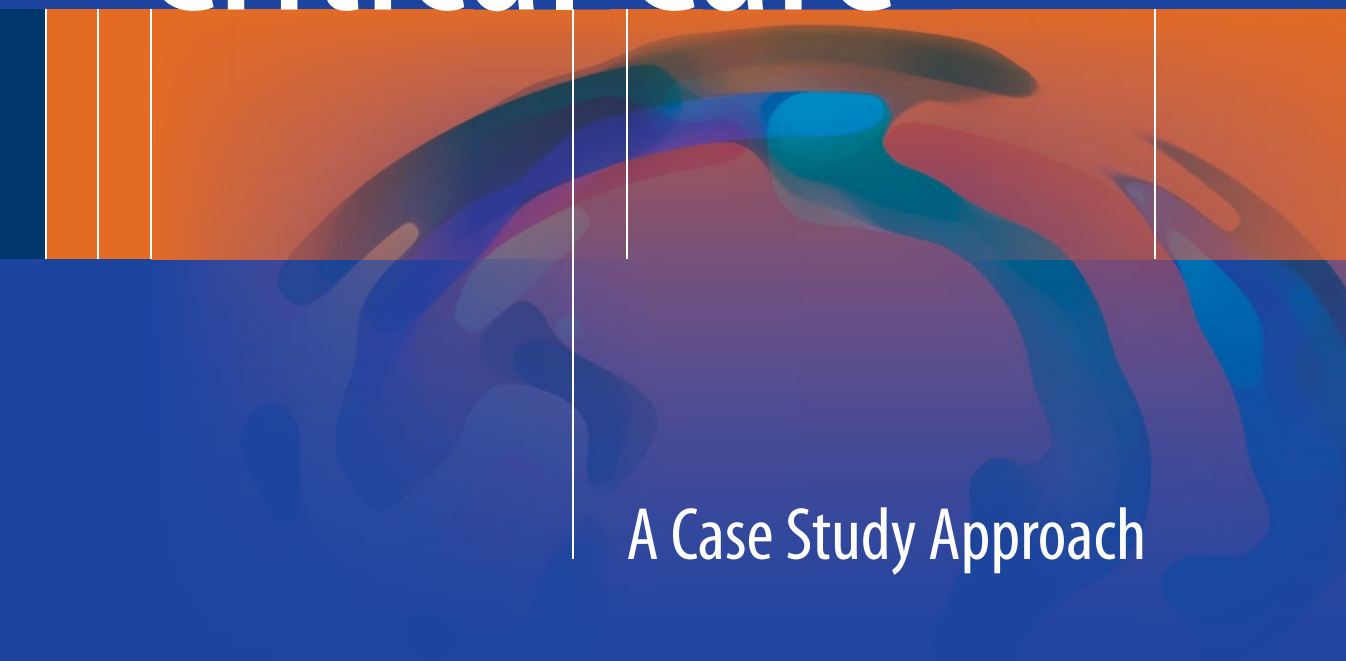
Robert C. Hyzy
Editor

Evidence-Based Critical Care



A Case Study Approach

EXTRAS ONLINE

Springer

Evidence-Based Critical Care

Robert C. Hyzy
Editor

Evidence-Based Critical Care

A Case Study Approach

Springer

Editor
Robert C. Hyzy
Division of Pulmonary and Critical Care
University of Michigan
Ann Arbor
MI
USA

ISBN 978-3-319-43339-4 ISBN 978-3-319-43341-7 (eBook)
DOI 10.1007/978-3-319-43341-7

Library of Congress Control Number: 2017931641

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

This book is dedicated to the memory of Eugene C. Hyzy, MD

Preface

Along with Springer International, I am pleased to offer you our new textbook entitled Hyzy's *Evidence-Based Critical Care Medicine: A Case Study Approach*. In medicine, "teachable moments" usually occur in clinical context, where the engagement in a real case exemplifies principles of diagnosis or therapy. We have created our new textbook with the teaching moment in mind: each chapter begins with a real case gleaned from the authors' clinical experience. In order to replicate the teaching dyad, each case poses a question which offers the reader to process and reflect on the components of the case before offering and answer.

While medical practice attempts to be evidence-based, common approaches to diagnosis and management incorporate not only evidence but heuristics and biases which await either validation or repudiation. Hence, we have divided the discussion section of each chapter into two segments: the "Principles of Management" section and the "Evidence Contour" section. In the "Principles of Management" section, the common approach to the care of patients having a given condition is presented. Here you will find the nuts and bolts of what you need to know about the condition and the usual approach to diagnosis and treatment. Evidence-based approaches are emphasized, where appropriate. However, medical knowledge is ever evolving. The approach to many aspects of the diagnosis and treatment of a condition remains the subject of controversy. In the "Evidence Contour" section, each author discusses the aspects of diagnosis and management which are the subject of ongoing debate in the medical literature. In the way, the reader will appreciate not only what appears to be known but also what is becoming known about a given topic.

We believe the approach we have taken with this textbook successfully bridges the gulf between the traditional encyclopedic sit-on-your-shelf textbook and the single-hit online reference, each of which lacks the contextual elements of effective learning. This is a new way to present knowledge in a medical textbook and should help critical care practitioners, fellows, residents, allied health professionals, and students expand their critical care knowledge in an efficient and effective manner. This approach should also benefit those preparing for board examinations.

I would like to thank the many friends, colleagues, and former fellows whose labors went to create this book. In particular, I would like to thank my section editors, Drs. Robert Neumar, David Morrow, Ben Olenchock, Romer Geocadin, John Kellum, Jonathan Fine, Robyn Scatena, Lena Napolitano,

and Marie Baldisseri. Without their thoughtful and insightful efforts, this book would not have been possible. I would also like to thank my editors at Springer, Connie Walsh and Grant Weston for their vision and for seeing this work through to fruition.

Ann Arbor, MI, USA Robert C. Hyzy, MD

Contents

Part I ER- ICU Shock and Resuscitation
Robert W. Neumar

1 Cardiac Arrest Management 3
Ronny M. Otero

2 Post-cardiac Arrest Management 13
Ronny M. Otero and Robert W. Neumar

3 Undifferentiated Shock. 25
Sage P. Whitmore

4 Hypovolemic Shock and Massive Transfusion 39
Joshua M. Glazer and Kyle J. Gunnerson

5 Acute Respiratory Failure: NIV Implementation and Intubation. 49
Torben K. Becker and John M. Litell

6 Diagnosis and Management of Tricyclic Antidepressant Ingestion 57
Patrick George Minges and Robert W. Shaffer

7 Management of Calcium Channel Blocker Poisoning. 65
David M. Black and Robert W. Shaffer

8 Diagnosis and Management of Ethylene Glycol Ingestion 73
Christine Martinek Brent and Robert W. Shaffer

9 Accidental Hypothermia 83
Carrie Harvey and Ivan Nathaniel Co

Part II Cardiac Disease
David A. Morrow and Benjamin A. Olenchock

10 Management of Cardiogenic Shock 95
Michael G. Silverman and Benjamin A. Olenchock

11 Management of Acute Heart Failure. 103
Gregory T. Means and Jason N. Katz

12 Management of Acute Coronary Syndrome 111
Arman Qamar and Benjamin M. Scirica

13 Complications of Myocardial Infarction 121
Brandon M. Jones and Venu Menon

14 Management of Cardiac Tamponade 129
David D. Berg, Gregory W. Barsness, and Benjamin A. Olenchock

15 Hypertensive Crises 135
Mark Schmidhofer

16 Atrial Fibrillation and Other Supraventricular Tachycardias 145
Daniel Sedehi

17 Ventricular Arrhythmias 153
Sohaib Tariq and Howard A. Cooper

18 Management of Acute Aortic Syndromes 163
Carol H. Choe and Rohan R. Arya

19 Management of Endocarditis 171
Janek Manoj Senaratne and Sean van Diepen

Part III Respiratory Disease
Robert C. Hyzy

20 Community Acquired Pneumonia 181
Richard G. Wunderink and Mark W. Landmeier

21 Management of Acute Respiratory Distress Syndrome 189
Robert C. Hyzy

22 Acute Exacerbation of COPD: Non-invasive Positive Pressure Ventilation 199
Kristy A. Bauman

23 Management of Status Asthmaticus 205
Jacob Scott and Ryan Hadley

24 Immunocompromised Pneumonia 215
Robert P. Dickson

25 Venous Thromboembolism in the Intensive Care Unit 221
Scott J. Denstaedt and Thomas H. Sisson

26 Massive Hemoptysis 233
Andrew M. Namen, Norman E. Adair, and David L. Bowton

27 Sedation and Delirium 241
Timothy D. Girard

28 Prolonged Mechanical Ventilation 251
Thomas Bice and Shannon S. Carson

29 Ventilator-Associated Pneumonia and Other Complications 257
Jennifer P. Stevens and Michael D. Howell

30 Respiratory Failure in a Patient with Idiopathic Pulmonary Fibrosis 265
Ryan Hadley

31 Weaning from Mechanical Ventilation 273
Ayodeji Adegunsoye and John P. Kress

32 The Post-intensive Care Syndrome 281
Jason H. Maley and Mark E. Mikkelsen

33 Management of Decompensated Right Ventricular Failure in the Intensive Care Unit 287
Rana Lee Adawi Awdish and Michael P. Mendez

34 Diffuse Alveolar Hemorrhage 295
Joshua Smith and Mark Daren Williams

Part IV Neurologic Disease
Romergryko G. Geocadin

35 Acute Stroke Emergency Management 303
Pravin George and Lucia Rivera Lara

36 Bacterial Meningitis in the ICU 315
Jennifer S. Hughes and Indhu M. Subramanian

37 Management of Intracerebral Hemorrhage 325
Shamir Haji and Neeraj Naval

38 Status Epilepticus 333
Jharna N. Shah and Christa O'Hana V. San Luis

39 Neuroleptic Malignant Syndrome 343
Kathryn Rosenblatt

40 Traumatic Brain Injury 355
Yogesh Moradiya and Romergryko G. Geocadin

41 Management of Anoxic Brain Injury 363
Maximilian Mulder and Romergryko G. Geocadin

Part V Renal Disease
John A. Kellum

42 Traditional and Novel Tools for Diagnosis of Acute Kidney Injury 375
Fadi A. Tohme and John A. Kellum

43 Management of Acute Kidney Injury 383
Fadi A. Tohme and John A. Kellum

44 Rhabdomyolysis 393
Saraswathi Gopal, Amir Kazory, and Azra Bihorac

45 Hyponatremia 401
Christian Overgaard-Steensen and Troels Ring

Part VI Endocrine Disease
Jonathan M. Fine and Robyn Scatena

46 Management of Severe Hyponatremia and SIADH 413
Robyn Scatena

47 Diabetic Ketoacidosis 419
Neal Hakimi and Jonathan M. Fine

48 Thyroid Storm 425
Matthew E. Schmitt and Robyn Scatena

49 Adrenal Insufficiency 433
Amy M. Ahasic and Anuradha Ramaswamy

50 Management of Hyperglycemic Hyperosmolar Syndrome 441
Elaine C. Fajardo

51 Management of Myxedema Coma 447
Aydin Uzun Pinar

Part VII Infectious Disease
Robert C. Hyzy

52 Urosepsis 453
Benjamin Keveson and Garth W. Garrison

53 Management of Sepsis and Septic Shock 457
Rommel Sagana and Robert C. Hyzy

54 Invasive Aspergillus 471
Elaine Klinge Schwartz

55 Management of Strongyloides Hyperinfection Syndrome 479
Shijing Jia, Hedwig S. Murphy, and Melissa A. Miller

56 Treatment of Viral Hemorrhagic Fever in a Well-Resourced Environment 485
Amit Uppal and Laura Evans

57 Management of Severe Malaria 495
Jorge Hidalgo, Pedro Arriaga, and Gloria M. Rodriguez-Vega

58 Dengue 509
Pedro Arriaga, Jorge Hidalgo, and Gloria M. Rodriguez-Vega

59 Chikungunya 513
Pedro Arriaga and Jorge Hidalgo

60 Leptospirosis 517
Jorge Hidalgo, Gloria M. Rodriguez-Vega, and Pedro Arriaga

Part VIII Gastrointestinal Disease
Robert C. Hyzy

61 Management of Acute Upper Gastrointestinal Hemorrhage 527
David Schrift and Carol H. Choe

62 Variceal Hemorrhage 535
Elizabeth A. Belloli and Steven E. Gay

63 Acute Pancreatitis 545
Margaret F. Ragland and Curtis H. Weiss

64 Management of Acute Liver Failure 551
Jessica L. Mellinger and Robert J. Fontana

65 Acute Lower Gastrointestinal Bleeding 561
Ali Abedi and Anoop M. Nambiar

66 Diagnosis and Management of Clostridium Difficile Infection (CDI) 569
Paul C. Johnson, Christopher F. Carpenter, and Paul D. Bozyk

67 Principles of Nutrition in the Critically Ill Patient 575
Jacqueline L. Gierer, Jill Gualdoni, and Paul D. Bozyk

68 Spontaneous Bacterial Peritonitis 581
Abdul W. Raif Jawid and Indhu M. Subramanian

69 ICU Management of the Patient with Alcoholic Liver Disease 589
Jessica L. Mellinger and Robert J. Fontana

Part IX Hematologic Disease
Robert C. Hyzy

70 Diagnosis and Management of Thrombotic Thrombocytopenic Purpura 605
Bravein Amalakuhan and Anoop M. Nambiar

71 Acute Leukemia Presentation with DIC 615
Laurie A. Manka and Kenneth Lyn-Kew

72 Disseminated Intravascular Coagulation 619
Mario V. Fusaro and Giora Netzer

73 Hemophagocytic Lymphohistiocytosis 625
Benjamin H. Singer and Hillary A. Loomis-King

74 ICU Complications of Hematopoietic Stem Cell Transplantation Including Graft Versus Host Disease 631
Peter C. Stubenrauch, Kenneth Lyn-Kew, and James Finigan

75 Tumor Lysis Syndrome 641
Himaja Koneru and Paul D. Bozyk

76 Management of Hyperviscosity Syndromes 647
Brian P. O'Connor and Indhu M. Subramanian

Part X Surgical
Lena M. Napolitano

77 Thoracic Trauma 657
Katherine M. Klein and Krishnan Raghavendran

78 Blunt Abdominal Trauma 665
Elizabeth C. Gwinn and Pauline K. Park

79 Abdominal Sepsis and Complicated Intraabdominal Infections 673
Sara A. Buckman and John E. Mazuski

80 Intestinal Obstruction: Small and Large Bowel 681
Joseph A. Posluszny Jr. and Fred A. Luchette

81 Management of Acute Compartment Syndrome 687
Ming-Jim Yang, Frederick A. Moore, and Janeen R. Jordan

82 Extracorporeal Membrane Oxygenation (ECMO) and Extracorporeal CO_2 Removal ($ECCO_2R$) 693
Eric T. Chang and Lena M. Napolitano

83 Management of Acute Thermal Injury 701
Kavitha Ranganathan, Stewart C. Wang and Benjamin Levi

84 Acute Arterial Ischemia 707
Danielle Horne and Jonathan L. Eliason

85 Management of Necrotizing Soft Tissue Infection 713
Heather Leigh Evans and Eileen M. Bulger

86 Biliary Infections 719
Gregory A. Watson and Andrew B. Peitzman

Part XI Critical Care in Obstetrics
Marie R. Baldisseri

87 Peripartum Cardiomyopathy 729
Hayah Kassis, Maria Patarroyo Aponte, and Srinivas Murali

88 Management of Amniotic Fluid Embolism 737
Susan H. Cheng and Marie R. Baldisseri

89 Respiratory Diseases of Pregnancy 743
Nithya Menon and Mary Jane Reed

90 Preeclampsia, Eclampsia and HELLP Syndrome 749
Meike Schuster, Emmie Ruth Strassberg, and Mary Jane Reed

Part XII Other Conditions
Robert C. Hyzy

91 Management of Severe Skin Eruptions. 759
Jad Harb, Andrew Hankinson, and Garth W. Garrison

92 Management of Alcohol Withdrawal Syndromes 765
Lucas A. Mikulic and Garth W. Garrison

Part XIII Medical Ethics
Robert C. Hyzy

93 End of Life Care in the ICU. 773
Sameer Shah and Nicholas S. Ward

Index. 781

Contributors

Ali Abedi, MD, MSc Department of Medicine, Division of Pulmonary Diseases and Critical Care Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Norman E. Adair, MD Pulmonary, Allergy and Critical Care Medicine, Wake Forest University/Wake Forest Baptist Health, Winston-Salem, NC, USA

Ayodeji Adegunsoye, MD Section of Pulmonary & Critical Care, Department of Medicine, University of Chicago Medicine, Chicago, IL, USA

Amy M. Ahasic, MD, MPH Department of Internal Medicine, Section of Pulmonary, Critical Care and Sleep Medicine, Yale University School of Medicine, New Haven, CT, USA

Bravein Amalakuhan, MD Department of Medicine, Division of Pulmonary Diseases and Critical Care Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Maria Patarroyo Aponte, MD Cardiovascular Institute, Allegheny Health Network, Pittsburgh, PA, USA

Pedro Arriaga, MD Internal Medicine, Karl Heusner Memorial Hospital, Belize City, Belize

Rohan Arya, MD Medicine, Division of Pulmonary and Critical Care Medicine, University of South Carolina School of Medicine, Columbia, SC, USA

Rana Lee Adawi Awdish, MS, MD Department of Pulmonary and Critical Care Medicine, Henry Ford Health System, Detroit, MI, USA

Marie R. Baldisseri, MD, MPH, FCCM Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Gregory W. Barsness, MD Internal Medicine, Cardiovascular Diseases and Radiology, Mayo Clinic, Rochester, MN, USA

Kristy A. Bauman, MD Pulmonary and Critical Care Medicine, University of Michigan Health System, Ann Arbor, MI, USA

Torben Kim Becker, MD, PhD Department of Emergency Medicine, University of Michigan, Ann Arbor, MI, USA

Elizabeth A. Belloli, MD Internal Medicine, Division of Pulmonary & Critical Care Medicine, University of Michigan Health System, Ann Arbor, MI, USA

David D. Berg, MD Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Thomas Bice, MD, MSc Pulmonary and Critical Care Medicine, University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Azra Bihorac, MD, MS, FCCM, FASN Department of Anesthesiology/ Division of Critical Care Medicine, University of Florida College of Medicine, Gainesvile, FL, USA

David M. Black, MD Emergency Medicine, University of Michigan Health System, Ann Arbor, MI, USA

David L. Bowton, MD, FCCP, FCCM Department of Anesthesiology, Section of Critical Care, Wake Forest University/Wake Forest Baptist Health, Winston-Salem, NC, USA

Paul D. Bozyk, MD Medical Intensive Care Unit, Department of Medicine, Beaumont Health, Royal Oak, MI, USA

Christine Martinek Brent, MD Emergency Medicine, University of Michigan Health System, Ann Arbor, MI, USA

Sara A. Buckman, MD, PharmD Department of Surgery, Section of Acute and Critical Care Surgery, Washington University, St. Louis, MO, USA

Eileen M. Bulger, MD Surgery, University of Washington, Seattle, WA, USA

Christopher F. Carpenter, MD Section of Infectious Diseases and International Medicine, Department of Medicine, Oakland University, Beaumont Health, Royal Oak, MI, USA

Shannon S. Carson, MD Pulmonary and Critical Care Medicine, University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Eric T. Chang, MD General Surgery, University of Michigan, Ann Arbor, MI, USA

Susan H. Cheng, MD, MPH Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Carol H. Choe, MD Critical Care Medicine, Lexington Medical Center, West Columbia, SC, USA

Ivan Nathaniel Co, MD Department of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA

Howard A. Cooper, MD Inpatient Cardiology, Division of Cardiology, Westchester Medical Center, Valhalla, NY, USA

Scott J. Denstaedt, MD Pulmonary and Critical Care Medicine, University of Michigan Health System, Ann Arbor, MI, USA

Robert P. Dickson, MD Medicine (Pulmonary and Critical Care), University of Michigan Health System, Ann Arbor, MI, USA

Jonathan L. Eliason, MD Section of Vascular Surgery, University of Michigan, Ann Arbor, MI, USA

Heather Leigh Evans, MD, MS Surgery, University of Washington/ Harborview Medical Center, Seattle, WA, USA

Laura Evans, MD, MSc Division of Pulmonary, Critical Care, and Sleep Medicine, New York University School of Medicine, New York, NY, USA

Elaine C. Fajardo, MD Internal Medicine Department, Section of Pulmonary, Critical Care and Sleep Medicine, Yale University School of Medicine, New Haven, CT, USA

Johnathan M. Fine, MD Internal Medicine, Pulmonary and Critical Section, Norwalk Hospital, Norwalk, CT, USA

James Finigan, MD Department of Medicine, National Jewish Health, Denver, CO, USA

Robert J. Fontana, MD Division of Gastroenterology, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA

Mario V. Fusaro, MD Medicine, Division of Pulmonary and Critical Care, New York Medical College, Westchester Medical Center, Valhalla, NY, USA

Garth W. Garrison, MD Division of Pulmonary and Critical Care Medicine, University of Vermont Medical Center, Burlington, VT, USA

Steven E. Gay, MD Division of Pulmonary and Critical Care Medicine, University of Michigan Health System, Ann Arbor, MI, USA

Romergryko G. Geocadin, MD Neurology, Neurosurgery and Anesthesiology – Critical Care Medicine, Neurosciences Critical Care Division, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Pravin George, BA, DO Neuroscience Critical Care, Anesthesia Critical Care Medicine, The Johns Hopkins Hospital, Baltimore, MD, USA

Jacqueline L. Gierer, DO Internal Medicine, Beaumont Health, Royal Oak, MI, USA

Timothy D. Girard, MD, MSCI Division of Allergy, Pulmonary and Critical Care Medicine and Center for Health Services Research in the Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA

Geriatric Research, Education and Clinical Center (GRECC) Service and Medical Service, Department of Veterans Affairs Medical Center, Tennessee Healthcare System, Nashville, TN, USA

Joshua M. Glazer, MD Emergency Medicine, University of Michigan Health System, Ann Arbor, MI, USA

Saraswathi Gopal, MD Division of Nephrology Hypertension and Renal Transplantation, Department of Medicine, University of Florida, Gainesville, FL, USA

Jill Gualdoni, MD Internal Medicine, Beaumont Health, Royal Oak, MI, USA

Kyle J. Gunnerson, MD Emergency Medicine, Internal Medicine and Anesthesiology, Division of Emergency Critical Care, University of Michigan Health System, Ann Arbor, MI, USA

Elizabeth C. Gwinn, MD Acute Care Surgery, University of Michigan, Ann Arbor, MI, USA

Ryan Hadley, MD Pulmonary and Critical Care Medicine, Spectrum Health, Grand Rapids, MI, USA

Shamir Haji, MSc, MD Anesthesia and Critical Care Medicine, Johns Hopkins Hospital, Baltimore, MD, USA

Neal Hakimi, MD Medicine, Section of Pulmonary, Critical Care and Sleep Medicine, Yale University School of Medicine, New Haven, CT, USA

Andrew Hankinson, MD Dermatology, University of Vermont Medical Center, Burlington, VT, USA

Jad Harb, MD Pulmonary and Critical Care Medicine, University of Vermont Medical Center, Burlington, VT, USA

Carrie E. Harvey, MD Anesthesiology, University of Michigan Health System, Ann Arbor, MI, USA

Jorge Hidalgo, MD, MACP, MCCM, FCCP Adult Intensive Care, Critical Care Division, Karl Heusner Memorial Hospital, Belize City, Belize

Danielle Horne, MD, MS Section of Vascular Surgery, University of Michigan, Ann Arbor, MI, USA

Michael D. Howell, MD, MPH Center for Healthcare Delivery Science and Innovation, University of Chicago Medicine, Chicago, IL, USA

Jennifer S. Hughes, MD, MS Department of Internal Medicine, Highland Hospital, Alameda Health System, Oakland, CA, USA

Robert C. Hyzy, MD Critical Care Medicine Unit, Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA

Shijing Jia, MD Internal Medicine, Pulmonary and Critical Care, University of Michigan, Ann Arbor, MI, USA

Paul C. Johnson, MD Infectious Diseases, Beaumont Health, Royal Oak, MI, USA

Brandon M. Jones, MD Cardiovascular Medicine and Interventional Cardiology, Cleveland Clinic Foundation, Cleveland, OH, USA

Janeen R. Jordan, MD, FACS Department of Surgery, University of Florida, Gainesville, FL, USA

Hayah Kassis, MD Cardiovascular Institute, Allegheny Health Network, Pittsburgh, PA, USA

Jason N. Katz, MD, MHS Medicine, Mechanical Heart Program, Cardiac Intensive Care Unit, Cardiothoracic Intensive Care Unit & Critical Care Service, Cardiovascular Clinical Trials, University of North Carolina, Chapel Hill, NC, USA

Amir Kazory, MD Medicine/Nephrology, University of Florida, Gainesville, GA, USA

John A. Kellum, MD, MCCM, FACP Critical Care Research, Center for Critical Care Nephrology, Critical Care Medicine University of Pittsburgh, Pittsburgh, PA, USA

Benjamin Keveson, MD Division of Pulmonary and Critical Care Medicine, University of Vermont Medical Center, Burlington, VT, USA

Katherine M. Klein, MD Surgical Critical Care, General Surgery, Department of Surgery, University of Toledo, Toledo, OH, USA

Himaja Koneru, MD Internal Medicine, Beaumont Health, Royal Oak, MI, USA

John P. Kress, MD Medical Intensive Care Unit, Section of Pulmonary & Critical Care, Department of Medicine, University of Chicago Medicine, Chicago, IL, USA

Mark W. Landmeier, MD Department of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Benjamin Levi, MD Department of Surgery, University of Michigan Health Systems, Ann Arbor, MI, USA

John M. Litell, DO Department of Emergency Medicine, Division of Emergency Critical Care, University of Michigan Health System, Ann Arbor, MI, USA

Hillary A. Loomis-King, MD Internal Medicine, Division of Pulmonary and Critical Care Medicine, University of Michigan Health System, Ann Arbor, MI, USA

Fred A. Luchette, MD, MSc Department of Surgery, Stritch School of Medicine, Loyola University of Chicago, VA Affairs, Surgical Service Lines, Edward Hines Jr., Veterans Administration Medical Center, Maywood, IL, USA

Kenneth Lyn-Kew, MD Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, CO, USA

Jason H. Maley, MD Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Laurie A. Manka, MD Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Denver, CO, USA

John E. Mazuski, MD, PhD Department of Surgery, Washington University in Saint Louis School of Medicine, Saint Louis, MO, USA

Gregory T. Means, MD Cardiology, Department of Medicine, University of North Carolina, Chapel Hill, NC, USA

Jessica L. Mellinger, MD, MSc Division of Gastroenterology, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA

Michael P. Mendez, MD Department of Pulmonary and Critical Care Medicine, Henry Ford Health System, Detroit, MI, USA

Nithya Menon, MBBS, MD Pulmonary and Critical Care, Geisinger Medical Center, Danville, PA, USA

Venu Menon, MD Cardiovascular ICU, Cardiovascular Medicine and Cardiovascular Imaging, Cleveland Clinic Foundation, Cleveland, OH, USA

Mark E. Mikkelsen, MD, MSCE Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Lucas A. Mikulic, MD Pulmonary and Critical Care Medicine, University of Vermont Medical Center, Burlington, VT, USA

Melissa A. Miller, MD, MS Internal Medicine, University of Michigan Medical School, Ann Arbor VA Health System, Ann Arbor, MI, USA

Patrick George Minges, MD, BS Department of Emergency Medicine, University of Michigan Hospitals, Ann Arbor, MI, USA

Frederick A. Moore, MD, FACS Department of Surgery, University of Florida, Gainesville, FL, USA

Yogesh Moradiya, MD Neurosurgery, Hofstra Northwell School of Medicine, Manhasset, NY, USA

David A. Morrow, MD, MPH Levine Cardiac Intensive Care Unit, TIMI Biomarker Program, TIMI Study Group, Department of Medicine, Cardiovascular Division, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA

Maximilian Mulder, MD Neurocritical Care Unit, Department of Critical Care, Abbott Northwestern Hospital, Minneapolis, MN, USA

Srinivas Murali, MD, FACC Cardiovascular Institute, Allegheny Health Network Cardiovascular Medicine, Allegheny General Hospital, Pittsburgh, PA, USA

Hedwig S. Murphy, MD, PhD Department of Pathology, University of Michigan and Veterans Affairs Ann Arbor Health System, Ann Arbor, MI, USA

Anoop M. Nambiar, MD Department of Medicine, Division of Pulmonary Diseases and Critical Care Medicine, University of Texas Health Science Center at San Antonio and the Audie L. Murphy VA Hospital, South Texas Veterans Health Care System, San Antonio, TX, USA

Andrew M. Namen, MD, FCCP, FAASM Pulmonary, Critical Care, Allergy & Immunology, Wake Forest University/Wake Forest Baptist Health, Winston-Salem, NC, USA

Lena M. Napolitano, MD Department of Surgery, Division of Acute Care Surgery, Trauma and Surgical Critical Care, University of Michigan Health System, Ann Arbor, MI, USA

Neeraj Naval, MD Inpatient Neurosciences & Neurocritical Care, Lyerly Neurosurgery, Baptist Neurological Institute, Jacksonville, FL, USA

Giora Netzer, MD, MSCE Medicine and Epidemiology, Division of Pulmonary and Critical Care Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

Robert W. Neumar, MD, PhD Department of Emergency Medicine, University of Michigan Medical School, Ann Arbor, MI, USA

Brian P. O'Connor, MD, MPH Department of Internal Medicine, Highland Hospital, Alameda Health System, Oakland, CA, USA

Benjamin A. Olenchock, MD, PhD Department of Medicine, The Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Ronny M. Otero, MD Emergency Medicine, University of Michigan Hospital, Ann Arbor, MI, USA

Christian Overgaard-Steensen, MD, PhD Department of Neuroanaesthesiology, Rigshospitalet, Copenhagen, Denmark, USA

Pauline K. Park, MD Acute Care Surgery, University of Michigan, Ann Arbor, MI, USA

Andrew B. Peitzman, MD Department of Surgery, Trauma and Surgical Services, University of Pittsburgh School of Medicine, UPMC-Presbyterian, Pittsburgh, PA, USA

Aydin Uzun Pinar, MD Medical Intensive Care Unit, Department of Medicine, Section of Pulmonary Critical Care and Sleep Medicine, Yale School of Medicine, New Haven, CT, USA

Joseph A. Posluszny, Jr., MD Surgery, Loyola University Stritch School of Medicine, Edward Hines Jr. Veterans Administration Medical Center, Maywood, IL, USA

Arman Qamar, MD Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Krishnan Raghavendran, MBBS, MS, FRCS Department of Surgery, University of Michigan, Ann Arbor, MI, USA

Margaret F. Ragland, MD, MS Department of Medicine, Northwestern Feinberg School of Medicine, Chicago, IL, USA

Abdul W. Raif Jawid, MD Department of Internal Medicine, Highland Hospital, Alameda Health System, Oakland, CA, USA

Anuradha Ramaswamy, MD, FACP Section of Pulmonary, Critical Care and Sleep Medicine, Yale University School of Medicine, New Haven, CT, USA

Kavitha Ranganathan, MD Department of Surgery, University of Michigan Health Systems, Ann Arbor, MI, USA

Mary Jane Reed, MD, FACS, FCCM, FCCP Critical Care Medicine, Geisinger Medical Center, Danville, PA, USA

Troels Ring, MD Nephrology, Aalborg University Hospital, Aalborg, Denmark, USA

Lucia Rivera Lara, MD Neurology, Johns Hopkins University, Baltimore, MD, USA

Gloria M. Rodríquez-Vega, MD, FACP, FCCP, FCCM Department of Critical Care Medicine, Hospital Hima – San Pablo – Caguas, Rio Piedras, PR, USA

Kathryn Rosenblatt, MD Anesthesiology & Critical Care Medicine, Division of Neuroanesthesia and Neurosciences Critical Care, Johns Hopkins Hospital, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Rommel Sagana, MD Pulmonary & Critical Care, University of Michigan, Ann Arbor, MI, USA

Christa O'Hana V. San Luis, MD Neurology, Division of Neurocritical Care, University of Mississippi Medical Center, Jackson, MS, USA

Robyn Scatena, MD Yale University School of Medicine, Department of Medicine, Section of Pulmonary, Critical and Sleep, Norwalk Hospital, Norwalk, CT, USA

Mark Schmidhofer, MS, MD Department of Medicine, University of Pittsburgh School of Medicine, Heart and Vascular Institute, UPMC Health System, Pittsburgh, PA, USA

Matthew E. Schmitt, MD Pulmonary, Critical Care and Sleep Medicine, Norwalk Hospital, Norwalk, CT, USA

David Schrift, MD Clinical Internal Medicine, Pulmonary and Critical Care Medicine, University of South Carolina School of Medicine, Columbia, SC, USA

Meike Schuster, DO Maternal Fetal Medicine, Geisinger Medical Center, Danville, PA, USA

Elaine Klinge Schwartz, MD, FCCP Department of Medicine, National Jewish Health, Denver, CO, USA

Benjamin M. Scirica, MD, MPH Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Jacob Scott, MD Pulmonary and Critical Care Medicine, Spectrum Health, Grand Rapids, MI, USA

Daniel Sedehi, MD Cardiovascular Medicine, Knight Cardiovascular Institute, Oregon Health and Science University, Portland, OR, USA

Janek Manoj Senaratne, MD, BMedSci Division of Cardiology, University of Alberta, Edmonton, AB, Canada

Robert W. Shaffer, MD Department of Emergency Medicine, University of Michigan Health System, Ann Arbor, MI, USA

Sameer Shah, MD Pulmonary and Critical Care Medicine, Medicine, Rhode Island Hospital/Brown University, Providence, RI, USA

Jharna N. Shah, MBBS, MPH Division of Neurosciences Critical Care, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Michael G. Silverman, MD Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA

Benjamin H. Singer, MD, PhD Internal Medicine, Division of Pulmonary and Critical Care Medicine, University of Michigan Medical School, Ann Arbor, MI, USA

Thomas H. Sisson, MD Pulmonary and Critical Care Medicine, University of Michigan Hospital and Health Systems, Ann Arbor, MI, USA

Joshua Smith, MD Internal Medicine – Division of Pulmonary and Critical Care Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

Jennifer P. Stevens, MD, MS Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

Emmie Ruth Strassberg, DO Maternal Fetal Medicine, Geisinger Health System, Danville, PA, USA

Peter C. Stubenrauch, MD Pulmonary and Critical Care Medicine, National Jewish Health, Denver, CO, USA

Indhu M. Subramanian, MD Pulmonary and Critical Care Faculty, Department of Internal Medicine, Highland Hospital, Alameda Health System, Oakland, CA, USA

Sohaib Tariq, MD Division of Cardiology, Westchester Medical Center, Valhalla, NY, USA

Fadi A. Tohme, MD Renal & Electrolyte Division, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Amit Uppal, MD Division of Pulmonary, Critical Care, and Sleep Medicine, New York University School of Medicine, New York, NY, USA

Sean van Diepen, MD, MSc Critical Care Medicine, Division of Cardiology, University of Alberta Hospital, Edmonton, AB, Canada

Stewart C. Wang, MD, PhD Burn Surgery, Department of Surgery, University of Michigan Health Systems, Ann Arbor, MI, USA

Nicholas S. Ward, MD Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Alpert/Brown Medical School, Providence, RI, USA

Gregory A. Watson, MD Surgery & Critical Care, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Curtis H. Weiss, MD, MS Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Sage P. Whitmore, MD Emergency Medicine, Division of Emergency Critical Care, University of Michigan Health System, Ann Arbor, MI, USA

Mark Daren Williams, MD, FCCM, FCCP Pulmonary/Critical Care Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

Richard G. Wunderink, MD Department of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Ming-Jim Yang, MD, MS Department of Surgery, University of Florida, Gainesville, FL, USA

Part I

ER- ICU Shock and Resuscitation

Robert W. Neumar

Cardiac Arrest Management

1

Ronny M. Otero

Introduction

It is currently estimated that over 300,000 out-of-hospital cardiac (OHCA) arrests occur in the United States. Over half of OHCA cases are managed by EMS systems [1]. The national average for survival from an OHCA is approximately 12 % however; there is considerable variation by region and EMS system [2, 3]. Factors associated with an improved survival from OHCA include crew witnessed arrest and bystander CPR [4]. Survival from witnessed VF arrest decreases by 8 % for every minute delay in CPR and defibrillation [5]. Overall outcomes correlate with early implementation of chest compression. There is a strong suggestion that bystander CPR whether with "chest compression only" or standard CPR is associated with better mortality and neurologic outcomes [6, 7].

Early effective chest compressions and attention to basic life support components are part of high quality CPR. Various organizations have revisited each of the components of cardiac arrest resuscitation over the last couple of years and thus the elements of high-quality CPR are "ever-evolving" [8]. Rapid activation of the "Chain of Survival" and meticulous attention to early defibrillation and chest compressions may lead to greater overall trends in survival.

Case Presentation

A 68 year-old male was playing cards at a casino when suddenly he clutched his chest and became unresponsive. Casino security arrived within less than a minute and applied an automated external defibrillator (AED). AED displayed an audio prompt that "no shock was advised". Bystander cardiopulmonary resuscitation (CPR) was begun within another 10 s. Paramedics arrived and provided two-rescuer CPR with a compression rate of 110 compressions/minute. In the ambulance rescuers used a mechanical compression device to administer continuous chest compressions at a rate of 110 and depth of 2.5 inches with manual ventilation using a bag mask valve. This support was continued until their arrival at the hospital in approximately 9 min. Patient was not intubated in the field. During CPR there was no evidence of an organized cardiac rhythm. Patient had received a total of 3 doses of epinephrine totaling 3 mg via humeral intra-osseous line. Upon arrival in the emergency department endotracheal intubation was performed without incident and capnography displayed a good waveform with an $ETCO_2$ of 15 mm Hg. On arrival emergency physicians administered another dose of epinephrine while continuing CPR. At this point the team leader

Electronic supplementary material The online version of this chapter (doi:10.1007/978-3-319-43341-7_1) contains supplementary material, which is available to authorized users.

R.M. Otero
Emergency Medicine, University of Michigan Hospital, Ann Arbor, MI, USA
e-mail: Oteror@umich.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_1

paused and solicited ideas from the team about possible etiologies for persistent pulseless electrical activity (PEA).

Question What are methods to assess the quality of chest compressions during CPR?

Answer Capnography, arterial blood pressure and coronary perfusion pressure

Components of high quality CPR include minimizing interruptions of chest compressions with a chest compression fraction of >60 %, correct chest compression rate and depth. Recommended chest compression rates are greater than 100 and a depth of 50 mm with allowance for chest recoil between compression and minimizing ventilations to no more than 10–12 breaths/minute [9–12]. The emphasis of chest compressions over positive pressure ventilation has been supported by studies, which have shown a mortality benefit of compression only CPR in witnessed arrest compared with traditional CPR with compressions and ventilation [13]. How well chest compressions are meeting the goal of providing circulatory flow to the brain and vital systems is often difficult to ascertain.

Of the readily available parameters capnography and arterial blood pressure monitoring are the most easily applied measurements to provide feedback of the quality of chest compressions. Close attention to the physiologic response to chest compressions is desirable, as studies indicate that even healthcare professionals have poor recall and variable quality when performing chest compressions [14].

Capnography has long-been seen as a potential surrogate for blood flow through heart and the pulmonary circulation [15]. As the technology has improved so has the portability. Capnography can now be measured by sidestream technology in non-intubated patients and or mainstream capnography in intubated patients. During cardiopulmonary resuscitation the goal of high quality chest compressions is to achieve an end-tidal CO_2 of 20 mm Hg or higher and to maintain an end-tidal CO_2 greater than 10 mm Hg at all times with compressions. A rapid rise in end-tidal CO_2 with chest compression to close to 35 mm Hg may signal return of spontaneous circulation (ROSC) [15–17].

Achieving a higher blood pressure during CPR makes intuitive sense, as thoracic compression and thus, cardiac output will be the driving force behind improving cerebral and systemic perfusion. However, the hemodynamics of cardiac arrest is complex and patient-specific factors may be responsible for the variable responses to chest compressions, vasopressors and ventilation. One of the main determinants of successful resuscitation is the coronary perfusion pressure (CPP), which is the difference between the right atrial pressure (or CVP) and aortic pressure during diastole (relaxation phase of chest compression). In the arrested patient there is a delay until there is a complete cessation of flow through the cardiac chambers and by 1 min there is no flow to the coronary arteries. In a human study a CPP < 15 mm Hg was associated with not achieving ROSC [18]. In animal studies it has been shown that higher levels of CPP are required to provide cerebral blood flow when CPR is delayed [19]. Moreover, in studies where ROSC was achieved in humans, it was closely tied to CPP and aortic diastolic pressure [20]. CPR guided by blood pressure has also shown improved outcomes [21]. In the observational human study evaluating coronary perfusion pressure as the correlate to ROSC a mean maximal aortic relaxation pressure (aka diastole) was 35.2 ± 11.5, thus the diastolic pressure target should be approximately 40 mm Hg [18]. In settings where a patient is instrumented with an arterial and a central venous line, aortic diastolic pressure and right atrial pressure can be substituted by arterial diastolic pressure and central venous pressure. The difference between arterial diastolic pressure and central venous pressure may provide a rough estimate of CPP [22]. When the ability to monitor CPP is unavailable a strategy to assess the efficacy of chest compressions may depend upon capnography and diastolic pressure.

Lastly, emerging technology, which provides instantaneous feedback about the quality of chest compressions is now available. This CPR-sensing feedback (FB) system often utilizes accelerome-

ters to detect rate and depth of compressions while delivering audio cues to the rescuer. Currently available CPR-FB systems include the Phillips Q-CPR ®, Zoll Real CPR Help ® and Physio-Control compression metronome and Code Stat ® [23]. It is not known at this time whether utilizing these CPR-FB systems improves outcomes.

Principles of Management

Standard Approach to Resuscitation

Introduction

Achieving optimal outcomes from cardiac arrest requires collaboration between several disciplines including pre-hospital providers, emergency physicians, cardiologists, cardiac interventionalist as well as several other medical professionals and specialists. All providers in this paradigm should understand each other's role as well as what measures can be expected to be offered to a victim of sudden cardiac arrest.

Recognition of Sudden Cardiac Arrest

The ability of laypersons as well as health professionals to detect a pulse has been reported to be extremely poor [14, 24]. Additionally, agonal breaths may be seen for several minutes after cardiac arrest confounding the confirmation that a patient has arrested. Despite these limitations it is best to activate emergency response system as soon as a patient is unresponsive with a faint or absent pulse.

Chest Compressions

After a pulse check of no more than 10 s chest compressions should be initiated at once. Health care providers should re-double their efforts to improve their knowledge and maintain technical skills relevant to chest compressions. Evidence for maintaining these skills may be gleaned from a multi-center study whereby healthcare providers often performed suboptimal chest compression rates. Specifically, the mean chest compression rate was below the recommended rate and lowest for patients without ROSC (79 ± 18) compared to patients with ROSC (90 ± 17) [3].

Specific goals of high quality CPR include achieving a compression rate of at least 100–120 compression/minute and a compression depth of at least 50 mm (2 inches) with an upper limit of 60 mm (2.4 inches) [9]. Additionally, high quality chest compressions should include a chest compression fraction >60 %, meaning when CPR is performed chest compressions should occupy at least 60 % of the resuscitation [9]. Patient positioning, vascular or intraosseous access, medication administration, airway establishment, rhythm analysis and defibrillation should occupy the remaining fraction of time. Maintaining a chest compression rate of 100–120 compressions/minute can lead to rescuer fatigue. Switching compressors every 2 min may minimize rescuer fatigue but lead to frequent interruptions and may negatively impact chest compression fraction. One suggestion to decrease this "hands-off" time is to have rescuers switch from opposite sides of the victim [25]. Between compressions there should be time allowed for full chest recoil in order for heart to refill with blood and maximizing CPP.

Adjuncts to CPR: Oxygen and Ventilation

During the initial rounds of chest compressions rescuers should focus on the quality of the compressions and use passive oxygenation with the highest concentration of oxygen available at the time. The delivery of this oxygen is dependent upon the systemic perfusion that may be established by chest compressions.

Attempts to establish a definitive airway should be postponed unless there is difficulty ventilating a patient with a bag valve mask. Furthermore, hyperventilation should be avoided as this has been tied to reducing cardiac output [26, 27]. When two providers are resuscitating a patient ventilations are delivered in a 30:2 compression-to-ventilation ratio until a definitive airway has been established [28]. Using a 1 L bag mask device a second provider should provide approximately 600 cc of tidal volume over 1 s. This should be performed a total of two times after every 30 compressions. With an advanced

airway in place rescuers may provide a breath every 6 s while chest compressions are performed continuously.

Defibrillation

Defibrillation is indicated for ventricular fibrillation or pulseless ventricular tachycardia. Although traditionally monophasic defibrillators have been used to administer a counter shock, biphasic defibrillators are preferred due to the greater first shock success. Newer waveforms have been studied which provide patient-specific impedance current delivery using biphasic truncated exponential, rectilinear biphasic or pulsed biphasic wave. At this time there is no specific recommendation regarding which waveform is superior. Current recommendations are to administer a single counter shock at an optimal energy level (between 120 and 360 J for biphasic defibrillators) with minimal interruptions in CPR before and after the shock [28]. In situations requiring repeated defibrillations use manufacturers' guidelines or consider escalating energy. For refractory VF and pulseless VT, administration of epinephrine and an anti-dysrhythmic agent should be instituted.

Search for Precipitating Cause of Cardiac Arrest

Ventricular Dysrhythmias

Survival to discharge for patients with an initial rhythm of VT or VF is between 15 and 23 % for out-of-hospital cardiac arrest and up to 37 % for patients with an in-hospital cardiac arrest [29, 30]. Resuscitation team leaders must simultaneously look for reversible etiologies while administering time-sensitive interventions. Ventricular fibrillation is usually found in patients with abnormal myocardial perfusion from a prior infarct or ongoing ischemia. Similarly ventricular tachycardia usually results from foci below the AV node which progresses into a wide and regular tachycardia. When confronted with these malignant ventricular dysrhythmias diagnostic considerations include medication toxicity, pre-existing channelopathy (Brugada syndrome) or an electrolyte abnormality. If medication toxicity and electrolyte abnormalities are ruled out persistence of these dysrhythmias should prompt search for myocardial ischemia.

Different forms of ventricular tachycardia exist including: monomorphic VT, polymorphic VT, torsade de pointes, right ventricular outflow tachycardia (idiopathic and arrhythmogenic right ventricular dysplasia), fascicular tachycardia, bidirectional VT and ventricular flutter. Monomorphic VT accounts for the majority of VT encountered. Most cases of monomorphic VT are associated with myocardial ischemia. Torsade de pointe is a specific form of polymorphic VT where there is progressive widening of the QT interval. Although most forms of VT are associated with myocardial ischemia there are forms of idiopathic VT. Of the idiopathic forms of VT, most cases are due to abnormalities in the outflow tract of the right ventricle. A small number of these have an anatomically identified focus termed "arrhythmogenic right ventricular dysplasia". Ventricular flutter is an extreme form of VT that has a sinusoidal appearance and may degrade into ventricular fibrillation. Ventricular flutter usually has a rate >200 beats/min. Thus when confronted with a patient with refractory ventricular dysrhythmias providers should strongly consider consulting a cardiology specialist to evaluate patient for the possibility of a diagnostic and percutaneous intervention.

Pulseless Electrical Activity (PEA)

Patients with PEA have a survival to discharge of 2.77 % for patients with out-of-hospital cardiac arrest as compared to patient in an in-hospital cardiac arrest of only 12 % [30, 31]. PEA is defined as the absence of a pulse when electrical cardiac activity is present. This is further classified as "true" PEA, which is when there is no pulse, the presence of an electrical signal but no evidence of cardiac activity usually detected by echocardiography. "Pseudo-PEA" is defined as the absence of a pulse, presence of an electrical signal and cardiac activity observed by echocardiography.

It is important to make these distinctions, as there is pathophysiologic and prognostic significance. True PEA is when electromechanical uncou-

pling of cardiac cells which propagate an electrical signal but the myocytes are unable to coordinate ventricular contraction. This situation is usually seen in severe hypoxia, acidosis or necrosis.

In pseudo-PEA, there is an electrical signal and weak cardiac contractions due to conditions such as hypovolemia, massive pulmonary embolism or other mechanical impediments to flow. In these situations the predominant rhythm is a tachydysrhythmia.

A mnemonic, which has been modified over the years to remind providers of the common precipitants of PEA, is "4Hs-4Ts". This mnemonic represents – hypoxia, hypovolemia, hypo/hyperkalemia and hypothermia as well as thrombosis (pulmonary emboli), tamponade (cardiac), toxins and tension pneumothorax [32].

Point of care ultrasound whenever possible should be used to assist clinicians to investigate many of the above-mentioned etiologies. For instance, a subcostal view on ultrasound may reveal a large pericardial effusion with diastolic collapse of right ventricle representing cardiac tamponade (Video 1.1). A parasternal short axis view may demonstrate bowing of the intra-ventricular septum, the so called "D-sign" appearance of the left ventricle being compressed by a volume-overloaded right ventricle contracting against a massive pulmonary embolism (Video 1.2).

Littman et al. proposes a diagnostic guide to evaluate causes of PEA which includes evaluating the width of the QRS complexes on EKG as well as combining sonographic findings to suggest whether a mechanical, ischemic or metabolic cause are to blame [33]. There is no randomized study to support ultrasound-guided resuscitations over resuscitations without ultrasound but a recent study has suggested a trend that when modifications in traditional approaches employ ultrasound there may be a higher rate of ROSC to hospital admission [34].

Quality Assurance

Every cardiac arrest should have some method to monitor the quality of the resuscitation. The ability of rescuers to retain critical resuscitation skills wanes after 6 months thus implementing simulated resuscitations may be useful in retaining skills [35]. Short debriefing sessions after performing a cardiac resuscitation have been shown to improve team performance and outcomes [36].

Evidence Contour

Are Outcomes with Mechanical Compressions Superior to Manual Compressions During Active CPR?

Based upon currently available data mechanical compressions do not appear to be superior to manual compressions in terms of outcomes. Manual compressions are the most readily applicable and commonly taught method of providing chest compressions. Despite this many prehospital and hospital systems have chosen to use mechanical compression devices to administer chest compression for various logistical reasons.

Over the last 40 years various technologies have emerged to provide high quality and consistency of chest compressions. These technologies are based upon one of two predominant theories of how chest compressions promote forward flow of blood into the thoracic aorta and systemic circulation. The so-called "cardiac pump" theory expounds that external chest compressions places pressure simultaneously on the right and left ventricle. During the active compression phase a pressure gradient pushes blood out of ventricles, while closing the atrio-ventricular valves and then to the pulmonary artery and the aorta. During the decompression phase blood re-enters the right and left atrium and feeds coronary arteries [37].

The "thoracic pump" theory relies upon the compliance of the whole thorax as the main pressure determinant of flow and not on compression of the heart. During compressions in the "thoracic pump" theory intra-thoracic pressure is increased driving blood into the thoracic, extra-thoracic aorta and other large arteries preferentially. This compression however does not seem to affect the venous system as much due to valves and the vast network of venous plexuses. During

Fig. 1.1 Thumper ™ piston driven chest compression device (Courtesy of Michigan Instruments, Inc.)

Fig. 1.2 LUCAS™ Chest compression device (Used with permission of Physio-Control, Inc.)

the decompression phase intra-thoracic pressure falls below the extra-thoracic pressure and blood flows to the lungs.

Mechanical compression devices became available for research and clinical applications during the 1970s with the Thumper ® created by Michigan Instrument which utilized a hydraulically powered piston to provide chest compressions similar to the "cardiac pump theory" (Fig. 1.1). Newer devices emerged including the Lund University Cardiac Arrest System (aka. LUCAS 1 and 2 ®) by Physio Control and the Auto Pulse ® by Zoll employ different mechanisms to enhance chest compressions namely through an active compression and decompression mode. The LUCAS ® device is predominantly a piston-driven device with a suction area which makes contact with the chest (Fig. 1.2). The Auto Pulse ® utilizing a load-distributing band which wraps around the torso and squeezes to increase intra-thoracic pressure (Fig. 1.3).

Fig. 1.3 Auto Pulse ™ Load distributing chest compression device (Courtesy of ZOLL Medical Corporation)

Despite various studies utilizing transthoracic and trans esophageal dopplers to investigate the hemodynamics during chest compressions there is no consistent data to support either the "cardiac pump or "thoracic pump" as the main mechanism of flow during CPR [19, 38]. It is possible that there are elements of both pump models active during CPR.

Advocates of mechanical compressions support its consistency of depth and compression rate. Mechanical compressions can maximize "hands on" time compared to manual compressions due to the fact that there is no need to switch

rescuers or halt compressions when performing defibrillation. Despite these theoretical advantages a study completed in 2014 did not show a mortality benefit of mechanical CPR over manual compressions [39]. This study, which used the LUCAS device showed no difference in survival or neurologic outcome. The added cost of these devices and their upkeep may prohibit widespread use however providers point to the advantage of reducing rescuer fatigue and diminishing risk to rescuers during transport while CPR is in progress [40, 41].

What Physiologic Parameters Can Guide the Administration of Vasoactive Medications and Provide Feedback Regarding Quality of CPR?

Hemodynamic Directed Resuscitation

Hemodynamic directed resuscitation (or patient-centric cardiopulmonary resuscitation) is a concept whereby the decision to administer a pharmacologic agents such as epinephrine is guided by hemodynamic variables. This concept may have developed due to various studies indicating that epinephrine may have several deleterious effects on the heart [42]. A strategy whereby resuscitation is guided by hemodynamic parameters rather than protocolized and repetitive administration of epinephrine may potentially minimize inadvertent epinephrine toxicity [42].

Ever since the seminal studies by Ewy and Paradis which tied successful resuscitation to coronary perfusion pressure (CPP) there has been a resurgence of interest in evaluating CPP or a "surrogate of CPP" during CPR [18, 43]. In an animal study which compared CPR guided by CPP vs. chest compressions at 33 mm depth plus standard dose epinephrine vs. chest compressions at 51 mm depth plus standard dose epinephrine the largest improvement in cerebral perfusion pressure was found in the group that was guided by CPP [44]. In another similar study, CPR guided by systolic blood pressure was associated with the highest 24-h survival compared to conventional guideline care [21]. Despite controversy surrounding the use of central venous oxygen saturation ($ScvO_2$) in the management of sepsis its application may be used as an estimate of tissue perfusion. $ScvO_2$ represents the residual oxygen content returning to the right side of the heart after systemic perfusion. Studies have shown that persistently low $ScvO_2$ correlates with decrease cardiac output. If available, chest compressions may be titrated to a $ScvO_2$ concentration greater than 30 % [45, 46].

Whether hemodynamic directed resuscitation leads to better outcomes in humans remains unknown but if efforts to improve the rate of bystander CPR and high quality chest compressions are successful there may be less dependence upon the pharmacologic treatment to achieve ROSC.

References

1. Daya MR, et al. Out of Hospital Cardiac Arrest survival improving over time: results from the Resuscitation Outcomes Consortium (ROC). Resuscitation. 2015;91:108–15.
2. Prevention, C.f.D.C.a. Cardiac Arrest Registry to Enhance Survival (CARES) National Summary Report: Non-Traumatic National Survival Report. 2014. https://mycares.net/sitepages/reports2014.jsp. Accessed 4 Jan 2016.
3. Abella BS, Sandbo N, Vassilatos P. Chest compression rates during cardiopulmonary resuscitation are suboptimal: a prospective study during in-hospital cardiac arrest. Circulation. 2005;111:428–34.
4. Hollenberg J, Herlitz J, Lindqvist J. Improved survival after out of hospital cardiac arrest is associated with an increase in proportion of emergency crew-witnessed cases and bystander cardiopulmonary resuscitation. Circulation. 2008;118:389–96.
5. Sutton R, Nadkarni V, Abella BS. "Putting it all together" to improve resuscitation quality. Emerg Med Clin N Am. 2012;30(1):105–22.
6. Bernard SA, Buist M. Induced hypothermia in critical care medicine: a review. Crit Care Med. 2003;31(7):2041–51.
7. Bohm K, et al. In patients with out-of-hospital cardiac arrest, does the provision of dispatch cardiopulmonary resuscitation instructions as opposed to no instructions improve outcomes: a systematic review of the literature. Resuscitation. 2011;82:1490–5.
8. Hazinski M, et al. Part 1: Executive Summary: 2015: International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Circulation. 2015;132:S2–39.

9. Neumar N, et al. Executive Summary Part 1: 2015 American Heart Association Guidelines Update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132 Suppl 2:S315–67.
10. Wik L, Kramer-Johansen J, Myklebust H. Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. JAMA. 2005;293(3):299–304.
11. Idris A, Guffey D, Pepe P. Chest compression rates and survival following out-of-hospital cardiac arrest. Crit Care Med. 2015;43(4):840–8.
12. Meaney P, Bobrow B, Mancini M. CPR quality: improving cardiac resuscitation outcomes both inside and outside the hospital. Circulation. 2013;128(4):417–35.
13. International Liaison Committee on Resuscitation. 2005 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Resuscitation. 2005;67:181–341.
14. Ochoa F, Ramalle-Gomara E, Carpintero J. Competence of health professionals to check carotid pulse. Resuscitation. 1998;37:173–5.
15. Sanders A, Atlas M, Ewy G. Expired PCO2 as an index of coronary perfusion pressure. Am J Emerg Med. 1985;1985(3):147–9.
16. Rieke H, et al. Virtual arterial blood pressure feedback improves chest compression quality during simulated resuscitation. Resuscitation. 2013;84:1585–90.
17. Vaillancourt C, et al. In out-of-hospital cardiac arrest patients, does the description of any specific symptoms to the emergency medical dispatcher improve the accuracy of the diagnosis of cardiac arrest: a systematic review of the literature. Resuscitation. 2011;82:1483–9.
18. Paradis N, et al. Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. JAMA. 1990;263:1106–13.
19. Andreka P, Frenneaux MP. Haemodynamics of cardiac arrest and resuscitation. Curr Opin Crit Care. 2006;12(3):198–203.
20. Sanders A, Ewy G. Prognostic and therapeutic importance of the aortic diastolic pressure in resuscitation from cardiac arrest. Crit Care Med. 1984;12(10): 871–3.
21. Sutton R, Friess S, Naim M. Patient-centric blood pressure-targeted cardiopulmonary resuscitation improves survival from cardiac arrest. Am J Resp Crit Care Med. 2014;190(11):1255–62.
22. Sutton R, Friess S, Maltese M. Hemodynamic-directed cardiopulmonary resuscitation during in-hospital cardiac arrest. Resuscitation. 2014;85: 983–6.
23. Vadeboncoeur T, Bobrow BJ, Cone DC, Chikani V, Abella BS. Instant replay: perform CPR with immediate feedback. JEMS. 2011;36(3):50–63.
24. Eberle B, Dick W, Schneider T. Checking the carotid pulse check: diagnostic accuracy of first responders in patients with and without a pulse. Resuscitation. 1996;33:107–16.
25. Kim Y, Lee J, Lee D. Differences in hands-off time according to the position of a second rescuer when switching compression in pre-hospital cardiopulmonary resuscitation provided by two bystanders: a randomized, controlled, parallel study. J Korean Med Sci. 2015;30:1347–53.
26. Aufderheide TP. Hyperventilation-induced hypotension during cardiopulmonary resuscitation. Circulation. 2004;109:1960.
27. Aufderheide TP, Lurie K. Death by hyperventilation: a common and life-threatening problem during cardiopulmonary resuscitation. Crit Care Med. 2004;32:S345.
28. Neumar RW, et al. 2010 "American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science". Circulation. 2010;122:S729–67.
29. Sasson C, et al. Predictors of survival from out of hospital cardiac arrest: a systematic review and meta-analysis. Circulation. Cardiovasc Quality Outcomes. 2010;3(1):63–81.
30. Meaney P, Nadkarni V, Kern K. Rhythms and outcomes of adult in-hospital cardiac arrest. Crit Care Med. 2010;38(1):101–8.
31. Thomas A, Newgard C, Fu R. Survival in out-of-hospital cardiac arrests with initial asystole or pulseless electrical activity and subsequent shockable rhythms. Resuscitation. 2013;84(9):1261–6.
32. Kloeck W. A practical approach to the aetiology of pulseless electrical activity. A simple 10-step training mnemonic. Resuscitation. 1995;30:157–9.
33. Littman L, Bustin D, Haley M. A simplified and structured teaching tool for the evaluation and management of pulseless electrical activity. Med Princ Pract. 2014;23:1–6.
34. Prosen G, Krizmaric M, Zavrsnik J. Impact of modified treatment in echocardiographically confirmed pseudo-pulseless electrical activity in out-of-hospital cardiac arrest patients with constant end-tidal carbon dioxide pressure during compression pauses. J Int Med Res. 2010;38:1458–67.
35. Niles D, Sutton R, Donoghue A. "Rolling Refreshers": a novel approach to maintain CPR psychomotor skill competence. Resuscitation. 2009;2009(80):909–12.
36. Edelson D, Litzinger B, Arora V. Improving in-hospital cardiac arrest process and outcomes with performance debriefing. Arch Intern Med. 2008; 168(10):1063–9.
37. Rudikoff M, Maughan W, Effron M. Mechanisms of blood flow during cardiopulmonary resucitation. Circulation. 1980;61(2):345–52.
38. Georgiou M, Papathanassoglou E, Xanthos T. Systematic review of the mechanisms driving effective blood flow during adult CPR. Resuscitation. 2014;85:1586–93.
39. Rubertsson S, et al. Mechanical chest compressions and simultaneous defibrillation vs conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest: the LINC randomized trial. JAMA. 2014;311(1):53–61.
40. Chang WT, Ma MH, Chien KL. Post resuscitation myocardial dysfunction: correlated factors and prognostic implications following prolonged ventricular

fibrillation and cardiopulmonary resuscitation. Intensive Care Med. 2007;33:88–95.
41. Brooks S, et al. Mechanical versus manual chest compressions for cardiac arrest. Cochrane Database Syst Rev. 2014;2:1–46.
42. Dumas F, Bougouin W, Geri G. Is epinephrine during cardiac arrest associated with worse outcomes in resuscitated patients. J Am Coll Cardiol. 2014;64(22):2360–7.
43. Go AS, et al. Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. Circulation. 2013;127:e6–245.
44. Friess S, Sutton R, French B. Hemodynamic directed CPR improves cerebral perfusion pressure and brain tissue oxygenation. Resuscitation. 2014;85(9): 1298–303.
45. Rivers E, et al. The clinical implications of continuous central venous oxygen saturation during human CPR. Ann Emerg Med. 1992;21:1094–101.
46. Snyder A, Salloum L, Barone J. Predicting short-term outcome of cardiopulmonary resuscitation using central venous oxygen tension measurements. Crit Care Med. 1991;19:111–3.

Post-cardiac Arrest Management

2

Ronny M. Otero and Robert W. Neumar

Introduction

This chapter will review the elements of cardiac arrest resuscitation that begin after return of spontaneous circulation (ROSC). In-hospital mortality of patients who achieve ROSC long enough to be admitted to an ICU averages 60 % with wide inter-institutional variability (40–80 %) [1]. The pathophysiology of post-cardiac arrest syndrome (PCAS) is composed of four major components: post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion response, and persistent precipitating pathology [2]. It is important to recognize that each component is potentially reversible and responsive to therapy. A comprehensive multidisciplinary management strategy that addresses all components of post-cardiac arrest syndrome is needed to optimize patient outcomes [3]. In addition, a reliable strategy to prognosticate neurologic outcome in persistently comatose patients is essential to prevent premature limitation of care and make possible appropriate stewardship of patient care resources [3].

R.M. Otero (✉)
Emergency Medicine, University of Michigan Hospital, Ann Arbor, MI, USA
e-mail: Oteror@umich.edu

R.W. Neumar
Department of Emergency Medicine, University of Michigan Medical School, Ann Arbor, MI, USA

Case Presentation

A 68-year old male was mowing his lawn, complained to his wife that he was having chest pain and then collapsed. She called “911” and when first responder EMTs arrived 5 min later, they found him to be unresponsive, not breathing and without a pulse. EMTs initiated cardiopulmonary resuscitation (CPR) and an automated external defibrillator (AED) was applied to the patient. The initial rhythm analysis advised a “shock”, and a shock was delivered. After two additional minutes of CPR the paramedics arrived and found the patient to have a palpable pulse, a systolic blood pressure of 70 mmHg, a narrow complex sinus tachycardia at a rate of 110 on the monitor, and agonal respirations. Prior to transport, a supraglottic airway was placed, bag-valve ventilation was performed using 100 % oxygen, an intravenous line was placed and 1-L normal saline bolus was initiated. Time from 911 call to return of spontaneous circulation (ROSC) was 9 min.

On arrival to the local hospital, the patient became pulseless again and the monitor revealed a rhythm of ventricular fibrillation. The patient was defibrillated with a biphasic defibrillator set at 200 J. Patient achieved return of spontaneous circulation (ROSC) with narrow complex tachycardia at a rate of 120 and a blood pressure of 75/40. The patient was given 500 cc IV crystalloid bolus and epinephrine infusion was initiated at titrated to MAP >65 mmHg. A femoral arterial

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_2

line and an internal jugular central venous line were placed. Endotracheal intubation was performed and placement confirmed with waveform capnography and the $P_{et}CO_2$ was 40 mmHg. The patient had no eye opening or motor response to painful stimuli and pupils were fixed and dilated. Arterial blood gas demonstrated the following: pH = 7.18 PCO_2 = 39 HCO_3^- = 16 PaO_2 = 340, SpO_2 = 100 %, Lactate = 4.0. FiO_2 was decreased to achieve SpO_2 94–96 %. A temperature sensing bladder catheter was placed and read 36.0 °C. A 12 lead ECG was immediately obtained (Fig. 2.1).

Question What interventions should be performed next?

Answer Immediate coronary angiography with percutaneous coronary intervention (PCI) and hypothermic targeted temperature management.

Twelve-lead ECG reveals an acute anteroseptal ST-segment elevation myocardial infarction (STEMI). The patient's history of chest pain and recurrent episodes of VF support acute coronary syndrome (ACS) as the cause of cardiac arrest. Cardiology was consulted and patient was taken immediately to the coronary catheterization lab. Coronary angiography revealed left anterior descending artery occlusion that was successfully treated with balloon angioplasty and stent placement (Fig. 2.2).

An intravascular cooling catheter placed in coronary angiography laboratory and target temperature was set at 33 °C. Patient was admitted to the cardiac ICU and hypothermic targeted temperature management was maintained for 24 h followed by rewarming to 37 °C over 16 h (0.25 °C/h). Sedation included propofol and fentanyl infusion. Continuous EEG revealed a reactive baseline with intermittent seizure activity after rewarming that was treated with IV lorazepam and valproic acid. Seventy-two hours after rewarming neurologic exam revealed reactive pupil and positive cornea reflex, with withdrawal from painful stimuli. Patient began following commands 96 h after rewarming and was extubated on the 6th admission day. He was discharged to short-term rehabilitation on the ninth day with neurologic deficits limited to mild short-term memory deficit.

Principles of Management

Overview of Post-cardiac Arrest Syndrome

Post cardiac arrest syndrome is a unique pathologic state where varying degrees of post-arrest brain injury, myocardial dysfunction, systemic ischemia and reperfusion response, and persistent precipitating pathology are observed [2]. The

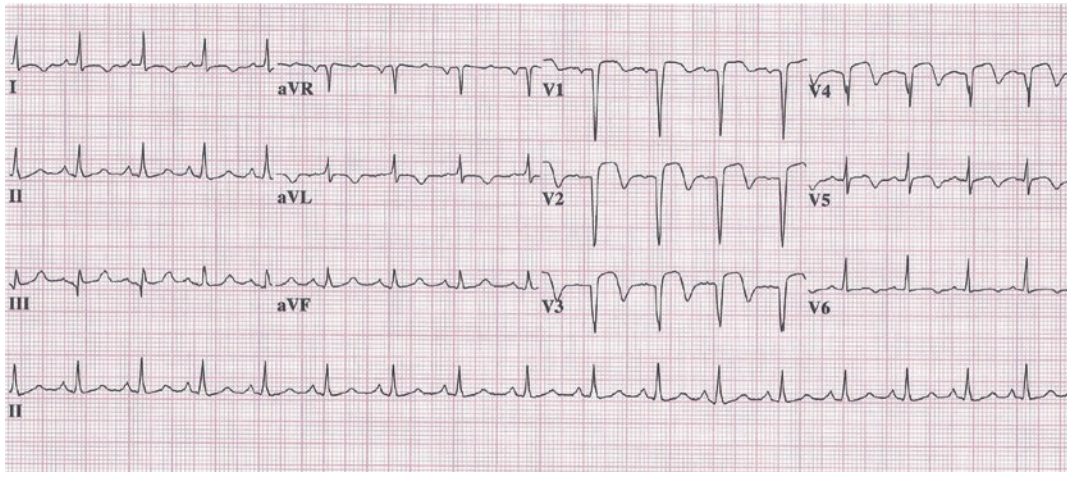


Fig. 2.1 Twelve lead ECG performed post-ROSC

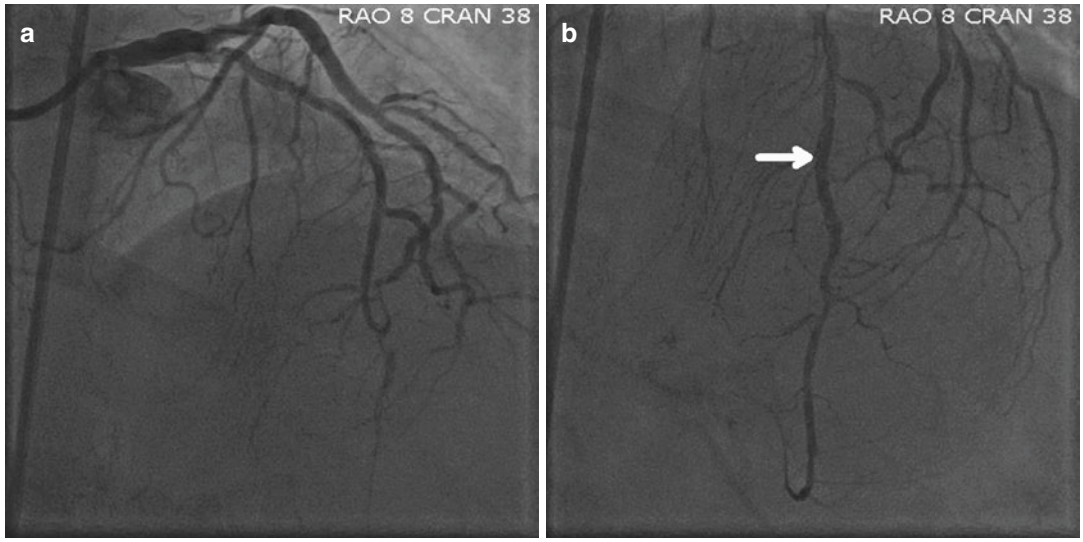


Fig. 2.2 (**a**) This is an image of a left anterior descending artery prior to angioplasty. (**b**) Left anterior descending artery (close up) after successful PCI with angioplasty indicated by increased flow below *arrow*

severity of these manifestations will vary in each patient. When ROSC is achieved rapidly PCAS can be limited or even absent while prolonged cardiac arrest can result in PCAS that is refractory to all interventions. Between these two extremes, each component of PCAS when present is potentially treatable and reversible. Some post-cardiac arrest interventions, such as hypothermic-targeted temperature management, appear to have a favorable impact on multiple components of PCAS while more focused interventions such at early PCI specifically address the precipitating pathology. A comprehensive multidisciplinary approach that addresses all PCAS components in the appropriate timeframe is the best strategy to optimize outcomes.

Post Cardiac Arrest Brain Injury

Post-cardiac arrest brain injury is a common cause of morbidity and mortality. One study reported that brain damage was the cause of death in 68 % of patients that died after ICU admission following out-of hospital cardiac arrest and in 23 % of patient that died after ICU admission following in-hospital cardiac arrest [4]. The unique vulnerability of the brain is attributed to its limited tolerance of ischemia as well as unique response to reperfusion. The most vulnerable regions of the brain include the hippocampus, cerebellum, caudoputamen, and cortex. The mechanisms of brain damage triggered by cardiac arrest and resuscitation are complex, and many pathways are executed over hours to days following ROSC. The relatively protracted time course of injury cascades and histological changes suggests a broad therapeutic window for neuroprotective strategies following cardiac arrest. Early clinical manifestations include coma, seizures, myoclonus and late manifestations ranging from mild short-term memory deficits to persistent vegetative state and brain death.

Post-cardiac Arrest Myocardial Dysfunction

Post-cardiac arrest myocardial dysfunction is a significant cause of morbidity and mortality after both in- and out-of-hospital cardiac arrest [4–6]. Myocardial dysfunction is manifest by tachycardia, elevated left ventricular end-diastolic pressure, decreased ejection fraction, reduced cardiac output and hypotension. Cardiac output tends to improve by 24 h and can return to near normal by 72 h in survivors in the absence of other pathology [6]. The responsiveness of post-cardiac arrest global myocardial dysfunction to inotropic drugs is well documented in animal studies [7, 8]. If

acute coronary syndrome or decompensated congestive heart failure were the precipitating pathology that caused cardiac arrest, the management of post-cardiac arrest myocardial dysfunction becomes more complex.

Systemic Ischemia/Reperfusion Response

The whole body ischemia/reperfusion of cardiac arrest with associated oxygen debt causes generalized activation of immunological and coagulation pathways increasing the risk of multiple organ failure and infection [9, 10]. This condition has many features in common with sepsis [11–14]. In addition, activation of blood coagulation without adequate activation of endogenous fibrinolysis may also contribute to microcirculatory reperfusion disorders after cardiac arrest [15, 16]. Finally, the stress of total body ischemia/reperfusion appears to adversely affect adrenal function [17, 18]. However, the relationship of adrenal dysfunction to outcome remains controversial. Clinical manifestations of systemic ischemic-reperfusion response include intravascular volume depletion, impaired vasoregulation, impaired oxygen delivery and utilization, as well as increased susceptibility to infection.

Persistent Precipitating Pathology

Post-cardiac arrest syndrome is commonly associated with persisting acute pathology that caused or contributed to the cardiac arrest itself. The diagnosis and treatment of acute coronary syndrome, pulmonary diseases, hemorrhage, sepsis, and various toxidromes is often complicated in the setting of post-cardiac arrest syndrome. However, early identification and effective therapeutic intervention is essential if optimal outcomes are to be achieved.

Hemodynamic Optimization

Post-cardiac arrest patients typically exhibit a mixed cardiogenic, distributive, and hypovolemic state of shock. In addition, persistence of the pathology that caused the cardiac arrest can cause a refractory shock state unless definitively treated. Early hemodynamic optimization is essential to prevent re-arrest, secondary brain injury and multi-organ failure. A goal-directed approach using physiologic parameters to achieve adequate oxygen delivery has been associated with improved outcomes [19, 20]. This involves optimizing preload, arterial oxygen content, afterload, ventricular contractility, and systemic oxygen utilization. Appropriate monitoring includes continuous intra-arterial pressure monitoring, arterial and central venous blood gases, urine output, lactate clearance, and bedside echocardiography. When feasible, diagnostic studies to rule out treatable persistent precipitating pathology should be performed, and treatment initiated while resuscitation is ongoing.

The optimal MAP for post-cardiac arrest patients has not been defined by prospective clinical trials, and should be individualize for each patient. Cerebrovascular auto regulation can be disrupted or right-shifted in post-cardiac arrest patients suggesting a higher cerebral perfusion pressure is needed to provide adequate brain blood flow [21]. In contrast, ongoing ACS and congestive heart failure can be exacerbated by targeting a MAP higher than what is needed to maintain adequate myocardial perfusion. Higher systolic and mean arterial pressures during the first 24 h after ROSC are associated with better outcomes in descriptive studies [22–24]. In terms of goal-directed strategies, good outcomes have been achieved in published studies where the MAP target range was low as 65–75 mmHg [20] to as high as 90–100 mm [25, 26] for patients admitted after out-of-hospital cardiac arrest.

For patients with evidence of inadequate oxygen delivery or hypotension, preload optimization is the first line intervention. Preload optimization is typically achieved using IV crystalloid boluses guided by non-invasive bedside assessment of volume responsiveness. Patients treated with a goal-directed volume resuscitation strategy following out-of-hospital cardiac arrest typically have positive fluid balance of 2–3 in the first 6 h and 4–6 L positive fluid balance in the first 24 h [19, 20].

Vasopressor and inotrope infusions should be initiated early in severe shock states and when

there is an inadequate response to preload optimization. No agent or combination of agents has been demonstrated to be superior or improve outcomes. A reasonable approach is norepinephrine as the first line vasopressor supplemented by dobutamine for inotropic support guided by bedside echocardiography.

When shock is refractory to preload optimization, vasopressors, and inotropes it is critical to identify and treat any persistent acute pathology that caused the cardiac arrest including acute coronary syndrome (ACS), pulmonary embolism (PE), or hemorrhage. If no such persistent pathology exists or the patient is not stable enough to undergo definitive intervention, then mechanical circulatory support should be considered (see section "Evidence Contour").

Ventilation and Oxygenation

The ventilation and oxygenation goals for post-cardiac arrest patients should be normoxia and normocarbia. Both low (<60 mmHg) and high (>300 mmHg) arterial PO_2 are associated with worse outcomes in post-cardiac arrest patients [27]. Low PaO_2 can cause secondary brain hypoxia while high PaO_2 can increase oxidative injury in the brain. The impact of $PaCO_2$ on cerebrovascular blood flow is maintained in post-cardiac arrest patients; therefore hypocarbia can cause secondary brain ischemia and is associated with worse outcomes [28, 29]. Currently there are no studies to specify which ventilator modes or tidal volumes are optimal in patients resuscitated from cardiac arrest but generally an approach using assist control mode with a tidal volume goal in 6–8 cc/kg range is considered standard. Titration of mechanical ventilation should be aimed at achieving a $PaCO_2$ of 45 mmHg and a range for PaO_2 between 75 and 150 mmHg.

Management of STEMI and ACS

Acute coronary syndrome is a common cause of out-of-hospital cardiac arrest, but making the diagnosis in an unconscious post-arrest patient presents unique challenges. A previous history of coronary artery disease, significant risk factors, and/or symptoms prior to arrest can contribute to clinical suspicion, but the absence of these does not exclude ACS as the cause. A standard 12-lead ECG should be obtained as soon as feasible after ROSC, with additional right-sided and/or posterior leads as indicated. Immediate PCI is indicated in post-ROSC patients meeting STEMI criteria regardless of neurologic status [3]. In addition, immediate coronary angiography should be considered in post-cardiac arrest patients that do not meet STEMI criteria but there is a high clinical suspicion for ACS (see section "Evidence Contour"). Medical management of ACS is the same as for non-post-cardiac arrest patients.

Hypothermic Targeted Temperature Management

Hypothermic-targeted temperature management (HTTM) is recommended for comatose adult patients who achieve ROSC following cardiac arrest independent of presenting cardiac rhythm (shockable vs. non-shockable) and location (Out of Hospital Cardiac Arrest (OHCA) vs. In-hospital Cardiac Arrest (IHCA)) [3]. Based on current clinical evidence, providers should select a constant target temperature between 32 and 36 °C and maintain that temperature for at least 24 h. Rewarming should be no faster than 0.5 C/h and fever should be prevented for at least 72 h after ROSC.

Although there are no absolute contraindications to HTTM after cardiac arrest, relative contraindications may include uncontrolled bleeding or refractory severe shock. Induction of hypothermia may lead to intense shivering, hyperglycemia, diuresis and associated electrolyte derangements such as hypokalemia and hypophosphatemia [30]. Rewarming may be associated with mild hyperkalemia and must be monitored closely.

When the decision is made to treat the comatose post-cardiac arrest patient with HTTM,

efforts to achieve and maintain target temperature should be as soon as feasible. In the ED, practical methods of rapidly inducing hypothermia include ice packs (applied to the neck, inguinal areas, and axilla), fan cooling of dampened exposed skin, cooling blankets underneath and on top of the patient, and disabling of ventilator warming circuits. Rapid intravenous infusion of limited volumes (1–2 L) of 4 °C saline facilitates induction of hypothermia, but additional measures are needed to maintain hypothermia. No one cooling strategy or device has been demonstrated to result in superior clinical outcomes. A number of automated surface cooling devices are now available that use chest and thigh pads and continuous temperature feedback from bladder or esophageal temperature probes. Although more invasive, automated endovascular cooling systems are also available that require placement of a central venous catheter and offer tighter control of temperature at target. Target core body temperature is best monitored by an indwelling esophageal temperature probe, but can be monitored by a temperature-sensitive bladder catheter if adequate urine output is present.

Shivering, which inhibits cooling, can be prevented with sedation and neuromuscular blockade. If neuromuscular blockade is continued during the maintenance phase of therapeutic hypothermia, continuous electroencephalographic monitoring is strongly encouraged to detect seizures, a common occurrence in post-cardiac arrest patients [3].

Glucose Control

Hyperglycemia is common in post-cardiac arrest patients, and average levels above 143 mg/dL have been strongly associated with poor neurologic outcomes [31]. One randomized trial in post-cardiac arrest patients compared strict (72–108 mg/dL) versus moderate (108–144 mg/dL) glucose control and found no difference in 30-day mortality [32]. Based on available evidence, moderate glucose management strategies in place for most critically ill patients do not need to be modified for post-cardiac arrest patients.

Seizure Management

Seizures, nonconvulsive status epilepticus, and other epileptiform activity occurs in 12–22 % of comatose post-cardiac arrest patients, and may contribute to secondary brain injury and prevent awaking from coma [3]. There is no direct evidence that post-cardiac arrest seizure prophylaxis is effective or improves outcomes. However, prolonged epileptiform discharges are associated with secondary brain injury in other conditions, making detection and treatment of nonconvulsive status epilepticus a priority [33]. Continuous EEG, initiated as soon as possible following ROSC, should be strongly considered in all comatose survivors of cardiac arrest treated with HTTM, to monitor for potentially treatable electrographic status epilepticus and to assist with neuroprognostication. In the absence of continuous EEG monitoring, an EEG for the diagnosis of seizure should be promptly performed and interpreted in comatose post-arrest patients. The same anticonvulsant regimens for the treatment of seizures and status epilepticus and myoclonus caused by other etiologies are reasonable to use in post-cardiac arrest patients.

Neuroprognostication

Accurate neuroprognostication can be extremely challenging in persistently comatose post-cardiac arrest patients, but is essential for appropriate patient care and resource utilization. Decisions to limit care based on neurologic prognosis should not be made before 72 h after ROSC and at least 12 h following rewarming and cessation of all sedative and paralytic medications [34]. Available neuroprognostication tools include clinical examination, electrophysiologic measurements, imaging studies, and serum biomarkers. The performance of these tools is highly dependent on the interval between the achievement of ROSC and the measurement. For example, bilateral absence of pupillary light reflex has a false positive rate (FPR) for predicting poor neurologic outcome of 32 % [95 % CI 19–48 %] at the time of hospital admission

versus a FPR of 1 % [0–3 %] when measured 72 h after ROSC [35]. In addition to timing, major confounders such as sedation and neuromuscular blockade, persistent hypothermia, severe hypotension, hypoglycemia and other profound metabolic derangements must be excluded before an assessment for neuroprognostication is performed. Finally, all available clinical data on the reliability of prognostication tools is limited by the potential for a self-fulfilling prophecy that occurs when these tools are used to limit care.

Most experts agree that recovery of Glasgow Motor Score (GMS) of flexion or better (i.e. >2) is a good prognostic sign that precludes the need for further prognostic evaluation. In patients that do not recover a GMS >2 by 72 h after ROSC, the most reliable predictors of poor neurologic outcome (defined by a Cerebral Performance Category score of 3–5) are listed in Table 2.1.

It is recommended that decisions to limit care never be based on the results of a single prognostication tool [3]. Although a number of published guidelines from professional societies are available, the field is rapidly evolving and therefore post-arrest neuroprognostication should be guided by consultation with an experienced neurocritical care specialist [34, 37]. Establishing a consistent institutional approach based on available resources and multidisciplinary expertise will optimize both resource utilization and patient outcomes.

Organ Donation

Patients that are initially resuscitated from cardiac arrest but subsequently die or meet brain death criteria should be evaluated as potential organ donors. Multiple studies have found no difference in immediate or long-term function of transplanted organs from donors who reach brain death after cardiac arrest when compared with donors who reach brain death from other causes [38]. In addition, patients who have withdrawal of life support after initial resuscitation from cardiac arrest based on reliable neuroprognostication of futility or as part of advanced directives are candidates for donation after cardiac death (DCD). The list of potential organs successfully donated from the patients has expanded from primarily kidneys and liver to include heart, lung and intestine. Finally, tissue donation (cornea, skin, and bone) is almost always possible if post-cardiac arrest patients die.

Evidence Contour

Patient Selection for Emergency Coronary Angiography

There are no prospective randomized controlled trials demonstrating benefit of immediate coronary angiography and PCI in post-cardiac arrest patients with or without STEMI. However,

Table 2.1 Most reliable predictors of poor neurologic outcome in comatose post-cardiac arrest patients [35]

Prognostication tool	Positive result measurement	Timing	FPR [95%CI]	Sensitivity [95%CI]
Clinical Exam	Bilaterally absent pupillary light reflexes [35]	≥72 h post-ROSC	1 % [0–3 %]	19 % [14–25 %]
	Status myoclonus [35]	During the first 72 h post-ROSC	0 % [0–4 %]	16 % [11–22 %]
Somatosensory evoked potentials (SSEPs)	Bilaterally absent N20 (cortical) SSEP wave [35]	After rewarming from HTTM	1 % [0–3 %]	45 % [41–50 %]
Electroencephalography (EEG)	Highly malignant pattern [36]	After rewarming from HTTM and 48–96 h after ROSC	0 % [0–12 %]	50 % [39–61 %]

A. Highly malignant EEG patterns are (1) suppressed background without discharges (amplitude, 10 mV, 100 % of the recording), (2) suppressed background with continuous periodic discharges, and (3) surest-suppression background with or without superimposed discharges (periods of suppression with amplitude <10 mV constituting >50 % of the recording)

multiple observational studies have reported better survival in both STEMI and NSTEMI post-cardiac arrest patients that undergo immediate coronary angiography and PCI (when indicated) compared to those that do not undergo immediate coronary angiography [39–41]. The strength of the recommendation for post-cardiac arrest patients that meet STEMI criteria is based on extrapolation of the positive survival benefits for non-cardiac arrest patients. Conversely, the reluctance of interventional cardiologists to perform immediate coronary angiography in NSTEMI patients is similarly based on lack of proven benefit in non-cardiac arrest patients. However, it should be recognized that the post-arrest patients are higher risk and do not always have ST-elevation with an acutely occluded culprit lesion [42]. In a large international post-cardiac arrest registry that included patients undergoing immediate coronary angiography with and without STEMI, an occluded culprit vessel was found in 74.3 % of patients with STEMI and 22.9 % of patients without STEMI [41]. This high incidence of occluded culprit lesions combined with post-cardiac arrest myocardial dysfunction and the need to maintain adequate cerebral perfusion pressure to prevent secondary brain injury argues strongly for immediate coronary angiography in any post-cardiac arrest patient when there is a clinical suspicion of ACS, especially when associated with hemodynamic instability.

Patient Selection for Hypothermic TTM

Although international guidelines consistently recommend treating all comatose post-cardiac arrest patients with hypothermic TTM, this practice has not been universally implemented. The two major clinical trials demonstrating efficacy of HTTM limited enrollment to witnessed out-of-hospital cardiac arrest with as shockable (VF/VT) presenting rhythm [26, 43]. There have been no prospective randomized clinical trials comparing HTTM to normothermia (or no active temperature management) in out-of-hospital cardiac arrest patients with non-shockable presenting rhythms or in in-hospital cardiac arrest patients with any presenting rhythm. Therefore these recommendations represent an extrapolation of the evidence in patients with witnessed out-of-hospital ventricular fibrillation. This extrapolation is supported by clinical observational studies that suggest benefit in these patient populations and robust body animal data demonstrating the neuroprotective effect of HTTM in cardiac arrest models regardless of arrest rhythm [44, 45]. In addition, HTTM has a relatively safe side effect profile limited primarily to shivering and electrolyte shifts. For intubated comatose cardiac arrest survivors managed in the ICU setting, the incremental intensity of care and cost is modest. One potential concern about treating all comatose post-cardiac arrest patients with HTTM is a delay in prognostication of poor outcome and decision to limit care. However, there is international consensus that neuroprognostication should not be performed before 72 after ROSC. So, awaiting completion of HTTM therapy does itself delay neuroprognostication. Moreover, HTTM could delay the metabolism of sedative and paralytic agents. Therefore, some experts have recommended delaying prognostication until 72 h after rewarming, which could cause significant delays in neuroprognostication. However, the initiation of HTTM should not impact decisions to limit care that are based criteria other than neurologic prognosis, such as terminal illness or previously unrecognized advanced directives. In such cases the decision to discontinue HTTM can be considered in the same way as the decision to discontinue mechanical ventilation or intravenous pressor therapy.

Optimizing Hypothermic TTM

Most experts agree that the optimal time to initiation, target temperature, and duration of HTTM is unknown. Although it theoretically makes sense to achieve target temperature as soon as feasible, there is no clinical data to support this approach. Even in the two landmark clinical trials, the time to target temperature was discordant. In the study by Bernard the time to target temperature was reported to be $\leq$2 h while in the HACA trial the

median time to target temperature was 8 h (IQR 4–16 h) [26, 43]. Rapid infusion of cold intravenous saline immediately after ROSC by paramedics in the field had no impact on outcomes in two randomized clinical trials [46, 47]. Observational studies examining time to target temperature are not informative because neurologically devastated patients are easier to cool due to loss of temperature auto regulation. Based on available evidence achieving target temperature within 4 h of ROSC is a reasonable goal.

The target temperature of 32–34 °C in the original guidelines was based on the target temperature used in the Bernard and HACA studies [26, 43]. Subsequent to that, a large multicenter studied published by Nielsen et al. did not detect superior outcomes in comatose post-cardiac arrest patients who were cooled to 33 °C compared to 36 °C [48]. It is for this reason that the recommended target temperature range was expanded to 32–36 °C. Although it is theoretically easier to use a higher target temperature, it does not obviate the need for use of active cooling techniques guided by continuous temperature monitoring. The recommended duration of therapy is again based on the durations used in major clinical trials. There have been no prospective comparisons of HTTM duration in randomized clinical trials. No specific cooling technique has been demonstrated to result in superior patient outcomes. Therefore the best strategy is the one that is most feasible to consistently implement at your own institution. Overall, the optimization of HTTM requires additional research, and it is likely that a personalized approach based on severity of injury and response to therapy will emerge as the best strategy.

Mechanical Support for Refractory Post-cardiac Arrest Cardiogenic Shock

In post-cardiac arrest patients with refractory cardiogenic shock a number of options can be considered for mechanical circulatory support. An intra-aortic balloon pump can enhance cardiac output by approximately 0.5 L/min in cardiogenic shock. Despite early evidence of improved outcomes when IABP was used post-MI, recent studies have not shown a 30-day or 12 month mortality benefit [49, 50]. The newer peripheral ventricular assist devices Tandem Heart™ PVAD (Fig. 2.3) and Impella™ Recovery

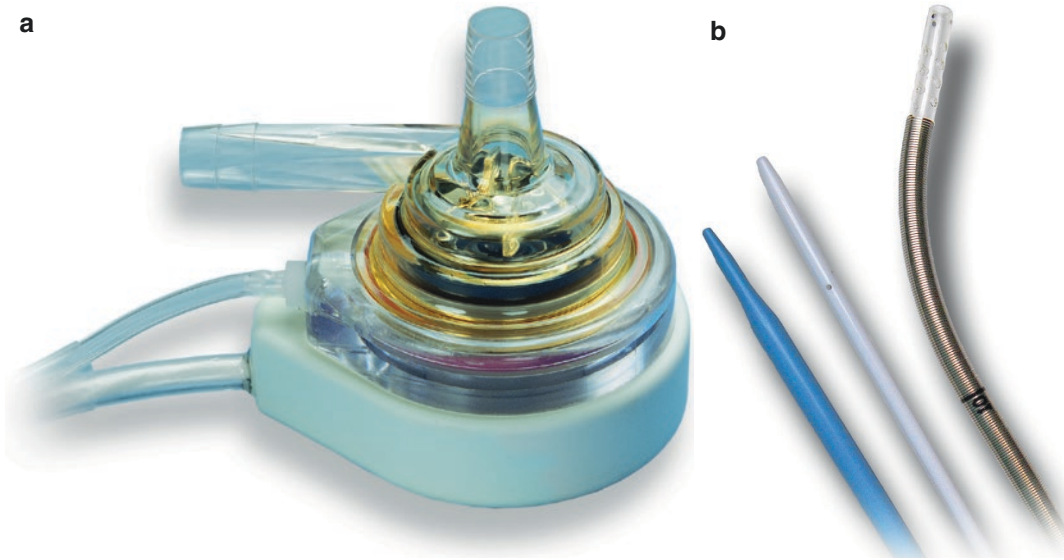


Fig. 2.3 (**a**, **b**) Thoratec Device™ Percutaneous ventricular assist device consisting of Tandem Heart pump™ and Tandem Heart cannulae™ with flow rates from 4 to 5.0 L/min depending on size of cannulae (With permission Cardiac Assist® Inc.)

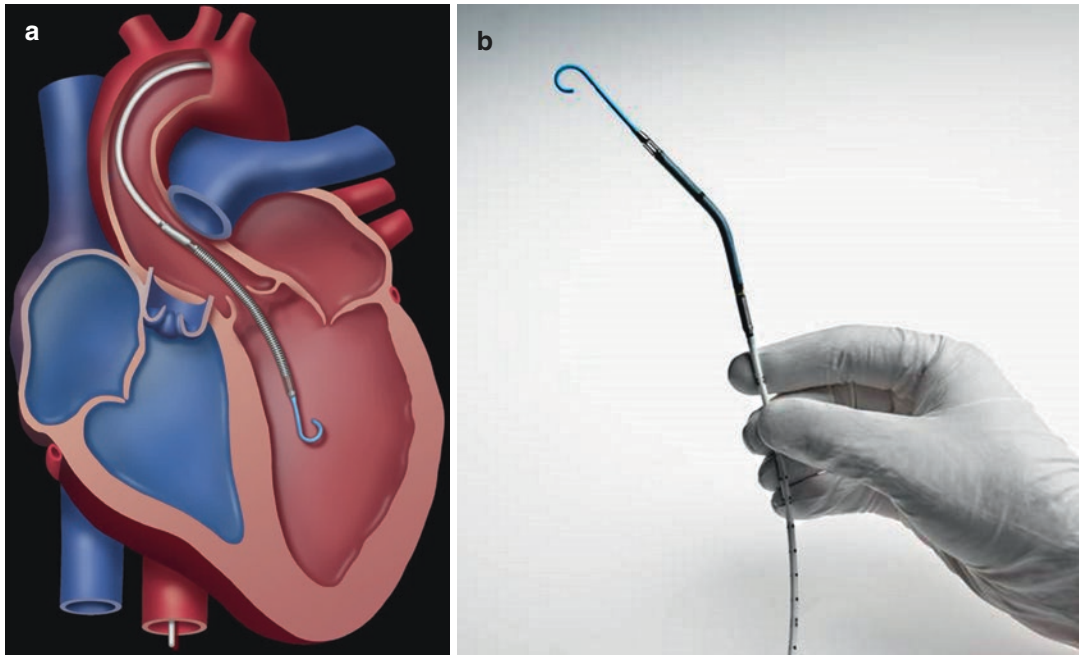


Fig. 2.4 (**a**, **b**) Impella Device ™ Device demonstrating retrograde insertion via aorta into left ventricle proprietary 9Fr catheter with 2.5 L/min flow rate. Inserted under fluoroscopic guidance. (**b** With permission Abiomed®)

(Fig. 2.4) are reported to augment cardiac output by 3.5 and 2.5 L/min, respectively. These devices gain access to the central circulation via large cannulas, which then use either a centrifugal pump (Tandem Heart™) or catheter motor with inlet and output (Impella™) via the aorta. In centers with specialty expertise complete circulatory support may be performed using veno-arterial extracorporeal membrane oxygenation (VA-ECMO) as a bridge to transplantation or bridge to recovery [51].

References

1. Carr B, Kahn J, Merchant RM. Inter-hospital variability in post-cardiac arrest mortality. Resuscitation. 2009;80:30–4.
2. Neumar R, Nolan JP, Adrie C. Post-Cardiac Arrest Syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa). Circulation. 2008;118(23):2452–83.
3. Callaway C, Donnino M, Fink E. Post Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132 Suppl 1:S465–82.
4. Laver S, Farrow C, Turner D. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med. 2004;30:2126–8.
5. Herlitz J, Ekstrom B, Wennerblom B. Hospital mortality after out-of-hospital cardiac arrest among patients found in ventricular fibrillation. Resuscitation. 1995;29(1):11–21.
6. Laurent I, Monchi M, Chiche J. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol. 2002;40(1):2110–6.
7. Kern KB, Hilwig R, Berg RA. Postresuscitation left ventricular systolic and diastolic dysfunction: treatment with dobutamine. Circulation. 1997;95(12): 2610–3.
8. Huang L, Weil M, Tang W. Comparison between dobutamine and levosimendan for management of postresuscitation myocardial dysfunction. Crit Care Med. 2005;33(3):487–91.
9. Cerchiari E, Safar P, Klein E. Visceral, hematologic and bacteriologic changes and neurologic outcome after cardiac arrest in dogs. The visceral post-resuscitation syndrome. Resuscitation. 1993;25:119–36.
10. Adams J. Endothelium and cardiopulmonary resuscitation. Crit Care Med. 2006;34(12):S45–465.

11. Adrie C, Adib-Conquy M, Laurent I. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. Circulation. 2002;106(5):562–8.
12. Adrie C, Laurent I, Monchi M. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? Curr Opin Crit Care. 2004;10(3):208–12.
13. Gando S, Nanzaki S, Morimoto Y. Out-of-hospital cardiac arrest increases soluble vascular endothelial adhesion molecules and neutrophil elastase associated with endothelial injury. Intensive Care Med. 2000; 26(1):38–44.
14. Geppert A, Zorn G, Karth G. Soluble selectins and the systemic inflammatory response syndrome after successful cardiopulmonary resuscitation. Crit Care Med. 2000;28(7):2360–5.
15. Bottinger B, Motsch J, Bohrer H. Activation of blood coagulation after cardiac arrest is not balanced adequately by activation of endogenous fibrinolysis. Circulation. 1995;92(9):2572–8.
16. Adrie C, Monchi M, Laurent I. Coagulopathy after successful cardiopulmonary resuscitation following cardiac arrest: implication of the protein C anticoagulant pathway. J Am Coll Cardiol. 2005;46(1):21–8.
17. Hekimian G, Baugnon T, Thuong M. Cortisol levels and adrenal reserve after successful cardiac arrest resuscitation. Shock. 2004;22(2):116–9.
18. Schultz C, Rivers EP, Feldkamp C. A characterization of hypothalamic-pituitary-adrenal axis function during and after human cardiac arrest. Crit Care Med. 1993;21(9):1339–47.
19. Gaieski DF, et al. Early goal directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. Resuscitation. 2009;80:418–24.
20. Sunde K, Pytte M, Jacobsen D. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation. 2007;73(1):29–39.
21. Sundgreen C, Larsen F, Herzog T. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. Stroke. 2001;32:128–32.
22. Kilgannon JH, et al. Early arterial hypotension is common in the post-cardiac arrest syndrome and associated with increased in-hospital mortality. Resuscitation. 2008;79(3):410–6.
23. Beylin ME, et al. Higher mean arterial pressure with or without vasoactive agents is associated with increased survival and better neurological outcomes in comatose survivors of cardiac arrest. Intensive Care Med. 2013;39(11):1981–8.
24. Kilgannon JH, et al. Arterial blood pressure and neurologic outcome after resuscitation from cardiac arrest. Crit Care Med. 2014;42:2083–91.
25. Oddo M, et al. From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. Crit Care Med. 2006;34(7):1865–73.
26. Bernard S, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002;346(8):557–63.
27. Kilgannon JH, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA. 2010;303(21): 2165–71.
28. Kagstrom E, Smith M, Siesjo B. Cerebral circulatory responses to hypercapnia and hypoxia in the recovery period following complete and incomplete cerebral ischemia in the rat. Acta Physiol Scand. 1983;118(3): 281–91.
29. Buunk G, van der Hoeven JG, Meinders AE. Cerebrovascular reactivity in comatose patients resuscitated from a cardiac arrest. Stroke. 1997;28: 1569–73.
30. Polderman K. Of ions and temperature: the complicated interplay of temperature, fluids, and electrolyte on myocardial function. Crit Care. 2013;17(6):1018.
31. Losert H, et al. Strict normoglycaemic blood glucose levels in the therapeutic management of patients within 12 h after cardiac arrest might not be necessary. Resuscitation. 2008;76(2):214–20.
32. Oksanen T, Skrifvars M, Varpula T. Strict versus moderate glucose control after resuscitation from ventricular fibrillation. Intensive Care Med. 2007;33(12): 2093–100.
33. Friedman D, Claassen J, Hirsch L. Continuous electroencephelogram monitoring in the intensive care unit. Anesth Analg. 2009;109(2):506–23.
34. Sandroni C, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Resuscitation. 2014;85:1779–89.
35. Callaway C, et al. Part 4: Advanced life support: 2015 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations [review]. Circulation. 2015;132(16 Suppl 1):S84–145.
36. Westhall E, Rossetti A, van Rootselaar A. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. Neurology. 2016;86(16):1482–90.
37. Cronberg T, Brizzi M, Liedholm L. Neurological prognostication after cardiac arrest – recommendations from the Swedish resuscitation Council. Resuscitation. 2013;84(7):867–72.
38. Orioles A, Morrison W, Rossano J. An underrecognized benefit of cardiopulmonary resuscitation: organ transplantation [review]. Crit Care Med. 2013;41(12):2794–9.
39. Callaway CW, et al. Early coronary angiography and induced hypothermia are associated with survival and functional recovery after out-of-hospital cardiac arrest. Resuscitation. 2014;85(5):657–63.
40. Dumas F, Bougouin W, Geri G. Is early PCI associated with a clinical benefit in post-cardiac arrest patients without STEMI pattern? Insights from the Parisian registry (PROCAT II). Resuscitation. 2015;96 Suppl 1:37.
41. Kern K, Lotun K, Patel N. Outcomes of comatose cardiac arrest survivors with and without ST-segment elevation myocardial infarction: importance of

coronary angiography. JACC Cardiovasc Interv. 2015;8(8):1031–40.
42. Spaulding CM, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. N Engl J Med. 1997;336(23):1629–33.
43. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346(8):549–56.
44. Testori C, Sterz F, Behringer W. Mild therapeutic hypothermia is associated with favourable outcomes in patients after cardiac arrest with non-shockable rhythms. Resuscitation. 2011;82(9):1162–7.
45. Perman S, Grossestreuer A, Wiebe D. The utility of therapeutic hypothemia for post-cardiac arrest syndrome patients with an initial nonshockable rhythm. Circulation. 2015;132(22):2146–51.
46. Bernard S, Smith K, Cameron P. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. Circulation. 2010;122(7):737–42.
47. Kim F, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. JAMA. 2014;311(1):45–52.
48. Nielsen N, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med. 2013;369(23):2197–206.
49. Thiele H, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med. 2012;367:1287–96.
50. Thiele H, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised open-label trial. Lancet. 2013;382:1638–45.
51. Stub D, et al. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). Resuscitation. 2015; 86:88–94.

Undifferentiated Shock

3

Sage P. Whitmore

Case Presentation

A 39-year-old woman with a history of rheumatoid arthritis and localized breast cancer status post lumpectomy was admitted to the intensive care unit (ICU) for suspected septic shock from a biliary source. She had presented with right upper quadrant abdominal pain worsening over the last 3 days. She endorsed lightheadedness, shortness of breath, and vomiting, and denied cough or fever. On initial examination, her vitals included a heart rate of 110, respiratory rate 22, blood pressure 86/58, SpO_2 94 % on room air, temperature 37.5 °C. She was ill appearing, anxious but alert, visibly dyspneic, with clear heart and lung sounds. She had tenderness with voluntary guarding of her right upper quadrant. Her extremities were cool with delayed capillary refill and 1+ pretibial edema bilaterally. Her electrocardiogram showed sinus tachycardia with small T wave inversions in the anterior leads and no ST elevations. Her chest radiograph showed a small right pleural effusion but was otherwise clear. Pertinent labs included: WBC 13,000, hemoglobin 11.9, platelets 180,000, creatinine 1.9 mg/dL, AST 250, ALT 300, alkaline phosphatase 110, total bilirubin 1.8, lipase 120, troponin-I 1.1 (negative <0.10), and INR 1.5. Arterial blood gas revealed pH 7.32, PCO_2 28, PO_2 64, and lactate 4.2 mmol/L. Pregnancy testing was negative. Urinalysis was pending as her urine output was poor. She was treated empirically with broad-spectrum antibiotics and intravenous fluids. After 1500 mL of saline, the patient's heart rate was 120, respiratory rate 26, blood pressure 80/54, and SpO_2 now 90 % on 2 L nasal cannula. While awaiting diagnostic imaging, a foley catheter, central venous catheter, and arterial line were placed.

Question How should the clinician determine this patient's shock type and the appropriate resuscitation strategy?

Answer Assessment of volume responsiveness plus bedside echocardiography

This patient presents with clinical features of, and risk factors for, multiple shock types with many possible etiologies. The differential diagnosis includes septic shock due to biliary, gastrointestinal, or genitourinary causes, severe pancreatitis, hemorrhagic shock possibly from a ruptured ovarian or hepatic cyst, adrenal crisis, massive pulmonary embolism, right ventricular failure, cardiac tamponade, or left ventricular failure. The fact that she is more hypotensive after fluids might suggest cardiac failure, or may be due to progression of septic shock. The indications for IV fluid boluses,

S.P. Whitmore
Emergency Medicine, Division of Emergency Critical Care, University of Michigan Health System, Ann Arbor, MI, USA
e-mail: swhitmor@med.umich.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_3

blood products, vasopressors, and inotropes differ widely among these possibilities, and both under-resuscitation and volume overload carry potential harm.

After placement of a left subclavian central line and radial arterial line, central venous pressure (CVP) averaged 10 mmHg, and a pulsus paradoxus was noted on the arterial pressure waveform. A 90-s bilateral passive leg raise resulted in a 12-point drop in systolic blood pressure. Based on this, intravenous fluids were discontinued. A bedside echocardiogram demonstrated a dilated inferior vena cava (IVC) with no respiratory variation, no pericardial effusion, massive dilation of the right ventricle (RV) with poor RV contractility, marked right-to-left interventricular septal bowing, and a small, hyperdynamic left ventricle (LV). A diagnosis of cardiogenic shock due to RV failure was made, and the patient was started on high-flow oxygen at 15 L/min with inhaled nitric oxide blended in at 20 parts per million. Norepinephrine and dobutamine infusions were initiated. After application of these therapies, her skin temperature and capillary refill improved, her blood pressure improved to 110/70, and urine output increased. A formal right upper quadrant ultrasound showed no gallstones, gallbladder wall thickening, or biliary dilation; her right upper quadrant pain was attributed to congestive hepatopathy. A CT of the chest showed no pulmonary embolism. She was scheduled for right heart catheterization for a suspected index presentation of pulmonary arterial hypertension.

Standard Approach to Undifferentiated Shock

Shock is defined as a state of inadequate oxygen delivery to tissues resulting in cellular dysoxia, which is often accompanied by, but may be completely independent of, decreased systemic arterial blood pressure [1]. The classic approach to determining shock type begins with utilizing history and cardiopulmonary and skin examinations to categorize the patient's condition into one of four shock types: hypovolemic, distributive, cardiogenic, or obstructive [1]. This can be quite challenging in patients with multiple comorbidities, difficult body habitus, or atypical physical exam findings (e.g. "cold" septic shock or "high output" cardiac failure).

In the past, static hemodynamic parameters such as central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), estimated stroke volume (SV), cardiac index (CI), and systemic vascular resistance (SVR) obtained invasively via central venous and pulmonary artery catheterization were used to attempt to differentiate cardiac failure, obstruction, hypovolemia, or inappropriate vasodilation. Various combinations of fluids, vasopressors, and inotropes would be then employed to target certain goals; for example, CVP of 8–12 mmHg, PAOP of 12–15 mmHg, and CI greater than 2.2. CVP-guided fluid management is still emphasized in a number of resuscitation protocols, including early goal directed therapy of septic shock and the post-cardiac arrest syndrome [2, 3], and utilization of the pulmonary artery catheter (PAC) remains a standard monitoring strategy for patients in cardiogenic shock or post cardiac surgery. As described in greater detail below, these parameters are notoriously unreliable in determining shock type and predicting response to intravenous fluid.

Shock Types

The basic phenotypes of shock are only three: hypovolemic, distributive, and cardiogenic; cardiogenic shock includes obstructive causes of RV failure (Fig. 3.1). In the modern approach to undifferentiated shock, it is essential to first recognize that a large proportion of patients in shock are suffering multiple insults resulting in *mixed shock phenotypes*, and therefore a linear approach to diagnosis and management is inappropriate. For example, patients with cardiogenic shock, post-cardiac arrest syndrome, or massive hemorrhage may also suffer distributive shock due to systemic inflammation and vasoplegia [4]; over half of patients with septic shock will develop cardiac dysfunction during their course [5]; and patients with hypotension and severe congestive

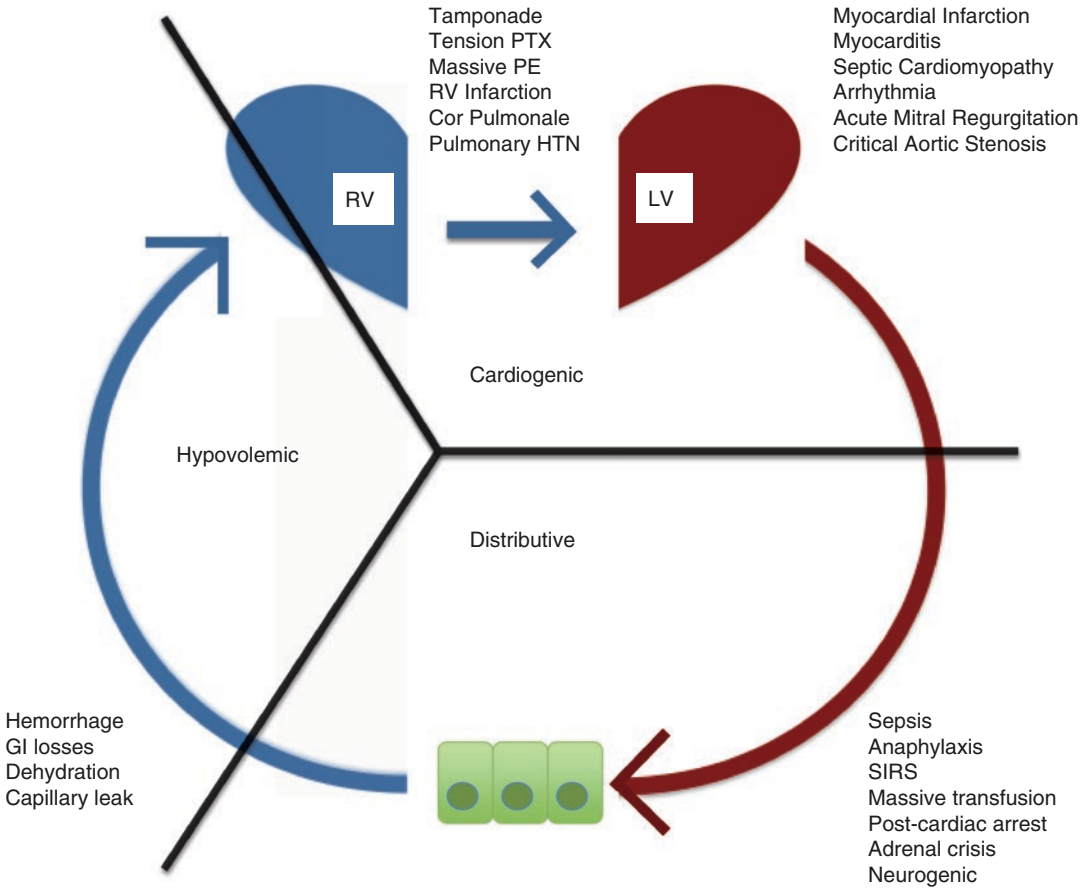


Fig. 3.1 Shock types and examples. *RV* right ventricle, *PTX* pneumothorax, *PE* pulmonary embolism, *HTN* hypertension, *LV* left ventricle, *SIRS* systemic inflammatory response syndrome, *GI* gastrointestinal

heart failure may in fact be initially volume responsive [6, 7], particularly if they are suffering concomitant gastrointestinal fluid losses, overdiuresis, or occult bleeding.

Hypovolemia is categorized as either hemorrhagic or non-hemorrhagic. Mechanistically, hypovolemic shock results from inadequate cardiac output due to diminished stroke volume, which itself is the result of decreased venous return. Venous return depends upon maintaining a gradient of blood flow from large capacitance veins in the body towards the right atrium, and this gradient depends in part on the difference between mean systemic pressure (P_{ms}) and right atrial pressure (Fig. 3.2) [8]. P_{ms} can be thought of as the intrinsic blood pressure within the venous system and depends on "stressed" intravascular volume—the volume of blood pressurized by the elasticity of the distended blood vessels in which it is contained. Normally when intravascular volume is lost, compensatory venoconstriction maintains an adequate stressed volume and thus adequate P_{ms}; however, when a patient becomes critically hypovolemic or is subject to inappropriate vasodilation, P_{ms} drops and venous return to the right atrium falls. The treatment is thus replacement of intravascular volume to restore P_{ms}. In the profoundly vasoplegic patient (e.g. advanced cirrhosis or anaphylaxis), venous return can be increased by using vasoconstrictors such as norepinephrine to increase venous tone and stressed volume [8, 9]; however, excessive vasoconstriction increases resistance to blood flow and may impede venous return.

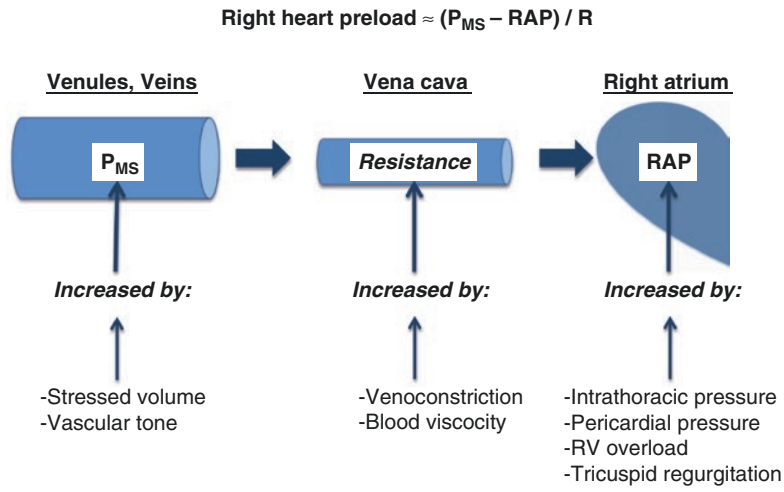


Fig. 3.2 Physiologic determinants of right heart preload. P_{MS} mean systemic pressure, *RAP* right atrial pressure, *R* resistance, *RV* right ventricle

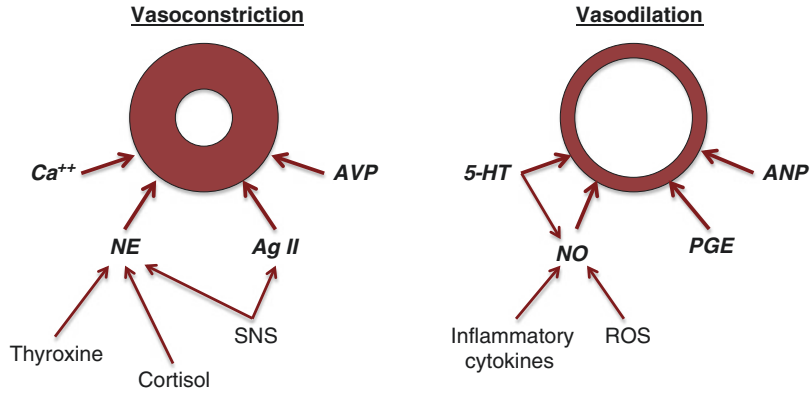


Fig. 3.3 Physiologic determinants of vascular tone. Ca^{++} calcium, *NE* norepinephrine, *Ag II* angiotensin, *AVP* arginine vasopressin, *SNS* sympathetic nervous system, *5-HT* serotonin, *NO* nitric oxide, *PGE* prostaglandin, *ANP* atrial natriuretic peptide, *ROS* reactive oxygen species

Distributive shock is due to vasoplegia, the failure to maintain vascular tone, and can occur via multiple mechanisms. Vascular smooth muscle tone is affected by a balance of several chemical mediators: catecholamines, vasopressin, angiotensin II, and free calcium cause vasoconstriction, while prostaglandins, histamine, atrial natriuretic peptide, and nitric oxide cause vasodilation (Fig. 3.3) [4, 10, 11]. Catecholamine induced vasoconstriction is influenced by the integrity of the sympathetic nervous system as well as by adrenal and thyroid function. Nitric oxide induced vasodilation is heightened by histamine, inflammatory cytokines, and possibly reactive oxygen species during ischemia-reperfusion. The interplay of these factors explains why such varied disease processes such as septic shock, anaphylactic shock, post-cardiopulmonary bypass, post-cardiac arrest syndrome, massive transfusion, adrenal failure, and high cervical spine injury may all result in distributive shock via different mechanisms. The mainstay of treatment is an adrenergic vasopressor agent such as norepinephrine or phenylephrine, and other intravenous agents such as ephedrine, vasopressin, angiotensin II, antihistamines, corticosteroids, thyroxine, and nitric oxide scavengers such as methylene blue may be indicated in certain clinical situations.

Cardiogenic shock is a broad category encompassing depressed cardiac output related to failure of either the right ventricle, left ventricle, or both. The causes of "obstructive shock" such as tension pneumothorax, cardiac tamponade, or massive pulmonary embolism, can be thought of as a subset of cardiogenic shock as they directly

impede the filling and/or output of the right heart. After a cautious trial of intravenous fluids, the mainstays of treatment are to support hemodynamics with a combination of vasopressors and inotropes while working to correct any potential mechanical lesion (e.g. pericardiocentesis for tamponade, tube thoracostomy for tension pneumothorax, thrombolysis for massive pulmonary embolism, percutaneous coronary intervention for ST-elevation myocardial infarction, emergent valve repair for severe regurgitation, etc.). Mechanical ventilation and mechanical circulatory devices such as implantable ventricular assist devices, intraaortic balloon counterpulsation, or extracorporeal life support may be needed until resolution or definitive therapy [6].

Evidence Contour

Rarely will one simple shock type exist in isolation, and one should approach shock as a potential combination of three simultaneous insults: hypovolemia, vasoplegia, and cardiac dysfunction. In all-comers with shock, these three parameters must be addressed systematically. The two most important maneuvers guiding the resuscitation of undifferentiated shock are (1) assessment of volume responsiveness and (2) bedside echocardiography.

Assessment of Volume Responsiveness

Accurate assessment of volume responsiveness is the most important first step in the resuscitation of a patient in shock, as it directly influences management in real time. Volume responsiveness is defined as a 10–15% increase in stroke volume (SV) or cardiac output (CO) after the administration of an intravenous fluid challenge, usually 250–500 mL of crystalloid, theoretically corresponding to the steep portion of the Starling curve (Fig. 3.4). There are many methods of assessment described, which are divided into static measurements of filling pressure or dynamic measurements of cardiopulmonary interaction.

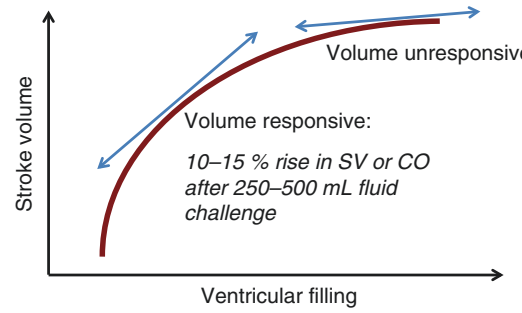


Fig. 3.4 Starling curve. *SV* stroke volume, *CO* cardiac output

When caring for patients in shock, the routine use of CVP or PAOP to guide fluid management is not recommended [1]. Despite their widespread use, static measurements such as CVP, PAOP, or estimated end-diastolic volumes do not accurately reflect volume responsiveness or intravascular volume status, even in combination, and even at extreme highs and lows [12–14]. Randomized trials and large systematic reviews have not demonstrated that targeting a specific CVP or routinely using a PAC are of benefit to critically ill patients [15–18]. Blindly administering intravenous fluids to increase CVP is not recommended, as there is a worrisome correlation between elevated CVP, positive fluid balance during resuscitation, and mortality, at least in septic shock [19].

Unlike static filling pressures, dynamic measures of cardiopulmonary interaction are highly accurate in determining volume responsiveness [20–25]. In mechanically ventilated patients, such dynamic measurements include pulse pressure variation (PPV), stroke volume variation (SVV), and plethysmography variation index (PVI). Variations in pulse pressure (PP), stroke volume (SV) or plethysmography amplitude indicate that cardiac output is linked to changes in ventricular filling that occur with swings in intrathoracic pressure, which reflects volume responsiveness. Respiratory variation of IVC diameter (ΔD_{IVC}) using bedside ultrasound may also be used to predict volume responsiveness, again linking changes in venous return and cardiac output with changes in intrathoracic pressure.

SVV, PPV, and PVI specifically predict left ventricle (LV) volume responsiveness. During a positive pressure breath, venous return from the pulmonary vascular bed to the LV is briefly increased; if the LV is volume-responsive, then PP, SV, and plethysmography amplitude will transiently increase immediately after each ventilator-delivered breath. However, a positive pressure breath at the same time impedes the cardiac output of the RV—the source of LV preload. If the LV is volume responsive, PP and SV will dip after several cardiac cycles to reflect this decrease in preload to the LV, and then return to baseline during exhalation (Fig. 3.5). There are several minimally invasive methods available to assess SV, including pulse contour analysis from arterial pressure tracings (e.g. FloTrac [Edwards Lifesciences, Irvine, CA], PiCCO [Philips, Netherlands], LiDCO [LiDCO Group PLC, London, UK], etc.), esophageal Doppler monitoring (EDM) of aortic blood flow (e.g. CardioQ-ODM, Deltex Medical, West Sussex, UK), and left ventricular outflow tract velocity-time integral (LVOT VTi) obtained by transthoracic echocardiography (TTE).

An end-expiratory occlusion (EEO) maneuver can be used to determine volume responsiveness of both the right and left ventricle together. This is essentially an end-expiratory hold for 15 s in a passive, mechanically ventilated patient, during which time preload to the right heart and then left heart increases. If both the RV and LV are volume responsive in parallel, then PP, SV, and CI will increase during this maneuver. Table 3.1 compares these techniques.

There are important limitations to these dynamic measurements. Most of these measurements have only been validated in patients who are in a sinus rhythm, completely passive, and receiving

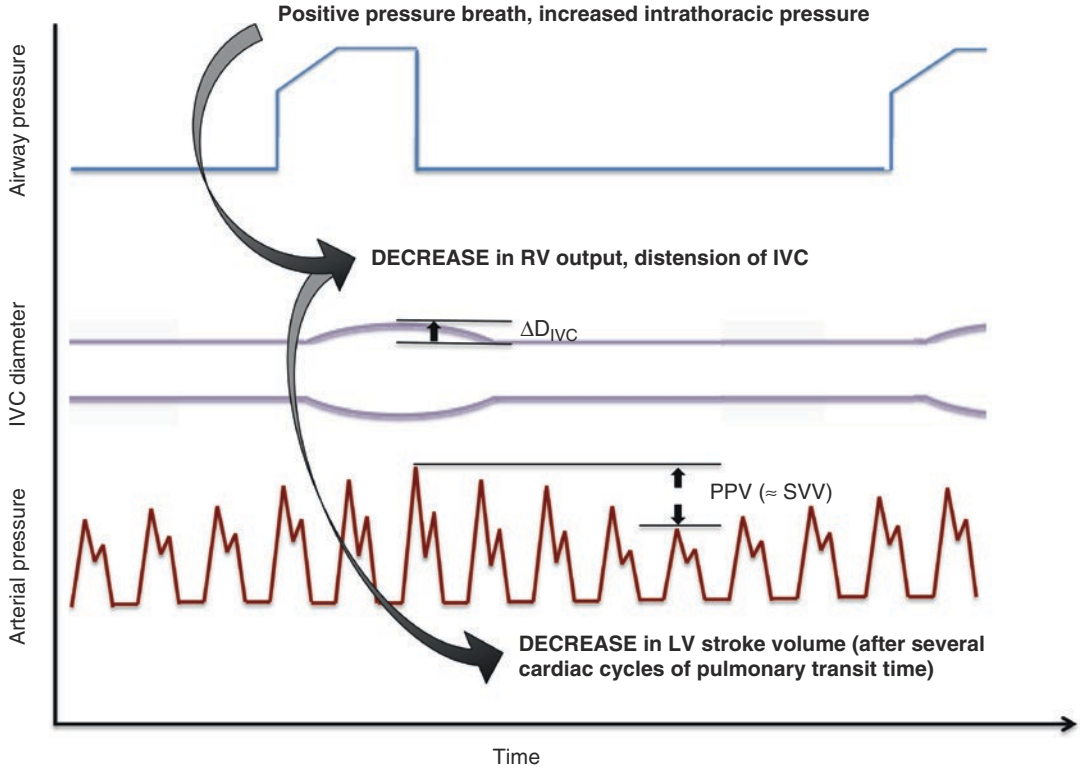


Fig. 3.5 Effects of positive pressure ventilation on IVC diameter and stroke volume variation. *RV* right ventricle, *IVC* inferior vena cava, ΔD_{IVC} change in diameter of IVC, *PPV* pulse pressure variation, *SVV* stroke volume variation, *LV* left ventricle

Table 3.1 Predictors of volume responsiveness during mechanical ventilation[a]

Measurement	Technique	Threshold for predicting volume responsiveness
PPV	Arterial waveform tracing	>13 %
SVV	Pulse contour analysis Esophageal Doppler monitor LVOT VTi using TTE	>10–13 %
PVI	Plethysmography	>10–15 %
ΔD_{IVC}	TTE	>12–18 %
ΔPP or ΔCI during EEO	Arterial waveform tracing PAC Pulse contour analysis Esophageal Doppler monitor	>5 % increase

PPV pulse pressure variation, *SVV* stroke volume variation, *LVOT* left ventricular outflow tract, *VTi* velocity-time integral, *TTE* transthoracic echocardiography, *PVI* plethysmography variation index, ΔD_{IVC} change in diameter of inferior vena cava, *ΔPP* change in pulse pressure, *ΔCI* change in cardiac output, *EEO* end-expiratory occlusion, *PAC* pulmonary artery catheter

[a]Requirements include: passive patient, tidal volume at least 8 mL/kg ideal body weight, sinus rhythm

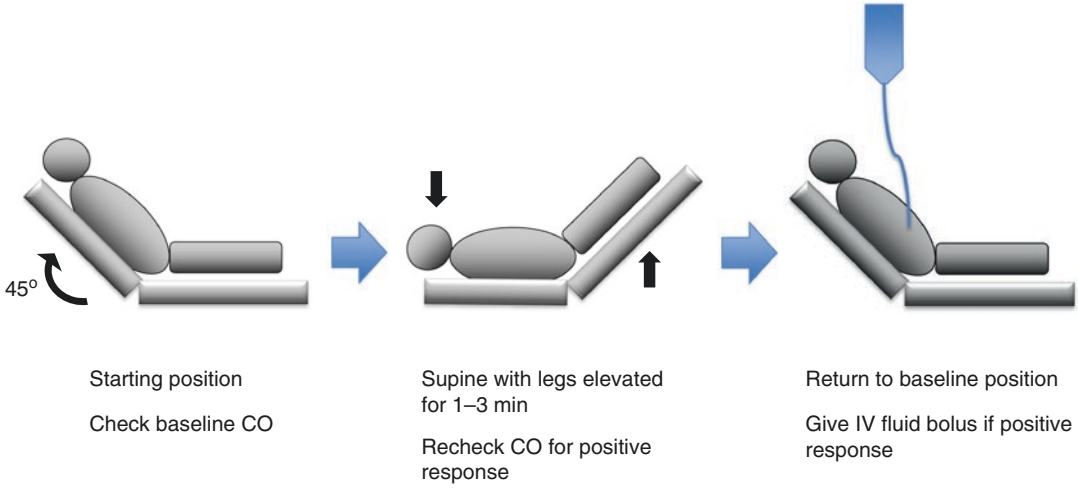


Fig. 3.6 Technique for positive passive leg raising. *CO* cardiac output

volume controlled breaths of at least 8 mL/kg tidal volume—conditions that apply to very few ICU patients in common practice. Furthermore, using indices of LV volume responsiveness in isolation may be misleading in patients with RV dysfunction (i.e. massive pulmonary embolism or pulmonary hypertension). These patients will have marked respiratory variation of SV and PP because the LV is relatively empty and preload dependent; however, the RV may be completely volume overloaded. If the RV itself is overloaded, giving intravenous fluid will not improve LV output and may cause hemodynamic deterioration (as seen in the case presentation). Combining SVV or PPV with an EEO maneuver or bedside echocardiography will help prevent this misinterpretation. Finally, decreased respiratory system compliance (e.g. severe ARDS, massive ascites, morbid obesity, etc.) may decrease the sensitivity of SVV or PPV; however, the accuracy of EEO appears unaffected by changes in compliance or positive end-expiratory pressure [26, 27].

Passive leg raising (PLR) may be the most accurate and widely applicable assessment of volume responsiveness (Fig. 3.6). For this test, a patient is laid supine and his/her legs are lifted up

Table 3.2 Thresholds for predicting volume responsiveness using passive leg raising (PLR)

Measurement	Technique	Threshold for predicting volume responsiveness
Pulse pressure	Arterial waveform tracing	Increase >12–15 %
Stroke volume	Pulse contour analysis Esophageal Doppler monitoring LVOT VTi using TTE PAC	Increase >12–15 %
Cardiac output, Cardiac index	Pulse contour analysis Esophageal Doppler monitoring LVOT VTi using TTE PAC	Increase >12–15 %
	Quantitative end tidal CO_2	Increase >5 %

LVOT left ventricular outflow tract, *VTi* velocity-time integral, *TTE* transthoracic echocardiography, *PAC* pulmonary artery catheter

to 45° and held up for 1–3 min; if SV, PP, CO or CI increase by 12–15 %, the patient is highly likely to be volume responsive (Table 3.2) [26, 28, 29]; continuous cardiac output monitoring is preferred for real-time assessments. As a surrogate for increased CO, a 5 % or more increase in $ECTO_2$ during PLR is also predictive of volume responsiveness, although this is not as sensitive [30]. The PLR retains its accuracy regardless of active respiratory efforts, tidal volume, level of sedation, or cardiac rhythm. Interpretation may be difficult in cases of massive ascites, abdominal compartment syndrome, or high pain response to the maneuver, and it should not be attempted in patients with elevated intracranial pressure.

Bedside Echocardiography

After assessment of volume responsiveness and initiating intravenous fluids as indicated, bedside echocardiography (BE) is the first test of choice to investigate undifferentiated shock [1]. Bedside echocardiography has been demonstrated to assist greatly in the determination of shock etiology in multiple clinical arenas. In the emergency setting, BE (along with multi-organ focused ultrasonography) can accurately differentiate between hypovolemic, cardiogenic, and obstructive causes of shock in patients with undifferentiated hypotension, and allow the examiner to correctly prioritize the most likely diagnoses in a timely fashion with high specificity and accuracy [31–34]. A simple, standardized approach to bedside ultrasound in undifferentiated hypotension has been shown to reduce diagnostic uncertainty, alter medical management, and influence the diagnostic or therapeutic plan in about one quarter of emergency cases [35].

In the ICU setting, BE within the first 24 h has been shown to significantly alter management in patients with hypotension, leading to less fluid administration and earlier use of inotropic support in many patients, reducing absolute mortality by 10 % in a small series [36]. In the perioperative, postoperative, and general ICU settings, echocardiography has been shown to accurately differentiate hypovolemia, volume overload, cardiac tamponade, and hemodynamically significant right or left ventricular dysfunction that otherwise may have otherwise gone undiagnosed [37–40].

There are several protocols for the use of point-of-care ultrasound in the hypotensive patient, and the key similarities among them are the systematic evaluation of cardiac function, pericardial effusion, IVC diameter and variability, pneumothorax, and sources of potential hemorrhage [41, 42]. When examining a hypotensive patient with ultrasound, the echocardiographic portion is the most important. The examiner should start with a subxiphoid view of the heart, determining any obvious decrease in global contractility as well as the presence of any significant pericardial effusion. A large pericardial effusion in the presence of hypotension is highly concerning for tamponade (Fig. 3.7). From the same location, the IVC should be located and assessed for respiratory variation, with a varying diameter or collapse suggestive of volume responsiveness (Fig. 3.8). Parasternal and apical

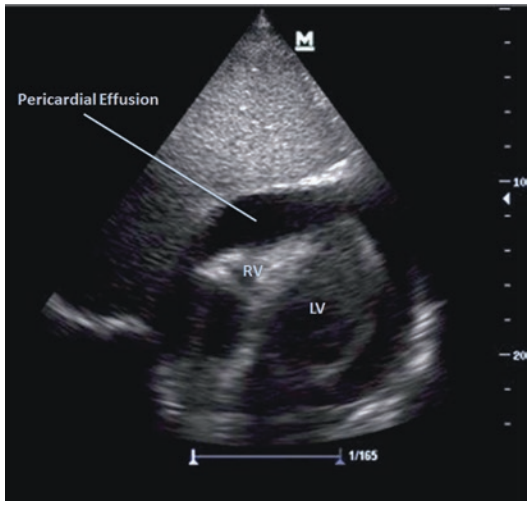


Fig. 3.7 Cardiac tamponade causing right ventricular collapse (transthoracic echocardiogram, subxiphoid view). *RV* right ventricle, *LV* left ventricle

views should be used to estimate global RV and LV systolic function (Fig. 3.9), RV size compared to LV size, and of utmost importance, the relationship of the interventricular septum (Fig. 3.10). Dilation of the RV (i.e. RV diameter approaching or exceeding LV diameter) and bowing of the septum from right to left suggests RV strain, which should prompt a search for pulmonary embolism or other causes of RV failure, as well as dissuade the clinician from using large fluid boluses or positive pressure ventilation if it can be helped [7]. After the cardiac portion, the examiner should look for bilateral lung sliding to rule out pneumothorax, free intraperitoneal fluid suggestive of hemorrhage, and abdominal aorta dilation >3 cm concerning for aneurysm. Echocardiographic patterns of shock type are summarized in Table 3.3.

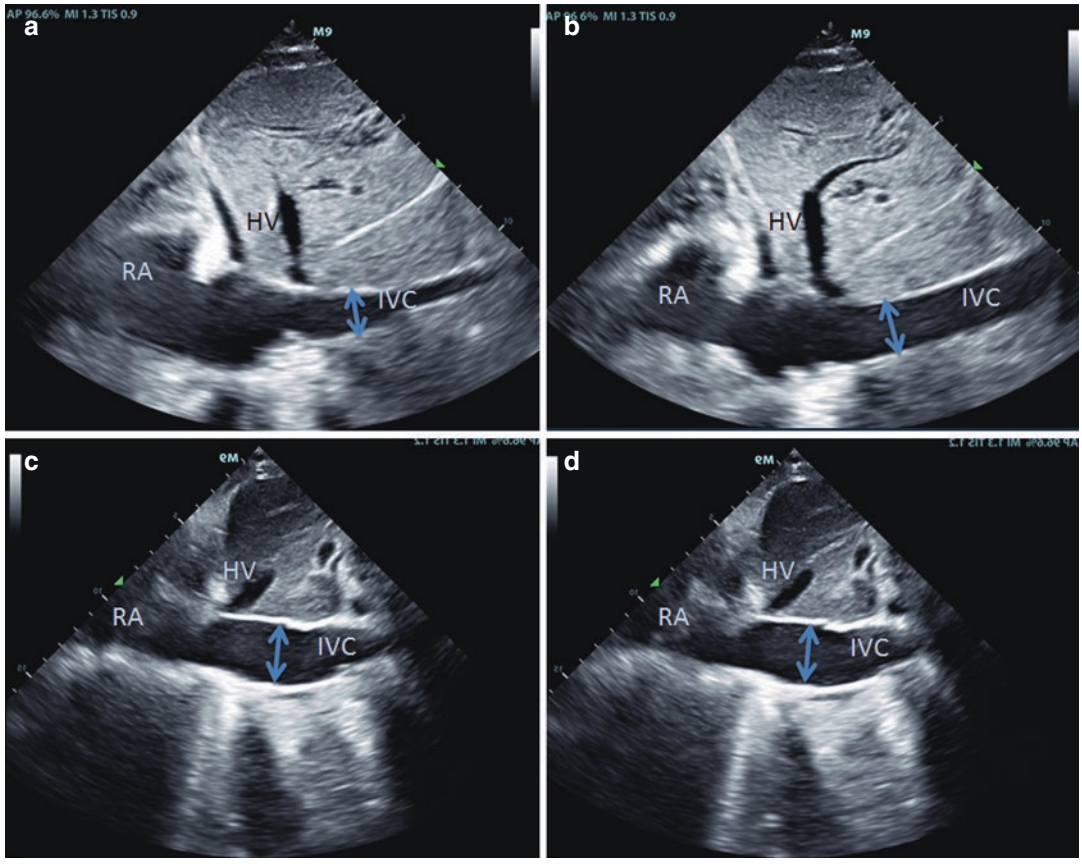


Fig. 3.8 IVC variation during respiration (transthoracic echocardiogram, subxiphoid view). **a** vs. **b**: roughly 50% IVC variation, suggests volume responsiveness. **c** vs. **d**: virtually no respiratory variation, suggests no response to fluid bolus. *IVC* inferior vena cava, *RA* right atrium, *HV* hepatic vein

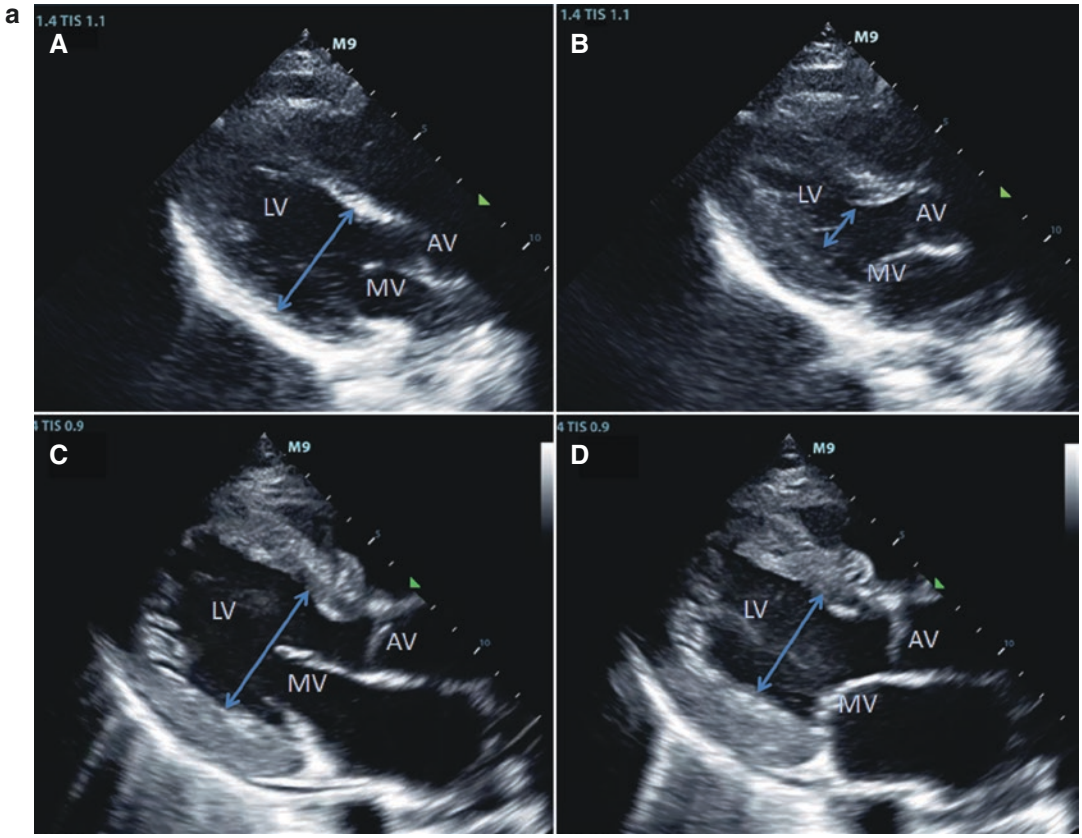


Fig. 3.9 (**a**) Global assessment of left ventricular contractility (transthoracic echocardiogram, parasternal long axis). *A* vs. *B*: roughly 50 % decrease in LV cavity, suggests normal contractility. *C* vs. *D*: roughly 25 % decrease in LV cavity, suggests moderately depressed contractility. *LV* left ventricle, *MV* mitral valve, *AV* aortic valve, *A and C* diastole, *B and D* systole. (**b**) Global assessment of left ventricular contractility (transthoracic echocardiogram, parasternal short axis). *A* vs *B*: roughly 40 % decrease in LV cavity, suggests mildly reduced contractility. *C* vs *D*: almost no decrease in LV cavity, suggests severely reduced contractility. *LV* left ventricle, *A and C* diastole, *B and D* systole

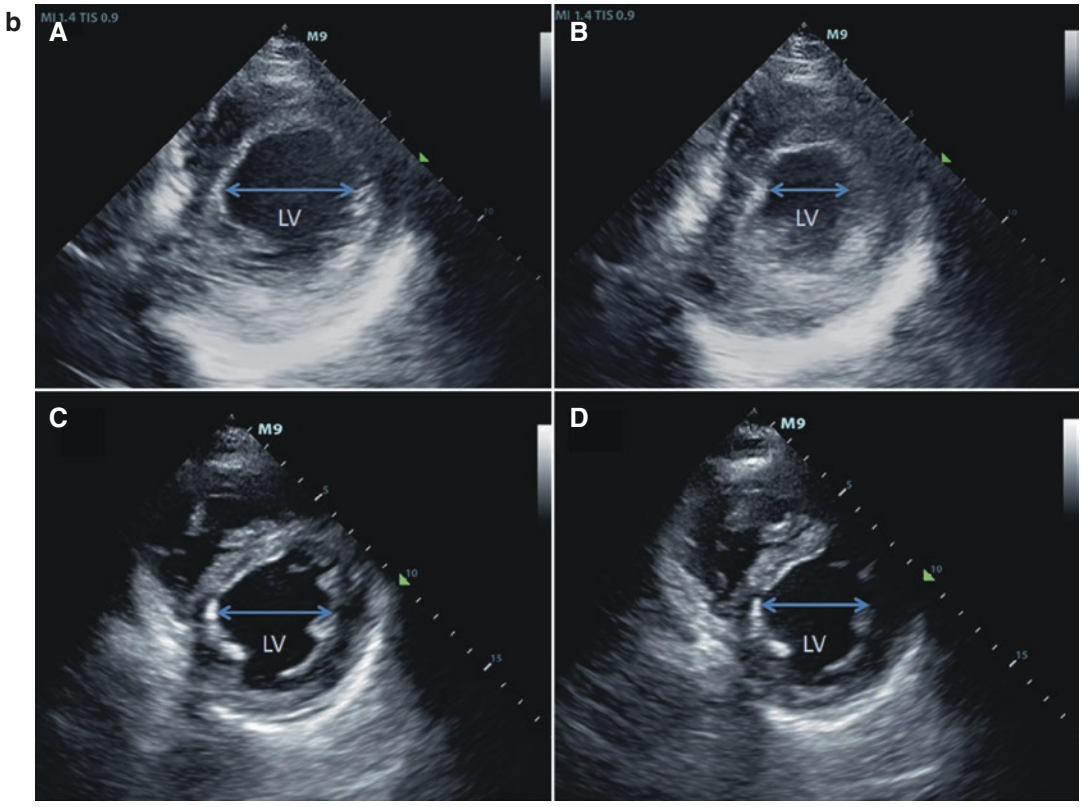


Fig. 3.9 (continued)

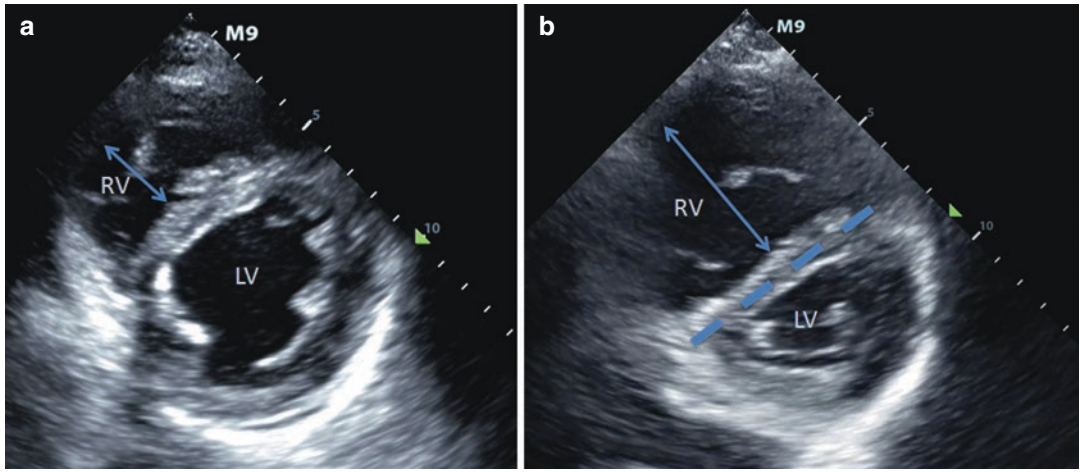


Fig. 3.10 RV-LV size relationship and position of intraventricular septum (transthoracic echocardiogram, parasternal short axis). (**a**) Normal relative RV and LV size, septum forms a contiguous circle with the LV. (**b**) Dilation of the RV with septal flattening ("D-sign") and compression of the LV, indicates RV strain/overload. *RV* right ventricle, *LV* left ventricle, *dashed line* flattened septum

Table 3.3 Echocardiographic patterns of shock types

Shock type	Suggestive echocardiographic findings
Hypovolemia	IVC collapsing on active inspiration Widely variable IVC diameter with respiration Hyperdynamic RV and LV
Distributive	IVC collapsing on active inspiration Widely variable IVC diameter with respiration Hyperdynamic RV and LV
Cardiogenic—Obstructive	*Pneumothorax*—absent lung sliding, identification of lung point *Tamponade*—pericardial effusion + distended, non-varying IVC ± RV collapse during diastole *Pulmonary Embolism*—distended, non-varying IVC, RV dilation, septal bowing, decreased RV contractility
Cardiogenic—RV	Distended, non-varying IVC RV dilation Septal bowing Decreased RV contractility
Cardiogenic—LV	Decreased LV contractility Dilated LV and/or LA ± distended, non-varying IVC

IVC inferior vena cava, *RV* right ventricle, *LV* left ventricle

Summary

Medically complex patients in shock should be assumed to have multiple shock types occurring simultaneously, and it may be difficult to differentiate these clinically. The use of static filling pressures such as CVP and PAOP are not helpful in determining which shock type(s) is/are present or in determining whether intravenous fluids will improve cardiac output. Targeting a specific CVP as a marker of adequate volume resuscitation is inappropriate, as positive fluid balance and elevated CVP have been associated with increased mortality, particularly in septic shock. The most important steps in the approach to undifferentiated shock are (1) determination of volume responsiveness, and (2) bedside echocardiography. There are multiple methods of determining volume responsiveness, with passive leg raising being the most accurate and widely applicable. After determining the appropriateness of a fluid challenge, bedside echocardiography should be used to look for IVC size and variation, pericardial effusion, RV size, and interventricular septal bowing, with added lung views for pneumothorax and abdominal views for free fluid and aorta caliber, to further differentiate shock type and guide the use of fluids, pressors, inotropes, or other specific therapies.

References

1. Cecconi M, DeBacker D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring: task force of the European Society of Intensive Care Medicine. Intens Care Med. 2014;40:1795–815.
2. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368–77.
3. Gaieski DF, Band RA, Abella BS. Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. Resuscitation. 2009;80(a4):418–24.
4. Omar S, Zedan A, Nugent K. Cardiac vasoplegia syndrome: pathophysiology, risk factors, treatment. Am J Med Sci. 2015;349(1):80–8.
5. Vieillard-Barron A, Cecconi M. Understanding cardiac failure in sepsis. Intens Care Med. 2014;40:1560–3.
6. Thiele H, Ohman EM, Desch S, et al. Management of cardiogenic shock. Eur Heart J. 2015;36(20):1223–30.
7. Piazza G, Goldhaber SZ. The acutely decompensated right ventricle: pathways for diagnosis and management. Chest. 2005;128(3):1836–52.
8. Funk DJ, Jacobsohn E, Kumar A. Role of the venous return in critical illness and shock—part I: physiology. Crit Care Med. 2013;41:255–62.

9. Monnet X, Jobot J, Maizel J, et al. Norepinephrine increased cardiac preload and reduces preload dependency by passive leg raising in septic shock patients. Crit Care Med. 2011;39:689–94.
10. Sharawy N. Vasoplegia in septic shock: do we really fight the right enemy? J Crit Care. 2014;29:83–7.
11. Lo JCY, Darracq MA, Clark RF. A review of methylene blue treatment for cardiovascular collapse. J Emerg Med. 2014;46(5):670–9.
12. Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. Crit Care Med. 2004;32(3):691–9.
13. Marik PE, Cavallazze R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. Crit Care Med. 2013;41(7):1774–81.
14. Osman D, Ridel C, Ray P, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. Crit Care Med. 2007;35(1):64–8.
15. Rajaram SS, Desai NK, Kalra A, et al. Pulmonary artery catheters for adult patients in intensive care. Cochrane Database Syst Rev. 2013;2:1–59.
16. Richard C, Warszawski J, Anguel N, et al. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2003;290(20):2713–20.
17. ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370(18):1683–93.
18. ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371(16):1496–506.
19. Boyd JH, Forbes J, Nakada TA, et al. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med. 2011;23(2):259–65.
20. Marik PE, Cavallazzi R, Vasu T, et al. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med. 2009;37(9):2642–7.
21. Sandroni C, Cavallaro F, Morano C, et al. Accuracy of plethysmographic indices as predictors of volume responsiveness in mechanically ventilated adults: a systematic review and meta-analysis. Intens Care Med. 2012;38:1429–37.
22. Monnet X, Osman D, Ridel C, et al. Predicting volume responsiveness by using the end-expiratory occlusion in mechanically ventilated intensive care unit patients. Crit Care Med. 2009;37(3):951–6.
23. Feissel M, Michard F, Faller JP, et al. The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. Intens Care Med. 2004;30(9):1834–7.
24. Barbier C, Loubieres Y, Schmit C, et al. Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated patients. Intens Care Med. 2004;30(9):1740–6.
25. Mandeville JC, Colebourn CL. Can transthoracic echocardiography be used to predict fluid responsiveness in the critically ill patient? A systematic review. Crit Care Res Pract. 2012;2012:1–9.
26. Monnet X, Bleibtreu A, Ferre A, et al. Passive leg raising and end-expiratory occlusion tests perform better than pulse pressure variation in patients with low respiratory system compliance. Crit Care Med. 2012;40(1):152–7.
27. Silva S, Jazwiak M, Teboul JL, et al. End-expiratory occlusion test predicts preload responsiveness independently of positive end-expiratory pressure during acute respiratory distress syndrome. Crit Care Med. 2013;41(7):1692–701.
28. Cavallaro F, Sandroni C, Marano C, et al. Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. In: Pinsky ME, Brochard L, Mancebo J, editors. Applied physiology in intensive care medicine. Berlin/Heidelberg: Springer; 2012.
29. Lamia B, Ochagavia A, Monnet X, et al. Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneous breathing activity. Intens Care Med. 2007;33:1125–32.
30. Monnet X, Bataille A, Magalhoes E, et al. End-tidal carbon dioxide is better than arterial pressure for predicting volume responsiveness by the passive leg raising test. Intens Care Med. 2013;39:93–100.
31. Jones AE, Tayal VS, Sullivan DM, et al. Randomized controlled trial of immediate versus delayed goal-directed ultrasound to identify the cause of non-traumatic hypotension in emergency department patients. Crit Care Med. 2004;32(8):1703–8.
32. Volpicelli G, Lamorte A, Tullio M, et al. Point-of-care multiorgan ultrasonography for the evaluation of undifferentiated hypotension in the emergency department. Intens Care Med. 2013;39:1290–8.
33. Jones AE, Craddock PA, Tayal VS, et al. Prognostic accuracy of left ventricular function for identifying sepsis among emergency department patients with non-traumatic symptoms of undifferentiated hypotension. Shock. 2005;24(6):513–7.
34. Ghane MR, Gharib M, Ebrahimi A, et al. Accuracy of early rapid ultrasound in shock (RUSH) examination performed by emergency physicians for diagnosis of shock etiology in critically ill patients. J Emerg Trauma Shock. 2015;8(1):5–10.
35. Shokoohi H, Boniface KS, Pourmand A, et al. Bedside ultrasound reduces diagnostic uncertainty

and guides resuscitation in patients with undifferentiated hypotension. Crit Care Med. 2015;43(12):2562–9.
36. Kanji HD, McCallum J, Sirounis D, et al. Limited echocardiography-guided therapy in subacute shock is associated with change in management and improved outcomes. J Crit Care. 2014;29:700–5.
37. Bouferrache K, Amiel JB, Chimot L, et al. Initial resuscitation guided by the Surviving Sepsis Campaign recommendations and early echocardiographic assessment of hemodynamics in intensive care unit septic patients: a pilot study. Crit Care Med. 2012;40(10):2821–7.
38. Shillcutt SK, Markin NW, Montzingo CR, et al. Use of rapid "rescue" perioperative echocardiography to improve outcomes after hemodynamic instability in non-cardiac surgical patients. J Cardiothorac Vasc Anesth. 2012;26(3):362–70.
39. Maltais S, Costello WT, Billings FT. Episodic monoplane transesophageal echocardiography impacts postoperative management of the cardiac surgery patient. J Cardiothorac Vasc Anesth. 2013;27(4):655–9.
40. Marcelino PA, Marum SM, Fernandes APM, et al. Routine transthoracic echocardiography in a general intensive care unit: an 18 month survey in 704 patients. Eur J Intern Med. 2009;20:e37–42.
41. Atkinson PRT, McAuley DJ, Kendall RJ, et al. Abdominal and cardiac evaluation with sonography in shock (ACES): an approach by emergency physicians for the use of ultrasound in patients with undifferentiated hypotension. Emerg Med J. 2009;26:87–91.
42. Perera P, Mailhot T, Riley D, et al. The RUSH exam: rapid ultrasound in shock in the evaluation of the critically ill. Emerg Med Clin N Am. 2010;28:29–56.

Hypovolemic Shock and Massive Transfusion

4

Joshua M. Glazer and Kyle J. Gunnerson

Case Presentation

A previously healthy 35 year old male presented as a Level I trauma after a motor vehicle accident in which he was the restrained driver. There was extensive intrusion on the front end of the vehicle requiring extrication of the patient. Airbag did not deploy. He was reportedly hypotensive and confused in the field. An 18 gauge IV was placed and a 500 mL NS bolus initiated prior to arrival. In the Emergency Department, his initial vitals were significant for a heart rate of 140 and blood pressure of 72/48. Primary survey demonstrated an intact airway, bilateral breath sounds, 2+ pulses in all four extremities, and a Glasgow Coma Score (GCS) of 11 with no obvious focal disability on full exposure. The patient was pale, had a large left-sided frontal scalp contusion, and had obvious bruising of the lower chest and right abdomen. A bedside Extended Focused Assessment with Ultrasound in Trauma (E-FAST) exam showed free fluid in Morison's pouch (Fig. 4.1). The remaining E-FAST views showed no evidence of hemopneumothorax, pericardial fluid, myocardial wall-motion abnormalities, or fluid in the splenorenal or rectovesicular spaces. Trauma-protocol chest and pelvis x-rays were negative.

Question What is the optimal approach to management of this patient's presumed traumatic hemorrhagic shock; specifically, how should intravascular access, fluid resuscitation, hemodynamic end-points, and definitive therapy be prioritized?

Answer Hemostatic resuscitation prioritizing damage control surgery & massive transfusion.

This patient is exsanguinating, presumably secondary to traumatic intraabdominal injury, and demonstrating physiology consistent with decompensated hemorrhagic shock. Injury mechanism and physical exam findings are also concerning for concurrent traumatic brain injury. As with all types of shock, prioritization is given to reversal of the inciting etiology and concurrent mitigation of tissue hypoperfusion caused by the precipitating shock state.

After confirming an intact airway and bilateral breath sounds, this patient's management appropriately focused on cardiovascular optimization and hemodynamic support. Two additional proximal 16 gauge peripheral IV's were placed. The crystalloids which were initiated in the field were discontinued. Non-crossed O+ packed red blood

J.M. Glazer
Emergency Medicine, University of Michigan Health System, Ann Arbor, MI, USA

K.J. Gunnerson (✉)
Emergency Medicine, Internal Medicine and Anesthesiology, Division of Emergency Critical Care, University of Michigan Health System, Ann Arbor, MI, USA
e-mail: kgunners@med.umich.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_4

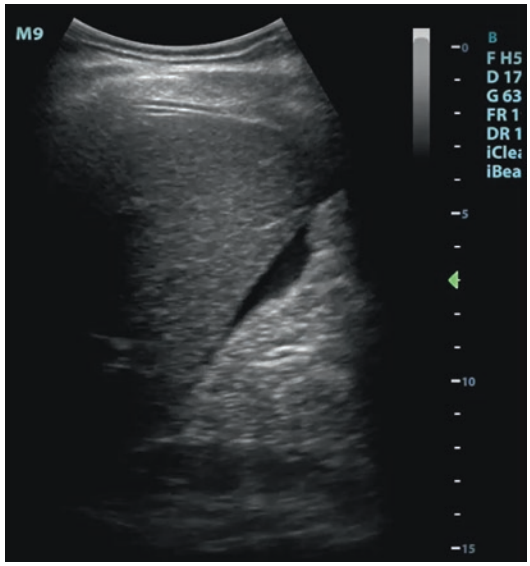


Fig. 4.1 Extended Focused Assessment with Ultrasound in Trauma (E-FAST) scan showing free fluid surrounding the liver border in a polytrauma patient (Reproduced with permission of Huang and Fung)

cells, along with fresh frozen plasma and pooled platelets, were rapidly hand-delivered and infused in a 1:1:1 ratio per the institutional massive transfusion protocol. As he is within the 3-h window, tranexamic acid is administered to inhibit fibrinolysis. Simultaneously, electrolytes were aggressively repleted and his acidosis corrected. A multidisciplinary Trauma team agreed on a mean arterial pressure goal of 75 mmHg in an effort to maintain cerebral perfusion pressure in the setting of probable traumatic brain injury, remaining cognizant to avoid overcorrection and resultant disruption of intrinsic/protective hemostatic mechanisms.

After initial evaluation/stabilization in the Emergency Department, the patient was transported first for head CT, which did not show intracranial hemorrhage, then to the operating room for exploratory laparotomy. Damage control surgery, including splenectomy and partial small bowel resection without reanastamosis, was performed. The patient was then transferred to the ICU with an abdominal wound vacuum device in place. Hemodynamic optimization was continued, utilizing a combination of blood products, pressors, and intravenous fluids. Markers of tissue perfusion, including central venous oxygen saturations ($ScvO_2$) and serial lactate levels, improved and the patient was taken back to the operating room for reanastamosis and closure.

Principles of Management

Hypovolemic Shock

We will first review fundamentals of the management of hypovolemic shock regardless of etiology, then focus on elements unique to treating patients with hemorrhagic shock.

Establish Adequate IV Access

Flow rates achieved for potential life-saving fluid resuscitation depend on the device used. In agreement with Poiseuille's law, the ideal cannula should be a short, large-bore (at least 18 g), and placed in a proximal large vein in the upper extremity. If a central venous catheter (CVC) is the only available access, the addition of a pressure bag makes a greater difference on flow rate than with an equivalent peripheral cannula [1]. However, in a resuscitation setting, intraosseous (IO) access has higher first pass success and shorter procedure times, making it preferable to CVC insertion if peripheral access cannot be rapidly obtained [2]. Of the three approved IO sites (proximal tibia, distal tibia, proximal humerus), the humerus seems to be the superior site in terms of flow rates, drug delivery, and management of infusion pain [3].

Consider Physiologic Reserve

Young healthy individuals can maintain end-organ perfusion and normotension despite significant intravascular loss as a result of their ability to sustain cardiac output through: peripheral vasoconstriction, compensatory tachycardia, and catecholamine surge. Thus, substantial tachycardia and cool extremities should be recognized as markers of imminent decompensation and cardiovascular collapse in these individuals [4]. Conversely, systemic diseases (e.g. chronic kidney disease, hypertension, diabetes, cirrhosis,

chronic heart failure) and/or pharmacotherapies (e.g. alcohol, antihypertensives, anti-arrhythmics, β-blockers, steroids, insulin) can both limit physiological reserve and also delay detection of shock when patients do not manifest classic signs of hypovolemia.

Monitor Volume Responsiveness

Fundamentally, "fluid responsiveness" means that stroke volume (and thus cardiac output, given stable heart rate) will improve if fluids are administered. Administering fluid to a volume unresponsive patient can negatively affect cardiac output directly and has other potential side effects such as pulmonary edema, abdominal compartment syndrome, and cerebral edema. Traditionally an increase in stroke volume of 10–15 % after receiving an adequate bolus (rapid infusion of at least 250 cc) is considered a positive test of volume responsiveness [5]. Several techniques and technologies exist to help make this determination without actually administering a volume expander, but each has its own unique challenges and limitations. Please refer to the "Undifferentiated Shock" chapter for a more detailed discussion.

Administer the Appropriate Fluid(s)

The ideal fluid used to replete intravascular depletion is very much dependent on the precipitating etiology. With gastrointestinal losses, thoughtful repletion of electrolytes is indicated. With acute blood loss, sanguineous resuscitation is clearly preferable. Importantly, tissue perfusion and oxygen delivery are the goals, and that optimization of cardiac output and oxygen carrying capacity are the means.

Track Endpoints of Resuscitation

Normalization of vital signs alone is insufficient evidence of resolution of shock; indeed, poor tissue perfusion can often persist and lead to ongoing accumulation of oxygen debt and tissue damage (see Fig. 4.2). More appropriate markers, which account for perfusion of the microcirculation, include central venous oxygen saturation (ScvO2) and lactate clearance [6, 7].

Hemorrhagic Shock

Hemostatic resuscitation refers to the process of restoring and sustaining normal tissue perfusion to the patient presenting in uncontrolled hemorrhagic shock, with an emphasis on preservation of effective clotting.

Expedite Anatomic Control of Bleeding

Immediate control of ongoing hemorrhage is always the first priority. This may simply require direct pressure or other straightforward maneuvers for brisk external bleeds (e.g. staple closure for scalp wound or nasal pack for epistaxis). Depending on the source, however, Gastroenterology, Interventional Radiology, or Surgery consultation may be required for specific hemostatic interventions.

Utilize Damage Control Surgery

The initial surgery on a hemodynamically unstable, actively bleeding patient should be focused on anatomic control of bleeding, with repair of less significant injuries or time-intensive procedures deferred. Once hemostasis is achieved, the patient is transferred to the intensive care unit for completion of resuscitation [8]. Subsequent operative interventions are later performed once the patient is hemodynamically stable.

Allow for Permissive Hypotension

While the goal of resuscitation in general is to restore normal systemic oxygen delivery, during early resuscitation the advantage of reducing ischemia must be weighed against the iatrogenic prolongation of hemorrhage. Indeed, attempting to achieve normotension during active hemorrhage consistently increases mortality [9, 10]. In penetrating trauma patients, resuscitation to a target minimum MAP of 50 mmHg, rather than 65 mmHg, significantly decreases postoperative coagulopathy and lowers the risk of early postoperative death and coagulopathy [11].

Correct and Reverse Augmenting Factors of Coagulopathy and Shock

In the exsanguinating patient, the so-called "lethal triad" of coagulopathy, acidosis, and hypothermia predict morality and must be corrected (see Fig. 4.3).

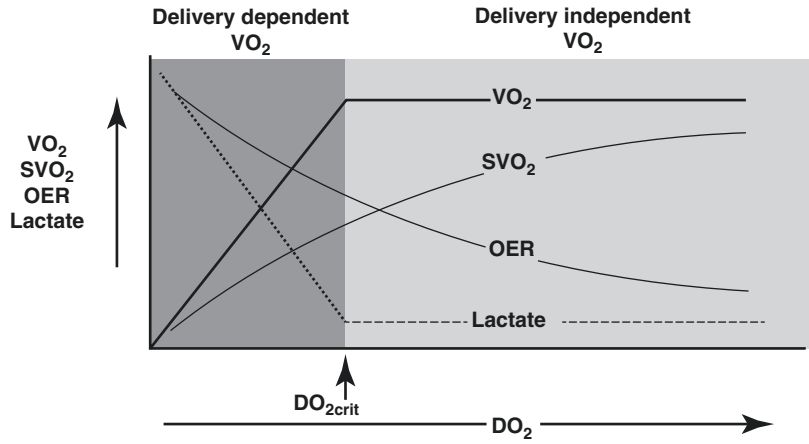


Fig. 4.2 The relationship between oxygen delivery and oxygen consumption in shock. When DO_2 decreases to less than the value for critical delivery (DO_2crit), oxygen consumption (VO_2) is linearly dependent on the delivery of oxygen to the tissues (DO_2). In the delivery-dependent region, oxygen extraction ratio is maximal and anaerobic metabolism increases with an associated increase in lactate and decrease in SVO_2. This region to the left of DO_2crit is where oxygen debt starts to accumulate. $DO_2 = CaO_2 \times CO$ (normal range: 460–650 ml/min/m^2); $VO_2 = CO \times (CaO_2 - CVO_2)$ (normal range: 96–170 ml/min/m^2); CaO_2 (arterial oxygen content) $= (Hb \times 1.34 \times SaO_2) + (0.003 \times PaO_2)$; $CVO_2 = (Hb \times 1.34 \times SVO_2) + (0.003 \times PVO_2)$. *CO* cardiac output, PaO_2 arterial oxygen tension, *Hb* hemoglobin. SVO2 normal range: 70% (±5%) [34]

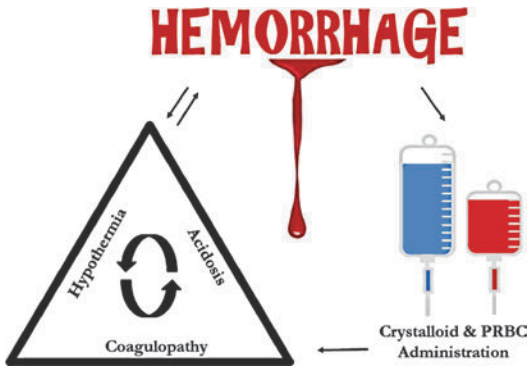


Fig. 4.3 The so-called "lethal triad" whereby the combination of hypothermia, acidosis, and coagulopathy contribute toward mortality in hemorrhagic shock. Iatrogenic etiologies for worsening hemorrhage include use of crystalloids and packed red blood cells (PRBC). Both directly worsen hypothermia if not warmed and contribute to dilutional coagulopathy, the latter if platelets and fresh frozen plasma are not concurrently infused

Several studies have demonstrated that patients with altered coagulation function at the time of hospital admission have substantially worse outcomes than similar patients who are not coagulopathic, even when controlling for degree of injury [12, 13].

Minimize Crystalloid Administration

Indiscriminate fluid administration during uncontrolled hemorrhage is associated with increased bleeding. Relative arterial hypertension caused by augmented cardiac output via the Frank-Starling relationship, forces more fluid out of the damaged circulation, and can "wash away" early clots. Furthermore, asanguineous crystalloids dilute the concentration of red cells, clotting factors, and platelets, impairing both oxygen carrying capacity and the clotting cascade [14]. Exogenous fluids are also likely to be cooler than body temperature, contributing to hypothermia. Finally, rapid administration of crystalloids damages the endothelial glycocalyx, leading to increased extravasation [15].

Preserve Formed Clot with Antifibrinolytics

The CRASH-2 trial randomized 20,000 trauma patients worldwide to receive either placebo or tranexamic acid, and demonstrated a significant survival benefit with this therapy when administered within 3 h of injury. Interestingly, there was no difference in transfusion requirements between the

groups, suggesting that tranexamic acid may have effects in addition to antifibrinolysis. The earlier the drug was administered, the more positive the effect [16].

Replace Losses via Transfusion Therapy

In the setting of brisk hemorrhage, the ideal fluid of choice is fresh whole blood (FWB). Blood provides the intravascular volume expansion needed to increase cardiac output, the red blood cells necessary for oxygen carrying capacity, and contains the platelets and clotting factors which enable hemostasis [17]. Importantly, hemoglobin and hematocrit do not change in acute hemorrhage; indeed, these measurements reflect concentrations of red blood cell content, and will not be affected until compensatory fluid shifts from the intra- and extra-cellular spaces dilute the blood.

Evidence Contour

Several aspects regarding the management of hypovolemic and hemorrhagic shock remain without clear consensus.

Hypovolemic Shock

The ideal fluid for hypovolemic shock secondary to asanguineous losses should reliably expand intravascular volume; have a sustained effect without accumulation in tissues, and replete whole-body deficits, while minimizing side-effects (electrolyte disturbances, third-spacing, acidosis, hemodilution) and cost. Unfortunately, no such fluid exists; so much debate exists surrounding which "non-ideal" fluid to use.

Normal Saline vs Balanced Solutions

Normal saline has traditionally been the most widely-used crystalloid in the United States. Increasing evidence, however, suggests that excessive chloride loads are associated with negative outcomes. Among patients with systemic inflammatory response syndrome (SIRS), chloride-restrictive fluid resuscitation is associated with lower in-hospital mortality [18]. Furthermore, implementation of a chloride-restrictive resuscitation is associated with a significant decrease in the incidence of acute kidney injury and use of renal replacement therapy [19]. Commercially available chloride-restrictive fluids include the crystalloids Lactated Ringers and Plasma-Lyte, as well as the colloids albumin and several synthetic gelatin- or hydroxyethyl starch (HES)-based preparations.

Role of Albumin

The Saline versus Albumin Fluid Evaluation (SAFE) study showed no significant difference in rate of death or development of organ failure among ICU patients randomized to normal saline or albumin resuscitation. Subgroup analysis suggests that use of albumin in patients with traumatic brain injury was associated with a significant increase in rate of death at 2 years while albumin is associated with a significant decrease in the rate of death at 28 days in patients with severe sepsis [20].

Use and Timing of Pressors

Even in patients with "pure" hypovolemic shock, vasopressors can and should be used as a bridge while volume is infused and then titrated off as the volume deficit is overcome [21]. The aim is to preserve coronary perfusion pressure (CPP) (aortic diastolic pressure (ADP) – pulmonary artery wedge pressure (PAWP)) and thus prevent ischemic injury and secondary cardiogenic shock. Many experts suggest that a target ADP of 35–40 mmHg is likely adequate; however, in patients with preexisting conditions that increase baseline PAWP (e.g. pulmonary hypertension), the ADP goal should be correspondingly increased [22, 23].

Hemorrhagic Shock

Adequately powered clinical trials addressing the question of optimal resuscitation of massively bleeding patients are lacking. Instead, a large number of retrospective studies and systematic reviews concerning this topic have been published,

although the interpretation of the currently available data differs substantially. Figure 4.4 demonstrates a theoretical framework for the treatment of hemorrhagic shock. Figure 4.5 incorporates this information with logistical considerations necessary for implementing an institutional massive transfusion protocol.

Massive Transfusion Protocol

Studies of both military and civilian trauma patients have demonstrated that those receiving high ratios of both fresh frozen plasma (FFP) and platelets (PLT) to red blood cells (RBC) have the highest survival, suggesting that the ideal transfusion ratio is 1:1:1 FFP:PLT:RBC. However, close inspection of many of these studies reveals important limitations in their interpretation, namely a prominent effect of survivor bias [24]. While the optimal massive transfusion protocol ratio remains elusive, it does appear that an early and more balanced approach to transfusion is associated with improved outcomes [25].

Ionized Calcium Repletion

Hypocalcemia can complicate massive transfusion as a result of the citrate anticoagulant in blood products (FFP&PLT>PRBC). Formation and stabilization of fibrin polymers is dependent

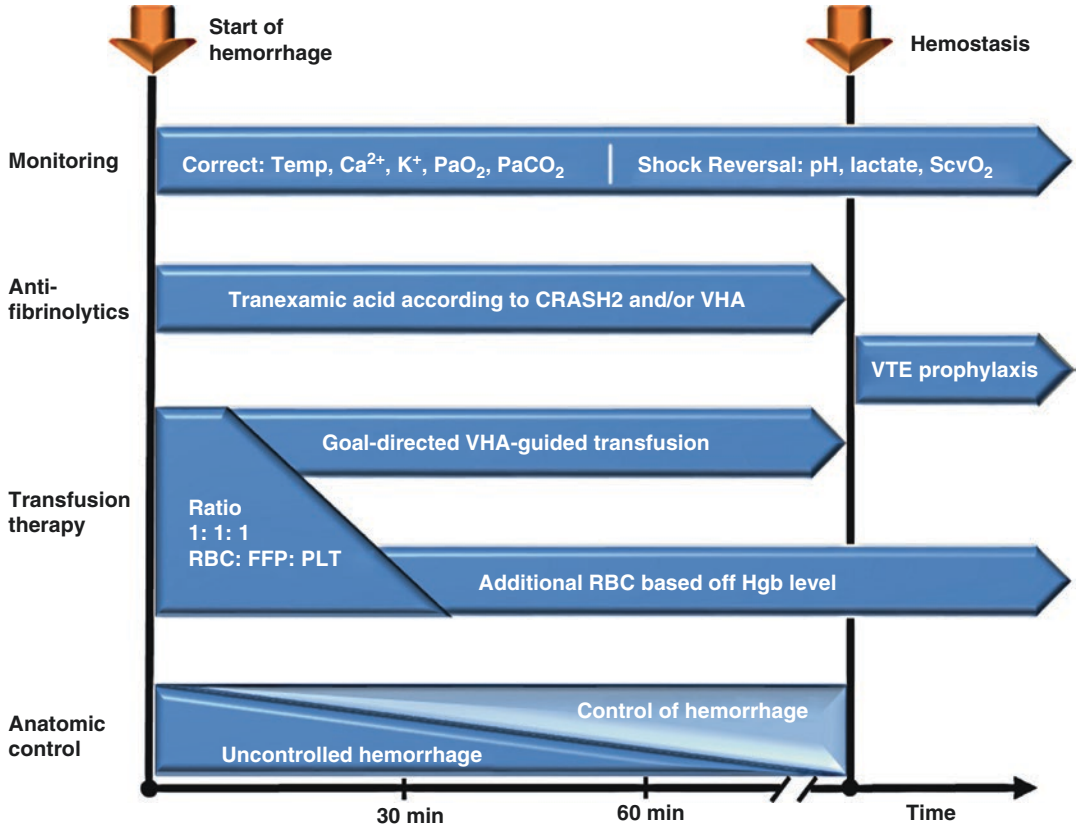


Fig. 4.4 One reasonable algorithm for treatment of hemorrhagic shock incorporating principles of hemostatic resuscitation. Of primary importance is anatomic control of bleeding. Concurrently, goal-directed transfusion of blood products and anti-fibrinolytics are administered to preserve cardiac output, oxygen carrying capacity, and the ability to form and preserve clots. As with any shock state correction of electrolyte abnormalities, hypothermia, and oxygenation/ventilation issues is indicated while tracking endpoints of resuscitation including serum pH, lactate, and $ScvO_2$. *RBC* red blood cells, *FFP* fresh frozen plasma, *PLT* platelets, *Hgb* hemoglobin, *VHA* viscoelastical hemostatic assay, *VTE* venous thromboembolism, Ca^{2+} serum calcium, K_+ serum potassium, PaO_2 partial pressure of oxygen in blood, $PaCO_2$ partial pressure of carbon dioxide in blood, $ScvO_2$ central venous oxygen saturation

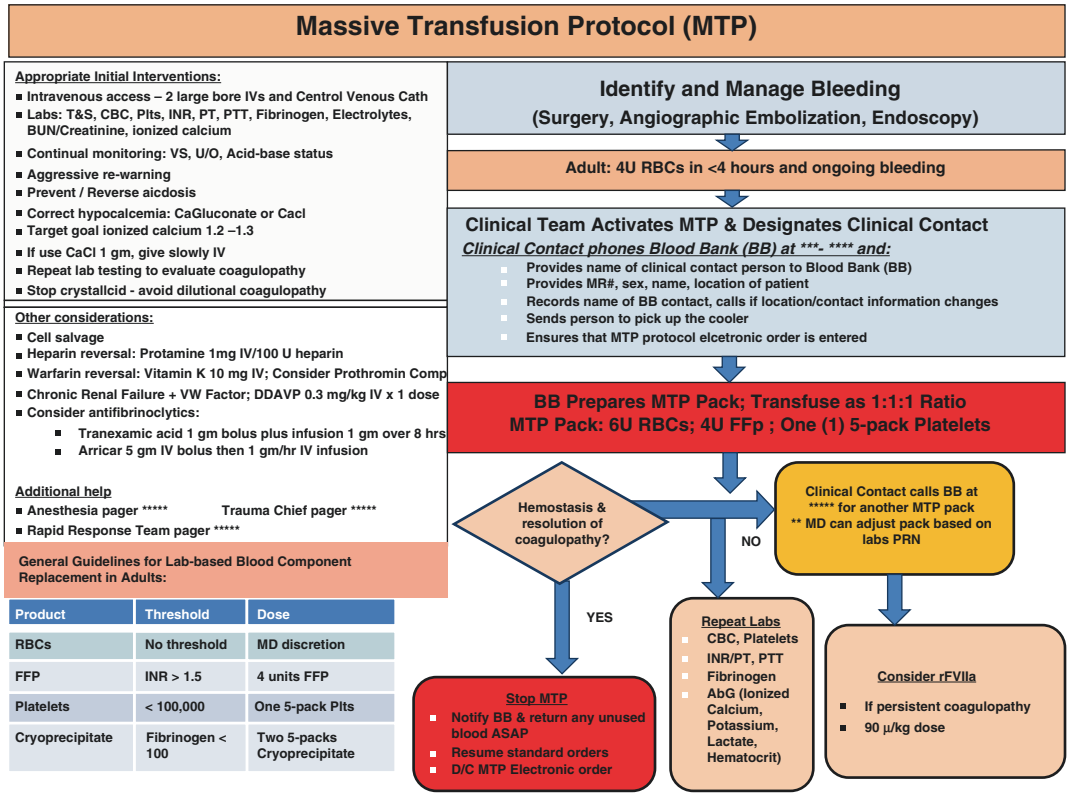


Fig. 4.5 An institutional Massive Transfusion Protocol detailing the initial stabilization steps, necessary contact information, relevant electronic medical record orders, component blood products, and triggers for activation and deactivation

on ionized calcium; additionally, decreased intracellular calcium concentration negatively affects all platelet-related activities. Equally importantly, myocardial contractility and systemic vascular resistance are compromised at low ionized calcium levels. Taking into account beneficial cardiovascular and coagulation effects, ionized calcium levels should be maintained above 0.9 mmol/l [26].

Point-of-Care Monitoring the Hemostatic System

Conventional laboratory tests of coagulation are insensitive in detection acquired coagulopathy or in guiding procoagulant therapy [27]. Viscoelastical hemostatic assays (VHAs), including thrombelastography (TEG®) and rotational thrombelastometry (ROTEM®), provide rapid information regarding platelet aggregation, clot strengthening, fibrin cross-linking, and fibrinolysis, and thus more accurately assess global hemostatic potential. Goal-directed transfusion utilizing VHAs have been reported to reduce bleeding, significantly diminish transfusion requirements, and improve outcomes in cohort studies [28].

Invasive Non-surgical Hemorrhage Control

In moribund or arresting patients with exsanguinating noncompressible hemorrhage in the chest, abdomen, or pelvis, resuscitative thoracotomy has traditionally been the intervention of choice in the emergent setting. Unfortunately, after controlling for relatively easily reversible causes of traumatic obstructive shock (tension pneumothorax and

hemopericardium with tamponade), outcomes are quite poor and the procedure itself places medical providers at risk of serious injury [29]. Resuscitative endovascular balloon occlusion of the aorta (REBOA) offers a less invasive alternative which effectively allows intravascular aortic cross-clamp thereby limiting further hemorrhage and redistributing blood supply to the heart and brain while definitive source control is performed [30].

Timing and Role of Vasopressors

Studies using animal models of profound hemorrhagic shock demonstrate improved survival when norepinephrine or vasopressin (AVP) is administered early; conversely, epinephrine and phenylephrine have been associated with worsened outcomes. In addition to improved cardiac perfusion pressure detailed previously, the splanchnic vasoconstriction caused by these drugs likely augments return of enteric blood volume to the central circulation and can also shunt blood away from commonly bleeding organs (e.g. lacerated liver) [31]. At present, a multicenter, randomized controlled trial (Vasopressin in Traumatic Hemorrhagic Shock—VITRIS study) is underway to evaluate the effects of AVP in prehospital management of hemorrhagic shock.

Hemostatic Resuscitation with Concurrent Head Injury

Hemorrhagic shock associated with moderate to severe head injury (GCS $\leq$ 12) compounds the clinical picture, and controversies exist between the so-called cerebral perfusion pressure (CPP) based therapy and intracranial pressure (ICP) based therapy [32]. Considering that cerebral ischemia is the single most important secondary factor influencing outcome following traumatic brain injury (TBI), maintenance of adequate cerebral perfusion pressure (CPP = MAP – ICP) is arguably the superior strategy in most cases. Outside the setting of impending herniation (where ICP must be rapidly lowered awaiting decompressive management), consensus guidelines recommend a CPP target of 50–70 mmHg [33]. When possible, monitoring cerebral oxygenation in individual patients can allow liberalization of CPP target and thus facilitate permissive hypotension in the polytrauma patient.

References

1. Reddick AD, Ronald J, Morrison WG. Intravenous fluid resuscitation: was Poiseuille right? Emerg Med J. 2011;28(3):201–2.
2. Leidel BA, Kirchhoff C, Bogner V, Braunstein V, Biberthaler P, Kanz KG. Comparison of intraosseous versus central venous vascular access in adults under resuscitation in the emergency department with inaccessible peripheral veins. Resuscitation. 2012;83(1):40–5.
3. Luck RP, Haines C, Mull CC. Intraosseous access. J Emerg Med. 2010;39(4):468–75.
4. Bonanno FG. Hemorrhagic shock: the "physiology approach". J Emerg Trauma Shock. 2012;5(4):285–95.
5. Monge Garcia MI, Gil Cano A, Gracia Romero M. Dynamic arterial elastance to predict arterial pressure response to volume loading in preload-dependent patients. Crit Care. 2011;15(1):R15.
6. Boulain T, Garot D, Vignon P, Lascarrou JB, Desachy A, Botoc V, et al. Prevalence of low central venous oxygen saturation in the first hours of intensive care unit admission and associated mortality in septic shock patients: a prospective multicentre study. Crit Care. 2014;18(6):609.
7. Odom SR, Howell MD, Silva GS, Nielsen VM, Gupta A, Shapiro NI, et al. Lactate clearance as a predictor of mortality in trauma patients. J Trauma Acute Care Surg. 2013;74(4):999–1004.
8. Pohlman TH, Walsh M, Aversa J, Hutchison EM, Olsen KP, Lawrence RR. Damage control resuscitation. Blood Rev. 2015;29(4):251–62.
9. Shoemaker WC, Peitzman AB, Bellamy R, Bellomo R, Bruttig SP, Capone A, et al. Resuscitation from severe hemorrhage. Crit Care Med. 1996;24(2 Suppl):S12–23.
10. Bickell WH, Wall Jr MJ, Pepe PE, Martin RR, Ginger VF, Allen MK, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med. 1994;331(17):1105–9.
11. Morrison CA, Carrick MM, Norman MA, Scott BG, Welsh FJ, Tsai P, et al. Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. J Trauma. 2011;70(3):652–63.
12. Hess JR, Lindell AL, Stansbury LG, Dutton RP, Scalea TM. The prevalence of abnormal results of conventional coagulation tests on admission to a trauma center. Transfusion. 2009;49(1):34–9.

13. MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. J Trauma. 2003;55(1):39–44.
14. Duchesne JC, Islam TM, Stuke L, Timmer JR, Barbeau JM, Marr AB, et al. Hemostatic resuscitation during surgery improves survival in patients with traumatic-induced coagulopathy. J Trauma. 2009; 67(1):33–7; discussion 7–9.
15. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. Anesthesiology. 2008;109(4):723–40.
16. Roberts I, Shakur H, Afolabi A, Brohi K, Coats T, Dewan Y, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet. 2011;377(9771):1096–101, 101.e1–2.
17. Nessen SC, Eastridge BJ, Cronk D, Craig RM, Berseus O, Ellison R, et al. Fresh whole blood use by forward surgical teams in Afghanistan is associated with improved survival compared to component therapy without platelets. Transfusion. 2013;53 Suppl 1:107s–13.
18. Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer CR. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. Intensive Care Med. 2014;40(12):1897–905.
19. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308(15):1566–72.
20. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350(22):2247–56.
21. Ellender TJ, Skinner JC. The use of vasopressors and inotropes in the emergency medical treatment of shock. Emerg Med Clin North Am. 2008;26(3):759–86, ix.
22. Reynolds JC, Salcido DD, Menegazzi JJ. Coronary perfusion pressure and return of spontaneous circulation after prolonged cardiac arrest. Prehosp Emerg Care. 2010;14(1):78–84.
23. Cruickshank JM. The role of coronary perfusion pressure. Eur Heart J. 1992;13 Suppl D:39–43.
24. Sihler KC, Napolitano LM. Massive transfusion: new insights. Chest. 2009;136(6):1654–67.
25. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015;313(5):471–82.
26. Lier H, Krep H, Schroeder S, Stuber F. Preconditions of hemostasis in trauma: a review. The influence of acidosis, hypocalcemia, anemia, and hypothermia on functional hemostasis in trauma. J Trauma. 2008; 65(4):951–60.
27. Haas T, Fries D, Tanaka KA, Asmis L, Curry NS, Schochl H. Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence? Br J Anaesth. 2015;114(2):217–24.
28. Kashuk JL, Moore EE, Wohlauer M, Johnson JL, Pezold M, Lawrence J, et al. Initial experiences with point-of-care rapid thrombelastography for management of life-threatening postinjury coagulopathy. Transfusion. 2012;52(1):23–33.
29. Rabinovici R, Bugaev N. Resuscitative thoracotomy: an update. Scand J Surg. 2014;103(2):112–9.
30. Biffl WL, Fox CJ, Moore EE. The role of REBOA in the control of exsanguinating torso hemorrhage. J Trauma Acute Care Surg. 2015;78(5):1054–8.
31. Cossu AP, Mura P, De Giudici LM, Puddu D, Pasin L, Evangelista M, et al. Vasopressin in hemorrhagic shock: a systematic review and meta-analysis of randomized animal trials. BioMed Res Int. 2014;2014:421291.
32. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Resuscitation of blood pressure and oxygenation. J Neurotrauma. 2000;17(6–7):471–8.
33. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol. 2008;7(8):728–41.
34. Huang R, Fung C. In: Neumar RW, Ward KR. Adult Resuscitation. In:Marx JA et al (eds) Rosen's emergency medicine: concepts and clinical practice. 5th ed. Mosby: Elsevier; 2002.

Acute Respiratory Failure: NIV Implementation and Intubation

5

Torben K. Becker and John M. Litell

Case Presentation

A 65 year-old woman with a history of ischemic cardiomyopathy and thromboembolic stroke presented with dyspnea, tachypnea (respiratory rate 36 breaths/minute), cough, fever, and oxygen desaturation to 85 % despite non-rebreather mask at 10 L/min. During her initial resuscitation she was treated with noninvasive ventilation via bilevel positive airway pressure (BPAP) ventilation. Thirty minutes later, the patient's oxygen saturation had steadily improved to 94 % on FiO_2 of 0.7, and her respiratory rate had decreased to 28, though she remained febrile. Initial diagnostics revealed a white blood cell count of 19,500. The chest x-ray is shown below in Fig. 5.1.

Question What is the next appropriate step in the management of this patient?

Answer Depending on her goals of care, this patient should most likely be intubated and undergo invasive ventilation.

While non-invasive ventilation has been shown to be effective and safe in patients with exacerbations of COPD and CHF, other conditions are more controversial. The use of NIV in patients with pneumonia who progress to acute respiratory failure has been associated with a high failure rate and rapid deterioration, leading to worse outcomes, including increased mortality. Both NIV (Fig. 5.2) and the use of high-flow, heated, humidified oxygen delivered by nasal cannula (Fig. 5.3) (see section "Evidence Contour") may improve respiratory and gas exchange parameters, but it is challenging to predict which patients will definitively improve with this strategy. Individualized care and continuous bedside reassessment are essential. In this case, the patient was emergently intubated and treated with broad-spectrum antibiotics prior to ICU admission. After 4 days, she was successfully extubated and transferred to the general medical ward, where she continued to improve prior to discharge on oral antibiotics.

Principles of Management

Definition

Acute respiratory failure manifests as hypoxemia and/or hypoventilation, which can lead to global ischemia and acid/base disturbances. Depending on patient factors and the type of respiratory failure, patients generally require some degree of respiratory support, ranging

T.K. Becker (✉)
Department of Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
e-mail: tbeckermd@gmail.com

J.M. Litell
Department of Emergency Medicine, Division of Emergency Critical Care, University of Michigan Health System, Ann Arbor, MI, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_5

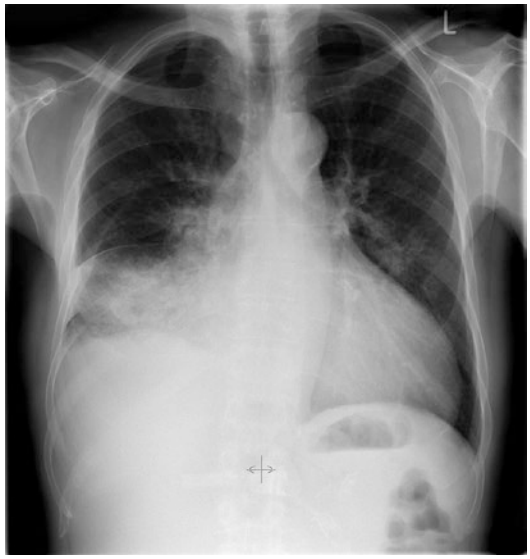


Fig. 5.1 Chest x-ray

from supplemental oxygen via nasal cannula to high-flow oxygen therapy, non-invasive ventilation, and invasive ventilation. High-flow oxygen therapy can be delivered via face mask or high flow nasal cannula (Fig. 5.3). The term non-invasive ventilation (NIV) encompasses all forms of mechanically assisted ventilation without an artificial airway in place. NIV refers to both negative pressure ventilation (no longer used in clinical practice) and positive pressure ventilation modes, which include continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP) ventilation. Both are typically delivered via a tightly-fitting mask, which can be fitted over the nose, nose and mouth, face, or entire head. CPAP delivers various air/oxygen ratios at a constant pressure throughout both inspiration and expiration, which can improve alveolar recruitment and capillary oxygen delivery. BPAP provides both this continuous level of baseline expiratory positive airway pressure (EPEP) and then a higher level during inspiration (IPAP). Depending on the settings, cycling between these two pressure levels is triggered by the patient and/or a pre-set rate chosen by the clinician.

Fig. 5.2 Non-invasive ventilation by full face mask

Fig. 5.3 Hi-flow nasal cannula

The theoretical benefit of BPAP over CPAP is this additional pressure support during inspiration, which can augment the patient's tidal volume and reduce the mechanical work of breathing [1]. Because of their impact on intrathoracic pressure, both of these modes of NIV can also have hemodynamic effects, including both preload and afterload reduction. Depending on the patient and pathology, these effects can offer additional therapeutic benefit, but can also exacerbate hemodynamic compromise.

Indications, Contraindications and Settings

The most widely accepted indications for the use of NIV in the acute setting include respiratory failure due to acute decompensated heart failure (ADHF) and acute exacerbations of chronic obstructive pulmonary disease (COPD). Early use of NIV is associated with improved survival in patients with these conditions [2, 3]. Common chronic indications include obstructive sleep apnea and restrictive diseases of the chest wall, such as muscular dystrophies and obesity hypoventilation syndrome. In order for NIV to be safe and effective, patients' mental status must not be altered to the point where they will not cooperate with the clinician or tolerate the face mask, nor should they have impaired inability to protect their airway from excessive secretions or emesis. Specifically, this includes all unresponsive and apneic patients, in whom intubation and invasive ventilation is the only reasonable mode of ventilatory support. Certain craniofacial abnormalities may also prevent an effective mask seal.

Patients with ADHF develop respiratory failure due in part to the presence of pulmonary edema [1]. CPAP is commonly used in these patients, as it can provide rapid preload and afterload reduction and augment alveolar recruitment, improving oxygenation and minimizing ongoing coronary ischemia [4]. CPAP is often initially set at 5 cm H_2O and titrated to a combination of patient tolerance and clinical effect. If they tolerate the mask, patients often describe an initial subjective improvement in their work of breathing. Objective clinical improvement, such as the resolution of pulmonary rales and jugular venous distension, usually lags somewhat behind.

BPAP can be a particularly helpful mode in patients with impaired gas exchange secondary to respiratory muscle fatigue, as commonly seen in patients with acute exacerbations of COPD. Beyond the alveolar recruitment conferred by the baseline EPAP, the addition of pressure support during inspiration can provide a mechanical advantage and thus further decrease the work of breathing, which otherwise consumes a tremendous amount of metabolic energy. Additional IPAP also creates more effective airway ventilation and CO_2 removal. Typical initial BPAP settings are an EPAP of 5 cm H_2O and an IPAP of 10 cm H_2O. In response to persistent respiratory acidosis, IPAP may be increased (usually in increments of 2 cm H_2O). This increases the difference between EPAP and IPAP, which is the primary contributor to augmented ventilation. In response to persistent hypoxemia, EPAP may also be increased in increments of 2 cm H_2O. This is most likely to augment alveolar recruitment and oxygenation. Clinicians should be mindful that the pressure required to overcome the tone of the lower esophageal sphincter is approximately 20–22 cm H_2O. Keeping the IPAP below this level may reduce the risk of accidental gastric insufflation, vomiting, and possible aspiration.

Predictors of Failure of Non-invasive Ventilation

It is important to recognize when a patient may not improve with NIV. Very limited evidence is available to guide decision-making in these patients. In a 2003 prospective cohort study of severe dyspnea due to decompensated heart failure, Giacomini and colleagues derived a crude

protocol that addresses the transition from the emergency department to inpatient care for patients stabilized with NIV. After a 90-min trial of NIV, patients who felt subjectively better and tolerated at least a 15-min period of oxygen by reservoir mask were admitted to a general care ward. None of these "responder" patients were subsequently intubated or transferred to ICU [5]. Patients who remained tachypneic, acidemic, or hypoxemic after a trial of NIV (60–90 min), and those who developed hypotension, were unlike to improve. For these "non-responder" patients, endotracheal intubation and invasive ventilation should be strongly considered, as the role of prolonged acute treatment with NIV is still unclear.

Strong evidence outlining safe titration of NIV in other patient subgroups is lacking. Factors to consider include patient comorbidities and physiologic reserve, as well as the expected time course of reversibility for the cause of their acute respiratory failure.

Evidence Contour

Use in Patients with Pneumonia

The use of NIV in acute respiratory failure has been studied for indications other than decompensated heart failure and COPD [6–10]. Pneumonia is not considered an appropriate indication for the use of NIV for patients in acute respiratory failure. Although NIV offers a less invasive intervention for respiratory distress, the NIV failure rate in patients with pneumonia has been reported as high as 50% [7]. It is very difficult to predict which patients will improve and which will deteriorate [7], and among those who decline there is an increased incidence of peri-intubation complications and a significant increase in mortality [9, 10]. Several possible explanations for this have been proposed, such as the increased metabolic demands in patients with pneumonia, the inability to adequately clear respiratory secretions, and the protracted time course of pneumonia when compared to other common indications for NIV. Possible exceptions to the poor performance of NIV in patients with pulmonary infection include patients with pneumonia and COPD with hypercapnic respiratory failure. This may be due to overlap in diagnosis between COPD exacerbation and true infection [8]. Other possible exceptions include neutropenic patients with hematologic malignancy, or recent solid organ transplant recipients with suspected pneumonia, possibly because these patients have a higher incidence of viral pneumonia than immunocompetent patients [11–14]. Overall, these data are still relatively sparse. If NIV is attempted in these patients, the clinician should provide near-continuous bedside reassessment and not hesitate to intubate if there is no significant improvement.

Use in Patients with Asthma Exacerbation

NIV has also been used in patients with acute exacerbations of asthma, however there is only limited evidence to help guide the clinician. The available studies fail to demonstrate improvement in mortality or intubation rates, but show an apparent decrease in hospital admission rates, hospital length of stay, symptom severity, and indirect markers of severity, such as pulmonary functions tests or arterial blood gases [15–18]. However, the are no high-quality studies addressing the use of NIV in patients with the most severe forms of asthma exacerbation, limiting any conclusion regarding its impact on mortality and intubation rates in this patient population [19]. For patients with severe asthma exacerbations, NIV should be used with caution, in the context of maximal medical therapy and continuous bedside reassessment.

Use in Patients with ARDS

Limited evidence suggests that NIV might be associated with decreased intubation rates in select patients with early mild ARDS, however overall mortality rates seem to be unchanged, and very close clinical monitoring is required [20–22]. NIV is not appropriate as a first line approach for established ARDS, given the importance of

careful control of tidal volume and airway pressure in this syndrome [23].

Use of NIV in Patients with Altered Mental Status

As mentioned, one of the most common traditional contraindications for the use of NIV is significantly altered mental status, because of the concern that these patients have compromised airway protective reflexes and are not able to adequately manage pulmonary or oropharyngeal secretions. Vomiting into the positive pressure mask is potentially catastrophic in these patients. For intoxicated patients with respiratory distress NIV is almost never the safest alternative, because of unpredictable toxicokinetics and the risk of vomiting. Though NIV can be of great utility in patients with acute exacerbations of COPD, these patients frequently exhibit altered mental status due to hypercapnia. Low to moderate quality evidence suggests that select patients with hypercapnic encephalopathy may warrant a trial of NIV if very close monitoring is feasible [24, 25]. Any such attempt should be aborted if there is no significant improvement in mental status within a short period [24].

Use of NIV for Preoxygenation Prior to Intubation

In carefully selected patients NIV can be used to maximize preoxygenation prior to intubation for acute respiratory failure. By providing high fractional inspired concentrations of oxygen, eliminating alveolar nitrogen, and recruiting atelectatic lung regions, this approach has the potential to improve oxygenation prior to intubation, and extend the "safe apnea time" prior to oxygen desaturation [26]. Patients should generally meet the same entry criteria as for the regular use of NIV, and those who are apneic or whose airway protective reflexes are in doubt are likely not appropriate for this relatively novel use of NIV.

Use of NIV to Facilitate Weaning from Invasive Ventilation

In addition to its use in patients with acute respiratory failure, NIV has also shown some promise for its use in liberating patients from invasive ventilation. Some evidence supports extubation to NIV as a safe strategy in certain patients with resolving acute respiratory failure, such as COPD patients with acute on chronic hypercapnia [27]. This approach may reduce the incidence of some risks associated with prolonged intubation and invasive ventilation, such as ventilator-associated pneumonia and tracheostomy rates. NIV use in this context may also reduce the total duration of ventilation, as well as ICU and hospital length of stay, without a higher risk of reintubation [1, 27–29].

Palliative Care Indications

NIV has been used in an attempt to both enhance short term survival and to optimize comfort in dying patients and those who decline full resuscitative efforts. While mortality among these patients remains high, survivors report no decrease in their quality of life compared to their baseline after the hospitalization, and there are no apparent negative impacts of NIV on their psychological well-being [30, 31]. The topic remains challenging, in particular because it is difficult to predict in which patients there may be a benefit, as opposed to merely an extended dying process with limited ability to communicate, eat, and drink [32]. Decisions about the use of NIV at the end of life are likely best made on an individual patient level, in close collaboration with surrogate decision makers.

Use of High-Flow Nasal Cannula as an Alternative to NIV

The heated high-flow nasal cannula (HFNC) is a relatively new alternative oxygen delivery device that may be of benefit in carefully selected patients with non-hypercapnic acute hypoxic respiratory

failure. In contrast to conventional low-flow nasal cannulae, which provide oxygen flow rates up to approximately 6 L/min, HFNC can deliver flow rates in excess of 40 L/min. The physical characteristics of the device, as well as the addition of a humidifying apparatus and heating circuit, make this a surprisingly comfortable and well-tolerated method of delivering substantial oxygen support [33]. Because it does not involve a tight fitting mask, HFNC is often better tolerated than a conventional NIV interface. This technology is relatively new and the evidence supporting its use is still evolving. Generally speaking, HFNC appears to be a safe and effective alternative for alert patients with certain types of non-hypercapnic respiratory failure. There is probably insufficient ventilatory effect to rely on HFNC in patients with hypercapnia, and the device offers no airway protection. A 2015 multicenter, randomized, open label trial compared HFNC, NIV, and standard oxygen therapy in a relatively large cohort of hypoxemic patients [34]. Approximately 60–70 % of these patients had some type of pneumonia. Intubation rates did not differ between the groups, but 90-day mortality was significantly lower in the HFNC group. The reasons for this are unclear. Additionally, NIV confers no mortality or other benefit over oxygen therapy alone, including HFNC patients, in immunocompromised patients with hypoxemic respiratory failure [35]. In the absence of additional evidence, the use of HFNC is probably best individualized to each patient. The overall concern about morbidity associated with delayed intubation in pneumonia patients supported with NIV probably applies equally to HFNC.

References

1. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. Lancet. 2009;374(9685):250–9. Epub 2009/07/21.
2. Cabrini L, Landoni G, Oriani A, Plumari VP, Nobile L, Greco M, et al. Noninvasive ventilation and survival in acute care settings: a comprehensive systematic review and meta-analysis of randomized controlled trials. Crit Care Med. 2015. Epub 2015/01/08.
3. Lindenauer PK, Stefan MS, Shieh MS, Pekow PS, Rothberg MB, Hill NS. Hospital patterns of mechanical ventilation for patients with exacerbations of COPD. Ann Am Thorac Soc. 2015;12(3):402–9.
4. Weitz G, Struck J, Zonak A, Balnus S, Perras B, Dodt C. Prehospital noninvasive pressure support ventilation for acute cardiogenic pulmonary edema. Eur J Emerg Med. 2007;14(5):276–9. Epub 2007/09/08.
5. Giacomini M, Iapichino G, Cigada M, Minuto A, Facchini R, Noto A, et al. Short-term noninvasive pressure support ventilation prevents ICU admittance in patients with acute cardiogenic pulmonary edema. Chest. 2003;123(6):2057–61. Epub 2003/06/11.
6. Carrillo A, Gonzalez-Diaz G, Ferrer M, Martinez-Quintana ME, Lopez-Martinez A, Llamas N, et al. Noninvasive ventilation in community-acquired pneumonia and severe acute respiratory failure. Intensive Care Med. 2012;38(3):458–66. Epub 2012/02/10.
7. Carron M, Freo U, Zorzi M, Ori C. Predictors of failure of noninvasive ventilation in patients with severe community-acquired pneumonia. J Crit Care. 2010;25(3):540.e9–14. Epub 2010/05/04.
8. Confalonieri M, Potena A, Carbone G, Porta RD, Tolley EA, Umberto MG. Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. Am J Respir Crit Care Med. 1999;160(5 Pt 1):1585–91. Epub 1999/11/11.
9. Wood KA, Lewis L, Von Harz B, Kollef MH. The use of noninvasive positive pressure ventilation in the emergency department: results of a randomized clinical trial. Chest. 1998;113(5):1339–46. Epub 1998/05/22.
10. Ferrer M, Cosentini R, Nava S. The use of noninvasive ventilation during acute respiratory failure due to pneumonia. Eur J Intern Med. 2012;23(5):420–8. Epub 2012/06/26.
11. Antonelli M, Conti G, Bufi M, Costa MG, Lappa A, Rocco M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. JAMA. 2000;283(2):235–41. Epub 2000/01/14.
12. Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med. 2001;344(7):481–7. Epub 2001/02/15.
13. Hilbert G, Gruson D, Vargas F, Valentino R, Chene G, Boiron JM, et al. Noninvasive continuous positive airway pressure in neutropenic patients with acute respiratory failure requiring intensive care unit admission. Crit Care Med. 2000;28(9):3185–90. Epub 2000/09/29.
14. Gristina GR, Antonelli M, Conti G, Ciarlone A, Rogante S, Rossi C, et al. Noninvasive versus invasive ventilation for acute respiratory failure in patients with hematologic malignancies: a 5-year multicenter observational survey. Crit Care Med. 2011;39(10):2232–9. Epub 2011/06/15.
15. Brandao DC, Lima VM, Filho VG, Silva TS, Campos TF, Dean E, et al. Reversal of bronchial obstruction with bi-level positive airway pressure

and nebulization in patients with acute asthma. J Asthma. 2009;46(4):356–61. Epub 2009/06/02.
16. Gupta D, Nath A, Agarwal R, Behera D. A prospective randomized controlled trial on the efficacy of noninvasive ventilation in severe acute asthma. Respir Care. 2010;55(5):536–43. Epub 2010/04/28.
17. Lim WJ, Mohammed Akram R, Carson KV, Mysore S, Labiszewski NA, Wedzicha JA, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. Cochrane Database Syst Rev. 2012;12, CD004360. Epub 2012/12/14.
18. Soroksky A, Stav D, Shpirer I. A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. Chest. 2003;123(4):1018–25. Epub 2003/04/10.
19. Landry A, Foran M, Koyfman A. Does noninvasive positive-pressure ventilation improve outcomes in severe asthma exacerbations? Ann Emerg Med. 2013;62(6):594–6. Epub 2013/06/19.
20. Pichot C, Petitjeans F, Ghignone M, Quintin L. Swift recovery of severe acute hypoxemic respiratory failure under non-invasive ventilation. Anaesthesiol ntens Ther. 2014. Epub 2014/10/24.
21. Zhan Q, Sun B, Liang L, Yan X, Zhang L, Yang J, et al. Early use of noninvasive positive pressure ventilation for acute lung injury: a multicenter randomized controlled trial. Crit Care Med. 2012;40(2):455–60. Epub 2011/10/25.
22. Luo J, Wang MY, Zhu H, Liang BM, Liu D, Peng XY, et al. Can non-invasive positive pressure ventilation prevent endotracheal intubation in acute lung injury/acute respiratory distress syndrome? A meta-analysis. Respirology. 2014;19(8):1149–57. Epub 2014/09/12.
23. Rana S, Jenad H, Gay PC, Buck CF, Hubmayr RD, Gajic O. Failure of non-invasive ventilation in patients with acute lung injury: observational cohort study. Crit Care. 2006;10(3):R79. Epub 2006/05/16.
24. Diaz GG, Alcaraz AC, Talavera JC, Perez PJ, Rodriguez AE, Cordoba FG, et al. Noninvasive positive-pressure ventilation to treat hypercapnic coma secondary to respiratory failure. Chest. 2005;127(3):952–60. Epub 2005/03/15.
25. Scala R. Hypercapnic encephalopathy syndrome: a new frontier for non-invasive ventilation? Respir Med. 2011;105(8):1109–17. Epub 2011/03/01.
26. Weingart SD, Trueger NS, Wong N, Scofi J, Singh N, Rudolph SS. Delayed sequence intubation: a prospective observational study. Ann Emerg Med. 2015;65(4):349–55. Epub 2014/12/03.
27. Burns KE, Meade MO, Premji A, Adhikari NK. Noninvasive positive-pressure ventilation as a weaning strategy for intubated adults with respiratory failure. Cochrane Database Syst Rev. 2013;12, CD004127. Epub 2013/12/11.
28. Ornico SR, Lobo SM, Sanches HS, Deberaldini M, Tofoli LT, Vidal AM, et al. Noninvasive ventilation immediately after extubation improves weaning outcome after acute respiratory failure: a randomized controlled trial. Crit Care. 2013;17(2):R39. Epub 2013/03/19.
29. Vaschetto R, Turucz E, Dellapiazza F, Guido S, Colombo D, Cammarota G, et al. Noninvasive ventilation after early extubation in patients recovering from hypoxemic acute respiratory failure: a single-centre feasibility study. Intensive Care Med. 2012;38(10):1599–606. Epub 2012/07/25.
30. Azoulay E, Kouatchet A, Jaber S, Lambert J, Meziani F, Schmidt M, et al. Noninvasive mechanical ventilation in patients having declined tracheal intubation. Intensive Care Med. 2013;39(2):292–301. Epub 2012/11/28.
31. Nava S, Ferrer M, Esquinas A, Scala R, Groff P, Cosentini R, et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomised feasibility trial. Lancet Oncol. 2013;14(3):219–27. Epub 2013/02/15.
32. Azoulay E, Demoule A, Jaber S, Kouatchet A, Meert AP, Papazian L, et al. Palliative noninvasive ventilation in patients with acute respiratory failure. Intensive Care Med. 2011;37(8):1250–7. Epub 2011/06/10.
33. Ward JJ. High-flow oxygen administration by nasal cannula for adult and perinatal patients. Respir Care. 2013;58(1):98–122.
34. Frat J-P, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372(23):2185–96.
35. Lemiale V, Mokart D, Resche-Rigon M, et al. Effect of noninvasive ventilation vs oxygen therapy on mortality among immunocompromised patients with acute respiratory failure: a randomized clinical trial. JAMA. 2015;314:1711–9.

6 Diagnosis and Management of Tricyclic Antidepressant Ingestion

Patrick George Minges and Robert W. Shaffer

Introduction

Tricyclic antidepressant (TCA) overdoses have become less common over the last 20 years as their overall use has decreased with the advent of safer and more effective antidepressants. Despite their declining popularity in the management of depression, they continue to be used clinically for conditions including the management of neuropathic and chronic pain, cyclic vomiting, nocturnal enuresis, OCD and ADHD. These medications continue to be a leading cause of mortality from intentional ingestions, and account for nearly half of all antidepressant-related deaths [1]. Common tricyclic antidepressants in use today include amitriptyline, nortriptyline, imipramine, desipramine and doxepin.

The management of tricyclic antidepressant poisonings can be quite challenging. Since they exert their toxicity through several different mechanisms an understanding of their pharmacology is imperative. TCAs all have inherent anticholinergic effects that may cause tachycardia, altered mental status and seizures. They can cause profound hypotension through alpha-adrenergic blockade as well as catecholamine depletion through reuptake inhibition. Finally, they block fast sodium channels in the cardiac conduction system leading to myocardial depression and ventricular arrhythmias [2].

Successful treatment of patients poisoned by tricyclic antidepressants hinges on prompt diagnosis and recognition of the classic EKG findings associated with their toxicity. GI decontamination should be considered when patients present within the first 1–2 h following an overdose. Serum alkalinization with sodium bicarbonate is considered the first-line treatment when signs of cardiotoxicity develop. Patients with refractory hypotension may require vasopressor support.

Case Presentation

A 32 year old female with a history notable for depression, migraine headaches, and chronic pelvic pain arrived to the emergency department 90 min after ingesting approximately sixty 75 mg tablets of amitriptyline. On arrival, she was noted to be agitated and confused. Her presenting vital signs included the following: BP 96/62, P 122, RR18, T37.8, O_2 sat (RA) 99 %, GCS 13. An EKG showed sinus tachycardia with normal intervals and normal axis. Blood glucose was normal, and serum lactate was 3.7. Serum and urine tox screening was negative. Shortly after

P.G. Minges
Department of Emergency Medicine, University of Michigan Hospitals, Ann Arbor, MI, USA

R.W. Shaffer (✉)
Department of Emergency Medicine, University of Michigan Health System, Ann Arbor, MI, USA
e-mail: rshaffer@med.umich.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_6

arrival, the patient had a generalized tonic-clonic seizure that was successfully aborted with 2 mg IV Ativan. She was subsequently intubated for airway protection, and 50 g of activated charcoal was administered through a nasogastric tube. Upon arrival to the ICU, her blood pressure fell to 65/32 and a repeat EKG was obtained (Fig. 6.1).

Question How would you proceed in the management of this patient?

Answer This patient now exhibits EKG findings that are consistent with fast sodium channel blockade due to tricyclic antidepressant toxicity (Table 6.1).

The patient was immediately given 2 meq/kg of IV sodium bicarbonate as a bolus and hydrated aggressively with 3 l of normal saline. A sodium bicarbonate drip was initiated to maintain a goal serum pH within the range of 7.45–7.55. Ventilator settings were managed accordingly to prevent hypercarbia. A repeat EKG was obtained once serum alkalinization was achieved and demonstrated improvement of the QRS duration to 90 ms, but the patient remained hypotensive. A norepinephrine drip was initiated and blood pressure improved. Over the ensuing 48 h, norepinephrine and sodium bicarbonate were successfully weaned. She was successfully extubated and transferred to the inpatient psychiatric service.

Principles of Management

Diagnosis

Tricyclic antidepressants have a narrow therapeutic index, and significant CNS and cardiovascular toxicity may be seen with ingestions that exceed therapeutic doses by as little as three-fold.

Tricyclic Antidepressant Side Effects

- Anticholinergic
  - Mucosal dryness
  - Constipation
  - Urinary retention
  - Confusion
  - Blurred vision
  - Aggravation of narrow angle glaucoma
- Anti-alpha-adrenergic
  - Orthostatic hypotension
- Antihistaminic
  - Sedation
- Quinidine-like
  - Cardiac arrhythmias and block

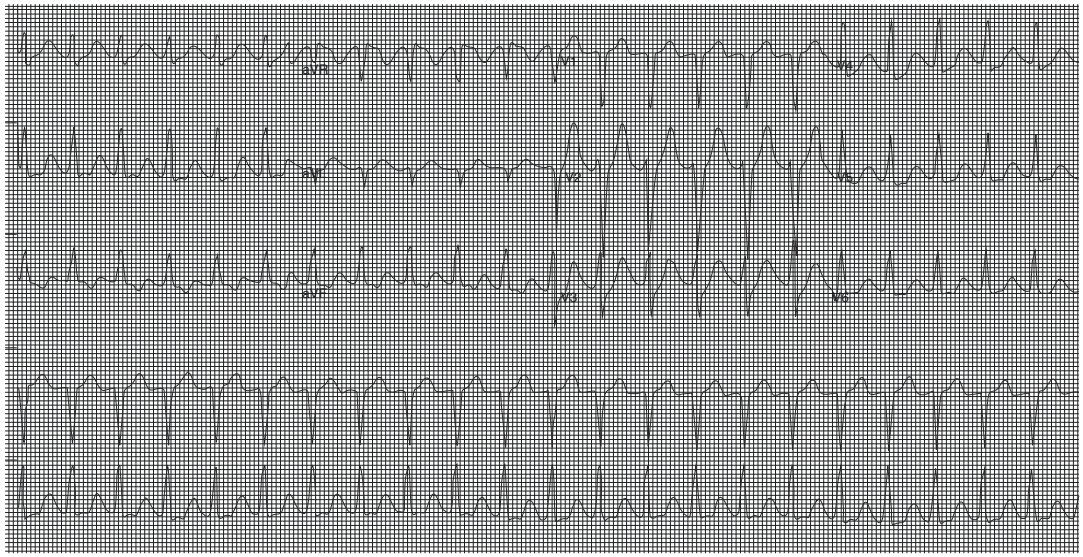


Fig. 6.1 12-Lead Electrocardiogram obtained at time of patients presentation

Table 6.1 Clinical features associated with specific toxidromes

	HR & BP	RR	Temp	Pupils	Bowel sounds	Diaphoresis
Anticholinergic Low potency antipsychotics Oxybutinin, Ipratropium Antihistamines ACh receptor antagonists	↑	⇔	↑	↑	↓	↓
Cholinergic ACh receptor agonists AChEls i.e. Donepezil	⇔	⇔	⇔	↓	↑	↑
Opioid Morphine Heroin Hydromorphone	↓	↓	↓	↓	↓	↓
Sympathomimetic Epinephrine Cocaine Amphetamine & Methylphenidate	↑	↑	↑	↑	↑	↑
Sedative-Hypnotic Benzos & barbs "Z-drugs" (i.e. Zopiclone)	↓	↓	↓	⇔	↓	↓

Mental status on presentation has been shown to be predictive of patient outcomes, and most life-threatening arrhythmias occur within the first 24 h after ingestion [2]. Owing to rapid GI absorption, patients may initially appear well and then deteriorate rapidly. Serum drug assays that measure specific serum tricyclic antidepressant levels are not widely available and should not be relied on when managing suspected overdose. Because these drugs are highly lipophilic and have high volumes of distribution, concentrations in brain and myocardium may exceed serum concentrations by as much as 40 to 200-fold, and serum drug levels have not been shown to predict the clinical course [1, 3].

The single most useful test in identifying tricyclic antidepressant toxicity is the electrocardiogram. The most common early EKG finding in overdoses is sinus tachycardia, due to anticholinergic effects and initial transient catecholamine excess. As toxicity progresses, tricyclic antidepressants block fast sodium channels in the cardiac conduction system thereby slowing depolarization and decreasing contractility. This results in a widened QRS complex. Prolongation of the QRS complex >100 ms has been shown to predict risk for seizures, and prolongation >160 ms predicts a risk for ventricular arrhythmias [4]. Owing to the greater susceptibility of the right ventricular conduction system to the effects of sodium channel blockade, a rightward axis shift of the terminal 40 ms of the QRS axis in the frontal plane will develop; but this finding may be difficult to detect [3]. A more practical means for identifying this rightward axis shift is by noting the presence of a larger than expected R wave amplitude in aVR (Fig. 6.2). An amplitude of the R wave in this lead in excess of 3 mm has been shown to predict risk for seizures and arrhythmias [5].

Gastrointestinal Decontamination

Activated charcoal has been shown to effectively bind tricyclic antidepressants. In a study of healthy volunteers activated charcoal given 5 min after oral administration of therapeutic doses of amitriptyline decreased GI absorption by 99 % [6]. Activated charcoal probably has the most benefit when administered within 1 h of a toxic ingestion, but may be considered for up to 2 h

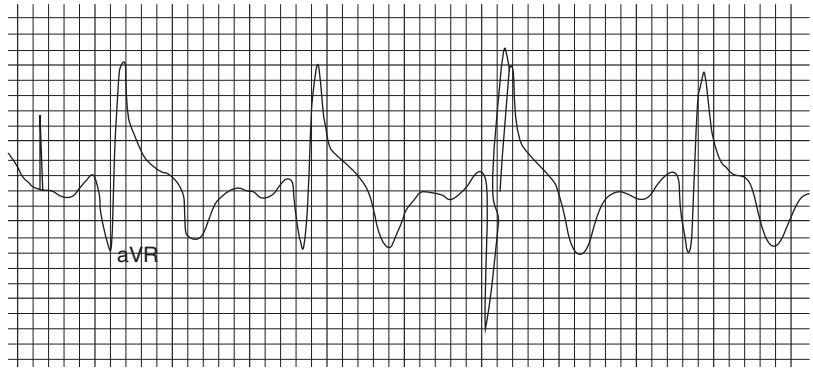


Fig. 6.2 Prominent terminal R wave (>3 mm amplitude) in lead aVR from electrocardiogram obtained from a patient experiencing TCA overdose

since the anticholinergic effects of the drug may delay gastric emptying [7].

Gastric lavage carries risks such as aspiration, and is not routinely recommended following tricyclic antidepressant ingestion. One randomized study demonstrated no significant difference in patient outcomes when gastric lavage was combined with the use of activated charcoal [8].

Whole bowel irrigation is typically reserved for overdoses involving sustained-release preparations or in cases where the drug binds poorly to activated charcoal. Therefore, its use is unlikely to provide any benefit [7].

Plasma Alkalinization

Although no randomized-controlled clinical trials exist in support of sodium bicarbonate therapy in the setting of tricyclic antidepressant poisoning, numerous animal studies and human case reports support its use as a first-line treatment [9–11]. Sodium bicarbonate has been shown to both prevent and terminate ventricular dysrhythmias. The benefits of serum alkalinization through the use of sodium bicarbonate are likely multifactorial. The fraction of drug that is protein-bound increases with alkalinity, and therefore the use of sodium bicarbonate would be expected to decrease the amount of free drug available for inhibition of sodium channels [2]. Additionally, increasing serum sodium concentrations may overwhelm the sodium channel blockade by increasing the gradient between the intracellular and extracellular space [2]. The net effect is improved myocardial contractility, narrowing of the QRS complex, and improved electrical stability.

Dosing and titration guidelines for sodium bicarbonate have not been well-studied, but most recommend initiating a bolus of 1–2 meq/kg followed by a continuous infusion to maintain a goal serum pH within 7.45–7.55 and titrating to a goal QRS duration of less than 100 ms [2, 10]. The prophylactic use of sodium bicarbonate is not supported when EKG abnormalities are absent [10]. Serum pH must be monitored closely, and while optimum pH has not been studied, it is reasonable to not exceed a pH of 7.6. Risks of marked alkalosis may include impaired tissue oxygenation due to shifts in the oxygen dissociation curve, cerebral vasoconstriction, reduction in ionized calcium concentration, intracellular shift of potassium, and an increased myocardial sensitivity to catecholamines [10].

Management of Hypotension and Vasopressor Support

Hypotension is a common feature of tricyclic antidepressant toxicity. These medications decrease systemic vascular resistance through alpha-adrenergic blockade. Relative catecholamine depletion may occur through their effects on norepinephrine reuptake. Additionally, hypotension may occur as a direct result of decreased cardiac inotropy [2]. Profound hypotension may be refractory to fluid resuscitation and alkalinization therapy, and vasopressors may be indicated. There are very few

studies evaluating the benefit of one such agent over another [12]. One retrospective case series suggested norepinephrine may be superior to dopamine in these instances [13]. A single case report showed that vasopressin stabilized blood pressure in a patient with hypotension that failed to respond to high-dose norepinephrine [14].

Extracorporeal Elimination

Because tricyclic antidepressants are lipophilic and highly protein-bound, extracorporeal elimination methods such as hemodialysis are ineffective [1].

Seizure Management

Seizures are common in the setting of significant tricyclic antidepressant overdose and are a predictor of poor outcomes. Seizures may precipitate an undesired acidosis that increases TCA toxicity. There is little high quality evidence describing first line anticonvulsant therapy for seizures secondary to TCA overdose. Seizures associated with TCA overdose are often brief and resolve before abortive medications can be administered. The use of benzodiazepines has been proposed as first line therapy. Barbiturates and propofol are second-line agents that have been noted to be effective in case reports. These therapies should be used in conjunction with the treatment strategies previously described [15, 16].

Evidence Contour

Intravenous Lipid Emulsion

The use of intravenous lipid emulsions were first reported in the 1990s as an antidote for systemic toxicity from local anesthetic agents. Since that time, the use of intravenous lipid emulsion therapy has been reported in the setting of overdoses of other lipophilic drugs including calcium channel blockers, beta blockers, and tricyclic antidepressants [17]. Several proposed mechanisms for the benefit of lipid emulsion use in tricyclic antidepressant poisonings have been described. Lipid emulsions may serve as a "lipid sink", sequestering intravascular drug from the aqueous phase of plasma. Secondly, the lipids themselves may directly provide a supplemental fuel source to the stressed myocardium. Lastly, a positive inotropic effect might be seen from increased intracellular calcium shifts [17, 18]. A few animal studies have been conducted using intravenous lipid emulsions for the management of tricyclic antidepressant toxicity, and the reported benefits on hemodynamic stability and mortality were mixed [18–20]. There are, however, several human case reports of patients being successfully managed with lipid emulsions in the setting of refractory hemodynamic instability when the use of traditional therapeutic modalities failed [21–24]. Dosing guidelines for intravenous lipid emulsion therapy for tricyclic antidepressant toxicity have not been established. Recommended dosing in the setting of systemic toxicity from local anesthetics have been proposed where a 20% emulsion is administered at a loading dose of 1.5 ml/kg based on lean body mass followed by a continuous infusion of 15 ml/kg/h until clinical response is achieved [17, 25]. It is unclear how to extrapolate dosing of lipid emulsions for management of tricyclic antidepressant overdose given their different pharmacokinetics. The use of lipid emulsion in the management of overdoses carry theoretical risks including infection, but serious adverse events have not been reported [17]. Intravenous lipid therapy may be considered in cases of refractory cardiovascular collapse when more traditional treatments fail.

Hypertonic Saline

One animal study suggested that the use of hypertonic saline in the management of tricyclic antidepressant poisonings, when compared to sodium bicarbonate, produced a statistically significant improvement in systolic blood pressure and narrowing of the QRS complex [26]. One human case report exists for a patient with refractory ventricular ectopy and widened QRS complex despite sodium bicarbonate therapy

that stabilized upon administration of hypertonic saline [27]. Clinical studies supporting its use, however, do not exist [2].

Antiarrhythmic Drugs

Occasionally, ventricular dysrhythmias may not respond to serum alkalinization, and the use of antiarrhythmic medications may be necessary. Class I antiarrhythmic medications are contraindicated in the setting of tricyclic antidepressant overdose since they act to inhibit cardiac sodium channels in a similar manner [9]. Other antiarrhythmic drugs have negative inotropic effects, which may worsen hypotension in the setting of these overdoses. Lidocaine has traditionally been considered the most reasonable agent in these instances, but the efficacy is limited to case series [28]. Theoretically, lidocaine's rapid binding to sodium channels may displace the effects of tricyclic antidepressants and improve cardiac conduction. Lidocaine has a stabilizing effect on the myocardium, but unfortunately may slow conduction and depress contractility [29]. Furthermore, one must take into consideration the fact that lidocaine may lower the seizure threshold [30].

Magnesium is an alternative antiarrhythmic that has been investigated with some promise. A study in rats sought to evaluate magnesium sulfate's ability to terminate arrhythmias when compared with lidocaine and demonstrated favorable results [29]. One small randomized human trial suggested that use of magnesium in addition to traditional therapeutics decreased ICU length of stay and mortality, and several case reports describe the successful use of magnesium to abort ventricular arrhythmias [31–33].

References

1. Yates C, Galvao T, Sowinski KM, et al. Extracorporeal treatment for tricyclic antidepressant poisoning: recommendations from the EXTRIP Workgroup. Semin Dial. 2014;27(4):381–9.
2. Agrawal P, Nadel ES, Brown DF. Tricyclic antidepressant overdose. J Emerg Med. 2008;34(3):321–5.
3. Harrigan RA, Brady RJ. ECG abnormalities in tricyclic antidepressant ingestion. Am J Emerg Med. 1999;17(4):387–93.
4. Boehnert MT, Lovejoy Jr FH. Value of the QRS duration versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. N Engl J Med. 1985;313(8):474–9.
5. Wolfe TR, Caravati EM, Rollins DE. Terminal 40-ms frontal place axis as a marker for tricyclic antidepressant overdose. Ann Emerg Med. 1989;18:348–51.
6. Karkkainen S, Neuvonen PJ. Pharmacokinetics of amitriptyline influenced by oral charcoal and urine pH. Int J Clin Pharmacol Ther Toxicol. 1986;24:326–32.
7. Dargan PI, Colbridge MG, Jones AL. The management of tricyclic antidepressant poisoning : the role of gut decontamination, extracorporeal procedures and fab antibody fragments. Toxicol Rev. 2005;24(3):187–94.
8. Bosse GM, Barefoot JA, Pfeifer MP, Rodgers GC. Comparison of three methods of gut decontamination in tricyclic antidepressant overdose. J Emerg Med. 1995;13(2):203–9.
9. Sasyniuk BI, Jhamandas V, Valois M. Experimental amitriptyline intoxication: treatment of cardiac toxicity with sodium bicarbonate. Ann Emerg Med. 1986;15(9):1052–9.
10. Blackman K, Brown SF, Wilkes GJ. Plasma alkalinization for tricyclic antidepressant toxicity: a systematic review. Emerg Med. 2001;13:204–10.
11. Hoffman JR, McElroy CR. Bicarbonate therapy for dysrhythmia and hypotension in tricyclic antidepressant overdose. Western J Med. 1981;134(1):60–4.
12. Vernon DD, Banner W, Garrett JS, Dean JM. Efficacy of dopamine and norepinephrine for treatment of hemodynamic compromise in amitriptyline intoxication. Crit Care Med. 1991;19(4):544–9.
13. Tran TP, Panacek EA, Rhee KJ, Foulke GE. Response to dopamine vs norepinephrine in tricyclic antidepressant-induced hypotension. Acad Emerg Med. 1997;4(9):864–8.
14. Barry JD, Durkovich DW, Williams SR. Vasopressin treatment for cyclic antidepressant overdose. J Emerg Med. 2006;31(1):65–8.
15. Ellison DW, Pentel PR. Clinical Features and consequences of seizures due to cyclic antidepressant overdose. Am J Med. 1989;7(1):5–10.
16. Merigian KS, Browning RG, Leeper KV. Successful treatment of amoxapine-induced refractory status epilepticus with propofol. Acad Emerg Med. 1995;2(2):128–33.
17. Ozcon MS, Weinberg G. Intravenous lipid emulsion for the treatment of drug toxicity. J Intensive Care Med. 2014;29(2):59–70.
18. Varney SM, Bebarta VS, Vargas TE, Boudreau S, Castaneda M. Intravenous lipid emulsion therapy does not improve hypotension compared to sodium bicarbonate for tricyclic antidepressant toxicity: a randomized, controlled pilot study in a swine model. Acad Emerg Med. 2014;21(11):1212–9.

19. Harvey M, Cave G. Intralipid outperforms sodium bicarbonate in a rabbit model of clomipramine toxicity. Ann Emerg Med. 2007;49(2):178–85, 185.e1–4.
20. Litonius E, Niiya T, Neuvonen PJ, Rosenberg PH. No antidotal effect of intravenous lipid emulsion in experimental amitriptyline intoxication despite significant entrapment of amitriptyline. Basic Clin Pharmacol Toxicol. 2012;110(4):378–83.
21. Blaber MS, Khan JN, Brebner JA, Mccolm R. "Lipid rescue" for tricyclic antidepressant cardiotoxicity. J Emerg Med. 2012;43(3):465–7.
22. Kiberd MB, Minor SF. Lipid therapy for the treatment of a refractory amitriptyline overdose. CJEM. 2012;14(3):193–7.
23. Agarwala R, Ahmed SZ, Wiegand TJ. Prolonged use of intravenous lipid emulsion in a severe tricyclic antidepressant overdose. J Med Toxicol. 2014;10:210–4.
24. Engels PT, Davidow JS. Intravenous fat emulsion to reverse haemodynamic instability from intentional amitriptyline overdose. Resuscitation. 2010;81(8):1037–9.
25. Weinberg GL. Lipid emulsion infusion: resuscitation for local anesthetic and other drug overdose. Anesthesiology. 2012;117(1):180–7.
26. McCabe JL, Cobaugh DJ, Menegazzi JJ, Fata J. Experimental tricyclic antidepressant toxicity: a randomized, controlled comparison of hypertonic saline solution, sodium bicarbonate, and hyperventilation. Ann Emerg Med. 1996;32(3):329–33.
27. Mckinney PE, Rasmussen R. Reversal of severe tricyclic antidepressant-induced cardiotoxicity with intravenous hypertonic saline. Ann Emerg Med. 2003;42(1):20–4.
28. Foianini A, Weigand TJ, Benowitz N. What is the role of lidocaine or phenytoin in tricylic antidepressant-induced cardiotoxicity. Clin Toxicol. 2010;48(4):325–30.
29. Knudsen K, Abrahamsson J. Effects of magnesium sulfate and lidocaine in the treatment of ventricular arrhythmias in experimental amitriptyline poisoning in the rat. Crit Care Med. 1994;22(3):494–8.
30. Pentel PR, Benowitz NL. Tricyclic antidepressant poisoning—management of arrhythmias. Med Toxicol. 1986;1:101–21.
31. Emamhadi M, Mostafazadeh B, Hassanijirdehi M. Tricyclic antidepressant poisoning treated by magnesium sulfate: a randomized, clinical trial. Drug Chem Toxicol. 2012;35(3):300–3.
32. Sarisoy O, Babaoglu K, Tukay S, et al. Effect of magnesium sulfate for treatment of ventricular tachycardia in amytriptyline intoxication. Pediatr Emerg Care. 2007;23:646–8.
33. Knudsen K, Abrahamsson K. Magnesium sulfate in the treatment of ventricular fibrillation in amitriptyline poisoning. Eur Heart J. 1997;18(5):881.

Management of Calcium Channel Blocker Poisoning

7

David M. Black and Robert W. Shaffer

Introduction

Calcium channel blocker poisonings are the leading cause of death from cardiovascular medication-related overdoses [1, 2]. Clinical effects in the poisoned patient may include hypotension, bradycardia, atrioventricular conduction disturbances, pulmonary edema, stroke, bowel ischemia, altered mental status, and cardiac arrest. Many immediate and sustained-release preparations exist, hence pharmacokinetics are highly variable. Calcium channel blockers are generally lipophilic and highly-protein bound, rendering traditional extracorporeal elimination methods such as hemodialysis largely ineffective.

Dihydropyridines
- Nicardipine
- Nifedipine
- Isradipine
- Amlodipine
- Felodipine
- Nimodopine
- Nisoldipine
- Nitrendipine

Non-Dihydropyridines
- Verapamil
- Diltiazem
- Bepridil

Calcium channel blockers act at L-type calcium channels and are generally divided into two unique pharmacologic classes based on their preferred sites of action.

Dihydropyridine (i.e. nifedipine, amlodipine) overdoses primarily cause hypotension with reflex tachycardia through their peripheral vasodilatory effects on vascular smooth muscle. The toxicity from non-dihydropyridines (i.e. verapamil, diltiazem), tends to be more severe owing to their primary effects on the myocardium [3]. This may lead to bradydysrhythmias, depressed myocardial contractility, and circulatory collapse [4]. It should be noted that in severe poisonings from either class, this selectivity may be lost [2].

The management of hemodynamically unstable patients with calcium channel blocker toxicity

D.M. Black
Emergency Medicine, University of Michigan Health System, Ann Arbor, MI, USA

R.W. Shaffer (✉)
Department of Emergency Medicine, University of Michigan Health System, Ann Arbor, MI, USA
e-mail: rshaffer@med.umich.ed

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_7

can be quite challenging, and responses to therapeutic interventions can be variable. Traditional therapies include intravenous fluid resuscitation, and the administration of calcium salts, glucagon, and vasopressor agents. Refractory bradycardia and atrioventricular nodal blocks may necessitate the use of atropine and temporary pacemakers. More contemporary treatment strategies including the use of intravenous lipid emulsions and high-dose insulin euglycemic therapy have shown great promise.

Case Presentation

A 47 year old female with a history of depression and chronic migraine headaches was brought to the emergency department by her spouse immediately following a witnessed intentional ingestion of approximately sixty 120 mg sustained-release verapamil tablets. On arrival, she was alert and oriented. Vital signs were as followed: pulse 62, blood pressure 95/62, respiratory rate 16, temperature 37.2, and pulse oximetry 99 % on room air. Her EKG showed normal sinus rhythm with normal intervals. IV access was established and a liter of normal saline was administered. Laboratory studies that include routine toxicologic screening tests were unremarkable. She was treated with 50 g of oral activated charcoal and admitted to the intensive care unit for close monitoring. Upon arrival to the ICU, her repeat vital signs revealed a pulse of 42 and blood pressure of 74/42. Her repeat EKG is shown below (Fig. 7.1). An arterial blood gas was obtained: pH 7.12, pCO_2 26, HCO_3 12, lactate 7.2 and glucose 350. An additional 2 L of normal saline were rapidly infused. She was treated with 2 g of IV calcium gluconate, 5 mg of IV glucagon followed by a continuous infusion, and a norepinephrine drip that was titrated for a goal mean arterial pressure of 65. Despite these measures, she remained hypotensive and bradycardic.

Question What do you think is causing her hyperglycemia and what therapeutic intervention(s) could be considered at this point to improve her hemodynamic stability?

Answer Impaired insulin secretion due to calcium channel blocker inhibition of pancreatic Beta cells, coupled with increased stress-mediated glucose mobilization account for her hyperglycemia. High-dose insulin euglycemic therapy should be considered at this point. Her metabolic acidosis is secondary to both a lactic acidosis from impaired tissue perfusion, and ketoacidosis similar to that seen with DKA due to relative hypoinsulinemia.

Based on her weight of 50 kg, an insulin bolus of 50 units IV was given followed by an infusion of 50 units/h. Approximately 45 min after initiation of the insulin infusion, her pulse normalized to 65 and her blood pressure improved enough to gradually wean the norepinephrine drip. Her glucose was monitored every 30 min, and ultimately she did require a continuous dextrose infusion to maintain serum glucose concentrations above 150 mg/dL. Her metabolic acidosis improved over the course of several hours, as did her serum lactate. Serum electrolytes were monitored closely. She developed mild hypokalemia but repletion was not necessary. Approximately 24 h following admission, the insulin infusion was discontinued and her vitals remained stable. She was discharged the next morning to an inpatient psychiatric facility.

Principles of Management

Gastrointestinal Decontamination

Activated charcoal effectively binds calcium channel blockers and should be administered in patients with stable airways and preserved mental status who present within the first 2 h following ingestion. Although clinical evidence supporting the use of multi-dose activated charcoal is lacking, it is reasonable to consider repeat charcoal dosing when sustained-release preparations are involved [2, 5]. Gastric lavage is generally not recommended since the procedure may increase vagal tone, exacerbate hemodynamic instability, and can provoke cardiac arrest [6, 7]. Whole bowel irrigation may be considered in

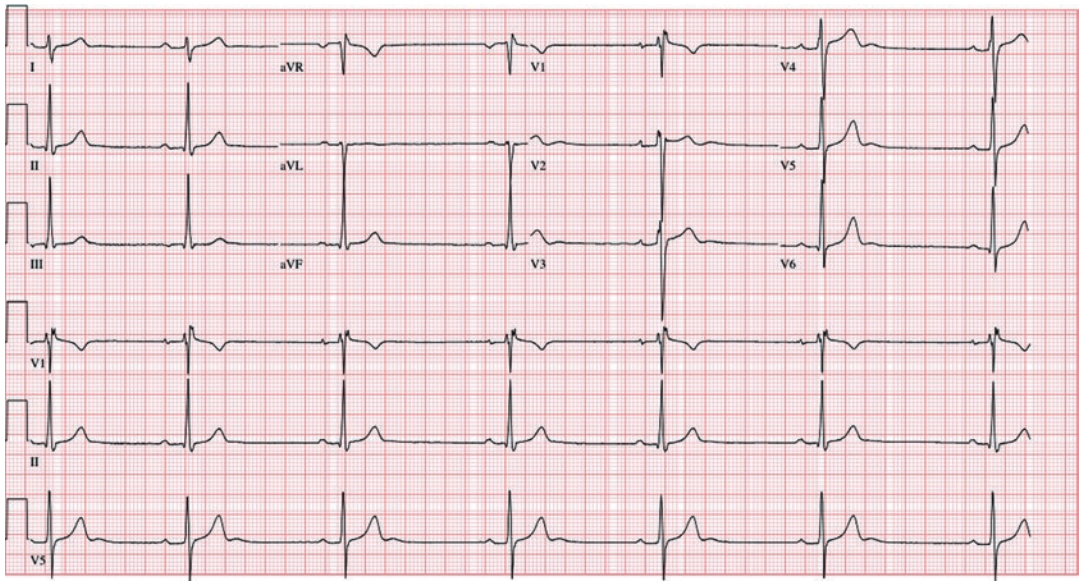


Fig. 7.1 12-lead EKG revealing sinus bradycardia

cases of sustained-release preparations, or when decontamination is delayed beyond a time-frame where activated charcoal would be of benefit [6]. Whole bowel irrigation should be avoided, however, in patients with depressed mental status, ileus, airway compromise, or hemodynamic instability [8].

Hemodynamic Support

The initial management of hypotension due to calcium channel blocker toxicity should include aggressive intravenous fluid resuscitation. In more severely poisoned patients, several therapeutic options may also be considered.

Calcium Salts

The use of calcium gluconate and calcium chloride in the management of calcium channel blocker toxicity seems intuitive. Increased serum calcium concentrations would be expected to overcome calcium channel blockade via a gradient effect, thereby improving myocardial contractility [6]. Animal studies suggest the use of calcium confers both hemodynamic benefits and improves mortality. Human studies are limited to case series, and the reported benefits are inconsistent [7, 9]. The response seen with calcium is often transient, and repeat dosing may be needed [2]. Despite conflicting evidence regarding benefit, use is generally recommended and adverse effects are rare.

Glucagon

Glucagon increases intracellular cyclic-AMP and has been shown in animal models to have positive inotropic and chronotropic effects. Furthermore, glucagon has been shown, in some cases, to reverse 2nd and 3rd degree heart blocks [10]. Evidence for its efficacy in humans is limited to case reports, and treatment failures have been described [2, 7]. Glucagon dosing is not well-established, but an initial dose of 3–5 mg IV followed by a continuous infusion has been suggested, with an additional dose of 4–10 mg IV 5 min after the initial dose if no response is achieved [6].

Atropine

Atropine may be considered for symptomatic bradycardia, but is often ineffective in the setting of severe poisonings. Standard advanced cardiac life support (ACLS) dosing guidelines should be used. Because of its anticholinergic effects on GI motility, it's use may potentiate absorption of

sustained-release calcium channel blocker formulations [6].

Vasopressor Support

When hemodynamic stability cannot be achieved through the use of fluid resuscitation and other initial pharmacologic strategies, vasopressor support may be necessary. Norepinephrine, dopamine, epinephrine, isoproterenol, dobutamine, and phenylephrine have all been used to achieve improvements in blood pressure, and no studies have demonstrated the superiority of one agent over another [2]. Multiple agents may be required simultaneously to achieve hemodynamic stability, and some have reported use of vasopressor doses far in excess of what would typically be considered the referenced maximum [4]. Although improvements in blood pressure are typically achieved, one must be mindful that the increase in systemic vascular resistance will also increase afterload. This may paradoxically lead to an undesirable decrease in cardiac output, as well as an increase in the cardiac oxygen requirement in an already energy-depleted myocardium [3, 6].

High-Dose Insulin Therapy

In recent years, high-dose insulin therapy for the treatment of calcium channel blocker poisonings has gained increasing attention. Calcium channel blockers directly inhibit the calcium channel-mediated release of insulin by the pancreas, leading to systemic hypoinsulinemia (Fig. 7.2). Because carbohydrates are the preferred metabolic substrate of myocardial cells when under duress, the impairment of intracellular glucose transport secondary to insulin depletion further worsens cardiac contractility already impaired by the calcium channel blockers themselves [11]. High-dose insulin restores myocardial glucose utilization and corrects systemic ketoacidosis when present. Insulin has also been shown to have direct positive inotropic effects on myocytes [11]. Furthermore, insulin has been shown to induce vasodilation which improves microvascular perfusion in tissues including the myocardium [12]. Insulin also promotes increased catecholamine sensitivity [11]. The combination of these effects may ameliorate the cardiogenic shock seen with calcium channel blocker toxicity.

Animal models suggest the mortality benefit from high-dose insulin therapy is superior to that seen with calcium salts, glucagon, and vasopressors. One human observational study showed that high-dose insulin therapy resulted in a >10 mmHg sustained increase in systolic blood pressure in all patients receiving high dose insulin boluses and infusions, and numerous case series and case reports detail beneficial hemodynamic responses [2, 13, 14].

Although definitive dosing guidelines have not been established, most recommend an initial insulin bolus be given at a dose of 1 U/kg IV followed by an infusion 1 U/kg/h which may be titrated upward [6]. Higher bolus doses of 10 U/kg and infusions up to 22 U/kg/h have been reported [3]. The clinical response to high-dose insulin may take 15–60 min. Many sources advocate initiation of high-dose insulin therapy very early on in the management of these patients (before they become unstable) [6, 14, 15]. Serum glucose should be monitored every 30 min during the initial course of treatment and supplemental dextrose should be administered, although supplementation may not be necessary if the initial glucose exceeds 300 mg/dL [6]. Mild hypokalemia should be anticipated due to intracellular shifts and may actually augment myocardial cellular function by improving intracellular calcium transport. Potassium repletion should be considered if serum levels fall below 2.8–3.0 mEq/L [12].

Invasive Circulatory Support

The use of temporary transcutaneous and transvenous pacemakers, and intra-aortic balloon pump counter pulsation therapy have been described in the setting of severe bradycardia and high-degree atrioventricular blocks in calcium channel blocker poisonings when medical management fails to adequately reverse cardiogenic shock [2, 6, 7]. At times, obtaining successful pacemaker capture may be difficult in these patients. Furthermore, improvement in hemodynamics may be variable owing to the persistent impaired cardiac inotropy, and it is unclear based

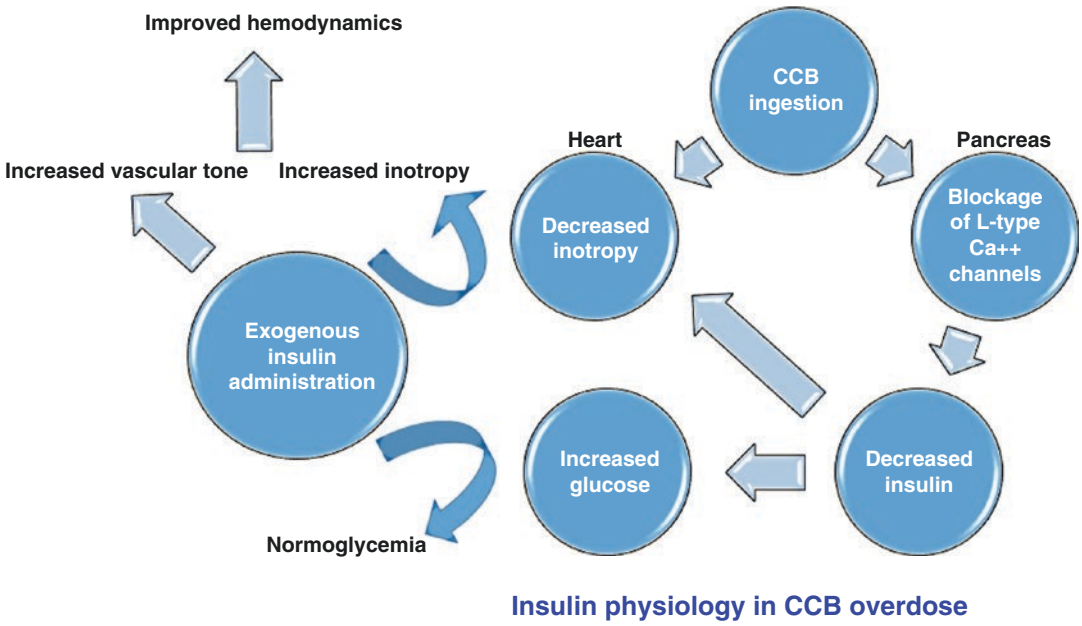


Fig. 7.2 *CCB* calcium channel blocker. L-type Ca++ channels: voltage-gated calcium channels

on case reports whether pacemakers improve clinical outcomes [7, 16]. There are reports describing the successful use of intra-aortic balloon pumps and extracorporeal life support in the setting of refractory shock due to severe calcium channel blocker poisonings, and these techniques may be considered on a case by case basis when other treatment strategies fail [17–19].

Evidence Contour

Intravenous Lipid Emulsions

The use of intravenous lipid emulsion therapy in the management of systemic toxicity from local anesthetics is well-described [6]. More recently, investigators have advocated for the use of intravenous lipid emulsions to treat poisonings due to other lipophilic drug classes including tricyclic antidepressants, beta blockers, and calcium channel blockers [20].

Intravenous lipid emulsion therapy in the context of calcium channel blocker toxicity may be beneficial for several reasons. One proposed mechanism is that lipid emulsions act as a "lipid sink", sequestering lipophilic toxins away from the aqueous plasma phase. In a case report of a verapamil overdose, plasma concentrations of this drug were nearly undetectable following administration of an intravenous lipid emulsion [21]. A second proposed benefit of intravenous lipid emulsions is that they directly stimulate insulin secretion [22]. Thirdly, lipids may promote an increased intracellular calcium concentration in myocytes counteracting the negative inotropic effects seen in these overdoses [23]. Lastly, lipids may serve as a supplementary fuel source for the myocardium, which prefers to derive energy from fatty acids under normal conditions [6].

The evidence supporting the use of intravenous lipid emulsions in calcium channel blocker poisonings is limited to animal studies and human case reports. Multiple animal studies demonstrate that intravenous lipid emulsions confer a survival benefit compared to placebo in verapamil overdoses [20]. Multiple human case reports suggest a temporal hemodynamic response when intravenous lipid emulsions were used as an adjunct to standard treatments [9, 20, 22, 24, 25]. Others report that required vasopressor support greatly diminished following initiation of intravenous

lipid emulsion therapy [23]. Because multiple confounding therapeutic strategies were used in all of these reported cases, the degree in which intravenous lipid emulsion therapy is beneficial remains unclear.

The optimal dosing for intravenous lipid emulsion has not been established, and recommendations are extrapolated from guidelines that exist for the management of local anesthetic toxicity. Typically, a 20 % lipid emulsion solution is administered at a bolus dose of 1.5 ml/kg based on ideal body weight. This is followed by a continuous infusion of 0.25 ml/kg/min until hemodynamic stability persists for at least 10 min. Some suggest that this bolus may be repeated twice and the infusion may be doubled when clinically necessary [6]. The lipemia resulting from this treatment may interfere with certain laboratory assays.

Sodium Bicarbonate

Acidosis is a common occurrence in calcium channel blocker toxicity secondary to diminished tissue perfusion and ketoacidosis. Correction of the acidosis could theoretically improve hemodynamic stability, but the role of bicarbonate therapy in these instances is unclear. In severe overdoses, a widened QRS complex from fast sodium channel blockade, similar to that seen in tricyclic antidepressant toxicity, may occur. The benefits of sodium bicarbonate in calcium channel blocker toxicity is largely anecdotal, but some advocate for its use when QRS complex prolongation occurs [2].

Methylene Blue

Methylene blue inhibits guanylate cyclase which subsequently decreases cGMP resulting in inhibition of vascular smooth muscle relaxation. Therefore, it might be expected to reverse some of the effects of the dihydropyridine class of calcium channel blockers. Experience with methylene blue in calcium channel blocker toxicity, however, is limited. One case report described an improvement in hemodynamic stability following methylene blue administration to a patient with an amlodipine overdose that had failed to respond to other measures [26]. Another case report demonstrated a similar effect in a mixed calcium channel/beta blocker overdose [27]. While adequate evidence supporting routine use does not exist, methylene blue might be considered as a rescue therapy in severe dihydropyridine poisonings that fail to respond to other treatment strategies [28].

Extracorporeal Albumin Dialysis

Because calcium channel blockers have high volumes of distribution and are largely protein-bound, traditional extracorporeal elimination strategies including hemodialysis and hemoperfusion are generally ineffective. Albumin dialysis with molecular absorbents recirculating system (MARS) therapy offers the ability to remove protein-bound toxins that would otherwise not be cleared by traditional hemodialysis. This technique was successfully in the management of three severely poisoned patients with refractory shock due to calcium channel blocker toxicity, and all three patients survived [29].

References

1. Mowry JB, Spyker DA, Cantilena Jr LR, McMillan N, Ford M. 2013 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st Annual Report. Clin Toxicol (Phila). 2014;52(10):1032–283.
2. Shenoy S, Lankala S, Adigopula S. Management of calcium channel blocker overdoses. J Hosp Med. 2014;9(10):663–8.
3. Siddiqi TA, Hill J, Huckleberry Y, Parthasarathy S. Non-cardiogenic pulmonary edema and life-threatening shock due to calcium channel blocker overdose: a case report and clinical review. Respir Care. 2014;59(2):e15–21.
4. Levine M, Curry SC, Padilla-Jones A, Ruha AM. Critical care management of verapamil and diltiazem overdose with a focus on vasopressors: a 25-year experience at a single center. Ann Emerg Med. 2013;62(3):252–8.
5. Thanacoody R, Caravati EM, Troutman B, Hojer J, Benson B, Hoppu K. Position paper update: whole

bowel irrigation for gastrointestinal decontamination of overdose patients. Clin Toxicol. 2015;53(1):5–12.
6. Jang DH, Spyres MB, Fox L, Manini AF. Toxin-inducedcardiovascular failure. Emerg Med Clin North Am. 2014;32(1):79–102.
7. St-Onge M, Dubé PA, Gosselin S, Guimont C, Godwin J, Archambault PM, Chauny JM, Frenette AJ, Darveau M, Le Sage N, Poitras J, Provencher J, Juurlink DN, Blais R. Treatment for calcium channel blocker poisoning: a systematic review. Clin Toxicol (Phila). 2014;52(9):926–44.
8. Cumpston KL, Aks SE, Sigg R, Pallasch P. Whole bowel irrigation and the hemodynamically unstable calcium channel blocker overdose: Primum non nocere. J Emerg Med. 2010;38(2):171–4.
9. Liang CW, Diamond SJ, Hagg DS. Lipid rescue of massive verapamil overdose: a case report. J Med Case Rep. 2011;5(1):399.
10. Bailey B. Glucagon in beta-blocker and calcium channel blocker overdose: a systematic review. J Toxicol Clin Toxicol. 2003;41(5):595–602.
11. Woodward C, Pourmand A, Mazer-Amirshahi M. High dose insulin therapy, an evidence based approach to betablocker/calcium channel blocker toxicity. Daru. 2014;22(1):36.
12. Engebretsen KM, Kaczmarek KM, Morgan J, Holger JS. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. Clin Toxicol (Phila). 2011;49(4):277–83.
13. Holger JS, Stellpflug SJ, Cole JB, Harris CR, Engebretsen KM. High-dose insulin: a consecutive case series in toxin-induced cardiogenic shock. Clin Toxicol (Phila). 2011;49(7):653–8.
14. Greene SL, Gawarammana I, Wood DM, Jones AL, Dargan PI. Relative safety of hyperinsulinaemia/euglycaemia therapy in the management of calcium channel blocker overdose: a prospective observational study. Intensive Care Med. 2007;33(11):2019–24.
15. Espinoza TR, Bryant SM, Aks SE. Hyperinsulin therapy for calcium channel antagonist poisoning: a seven-year retrospective study. Am J Ther. 2013;20(1):29–31.
16. McGlinchey PG, Mcneill AJ. Drug overdoses requiring temporary cardiac pacing; a study of six cases treated at Altnagelvin Hospital, Londonderry. Ulster Med J. 1998;67(1):13–8.
17. Janion M, Stepień A, Sielski J, Gutkowski W. Is the intra-aortic balloon pump a method of brain protection during cardiogenic shock after drug intoxication? J Emerg Med. 2010;38(2):162–7.
18. Masson R, Colas V, Parienti JJ, Lehoux P, Massetti M, Charbonneau P, Saulnier F, Daubin C. A comparison of survival with and without extracorporeal life support treatment for severe poisoning due to drug intoxication. Resuscitation. 2012;83(11):1413–7.
19. Daubin C, Lehoux P, Ivascau C, Tasle M, et al. Extracorporeal life support in severe drug intoxication: a retrospective cohort study of seventeen cases. Crit Care. 2009;13(4):R138.
20. Jamaty C, Bailey B, Larocque A, Notebaert E, Sanogo K, Chauny J. Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies. Clin Toxicol. 2010;48(1):1–27.
21. French D, Armenian P, Ruan W, Wong A, et al. Serum verapamil concentrations before and after Intralipid therapy during treatment of an overdose. Clin Toxicol. 2011;49(4):340–4.
22. Young AC, Velez LI, Kleinschmidt KC. Intravenous fat emulsion therapy for intentional sustained-release verapamil overdose. Resuscitation. 2009;80(5):591–3.
23. Ozcan MS, Weinberg G. Intravenous lipid emulsion for the treatment of drug toxicity. J Intensive Care Med. 2014;29(2):59–70.
24. Cevik S, Tasyurek T, Guneysel O. Intralipid emulsion treatment as an antidote in lipophilic drug intoxications. Am J Emerg Med. 2014;32(9):1103–8.
25. Doepker B, Healy W, Cortez E, Adkins EJ. High-dose insulin and intravenous lipid emulsion therapy for cardiogenic shock induced by intentional calcium- channel blocker and beta-blocker overdose: a case series. J Emerg Med. 2014;46(4):486–90.
26. Jang DH, Nelson LS, Hoffman RS. Methylene blue in the treatment of refractory shock from an amlodipine overdose. Ann Emerg Med. 2011;58(6):565–7.
27. Aggarwal N, Kupfer Y, Seneviratne C, Tessler S. Methylene blue reverses recalcitrant shock in β-blocker and calcium channel blocker overdose. BMJ Case Rep. 2013;18:2013.
28. Lo JC, Darracq MA, Clark RF. A review of methylene blue treatment for cardiovascular collapse. J Emerg Med. 2014;46(5):670–9.
29. Pichon N, Dugard A, Clavel M, Amiel J, François B, Vignon P. Extracorporeal albumin dialysis in three cases of acute calcium channel blocker poisoning with life-threatening refractory cardiogenic shock. Ann Emerg Med. 2012;59(6):540–4.

Diagnosis and Management of Ethylene Glycol Ingestion

8

Christine Martinek Brent and Robert W. Shaffer

Case Presentation

A 46 year old female with a history of depression arrived at the emergency department by EMS with altered mental status. Her husband found her in the garage of their home with confusion, incoherent slurred speech and an unsteady gait. By his report, she had seemed well 4 h earlier. Initial vital signs were as follows: HR 112, BP 145/91, RR 16, O_2 99 % on RA, and temperature 98.9. Glucose was 127 mg/dL. GCS was 14. There were no signs of trauma, and her physical exam, aside from the findings mentioned above, was unremarkable. Initial labs including CBC, chemistries and urinalysis were normal. Urine drug screen was negative. Salicylate, acetaminophen, and ethanol were not detected. Carboxyhemoglobin level was 1.2 %. ABG on room air revealed: pH 7.36, pO_2 88, pCO_2 35, HCO_3 21, lactate 2.7. Head CT and CXR were normal. EKG showed sinus tachycardia with normal intervals. IV fluids were initiated.

Over the next 2 h, her HR and RR increased to 125 and 24 respectively. She was placed on 4 L NC for a room air saturation of 87 %. She became more confused with a GCS of 10. Repeat labs were obtained which demonstrated a new anion gap of 22 (see below). A repeat ABG (on 4 L O_2) showed the following: pH 7.22, pO_2 58, PCO_2 26, HCO_3 15, lactate 3.2. Measured serum osmoles were obtained and an osmolal gap of 40 was calculated. CXR revealed pulmonary edema without cardiomegaly. Her hypoxia and tachypnea worsened despite increasing amounts of supplemental oxygen, including 100 % NRB.

Calculation and Differential Diagnosis of the Elevated Anion Gap with the Pneumonic "MUDPILES"

$$\text{Anion Gap} = [\text{Anions}] - [\text{Cations}][\text{AG}]$$
$$= [\text{Na}^+] - \left([\text{Cl}^-] + [\text{HCO}_3^-]\right)$$

Methanol

Uremia

Diabetic Ketoacidosis

Propylene Glycol
Paraldehyde
Propofol

C.M. Brent (✉)
Emergency Medicine, University of Michigan Health System, Ann Arbor, MI, USA
e-mail: martinek@med.umich.edu

R.W. Shaffer
Department of Emergency Medicine, University of Michigan Health System, Ann Arbor, MI, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_8

Infection
Iron
Isoniazid
Inborn Errors of Metabolism

Lactic Acidosis

Ethylene Glycol

Salicylates
Starvation ketoacidosis

Question How would you proceed in the management of this patient?

Answer The combination of altered mental status, progressive development of a high anion gap acidosis and the presence of a marked osmolal gap are highly suggestive of toxic alcohol ingestion, either methanol or ethylene glycol. Methanol is a common ingredient in windshield washer fluid and ethylene glycol is commonly found in antifreeze. Ingestion of isopropyl alcohol, the third common toxic alcohol ingestion, elevates the osmolar gap but does not result in an acidosis or significant elevation of the anion gap.

Given her decline in mental status and progressive failure of oxygenation secondary to development of pulmonary edema, she was intubated and mechanically ventilated. A loading dose of 15 mg/kg intravenous fomepizole treatment was immediately initiated to prevent further metabolism of the parent alcohol. The cofactors thiamine and pyridoxine were given. Her developing acidosis suggested that she had already metabolized a substantial portion of the parent alcohol into its toxic metabolites, and nephrology was consulted for emergent hemodialysis. Gas chromatography for toxic alcohols returned several hours later and revealed an ethylene glycol level of 257 mg/dL. Repeat urinalysis demonstrated calcium oxalate crystalluria (Fig. 8.1).

The patient underwent three runs of intermittent hemodialysis and was continued on IV fomepizole per protocol. Her gap acidosis normalized and her measured ethylene glycol fell below 20 mg/dL. Her renal function remained normal throughout her clinical course. Her pulmonary edema resolved and she was extubated on hospital day #2.

Principles of Management

Diagnosis

Ethylene glycol is an organic alcohol with multiple commercial and household purposes, and is typically the primary compound found in antifreeze. It is a colorless liquid, although dyes are often added by the manufacturer. The taste of ethylene glycol is often described as “sweet”, and therefore young children frequently fall victim to inadvertent ingestions [1]. Ethylene glycol is rapidly absorbed by the GI tract and clinical intoxication may be apparent within 20–30 min. Peak serum concentrations can be expected between 1 and 4 h post-ingestion [2]. Ingestions of as little as 1 mL/kg may lead to toxic serum concentrations [3].

Diagnosing ethylene glycol poisoning can be quite challenging, as the acute clinical presentation is typically non-specific and may appear quite similar to ethanol intoxication. Individuals with intentional ingestions may not be forthcoming, or may be too obtunded to provide a history of ingestion. Prompt initiation of treatment is imperative, and delays strongly correlate with the development of acidosis and renal failure once toxic metabolites accumulate (Fig. 8.2) [4, 5]. The gold standard for diagnosis uses gas chromatography to measure serum ethylene glycol levels, but may take 2–4 h to perform, and is not readily available at most medical facilities [2, 6]. Serum measurement of the glycolic acid metabolite has also been advocated by some, owing to its stronger correlation with the development of renal complications, but this also requires gas chromatography and therefore carries the same limitations [7]. Therefore, the clinician often must utilize surrogate markers when considering a toxic alcohol exposure.

Since ethylene glycol is an osmotically active substance, the osmolal gap (measured

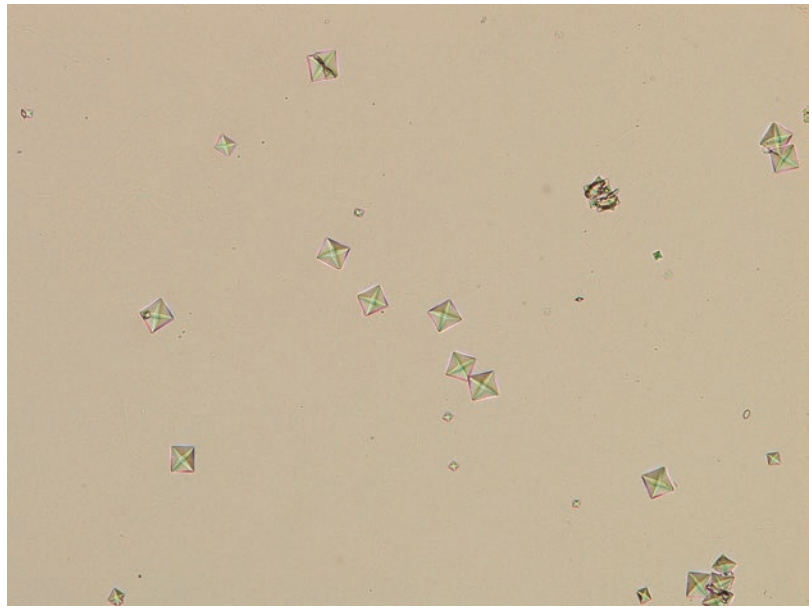


Fig. 8.1 Calcium oxalate crystals

osmoles – calculated osmoles) will typically be elevated during the initial phase following substantial ingestions. As the parent compound is metabolized, the osmolal gap will gradually decline and a metabolic anion gap acidosis will develop (Fig. 8.3) [9]. There are several caveats to note when interpreting an osmolal gap, however. Numerous formulas exist for calculating serum osmoles, and there is no consensus on which one is superior [2, 10, 11]. One commonly used formula is as follows:

$$\text{Osmc} = \left[2 \times \text{Na} + 1.15\left(\text{glucose}/18\right) + \text{BUN}/2.8 + \text{EtOH}/4.6\right]$$

An elevated osmolal gap is non-specific and may be seen with various conditions including ethanol intoxication, alcoholic ketoacidosis, DKA, renal failure, shock, and after use of other exogenous osmotically active compounds such as mannitol [10]. Additionally, since the normal reference range for a calculated osmolal gap may be as low as −10 mosm, the addition of measured osmoles from a toxic alcohol may not raise this gap beyond the accepted upper limit of +10 mosm. This can be understood when considering that an ethylene glycol level of 21 mg/dL (the threshold where treatment is recommended) would only be expected to increase serum osmoles by 4 mosm [2]. Despite these limitations, a large retrospective analysis suggested that an unexplained osmolal gap exceeding 50 was highly suggestive of a toxic alcohol ingestion, and that nearly 50 % of toxic ingestions had osmolal gaps greater than 30 [10].

In the initial phase following ethylene glycol poisoning, the anion gap is typically normal, and then begins to rise approximately 3 h post-ingestion [2]. When presentation or treatment is delayed, the parent alcohol is metabolized by alcohol dehydrogenase and aldehyde dehydrogenase into glycolic acid. Further metabolism of glycolic acid is very slow and therefore this compound progressively accumulates resulting in an anion gap acidosis. Cardiopulmonary manifestations are likely both due to the acidemia, as well as the direct toxic effect of glycolic acid. During this phase, patients may develop tachycardia,

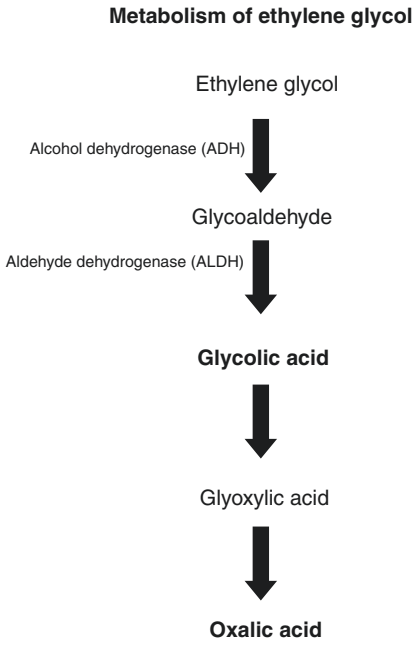


Fig. 8.2 Metabolism of ethylene glycol

hypotension, myocardial depression and congestive heart failure, cerebral edema, and an ARDS-type picture [3, 12].

A small portion of glycolic acid is then further metabolized into oxalate. Deposition of calcium oxalate crystals in renal tubules results in tubular necrosis and renal failure, and generally occurs 24–72 h post-ingestion. This can also lead to significant hypocalcemia [2]. Testing for calcium oxalate crystalluria as an adjunct to the diagnosis of ethylene glycol ingestions has been evaluated. Unfortunately, crystals are seen in only 33–63 % of those with known ingestions, and the baseline prevalence of crystalluria due to other causes such as dietary factors make this finding neither sensitive nor specific [2, 13].

Urine fluorescence is another strategy that has been evaluated by investigators to aid in determination of ethylene glycol ingestions. Fluorescein is often added to engine coolants by manufacturers to facilitate a mechanic's ability to detect radiator leaks using UV light [2]. In the setting of ingestions, fluorescein is excreted unchanged in the urine. However, not all antifreeze preparations contain this compound.

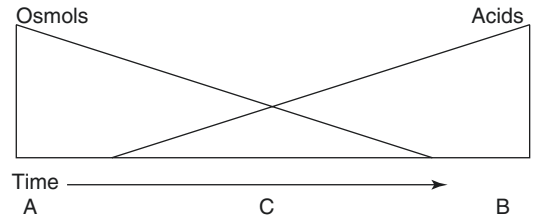


Fig. 8.3 The mountain: A visual schematic for clarifying the temporal relationship between the anion gap and osmole gaps in toxic alcohol poisoning. *A*: Ethylene glycol is the predominate form in the serum. Only an osmolar gap is present. No acidosis or anion gap yet noted. *C*: Ethylene glycol is being metabolized. Some glycolic acid is present. Both an osmolar gap and an anion gap acidosis are present. *B*: All the ethylene glycol has been metabolized to glycolic acid. Osmolar gap no longer exists. Large anion gap acidosis is present (From Mycyk and Aks [8]. Reprinted with permission from Elsevier Limited)

Furthermore, fluorescence is short-lived during the first few hours and may be difficult to detect. Inter-rater reliability when assessing urinary fluorescence is poor and fluorescein cannot be detected when urinary pH falls below 4.5. For these reasons, this screening test cannot be recommended [2, 6, 14].

As a result of the poor performance of any one marker for the diagnosis of toxic alcohol ingestion, it is recommended by the American Academy of Clinical Toxicology that the clinician maintain a high index of suspicion and low threshold for treatment [6]. Diagnostic criteria and indications for treatment are shown below [4, 6, 15].

Diagnostic Criteria and Indications for Treatment of Ethylene Glycol Poisoning

- Ethylene glycol level >20 mg/dL or
- Recent history of known ingestion AND osmolal gap >10 or
- Strong suspicion of ethylene glycol ingestion AND two of the following
  - pH, 7.3
  - serum bicarbonate <20
  - osmolal gap >10
  - Calcium oxalate crystalluria

Ventilator and Circulatory Support

Ethylene glycol exerts effects on GABA and Glutamate receptors in a similar manner to ethanol. In severe poisonings, respiratory depression and/or inability to adequately protect one's airway may necessitate intubation and mechanical ventilation. When an acidosis is present, attention to adequate minute ventilation is imperative to allow for adequate respiratory compensation.

Hypotension may result from direct vasodilatation caused by the toxic alcohol, or secondary to myocardial depression due to acidosis. In cases of congestive heart failure or impending circulatory collapse, vasopressor agents may be needed. Serial EKGs should be obtained to assess for prolongation of the QTc which may be seen when hypocalcemia is present. Calcium repletion should be limited to patients who are symptomatic (cardiac arrhythmias, seizures), as this may hasten calcium oxalate precipitation in the renal tubules [16]. The presence of hyperkalemia is often the result of extracellular shifts due to the metabolic acidosis, and treatment should be reserved for individuals with concerning EKG manifestations. An ARDS-like picture may rarely develop and should be managed with lung-protective ventilation.

Gastric Decontamination/Lavage/Charcoal

Gastrointestinal decontamination and gastric lavage have limited benefit following ethylene glycol absorption due to its very rapid absorption. Furthermore, toxic alcohols bind poorly to activated charcoal, and its use is not recommended [16].

Aldehyde Dehydrogenase (ADH) Blockade

Inhibition of ADH is the mainstay of treatment and prevents metabolism of ethylene glycol into its toxic metabolites, and it is generally accepted that treatment should be initiated for serum ethylene glycol concentrations in excess of 20 mg/dL [6]. The parent alcohol is then excreted largely unchanged in the urine. The elimination half-life of ethylene glycol ranges from 14 to 20 h in the setting of ADH inhibition [4, 6, 10]. The two ADH inhibitors that may be used are ethanol and fomepizole.

Prior to the advent of fomepizole, ethanol was historically used for ADH blockade. Ethanol is the natural substrate for ADH, and given its higher binding affinity over ethylene glycol, it serves as a competitive inhibitor to toxic alcohol metabolism. The generally accepted regimen for ethanol administration is a loading dose of 600 mg/kg of a 10 % solution IV through a central venous catheter, followed by a continuous infusion of 110 mg/kg/h. The drip is then titrated with a goal serum ethanol concentration between 100 and 125 mg/dL [6, 17]. This requires close monitoring, given the unpredictable pharmacokinetics of ethanol metabolism. Ethanol administration is not without side effects, and patients must be monitored for deterioration of mental status, hypoglycemia, hepatitis, and pancreatitis. When no IV ethanol formulation is available, PO ethanol can be considered using the same serum concentration goal.

Fomepizole (4-methylpyrazole, Antizole) was FDA approved in 1997 for use as a competitive inhibitor of ADH in the setting of toxic alcohol ingestions. Its efficacy was supported through a small prospective clinical sub-study of the Methylpyrazole for Toxic Alcohols (META) trial. Patients treated with fomepizole who had normal renal function at the time of treatment initiation had no subsequent kidney injury. It should be noted, however, that patients with serum ethylene glycol levels exceeding 50 mg/dL also underwent hemodialysis [13]. Fomepizole, when compared to ethanol, has the advantage of predictable pharmacokinetics. Its use is generally well-tolerated although patients occasionally report side-effects including headaches, nausea, and dizziness [13, 18]. A loading dose of 15 mg/kg IV is initiated, followed by 10 mg/kg every 12 h. Fomepizole may induce its own metabolism via the CYP450 pathway, and dosing should be increased to 15 mg/kg every 12 h for doses

beyond 48 h of treatment. In patients undergoing concurrent dialysis, the dosing frequency should be increased to every 4 h, or alternatively a continuous infusion of 1 mg/kg/h can be considered [4, 6, 18, 19]. Because ethanol metabolism is inhibited by fomepizole, ethanol treatment should not be used concurrently [20].

Hemodialysis

ADH blockade disrupts the initial metabolism of ethylene glycol. The development of an anion gap acidosis, or the presence of renal injury suggests significant metabolism of ethylene glycol into toxic substrates has already occurred. In these cases, hemodialysis may be required to correct the acidosis and thwart further deterioration of renal function [4, 6, 15, 21]. Although complications may occur, hemodialysis may shorten hospital length of stays [22]. Indications for hemodialysis were reported by the American Academy of Clinical Toxicology in 1999, and their guidelines have yet to be formally updated [6]. These include:

- Deteriorating vital signs despite supportive care.
- Severe metabolic acidosis (<7.25–7.30)
- Renal failure or severe electrolyte disturbances not responsive to conventional therapy
  4. Ethylene glycol level >50 mg/dL

The use of an ethylene glycol concentration threshold for hemodialysis has more recently been called into question [4, 23, 24].

Evidence Contour

Ethylene Glycol Treatment Threshold

Historically, a serum ethylene glycol concentration in excess of 20 mg/dL has been considered to be the potentially toxic level where ADH blockade was recommended [6]. This conservative threshold was likely extrapolated from case reports involving toxic methanol ingestions, and is based on opinion rather than evidence [25]. Furthermore, an absolute serum ethylene glycol concentration does not take into account how much metabolism has already occurred when presentations are delayed. Serum glycolate levels better correlate with the development of acidosis and renal injury, but again there is no established threshold for treatment [26].

Fomepizole vs Ethanol

Many toxicologists currently advocate fomepizole as the first-line agent for ADH-blockade [4, 19]. This may be, in part, related to less reported adverse events when compared to the use of ethanol [27]. To date, there have been no controlled clinical trials comparing the efficacy of fomepizole to ethanol, and there is a paucity of literature on the morbidity and mortality of patients treated with either intervention [5, 28, 29]. Recently, Beatty et al. conducted a systematic literature review that included 145 trials (none of which were randomized controlled studies) [28]. Two hundred ninety-five patients with ethylene glycol poisoning were identified who received either fomepizole, ethanol, or both. A higher mortality was seen in those treated with ethanol when compared to fomepizole (18 % vs 4.1 %). The author cautioned that extrapolated data was often poor or incomplete, and that literature reporting the use of fomepizole tended to be more current, and that recent advances in medical care may confound these results.

ADH Inhibition without Hemodialysis

The guidelines published in 1999 by the American Academy of Toxicology advocated initiation of hemodialysis (HD) when ethylene glycol levels exceed 50 mg/dL [6]. Since that time, there are growing reports of patients with significant ethylene glycol ingestions, some with serum levels exceeding 700 mg/dL, being treated with fomepizole alone when acidosis and renal impairment were absent [15, 24, 30, 31]. Some investigators

have even reported successful management with fomepizole alone when a mild acidosis was present [3, 32]. This has led some experts to advocate for the use of hemodialysis only in cases of significant acidosis or with signs of renal impairment, irrespective of the initial serum ethylene glycol level [4, 15, 19, 23, 32]. However, prospective studies are necessary to validate these recommendations.

Serum and Urine Alkalization

In methanol ingestions, there is some limited evidence that serum alkalization may promote deprotonation of toxic acids into their less toxic conjugate bases, and might also enhance urinary excretion [33]. This has not been proven to be of benefit in the setting of ethylene glycol intoxications, and alkalization for the sole purpose of enhancing elimination is not supported by evidence. Sodium bicarbonate therapy may be considered, however, in instances of refractory acidosis [6].

Cofactor Supplementation

Pyridoxine and thiamine are cofactors which facilitate conversion of glycolic acid to non-toxic metabolites via alternative metabolic pathways, potentially diverting metabolism away from the production of oxalate. While advocated by many, no clinical trials have substantiated this hypothetical benefit, and supplementation is unlikely to be useful in the absence of a pre-existing vitamin deficiency [6, 34].

Other Toxic Alcohols

Methanol

Methanol (aka "wood alcohol") was historically found in methylate spirits. It is now found in solvents, antifreeze, and certain fuels. The fatal dose is considered to be anywhere between 1 and 2 mL/kg [35], although deaths have been reported with doses as low as 0.1–0.4 mL/kg [35, 36]. Using the same enzymatic pathways as ethylene glycol, methanol is metabolized to formaldehyde then formate. Symptoms of acute ingestion are almost identical to those of ethylene glycol. Metabolic effects are also similar, including development of an osmolar gap followed by an anion gap acidosis. Metabolites of methanol are also profoundly more neurotoxic, and the optic nerve is particularly vulnerable which can result in permanent visual impairment [3, 35, 37, 38]. Production of formate is prevented by early use of fomepizole (preferred) or ethanol, and guidelines for initiation of these therapies are shown below [33].

Guidelines for Initiation of Therapies

1. Documented plasma methanol concentration > 20 mg/dL (200 mg/L)
2. Documented recent history of ingesting toxic amounts of methanol and osmolal gap >10 mOsm/kg
3. History or strong clinical suspicion of methanol poisoning and at least 2 of the following criteria:
   Arterial pH <7.3
   Serum bicarbonate <20 meq/L (20 mmol/L)
   Osmolal gap <10 mOsm/kg H_2O

Diagnostic Criteria and Indications for the Treatment of Methanol Poisoning

- Documented plasma methanol concentration > 20 mg/dL
- Documented recent history of ingesting methanol and osmolal gap >10 mOsm/kg
- History or strong clinical suspicion of methanol poisoning and at least two of the following criteria:
  - Arterial pH <7.3
  - Serum bicarbonate <20 meq/L (20 mmol/L)
  - Osmolal gap <10 mOsm/kg H_2O

Folic acid should be administered in toxic methanol ingestions since it serves as a cofactor in the breakdown of formate [39]. Acidosis should be corrected with sodium bicarbonate administration [33]. Recent guidelines recommend intermittent hemodialysis in severe ingestions for any of the following [40]:

- Seizures, coma, visual changes
- pH < 7.15, or any acidosis unresponsive to bicarbonate
- anion gap > 24 mmol/L
- [methanol]serum > 70 mg/dL in the setting of fomepizole treatment
- [methanol]serum > 60 mg/dL in the setting of ethanol treatment
- [methanol]serum > 50 mg/dL in the setting of no competitive inhibition
- Impaired kidney function
- Extracorporeal treatment can be discontinued when methanol concentration is <20–25 mg/dL [40].

Isopropyl Alcohol

Isopropyl alcohol (aka "rubbing alcohol") produces an acute clinical picture of CNS intoxication similar to that seen with ethanol, with greater relative potency. The primary metabolite of isopropyl alcohol is acetone. This compound elevates the osmolal gap and causes ketosis, but is not further metabolized to a toxic carboxylic acid and is therefore significantly less harmful than ethylene glycol and methanol. Management of acute ingestion thus consists of supportive care, and ethanol and fomepizole are not indicated [41].

References

1. Mowry JB, et al. 2012 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th annual report. Clin Toxicol. 2013;51:949–1229.
2. McQuade DJ, Dargan PI, Wood DM. Challenges in the diagnosis of ethylene glycol poisoning. Ann Clin Biochem. 2013;51(2):167–78.
3. Buchanan JA, Alhelail M, Cetaruk EW, Schaeffer TH, Palmer RB, Kulig K, et al. Massive ethylene glycol ingestion treated with fomepizole alone – a viable therapeutic option. J Med Toxicol. 2010;6(2):131–4.
4. Brent J. Fomepizole for ethylene glycol and methanol poisoning. N Engl J Med. 2009;360(21):2216–23.
5. Druteika DP, Zed PJ, Ensom MH. Role of Fomepizole in the management of ethylene glycol toxicity. Pharmacotherapy. 2002;22(3):365–72.
6. Barceloux DG, Krenzelok EP, Olson K, Watson W. American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. Clin Toxicol. 1999;37(5):537–60.
7. Porter WH, Rutter PW, Bush BA, Pappas AA, Dunnington JE. Ethylene glycol toxicity: the role of serum glycolic acid in hemodialysis. J Toxicol Clin Toxicol. 2001;39(6):607–15.
8. Mycyk MB, Aks SE. A visual schematic for clarifying the temporal relationship between the anion and osmol gaps in toxic alcohol poisoning. Am J Emerg Med. 2003;21(4):333–5.
9. Mycyk MB, Wills B, Mazor S, Deslauriers C, Metz J. Fomepizole use is often suboptimal in cases of toxic alcohol poisoning. Ann Emerg Med. 2004;44(4):S89.
10. Krasowski MD, Wilcoxon RM, Miron J. A retrospective analysis of glycol and toxic alcohol ingestion: utility of anion and osmolal gaps. BMC Clin Pathol. 2012;12(1):2–10.
11. Khajuria A, Krahn J. Osmolality revisited: deriving and validating the best formula for calculated osmolality. J Clin Biochem. 2005;38(6):514–9.
12. Catchings T, Beamer W, Lundy L, et al. Adult respiratory distress syndrome secondary to ethylene glycol ingestion. Ann Emerg Med. 1985;14:594–6.
13. Brent J, McMartin K, Phillips S, Burkhart KK, Donovan JW, Wells M, Kulig K, Methylpyrazole for Toxic Alcohols Study Group. Fomepizole for the treatment of ethylene glycol poisoning. N Engl J Med. 1999;340(11):832–8.
14. McStay CM, Gordon PE. Images in clinical medicine: urine fluorescence in ethylene glycol poisoning. N Engl J Med. 2007;356(6):611.
15. Velez LI, Shepard G, Lee YC, Keyes DC. Ethylene glycol ingestions treated only with fomepizole. J Med Toxicol. 2007;3(3):125–8.
16. Hall TL. Fomepizole in the treatment of ethylene glycol poisoning. Can J Emerg Med. 2002;4(3):199–204.
17. Peterson CD, Collins AJ, Himes JM, Bullock ML, Keane WF. Ethylene glycol poisoning: pharmacokinetics during therapy with ethanol and hemodialysis. N Engl J Med. 1981;304(1):21–3.
18. Howland MS. Antidotes in depth: fomepizole. In: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE, editors. Goldfrank's toxicologic emergencies. New York: McGraw-Hill; 2010.
19. Rehman H. Fomepizole for toxic alcohol poisoning. N Engl J Med. 2009;361(12):1213–4.
20. Butler GK. When is it appropriate to treat ethylene glycol intoxication with fomepizole alone without hemodialysis? Semin Dial. 2011;24(4):441–2.
21. Ting SM, Ching I, Nair H, Langman G, Suresh V, Temple RM. Early and late presentations of ethylene

glycol poisoning. Am J Kidney Dis. 2009;53(6): 1091–7.
22. Battistella M. Fomepizole as an antidote for ethylene glycol poisoning. Ann Pharmacother. 2002;36(6):1085–9.
23. Wedge MK, Mataajan S, Johanson C, Patel R, Kanji S. The safety of ethanol infusions for the treatment of methanol or ethylene glycol intoxication: an observational study. Can J Emerg Med. 2012;14(5):283–9.
24. Megarban B, Borron SW, Baud FJ. Current recommendations for treatment of severe toxic alcohol poisonings. Intensive Care Med. 2005;31(2):189–95.
25. Buller GK, Moskowit CB, Eckardt K. The role of hemodialysis and fomepizole in ethylene glycol intoxication. J Nephrol Therap. 2012;S10:4.
26. Kostic MA, Dart RC. Rethinking the toxic methanol level. J Toxicol Clin Toxicol. 2003;41:793–800.
27. Moreau CL, Kerns II W, Tomaszewski CA, McMartin KE, Rose SR, Ford MD, et al. Glycolate kinetics and hemodialysis clearance in ethylene glycol poisoning. Methylpyrazole for Toxic Alcohols Study Group. J Toxicol Clin Toxicol. 1998;36(7):659–66.
28. Beatty L, Green R, Magee K, Zed P. A systematic review of ethanol and fomepizole use in toxic alcohol ingestions. Emerg Med Int. 2013;2013:638057.
29. Watson WA. Ethylene glycol toxicity: closing in on rational, evidence-based treatment. Ann Emerg Med. 2000;36:139–41.
30. Levine M, et al. Ethylene glycol elimination kinetics and outcomes in patients managed without hemodialysis. Ann Emerg Med. 2012;59(6):527.
31. Borron SW, Megarbane B, Baud FJ. Fomepizole in treatment of uncomplicated ethylene glycol poisoning. Lancet. 1999;354:831.
32. Caravati EM, Heileson HL, Jones M. Treatment of severe pediatric ethylene glycol intoxication without hemodialysis. J Toxicol Clin Toxicol. 2004;42(3):255–9.
33. Barceloux DG, Bond GR, Krenzelok EP, Cooper H, Vale JA. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. J Toxicol Clin Toxicol. 2002;40(4): 415–46.
34. Lheureux P, Penaloza A, Gris M. Pyridoxine in clinical toxicology: a review. Eur J Emerg Med. 2005;12: 78–85.
35. Jammalamadaka D, Raissi S. Ethylene glycol, methanol, and isopropyl alcohol intoxication. Am J Med Sci. 2010;339(9):276–81.
36. Bennett IL, Cary FH, Mitchell GL, Cooper MN. Acute methyl alcohol poisoning: a review based on experiences in an outbreak of 323 cases. Medicine. 1953;32(4):431–63.
37. Sharma R, Marasini S, Sharma A, Shrestha J, Nepal B. Methanol poisoning: ocular and neurological manifestations. Opt Vis Sci. 2012;89(2):178–82.
38. Zakharov S, Pelclova D, Diblik P, Urban P, Kuthan P, Nurieva O, et al. Long-term visual damage after acute methanol poisonings: longitudinal cross-sectional study in 50 patients. Clin Toxicol. 2015;53(9): 884–92.
39. Noker P, Ells J, Tephly T. Methanol toxicity: treatment with folic acid and 5-formyl tetrahydrofolic acid. Alcoholism Clin Exp Res. 2008;4(4):378–83.
40. Roberts D, Yates C, Megarbane B, Winchester J, McClaren R, Gosselin S, et al. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. Extracorporeal Treatments in Poisoning Workgroup. Crit Care Med. 2015;43(2):461–72.
41. Slaughter R, Mason R, Beasley D, Vale J, Schep L. Isopropanol poisoning. Clin Toxicol. 2014;52(5): 470–8.

Accidental Hypothermia

9

Carrie Harvey and Ivan Nathaniel Co

Abbreviations

°C	Degrees Celsius
ACLS	Advanced Cardiac Life Support
AHA	American Heart Association
CAVR	Continuous arteriovenous rewarming
CPB	Cardiopulmonary bypass
CPR	Cardiopulmonary resuscitation
CVVHD	Continuous venovenous hemodiafiltration
CVVR	Continuous venovenous rewarming
CXR	Chest x-ray
ECG	Electrocardiogram
EMS	Emergency Medicine Services
IV	Intravenous
PRBC	Packed red blood cells
VA-ECMO	Venoarterial extracorporeal membrane oxygenation
VF	Ventricular fibrillation
VT	Ventricular tachycardia
VV-ECMO	Venovenous extracorporeal membrane oxygenation

C. Harvey (✉)
Department of Anesthesiology, University of Michigan Health System, Ann Arbor, MI, USA
e-mail: hcarrie@med.umich.edu

I.N. Co
Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA

Case Presentation

A 64 year old male with a history of hypertension and prostate cancer was found unresponsive by his wife around 0800 in their driveway in the middle of February in Toledo, OH. His wife had gone to bed before him the night prior and did not realize he was missing until approximately 9 h later. He was found on his side in a snow bank near the mailbox. Ambient temperature was approximately −2° Fahrenheit. He was unresponsive to painful stimuli. Emergency Medical Services (EMS) was called and the patient was transported to the nearest Level I Trauma center with full cardiac surgery capabilities. Transport vital signs included undetectable temperature by temporal probe, heart rate of 45 beats per minute, blood pressure of 60/palpation, and agonal respirations. En route, he received 2 L of warmed crystalloid and was intubated for airway protection. Vital signs on arrival to the Emergency Department were remarkable for heart rate of 20 beats per minute and blood pressure of 50/30. His axillary temperature was unable to be obtained. Foley catheter was placed and bladder temperature was 24 °C. Primary survey revealed clear breath sounds bilaterally, pupils 5 mm and fixed bilaterally, and Glascow Coma Scale (GCS) score of 3. His clothing was removed with no external signs of trauma. Cervical spine immobilization was maintained with a hard cervical collar applied by EMS prior to arrival. Electrocardiogram (ECG) was obtained with sample rhythm strip shown in

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_9

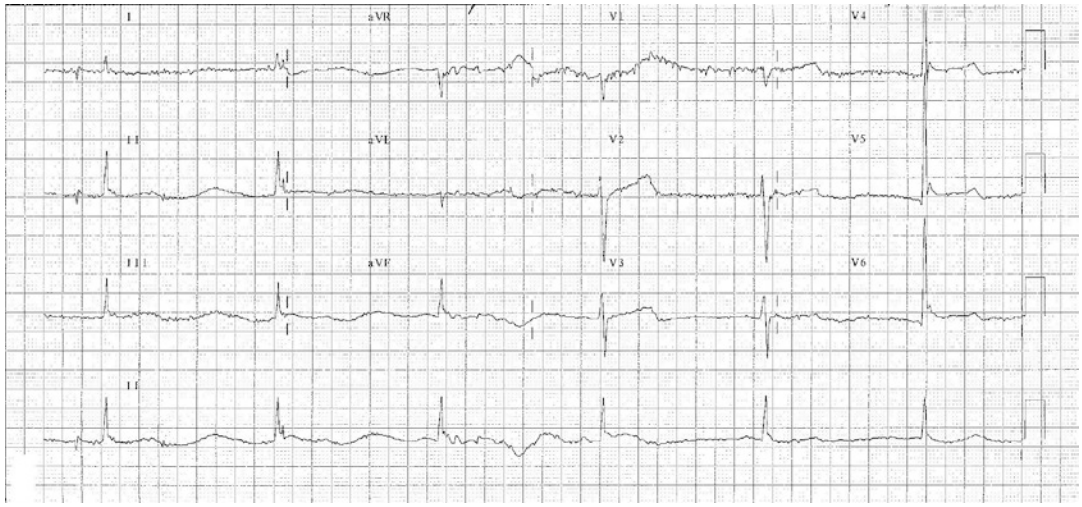


Fig. 9.1 Classic electrocardiogram findings in hypothermia. This EKG demonstrates three common findings in hypothermia, including bradycardia, shivering artifact, and J-waves (Image courtesy of lifeinthefastlane.com)

Fig. 9.1. Initial arterial blood gas on FiO_2 1.0 was as follows: pH 6.73, $paCO_2$ 50 mmHg, paO_2 259 mmHg, bicarbonate 4.8 mmol/L, base deficit −29.7, SaO_2 98%, potassium 5.2 mmol/L, and hemoglobin 13.6 mmol/L. Toxicology screen was negative. Active rewarming with warm humidified air, warm intravenous fluids, and warm fluid lavage of the stomach and bladder was initiated. After 30 min, pulse was unobtainable with ventricular fibrillation noted on telemetry. Cardiopulmonary resuscitation (CPR) was initiated and he was defibrillated once at 200 J. Ventricular fibrillation persisted and repeat core temperature was 25 °C.

Question What is the next best step in rewarming this patient?

Answer Initiate rewarming via extracorporeal cardiopulmonary resuscitation (ECPR)

When pulse and signs of life are absent in hypothermia, treatment with extracorporeal rewarming with extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass (CPB) is recommended. ECMO can be initiated in two modes: veno-venous (VV) or veno-arterial (VA) depending on the presence of innate and preserved cardiac function. This hospital has cardiac surgery available and consultation with the surgeon is necessary to determine which modality is best for the patient. Due to ongoing CPR, the decision was made to initiate VA ECMO with percutaneous venous and arterial cannulation at the bedside. The heater on the ECMO circuit was set to 37 °C and rewarming was started as soon as cannulation was complete. CPR continued until the patient was rewarmed to 30 °C, at which point defibrillation was again attempted with successful conversion to normal sinus rhythm. After 4 h of ECMO, his temperature and blood pressure had normalized. Repeat arterial blood gas on FiO_2 0.5 was: pH 7.38, $paCO_2$ 39 mmHg, paO_2 92 mmHg, bicarbonate 22.6 mmol/L, base deficit −2.2, SaO_2 99%, potassium 3.7 mmol/L, and hemoglobin 10.5 mmol/L. He received broad-spectrum antibiotics for high likelihood of aspiration and continued warm IV fluids due to presumed cold diuresis. After 24 h, the patient was awake and following commands with no evidence of acute respiratory distress syndrome. ECMO support was stopped and the patient was extubated the following day without incident. Neurologic exam was normal. He developed AKI requiring 3 days of dialysis, but had complete renal recovery. He was discharged home after 1 week with no functional or neurologic impairment.

Principles of Management

Diagnosis

Hypothermia is defined as a core body temperature of less than 35 °C (95 °F) and is classified by severity; mild, moderate, or severe (Table 9.1) [1]. Standard thermometers do not read below 34 °C, therefore, accurate measurement of core temperature should be obtained by esophageal, bladder, or rectal probes [2]. If core temperature cannot be readily measured, the Swiss staging system (Table 9.2) can be used to guide management based on clinical symptoms [3]. Additional risk factors for development of accidental hypothermia include extremes of age, ethanol abuse, and malnutrition [2].

With cold exposure, the body attempts to increase heat production by increasing circulating epinephrine, which leads to tachycardia, increased minute ventilation, peripheral vasoconstriction, and shivering [4]. If exposure persists, these compensatory mechanisms are overwhelmed, resulting in decreased metabolic demand, cessation of shivering, and ultimately death [3]. The effects of hypothermia by organ system are summarized in Table 9.3 and represent typical clinical findings.

Finally, any underlying medical conditions that may have contributed to development of hypothermia should be obtained by a focused history and physical exam. These include trauma, infection, toxic ingestion, endocrinopathy (e.g. myxedema coma), metabolic derangements, and stroke [1].

Table 9.1 Classification of hypothermia

Mild	35–32 °C
Moderate	<32 to 28 °C
Severe	<28 to 24 °C

Table 9.2 Swiss staging system of hypothermia

Stage	Clinical symptoms
I	Conscious, shivering
II	Altered mental status, no shivering
III	Unconscious, no shivering
IV	No vital signs[a]

Data from Brown et al. [3]
The estimated core temperature in stage I, II, and III correspond to mild, moderate, and severe hypothermia, respectively
[a]Loss of vital signs general occurs when the core temperature is below 24 °C

Patient Monitoring

Due to the dramatic hemodynamic changes that can occur with hypothermia and rewarming, all patients should be closely monitored with telemetry, continuous pulse oximetry, frequent blood pressure checks, and core temperature probe [3]. Pulse oximetry is often difficult to measure due to peripheral vasoconstriction and arterial blood gas may be the only way to assess oxygen content. There is also limited data to suggest that forehead pulse oximetry may be more accurate than fingertip devices in hypothermia [5]. The authors recommend pre-emptive placement of defibrillator pads if there is any concern for development of ventricular dysrhythmias. The prognostic value of end-tidal carbon dioxide monitoring in cardiac arrest secondary to accidental hypothermia has not been studied.

Adjunctive Testing

Once the diagnosis of hypothermia is confirmed by core temperature measurement, additional testing should include basic laboratory studies, toxicology screen, ECG, and chest radiograph (CXR). Typical laboratory findings are listed in Table 9.4. Slowed cardiac conduction manifests as a variety of ECG changes, the most common of which is the Osborne wave (Fig. 9.2), seen in approximately 80 % of hypothermic patients [7]. Baseline CXR is recommended due to the inherent risk of aspiration pneumonia in this patient population. CT head imaging in all hypothermic patients is not clearly indicated but should be considered if altered mental status is present despite temperature >32 °C or signs of head trauma are present [1]. Further workup should be pursued on an individual basis if associated

Table 9.3 Clinical findings in hypothermia

Organ system	Mild	Moderate	Severe
Neurologic	Apathy Confusion Ataxia	Dilated pupils Paradoxical undressing Stupor	Areflexia Coma
Cardiovascular	Tachycardia	Bradycardia Atrial fibrillation Hypotension	Ventricular dysrhythmias Asystole
Pulmonary	Tachypnea	Bradypnea	Pulmonary edema
Renal	High urine output	High urine output	Oliguria
Metabolic	Hyperglycemia No shivering Respiratory alkalosis	Variable blood glucose Shivering Mixed metabolic and respiratory acidosis	Hypoglycemia No shivering Mixed metabolic and respiratory acidosis

Data from Mulcahy and Watts [1]

trauma, infection, or other medical condition is suspected.

Rewarming

There are four general approaches to rewarming: passive, active external, active internal, and extracorporeal [8]. The best method depends on the severity of hypothermia and resources available to the provider, although there are no randomized, controlled trials regarding treatment approach. The average rates of rewarming for each method are listed in Table 9.5.

Passive rewarming is applicable to all hypothermic patients and should begin in the prehospital setting, with removal of wet clothing, application of blankets or foil insulator, and protection from the environment [9]. This method alone is only effective if shivering is present, otherwise, active rewarming is necessary.

Active external rewarming assumes circulation is intact and can return warmed blood to the core. Examples include warm blankets, radiant heat lamps, forced air device (e.g. Bair Hugger™), and warm water immersion [10].

Active internal rewarming includes warm humidified air (42 °C), warm intravenous (IV) fluids (42 °C), body cavity lavage (gastric, thoracic, peritoneal, bladder), intravascular devices, and peritoneal dialysis [1, 11]. If a commercial fluid warmer is not available, non-dextrose containing fluids can be warmed in a conventional microwave and then shaken to ensure uniform heating prior to infusion [12].

Table 9.4 Common laboratory derangements in hypothermia

Test	Typical result	Comments
Hematocrit	High	Due to hemoconcentration from cold dieresis
Potassium	High	Potassium > 12 mmol/L considered universally fatal [3, 6]
Creatinine	High	
Creatine kinase	High	Should be checked routinely as time down often unknown
PT/PTT	High	Due to coagulation cascade enzyme denaturation at colder temperature; reported values may be normal as blood heated prior to testing
Arterial blood gas	Variable	Recommend using uncorrected values [1]
Lactate	High	

Extracorporeal rewarming is the most effective method, with up to 6 °C/h rate of rewarming, but also the most invasive and resource intensive [13, 14]. Hemodialysis is generally the most readily available, but requires an adequate blood pressure to tolerate the procedure. Continuous arteriovenous rewarming (CAVR) or continuous venovenous rewarming (CVVR) can be achieved via percutaneous access and a countercurrent

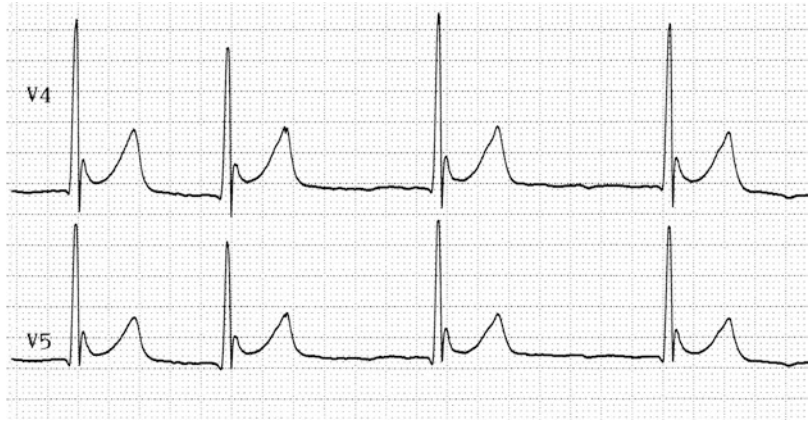


Fig. 9.2 Osborne wave. Osborne wave, or J wave, is frequently seen in hypothermia, although it is not pathognomonic for the condition. It is characterized by a positive deflection at the J point (negative in aVR and V1) and is usually seen best in the precordial leads. The height of the J wave generally corresponds to the degree of hypothermia [7] (Image courtesy of lifeinthefastlane.com)

Table 9.5 Rewarming techniques

Technique	Rate (°C/h)
Removal of wet clothing, insulation	0.5
Warm environment, warm oral fluids, active movement	2
Forced-air heating device, warm IV fluids	0.1–3.4
Peritoneal dialysis	1–3
Hemodialysis	2–4
Thoracic lavage	3
Venovenous ECMO	4
Venoarterial ECMO	6
Cardiopulmonary bypass	9

Data from Brown et al. [3]

heat exchanger (e.g. Belmont® Rapid Infuser) [15, 16]. Both methods utilize the patient's blood pressure to drive the blood through the device. CVVR by continuous venovenous hemodiafiltration (CVVHD) has also been shown to be effective in a case report [17]. Veno-arterial ECMO and CPB require the most resources and expertise, but bypasses the native circulation and can therefore be used in patients in cardiac arrest.

For patients with stable hemodynamic parameters, active rewarming with a forced air device, warm humidified air, and warm IV fluids is generally sufficient to achieve normothermia [18]. If these initial measures are not sufficient, a patient can undergo more invasive rewarming. Thoracic lavage and ECMO carry considerable risk and should be reserved for those patients with cardiac instability [11]. Expert opinion recommends ECMO if required resources are available [3, 11].

Hypothermia Without a Pulse

The 2010 American Heart Association (AHA) guidelines provide recommendations on advanced cardiac life support (ACLS) modifications in hypothermia, although these are based on expert opinion and case reports only (level of evidence C):

(a) If a patient does not have a pulse, ACLS should be immediately initiated, unless one of the following is present: valid Do Not Resuscitate order, patient is frozen solid, there is ice in the airway, core temperature is <10 °C, the patient was submerged for more than 1 h, or there is obvious lethal injury [1, 3, 19].

(b) If ventricular fibrillation (VF) or ventricular tachycardia (VT) is present, defibrillation should be attempted [20]. The number of attempts that should be made if VF or VT persists has not been established. The AHA guidelines state that it may be reasonable to perform further defibrillation (Class IIb recommendation), while most treatment algorithms recommend only one shock until the patient is rewarmed to 30 °C [1, 3].

(c) There is a theoretical concern for toxic accumulation of ACLS drugs due to reduction in drug metabolism in severe hypothermia. The AHA guidelines state that the safety of administration or withholding of medication is unclear, but that it is reasonable to consider administration of a vasopressor according to standard ACLS guidelines (Class IIb recommendation). Similarly,

expert opinion recommends up to three doses of epinephrine, with re-evaluation once the patient is rewarmed to 30 °C [3, 18].

In patients with return of spontaneous circulation after cardiac arrest, multi-organ failure should be anticipated and treated similar to any other critically ill patient.

Other Supportive Care

The majority of patients will present with hypovolemia secondary to cold diuresis and will consequently require aggressive fluid resuscitation. In one study of 38 severely hypothermic patients who received warmed IV fluids, the average volume load was 4.8 L [20]. Hyperglycemia (mild hypothermia) and hypoglycemia (severe hypothermia) are also common, thus, serum glucose level should be obtained and treated accordingly. Alcohol intoxication should prompt consideration of thiamine and alert the provider to the potential for alcohol withdrawal. It is recommended that broad-spectrum antibiotics be given to those patients at risk for associated infection, such as neonates, the elderly, and the homeless, as those with infection often respond poorly to rewarming [21]. There is no evidence for empiric steroids, unless there is high clinical suspicion for adrenal insufficiency as the cause of hypothermia [1].

Disposition

Those patients who presented with mild hypothermia that responded to rewarming methods, have a clear history of cold exposure, and have no evidence of an underlying disease or injury can be safely discharged home. All other patients require hospital admission, usually to the intensive care unit (ICU), for continued monitoring and supportive care.

In patients with cardiac arrest, the survival rate without neurologic impairment is higher in patients treated with ECMO (47–63%) as compared to those without (<37%) [3, 22, 23]. Therefore, patients with cardiac instability or arrest should be taken to the nearest facility capable of these interventions whenever possible. There are no guidelines regarding inter-hospital transfer and this decision should be made on a case-by-case basis with the consulting cardiac surgeon.

As mentioned above, there are certain circumstances in which CPR should not be initiated. Some experts also provide recommendations on when to stop an ongoing resuscitation. All experts agree that a patient should receive aggressive resuscitation including CPR until core temperature is at least 30 °C. A recent review article suggests that if asystole secondary to hypothermia persists despite rewarming to 32 °C, termination of CPR should be considered as the cardiac arrest is likely irreversible [3]. Similarly, markedly elevated potassium is considered a marker of hypoxia before hypothermia and therefore negatively associated with outcome. Most experts agree that resuscitation is futile if the potassium level is >12 mmol/L [3, 6]. The highest potassium level in patients that survived was 7.9 mmol/L in an adult [23] and 11.8 mmol/L in a child [24].

Pediatric Patients

In general, the management of pediatric accidental hypothermia is the same as adults. Pediatric Advanced Life Support (PALS) should be used in place of the ACLS algorithm. Pathophysiology and principles of rewarming are similar, with successful resuscitation via ECMO and CPB reported in the pediatric population. Hypothermia secondary to submersion is more common in pediatric patients and carries a worse prognosis due to associated asphyxia. The longest duration of submersion with full neurologic recovery was 66 min and used ECMO for rewarming [25]. Guidelines for cessation of resuscitation are similar to adults.

Evidence Contour

Withholding CPR

As stated above, the 2010 AHA guidelines recommend ACLS if a pulse cannot be palpated. However, it can be difficult to palpate a pulse in a

cold, stiff patient and many experts now advocate that CPR should be held if other signs of life are present, which include spontaneous respirations, spontaneous movement, or adequate cardiac activity is visualized on bedside echocardiography [1, 3]. Given the profound decrease in metabolic demand, it is hypothesized that any organized rhythm (i.e. bradycardia or adequate echocardiographic evidence of cardiac activity) provides enough perfusion to the body in hypothermia. Additionally, there is a long-standing belief that sudden movement of a hypothermic patient may irritate the myocardium and induce a dysrhythmia, such as in CPR [26]. This hypothesis has never been directly studied in humans. Thus, in a hypothermic patient with a pulse, spontaneous movement and/or respiration, or with bedside echo evidence of adequate cardiac activity, ACLS should be held. Otherwise, continuation of ACLS should be initiated per the AHA guidelines.

Degree of Rewarming in Cardiac Arrest

Given the neuroprotective effect of induced hypothermia following cardiac arrest, it is recommended that a patient with accidental hypothermia and cardiac arrest undergo therapeutic hypothermia for 24 h.

Timing of Extracorporeal Support

It remains unclear if aggressive extracorporeal rewarming with VA or VV ECMO should be initiated in patients without associated cardiac arrest. Some authors do recommend ECMO in patients with hemodynamic instability who do not respond to initial medical management [3]. Conversely, one prospective study of 38 patients with severe hypothermia without cardiac arrest found that 92 % of the patients could be successfully rewarmed to normothermia via forced air device, warmed inhaled oxygen, and warmed IV fluids within 10 h, including 14 of 17 patients with unstable hemodynamic parameters [20].

Selection of Extracorporeal Support

There are no randomized controlled trials comparing the various rewarming modalities. Expert opinion recommends that a hypothermic patient who has hemodynamic instability following accidental hypothermia should undergo extracorporeal support. VA ECMO is the mode of ECMO preferred as it provides cardiac support in addition to rewarming [27]. Selection of modality for rewarming will depend on resources available at the physician's institution.

Transcutaneous Pacing

Classic teaching in hypothermia has been to avoid any manipulation of the heart rate due to concern of inducing a ventricular dysrhythmia. However, a case report of two patients reported successful rewarming using CAVR with concomitant transcutaneous pacing [28]. In both cases, pacing was required to maintain blood pressure so that CAVR could be used. There were no reported dysrhythmias and both patients had normal neurologic outcomes. Still, it is hypothesized that bradycardia and hypotension in hypothermia may not be harmful due to the reduced metabolic requirements. A trial of transcutaneous pacing is reasonable but should not delay the initiation of rewarming.

Endovascular Rewarming

Successful rewarming of a patient using an endovascular device has been reported [29, 30]. This device is the same as those used for therapeutic hypothermia following cardiac arrest, which requires only percutaneous central venous access. This method had a rewarming rate of 3 °C/h, which is similar to thoracic lavage and may therefore be an efficient, less invasive alternative in facilities in which extracorporeal rewarming is not available. Similar to other active internal methods, the endovascular approach requires that the patient have a pulse.

Core Afterdrop

A commonly taught phenomenon of active external rewarming is core afterdrop, which is defined as continued core cooling despite rewarming. The prevailing theory was that peripheral vasodilation from external rewarming could lead to both distributive shock and return of peripheral acidemic blood to the core. This has largely been refuted by subsequent studies that argue that shock occurs secondary to inadequate fluid resuscitation in the context of cold diuresis. Studies in which active external rewarming is paired with accurate core temperature measurement with an esophageal probe and concurrent warm IV fluid administration do not report afterdrop [10, 20].

References

1. Mulcahy A, Watts M. Accidental hypothermia: an evidence-based approach. Emergency Medicine Practice, EBMedicine.net. 2009;11(1).
2. Auerbach PS. Wilderness medicine. 6th ed. Philadelphia: Mosby; 2012.
3. Brown DJA, Brugger H, Boyd J, Paal P. Accidental hypothermia. N Engl J Med. 2012;367(20):1930–8.
4. Sessler DI. Thermoregulatory defense mechanisms. Crit Care Med. 2009;37(7 Suppl):S203–10.
5. MacLeod DB, Cortinez LI, Keifer JC, Cameron D, Wright DR, White WD, et al. The desaturation response time of finger pulse oximeters during mild hypothermia. Anaesthesia. 2005;60(1):65–71.
6. Monika BM, Martin D, Balthasar E, Stefan L, Roland D, Lars E, et al. The Bernese Hypothermia Algorithm: a consensus paper on in-hospital decision-making and treatment of patients in hypothermic cardiac arrest at an alpine level 1 trauma centre. Injury. 2011;42(5):539–43.
7. Mustafa S, Shaikh N, Gowda RM, Khan IA. Electrocardiographic features of hypothermia. Cardiology. 2005;103(3):118–9.
8. Van der Ploeg G-J, Goslings JC, Walpoth BH, Bierens JJLM. Accidental hypothermia: rewarming treatments, complications and outcomes from one university medical centre. Resuscitation. 2010;81(11):1550–5.
9. Lundgren P, Henriksson O, Naredi P, Björnstig U. The effect of active warming in prehospital trauma care during road and air ambulance transportation – a clinical randomized trial. Scand J Trauma Resusc Emerg Med. 2011;19:59.
10. Kornberger E, Schwarz B, Lindner KH, Mair P. Forced air surface rewarming in patients with severe accidental hypothermia. Resuscitation. 1999;41(2):105–11.
11. Plaisier BR. Thoracic lavage in accidental hypothermia with cardiac arrest – report of a case and review of the literature. Resuscitation. 2005;66(1):99–104.
12. Lindhoff GA, MacG Palmer JH. An assessment of the thermal safety of microwave warming of crystalloid fluids. Anaesthesia. 2000;55(3):251–4.
13. Husby P, Andersen KS, Owen-Falkenberg A, Steien E, Solheim J. Accidental hypothermia with cardiac arrest: complete recovery after prolonged resuscitation and rewarming by extracorporeal circulation. Intensive Care Med. 1990;16(1):69–72.
14. Tiruvoipati R, Balasubramanian SK, Khoshbin E, Hadjinikolaou L, Sosnowski AW, Firmin RK. Successful use of venovenous extracorporeal membrane oxygenation in accidental hypothermic cardiac arrest. ASAIO. 2005;51(4):474–6.
15. Bräuer A, Wrigge H, Kersten J, Rathgeber J, Weyland W, Burchardi H. Severe accidental hypothermia: rewarming strategy using a veno-venous bypass system and a convective air warmer. Intensive Care Med. 1999;25(5):520–3.
16. Gentilello LM, Cobean RA, Offner PJ, Soderberg RW, Jurkovich GJ. Continuous arteriovenous rewarming: rapid reversal of hypothermia in critically ill patients. J Trauma. 1992;32(3):316–25; discussion 325–7.
17. Komatsu S, Shimomatsuya T, Kobuchi T, Nakajima M, Amaya H, Konishi S, et al. Severe accidental hypothermia successfully treated by rewarming strategy using continuous venovenous hemodiafiltration system. J Trauma. 2007;62(3):775–6.
18. Soar J, Perkins GD, Abbas G, Alfonzo A, Barelli A, Bierens JJLM, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 8. Cardiac arrest in special circumstances: Electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. Resuscitation. 2010;81(10):1400–33.
19. Vanden Hoek TL, Morrison LJ, Shuster M, Donnino M, Sinz E, Lavonas EJ, et al. Part 12: cardiac arrest in special situations: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122(18 Suppl 3):S829–61.
20. Röggla M, Frossard M, Wagner A, Holzer M, Bur A, Röggla G. Severe accidental hypothermia with or without hemodynamic instability: rewarming without the use of extracorporeal circulation. Wien Klin Wochenschr. 2002;114(8–9):315–20.
21. Delaney KA, Vassallo SU, Larkin GL, Goldfrank LR. Rewarming rates in urban patients with hypothermia: prediction of underlying infection. Acad Emerg Med. 2006;13(9):913–21.
22. Farstad M, Andersen KS, Koller ME, Grong K, Segadal L, Husby P. Rewarming from accidental hypothermia by extracorporeal circulation. A retrospective study. Eur J Cardiothorac Surg. 2001;20(1):58–64.
23. Walpoth BH, Walpoth-Aslan BN, Mattle HP, Radanov BP, Schroth G, Schaeffler L, et al. Outcome of

survivors of accidental deep hypothermia and circulatory arrest treated with extracorporeal blood warming. N Engl J Med. 1997;337(21):1500–5.
24. Dobson JA, Burgess JJ. Resuscitation of severe hypothermia by extracorporeal rewarming in a child. J Trauma. 1996;40(3):483–5.
25. Bolte RG, Black PG, Bowers RS, Thorne JK, Corneli HM. The use of extracorporeal rewarming in a child submerged for 66 minutes. JAMA. 1988;260(3):377–9.
26. Aslam AF, Aslam AK, Vasavada BC, Khan IA. Hypothermia: evaluation, electrocardiographic manifestations, and management. Am J Med. 2006;119(4):297–301.
27. Ruttmann E, Weissenbacher A, Ulmer H, Müller L, Höfer D, Kilo J, et al. Prolonged extracorporeal membrane oxygenation-assisted support provides improved survival in hypothermic patients with cardiocirculatory arrest. J Thorac Cardiovasc Surg. 2007;134(3):594–600.
28. Ho JD, Heegaard WG, Brunette DD. Successful transcutaneous pacing in 2 severely hypothermic patients. Ann Emerg Med. 2007;49(5):678–81.
29. Laniewicz M, Lyn-Kew K, Silbergleit R. Rapid endovascular warming for profound hypothermia. Ann Emerg Med. 2008;51(2):160–3.
30. Taylor EE, Carroll JP, Lovitt MA, Petrey LB, Gray PE, Mastropieri CJ, et al. Active intravascular rewarming for hypothermia associated with traumatic injury: early experience with a new technique. Proc Bayl Univ Med Cent. 2008;21:120–6.

Part II

Cardiac Disease

David A. Morrow and Benjamin A. Olenchock

Management of Cardiogenic Shock

10

Michael G. Silverman and Benjamin A. Olenchock

Case Presentation

A 60 year-old man with known coronary artery disease complained to coworkers of intermittent chest pain for several days prior to admission. On the morning of admission, he developed crushing chest pain at work and then lost consciousness. Coworkers phoned 911 and performed CPR. Emergency Medical Technicians arrived 15 min later, and reported an initial cardiac rhythm of ventricular fibrillation. He was successfully resuscitated, and a post arrest ECG was then performed (Fig. 10.1). The hospital's ST-elevation myocardial infarction (STEMI) team was activated from the field, and the patient was transported to the Emergency Department. Upon arrival he was hypoxemic and hypotensive. He was intubated prior to emergent coronary angiography. Coronary angiogram revealed a complete occlusion at the site of a prior proximal left anterior descending (LAD) coronary artery stent (Fig. 10.2) as well as a 70 % stenosis of the mid right coronary artery. After much difficulty, a wire was passed through the proximal LAD blockage and the artery was re-stented with restoration of normal flow. The patient remained hypotensive, requiring vasopressor support with norepinephrine to maintain a blood pressure of 80/60 mmHg.

Question What is the next step in management to optimize this patient's hemodynamics and treat his shock?

Answer Initiation of mechanical circulatory support.

For patients in cardiogenic shock (CS) from an acute myocardial infarction (MI) who continue to have hypotension and inadequate cardiac output despite revascularization and pharmacotherapy, it is reasonable to consider the use of mechanical circulatory support. This patient underwent placement of an intra-aortic balloon pump (IABP) and placement of a flow-directed pulmonary artery catheter for invasive hemodynamic monitoring. His initial hemodynamics were notable for an elevated pulmonary capillary wedge pressure (PCWP) of 29 mmHg and a low cardiac index of 1.5 L/min, confirming the diagnosis of CS. With placement of the IABP there was mild improvement in his hemodynamics, and he was admitted to the Cardiac Intensive Care Unit (CICU) for ongoing management. A transthoracic echocardiogram was obtained, which demonstrated a severely reduced ejection fraction of 15 % with anterior and anteroseptal wall akinesis and global hypokinesis of the remaining wall segments. Over the next 12–18 h, despite the IABP and increasing

M.G. Silverman • B.A. Olenchock (✉)
Division of Cardiovascular Medicine, Department of Medicine, The Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
e-mail: bolenchock@partners.org

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_10

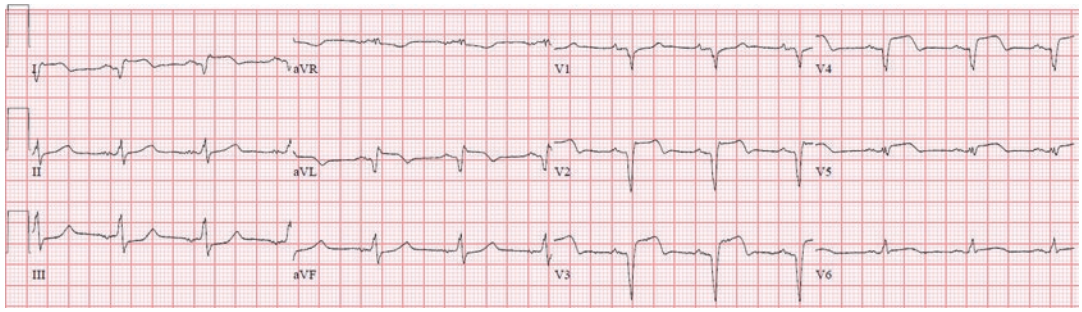


Fig. 10.1 Admission ECG

doses of pharmacologic support with vasopressors/inotropes, his hemodynamics remained marginal with worsening renal failure. In the setting of progressive shock, the patient was brought back to the catheterization lab to upgrade his mechanical circulatory support to a TandemHeart® percutaneous left ventricular assist device (LVAD). Although his filling pressures and cardiac output improved with the increased mechanical circulatory support, his overall clinical picture continued to deteriorate, and his family ultimately decided to transition his goals of care to comfort measures only. His mechanical and pharmacologic supports were withdrawn and he expired.

Principles of Management

Diagnosis

Cardiogenic shock (CS) occurs in roughly 8% of individuals who present with STEMI, while 80% of CS cases are due to an acute MI [1, 2]. The diagnosis of CS can be made based on the following established clinical criteria: (1) Hypotension – systolic blood pressure < 90 mmHg for more than 30 min or the need for vasopressor/mechanical support to achieve this blood pressure; (2) pulmonary edema or evidence of elevated left ventricular filling pressures; (3) evidence of end-organ hypoperfusion with at least one of the following: altered mental status, cold clammy skin or extremities, urine output less than 30 ml/h, or elevated serum lactate greater than 2 mmol/L [2–4]. The hemodynamic criteria for CS include a cardiac index (CI) of less than 2.2 L/min/m^2 as well as a PCWP greater than 18 mmHg [3]. Invasive hemodynamics with a pulmonary arterial catheter have been recommended and are often used to help confirm the diagnosis of CS and help guide management [3, 5, 6].

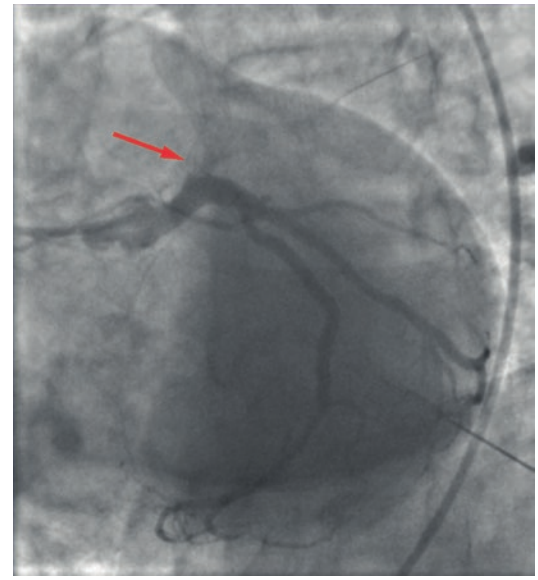


Fig. 10.2 Coronary angiogram, LAO Caudal view, demonstrating stent thrombosis of LAD (*arrow*)

Early Revascularization

The most significant advance in treatment of CS has been the implementation of early revascularization of the infarct-related artery, which has led to a significant decrease in mortality [4]. The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK)

trial randomized 302 patients with CS from an acute MI to undergo either emergency revascularization (152 patients) or initial medical stabilization (150 patients) [7]. Patients underwent revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Although the primary endpoint of 30 day all-cause mortality was not significantly different between the revascularization and the medical-therapy groups (46.7 % and 56.0 % respectively, p = 0.11), there was a significant difference between the respective groups at 6 months favoring the revascularization group (50.3 % versus 63.1 %, p = 0.027). The 13 % absolute risk reduction persisted at longer term follow up of 1 and 6 years [7, 8]. As a result of this trial, current guidelines give early revascularization with either PCI or CABG a class Ib recommendation [3, 5, 9].

Vasopressors/Inotropes

Vasopressors and inotropes are often required to treat patients with CS [2]. Dopamine and Norepinephrine are commonly used vasopressors that were compared in a randomized control trial including 1,679 patients with shock, of whom 280 were classified as having CS. The overall trial demonstrated an increased burden of arrhythmic events in the dopamine treated group compared with the norepinephrine treated group, although there was no difference in the primary endpoint of all-cause mortality. However, in the predefined subgroup of 280 patients with CS, norepinephrine was associated with a significantly lower death rate compared to dopamine [10]. As a result, the European Society of Cardiology (ESC) guidelines recommend norepinephrine over dopamine for medical management of hypotension from CS, and the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines caution that there may be, “excess hazard” associated with the use of dopamine in CS [3, 5].

Inotropic support with dobutamine increases heart rate, stroke volume, and cardiac output, while decreasing left ventricular filling pressures and systemic vascular resistance [11]. Since dobutamine can decrease blood pressure, it is often used in conjunction with vasopressors to improve cardiac output in the setting of CS from acute MI [2, 4]. Milrinone also increases heart rate, stroke volume, and cardiac output while decreasing left ventricular filling pressures and systemic vascular resistance. However, because milrinone can cause more significant vasodilation and hypotension, it is not a preferred inotropic agent in CS from acute MI [4]. Although inotropes and vasopressors can improve cardiac output and blood pressure, they also increase myocardial oxygen demand, increase risk for arrhythmias, and can impair microcirculation; therefore their use should be limited to the lowest dose for the shortest duration possible [2, 4, 11].

The goal of inotropic/vasopressor support is to maintain end-organ perfusion. In general, a target of a mean arterial pressure >=65 mmHg is reasonable. However, evidence of organ function (mental status, renal function, absence of biochemical evidence of organ ischemia) is more important.

Percutaneous Mechanical Circulatory Support

Given the limitations of pharmacologic support with vasopressors and inotropes to maintain adequate blood pressure and tissue perfusion, there has been much interest in the use of percutaneous mechanical circulatory support (MCS). There are now multiple device options, and over the past several years there has been a significant increase in the use of percutaneous MCS [12]. Currently available devices include the intra-aortic balloon pump (IABP), the Impella® micro-axial rotary pumps (2.5, CP, and 5.0), the TandemHeart® continuous flow centrifugal pump, and percutaneous venoarterial extracorporeal membrane oxygenation (v-a ECMO). These devices all require anticoagulation and have been associated with adverse events including limb ischemia, stroke, infection, and hemolysis. The ACC/AHA guidelines give a class IIa recommendation for

Table 10.1 Comparison of device characteristics and hemodynamics

	IABP	Impella® 2.5	Impella® CP	Impella® 5.0	TandemHeart™	ECMO
Hemodynamic support (L/min)	0.5–1.0	2.5	3.7–4.0	5.0	4.0	4.0–7.0
Pump mechanism	Pneumatic	Axial flow	Axial flow	Axial flow	Centrifugal	Centrifugal
Effect on LV pre-load	Reduced	Reduced	Reduced	Reduced	Reduced	Reduced
Effect on LV afterload	Reduced	Neutral	Neutral	Neutral	Increased	Increased

IABP intra-aortic balloon pump, *ECMO* extracorporeal membrane oxygenation, *LV* left ventricle

the use of IABP in patients with CS after STEMI, whereas the ACC/AHA and the ESC give a IIb recommendation for the use of alternative percutaneous left ventricular assist devices (LVADs) in patients with CS [3, 5, 9]. The different devices are discussed here and in Table 10.1.

Intra-Aortic Balloon Pump

The IABP is placed in the descending thoracic aorta via femoral arterial access. The pneumatic device inflates during diastole, raising diastolic blood pressure, and deflates during systole, lowering left ventricular afterload. Figure 10.3 demonstrates the typical IABP waveforms. The IABP can increase stroke volume and cardiac output up to 0.5–1.0 L/min [4]. The IABP is widely available and is the most commonly used mechanical support device, although it provides limited hemodynamic support [2].

Impella® 2.5, CP, and 5.0

The axial flow device is typically placed via femoral arterial access retrograde across the aortic valve and provides support by aspirating blood from the left ventricle and pumping it into the ascending aorta (Fig. 10.4). The 2.5 and CP can provide up to 2.5 L/min and 3.7–4.0 L/min of support, respectively, and both can be placed percutaneously. The 5.0 can provide up to 5.0 L/min of support, but requires a surgical cut down of either the femoral or axillary artery [2, 4].

TandemHeart®

This continuous flow centrifugal device is placed percutaneously and can deliver up to 4.0 L/min of circulatory support. The inflow cannula is placed in the left atrium via femoral venous access and transseptal puncture (Fig. 10.4). The outflow cannula is placed in the lower abdominal aorta or the iliac artery via femoral arterial access. Oxygenated blood is aspirated from the left atrium into the inflow cannula, and is then pumped into the lower abdominal aorta or the iliac artery via the outflow cannula. The TandemHeart® increases afterload because blood is pumped retrograde towards the left ventricle [2, 4].

Venoarterial Extracorporeal Membrane Oxygenation (v-a ECMO)

The percutaneous v-a ECMO system includes a centrifugal pump, heat exchanger, and oxygenator. The inflow cannula is placed in the right atrium via femoral venous access, and the outflow cannula is placed in the descending thoracic aorta via femoral arterial access. V-a ECMO can provide up to 4.0–7.0 L/min of biventricular circulatory support (bypasses both the right and left ventricle) as well as respiratory support. Limitations are that it does not directly unload the left ventricle, it increases afterload, and requires additional staffing [2, 4].

Temporary Surgical Mechanical Circulatory Support

When percutaneous MCS is inadequate, temporary surgical MCS with a surgically placed VAD can provide support for both the right and left ventricle with increased flow (up to 10 L/min) [13]. These surgically placed VADs can also be

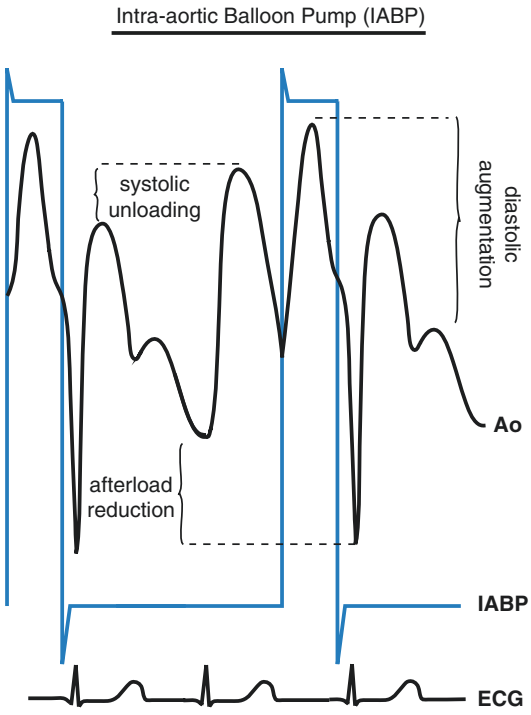


Fig. 10.3 Intra-aortic balloon pump (IABP) pressure waveforms, with IABP inflation set to 2:1. The IABP is inflated in early diastole at the timing of the dichrotic notch, augmenting blood pressure during diastole, thus augmenting coronary perfusion pressure. The balloon deflates in late diastole, lowering aortic end diastolic pressure, decreasing afterload on the left ventricle, and unloading the left ventricle during systole

left in place for weeks to months if necessary, providing a longer term temporary solution while waiting for recovery or as a bridge to transplant. The CentriMag® VAD (magnetically levitated rotor) and the Abiomed AB5000™ (pneumatically driven external ventricle) are two examples of temporary surgical MCS.

There are three outcomes of Mechanical Circulatory Support: (1) Recovery, i.e. improvement in hemodynamics such that MCS can be removed. (2) Implantation of a durable LVAD, or in rare circumstances, heart transplantation. (3) Progressive multisystem organ dysfunction and death. There are little data regarding the optimal patient selection and timing of percutaneous MCS, and we recommend that each patient be evaluated on an individualized basis with input from a multidimensional team.

Evidence Contour

There are several aspects in the management of patients with CS from an acute MI for which clinical equipoise still exists.

Multivessel Revascularization

Although the SHOCK trial demonstrated the benefit of early culprit vessel revascularization in CS from STEMI, the optimal revascularization strategy among individuals with multivessel disease remains unclear. A critical eye toward these data will note that the primary endpoint was not met and thus all additional analyses in the SHOCK trial were inherently exploratory. Nonetheless, since no other strategies have proven effective in CS, early revascularization remains the paradigm. Nearly ¾ of individuals who present with CS from acute MI have multivessel coronary disease [14]. Current ESC guidelines recommend multivessel PCI (class IIa) for individuals with CS who have multivessel coronary artery disease [9]. The ACC/AHA guidelines do not give an overt recommendation, but do recognize shock or severe heart failure as a clinical scenario in which acute revascularization of significant stenosis in noninfarct arteries can be justified [5]. The current evidence as it relates to patients with CS comes from nonrandomized studies looking at outcomes associated with multivessel PCI in CS from acute MI. Two of these trials demonstrated significant harm associated with multivessel PCI, one trial demonstrated significant benefit, and one demonstrated no change in mortality [14–17]. There is an ongoing prospective randomized control trial in Europe, the CULPRIT-SHOCK trial (Clinicaltrials.gov: NCT01927549), which seeks to answer this question.

Mechanical Circulatory Support

Although the use of percutaneous mechanical circulatory support is increasing, there are limited data supporting this practice. The Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II)

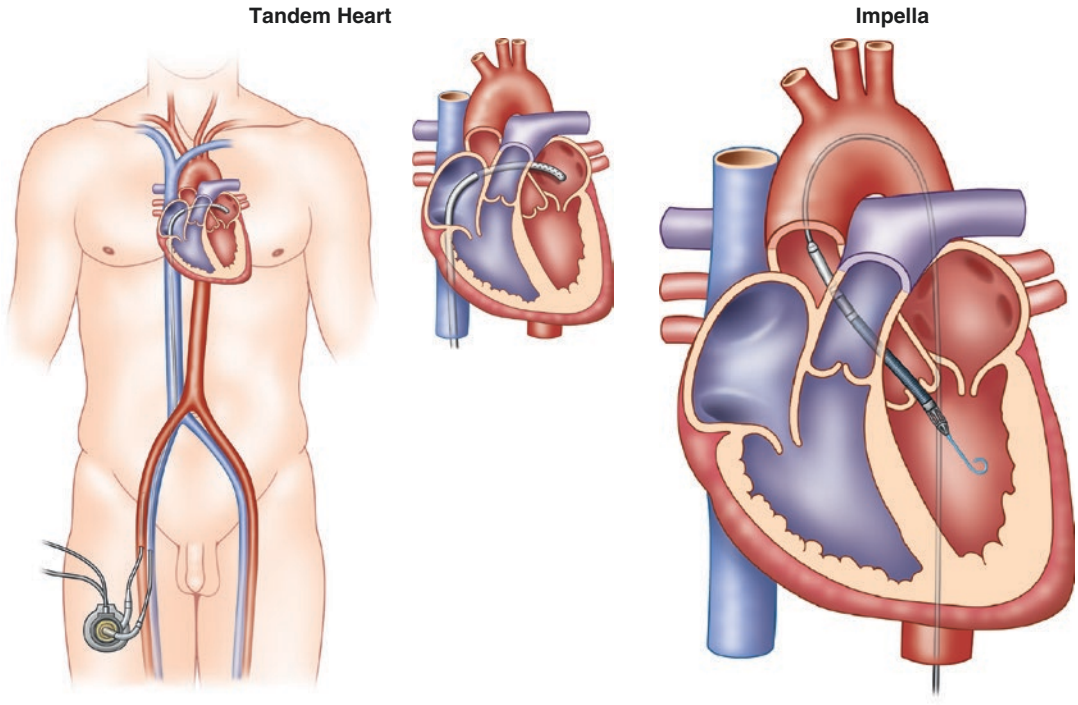


Fig. 10.4 Images of percutaneous LVADs: Tandem Heart® and Impella®

Trial randomized 600 patients with CS from acute MI to IABP versus no IABP. All participants were supposed to undergo early revascularization and receive guideline driven medical therapy. At 30 days there was no difference in the primary endpoint of all-cause mortality, and these results persisted at 12 month follow up [18, 19]. As a result, the ESC has recently changed their recommendation for IABP in CS from acute MI to a class III indication [9].

A meta-analysis was published in 2009 comparing the effect of percutaneous left ventricular assist devices (LVADs) versus IABP on hemodynamics and 30-day mortality [20]. The meta-analysis included two trials comparing the TandemHeart® to IABP and one comparing the Impella® to IABP. There was a significant improvement in hemodynamics (higher cardiac index, higher MAP, and lower PCWP) with percutaneous LVADs compared to IABP. However, there was no difference in 30 day mortality, and there was a significantly increased risk of bleeding in patients with percutaneous LVADs versus IABP. Importantly, the Impella® device used in the randomized control trial was the 2.5. It remains unclear if the higher flow Impella® devices (CP and 5.0) would be associated with lower mortality when compared to IABP. There are no randomized control trials that have evaluated the use of v-a ECMO in CS despite its widespread use for this indication.

Despite the lack of evidence, both the ACC/AHA and the ESC recommend consideration of mechanical circulatory support for patients with CS from acute MI [3, 5]. Given the high mortality rate associated with CS in acute MI, it is likely that the use of percutaneous mechanical circulatory support will continue notwithstanding the lack of hard outcome data. Additionally, these devices improve hemodynamic parameters and provide a critical bridge to further clinical decision making, including considerations of durable VADs, cardiac transplant evaluations, and goals of care discussions

with the patient's family and proxies. Future clinical trials are needed to better define patient selection, choice of mechanical support, and optimal timing for device placement.

References

1. Kolte D, Khera S, Aronow WS, Mujib M, Palaniswamy C, Sule S, Jain D, Gotsis W, Ahmed A, Frishman WH, Fonarow GC. Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. J Am Heart Assoc. 2014;3, e000590. doi:10.1161/JAHA.113.000590.
2. Thiele H, Ohman EM, Desch S, Eitel I, de Waha S. Management of cardiogenic shock. Eur Heart J. 2015;36(20):1223–30.
3. Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, Van't Hof A, Widimsky P, Zahger D. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569–619.
4. Werdan K, Gielen S, Ebelt H, Hochman JS. Mechanical circulatory support in cardiogenic shock. Eur Heart J. 2014;35:156–67.
5. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX. 2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:e362–425.
6. Reynolds HR, Hochman JS. Cardiogenic shock. Current concepts and improving outcomes. Circulation. 2008;117:686–97.
7. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med. 1999;341:625–34.
8. Hochman JS, Sleeper LA, Webb JG, Dzavik V, Buller CE, Aylward PE, Col J, White HD. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA. 2006;295:2511–5.
9. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A, Authors/Task Force m. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014;35:2541–619.
10. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362:779–89.
11. Nativi-Nicolau J, Selzman CH, Fang JC, Stehlik J. Pharmacologic therapies for acute cardiogenic shock. Curr Opin Cardiol. 2014;29:250–7.
12. Stretch R, Sauer CM, Yuh DD, Bonde P. National trends in the utilization of short term mechanical circulatory support: incidence, outcomes, and cost analysis. J Am Coll Cardiol. 2014;64:1407–15.
13. Westaby S, Anastasiadis K, Wieselthaler GM. Cardiogenic shock in ACS. Part 2: role of mechanical circulatory support. Nat Rev Cardiol. 2012;9:195–208.
14. Webb JG, Lowe AM, Sanborn TA, White HD, Sleeper LA, Carere RG, Buller CE, Wong SC, Boland J, Dzavik V, Porway M, Pate G, Bergman G, Hochman JS. Percutaneous coronary intervention for cardiogenic shock in the SHOCK trial. J Am Coll Cardiol. 2003;42:1380–6.
15. Zeymer U, Hochadel M, Thiele H, Andresen D, Schühlen H, Brachmann J, Elsässer A, Gitt A, Zahn R. Immediate multivessel percutaneous coronary intervention versus culprit lesion intervention in patients with acute myocardial infarction complicated by cardiogenic shock: results of the ALKK-PCI registry. EuroIntervention. 2015;11(3):280–5. doi:10.4244/EIJY4214M4208_4204.
16. Mylotte D, Morice M-C, Eltchaninoff H, Garot J, Louvard Y, Lefevre T, Garot P. Primary percutaneous coronary intervention in patients with acute myocardial infarction, resuscitated cardiac arrest, and cardiogenic shock. The role of primary multivessel revascularization. JACC Cardiovasc Interv. 2013;6:115–25.
17. Yang JH, Hahn JY, Song PS, Song YB, Choi SH, Choi JH, Lee SH, Jeong MH, Choi DJ, Kim YJ, Gwon HC. Percutaneous coronary intervention for nonculprit vessels in cardiogenic shock complicating

ST-segment elevation acute myocardial infarction. Crit Care Med. 2014;47:17–25.
18. Thiele H, Zeymer U, Neumann F-J, Ferenc M, Olbrich H-G, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Böhm M, Ebelt H, Schneider S, Schuler G, Werdan K. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med. 2012;367:1287–96.
19. Thiele H, Zeymer U, Neumann F-J, Ferenc M, Olbrich H-G, Hausleiter J, deWaha A, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Lauer B, Böhm M, Ebelt H, Schneider S, Werdan K, Schuler G. Intraaortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock. Final 12-month results of the randomised IntraAortic Balloon Pump in cardiogenic shock II (IABP-SHOCK II) Trial. Lancet. 2013;382:1638–45.
20. Cheng JM, den Uil CA, Hoeks SE, van der Ent M, Jewbali LSD, van Domburg RT, Serruys PW. Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. Eur Heart J. 2009;30:2102–8.

Management of Acute Heart Failure

11

Gregory T. Means and Jason N. Katz

Case Presentation

A 55 year old male with history of coronary artery disease (CAD), chronic systolic heart failure, and chronic obstructive pulmonary disease (COPD) presented to the hospital with 5 days of cough, exertional dyspnea, and fatigue. The patient's past medical history was notable for a remote history of emergent percutaneous coronary intervention for an acute anterior myocardial infarction complicated by systolic heart failure. His left ventricular ejection fraction (LVEF) was most recently noted to be 25 %. He had an implantable cardioverter-defibrillator (ICD) for primary prevention. He had not been seen by his cardiologist in several years.

Upon arrival to the emergency department, the patient was found to have a white blood cell count of 15 K, serum sodium of 123 mEq/L, creatinine of 1.6 mg/dL, and NT-pro-B-type natriuretic peptide level of 4800 ng/mL. An electrocardiogram showed sinus tachycardia with a chronic left bundle branch block. Initial cardiac enzymes were negative. He was short of breath and mildly hypoxic, with a room air oxygen saturation of 90 %. A chest x-ray showed a right-sided pleural effusion and some subtle interstitial infiltrates bilaterally. The patient was admitted to the inpatient hospitalist service, where he was treated with intravenous (IV) ceftriaxone for community-acquired pneumonia, bronchodilators and oral prednisone for a COPD flare, and given some IV fluids to treat acute renal failure presumed to have been pre-renal in etiology.

Over the course of several days, the patient became increasingly more short of breath. He was also noted to be more lethargic and less responsive. Laboratory analysis revealed an increasing serum creatinine and persistent hyponatremia. Serial electrocardiograms (ECGs) revealed no dynamic changes suggestive of ischemia, and cardiac biomarkers demonstrated a low-level elevation in cardiac-specific troponin. He was transferred to the intensive care unit (ICU) for management of hypotension and respiratory distress. There he was tachypneic and a blood gas analysis revealed new metabolic acidosis with associated respiratory compensation. His extremities were cool. A Foley catheter was placed with no return of urine.

The patient was placed on supplemental oxygen, given intermittent IV furosemide, and started

Electronic supplementary material The online version of this chapter (doi:10.1007/978-3-319-43341-7_11) contains supplementary material, which is available to authorized users.

G.T. Means (✉)
Cardiology, Department of Medicine, University of North Carolina, Chapel Hill, NC, USA
e-mail: gmeans@unch.unc.edu

J.N. Katz
Medicine, Mechanical Heart Program, Cardiac Intensive Care Unit, Cardiothoracic Intensive Care Unit & Critical Care Service, Cardiovascular Clinical Trials, University of North Carolina, Chapel Hill, NC, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_11

on a dopamine infusion for hypotension. Despite increasing dosages of dopamine and furosemide, the patient remained hypotensive and anuric. Given an increasing work of breathing, he was intubated and mechanically ventilated.

Question What complications should be considered when instituting invasive mechanical ventilation for this patient?

Answer Worsening acidosis and progressive cardiovascular collapse.

The decision to pursue intubation and mechanical ventilation for a patient with cardiogenic shock should not be taken lightly. While hemodynamic instability and refractory respiratory failure may make invasive ventilation unavoidable, complications should be anticipated. The patient was given benzodiazepines and neuromuscular blockade to facilitate intubation. Shortly after this, he became considerably more hypotensive. He was placed on the ventilator with an assist-control mode and 100 % FIO_2. His dopamine dosing was rapidly escalated and he was given an ampule of sodium bicarbonate. His respiratory rate was initially set at 15 breaths per minute, but when an ABG showed a pH of 7.2 and worsening metabolic acidosis, his ventilator rate was quickly increased to provide more appropriate respiratory compensation.

Given his unrelenting cardiogenic shock, an intra-aortic balloon pump (IABP) was placed emergently at the bedside. This resulted in an immediate improvement in the patient's mean arterial blood pressure. A dobutamine infusion was then added to his pharmacologic regimen for simultaneous afterload reduction and inotropic support. An hour after balloon counterpulsation and inotropic therapy, the patient's metabolic acidosis had completely resolved. A serum lactate – which was initially markedly elevated – had returned to the normal range. Serial ABGs demonstrated resolution of his systemic acidosis and improvement in his hypoxemia, thus allowing his ventilator to be weaned. Additionally, the patient's urine output improved over several hours, supported by high-dose parenteral diuretic therapy.

A swan-ganz catheter was placed in order to assess the patient's invasive hemodynamics, on his present level of circulatory support, and revealed a pulmonary artery (PA) pressure of 50/30, mean PA pressure of 37 mmHg, central venous pressure of 13 mmHg, Fick cardiac output of 6.2 L/min, Fick cardiac index of 2.8 L/min/m^2, and a mixed venous oxygen saturation of 68 %. Over the next 3 days, IABP support was gradually weaned from a 1:1 to 1:3 assist ratio to ensure the patient would maintain stable hemodynamics off mechanical support. Subsequently, the device was removed while systemic anticoagulation was held. On the fifth ICU day, the patient was successfully liberated from mechanical ventilation and transitioned to a nasal cannula. Unfortunately, multiple attempts to wean his dobutamine infusion resulted in hemodynamic perturbation and worsening renal dysfunction. He was ultimately transferred out of the ICU for ongoing care, with plans to consider more durable advanced heart failure therapies including home inotropic support, implantable left ventricular assist device, or heart transplantation.

Principles of Management

Diagnosis

Acute Heart Failure (AHF) is a complex clinical syndrome which results from any structural or functional impairment of ventricular filling or ejection of blood. AHF may occur either due to heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF). While HFrEF is simply characterized by decreased cardiac contractility, HFpEF is commonly a result of diastolic dysfunction represented by impaired left ventricular relaxation and/or increased left ventricular filling pressures. HFpEF is often seen in association with comorbidities such as chronic hypertension and diabetes, and its prevalence increases with age. Diagnosis of HFpEF is aided

by echocardiography which can show abnormal trans-mitral valve and/or pulmonary vein flow hemodynamics or impaired mitral annular relaxation.

Dietary indiscretions, medication non-compliance, uncontrolled hypertension, arrhythmias, infections, catecholamine surge, valvular dysfunction, and ischemia are just a few of the known triggers of acute decompensation. Elevated cardiac filling pressures classically produce symptoms of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Patients may also have evidence of peripheral or pulmonary edema. Potential etiologies for AHF include, but are not limited to, myocardial ischemia/infarction, acute on chronic HFpEF or HFrEF, acute or fulminant myocarditis, myocardial contusion, septic shock with myocardial depression, acute valvular heart disease, cardiac arrhythmias, drug-related cardiotoxicity, profound metabolic derangements, peripartum cardiomyopathy, or stress-induced cardiomyopathy [1, 2].

A thorough history and physical examination are necessary to determine a cause of acute heart failure in order to develop a comprehensive diagnostic and management plan for each affected patient. Complementary studies include laboratory evaluation to risk-stratify the individual with AHF (Fig. 11.1), ECG, and imaging modalities (including echocardiography [Video 11.1] and chest radiography). An ischemic evaluation with myocardial perfusion imaging or cardiac catheterization can often be helpful in determining whether ischemia is contributing to cardiac decompensation. Interrogating a patient's ICD, if present, can also help to elucidate if arrhythmias may be precipitating or preceding heart failure.

Diuretic Therapy

Fluid removal through intravenous diuresis is an essential management strategy for AHF patients that present with congestion (2013 American College of Cardiology (ACC)/American Heart Association (AHA) Heart Failure Management Guidelines Class I, Level of Evidence (LOE) B). If unable to achieve effective diuresis with escalating doses of loop diuretics, a second diuretic agent (e.g. metolazone, chlorothiazide) may be added (ACC/AHA Class IIA, LOE B). Use of a continuous diuretic infusion has not been shown to be more effective than bolus therapy but may be considered for ease of dosing. Potential diuretic-related side effects that can negatively impact patient outcomes include electrolyte disturbances (hyponatremia, hypokalemia, and hypomagnesemia), metabolic alkalosis, ototoxicity, hyperuricemia, and hypotension. It is important to serially monitor clinical signs, daily weights, urine output, and electrolytes during treatment to determine the adequacy of decongestion and to avoid the untoward consequences of volume contraction (ACC/AHA Class I, LOE C). Under-treatment is common among hospitalized patients as seen in the Acute Decompensated Heart Failure National Registry (ADHERE), and failure to achieve adequate volume removal can be considered an important risk factor for hospital readmission [3].

Intravenous Vasodilators

Nitrates, such as nitroglycerin (10–350 mcg/minute) and sodium nitroprusside (5–300 mcg/minute) promote smooth muscle relaxation, resulting in decongestion and reduced cardiac filling pressures. Unpredictable patient responses to therapy and the risk for associated hypotension, however, mandate careful hemodynamic monitoring during treatment and the consideration of ICU admission for all individuals receiving parenteral nitrates. Nitroprusside has been shown to improve cardiac output, maintain adequate mean arterial pressures, and improve clinical outcomes in patients with acutely decompensated heart failure [4]. Nitroglycerin has a relatively short half-life and rapid onset of action. In AHF with significant pulmonary congestion, nitroglycerin can improve arterial oxygenation and hemodynamics through venous vasodilation. Duration of vasodilator therapy may be limited by hypotension, drug tachyphylaxis (nitroglycerin), and thiocyanate toxicity (nitroprusside).

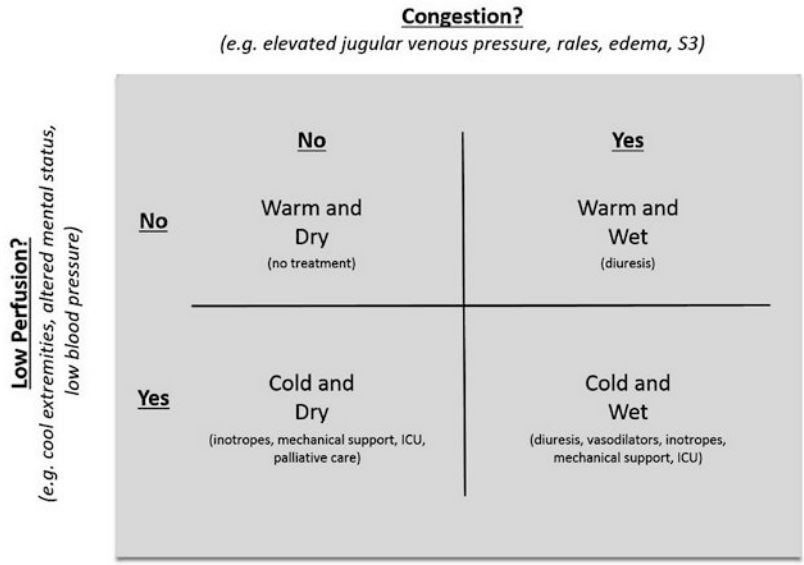


Fig. 11.1 Acute decompensated heart failure patient classification (Adapted from Nohria and Lewis [20], with permission)

Emergent Mechanical Circulatory Support

In situations of hemodynamic instability and reduced cardiac output that is refractory to pharmacologic intervention, mechanical circulatory support may be needed to reduce afterload and augment diastolic perfusion pressure (see Chap. 10, Management of Cardiogenic Shock).

Evidence Contour

Pulmonary Artery (PA) Catheters

PA catheterization allows direct measurement of cardiac filling pressures, pulmonary arterial pressures, cardiac output, and calculation of both systemic and pulmonary vascular resistance. Widespread adoption of this technology in all critically ill patients was tempered by findings which suggested an increased cost, mortality, and length of stay [5]. Specific to the heart failure population, the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial was conducted to assess the role of PA catheter-guided therapy in hospitalized individuals with AHF. Similar to other studies, there was no suggestion that PA catheters improved mortality; it did, however, result in increased adverse events such as infection, pulmonary infarction, and bleeding [6]. It has widely been assumed that the morbidity of PA catheterization is primarily related to operator experience [7]. Despite their unproven mortality benefit, PA catheters remain a viable diagnostic tool particularly in challenging cases of AHF. The 2013 ACC/AHA guidelines for heart failure management recommend PA catheter use in cases of refractory hypotension, difficult volume status determination, renal function deterioration despite therapy, and to guide inotrope therapy titration (Class IIA (LOE C)) [2].

Inotropic Agents

Management of AHF is often limited by low blood pressure and systemic hypoperfusion. Inotropic agents (e.g. dopamine, dobutamine, and milrinone) can augment contractility and chronotropy, resulting in increased stroke volume and cardiac output (Table 11.1). These goals are often accomplished with a tradeoff of increasing myocardial oxygen demand, increased heart rate, and increased risk for tachyarrhythmias. Improved hemodynamic response, however, has

Table 11.1 Intravenous inotropic agents used in management of HF

Adrenergic agonists	Typical infusion dose (mcg/kg/min)	CO	HR	SVR	PVR	Possible adverse effects
Dopamine	5–10	↑	↑	↔	↔	Headache, nausea, arrhythmia
	10–15	↑	↑	↑	↔	
Dobutamine	2.5–5	↑	↑	↓	↔	Hyper- or hypotension, headache, arrhythmia, hypersensitivity
	5–20	↑	↑	↔	↔	
PDE inhibitor						
Milrinone	0.125–0.75	↑	↑	↓	↓	Hypotension, arrhythmia

Adapted from Yancy et al. [21]. With permission from Wolters Kluwer Health, Inc.
Abbreviations: *CO* cardiac output, *HR* heart rate, *PDE* phosphodiesterase, *PVR* pulmonary vascular resistance, *SVR* systemic vascular resistance

not always translated into improved patient survival. The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) investigators and data from the ADHERE registry showed that these agents may actually increase mortality when compared to standard diuretic or vasodilator therapies in AHF patients [8–10]. Therefore, inotropes are best used for short periods in the ICU in situations suggestive of emerging cardiogenic shock and end-organ failure. Inotropes can also be employed as a bridge to other definitive management strategies or used for palliative care purposes.

Diuretic Dosing – Intermittent Versus Continuous

Patients presenting with AHF and congestion should receive intravenous loop diuretics as progressive bowel wall edema may limit oral diuretic absorption and efficacy. Less well understood is the differences between adopting a continuous infusion or interval dosing diuretic strategy. The Diuretic Optimization Strategies Evaluation (DOSE) trial compared intermittent IV diuresis to a continuous infusion strategy, and found them to have a similar effect on subjective symptoms and renal function [11]. A more recent meta-analysis evaluating ten randomized control trials similarly found no difference in resulting renal function, electrolyte disturbances, length of hospitalization, or cardiac or all-cause mortality between these two approaches [12].

Ultrafiltration

The use of ultrafiltration (UF) to enhance cardiac decongestion has been examined extensively as an adjunct to diuresis. UF can remove excess fluid and small solutes via a dialysis circuit. Initial small randomized controlled trials have supported the utility and safety of UF when compared to traditional loop diuretics [13]. A follow-up trial, the Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) study, found that UF achieved greater net weight loss and reduced re-hospitalization rates at 90 days [14]. However, subsequent studies have not consistently corroborated these findings [15], and have suggested a potentially greater adverse-event rate and cost-of-care among UF-treated individuals. The financial implications and potential morbidity of UF must therefore be weighed carefully in any decision to initiate therapy. The most recent AHA/ACC guidelines maintain a Class IIA (LOE B) recommendation for UF in patients refractory to standard diuresis.

Nesiritide

Nesiritide, a form of synthetic B-type natriuretic peptide (BNP), is a potent vasodilating agent that may reduce cardiac filling pressures and improve ventricular unloading. Reported side-effects of this drug have included hypotension and acute renal failure. In a large, multicenter, randomized trial, the Acute Study of the Clinical Effectiveness of

Nesiritide in Decompensated Heart Failure (ASCEND-HF) study found that use of this drug did not improve patient survival, reduce readmission rates, or augment end-organ function when compared to placebo [16]. Therefore, while still available, its routine use has been discouraged, and it is often only considered for patients with substantially elevated systemic vascular resistance in whom intensive vasodilation may be advantageous.

Renal-Dose Dopamine

At lower doses (1–2.5 mg/kg/min), dopamine predominantly activates renal dopamine receptors, with little systemic adrenergic stimulation. Diuresis in AHF is often limited by deteriorating renal function, hypokalemia, and hyponatremia. Therefore, a low-dose dopamine strategy has been considered a possible treatment for diuretic-refractory patients. In 2010, results of the Dopamine in Acute Decompensated Heart Failure (DAD-HF) trial showed that low-dose furosemide plus low-dose dopamine resulted in less hypokalemia and less renal insufficiency, but with similar 60-day mortality, rates of readmission, and hospital lengths-of-stay [17]. A follow-up investigation – the Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) trial – was stopped prematurely after finding that the dopamine arm had a greater incidence of tachycardia with no demonstrable effect on the primary endpoint of all-cause mortality or re-hospitalization [18]. More recently, the Renal Optimization Strategies Evaluation (ROSE-AHF) trial similarly evaluated the use of low-dose dopamine (2 mcg/kg/min) in patients hospitalized with AHF [19]. In this case, low-dose dopamine failed to improve urine output or renal function. Despite limited supporting evidence in AHF, however, low-dose dopamine continues to be used clinically and carries a Class IIB (LOE B) designation.

References

1. Hollenberg SM, Kavinsky CJ, Parrillo JE. Cardiogenic shock. Ann Intern Med. 1999;131:47.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA Guideline for the Management of Heart Failure. Circulation. 2013;128:e240–327.
3. Fonarow GC, ADHERE Scientific Advisory Committee. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. Rev Cardiovasc Med. 2003;4 Suppl 7:S21–30.
4. Mullens W, Abrahams Z, Francis GS, Skouri HN, Starling RC, Young JB, Taylor DO, Tang WH. Sodium nitroprusside for advanced low-output heart failure. J Am Coll Cardiol. 2008;52(3):200–7.
5. Connors Jr AF, Speroff T, Dawson NV, Thomas C, Harrell Jr FE, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson Jr WJ, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA. The effectiveness of right heart catheterization in the initial care of critically ill patients SUPPORT Investigators. JAMA. 1996;276(11):889–97.
6. Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, Stevenson LW, Francis GS, Leier CV, Miller LW, ESCAPE Investigators and ESCAPE Study Coordinators. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA. 2005;293:572–80.
7. Iberti TJ, Fischer EP, Leibowitz AB, Panacek EA, Silverstein JH, Albertson TE. A multicenter study of physicians' knowledge of the pulmonary artery catheter. Pulmonary Artery Catheter Study Group. JAMA. 1990;264:2928–32.
8. Cuffe MS, Califf RM, Adams Jr KF, Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, Silver MA, Gheorghiade M, Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA. 2002;287(12):1541–7.
9. Abraham WT, Adams KF, Fonarow GC, Costanzo MR, Berkowitz RL, LeJemtel TH, Cheng ML, Wynne J, ADHERE Scientific Advisory Committee and Investigators, ADHERE Study Group. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Am Coll Cardiol. 2005;46(1):57–64.
10. Stevenson LW. Clinical use of inotropic therapy for heart failure: looking backward or forward? Part II: chronic inotropic therapy. Circulation. 2003;108(4):492–7.
11. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH,

Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM, NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9):797–805.
12. Wu M, Chang NC, Su CL, Hsu YH, Chen TW, Lin YF, Wu CH, Tam KW. Loop diuretic strategies in patients with acute decompensated heart failure: a meta-analysis of randomized controlled trials. J Crit Care. 2014;29(1):2–9.
13. Bart BA, Boyle A, Bank AJ, Anand I, Olivari MT, Kraemer M, Mackedanz S, Sobotka PA, Schollmeyer M, Goldsmith SR. Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial. J Am Coll Cardiol. 2005;46(11):2043–6.
14. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, Jaski BE, Fang JC, Feller ED, Haas GJ, Anderson AS, Schollmeyer MP, Sobotka PA, UNLOAD Trial Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol. 2007;49(6):675–83.
15. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E, Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med. 2012;367(24):2296–304.
16. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med. 2011;365(1):32–43.
17. Giamouzis G, Butler J, Starling RC, Karayannis G, Nastas J, Parisis C, Rovithis D, Economou D, Savvatis K, Kirlidis T, Tsaknakis T, Skoularigis J, Westermann D, Tschöpe C, Triposkiadis F. Impact of dopamine infusion on renal function in hospitalized heart failure patients: results of the Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial. J Card Fail. 2010;16(12):922–30.
18. Giamouzis G, et al. The dopamine in acute decompensated heart failure II trial. Late Breaking Trials 2, Heart Failure 2013; abstract 285. http://clinicaltrials.gov/show/NCT01060293.
19. Chen HH, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ, Goldsmith SR, Bart BA, Bull DA, Stehlik J, LeWinter MM, Konstam MA, Huggins GS, Rouleau JL, O'Meara E, Tang WH, Starling RC, Butler J, Deswal A, Felker GM, O'Connor CM, Bonita RE, Margulies KB, Cappola TP, Ofili EO, Mann DL, Dávila-Román VG, McNulty SE, Borlaug BA, Velazquez EJ, Lee KL, Shah MR, Hernandez AF, Braunwald E, Redfield MM, NHLBI Heart Failure Clinical Research Network. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. JAMA. 2013;310(23):2533–43.
20. Nohria A, Lewis E, Stevenson LW. Medical management of advanced heart failure. JAMA. 2002;287(5):628–40.
21. Yancy CW, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240–327.

Management of Acute Coronary Syndrome

12

Arman Qamar and Benjamin M. Scirica

Case Presentation

A 65 year-old man with history of hypertension, hypercholesterolemia and diabetes mellitus presented with two hours of severe substernal chest pain radiating to left arm in addition to diaphoresis and nausea. At the time of presentation to the emergency department, his electrocardiogram showed inferior and posterior ST-segment elevations (Fig. 12.1) and serum troponin T was 0.30 ng/mL (reference range <0.01 ng/mL). He was treated with aspirin, intravenous nitroglycerin, ticareglor, metoprolol, atorvastatin, and heparin.

Question What approach should guide this patient's further management?

Answer All patients with acute coronary syndrome with ST-segment elevation myocardial infarction (STEMI) should undergo emergent reperfusion therapy with primary percutaneous coronary intervention (PCI) or fibrinolysis.

This patient underwent emergent invasive coronary angiography, which revealed a discrete 90 % lesion in the proximal right coronary artery. He was treated by primary PCI with drug-eluting stent placement. The patient had an uneventful hospital course and was discharged on aspirin, ticagrelor, metoprolol, atorvastatin and lisinopril.

Principles of Management

Diagnosis

Acute coronary syndrome (ACS) refers to spectrum of conditions associated with acute myocardial ischemia and/or infarction that are most frequently due to sudden decrease in coronary blood flow from an atherothrombotic obstruction. The first step in the management of patients with ACS is prompt recognition, as beneficial effects of therapy are greater when started soon after presentation, and steadily decline in the hours that follow the first signs of myocardial injury. The most common symptom that prompts the diagnostic evaluation of ACS is chest discomfort. Classification of patients presenting with ACS is based on electrocardiogram. Patients with persistent ST-segment elevation are deemed as having ST-segment elevation ACS (STE-ACS) due to the presumed acute complete coronary occlusion and are candidates for immediate reperfusion therapy with either primary angioplasty or fibrinolysis. Absence of ST-segment elevation in a patient with ACS suggests non-ST segment elevation ACS (NSTE-ACS) (Fig. 12.2), which is further classified on the basis of biomarkers of myocardial

A. Qamar • B.M. Scirica (✉)
Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
e-mail: bscirica@partners.org

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_12

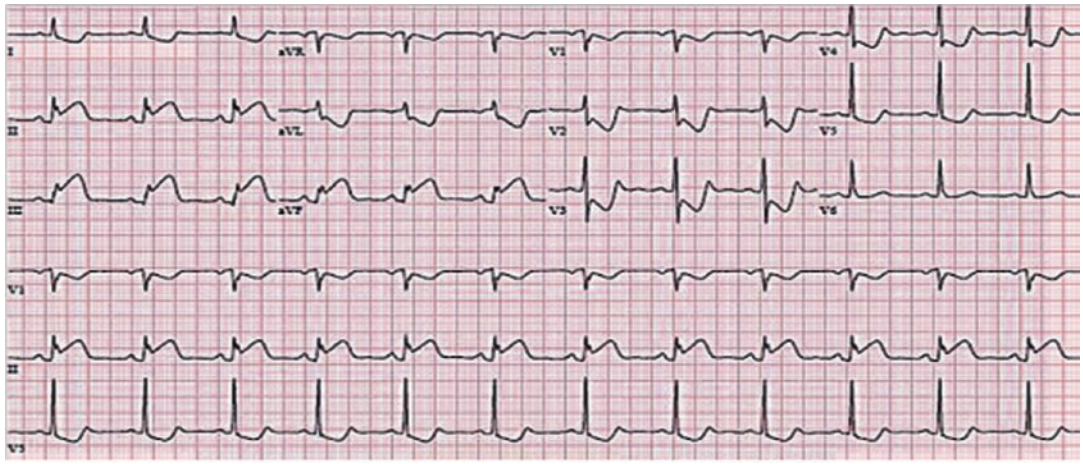


Fig. 12.1 EKG demonstrating inferior and posterior ST-segment elevations in a patient with STEMI

necrosis. In an appropriate clinical setting, if the biomarkers are elevated the patient is classified as having a non-ST segment elevation MI (NSTEMI), otherwise, without elevated biomarkers; the patient should be diagnosed with unstable angina (UA) (Fig. 12.3). The primary diagnostic biomarkers of ACS are Troponin T and Troponin I. With contemporary troponin assays, CK-MB and myoglobin are less useful for diagnosis of ACS. However, patients with end-stage-renal disease and no clinical evidence of ACS could have chronically elevated troponins. With conventional assays, this is more common with cardiac troponin T than cardiac troponin I. In the diagnosis of ACS, cardiac troponin values must manifest an acute pattern consistent with the ischemic symptoms and electrocardiographic changes.

ECG abnormalities and elevated biomarkers in isolation are insufficient to make the diagnosis of ACS, and must be interpreted in an appropriate clinical context. MI must be discriminated from other acute and chronic causes of myocardial injury, such as pulmonary embolism, severe sepsis, and end-stage renal disease, which occur commonly in the intensive care setting. Moreover, MI may be further classified into those caused by acute atherothrombotic coronary events (Type 1 MI) and those caused by supply–demand mismatch, as is seen in instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between oxygen demand and supply, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy (Type 2 MI). We typically reserve the term acute coronary syndrome for patients with acute atherothrombosis (Type 1 MI).

Once the diagnosis of STEMI, NSTEMI or unstable angina is made, the acute management of the patient involves achievement of several goals followed by initiation of therapy that may improve the long-term prognosis.

Initial Assessment and Early Risk Stratification

Clinical assessment of a patient with ACS should begin as soon as the patient arrives in the emergency department and continues in hospital wards or the intensive care units. Initial assessment includes evaluation for hemodynamic stability and early risk stratification. A 12-lead ECG should be obtained in all patients with suspected ACS within 10 min after first medical contact and immediately read by an experienced physician.

Early risk stratification in patients with ACS is critical to identify those at higher risk of adverse

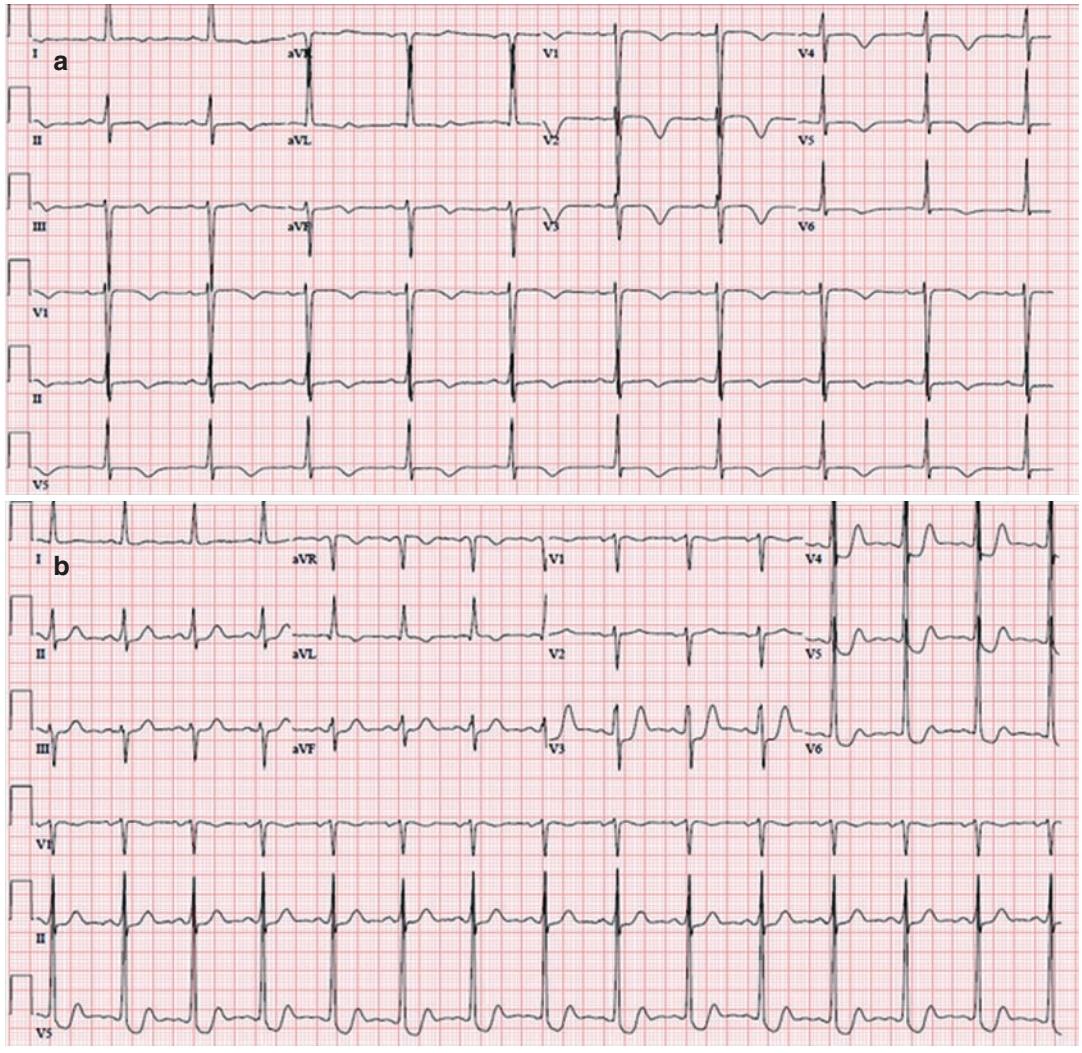


Fig. 12.2 EKG demonstrating diffuse T wave inversion **(a)** and ST depression in patients with NSTE-ACS **(b)**

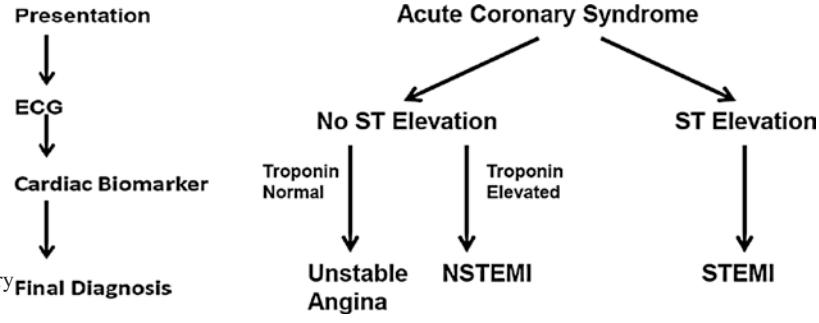


Fig. 12.3 Acute coronary syndromes

cardiac events and may benefit from a more aggressive therapeutic approach [1–4]. Analyses from several large clinical trials have established a number of predictors of adverse outcomes among patients with STEMI, NSTEMI and unstable angina. However, with need for emergent reperfusion therapy through primary angioplasty or fibrinolysis in patients with STEMI, their clinical utility in early therapeutic decision-making is less relevant to STEMI patients. Some of the early predictors of poor outcome from STEMI include age, tachycardia, low blood pressure, Killip class (Table 12.1), time to reperfusion, diabetes mellitus, anterior infarct location, smoking status, renal function and elevated biomarker. Examples of validated risk score include the TIMI risk score for STEMI [5] and NSTEMI/UA [6] and the GRACE Risk Score [7].

Initial Medical Therapy

Patients with STEMI, NSTEMI and unstable angina are treated with similar medical regimens, with the exception of fibrinolysis, which should be limited to STEMI patients. The timing of initiation of medication may vary between STEMI and NSTEMI/UA.

Anti-ischemic Therapy

Oxygen Supplemental oxygen should be administered to patients with ACS with arterial oxygen saturation less than 90%, respiratory distress, cyanosis or other higher risk features of hypoxemia. The value of supplemental oxygen therapy in ACS patients without hypoxia is unclear, as several studies have suggested that supplemental oxygen in normoxic patients with ACS may increase myocardial injury and mortality [8, 9].

Table 12.1 Killip classification of acute myocardial infarction

Class I	No evidence of heart failure
Class II	Findings consistent with mild to moderate heart failure (S3 gallop, lung rales less than one-half way up the posterior lung fields or jugular venous distension)
Class III	Overt pulmonary edema
Class IV	Cardiogenic shock

Nitrates Patients with continuing chest pain should be initially treated with sublingual nitroglycerin (0.3–0.4 mg) every 5 min for up to three doses. If ischemic pain persists, intravenous nitroglycerin should be considered if not contraindicated. Nitrates should not be administered to patients with severe aortic stenosis, or patients who received a phosphodiesterase-5 inhibitor, and should be cautiously used in patients with suspected right ventricular infarction due to their dependence on pre-load [10].

Morphine In patients with ACS, it is reasonable to administer intravenous morphine for analgesia if the patient has continued chest pain despite maximally tolerated anti-ischemic medications. NSAIDS (except aspirin) in patients with ACS are associated with increased risk of major adverse cardiac events; therefore, its use in ACS patients is not recommended [11].

Beta-Adrenergic Blockers In patients with ACS beta-blockers decrease myocardial ischemia and frequency of ventricular arrhythmias and increase long term survival [12]. Oral beta-blocker therapy should be initiated within the first 24 h in patients who do not have signs of HF, evidence of low-output state, increased risk for cardiogenic shock (>70 years of age, systolic blood pressure <120 mmHg, heart rate >110 bpm or heart rate <60 bpm) or other contraindications to beta-blockade (e.g., PR interval >0.24 s, second- or third-degree heart block without a cardiac pacemaker, active asthma, or documented reactive airway disease). Beta-blockers should be titrated to decrease the heart rate to less than 70/min while maintaining a systolic blood pressure above 120 mmHg. A non-dihydropyridine calcium channel blocker (CCB) (e.g., verapamil or diltiazem) should be considered in patients in whom beta-blockers are contraindicated.

Statin therapy High-intensity statin (atorvastatin 80 mg or rosuvastatin 40 mg) should be started or continued in all patients with ACS

Recommendations	Dosing and Special Considerations	COR	LOE
Aspirin			
• Non-enteric-coated aspirin to *all* patients promptly after presentation	162 mg–325 mg	I	A
• Aspirin maintenance dose continued indefinitely	81 mg/d–325 mg/d*	I	A
$P2Y_{12}$ inhibitors			
• Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin	75 mg	I	B
• $P2Y_{12}$ inhibitor, in addition to aspirin, for up to 12 mo for patients treated initially with either an early invasive or initial ischemia-guided strategy: – Clopidogrel – Ticagrelor*	300-mg or 600-mg loading dose, then 75 mg/d 180-mg loading dose, then 90 mg BID	I	B
• $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) continued for at least 12 mo in post-PCI patients treated with coronary stents	N/A	I	B
• Ticagrelor in preference to clopidogrel for patients treated with an early invasive or ischemia-guided strategy	N/A	IIa	B
GP IIb/IIIa inhibitors			
• GP IIb/IIIa inhibitor in patients treated with an early invasive strategy and DAPT with intermediate/high-risk features (e.g., positive troponin)	Preferred options are eptifibatide or tirofiban	IIb	B
Parenteral anticoagulant and fibrinolytic therapy			
• SC enoxaparin for duration of hospitalization or until PCI is performed	• 1 mg/kg SC every 12 h (reduce dose to 1 mg/kg/d SC in patients with CrCl <30 mL/min) • Initial 30 mg IV loading dose in selected patients	I	A
• Bivalirudin until diagnostic angiography or PCI is performed in patients with early invasive strategy only	• Loading dose 0.10 mg/kg loading dose followed by 0.25 mg/kg/h • Only provisional use of GP IIb/IIIa inhibitor in patients also treated with DAPT	I	B
• SC fondaparinux for the duration of hospitalization or until PCI is performed	2.5 mg SC daily	I	B
• Administer additional anticoagulant with anti-IIa activity if PCI is performed while patient is on fondaparinux	N/A	I	B
• IV UFH for 48 h or until PCI is performed	• Initial loading dose 60 IU/kg (max 4,000 IU) with initial infusion 12 IU/kg/h (max 1,000 IU/ h) • Adjusted to therapeutic aPTT range	I	B
• IV fibrinolytic treatment not recommended in patients with NSTE-ACS	N/A	III: Harm	A

Fig. 12.4 AHA/ACC recommendations for initial anti-thrombotic therapy in NSTE-ACS (From Amsterdam et al. [2]. Reprinted with permission from Elsevier Limited)

without contraindication. Statins in ACS reduces cardiac deaths, recurrent MI, need for repeat revascularization, and stroke [13].

Anti-thrombotic Therapy

All patients with ACS, in the absence of contraindications, should receive aspirin, a second antiplatelet agent, and an anticoagulant. The AHA/ACC guidelines for anti-thrombotic medical management of NSTE-ACS is provided in Fig. 12.4.

Antiplatelet Therapy

In the absence of an absolute contraindication, antiplatelet therapy with aspirin and a P2Y12 inhibitor is indicated in all patients with ACS.

Aspirin Uncoated aspirin (325 mg) should be administered to all patients with ACS without contraindications as early as possible on presentation, and a maintenance dose of aspirin (81–162 mg daily) should be continued indefinitely.

P2Y12 receptor inhibitors P2Y12 receptor inhibitors are administered to patients with ACS according to the type of presentation and how they are treated:

- **STEMI patients**
  - Primary PCI - In patients with STEMI treated with primary PCI, a loading dose of a P2Y12 receptor inhibitor should be given as early as possible (clopidogrel [600 mg followed by 75 mg/day], ticagrelor [180 mg followed by 90 mg BID], or prasugrel [60 mg followed by 10 mg/day]). Ticagrelor as compared with clopidogrel significantly reduces rate of death from vascular causes, MI, or stroke [14].
  - Fibrinolysis - In patients with STEMI treated with fibrinolysis, clopidogrel [300 mg loading dose for age<=75 year old or 75 mg for >75 year old, followed by 75 mg/day] should be administered at the time of presentation.
- NSTEMI/UA patients
  - PCI - In patients with NSTEMI/UA undergoing PCI with stenting should receive a loading dose of a P2Y12 inhibitor at the time of the procedure (clopidogrel [600 mg followed by 75 mg/day], ticagrelor [180 mg followed by 90 mg BID], or prasugrel [60 mg followed by 10 mg/day]). Ticagrelor and Prasugrel, as compared with clopidogrel, significantly reduce rate of death from vascular causes, MI, or stroke [14, 15].
  - Other NSTEMI/UA patients - In patients with NSTEMI/UA treated with either an early invasive approach or an ischemia driven approach should receive either clopidogrel (600 mg followed by 75 mg/day) or ticagrelor (180 mg followed by 90 mg BID), or prasugrel (60 mg followed by 10 mg/day). Ticagrelor as compared with clopidogrel significantly reduces rate of death from vascular causes, MI, or stroke [14].
- In addition to aspirin, a P2Y12 inhibitor should be administered for at least 12 months to all patients with ACS [16].

Glycoprotein IIb/IIIa Inhibitors In patients with very high risk features including, markedly elevated troponin, recurrent ischemic discomfort, dynamic ECG changes, or hemodynamic instability not treated with a P2Y12 inhibitor, a IIb/IIIa inhibitor (abciximab, eptifibatide or tirofiban) may be considered at the time of PCI.

Anticoagulation In patients with ACS, anticoagulation is recommended for all patients, in addition to antiplatelet therapy irrespective of initial treatment strategy. Anticoagulation is continued for 48 h or until PCI is performed. Anticoagulation options include:

- Unfractionated heparin (UFH) (initial loading dose of 60 IU/kg (maximum 4,000 IU) with initial infusion of 12 IU/kg per hour (maximum 1,000 IU/h) adjusted per activated partial thromboplastin time),
- Low-molecular weight heparin (LMWH) (1 mg/kg subcutaneous (SC) every 12 h (reduce dose to 1 mg/kg SC once daily in patients with creatinine clearance [CrCl] <30 mL/min)). LMWH has been shown to be superior to UFH in STEMI patients treated with fibrinolysis.
- Bivalirudin (0.10 mg/kg loading dose followed by 0.25 mg/kg per hour [only in patients managed with an early invasive strategy]), or
- Fondaparinux (2.5 mg SC daily [only in NSTEMI/UA; additional heparin needed if patients received PCI]).

Early Reperfusion and Revascularization

STEMI

In patients with STEMI, rapid restoration of myocardial blood flow reduces mortality [17]. Current guidelines recommend primary PCI within 90 min or less for STEMI patients with symptom onset within 12 h, who arrive at PCI-capable hospital or 120 min or less for those who initially present to a non-PCI capable hospital and are then transferred to a PCI-capable hospital [1, 4]. Figure 12.5 provides a flow diagram for revascularization decisions in STEMI patient. Fibrinolytic therapy, unless contraindicated should be initiated in patients with STEMI who cannot receive primary PCI within 120 min of first medical contact (Table 12.2). Decisions whether to transfer a patient for PCI vs. immediate administration of a fibrinolytic should take into account (1) the risk of complications of the STEMI; (2) the risks associated with fibrinolytic; (3) the timing of presentation relative to symptom onset; and (4) the anticipated transfer time for primary PCI. In general, fibrinolysis may be preferred in early presenting patients, particularly when accompanied by a large myocardial territory at risk, and the time to PCI is anticipated to be longer than 90–120 min. Primary PCI should be favored in late presenters, those with shock, and when the diagnosis of STEMI is in doubt, or contraindications to fibrinolysis exist.

NSTE-ACS

In patients with NSTE-ACS who have refractory angina, hemodynamic or electrical instability an immediate invasive coronary angiography should be performed with intent to perform revascularization if appropriate based on coronary anatomy. Furthermore, NSTE- ACS patients who have an elevated risk of adverse cardiac events should be treated with an early invasive strategy (coronary

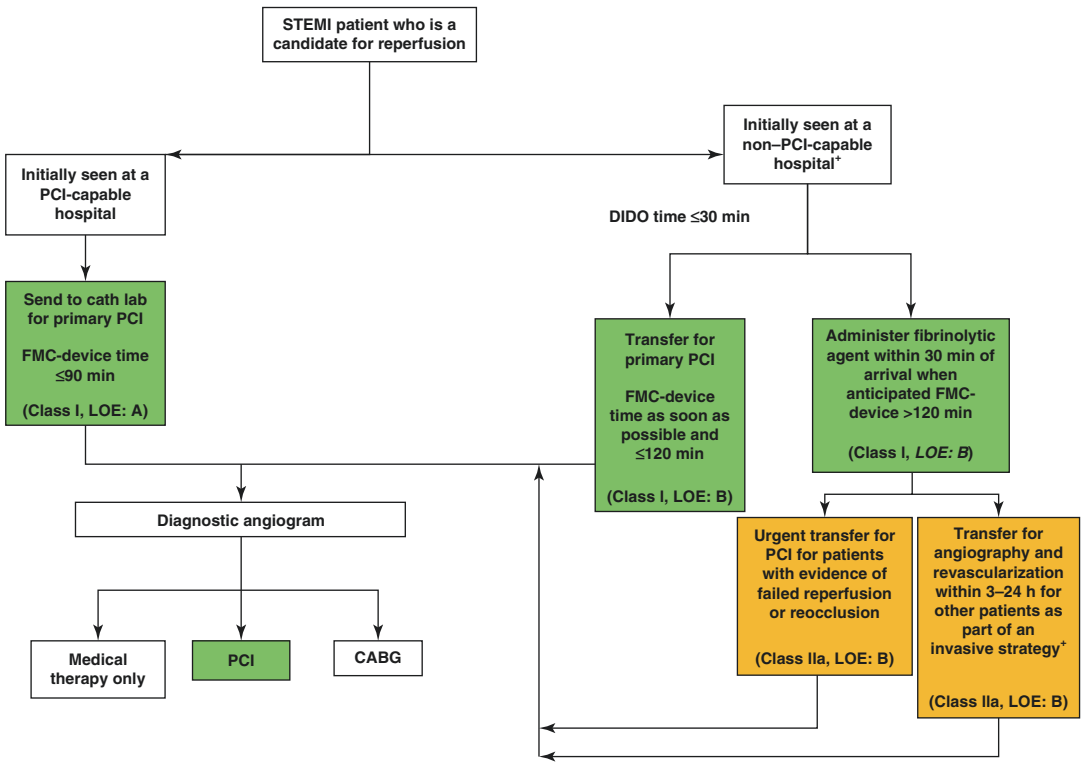


Fig. 12.5 AHA/ACC recommendations for reperfusion therapy choice in STEMI (From O'Gara et al. [1]. Reprinted with permission from Elsevier Limited)

Table 12.2 Fibrinolytic regimens for STEMI

Fibrinolytic agent	Dose	Fibrin specificity[a]	Antigenic	Patency rate (90-min TIMI 2 or 3 flow)
Fibrin-specific				
Tenecteplase (TNK-tPA)	Single IV weight-based bolus[b]	++++	No	85 %
Reteplase (rPA)	10 U + 10-U IV boluses given 30 min apart	++	No	84 %
Alteplase (tPA)	90-min weight-based infusion[c]	++	No	73–84 %
Non-fibrin-specific				
Streptokinase[d]	1.5 million units IV given over 30–60 min	No	Yes[e]	60–68 %

From O'Gara et al. [1]. Reprinted with permission from Elsevier Limited
IV indicates intravenous, *rPA* reteplase plasminogen activator, *TIMI* thrombolysis in myocardial infarction, *TNK-tPA* tenecteplase tissue-type plasminogen activator, *tPA* tissue-type plasminogen activator
[a]Strength of fibrin specificity; "++++" is more strong, "++" is less strong
[b]30 mg for weight <60 kg; 35 mg for 60–69 kg; 40 mg for 70–79 kg; 45 mg for 80–89 kg; and 50 mg for ≥90 kg
[c]Bolus 15 mg, infusion 0.75 mg/kg for 30 min (maximum 50 mg), then 0.5 mg/kg (maximum 35 mg) over the next 60 min; total dose not to exceed 100 mg
[d]Streptokinase is no longer marketed in the United States but is available in other countries
[e]Streptokinase is highly antigenic and absolutely contraindicated within 6 months of previous exposure because of the potential for serious allergic reaction

angiography with intent to perform revascularization within 24 h of admission) [18]. However, a delayed invasive strategy (coronary angiography with intent to perform revascularization within 25–72 h of admission) is reasonable for NSTE-ACS patients at low risk of adverse clinical events. Fibrinolytic therapy should not be used for reperfusion in patients with NSTE-ACS [19].

Evidence Contour

Several aspects of management in a patient with ACS remain without consensus. Recent trials have attempted to settle uncertainty behind many approaches involved in the care of patients with ACS.

Routine Early PCI After Successful Thrombolysis in STEMI

Many patients with STEMI present to hospitals that are not PCI-capable and cannot undergo PCI within the timelines suggested in current guidelines, instead, they are treated with fibrinloysis as the initial reperfusion therapy. Initial studies showed no clinical benefit with routine early PCI after successful fibrinolysis [20]. However, one study showed a strategy of immediate transfer to a PCI-capable hospital within 6 h after successful fibrinolysis for PCI to be associated with lower incidence of primary composite endpoint of death, recurrent MI, heart failure or cardiogenic shock compared to standard therapy alone with delayed coronary angiography or rescue PCI when indicated [21]. A strategy of routine transfer and angiography at 3–24 h is reasonable in patients who have undergone initial reperfusion therapy with a fibrinolytic.

Culprit Only vs Complete Revascularization in STEMI

STEMI patients with obstructive non-culprit lesions are at increased risk of major adverse cardiac events. However, past guidelines recommend revascularization of culprit lesions only unless complicated by cardiogenic shock. Results from observational and small randomized controlled

trials (RCTs), though suggest potential benefit with complete revascularization in STEMI patients with obstructive non-culprit lesions. Such a strategy may be reasonable in selected patients who have residual critical disease after primary PCI. Data from ongoing large RCTs will help to define any role and timing of routine PCI of non-culprit stenoses in patients with STEMI [22].

Manual Thrombectomy During Primary PCI in STEMI

Based on prior studies, past practice guidelines [1] recommended routine manual thrombectomy to prevent distal embolization, improve coronary perfusion and reduce adverse events. Subsequent studies, however, found that a strategy of routine manual thrombectomy compared with PCI not only did not reduce cardiovascular deaths, recurrent MI, cardiogenic shock or heart failure but led to possibly increased rates of stroke [23]. Therefore, routine manual thrombectomy is not recommended for all patients undergoing primary PCI.

Ezetimibe in Acute Coronary Syndromes

Ezetimibe, a nonstatin drug that decreases intestinal absorption of cholesterol was found to reduce adverse cardiac events when added to simvastatin in a larger trial of patients with ACS [24]. This is a first trial showing a net benefit with addition of a nonstatin LDL-C lowering agent to statin therapy and suggests a promising role of other novel interventions including recently improved PCSK9 inhibitors in lowering LDL-C and improving cardiovascular outcomes.

Optimal Duration of Dual Antiplatelet Therapy (DAPT)

Large proportions of patients with ACS are treated with invasive strategy and undergo PCI with drug-eluting stents (DES). Current practice guidelines recommend DAPT with aspirin and a P2Y12 inhibitor for 12 months in patients treated with a DES. Two recent randomized trials have demonstrated that dual antiplatelet therapy beyond 12 months, compared with aspirin alone, reduced risk of stent thrombosis and major cardiac events, in particular in those patients with prior ACS [25, 26].

References

1. O'Gara PT, Kushner FG, Ascheim DD, Casey Jr DE, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61(4):e78–140.
2. Amsterdam EA, Wenger NK, Brindis RG, Casey Jr DE, et al. 2014 AHA/ACC guideline for the management of patients with Non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64(24):2645.
3. Hamm CW, Bassand JP, Agewall S, Bax J, et al. ESC Committee for Practice Guidelines. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(23):2999–3054.
4. Steg PG, James SK, Atar D, Badano LP, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). Eur Heart J. 2012;33(20):2569–619.
5. Morrow DA, Antman EM, Parsons L, de Lemos JA, Cannon CP, Giugliano RP, McCabe CH, Barron HV, Braunwald E. Application of the TIMI risk score for ST-elevation MI in the National Registry of Myocardial Infarction 3. JAMA. 2001;286(11):1356.
6. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA. 2000;284(7):835.
7. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA, Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003;163(19):2345–53.

8. Moradkhan R, Sinoway LI. Revisting the role of oxygen therapy in cardiac patients. J Am Coll Cardiol. 2010;56:1013–6.
9. Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, Cameron P, Barger B, Ellims AH, Taylor AJ, Meredith IT, Kaye DM, AVOID Investigators. Air versus oxygen in ST-segment-elevation myocardial infarction. Circulation. 2015;131(24):2143–50.
10. Levine GN, Steinke EE, Bakaeen FG, et al. Sexual activity and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2012;125:1058–72.
11. Gislason GH, Jacobsen S, Rasmussen JN, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal anti-inflammatory drugs after acute myocardial infarction. Circulation. 2006;113:2906–13.
12. Ryden L, Ariniego R, Arnman K, et al. A double-blind trial of metoprolol in acute myocardial infarction. Effects on ventricular tachyarrythmias. N Engl J Med. 1983;308:614–8.
13. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350(15):1495–504.
14. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045–57.
15. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM, TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20):2001–15.
16. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345:494–502.
17. Anderson JL, Karagounis LA, Califf RM. Metaanalysis of five reported studies on the relation of early coronary patency grades with mortality and outcomes after acute myocardial infarction. Am J Cardiol. 1996;78(1):1.
18. Morrow DA, Cannon CP, Rifai N, Frey MJ, Vicari R, Lakkis N, Robertson DH, Hille DA, DeLucca PT, DiBattiste PM, Demopoulos LA, Weintraub WS, Braunwald E, TACTICS-TIMI 18 Investigators. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomized trial. JAMA. 2001;286(19):2405–12.
19. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation. 1994;89(4):1545–56.
20. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) phase II trial. N Engl J Med. 1989;320(10):618–27.
21. Cantor WJ, Fitchett D, Borgundvaag B, Ducas J, Heffernan M, Cohen EA, Morrison LJ, Langer A, Dzavik V, Mehta SR, Lazzam C, Schwartz B, Casanova A, Goodman SG, TRANSFER-AMI Trial Investigators. Routine early angioplasty after fibrinolysis for acute myocardial infarction. N Engl J Med. 2009;360(26):2705–18.
22. Qamar A, Bhatt DL. Culprit-only vs. complete revascularization during ST-segment elevation myocardial infarction. Prog Cardiovasc Dis. 2015;58(3):260–6.
23. Jolly SS, Cairns JA, Yusuf S, Meeks B, et al. TOTAL Investigators. Randomized trial of primary PCI with or without routine manual thrombectomy. N Engl J Med. 2015;372(15):1389–98.
24. Cannon CP, Blazing MA, Giugliano RP, McCagg A, et al. for the IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–97.
25. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, et al. DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014;371(23):2155–66.
26. Bonaca MP, Bhatt DL, Cohen M, Steg PG, et al.; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;372(19):1791–800.

Complications of Myocardial Infarction

13

Brandon M. Jones and Venu Menon

Case Presentation

A 61 year old woman with a history of hypertension, tobacco abuse, and Wolf-Parkinson-White syndrome with prior ablation 15 years ago, presented to the emergency department via ambulance with 4 days of indigestion and generalized chest discomfort, with more severe pain lasting several hours. EMS noted her to be tachycardic with HR 102 bpm, and hypotensive with BP 83/61 mmHg. The following 12-lead ECG was obtained (Fig. 13.1).

The initial physical exam was notable for an anxious and diaphoretic patient with elevated jugular venous pressure, crackles at the lung bases, and a left ventricular S3 with a soft systolic murmur adjacent to the lower left sternal boarder. Initial blood tests showed WBC 12.5, hemoglobin 15.5 mg/dL, serum creatinine 1.2 mg/dl, and cardiac troponin I 6.06 ug/L. She was brought emergently to the cardiac catheterization laboratory where she was found to have 100 % occlusion of a dominant, mid-left circumflex artery. She underwent successful PCI with placement of two overlapping drug-eluting stents, and restoration of TIMI 3 flow to the infarct related artery (Table 13.1). At the conclusion of the case, the patient became agitated and pulse oximetry showed 88 % saturation despite administering 100 % oxygen by non-rebreather facemask. Blood-pressure was 78/58 mmHg at this time, and the patient required endotracheal intubation and the initiation of vasopressor medications to stabilize her blood pressure.

Question What is the differential diagnosis for the patient's hemodynamic and respiratory decompensation, and what should be done next to confirm the diagnosis?

Answer The differential diagnosis must include mechanical complications of AMI including ventricular septal rupture (VSR) (Video 13.1), papillary muscle rupture leading to acute mitral regurgitation (MR) (Video 13.2), or free-wall rupture leading to pseudoaneurysm or cardiac tamponade (Video 13.3). Other etiologies to be considered include RV infarction, acute blood loss, iatrogenic hypotension secondary to medication, and cath lab complications such as aortic dissection or coronary perforation. **The most**

Electronic supplementary material The online version of this chapter (doi:10.1007/978-3-319-43341-7_13) contains supplementary material, which is available to authorized users.

B.M. Jones
Cardiovascular Medicine and Interventional Cardiology, Cleveland Clinic Foundation, Cleveland, OH, USA

V. Menon (✉)
Pulmonary and Critical Care, Geisinger Medical Center, Danville, PA, USA
e-mail: menonv@ccf.org

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_13

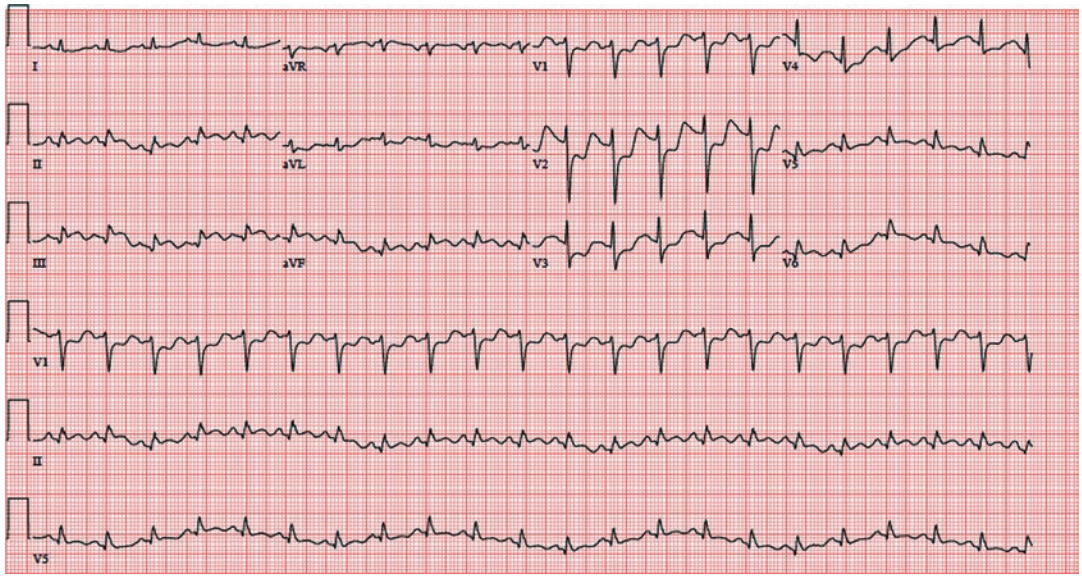


Fig. 13.1 12-lead ECG

Table 13.1 TIMI flow definitions

TIMI Grade 0 (no perfusion)	There is no antegrade flow beyond the point of occlusion
TIMI Grade 1 (penetration without perfusion)	The contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence
TIMI Grade 2 (partial perfusion)	The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel – e.g., the opposite coronary artery or the coronary bed proximal to the obstruction
TIMI Grade 3 (complete perfusion)	Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery

Data from Chesebro et al. [16]

rapid way to confirm the diagnosis is with immediate, trans-thoracic echocardiography.

The patient has demonstrated hemodynamic instability despite patency of the infarct related artery in the setting of a delayed presentation of acute myocardial infarction (AMI). Based on her clinical and hemodynamic findings she is now Killip Class IV (Table 13.2). Understanding the etiology of her hemodynamic instability is now crucial to guide further management. While this may represent LV failure in the setting of a large MI, it is unusual that an isolated infarction in the distribution described will account for these findings. Mechanical complications of MI, as listed above, must be considered and rapidly identified or excluded. In this specific case, the bedside echo demonstrated a severe, eccentric jet of mitral regurgitation. On a subsequent trans-esophageal echocardiogram (TEE), the diagnosis was confirmed to be due to rupture and flail of the papillary muscle with prolapse into the left atrium during systole. An image from the trans-esophageal echocardiogram obtained in the standard 4-chamber view is provided in Fig. 13.2. The patient was taken emergently to the operating room where a bioprosthetic mitral valve replacement was performed. The patient was successfully

discharged to a sub-acute nursing facility on hospital day 15, and made a full recovery.

Standard Approach to Management

Epidemiology

Cardiogenic shock in the peri-infarct setting is defined as inadequate tissue perfusion and sustained hypotension despite adequate intravascular volume. Cardiogenic shock complicates between 5 and 8 % of cases of AMI in contemporary databases and trials. Mortality for AMI in general is <5 % in contemporary series, but can exceed 50 % in patients with shock [1]. The most common cause of shock after AMI is left ventricular (LV) failure which represents 80 % of cases, but mechanical complications of AMI must be considered including isolated right ventricular (RV) infarct, ventricular septal rupture (VSR), free-wall rupture with ensuing cardiac tamponade, and papillary muscle rupture leading to acute mitral regurgitation (MR). Data from the SHOCK trial and the subsequent SHOCK registry documented the most common etiologies of cardiogenic shock among 1,422 patients after AMI (Fig. 13.3) [2].

Table 13.2 Killip Class definitions

	Definition	30-day mortality (in 1967) (%)
Killip Class I	No clinical signs of heart failure	<6
Killip Class II	Signs of heart failure including rhales or crackles in the lower lung fields, an S3, or elevated jugular venous pressure	<17
Killip Class III	Frank, acute pulmonary edema.	38
Killip Class IV	Cardiogenic shock or hypotension (measured as systolic blood pressure < 90 mmHg) and evidence of peripheral vasoconstriction (oliguria, cyanosis, or sweating)	81

Data from Killip and Kimball [17]

Diagnosis

The first step in managing patients with cardiogenic shock after AMI is to identify the cause. Specifically, one must attempt to differentiate between mechanical complications that require immediate operative treatment as compared to LV failure alone. A rapid but thorough physical examination is important in any patient with AMI and shock. Cardiac auscultation may reveal the

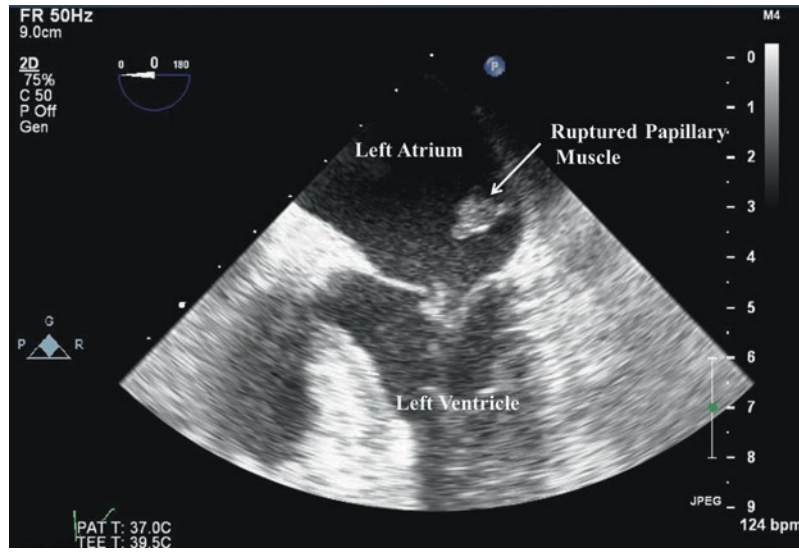


Fig. 13.2 Transesophageal echocardiogram

characteristic, harsh, holosystolic murmur of a VSR or a softer, apical murmur consistent with acute mitral regurgitation. Cardiac tamponade may be suspected based on jugular venous distention (JVD) and a pulsus paradoxus, or Beck's triad of hypotension, distended neck veins, and muffled heart sounds. Patients with RV infarction may display a pulsus paradoxus along with the Kussmaul sign (increase in JVD with inspiration) which is usually absent in patients with cardiac tamponade. Physical exam may be challenging due to the degree of hypotension, the need for mechanical ventilation, and the physical environment. The murmur of acute MR may be soft and difficult to appreciate due to rapid elevation in left atrial pressures. Similarly a large VSR in the setting of hypotension may also be under appreciated.

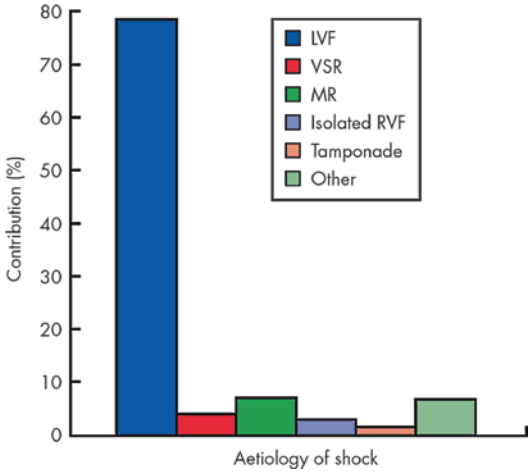
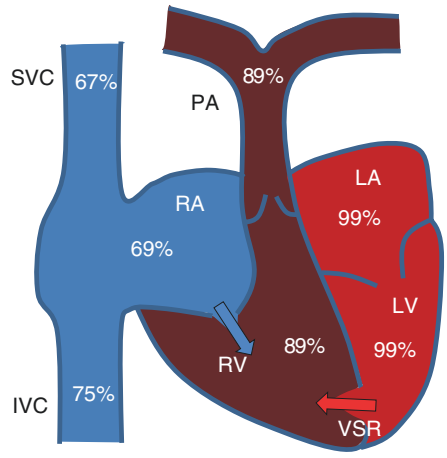


Fig. 13.3 Etiology of suspected cardiogenic shock in the combined SHOCK trial registry and trial (total n = 1422, only first 232 trial patients are included). "Other" includes shock caused by prior severe valvular disease, dilated cardiomyopathy, excess beta-blockade/calcium channel blockade, hemorrhage, and procedural complications. Aortic dissection, pulmonary embolism, and dynamic subaortic outflow obstruction should also be considered. *LVF* left ventricular failure, *MR* mitral regurgitation, *RVF* right ventricular failure, *VSR* ventricular septal rupture (Reproduced with permission from Menon, Heart, 2002 [2] with permission from BMJ Publishing Group Ltd)

Practically speaking, most mechanical complications of AMI can be definitively diagnosed by prompt, bedside, trans-thoracic echocardiography (TTE). In patients who are brought immediately to the cardiac catheterization lab and/or in whom echocardiography is not immediately available or is inconclusive, the diagnosis can be made by LV angiography and/or right heart catheterization. Using a balloon-tipped catheter, VSR can usually be confirmed by demonstrating a "step-up" in the oxygen saturation of blood sampled from the right ventricle or pulmonary artery as compared to the right atrium, reflecting shunting of oxygenated blood from the LV to the RV through the ruptured septum, and subsequent mixing with relatively deoxygenated blood returning to the right side of the heart (Fig. 13.4). Comparatively, patients with severe mitral regurgitation will likely have tall v-waves in the pulmonary capillary wedge tracing without a significant step-up in oxygen saturations. Importantly, not all mitral regurgitation in the setting of AMI is due to papillary muscle rupture, and it is important to distinguish MR due to LV



$$\text{Qp/Qs} = \frac{\%\ \text{Sat Artery} - \%\ \text{Sat RA}}{\%\ \text{Sat Artery} - \%\ \text{Sat PA}}$$

$$\text{Qp/Qs} = \frac{99\% - 69\%}{99\% - 89\%}$$

$$\text{Qp/Qs} = \frac{30\%}{10\%}$$

$$\text{Qp/Qs} = 3$$

Fig. 13.4 Oximetry run and shunt fraction calculation in a patient with an apical VSR showing a "step up" in the RV where there is mixing of venous blood with oxygenated blood from the left ventricle that is crossing the apical septal defect. Note: RA sat can be estimated by (3× SVC + IVC)/4. Note: A peripheral arterial sat is usually used as a surrogate for LV saturation

dilation or posterior mitral leaflet restriction in the setting of an akinetic inferior wall (Video 13.4), neither of which would typically be managed with emergent surgery. Thus, there should be a low threshold to proceed to trans-esophageal echocardiography (TEE) when the mechanism for the MR is ambiguous on surface echocardiogram.

Management of LV Failure

When LV failure is felt to be responsible for cardiogenic shock, the next step in management is to ensure complete revascularization, as was clearly demonstrated in the SHOCK trial [1]. Patients with ongoing hemodynamic embarrassment despite revascularization may require urgent mechanical support, most commonly in the form of an intra-aortic balloon pump (IABP). Inotropic and vasopressor agents are sometimes used in emergent situations to stabilize hemodynamics, but have not been shown to improve hospital survival. Other mechanical support devices that have been used include the TandemHeart, Impella, and veno-arterial extra-corporeal membrane oxygenation (ECMO). In this emergent setting, mechanical support is usually utilized as a bridge to decision. In those who stabilize and recover, support is subsequently withdrawn. In others who continue to be unstable, destination support with an LVAD or consideration of the LVAD as a bridge to transplantation may be considered. Finally in the group of patients where care may be deemed futile, support is not performed or may be subsequently withdrawn.

Management of Mechanical Complications

Mechanical complications of AMI have become less common in the era of early reperfusion, but mortality for these patients remains high (Fig. 13.5) [3]. Medical management of papillary

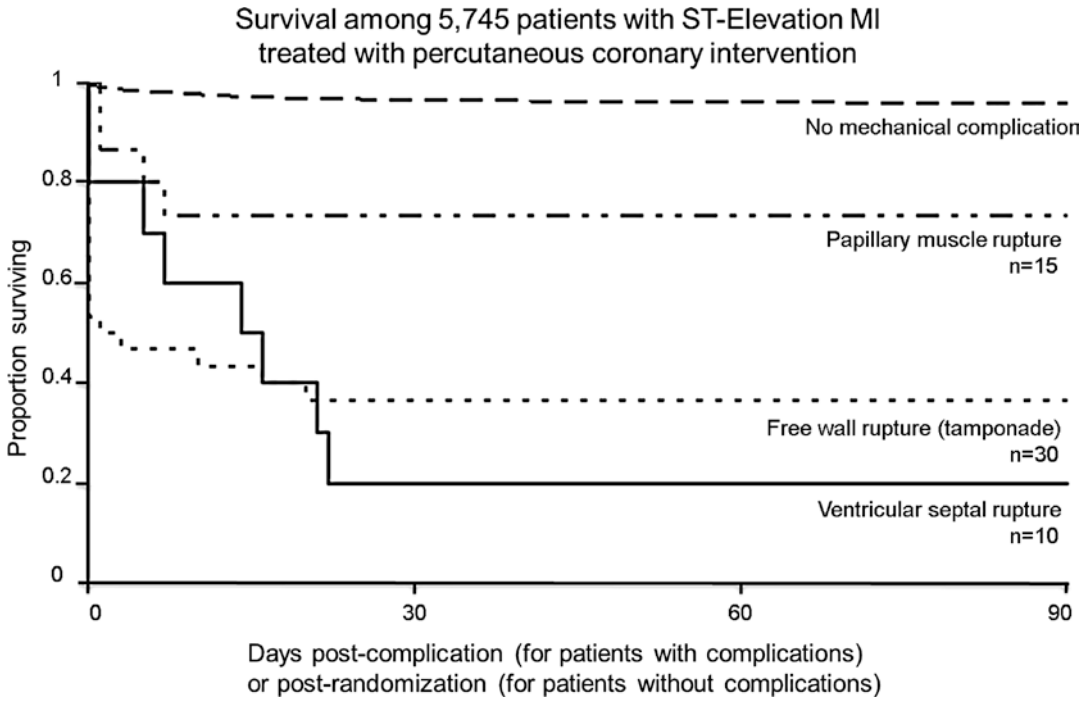


Fig. 13.5 Survival among 5,745 patients undergoing primary percutaneous coronary intervention (PCI) after ST-elevation myocardial infarction in the APEX-AMI trial. A total of 52 patients (0.91 %) had a mechanical complication of which 15 were papillary muscle rupture, 30 were free wall rupture with tamponade, and 10 were ventricular septal rupture (Adapted from French [3] with permission from Elsevier Limited)

muscle rupture and VSR is limited, but involves afterload reduction with intravenous sodium nitroprusside. IABP placement is considered routine care in hemodynamically unstable patients. The only definitive management strategy is surgical repair, although a variety of mechanical support devices have been used to temporarily stabilize hemodynamically unstable patients who were not initially felt to be candidates for surgery. When the diagnosis of a mechanical complication can be made prior to primary percutaneous coronary intervention (PCI), immediate collaboration between the interventional cardiologist and cardiac surgeon is needed to determine the optimal approach for prompt restoration of coronary flow, while also considering the competing need to limit the administration of dual-antiplatelet therapy in patients undergoing emergent surgery. In some cases, balloon angioplasty without stent placement, followed by combined coronary artery bypass graft placement with immediate mechanical repair, may be the preferred option.

Evidence Contour

Timing of Surgery in Ventricular Septal Rupture

The optimal timing for surgery in unstable patients with ventricular septal rupture is controversial given the exceedingly high mortality of patients who are operated on in the immediate, post-infarct period [4]. Complexity of the operation, relative surgical inexperience, acute right ventricular dysfunction from infarction, ischemia or volume overload, patient comorbidities, or exposure to potent antiplatelet treatment prior to surgery may all contribute towards this finding. The overall mortality of patients in the Society of Thoracic Surgeons National Database for patients with VSR was 42.9%, but was significantly higher (>60%) in patients who underwent surgery in the first 24 h, as compared to 18.4% in patients in whom the repair was delayed until after 7 days [5]. Unfortunately, unstable patients are very unlikely to survive long enough for surgery to be done electively, so this data is mostly reflective of survival bias. Many have hypothesized however that the particularly poor outcomes with immediate surgery may be in part due to the weak, friable tissue of an acute infarct which holds sutures poorly. Thus, some experienced centers have attempted a strategy of full mechanical support with a planned, delayed surgery in select patients, although the success of this strategy is currently limited to case reports [6, 7]. In general, patients who are considered acceptable candidates for immediate repair based on factors including comorbidities, willingness of the patient to pursue an aggressive strategy, and comfort of the surgeon/medical center in managing the patient, should undergo surgical repair without delay.

Percutaneous Closure of VSR

Given the exciting evolution of structural cardiac interventions over the past decade, many have considered options for percutaneous closure of acute VSR, either as a definitive strategy, or as a bridge to surgery after initial stabilization. This strategy has been attempted for both primary closure and in the treatment of residual shunts after surgical repair. Unfortunately, when attempted in the immediate, post-infarct period, or in patients with cardiogenic shock, mortality remains high, similar to surgical series [8]. The procedure can be done safely however, and with technical success in the overwhelming majority of cases. Thus, procedures done in the acute setting should likely be limited to patients who are not initially surgical candidates, and undertaken with the goal of reducing shunt fraction and improving hemodynamic stability as a bridge to a more definitive surgical repair. For patients in the sub-acute to chronic period whose comorbidities continue to prevent definitive repair, percutaneous closure is an especially attractive option, and initial clinical series have shown excellent success and low 30-day mortality in these populations [9–13].

Intra-aortic Balloon Pump

IABP use in patients with cardiogenic shock after AMI has come under scrutiny given the results of the IABP-SHOCK II trial which failed to show a difference in 30-day mortality among patients that were randomized to IABP placement vs. open label controls [14]. Although well performed, IABP placement in this study was performed only after revascularization and it included large subsets of patients with NSTEMI ACS and post cardiac arrest. Criticisms of this study have also included a high cross-over rate with 10% of patients undergoing IABP placement despite randomization to the control group, and a trend toward higher utilization of LV assist devices in the control group. Most clinicians feel that IAPB utilization continues to be a useful adjunct in the hemodynamically unstable patient with AMI. Based on the IABP –SHOCK II trial however, its utilization has been downgraded to a Class IIa LOE B recommendation from the 2013 ACCF/AHA guidelines on management of ST-elevation MI [15]. Importantly, the IABP-Shock II trial was not powered to look at the utility of IABP placement in the setting of VSR, where it is considered routine care.

References

1. Hochman JS, Sleeper LA, White HD, Dzavik V, Wong SC, Menon V, et al. One-year survival following early revascularization for cardiogenic shock. JAMA. 2001; 285(2):190–2.
2. Menon V, Hochman JS. Management of cardiogenic shock complicating acute myocardial infarction. Heart. 2002;88(5):531–7.
3. French JK, Hellkamp AS, Armstrong PW, Cohen E, Kleiman NS, O'Connor CM, et al. Mechanical complications after percutaneous coronary intervention in ST-elevation myocardial infarction (from APEX-AMI). Am J Cardiol. 2010;105(1):59–63.
4. Jones BM, Kapadia SR, Smedira NG, Robich M, Tuzcu EM, Menon V, et al. Ventricular septal rupture complicating acute myocardial infarction: a contemporary review. Eur Heart J. 2014;35(31):2060–8.
5. Arnaoutakis GJ, Zhao Y, George TJ, Sciortino CM, McCarthy PM, Conte JV. Surgical repair of ventricular septal defect after myocardial infarction: outcomes from the Society of Thoracic Surgeons National Database. Ann Thorac Surg. 2012;94(2):436–43; discussion 43–4.
6. Tsai MT, Wu HY, Chan SH, Luo CY. Extracorporeal membrane oxygenation as a bridge to definite surgery in recurrent postinfarction ventricular septal defect. ASAIO J. 2012;58(1):88–9.
7. Neragi-Miandoab S, Michler RE, Goldstein D, D'Alessandro D. Extracorporeal membrane oxygenation as a temporizing approach in a patient with shock, myocardial infarct, and a large ventricle septal defect; successful repair after six days. J Card Surg. 2013;28(2):193–5.
8. Thiele H, Kaulfersch C, Daehnert I, Schoenauer M, Eitel I, Borger M, et al. Immediate primary transcatheter closure of postinfarction ventricular septal defects. Eur Heart J. 2009;30(1):81–8.
9. Assenza GE, McElhinney DB, Valente AM, Pearson DD, Volpe M, Martucci G, et al. Transcatheter closure of post-myocardial infarction ventricular septal rupture. Circ Cardiovasc Interv. 2013;6(1):59–67.
10. Holzer R, Balzer D, Amin Z, Ruiz CE, Feinstein J, Bass J, et al. Transcatheter closure of postinfarction ventricular septal defects using the new Amplatzer muscular VSD occluder: Results of a U.S. Registry. Catheter Cardiovasc Interv. 2004;61(2):196–201.
11. Maltais S, Ibrahim R, Basmadjian AJ, Carrier M, Bouchard D, Cartier R, et al. Postinfarction ventricular septal defects: towards a new treatment algorithm? Ann Thorac Surg. 2009;87(3):687–92.
12. Bialkowski J, Szkutnik M, Zembala M. Ventricular septal defect closure – importance of cardiac surgery and transcatheter intervention. Kardiol Pol. 2007; 65(8):1022–4.
13. Demkow M, Ruzyllo W, Kepka C, Chmielak Z, Konka M, Dzielinska Z, et al. Primary transcatheter closure of postinfarction ventricular septal defects with the Amplatzer septal occluder- immediate results and up-to 5 years follow-up. EuroIntervention. 2005;1(1):43–7.
14. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med. 2012;367(14):1287–96.
15. O'Gara PT, Kushner FG, Ascheim DD, Casey Jr DE, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61(4):e78–140.
16. Chesebro JH, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation. 1987;76(1):142–54.
17. Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. Am J Cardiol. 1967;20(4): 457–64.

Management of Cardiac Tamponade

14

David D. Berg, Gregory W. Barsness, and Benjamin A. Olenchock

Case Presentation

A 64-year-old man with a remote history of stage IIIa adenocarcinoma of the lung treated with chemotherapy and radiation presented to the emergency department complaining of left-sided chest pain and dyspnea. He had been diagnosed with a pulmonary embolism 2 weeks prior and was started on warfarin at that time. He felt well until the night before his current presentation when he became acutely dyspneic while lying in bed. His triage vital signs were notable for a heart rate of 106 beats per minute (bpm), blood pressure of 92/70 mmHg, and respiratory rate of 28 breaths per minute. A pulsus paradoxus of 18 mmHg was measured by manual sphygmomanometer. A 12-lead ECG showed sinus tachycardia with low-normal QRS voltages (Fig. 14.1). A chest x-ray showed stable reticular opacities in the right middle and lower lobes at the sites of prior radiation treatment, as well as a prominent cardiomediastinal silhouette. A bedside echocardiogram was performed which showed a large circumferential pericardial effusion with early right ventricular (RV) diastolic collapse and exaggerated reciprocal respiratory variation in mitral and tricuspid early-diastolic inflow velocities (Fig. 14.2 and Video 14.1).

Question What is the appropriate next step in the management of the patient's pericardial effusion?

Answer With few exceptions, patients with clinical and supportive echocardiographic evidence of cardiac tamponade should undergo emergent drainage of the pericardial effusion by percutaneous needle pericardiocentesis. Isotonic fluids can modestly increase cardiac output and mean arterial pressure in about half of patients with tamponade [1], but the results are generally transient, and this intervention should not substitute for or delay pericardiocentesis.

In this case, the patient was given a 500 mL bolus of normal saline over 10 min with transient improvement in his systolic blood pressure. The cardiac catheterization laboratory was activated and the patient was given two units of fresh

Electronic supplementary material The online version of this chapter (doi:10.1007/978-3-319-43341-7_14) contains supplementary material, which is available to authorized users.

D.D. Berg • B.A. Olenchock (✉)
Department of Medicine, Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School,
Boston, MA, USA
e-mail: bolenchock@partners.org

G.W. Barsness
Department of Cardiovascular Diseases, Division of Ischemic Heart Disease and Critical Care Cardiology, Mayo Clinic, Rochester, MN, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_14

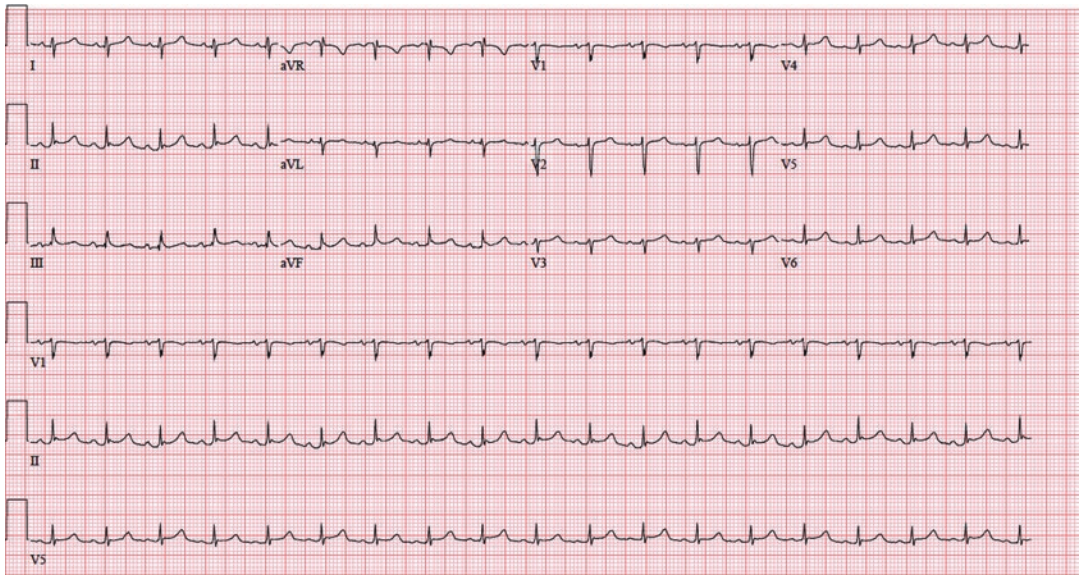


Fig. 14.1 Admission ECG

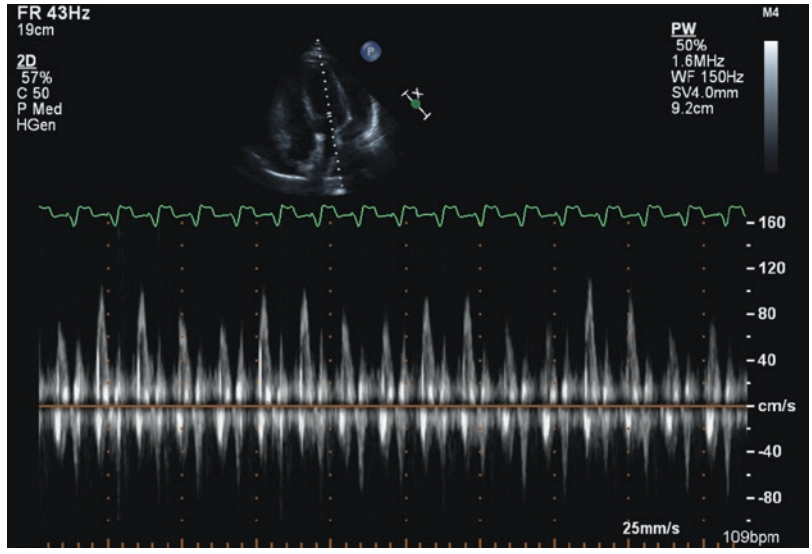


Fig. 14.2 Pulse-wave Doppler of mitral inflow in the apical four chamber view, showing >25 % respirophasic variation in diastolic inflow velocities

frozen plasma to reverse a supratherapeutic INR of 4.2. The pericardial space was accessed through a subxiphoid approach using echocardiographic and fluoroscopic guidance. The pericardial pressure was measured at 24 mmHg. A pericardial drain was placed, 850 mL of bloody fluid was removed, and the pericardial pressure was reduced to 0 mmHg. His symptoms dramatically improved and his blood pressure increased to 132/78 mmHg. He was admitted to the cardiac intensive care unit for ongoing monitoring, and over the ensuing 48 hours, the output from his pericardial drain tapered off to zero. A repeat transthoracic echocardiogram showed a small residual pericardial effusion without evidence of tamponade, and the drain was removed. Pericardial fluid analysis revealed a markedly elevated red blood cell count (2 million/μl) with negative culture and cytology. The clinical picture was felt to be consistent with a hemorrhagic

pericardial effusion due to excessive anticoagulation in the setting of subclinical radiation-induced pericardial disease.

Principles of Management

Hemodynamic Derangements

Cardiac tamponade occurs when fluid accumulates in the intrapericardial space, increasing intrapericardial pressure and impairing cardiac filling [2]. Tamponade is a continuum from mild impairment in cardiac filling to complete circulatory collapse [3]. The primary determinant of the hemodynamic significance of a pericardial effusion is the intrapericardial pressure, which is related to the volume of the effusion and the pericardial pressure-volume relationship. The latter is heavily influenced by the chronicity of the effusion, and hence slowly accumulating pericardial fluid can lead to a large effusion without the development of tamponade [4]. As intrapericardial pressure increases, right and left-sided atrial and ventricular pressures also increase to maintain end-diastolic volume. At some point, generally in the range of 15–20 mmHg, the intrapericardial pressure approaches intracavitary pressures with consequent reduction in ventricular transmural pressure and end-diastolic volume [5]. The heart attempts to maintain cardiac output by increasing contractility and heart rate, but these compensatory mechanisms are quickly exhausted and progressive circulatory collapse ensues.

Clinical Findings

The classical findings of cardiac tamponade were reported in 1935 by a thoracic surgeon named Claude Beck, who described the triad of hypotension, elevated jugular venous pressure, and muffled heart sounds in a series of surgical patients with cardiac tamponade due to intrapericardial hemorrhage [6]. Although this constellation of symptoms has remained the core clinical triad of tamponade, individual components may not be seen in all patients and often do not occur simultaneously within the same patient. A variant form of cardiac tamponade associated with systemic hypertension has also been described [7], and pericardial friction rubs can sometimes be heard in lieu of muffled heart sounds in patients with concomitant pericarditis [8].

The hallmark of cardiac tamponade is a paradoxical pulse (i.e., pulsus paradoxus), which is defined by a drop in systolic arterial pressure of greater than 10 mmHg during inspiration [2]. This occurs because the total intracardiac volume is relatively fixed due to the elevated intrapericardial pressure. As venous return to the right side of the heart increases with inspiration, the interventricular septum shifts to the left in an exaggerated fashion that further reduces left ventricular (LV) stroke volume. The pulsus paradoxus can be measured in the intensive care unit by cuff sphygmomanometry, pulse oximetry waveform analysis, or arterial waveform analysis when an arterial line is present [9]. The patient should not be asked to breathe deeply during blood pressure measurement since this can falsely exaggerate blood pressure variation over the respiratory cycle. It is important to remember that several other conditions can produce a pulsus paradoxus, including constrictive pericarditis, pulmonary embolism, hypovolemic shock, and severe obstructive lung disease.

Non-invasive Diagnostic Testing

A 12-lead electrocardiogram (ECG) should be obtained in all patients with suspected cardiac tamponade. The characteristic abnormalities seen on ECG are decreased QRS voltage and electrical alternans. Low QRS voltage is a non-specific finding that is also seen in infiltrative myocardial disease, pulmonary disease, and obesity. Electrical alternans, defined as beat-to-beat variation in QRS amplitude related to anterior-posterior swinging of the heart, is not sensitive but is relatively specific for cardiac tamponade [10]. The combination of P wave and QRS alternans further increases specificity [10].

Transthoracic echocardiography is the imaging modality of choice for evaluating the size,

location, and degree of hemodynamic impairment caused by a pericardial effusion [11, 12]. Several echocardiographic findings support the diagnosis of tamponade [12, 13]:

1. Right atrial inversion for greater than one-third of systole
2. Right ventricular diastolic collapse (best appreciated in the parasternal long-axis and subcostal views)
3. Reciprocal respiratory variation in RV and LV volumes and consequent septal shifting (best appreciated in the apical four-chamber view)
4. Exaggerated reciprocal respiratory variation (>25 %) in mitral and tricuspid early-diastolic inflow velocities (i.e., E velocities)
5. Increase in the flow velocity integral in the pulmonary artery and decrease in the flow velocity integral in the aorta during inspiration (i.e., "echocardiographic pulsus paradoxus")
6. Reduced early-diastolic mitral annular tissue Doppler velocity (i.e., E' velocity)
7. Severe dilation of the inferior vena cava (IVC) (i.e., IVC plethora)

It is important to remember that cardiac tamponade is a clinical and hemodynamic diagnosis. If the clinical picture is consistent with cardiac tamponade, the most important echocardiographic finding is the presence of a pericardial effusion. In this case, Doppler evaluation should not delay expeditious treatment.

Invasive Diagnostic Testing

Invasive hemodynamic monitoring with a pulmonary arterial catheter can provide additional evidence for the diagnosis of cardiac tamponade. Supportive findings include equalization of diastolic pressures between cardiac chambers, which produces a characteristic "blunted" y-descent in the right atrial tracing (Fig. 14.3), and reciprocal respirophasic variation in right and left-sided filling pressures [10]. Invasive monitoring is

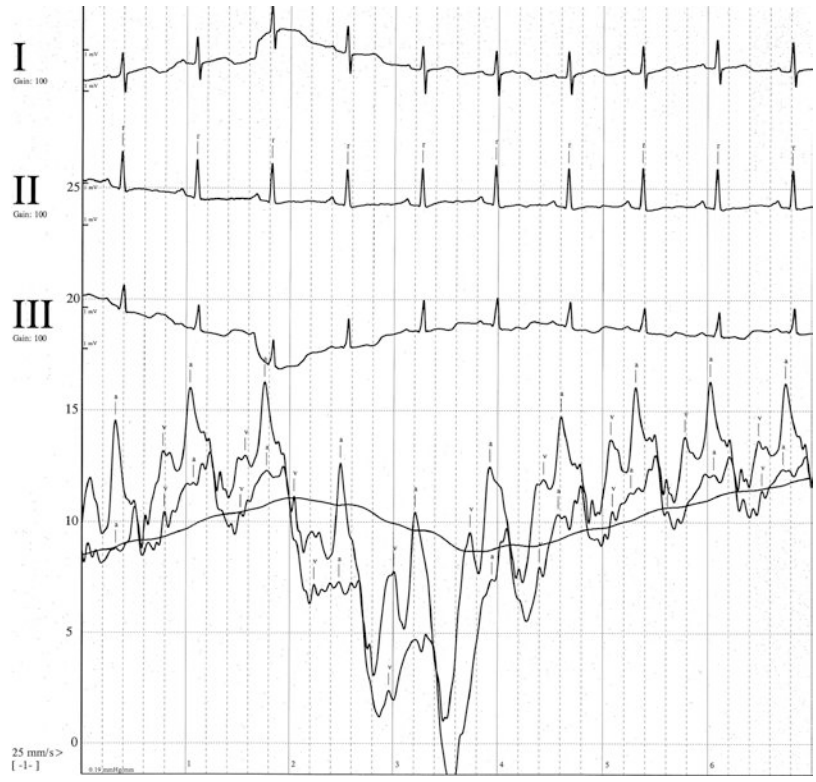


Fig. 14.3 Right atrial tracing demonstrating blunted y-descent in a patient with cardiac tamponade

generally not necessary for diagnosing tamponade, and should be reserved for circumstances in which there is diagnostic uncertainty (e.g., hypertensive cardiac tamponade). It is also necessary for the diagnosis of effusive-constrictive pericarditis (see section "Evidence Contour") [14].

Closed Pericardiocentesis

In most cases, the treatment of cardiac tamponade should be oriented toward emergent drainage of the pericardial effusion by percutaneous needle pericardiocentesis. Intravascular volume expansion with isotonic fluid resuscitation can lead to modest and transient increases in cardiac output and systolic blood pressure in about half of patients. Since volume expansion also acutely increases left ventricular diastolic pressures, it is generally recommended that no more than 500 mL be administered [1, 15]. Positive inotropes are of limited efficacy because endogenous adrenergic activation is generally near maximal [2]. Intubation should be avoided because positive-pressure mechanical ventilation will further reduce ventricular transmural pressure and diastolic filling [10].

Before proceeding with closed pericardiocentesis, it should be confirmed that there is clear clinical evidence of tamponade (including a pulsus paradoxus >10 mmHg), and that the effusion is large enough anteriorly to safely access the fluid via a percutaneous approach. Whenever possible, the procedure should be performed by an experienced provider in the cardiac catheterization laboratory. In the setting of circulatory collapse, a bedside pericardiocentesis may be performed emergently. Real-time transthoracic echocardiographic guidance is often used to identify the optimal percutaneous approach (generally subxiphoid), and has been shown to reduce procedural complications including myocardial puncture [16, 17]. When the procedure is done in the cardiac catheterization laboratory, fluoroscopic guidance and invasive hemodynamic monitoring can also be useful. Once the pericardial space has been accessed, a guidewire is passed through the sheath to facilitate introduction of a pigtail catheter [18]. Intrapericardial pressure should be measured prior to fluid removal, and the pericardial fluid analysis should include specific gravity, cell count and differential, total protein content, gram stain and culture for detection of bacteria (including tuberculosis) and fungi, and cytology. When the amount of pericardial fluid drained decreases to less than 50 mL per day, the catheter can generally be removed [10]. In rare cases, paradoxical hemodynamic deterioration and pulmonary edema associated with ventricular dysfunction have been reported after pericardial drainage. Known as pericardial decompression syndrome (PDS), this complication remains poorly understood [19].

Surgical Drainage

Open pericardiocentesis is the preferred approach for treating tamponade that results from intrapericardial bleeding due to myocardial rupture or aortic dissection. Loculated effusions and effusions with excessive fibrinous material (e.g., clotted hemopericardium) may also require a surgical approach. In these cases, surgery is generally performed through a limited subxiphoid incision.

Most malignant pericardial effusions can be treated with closed pericardiocentesis with a low recurrence rate [20]. When hemodynamically significant malignant effusions do recur, they should generally be treated with open pericardiocentesis and creation of a pericardial window [18]. Multiple pericardial biopsies, with or without pericardioscopic guidance, should be obtained at the time of surgery [21].

Evidence Contour

Effusive-Constrictive Pericarditis

Effusive-constrictive pericarditis (ECP) is a clinical syndrome in which constriction of the visceral pericardium occurs in the presence of a tense pericardial effusion. It has been best characterized in patients presenting with cardiac tamponade who have persistently elevated right atrial pressure (i.e., failure to fall by 50 % or to a new level below 10 mmHg) after removal of the

pericardial fluid [22]. It is estimated that ECP complicates 5–10 % of cases of clinical tamponade, though there is significant geographic variation in the prevalence [22]. In most cases, the definitive treatment of ECP is pericardiectomy.

Since invasive hemodynamic monitoring is not routinely needed to diagnose cardiac tamponade, there is interest in developing non-invasive criteria to identify patients at higher risk of ECP who should undergo cardiac catheterization at the time of pericardiocentesis [14]. Echocardiography and cardiac magnetic resonance imaging have been explored but not yet systematically correlated with invasive parameters [14]. In addition, it has been suggested that patients with ECP have a distinct pattern of immune activation when compared with patients who have effusive but non-constrictive pericardial disease [23]. Further investigation into these differences may ultimately lead to the identification of novel serum or pericardial biomarkers for the diagnosis of ECP.

References

1. Sagrista-Sauleda J, Angel J, Sambola A, Permanyer-Miralda G. Hemodynamic effects of volume expansion in patients with cardiac tamponade. Circulation. 2008;117(12):1545–9.
2. Little WC, Freeman GL. Pericardial disease. Circulation. 2006;113(12):1622–32.
3. Reddy PS, Curtiss EI, Uretsky BF. Spectrum of hemodynamic changes in cardiac tamponade. Am J Cardiol. 1990;66(20):1487–91.
4. Imazio M, Adler Y. Management of pericardial effusion. Eur Heart J. 2013;34(16):1186–97.
5. Shabetai R. Pericardial and cardiac pressure. Circulation. 1988;77(1):1–5.
6. Beck C. Two cardiac compression triads. JAMA. 1935;104:714–6.
7. Brown J, MacKinnon D, King A, Vanderbush E. Elevated arterial blood pressure in cardiac tamponade. N Engl J Med. 1992;327(7):463–6.
8. Spodick DH. Pericardial rub. Prospective, multiple observer investigation of pericardial friction in 100 patients. Am J Cardiol. 1975;35(3):357–62.
9. Sulzbach LM. Measurement of pulsus paradoxus. Focus Crit Care/Am Assoc Crit Care Nurses. 1989; 16(2):142–5.
10. Spodick DH. Acute cardiac tamponade. N Engl J Med. 2003;349(7):684–90.
11. Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). Circulation. 2003;108(9):1146–62.
12. Authors/Task Force M, Adler Y, Charron P, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015;36(42):2921–64.
13. Wann S, Passen E. Echocardiography in pericardial disease. J Am Soc Echocardiogr. 2008;21(1):7–13.
14. Syed FF, Ntsekhe M, Mayosi BM, Oh JK. Effusive-constrictive pericarditis. Heart Fail Rev. 2013;18(3): 277–87.
15. Sagrista-Sauleda J, Angel J, Sambola A, Alguersuari J, Permanyer-Miralda G, Soler-Soler J. Low-pressure cardiac tamponade: clinical and hemodynamic profile. Circulation. 2006;114(9):945–52.
16. Silvestry FE, Kerber RE, Brook MM, et al. Echocardiography-guided interventions. J Am Soc Echocardiogr. 2009;22(3):213–31; quiz 316–7.
17. Vayre F, Lardoux H, Pezzano M, Bourdarias JP, Dubourg O. Subxiphoid pericardiocentesis guided by contrast two-dimensional echocardiography in cardiac tamponade: experience of 110 consecutive patients. Eur J Echocardiogr. 2000;1(1):66–71.
18. Tsang TS, Enriquez-Sarano M, Freeman WK, et al. Consecutive 1127 therapeutic echocardiographically guided pericardiocenteses: clinical profile, practice patterns, and outcomes spanning 21 years. Mayo Clin Proc. 2002;77(5):429–36.
19. Pradhan R, Okabe T, Yoshida K, Angouras DC, DeCaro MV, Marhefka GD. Patient characteristics and predictors of mortality associated with pericardial decompression syndrome: a comprehensive analysis of published cases. Eur Heart J Acute Cardiovasc Care. 2015;4(2):113–20.
20. El Haddad D, Iliescu C, Yusuf SW, et al. Outcomes of cancer patients undergoing percutaneous pericardiocentesis for pericardial effusion. J Am Coll Cardiol. 2015;66(10):1119–28.
21. Seferovic PM, Ristic AD, Maksimovic R, Tatic V, Ostojic M, Kanjuh V. Diagnostic value of pericardial biopsy: improvement with extensive sampling enabled by pericardioscopy. Circulation. 2003;107(7): 978–83.
22. Sagrista-Sauleda J, Angel J, Sanchez A, Permanyer-Miralda G, Soler-Soler J. Effusive-constrictive pericarditis. N Engl J Med. 2004;350(5):469–75.
23. Ntsekhe M, Matthews K, Syed FF, et al. Prevalence, hemodynamics, and cytokine profile of effusive-constrictive pericarditis in patients with tuberculous pericardial effusion. PLoS One. 2013;8(10), e77532.

Hypertensive Crises

15

Mark Schmidhofer

Case Presentation

A 67-year-old man was driven to the emergency room by his wife when he began acting strangely and massaging his sternum. He previously had been reasonably healthy, with past medical history significant for hypertension and hyperlipidemia. His prescribed medications included hydrochlorothiazide 12.5 mg daily, enalapril 5 mg twice daily, amlodipine 10 mg daily, clonidine 0.3 mg twice daily, combination simvastatin and ezetimibe, 81 mg of aspirin, and prn ibuprofen. His wife reported that his prescriptions all ran out 2 days prior to admission.

Physical examination revealed an overweight, restless man who was oriented to name and location but not the date. When asked if he was having chest discomfort, he looked up quizzically and rubbed his forehead. He was afebrile, respiratory rate was 28 breaths per minute, heart rate was 115 beats per minute, and blood pressure was 235/130. His lungs were clear to auscultation. Cardiac exam revealed a regular S1 and S2, an S3 and prominent S4, but no murmurs. His abdomen was soft and non-tender. He had no edema. Neurologic exam revealed no focal deficits.

M. Schmidhofer
Department of Medicine, University of Pittsburgh School of Medicine, Heart and Vascular Institute, UPMC Health System, Pittsburgh, PA, USA
e-mail: schmidhoferm@upmc.edu

Bedside ultrasound showed his optic nerve sheath to be 5.3 mm in diameter, B lines in both lung fields, and hyperdynamic left ventricular function without regional wall motion abnormalities or valvular dysfunction. His electrocardiogram (ECG) is shown in Fig. 15.1.

Basic metabolic profile demonstrated a plasma glucose of 139, creatinine of 1.4 mg/dL and a BUN of 30 mg/dL. His CBC was within normal limits. Urinalysis showed trace proteinuria, modest red blood cells, and no casts. His cardiac troponin was normal.

Question What is the diagnosis?

Answer Hypertensive crisis.

The patient presented with significant hypertension and end-organ dysfunction including hypertensive encephalopathy, acute kidney injury, and myocardial ischemia by ECG. He was treated with IV labetalol and intravenous nitroglycerin. Within the first hour, his blood pressure was reduced to 210/115. Labetalol and nitroglycerin were both uptitrated and furosemide was administered. Head CT showed no acute abnormalities. Upon obtaining further history, his wife mentioned that he was a recreational drug user, and the previous day had used cocaine. Urine drug screen was positive. Benzodiazepines were started. An arterial line was placed for invasive blood pressure monitoring. A repeat cardiac troponin was elevated at 4.3.

Over the course of the next 24 h, his blood pressure came down to 175/100 and heart rate

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_15

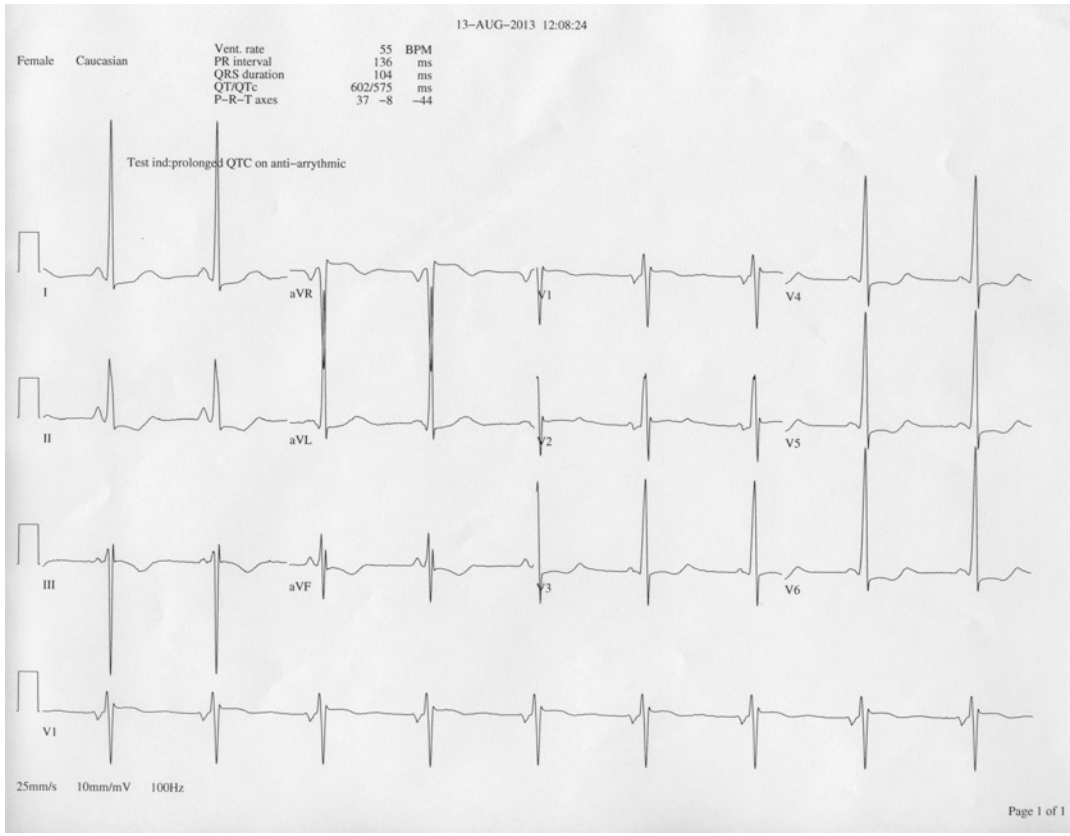


Fig. 15.1 Admission EKG

to 90. His mentation improved, he said he was having no chest discomfort, his lungs were clear to auscultation, and the S3 was no longer audible. The following day his previous oral anti-hypertensive regimen was reinstituted. 2 days later, he had an exercise stress SPECT myocardial perfusion study, which demonstrated no evidence of ischemia, and an ejection fraction of 60 %. He was discharged home the following day.

Principles of Management

Diagnosis

Hypertensive crisis is defined as uncontrolled hypertension (diastolic blood pressure ≥120 mmHg and/or systolic blood pressure ≥180 mmHg) accompanied by evidence of acute end organ involvement, most commonly manifested by mental status changes, stroke, aortic dissection, or renal dysfunction. The initial differential diagnosis should include acute myocardial infarction, aortic dissection, stroke (ischemic or hemorrhagic), subarachnoid hemorrhage, renal disease, drugs (such as amphetamines, cocaine, or dietary indiscretion with MAO inhibitors), head trauma, and other causes of autonomic overactivity such as pheochromocytoma, autonomic dysfunction, or antihypertensive drug withdrawal [1].

Traditionally, fundoscopic examination is used to identify papilledema and other hallmarks of hypertension. However, few non-ophthalmologists are skilled at fundoscopic examination, and neuro-ophthalmologists only agree on the Frisen grading of 36 % of the time [2].

Modified Frisen Scale
Papilledema Grade, major findings

0 (Normal)
1 (Minimal degree of edema) C shaped halo that is subtle and grayish, with a temporal gap; obscures underlying retinal details
2 (Low degree of edema) Circumferential halo
3 (Moderate degree of edema) Obscuration of ≥1 segment of major blood vessels leaving disc
4 (Marked degree of edema) Total obscuration on the disc of a segment of a major blood vessel on the disc
5 (Severe degree of edema) Obscuration of all vessels on the disc and leaving the disc

Modified from Scott CJ Arch Ophthalmol 2010;128(6):705

Optic disk diameter greater than 5 mm by ocular ultrasound (Fig. 15.2) has been shown to detect intracranial pressure greater than 20 with an AUC of 0.93 [3].

The patient in this case had evidence of pulmonary edema and thus received diuretics; however, many patients with hypertensive crises are volume depleted, and in the absence of obvious volume overload, diuretics should generally be avoided [5]. Renal injury from hypertensive crisis is manifest clinically by hematuria and creatinine elevation. Pathologically, renal injury is described as hypertensive nephrosclerosis, with necrosis of renal capillaries and "onion skinning" of small renal arterioles.

Withdrawal syndromes from cessation of antihypertensive therapy are common. Mechanisms are different depending on the discontinued medication. Clonidine withdrawal is seen commonly, and attributed to a rapid return of catecholamine secretion that has been suppressed during treatment. Symptoms from beta blocker withdrawal are related to drug half-life versus the speed of down regulation of adrenergic receptors that had previously been up regulated due to beta-blockade. Thus, withdrawal is more commonly seen with cessation of short acting as opposed to long acting agents [6].

The diagnosis of hypertensive encephalopathy is one of exclusion. Posterior reversible encephalopathy syndrome (PRES) presents with headache, vomiting, altered mental status and seizures, with loss of gray-white differentiation and cerebral edema, largely in the posterior portions of the brain (Fig. 15.3) [7]. While it usually resolves with treatment, there can be permanent deficits if not treated promptly.

Treatment of Hypertensive Crises

Patients with hypertensive crisis require intensive care unit admission and careful monitoring; given the usual need for parenteral treatment, an arterial line for continuous monitoring of the response to therapy should be placed in most cases. Selection of a specific agent(s) is tailored to the clinical scenario. Treatment goal is a reduction of systolic blood pressure by 10% during the first hour, and 25% during the first 24 h. In most instances the goal is not to quickly normalize the blood pressure, but to lower it in order to abort the crisis. Many patients have had long-standing hypertension and have auto-regulated their vasculature, and therefore a higher than normal blood pressure may be needed for adequate organ perfusion. After about 24 h of adequate control, patients are switched to an oral regimen. Management of acute aortic dissection and ischemic stroke are exceptions to these goals (see Chapters 11 and 12).

Pharmacotherapy (Table 15.1)

(a) Esmolol as an ultra-short acting beta blocker with an almost immediate onset, and the half-life is only 9 min.
(b) Labetalol is a combined alpha- and beta-adrenergic receptor blocker with a rapid onset. It is considered safe in patients with active coronary disease because its beta-blockade does not cause reflex tachycardia.

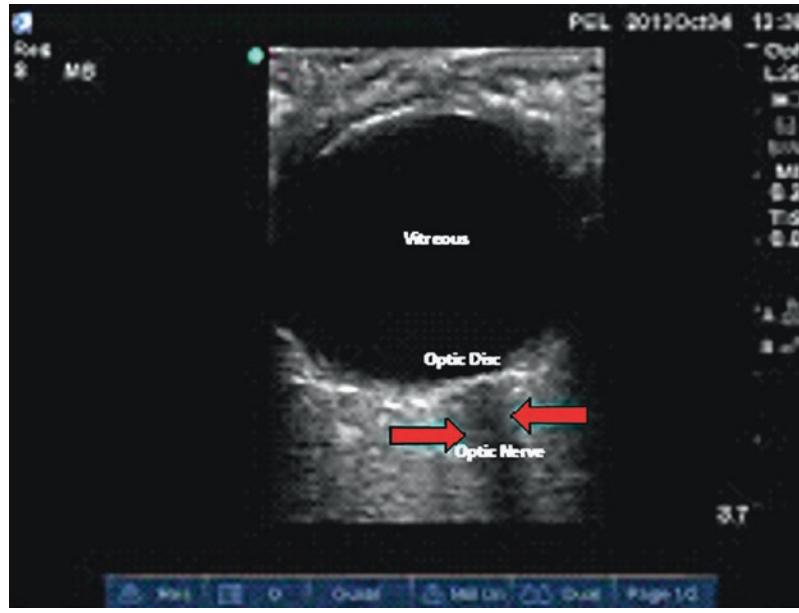


Fig. 15.2 Ocular ultrasound with optic nerve measurement 3 mm posterior to retina *arrows* indicate edges of the optic nerve (Image courtesy of Phil Lamberty, MD)

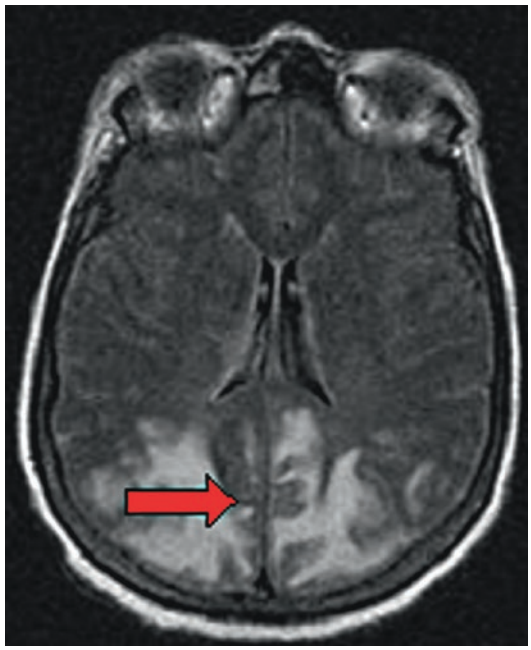


Fig. 15.3 Axial flair image of MRI of patient with PRES, demonstrating high signal activity (*arrow*) confined to the white matter in a posterior distribution (Image courtesy of Barton F Branstetter IV, MD)

(c) Sodium nitroprusside is a potent arteriolar vasodilator that has onset within a minute, and lasts for about 10 min. It is metabolized to cyanide and can lead to cyanide or thiocyanate toxicity especially (but not only) when used at high doses, for periods longer than 24–48 h, or in renal insufficiency.

(d) Nitroglycerin is predominantly a venodilator, though intravenously at higher doses it also has arteriolar dilating effects. Its antihypertensive effects are less potent than nitroprusside. Prolonged use can cause methemoglobinemia.

(e) Nicardipine is a calcium channel antagonist, and is an effective drug, but it has a longer onset of action and half-life. It is used in subarachnoid and intracranial hemorrhage because it may reduce cerebral vasospasm, and does not increase intracranial pressure as may occur with nitroprusside.

(f) Hydralazine as a direct arteriolar dilator. It can cause reflex tachycardia. Its use is generally limited to pregnant women who cannot use other agents.

(g) Less commonly used agents:
- Clevidipine is a short acting dihydropyridine calcium channel blocker, with an elimination time of between 5 and 15 min. It is an arteriolar dilator, and it is administered in a lipid emulsion, and is contraindicated in patients with allergies to eggs or soy products [9].

Table 15.1 Drugs used for the treatment of hypertensive crises

Drug	Dose	Onset	Duration	Role	Contraindications and Caveats	Adverse effects	Cost/Day
Sodium nitroprusside	0.25 μg/kg/min to max of 8 μg/kg/min	Seconds	1–2 min after stopping	Aortic dissection (in conjunction with beta-blocker), hyperadrenergic conditions, encephalopathy	Avoid with CVA, ICH, SAH. Caution in renal insufficiency – rates >4 μg/kg/min can cause toxic levels in 3 h (15)	Nausea, cyanate & thiocyanate toxicity, increased intracranial pressure, decreased cerebral blood flow, coronary steal	$12–$252
Nitroglycerine	5 μg/min titrate by 5 μg/min every 15 min to max of 100 μg/min	2–5 min	5–10 min	Cardiac ischemia, CHF, hyperadrenergic states, encephalopathy, renal failure	Concurrent use PDE-5 inhibitors. NTG is mostly a venodilator until high doses, care in patients who are volume depleted, tachyphylaxis common	Decreased CO headache, dizziness	$4–$12
Nicardipine	5 mg/h increase by 2.5 mg increments q 20 min to max of 15 mg/h	5–10 min	2–4 h	Aortic dissection in conjunction with beta blocker, cardiac ischemia, stroke, CNS bleed, hyperadrenergic conditions, encephalopathy, renal failure	Tachyphylaxis, avoid calcium channel blockers in CHF	Headache, flushing, nausea, reflex tachycardia, edema	$87–$262
Clevidipine	1–2 mg/h double every 90 s to max of 16 mg/h	2–4 min	5–20 min	Conjunction with beta blocker, CHF, cardiac ischemia, stroke, CNS bleed, hyperadrenergic conditions, encephalopathy, renal failure	Egg or soy allergy	Headache, flushing, nausea, reflex tachycardia	$260–$1300
Fenoldopam	0.1–0.6 μg/kg/min titrate q15 min	5–10 min	10–15 min	Renal failure aortic dissection in conjunction with beta blocker	Glaucoma	Hypotension, headache, tachycardia, nausea, flushing	$163–$985

(continued)

Table 15.1 (continued)

Drug	Dose	Onset	Duration	Role	Contraindications and Caveats	Adverse effects	Cost/Day
Labetolol	20 mg bolus; repeat boluses of 20–80 mg q10 min or 2 mg/min drip to total of 300 mg/day	5–10 min	3–6 h	Myocardial ischemia; hyperadrenergic states, aortic dissection, encephalopathy		Bradycardia, heart block, bronchospasm	$276
Esmolol	50 μg/kg load over 1 min; infusion at 20–50 μg/kg/min titrate by 25 μg/kg/min q 10 min to max of 300 μg/kg/min	1–5 min	15–30 min	Myocardia ischemia, hyperadrenergic states, aortic dissection, encephalopathy		Bradycardia, heart block, bronchospasm	$1270–$19,501
Enalaprilat	1.25 mg over 5 min titrate by 1.25 mg increments q12 h to max of 5 mg q6 h	15 min	4–6 h		Caution with renal insufficiency	Renal insufficiency, hyperkalemia. Unpredictable results depending on plasma renin levels	$5–$20
Phentolamine	5–10 mg repeat q5–15 min or drip at 0.2–5 mg/min	1–2 min	5–10 min	Adrenergic crisis		Reflex tachycardia, headache, nausea	$6902–$172,000
Hydralazine	10–20 mg bolus q30 min until target BP reached	10 min	2–6 h	Pregnancy		Reflex tachycardia results inconsistent prolonged effect	$25

Costs are as of 2015 in a single teaching hospital

- Fenoldopam as a dopamine agonist, and is the only intravenous agent that increases renal blood flow. It can increase intraocular pressure so should not be used in patients with glaucoma [10].
- Phentolamine is a nonselective alpha-adrenergic receptor blocker, and its use is largely in patients with pheochromocytoma or tyramine ingestion in patients who are on monoamine oxidase inhibitors. In these latter instances, one should not use beta-blockers until sufficient alpha blockade has been achieved; doing so could remove the vasodilatation of beta-1 stimulation, making the alpha mediated constriction worse.
- Enalaprilit is an intravenous form of enalapril. The blood pressure response to this agent can be variable because its action is dependent on plasma volume and renin activity. If the patient is hypovolemic with high plasma renin, excessive hypotension has been reported.

(h) Suggested drugs for specific clinical scenarios are shown in Table 15.2.

Evaluation for Secondary Causes of Hypertension

The prevalence of secondary hypertension is higher in patients who have presented with a hypertensive crisis compared with those who have not. Evaluation should be considered as guided by clinical presentation. Ten to forty-five percent of patients with hypertensive crises have renal artery stenosis [11]. Common secondary causes and suggested diagnostic strategies are outlined in Table 15.3.

Treatment of cocaine-induced hypertension includes benzodiazepines to reduce the central stimulatory effects of the cocaine, calcium antagonists, alpha blockers, and either nitroglycerin, nitroprusside, or clevidipine. Beta blockers are generally avoided because of the risk of removing beta-1 mediated vasodilation [12].

Evidence Contour

There are few high quality studies comparing various treatment modalities and outcomes for hypertensive crises. Those studies that are avail-

Table 15.2 Suggested drugs in particular clinical scenarios

Clinical scenario	Suggested drugs
Cardiac ischemia	Nitroglycerin, nitroprusside, or nicardipine plus a beta blocker such as esmolol, labetalol, or metoprolol
Pulmonary edema/congestive heart failure	Nitroglycerin, nitroprusside, or clevidipine; add beta blocker if tachycardic
Aortic dissection	Nitroprusside, clevidipine, or fenoldopam plus beta blocker such as labetalol or esmolol
Renal dysfunction (hematuria or worsening creatinine)	Fenolodopam [16]
Catecholamine excess (pheochromocytoma, drug withdrawal, cocaine, amphetamines)	Nicardipine, clevidipine, nitroprusside; benzodiazepines for cocaine
Hypertensive encephalopathy	Nicardipine, clevidipine, fenoldopam
Ischemic stroke (if BP >220/120 if not receiving thrombolytics, or >185/110 if receiving thrombolytics)	Nicardipine, clevidipine, fenoldopam
Intracerebral hemorrhage (if BP >200 or mean >150)	Nimodopine, nicardipine, clevidipine, fenoldopam
Subarachnoid hemorrhage (if BP >160)	Labetalol, nicardipine, clevidipine plus PO nimodopine for spasm reduction
Pregnancy (>150/100)	Labetalol, hydralazine, nitroglycerine if associated pulmonary edema

Table 15.3 More common causes of secondary hypertension and suggested testing strategies

Cause	Screening test	Definitive test
Chronic renal disease	UA/creatinine/renal ultrasound	
Renovascular disease	Duplex Doppler	MRI, CT angiography
Coarctation of aorta	BP arms and legs	Echo, MRI, CT angiography
Primary aldosteronism	Plasma and urinaryK Plasma aldosterone/renin ratio	Urinary aldosterone after salt load; adrenal CT; adrenal vein sampling
Cushing's disease	Dexamethasone suppression	
Pheochromocytoma	Plasma free metanephrines Urine metanephrines, catecholamines (falsely elevated during stress)	

able generally are observational, demonstrating the ability of an agent to achieve target blood pressures in what timeframe, or comparing a newer drug with an established agent, (e.g., clevidipine versus nitroprusside, or nicardipine with labetalol); in general, they demonstrate that all agents described in this chapter have utility in appropriate circumstances, without clear superiority of one versus another.

Specific Subsets of Patients with Hypertensive Crisis May Warrant Specific Treatment Approaches

(a) Blood pressure control for acute neurologic syndromes. As discussed above, recommended target blood pressures vary in different neurologic syndromes, and clear guidance is not available for any of them (see Chapter 34) [8, 13].

(b) The use of beta blockers in cocaine intoxication is unclear. The concern is that beta-blockade removes the beta mediated vasodilatation and thus can make the hypertension worse, and can make vasospasm worse. Given the significant recidivism rate, having patients on chronic beta-blockade may be unwise. However, in the presence of LV dysfunction or significant arrhythmias, the benefits may outweigh the risk, and at least one study raises the possibility that beta-blockers are not detrimental [14]. In general, however, most physicians avoid beta blockers.

References

1. Elliott WJ. Clinical features in the management of selected hypertensive emergencies. Prog CV Dis. 2006;48(5):316–25.
2. Sinclair AJ, Burdon MA, Matthews TD, Jacks A, Lawdwn M, Sivaguru A, Ball AK. Rating papilloedema: an evaluation of the Frisen classification in idiopathic intracranial hypertension. J Neurol. 2012;259(7):1406–12.
3. Kimberly HH, Shah S, et al. Correlation of optic nerve sheath diameter with direct measurement of intracranial pressure. Acad Emerg Med. 2008;15:201–4.
4. Marik PR, Varon J. Hypertensive crises. Chest. 2007;131:1949–62.
5. Hart GR. Withdrawl syndromes and the cessation of anti-hypertensive therapy. Arch Int Med. 1981;141:1125–7.
6. Servillo G, Bifulco F, DeRobertis E, Piazza O, Striano P, Tortora F, Striajno S, Tufano R. Posterior reversible encephalopathy syndrome in intensive care medicine. Intensive Care Med. 2007;33:230–6.
7. Jauch EC, Saver JL, Adams HP, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H. Guidelines for the early management of patients with acute stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:870–947.
8. Varon J. Treatment of acute severe hypertension. Drugs. 2008;68(3):283–97.
9. Elliot WJ, Weber RR, Roy F, Nelson KS, Oliner CM, Fumo MT, Gretler D, Mccray G, Murphy MB. Renal

and hemodynamic effects of fenoldopam versus nitroprusside in severe hypertension. Circulation. 1990;81:970–7.
10. Kitiyakara C, Guzman NJ. JASN. 1998;9(1):133–42.
11. Maraj S, Figueredo V, Morris L. Cocaine and the heart. Clin Cardiol. 2010;33(5):264–9.
12. Rothwell PM. Blood pressure in acute stroke; what questions remain? Lancet. 2015;385:582–5.
13. Dattilo PB, Hailpern SP, Fearon K, Sohal D, Nordin C. Beta blockers are associated with reduced risk of MI after cocaine use. Ann Emerg Med. 2008;51:117–25.
14. Shusterman NH, Elliott WJ, White WB. Fenoldopam but not nitroprusside improves renal function in severely hypertensive patients with normal or impaired baseline creatinine. Am J Med. 1993;95:161–8.

Atrial Fibrillation and Other Supraventricular Tachycardias

16

Daniel Sedehi

Case Presentation

A 49 year old male with a history of non-ischemic cardiomyopathy presented with worsening dyspnea on exertion, nausea, and three days of altered sensorium. A recent echocardiogram demonstrated severely reduced left ventricular ejection fraction (LVEF) of 15–20 %, moderate-to-severe functional mitral regurgitation, a dilated left ventricle, and a severely enlarged left atrium. At his prior office visits, electrocardiograms demonstrated sinus rhythm. He had been on a stable medical regimen of carvedilol 12.5 mg twice daily, lisinopril 40 mg daily, spironolactone 25 mg daily, furosemide 40 mg twice daily and he has not missed any of his medications. He denied dietary indiscretion or symptoms of infection. His heart rate was 106 beats per minute, blood pressure 88/60 mmHg, respiratory rate 26, temperature 98.8 F, and oxygen saturation 90 % on room air. On examination, he had cool extremities, elevated jugular venous pressure to the mandible while seated at 90°, bilateral rales half way up his lung fields, a prominent S3 gallop, a 3/6 holosysolic murmur best at the apex radiating to the axilla, and irregularly irregular, thready central pulses. He had 2+ pitting edema to his knees. He had no focal neurological deficits and his abdominal exam was unremarkable. His labs demonstrated a creatinine at 1.8 mg/dL, a sodium of 130 mmol/L, a potassium of 4.3 mmol/L, and a magnesium of 2.3 mg/dL. His lactate was 2.5. ECG is shown in Fig. 16.1.

Question What is this rhythm?

Answer Atrial fibrillation

This ECG demonstrates an irregularly irregular rhythm without discernable p-waves, consistent with atrial fibrillation (AF). The patient presented in cardiogenic shock. It was uncertain whether the AF was simply one manifestation of his decompensated heart failure or whether the onset of AF with a rapid ventricular rate was the primary reason for his decompensation, due to the rapid rate and loss of atrial contribution to ventricular filling. The duration of the arrhythmia was unknown, so the patient could not safely undergo elective cardioversion without anticoagulation and transesophageal echocardiography (TEE) to verify the absence of atrial thrombus. Because he was not hypotensive, immediate direct current cardioversion (DCCV) was not performed. Options for control of the ventricular rate were limited by his cardiogenic shock. He was admitted to the ICU where a heparin drip was initiated, and he was treated with intravenous furosemide. With diuresis alone, his shock state resolved, his

D. Sedehi
Cardiovascular Medicine, Knight Cardiovascular Institute, Oregon Health and Science University, Portland, OR, USA
e-mail: sedehi@ohsu.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_16

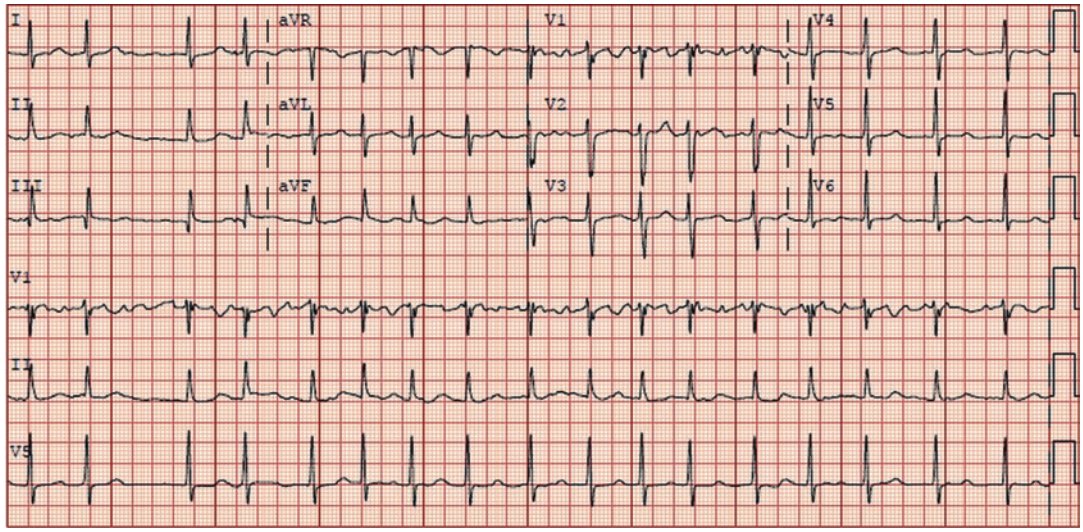


Fig. 16.1 12 Lead ECG with atrial fibrillation

creatinine, sodium, and lactate normalized, but his symptoms of dyspnea persisted. He underwent a TEE guided cardioversion, restoring sinus rhythm. He ultimately was discharged home with follow up with electrophysiology.

Principles of Management

Diagnosis

Conditions which increase the risk for new onset AF:

Triggers for Atrial Fibrillation

Acute/chronic pulmonary: pneumonia, pulmonary embolism, COPD exacerbation, sleep apnea

Heart failure, myocardial infarction, mitral valve disease

Cardiac or thoracic surgery

Acute or chronic hyperthyroidism, alcohol use

The incidence of AF increases steadily with advancing age. AF is commonly classified into three categories: paroxysmal, persistent (sustained longer than 7 days), or permanent [1]. Physical exam demonstrates an irregularly irregular heart rate on auscultation of the heart and palpation of the pulse. ECG findings include a variable R-R interval, with no discernable P-wave preceding each QRS complex. R-R variability may be less apparent at elevated heart rates (Fig. 16.2).

Echocardiograms demonstrate absence of A waves on pulse- and continuous-wave Doppler of the mitral valve in the apical views, along with a single E wave on M-Mode of the mitral valve in the parasternal long axis view (Fig. 16.3).

AF may be asymptomatic or associated with a spectrum of symptoms ranging from palpitations to those of heart failure or cardiogenic shock, severe dyspnea, and lack of energy.

Physiologic Effects

The deleterious effects of AF come in two primary categories: hemodynamic embarrassment and cardioembolism. Hemodynamically, AF results in the lack of mechanical contraction of the left atrium, resulting in depressed preload of the left ventricle. In the setting of heart failure with reduced ejection fraction (HFrEF) or severe aortic stenosis, this acute loss of atrial "kick" can

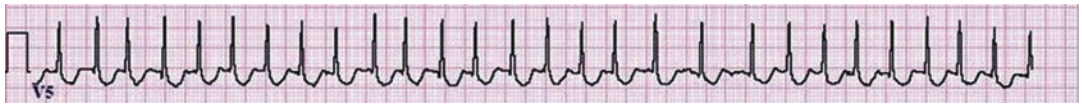


Fig. 16.2 R-R variability with very high ventricular rates

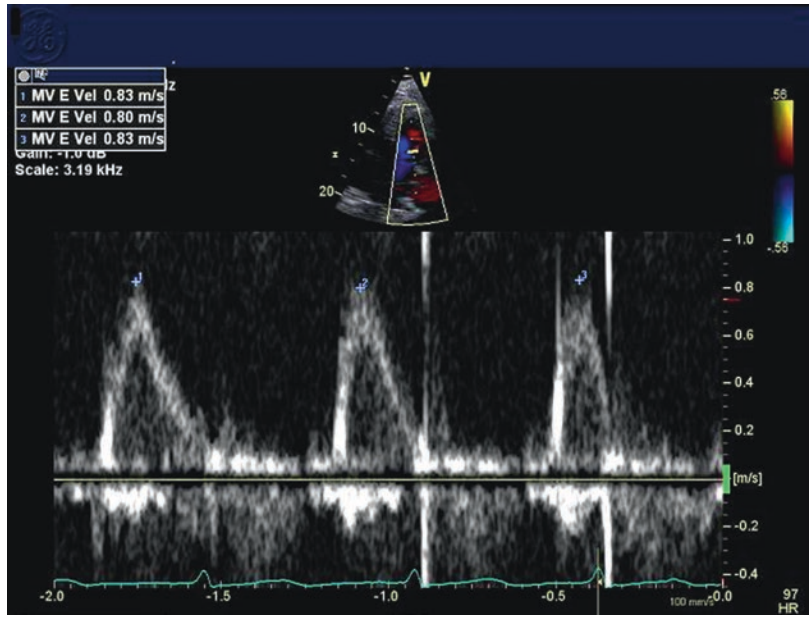


Fig. 16.3 Mitral inflow pattern in atrial fibrillation, with no atrial contraction, just passive filling (E wave only, no A wave)

result in a meaningful decline in cardiac stroke volume and cardiac output [2]. Patients with heart failure with preserved ejection fraction (HFpEF) are exquisitely sensitive to preload so acutely lowering their preload conditions can have rapid deleterious effects on their cardiac function. The same principle applies to patients with hypertrophic obstructive cardiomyopathy (HOCM) and pulmonary hypertension [3]. In structurally normal hearts, some patients may be quite symptomatic from the loss of the atrial "kick", and others may be asymptomatic. In many asymptomatic patients, their first sign of the arrhythmia is an embolic event such as a stroke [4].

A patient's risk of embolic events such as cerebrovascular accidents (CVAs) or ischemic bowel can be calculated using a prognostic model such as the CHADS2-Vasc score that is available through a variety of online risk calculators (e.g. http://www.mdcalc.com/cha2ds2-vasc-score-for-atrial-fibrillation-stroke-risk/) (Table 16.1) [5]. This model has been validated and helps clinicians and patients understand the long term risk for embolic events [6].

Another model, the HAS-BLED score, uses similar inputs, but can help calculate the possibility of a severe bleeding event during anticoagulation (e.g. http://www.mdcalc.com/has-bled-score-for-major-bleeding-risk/) (Table 16.2) [7]. These models help predict risk of ischemic events over the course of years, so apply less to the acute inpatient management of patients with AF.

Treatment Strategies

Aligned with physiologic effects, treatment of AF has two main goals: hemodynamic and embolic risk mitigation. There are two potential strategies to mitigate the hemodynamic impact of AF rate control and rhythm control. Long-term outpatient management of AF was assessed in the AFFIRM trial and despite long-standing

Table 16.1 CHADS2-Vasc score [5]

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65–74 y	1
Sex **c**ategory (i.e. female gender)	1

Table 16.2 HAS-BLED score [7]

Letter	Clinical characteristic	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly	1
D	Drugs or alcohol (1 point each)	1 or 2

debate as to the applicability of the outcome, no significant mortality benefit to rhythm control was identified [8]. Inpatient management of AF is more guided by symptoms and clinical presentation.

Rate Control

Patients with AF frequently present with rapid ventricular rates which drive their symptoms. Heart rate control is achieved by two main classes of medications: beta-blockers and calcium channel blockers. Both classes of medications slow AV nodal conduction and exert negative inotropic effects. Care must be exercised with the use of these agents, particularly in patients with HFrEF, because of their negative inotropic effects. Diltiazem carries a greater risk of inducing cardiogenic shock and even death in patients with HFrEF, especially if they are in a decompensated state, versus metoprolol. Esmolol may be a reasonable option with very rapid offset that can be trialed in patients who may not tolerate rate controlling agents with negative inotropic effects. Digoxin has modest efficacy but is sometimes the best alternative when beta-blockers and calcium channel blockers are not tolerated. Extrapolation of data from the RACE 2 trial suggests that targeting a heart rate of less than 110 bpm is a safe management strategy, assuming hemodynamic stability (Table 16.3) [9].

Rhythm Control

This method is preferred for patients with acute hemodynamic collapse, acute severe symptomatic AF with controlled rates, and patients in whom AF worsens their symptoms from heart failure. The options for rhythm control include antiarrhythmic medications, direct current cardioversion (DCCV), and/or catheter ablation. DCCV should be considered in patients who are displaying evidence of cardiogenic shock, not solely defined as low blood pressures, but with evidence of end organ hypoperfusion possibly contributed to by loss of atrial contraction. This can be particularly important in preload dependant states such as severe aortic stenosis and hypertrophic obstructive cardiomyopathy. Antiarrhythmic medications are used in accordance with ACC/AHA guidelines and emphasize the importance of structural heart disease and coronary artery disease in the selection of the safest and most effective medication (Fig. 16.4; see ACCF/AHA guidelines http://content.onlinejacc.org/article.aspx?articleid=1854230) [1].

Stroke Prevention

Anticoagulation is critical in patients with AF. Commonly used medications include intravenous unfractionated heparin or subcutaneous low-molecular weight heparin. Prior to undergoing DCCV or chemical cardioversion, patients need to be therapeutic on anticoagulation and most should undergo a TEE, assessing for the presence of left atrial appendage thrombus, if a prolonged period of anticoagulation (≥4 weeks) is not possible prior to elective cardioversion [10]. If an atrial thrombus is present, it is recommended to maintain therapeutic anticoagulation for at least 1 month, after which a repeat TEE should be performed to assess for resolution of the thrombus [11]. With no thrombus present

Table 16.3 Common dosage of intravenous medications for rate control of AF

	Intravenous administration	Usual oral maintenance dose
Beta blockers		
Metoprolol tartrate	2.5–5.0 mg IV bolus over 2 min; up to 3 doses	25–100 mg BID
Esmolol	500 mcg/kg IV bolus over 1 min, then 50–300 mcg/kg/min IV	N/A
Nondihydropyridine calcium channel antagonists		
Verapamil	0.075 – 0.15 mg/kg IV bolus over 2 min; may give an additional 10.0 mg after 30 min if no response, then 0.005 mg/kg/min infusion	180–480 mg QD (ER)
Diltiazem	0.25 mg/kg IV bolus over 2 min, then 5–15 mg/h	120–360 mg QD (ER)
Others		
Digoxin	0.25 mg IV with repeat dosing to a maximum of 1.5 mg over 24 h	0.125–0.25 mg QD
Amiodarone[a]	300 mg IV over 1 h, then 10–50 mg/h over 24 h	100–200 mg QD

[a]Amiodarone should not be used when cardioversion is contraindicated such as in patients not previously anticoagulated

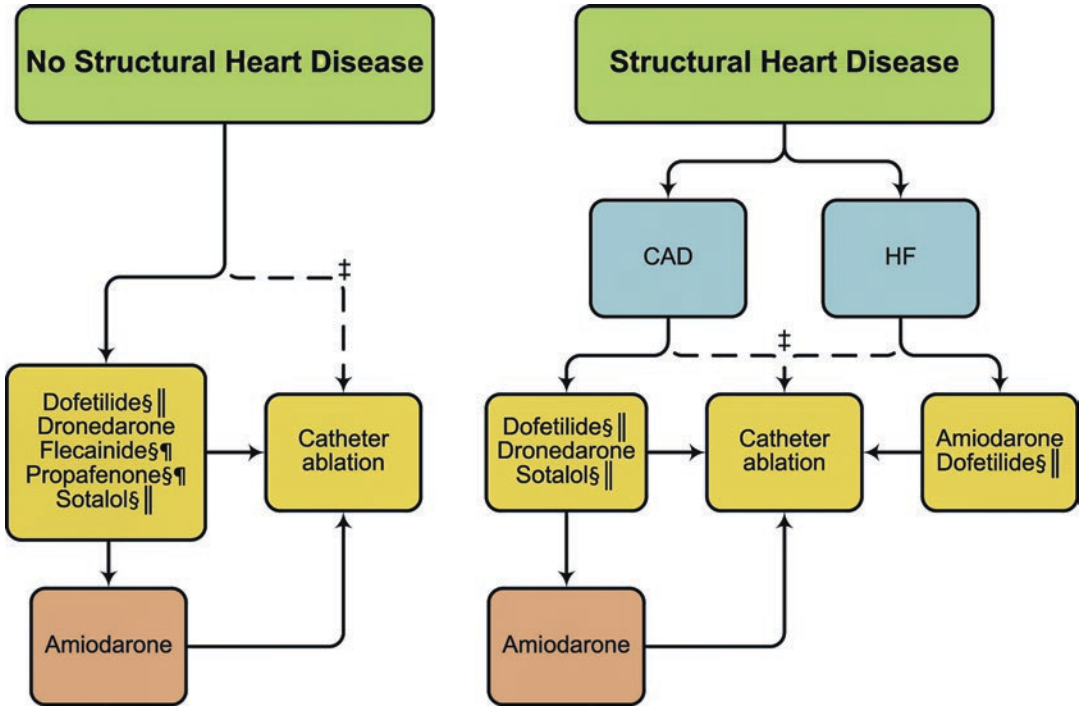


Fig. 16.4 ACCF/AHA guidelines for selection of antiarrhythmic drug therapy for AF

in the left atrial appendage, DCCV can be performed safely while on anticoagulation. The highest risk of embolic phenomena is present within the first month after DCCV, so diligence must be applied to anticoagulation during this period. For patients who acutely develop AF within the hospital or the exact time of onset is known via symptomatology, risk benefit ratio lies in favor of DCCV without TEE guidance if done within the first 48 hours [1].

Other Supraventricular Tachycardias (SVT)

Aside from AF, other non-sinus supraventricular tachycardias are common in critically ill patients. Like AF, these are narrow complex tachycardias unless there is aberrant conduction. These are typically divided according to the relationship between the R-wave and the P-wave, so called short- or long-RP tachycardia. See Table 16.4 and Fig. 16.5 for the differential of short- and long-RP tachycardia.

Hemodynamically, these SVTs can have similar features to AF. In the setting of hemodynamic instability and hypotension, DCCV is an appropriate first response. Diagnosis and acute management often fall under the same action, as many SVTs rely on the AV node for completing their circuit. Breaking that circuit, either with a vagal maneuver or administration of intravenous adenosine, can both reveal and abolish the re-entrant rhythm (Fig. 16.6).

To identify the rhythm, it is recommended to have a 12 lead rhythm strip recording while administering adenosine, so as to capture the termination of the rhythm and possibly to reveal underlying re-entrant rhythm by unveiling flutter waves (Table 16.5).

Certain rhythms, such as atrial flutter, can benefit from a standard catheter ablation, otherwise, treatment with beta-blockers is recommended for short and long term management. If these do not maintain sinus rhythm, catheter ablation may be attempted.

Table 16.4 Differential of short- and long-RP tachycardias

Short RP tachycardias	Long RP tachycardias
Typical AV nodal reentrant tachycardia	Atrial tachycardia
AV reentrant tachycardia using accessory pathway	Sinus tachycardia
Atrial tachycardia with first degree AV block	Atrial flutter
Junctional tachycardia	AV reentrant tachycardia

Evidence Contour

Despite the prevalence of AF (>9 % of Medicare patients in 2010) management still is quite challenging [12]. Certain populations of patients present challenges in dealing with this disease.

High Bleeding Risk in Post-operative Cardiac Surgery Patients

Some studies have demonstrated a near 25 % risk for the development of post-operative AF in patients undergoing cardiothoracic surgery [13]. The development of AF increases hospital length of stay and morbidity [14]. Strategies here often focus on rhythm control, most often achieved with the antiarrhythmic amiodarone [15]. Anticoagulation with heparin products may pose a prohibitive risk for bleeding, so discussion with the surgical team is recommended prior to initiation of anticoagulation in these patients.

Concurrent Inotropic Support

The onset of AF can complicate management of patients with cardiogenic shock on intravenous inotropic support. In these patients, rhythm control is not always possible as the adrenergic stimulus from the inotropic infusions is significantly arrhythmogenic. Rapid ventricular rates are frequently encountered, and rate control is both a challenge and there are no clinical studies to serve as a guide to therapy. Amiodarone and digoxin can be used in these cases, mainly for their rate control effects. Care must be exercised with digoxin in elderly patients, along with those impaired kidney function. Amiodarone should be used with caution in patients with underlying lung, liver, or thyroid disease.

Rhythm Control in HFrEF

In a subset of the AFFIRM trial, rhythm control was preferred in patients with HFrEF [16]. In patients with HFrEF and cardiac resynchronization therapy devices, rhythm control has a lower mortality [17]. For these reasons, it is recommended to try a rhythm control strategy for patients with HFrEF who are still symptomatic with rate controlled AF [1].

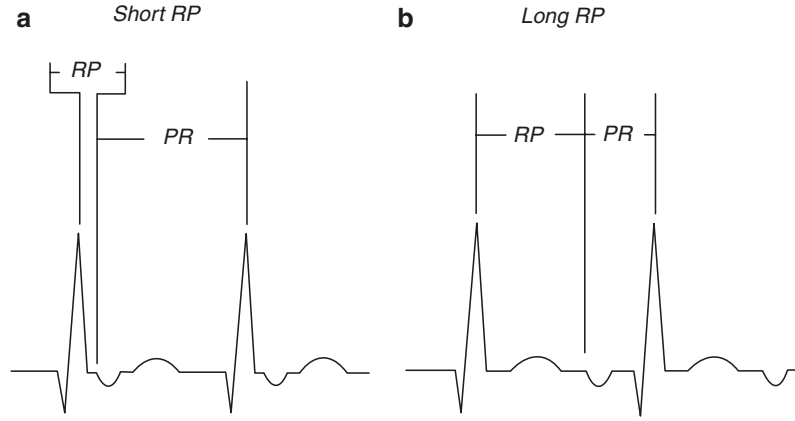


Fig. 16.5 (**a**) Short RP tachycardia, (**b**) Long RP tachycardia (Courtesy: Icyberrounds.com)

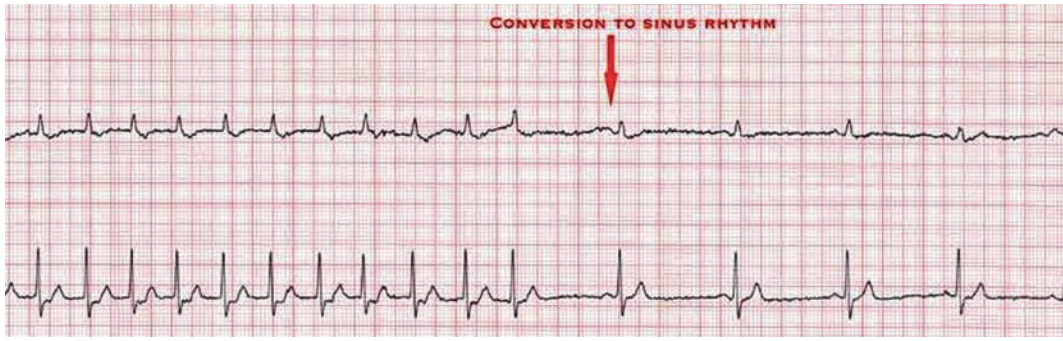


Fig. 16.6 Termination of SVT with adenosine (Courtesy: emedu.org)

Table 16.5 Effect of adenosine on short RP and long RP tachycardias

Short RP tachycardias	Effect of adenosine	Long RP tachycardias	Effect of adenosine
Typical AV nodal reentrant tachycardia	Terminates	Atrial tachycardia	Creates AV-block revealing underlying atrial tachycardia and slowing the ventricular rate
AV reentrant tachycardia using accessory pathway	Terminates	Sinus tachycardia	Creates AV-block revealing underlying atrial rhythm and slowing the ventricular rate
Atrial tachycardia with first degree AV block	Creates AV-block revealing underlying atrial tachycardia and slowing the ventricular rate	Atrial flutter	Creates AV-block revealing underlying atrial flutter and slowing the ventricular rate
Junctional tachycardia	Terminates	AV reentrant tachycardia	Terminates

References

1. Fuster V, Rydén LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the North American Society of Pacing and Electrophysiology. JAC J Am Coll Cardiol. 2001;38(4):1231–65.
2. Maganti K, Rigolin VH, Sarano ME, Bonow RO. Valvular heart disease: diagnosis and management. Mayo Clin Proc. 2010;85(5):483–500.

3. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation. 2001;104(21):2517–24.
4. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366(2):120–9.
5. Lip G, Nieuwlaat R, Pisters R. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263–72.
6. Ntaios G, Lip GYH, Makaritsis K, Papavasileiou V, Vemmou A, Koroboki E, et al. CHADS2, CHA2DS2-VASc, and long-term stroke outcome in patients without atrial fibrillation. Neurology. 2013;80(11):1009–17.
7. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093–100. American College of Chest Physicians.
8. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347(23): 1825–33.
9. Van Gelder IC, Groenveld HF, Crijns HJGM, Tuininga YS, Tijssen JGP, Alings AM, et al. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med. 2010;362(15):1363–73.
10. Klein AL. Cardioversion guided by transesophageal echocardiography: the ACUTE Pilot Study: a randomized, controlled trial. Ann Intern Med. 1997;126(3):200–9. American College of Physicians.
11. Klein AL, Murray RD, Grimm RA. Role of transesophageal echocardiography-guided cardioversion of patients with atrial fibrillation. JAC J Am Coll Cardiol. 2001;37(3):691–704.
12. McManus DD, Rienstra M, Benjamin EJ. An update on the prognosis of patients with atrial fibrillation. Circulation. 2012;126(10):e143–6.
13. Imazio M, Brucato A, Ferrazzi P, Rovere ME, Gandino A, Cemin R, et al. Colchicine Reduces Postoperative Atrial Fibrillation. Circulation. 2011;124(21):2290–5.
14. Mathew JP, Parks R, Savino JS, Friedman AS, Koch C, Mangano DT, et al. Atrial fibrillation following coronary artery bypass graft surgery: predictors, outcomes, and resource utilization. MultiCenter Study of Perioperative Ischemia Research Group. JAMA. 1996;276(4):300–6.
15. Mitchell LB, Exner DV, Wyse DG, Connolly CJ, Prystai GD, Bayes AJ, et al. Prophylactic oral amiodarone for the prevention of arrhythmias that begin early after revascularization, valve replacement, or repair: PAPABEAR: a randomized controlled trial. JAMA American Medical Association. 2005;294(24):3093–100.
16. Guglin M, Chen R, Curtis AB. Sinus rhythm is associated with fewer heart failure symptoms: insights from the AFFIRM trial. Heart Rhythm. 2010;7(5):596–601.
17. Gasparini M, Leclercq C, Lunati M, Landolina M, Auricchio A, Santini M, et al. Cardiac resynchronization therapy in patients with atrial fibrillation: the CERTIFY study (Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry). JACC Heart Fail. 2013;1(6):500–7.

Ventricular Arrhythmias

17

Sohaib Tariq and Howard A. Cooper

Case Presentation

A 71 year old male with a history of hypertension, hyperlipidemia, and coronary artery disease, with coronary artery bypass grafting 15 years earlier, presented with repeated episodes of lightheadedness over the course of several hours. In the emergency department he was found to be in monomorphic VT at a rate of 206 beats per minute (Fig. 17.1). He was urgently cardioverted to normal sinus rhythm and administered a 150 mg bolus of intravenous amiodarone followed by a continuous infusion. A 12-lead electrocardiogram revealed non-specific T-wave abnormalities. Subsequently, he had intermittent episodes of third degree atrioventricular block with a ventricular escape rhythm at 50 beats per minute. Initial laboratory investigation was significant for potassium of 3.9 mEq/L, magnesium of 1.8 mg/dL, white blood cell count of 22.6 K, and cardiac troponin I of 0.13 ng/mL. He was transferred to the cardiac intensive care unit where he continued to have frequent episodes of monomorphic VT.

S. Tariq
Division of Cardiology, Westchester Medical Center, Valhalla, NY, USA

H.A. Cooper (✉)
Inpatient Cardiology, Division of Cardiology, Westchester Medical Center, Valhalla, NY, USA
e-mail: howard.cooper@wmchealth.org

Question What approach should be taken in management of multiple recurrences of ventricular arrhythmias over a short period of time, i.e. VT storm?

Answer Antiarrhythmic medications and correction of the arrhythmia trigger(s).

The patient was initially treated with intravenous amiodarone and external defibrillation for episodes of VT. A temporary transvenous pacemaker was inserted to prevent bradycardia in the setting of intermittent complete atrioventricular block. Electrolytes were repleted. Intravenous lidocaine was added for breakthrough episodes of VT. Benzodiazepines were administered to ameliorate anxiety. Echocardiography showed left ventricular systolic dysfunction, with an estimated ejection fraction of 30%. Right heart catheterization revealed elevated intracardiac filling pressures and a cardiac index of 1.9 L/min/m^2. An endomyocardial biopsy was negative for signs of inflammation or myocarditis. Left heart catheterization demonstrated severe native three vessel disease with an atretic left internal mammary artery (LIMA) graft to the left anterior descending (LAD) coronary artery, and patent vein grafts to obtuse marginal (OM2), diagonal branch (D1), and right coronary artery (RCA). A drug eluting stent was placed in mid LAD. There was no significant elevation in serum troponin levels. No further episodes of VT were observed, even after discontinuation

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_17

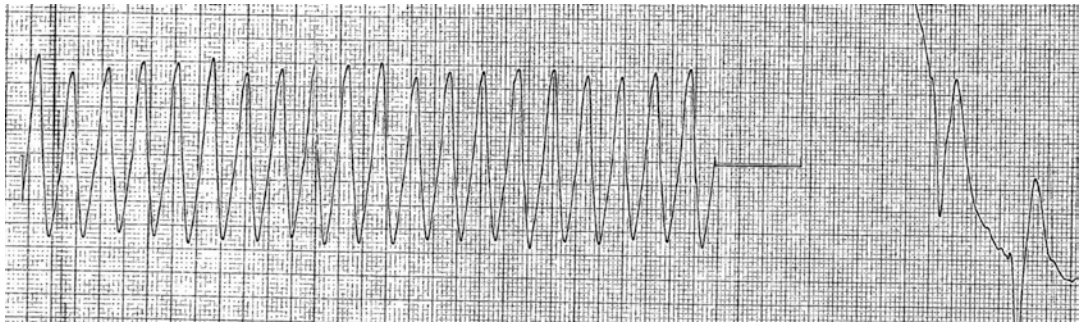


Fig. 17.1 Monomorphic ventricular tachycardia

of lidocaine. The patient received an implantable cardioverter defibrillator (ICD) and was discharged home on a long-acting beta blocker.

Three weeks later the patient presented with pre-syncope and palpitations. ICD interrogation revealed multiple episodes of VT resulting in defibrillator shocks. Intravenous amiodarone was initiated, but VT continued to recur. An intra-aortic balloon pump was placed with subsequent resolution of the VT. He then underwent electro-anatomic mapping followed by radiofrequency catheter ablation, after which he had no further VT.

Principles of Management

Diagnosis

Ventricular arrhythmias include a broad spectrum of rhythm disorders, which may have no clinical consequence or may result in sudden cardiac death. Patients at high risk for ventricular arrhythmias are those with ischemic heart disease, myocarditis, underlying structural heart disease, inherited or acquired channelopathies, drug intoxication, electrolyte derangement, and hyperthyroidism (Table 17.1). However, ventricular arrhythmias may occur in the absence of any of these predisposing factors. The diagnosis of ventricular arrhythmias may be suggested by the clinical presentation, but confirmation requires electrocardiographic recording.

Classification of VT

Ventricular arrhythmias are subdivided into non-sustained (premature ventricular contractions and non-sustained VT) and sustained (defined as VT lasting for more than 30 s or VF). VT may be monomorphic or polymorphic, with *torsades de pointes* representing a specific form of polymorphic VT occurring in the setting of a prolonged QT interval. Electrical storm is defined as 3 or more episodes of sustained VT, VF, or appropriate ICD therapies during a 24-h period. This condition has variably been referred to as "VT storm" or "VT cluster". An important subgroup of electrical storm is incessant VT, which refers to repeated recurrence within 5 min of a technically successful therapy. Management of sustained ventricular arrhythmias is essential aspect of critical care medicine.

Monitoring and Testing

Patients presenting with a suspicion of ventricular arrhythmias should undergo continuous electrocardiographic monitoring in a setting in which appropriate care can be rapidly deployed. A 12-lead ECG should be obtained at baseline and assessed for evidence of ischemia, underlying structural heart disease, and the various channelopathies, such as long QT syndrome or Brugada syndrome (Fig. 17.2). Every attempt should be made to obtain a 12-lead ECG during the occurrence of a ventricular arrhythmia. Confirmation of the presence of a ventricular arrhythmia may require prolonged electrocardiographic monitoring (inpatient or

Table 17.1 Approach to common etiologies of ventricular arrhythmias

Etiology	History	Evaluation	Treatment
Myocardial ischemia	Chest pain, dyspnea	ECG, echocardiography, stress testing, coronary angiography	Coronary revascularization, beta blockers, intra-aortic balloon pump, ablation
Channelopathies	Syncope, family history of sudden death	ECG, exercise testing, provocative pharmacological testing	Removal of QT-prolonging drugs, intravenous magnesium, potassium replacement, temporary pacing, sympathectomy, ICD
Myocarditis	Flu-like symptoms, chest pain	ECG, echocardiography, cardiac MRI, endomyocardial biopsy	Amiodarone, beta blockers, ICD, steroids in selected cases where indicated for subtypes of myocarditis
Electrolyte imbalance	Renal failure, dehydration	Serum electrolytes, ECG	Correction of electrolytes
Cardiomyopathy	Symptoms of heart failure	Echocardiography, coronary angiography, cardiac MRI	Amiodarone, beta blockers, ICD
Sarcoidosis	Lung involvement	Cardiac MRI, biopsy	Steroid therapy, immunomodulating agents, ICD
Arrhythmogenic right ventricular cardiomyopathy	Palpitations, syncope, dyspnea, family history	ECG, cardiac MRI, genetic testing	Beta blockers, ICD, amiodarone
Drug intoxication	Drug abuse, use of QT prolonging medications or digoxin	ECG, serum drug levels	Stop offending agent
Hyperthyroidism	Anxiety, palpitations, heat intolerance	Thyroid hormone studies	Beta blockers, glucocorticoids, anti-thyroid medications

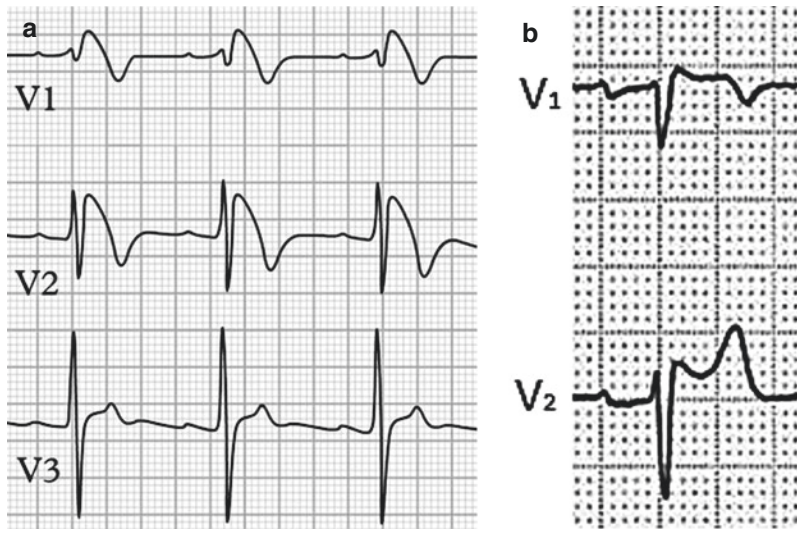


Fig. 17.2 Electrocardiographic tracings in Brugada syndrome. (**a**) Type 1; "coved type" ST-T segment configuration. (**b**) Type 2; "saddle back" pattern

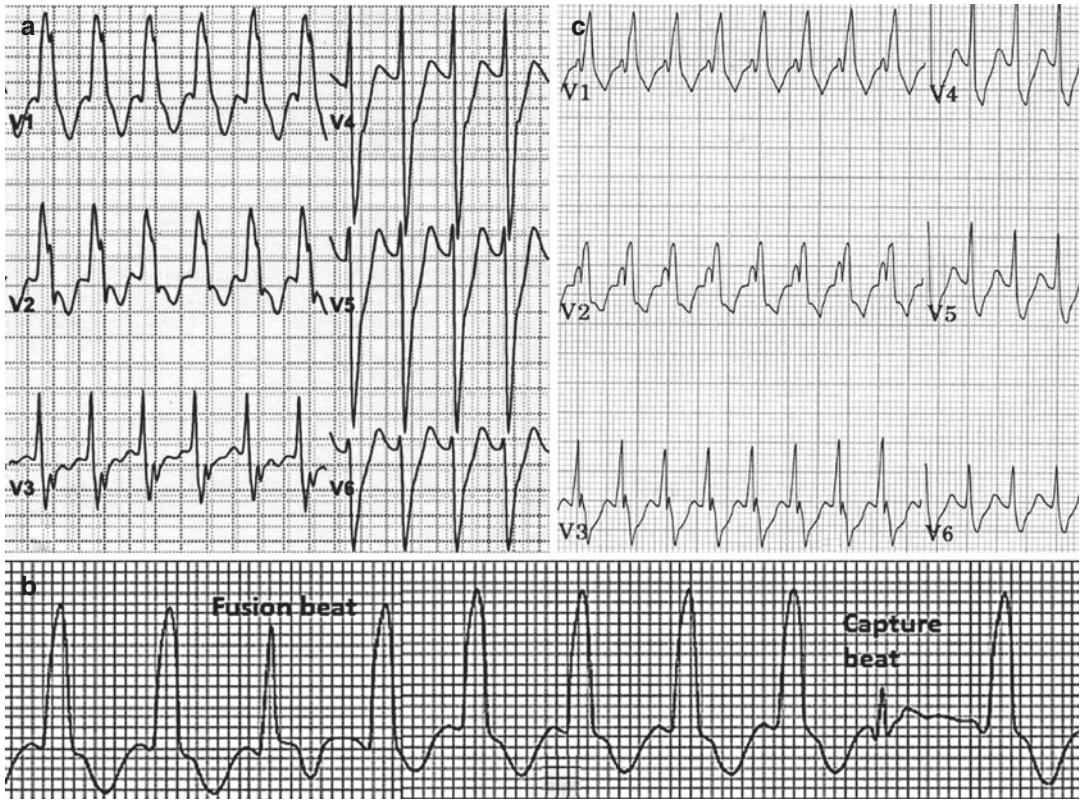


Fig. 17.3 (**a**) Monomorphic ventricular tachycardia. Atrioventricular dissociation can be seen. (**b**) Ventricular tachycardia with fusion beat (hybrid complex of supraventricular and ventricular activation) followed by a capture beat. (**c**) Supraventricular tachycardia with aberrancy. Atrioventricular dissociation and fusion beats are absent. RS complexes in precordial leads are evident

outpatient) (Fig. 17.3), or invasive electrophysiologic testing. Once the diagnosis of a ventricular arrhythmia has been confirmed, further studies should be obtained as clinically indicated in order to elucidate the underlying cause. These may include: serum electrolyte testing, thyroid studies, screening for drugs of abuse, echocardiography, cardiac magnetic resonance imaging, coronary angiography, endomyocardial biopsy, exercise electrocardiography, and provocative pharmacological testing. A family medical history should be assessed for sudden death or known cardiomyopathies. Myocardial ischemia should be considered in all cases of polymorphic VT and ventricular fibrillation with coronary angiography being appropriate early in the evaluation in most cases.

General Measures

Non-sustained VT (Fig. 17.4) is encountered very commonly in the intensive care unit among patients with structural heart disease. In general, no specific therapy is required for asymptomatic patients other than electrolyte repletion and treatment of the underlying condition. For frequent or symptomatic non-sustained VT, however, treatment with beta blockers should be considered. Patients who are not otherwise candidates for an ICD for primary prevention of sudden death, for example, those with non-sustained VT, a history of MI, and moderate left ventricular systolic dysfunction (EF >35 to 40 %), may be considered for electrophysiology study (EPS) when stable in order to determine if an ICD is indicated.

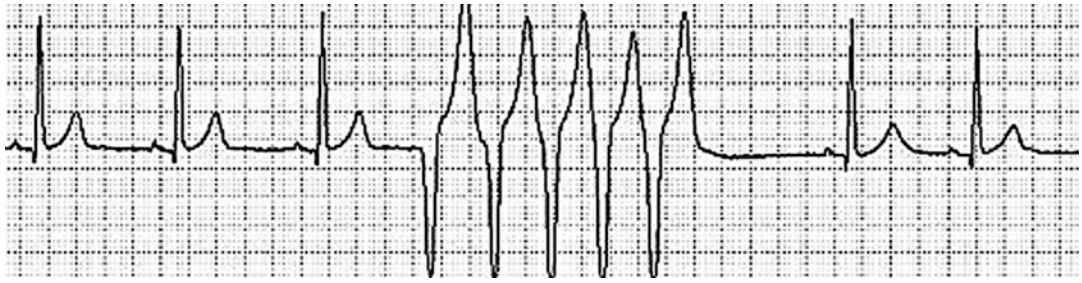


Fig. 17.4 Non-sustained ventricular tachycardia

In patients with sustained ventricular arrhythmias, it is essential that diagnostics and treatments be implemented simultaneously (Fig. 17.5). For patients with cardiac arrest from pulseless VT or VF, guideline-directed ACLS – including rapid defibrillation – should be implemented immediately. When an ICD is present, device interrogation and, if necessary, reprogramming should be performed by a qualified practitioner to ensure the delivery of appropriate therapy and to avoid shocks for non-life-threatening arrhythmias [1]. Triggers of ventricular arrhythmias such as ischemia, electrolyte imbalances, decompensated heart failure, bradycardia, drug intoxication, and hyperthyroidism, should be identified and treated. Heart failure is an under-recognized trigger for new or a significant change in pattern of ventricular arrhythmias in patients with structural heart disease. In patients with VT storm requiring multiple shocks, pain control and sedation with narcotics and/or benzodiazepines should be provided to aid in reducing sympathetic tone. In patients with VT that is refractory to these measures, it is often beneficial to intubate and deeply sedate such patients to further suppress sympathetic activation from pain and anxiety.

A multi-disciplinary approach is appropriate for most patients with sustained ventricular arrhythmias requiring intensive care. The critical care specialist should work closely with the electrophysiology team, and also consider consultation with interventional cardiologists and/or specialists in advanced heart failure as dictated by the specific needs of the patient.

Beta Blockers

Beta blockers should be used in the initial phase of treatment for most patients with ventricular arrhythmias [2]. These drugs play an important role in reducing ischemia, decreasing sympathetic tone, and increasing the fibrillation threshold. Nonrandomized data suggests that intravenous propranolol may be the beta blocker of choice in this setting. However, short-acting metoprolol is a reasonable alternative that is used commonly in clinical practice. In patients with relative hypotension, esmolol is preferred due to its very short half-life [3]. The beta blocker dose should be titrated to maintain a heart rate of 45–60 beats per minute. Insufficient advancement of beta blocking agents is a common error in the management of patients with symptomatic VT. Nevertheless, beta blocker therapy may be limited by bradycardia, hypotension, heart block, and bronchospasm.

Amiodarone

Intravenous amiodarone blocks fast sodium channels and L-type calcium channels, and inhibits norepinephrine release. Amiodarone is highly effective, and has been proven to be superior to other antiarrhythmic agents in suppressing ventricular arrhythmias [4–6]. Amiodarone is given as 150 mg bolus over 10 min (300 mg IV push for cardiac arrest) followed by a continuous infusion, with supplemental boluses given as needed for arrhythmia recurrence. Because of its potential to cause severe phlebitis, intravenous amiodarone

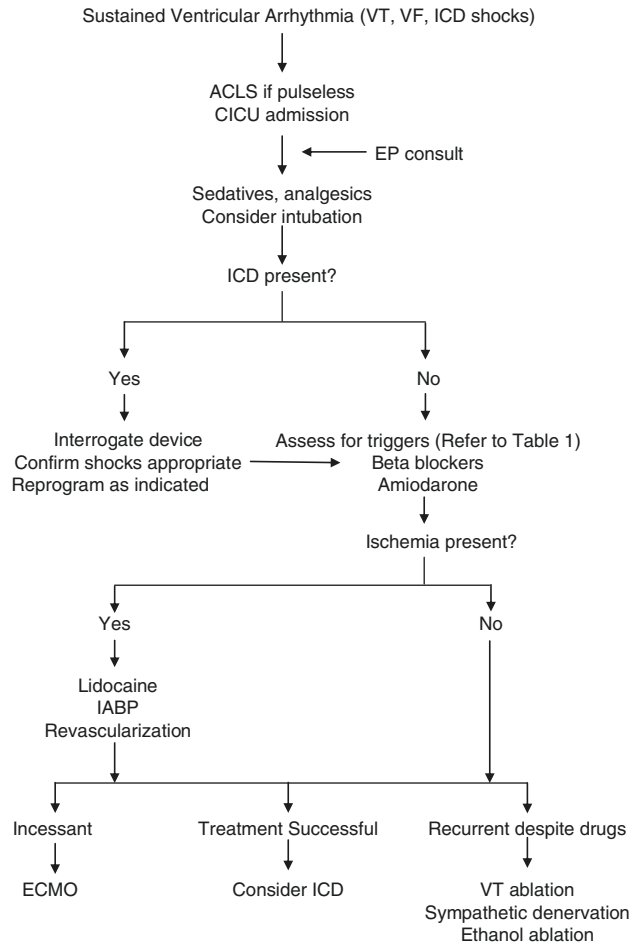


Fig. 17.5 Algorithm for assessment and management of sustained ventricular arrhythmias. *VT* ventricular tachycardia, *VF* ventricular fibrillation, *ACLS* advanced cardiac life support, *CICU* cardiac intensive care unit, *EP* electrophysiology, *ICD* implantable cardioverter defibrillator, *IABP* intra-aortic balloon pump, *ECMO* extracorporeal membrane oxygenation

should be administered via central venous access whenever possible. During short-term use, amiodarone has few side effects but can occasionally cause hypotension. Although amiodarone can increase the QTc interval, precipitation of *torsades de pointes* occurs rarely (<1.0 %) [7].

Lidocaine

Lidocaine blocks fast sodium channels in a use-dependent fashion and does not prolong the QT interval. It is effective in suppressing ventricular arrhythmias occurring in the setting of acute ischemia, but otherwise lidocaine has weak antiarrhythmic properties [5]. In patients resuscitated from VF, administration of lidocaine was associated with reduced survival compared to amiodarone [8]. In the absence of acute ischemia, lidocaine use should be considered if sustained ventricular arrhythmias are refractory to beta blockers and amiodarone. Lidocaine is administered as a bolus dose of 0.5–0.75 mg/kg every 5–10 min (maximum 300 mg total) until the arrhythmia is suppressed, followed by an infusion at 1–4 mg/min. A second bolus of lidocaine 0.5 mg/kg after 20–40 min should be considered because of significant redistribution of the drug. Notable side effects include bradycardia and central nervous system toxicity. Lidocaine is metabolized in the liver and excreted in the urine. Lidocaine should be administered with caution and the mainte-

nance dose adjusted downward in patients with liver disease or decompensated heart failure. Daily serum lidocaine levels should be monitored (therapeutic range: 1.5–5 mcg/mL) and the dose adjusted accordingly.

Digoxin Immune Fab

In patients with sustained ventricular arrhythmias due to digoxin toxicity, anti-arrhythmic drugs are not effective. Digoxin specific Fab antibody should be administered, and temporary pacing should be instituted in the presence of advanced AV block. Common arrhythmias due to digoxin toxicity are:

- Atrioventricular block
- Ectopic atrial tachycardia
- Junctional rhythm
- Ventricular premature beats
- Ventricular tachycardia
- Ventricular fibrillation
- Sinus bradycardia
- Sinoatrial block

Evidence Contour

There are very few randomized trials addressing the acute management of ventricular arrhythmias. Therefore, much of the treatment is based on expert opinion and experience. In particular, the treatment of ventricular arrhythmias which are refractory to the standard treatments outlined above remains an area of great uncertainty.

Anti-arrhythmic Drug Therapy

There are limited randomized data to guide anti-arrhythmic drug therapy of VT. Intravenous amiodarone is widely used as the initial anti-arrhythmic agent due to its high efficacy and excellent short-term safety profile. Beta blockers play an essential role in suppressing sympathetic activity and should be used in addition to amiodarone to maintain rhythm stability. Other than in the setting of acute ischemia, intravenous lidocaine is only modestly effective in terminating ventricular arrhythmias but may be a useful adjunct when amiodarone and beta blockade have been unsuccessful.

Mechanical Circulatory Support – IABP

Placement of an IABP may be useful in the short-term management of patients with refractory ventricular arrhythmias, particularly in the setting of acute ischemia and/or decompensated heart failure, when initial pharmacotherapy and reversal of identified triggers have been unsuccessful. The IABP is placed percutaneously, and may be implanted at the bedside in unstable patients. IABPs increase coronary perfusion, relieve ischemia, and unload the left ventricle, potentially serving as a bridge until a more definitive treatment may be implemented. The effectiveness of the IABP in refractory ventricular arrhythmias has been demonstrated in several case series [9]. Adverse effects are uncommon, but include bleeding, infection, and limb ischemia.

Advanced Mechanical Circulatory Support – ECMO

In rare cases, when VT is incessant and hemodynamically significant, complete mechanical circulatory support may become necessary. Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) involves using a centrifugal pump to remove blood from the venous system, circulate it through an oxygenator, and return oxygenated blood to the arterial circulation. ECMO can be instituted either percutaneously or surgically. In case series, ECMO has shown to facilitate termination of ventricular arrhythmias when other treatments had been exhausted [10].

In addition, ECMO supports the coronary circulation, relieves hypoxia, preserves vital organ perfusion, and allows time to proceed to other definitive treatments. Complications are fairly common, particularly bleeding and limb ischemia.

Radiofrequency Catheter Ablation

Catheter ablation alters the substrate for reentry, and may be useful in critically ill patients with ventricular arrhythmias in whom other modalities have been unsuccessful. This technique, including endocardial and/or epicardial ablation, can be technically challenging, particularly in the setting of multiple reentry circuits or unstable ventricular arrhythmias. Mechanical circulatory support is often useful to allow for proper mapping when the VT is poorly tolerated. Catheter ablation has been demonstrated to be efficacious in treating refractory electrical storm, with a reduction in recurrent VT and cardiac death [11, 12]. Vascular injury, thromboembolism, and cardiac tamponade are potential complications.

Transcoronary Ethanol Ablation

In patients with recurrent VT despite drug therapy and catheter ablation, transcoronary ethanol ablation may be used to treat VT of deep intramyocardial origin. The technique involves the infusion of ethanol – which is toxic to the myocardium – into the coronary artery branch supplying the reentry circuit [13]. Transcoronary ethanol ablation has been shown to prevent the recurrence of VT in a small group of highly selected patients after failed radiofrequency ablation [14]. Complications include myocardial injury, heart block, and ventricular rupture.

Cardiac Sympathetic Denervation

Limited data suggests that surgical sympathectomy may be of benefit in cases of refractory ventricular arrhythmias and VT storm. In a recently published case series involving 41 patients who had previously failed anti-arrhythmic drug therapy and VT ablation, bilateral surgical cardiac sympathetic denervation resulted in a clinically significant reduction in the number of ICD shocks in 90 % of patients and a shock-free survival rate of 50 % at 1 year [15].

References

1. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, et al. Reduction in inappropriate therapy and mortality through icd programming. N Engl J Med. 2012;367:2275–83.
2. Nademanee K, Taylor R, Bailey WE, Rieders DE, Kosar EM. Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. Circulation. 2000;102:742–7.
3. Brodine WN, Tung RT, Lee JK, Hockstad ES, Moss AJ, Zareba W, et al. Effects of beta-blockers on implantable cardioverter defibrillator therapy and survival in the patients with ischemic cardiomyopathy (from the multicenter automatic defibrillator implantation trial-ii). Am J Cardiol. 2005;96:691–5.
4. Connolly SJ, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, et al. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the optic study: a randomized trial. J Am Med Assoc. 2006;295:165–71.
5. Desouza IS, Martindale JL, Sinert R. Antidysrhythmic drug therapy for the termination of stable, monomorphic ventricular tachycardia: a systematic review. Emerg Med J. 2013;68:392–7.
6. Levine JH, Massumi A, Scheinman MM, Winkle RA, Platia EV, Chilson DA, et al. Intravenous amiodarone for recurrent sustained hypotensive ventricular tachyarrhythmias. Intravenous Amiodarone Multicenter Trial Group. J Am Coll Cardiol. 1996;27(1):67–75.
7. Hohnloser SH, Klingenheben T, Singh BN. Amiodarone-associated proarrhythmic effects. A review with special reference to torsade de pointes tachycardia. Ann Intern Med. 1994;121(7):529–35.
8. Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. N Engl J Med. 2002;346:884–90.
9. Fotopoulos GD, Mason MJ, Walker S, Jepson NS, Patel DJ, Mitchell AG, et al. Stabilisation of medically refractory ventricular arrhythmia by intra-aortic balloon counterpulsation. Heart. 1999;82(1):96–100.
10. Tsai FC, Wang YC, Huang YK, Tseng CN, Wu MY, Chu JJ, et al. Extracorporeal life support to terminate refractory ventricular tachycardia. Crit Care Med. 2007;35:1673–6.
11. Calkins H, Epstein A, Packer D, Arria AM, Hummel J, Gilligan DM, Cooled RF, et al. Multi Center Investigators

Group. Catheter ablation of ventricular tachycardia in patients with structural heart disease using cooled radiofrequency energy: results of a prospective multicenter study. J Am Coll Cardiol. 2000;35:1905–14.
12. Carbucicchio C, Santamaria M, Trevisi N, Maccabelli G, Giraldi F, Fassini G, et al. Catheter ablation for the treatment of electrical storm in patients with implantable cardioverter-defibrillators: short- and long-term outcomes in a prospective single center study. Circulation. 2008;117:462–9.
13. Sacher F, Sobieszczyk P, Tedrow U, Eisenhauer AC, Field ME, Selwyn A, et al. Transcoronary ethanol ventricular tachycardia ablation in the modern electrophysiology era. Heart Rhythm. 2008;5:62–8.
14. Tokuda M, Sobieszczyk P, Eisenhauer AC, Kojodjojo P, Inada K, Koplan BA, et al. Transcoronary ethanol ablation for recurrent ventricular tachycardia after failed catheter ablation: an update. Circ Arrhythm Electrophysiol. 2011;4:889.
15. Vaseghi M, Gima J, Kanaan C, Ajijola O, Marmureanu A, Mahajan A, et al. Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: intermediate and long-term follow-up. Heart Rhythm. 2014;11:360.

Management of Acute Aortic Syndromes

18

Carol H. Choe and Rohan R. Arya

Case Presentation

A 42-year-old man with a history of hypertension presented to the Emergency Department (ED) with complaints of severe chest and back pain. He reported the pain started shortly after lifting his wife in a bear hug while celebrating Valentine's Day. He had no relief of his symptoms with acetaminophen or ibuprofen, so his wife called emergency medical services. On arrival to the ED, he was noted to be hypertensive (172/101 mmHg), diaphoretic, and complaining of severe, sharp chest pain radiating to his back. He had nausea and progressively worsening shortness of breath. His blood work was unremarkable, including cardiac troponin. ECG showed mild non-specific ST segment abnormalities. Initial chest roentogram (CXR) was significant for pulmonary edema and a widened mediastinum (Fig. 18.1). CTA of the chest was done and shown in Fig. 18.2.

Question What is the initial approach to the management of a patient with acute aortic dissection?

Answer Blood pressure control, evaluation for involvement of the aortic root, or end-organ malperfusion.

Acute aortic dissection, regardless of the location, requires strict blood pressure control and admission to an intensive care unit (ICU). Ascending aortic dissections are a surgical emergency and need immediate evaluation by

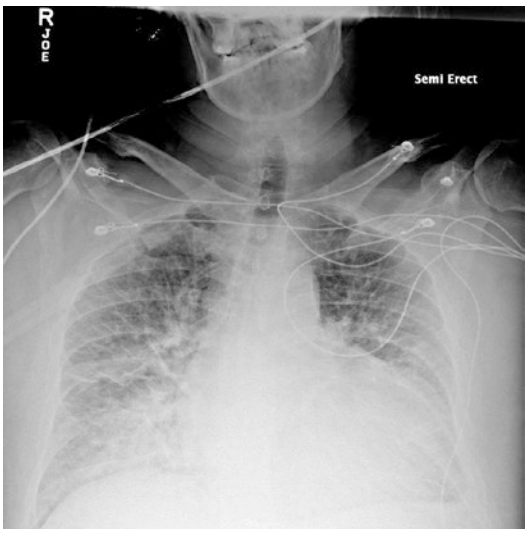


Fig. 18.1 Initial chest x-ray with evidence of pulmonary edema and widened mediastinum

Electronic supplementary material The online version of this chapter (doi:10.1007/978-3-319-43341-7_18) contains supplementary material, which is available to authorized users.

C.H. Choe (✉)
Critical Care Medicine, Lexington Medical Center, West Columbia, SC, USA
e-mail: chchoe@lexhealth.org

R.R. Arya
Medicine, Division of Pulmonary and Critical Care Medicine, University of South Carolina School of Medicine, Columbia, SC, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_18

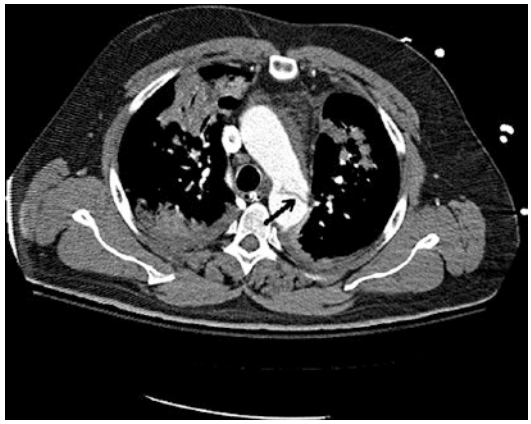


Fig. 18.2 CTA chest showing the dissection flap (black arrow) at the level of the descending aorta

cardiothoracic surgeons with emergent repair. All other dissections are usually managed with strict blood pressure control and urgent Cardiothoracic and Vascular Surgery consultations, unless there is evidence of end-organ hypoperfusion [1–3].

As pain can contribute to elevated blood pressures, the patient was given 4 mg Morphine IV with a modest improvement in his pain. However, he continued to have significant anxiety, shortness of breath and diaphoresis. After a discussion with the patient and his family, he was orotracheally intubated. An arterial line was placed into his right radial artery and his pressures were noted to be 170/100 s mmHg. Bilateral upper extremity cuff pressures correlated with pressures obtained from his arterial line. He was started on an esmolol drip at 10 mcg/kg/minute. This agent was quickly titrated up to 150 mcg/kg/minute (maximum infusion rate of 300 mcg/kg/minute) in order to obtain a goal heart rate <60 beats per minute (bpm) and a systolic blood pressure <120 mmHg. Despite high doses of esmolol with a heart rate <60 bpm, the patient's blood pressure remained uncontrolled so a nitroprusside infusion was started at 0.25 mcg/kg/minute and increased up to 0.35 mcg/kg/minute (maximum dose 2 mcg/kg/minute). Blood pressures remained poorly controlled with the two agents and so a third agent, labetalol was added at 1 mg/minute and increased up to 6 mg/minute. The initiation of labetalol improved his BP and the esmolol drip was weaned off.

Concurrent to the patient's blood pressure control, a STAT CTA chest was obtained upon the patient's arrival, and was read as a dissection of the aortic arch starting at the innominate artery (brachiocephalic trunk) and extending to the descending aorta. Cardiothoracic Surgery and Vascular Surgery evaluated the patient and opted to medically manage him as the ascending aorta was not involved. Twelve hours later, a transthoracic echocardiogram (TTE) was performed and was concerning for aortic valve involvement. A transesophageal echocardiogram (TEE) was immediately performed which confirmed ascending aortic dissection with aortic insufficiency without pericardial tamponade (Figs. 18.3, 18.4, and 18.5, Video 18.1 and 18.2).

Principles of Management

Definition

Acute aortic syndromes comprise a spectrum of disease involving the aorta, including penetrating aortic ulcers (PAU), intramural hematomas (IMH), and aortic dissection [2, 4]. Intramural hematomas develop as a result of a micro-tear within the vasa vasorum resulting in an intramedial hematoma that is characterized by the absence of an aortic entry or exit tear. The prevalence of IMH in patients found to have aortic dissections ranges from 4 to 22%. The IMH may evolve to overt dissection or even rupture, with progression that may occur suddenly or be heralded by ongoing acute aortic syndrome. Fifty to 80% may resolve completely but patients may also progress to dissection or develop an aneurysm later in their disease course. Resolution occurs more often in younger patients, and those with aortic diameter<4–4.5 cm, hematoma thickness <1 cm, and therapy with beta-blockers [1, 2, 5, 6].

Penetrating aortic ulcers represent atherosclerotic plaques that have ulcerated into the medial layer of the aortic wall. The high pressure pulsatile flow of blood through the aorta can cause further erosion of this ulcerated plaque which, in turn, can result in instability of the aortic wall and can lead to IMH, dissection, and even aortic

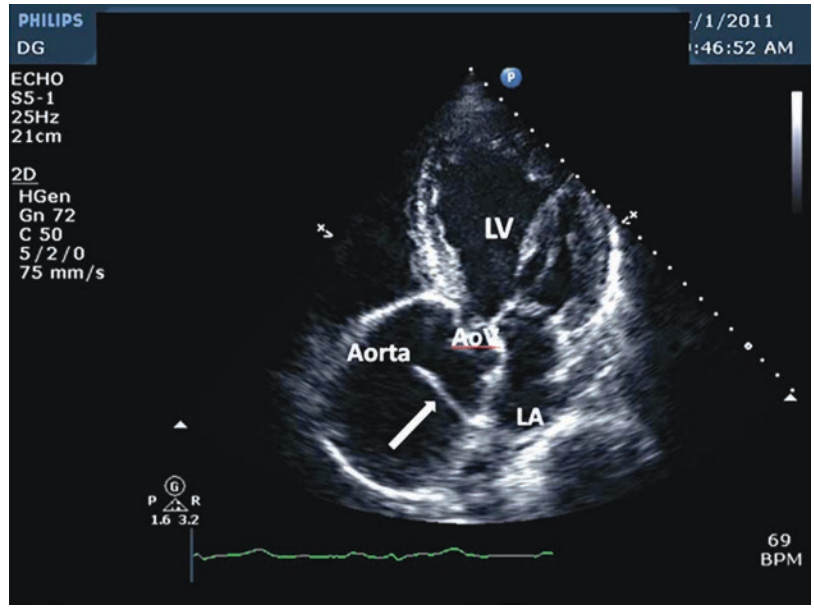


Fig. 18.3 Apical 5 chamber view demonstrating marked dilatation of the proximal ascending aorta and dissection flap (*arrow*). *AoV* aortic valve, *LV* left ventricle, *LA* left atrium (Image courtesy of Priscilla Peters, BA, RDCS, FASE)

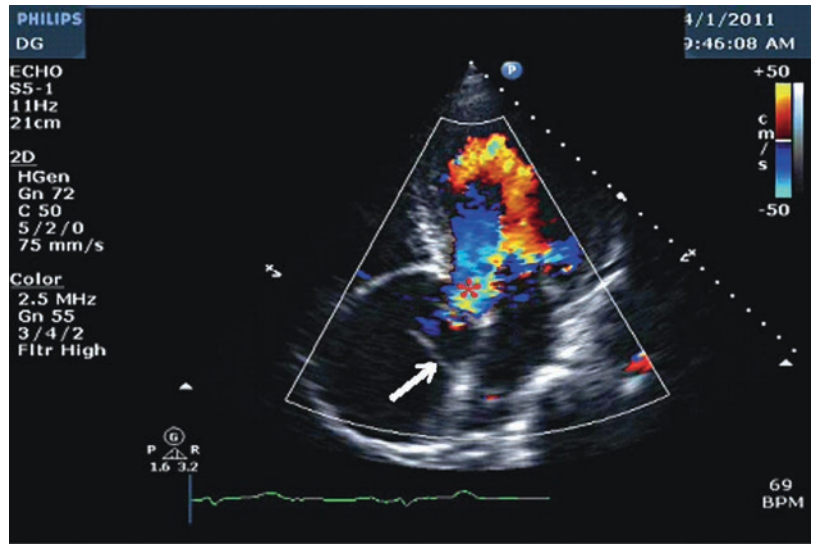


Fig. 18.4 Apical 5 chamber view revealing aortic regurgitation. *White arrow* points to the dissection flap. *Red asterisk* (*) at area of aortic regurgitation (Image courtesy of Priscilla Peters, BA, RDCS, FASE)

rupture. These lesions are uncommon in the ascending aorta because high flow is protective against atherosclerosis. However, if present, they usually rupture and are commonly fatal. Lesions in the ascending aorta can initially be treated medically with close observation. PAUs more commonly arise in the descending thoracic aorta [2, 4–6].

Anatomically, the ascending aorta is the section proximal to the brachiocephalic trunk and the descending aorta is distal to the left subclavian artery. The DeBakey and the Stanford classifications are the two most frequently utilized classification systems. The DeBakey classification system divides the dissection into 3 types. Type I involves both the ascending and descending aorta; Type II affects the ascending aorta only; and Type III is a dissection distal to the left subclavian artery. The Stanford classification simplifies this further. The dissection either affects the ascending

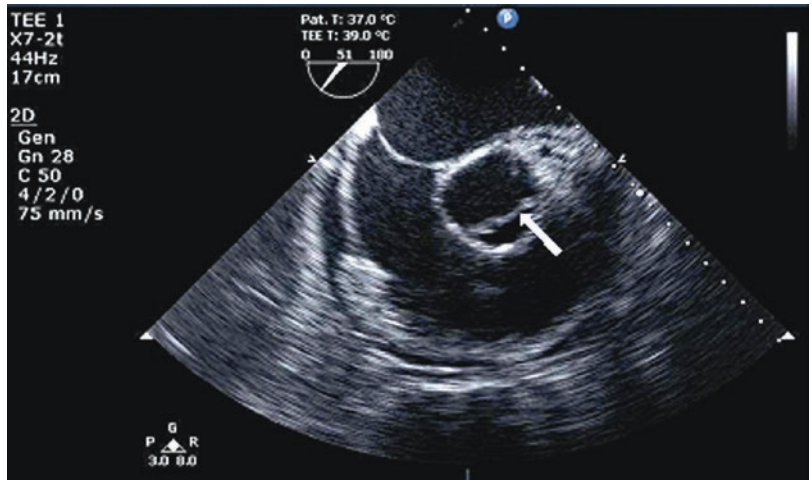


Fig. 18.5 Off-axis transesophageal echocardiogram revealing an ascending aortic dissection with a dissection flap (*arrow*)

aorta (Type A) or it remains distal to the left subclavian (Type B) [7]. Isolated aortic arch dissections do not fit neatly into any of these classification types, and there is debate as to whether they should be grouped with Type A or Type B dissections. Some have argued that the natural history approximates more closely that of Type B dissections and as such, isolated arch dissections do not require emergent surgical intervention. Other experts disagree [7, 8] (Fig. 18.6).

Risk factors for acute aortic dissection are varied. Hypertension is a predominant risk factor [9] but other factors include bicuspid aortic valve, cocaine use, Marfan syndrome (and other connective tissue disorders), blunt trauma, pregnancy, weight lifting (Valsalva maneuvers), previous aortic surgery, and large-vessel vasculitis, among others [1].

Diagnosis

Chest pain is a ubiquitous presenting complaint. In a patient with hypertension and chest pain radiating to the back, acute aortic syndrome must be considered and ruled out. While angiography had previously been the gold standard, CTA of the chest is now the standard of care to diagnose aortic dissection given its widespread availability and ease of use. MRI may also be used to augment findings although it is not the diagnostic study of choice for emergently imaging the aorta due to lesser availability and longer duration of image acquisition. TTE and TEE are other modalities that may be used to evaluate the aorta, particularly in a hemodynamically unstable patient for whom transport out of the department would be unsafe [2, 10, 11]. Although the quality of echocardiograms is operator dependent, TTE generally has a sensitivity of 59–83 % and a specificity of 63–93 % for diagnosing an ascending aortic dissection [5]. TEE has a sensitivity of close to 100 % with a specificity of 89 % for identifying an ascending aortic dissection, although it can be as low as 31–55 % for descending aortic aneurysms [6].

Medical Management

All Type B dissections, and rarely Type A dissections, are initially medically-managed with strict blood pressure control. Although no randomized trials have been conducted, beta-blockers have been the mainstay of treatment. An esmolol, labetalol, or propranolol continuous infusion is initiated in order to reduce shear force (dP/dt) exerted on the aortic wall. Unless hypotension is present, the goal systolic blood pressure is 100–120 mmHg and the target heart rate is 50–60 beats per minute [1, 3]. Esmolol is often favored as the initial agent as it is short-acting and can be rapidly weaned off if the patient experiences severe hypotension or bronchospasm (patients

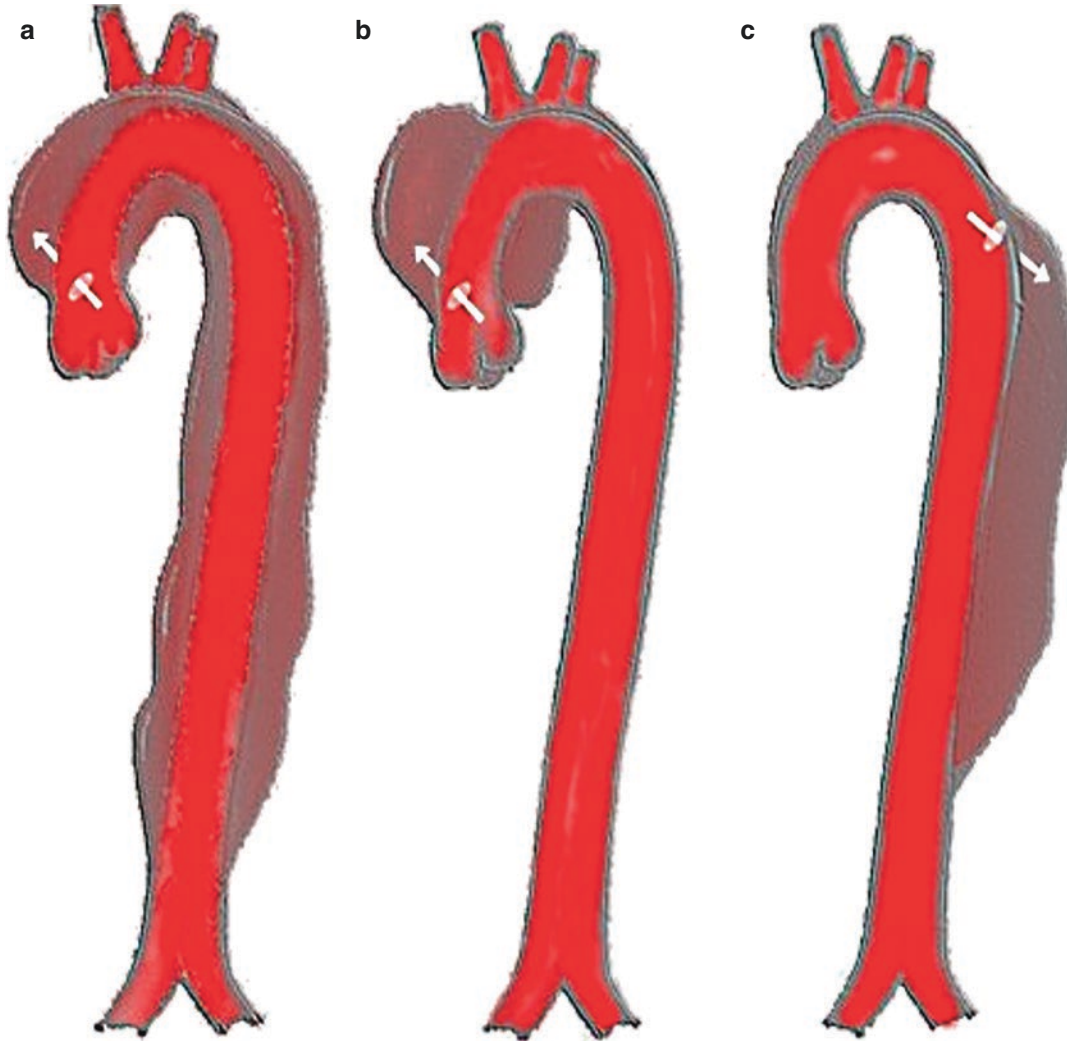


Fig. 18.6 Different types of aortic dissection. *DeBakey classification*: (**a**) DeBakey Type 1. (**b**) DeBakey Type 2. (**c**) DeBakey Type 3. *Stanford classification*: (**a**, **b**) Stanford Type A. (**c**) Stanford type B (Image courtesy of J. Heuser/Creative Commons)

with severe COPD or asthma). If blood pressure is still poorly controlled with intravenous beta-antagonist agents, nitroprusside may be added. Nitroprusside should never be started as the initial agent as it may promote reflex tachycardia and increase dP/dt, thus propagating the dissection flap. If blood pressures are still poorly controlled or if beta-blocker use is contraindicated, an infusion of a non-dihydropyridine calcium-channel blocker may be used [1].

Patients with PAU and IMH are treated with blood pressure control similar to that used in aortic dissection. Surgery may be necessary if there is refractory chest pain or extension. Both conditions should be recognized as part of the spectrum of acute aortic diseases that require close monitoring and treatment. They require lifelong anti-hypertensive therapy and repeat aortic imaging at 3, 6, 9 and 12 months based on the size of the aorta [2, 5].

Upon discharge, beta-blocking agents, calcium-channel blockers, or angiotensin-converting enzyme inhibitors should be prescribed to maintain blood pressure control. The

International Registry of Acute Aortic Dissection (IRAD) researchers found that, in general, beta-blockers were associated with mortality benefit in Type A dissections and in patients that were treated surgically, while patients with medically-managed Type B dissections had improved survival if discharged home with calcium channel blockers [3].

Surgical Intervention

Dissections involving the ascending aorta confer a high early mortality risk [12]. Previous studies reported a 1 % per hour mortality risk in patients with an untreated acute Type A aortic dissection [13]. Mortality is reduced from 90 % without surgical intervention to less than 20 % with surgery [13, 14]. Type B dissections are initially managed conservatively with strict blood pressure control unless there is evidence of malperfusion, persistent pain, or refractory hypertension; in such cases, emergent vascular surgery consultation and intervention is warranted. Delayed surgical intervention via endovascular repair is preferred to the open approach [9, 15, 16].

Complications

Aortic rupture and complications such as hypotension, neurologic deficits, shock, cardiac tamponade, pulse deficits, and kidney failure confer an even higher mortality rate [12]. Also, visceral malperfusion and extremity ischemia may occur.

Evidence Contour

A guideline-based approach to the management of patients with aortic dissection is provided in Fig. 18.7. However, the optimal approaches to diagnose and manage aortic dissection are still under investigation. Although no randomized control trials have been conducted to evaluate the best anti-hypertensive medication(s) to treat acute aortic syndromes, the mainstay of treatment is to start with an agent that will reduce shear stress and decrease heart rate. Other aspects of diagnosing and treating dissections, however, are still under significant debate.

Diagnosis of Aortic Dissection

Various biomarkers have been evaluated to determine their usefulness in ruling out aortic dissection. Of the possible biomarkers, D-dimer seems to have the most clinical utility. D-dimer assays may be significantly elevated (greater than 1600 ng/mL) in the first 6 h [3, 4] and may be used to assist in the assessment of patients with suspected dissection. A low D-dimer level (<500 ng/mL) may offer a sufficiently high negative predictive value to rule out aortic dissection [17]. However, professional guidelines do not endorse routine use of d-dimer for this purpose. Other novel biomarkers are currently under investigation.

Medical Management of Type A Dissection

While surgical intervention has been established as the standard of care for an ascending aortic dissection, some proponents recommend that in patients with advanced age, coma, acute renal failure, shock, or need for re-do operation, medical management alone may be warranted as the risk of surgery is prohibitive [18, 19]. Other considerations for medical management are given to patients with completed stroke, co-morbid conditions that preclude a good quality of life, prior aortic valve replacement, and presentation to the hospital more than 48–72 h after onset of aortic dissection [19].

Surgical Intervention for Aortic Arch Dissections

Treatment of aortic arch dissections is a matter of some controversy. In the DeBakey classification system, the aortic arch is a separate entity that is not clearly accounted for. As such, several studies

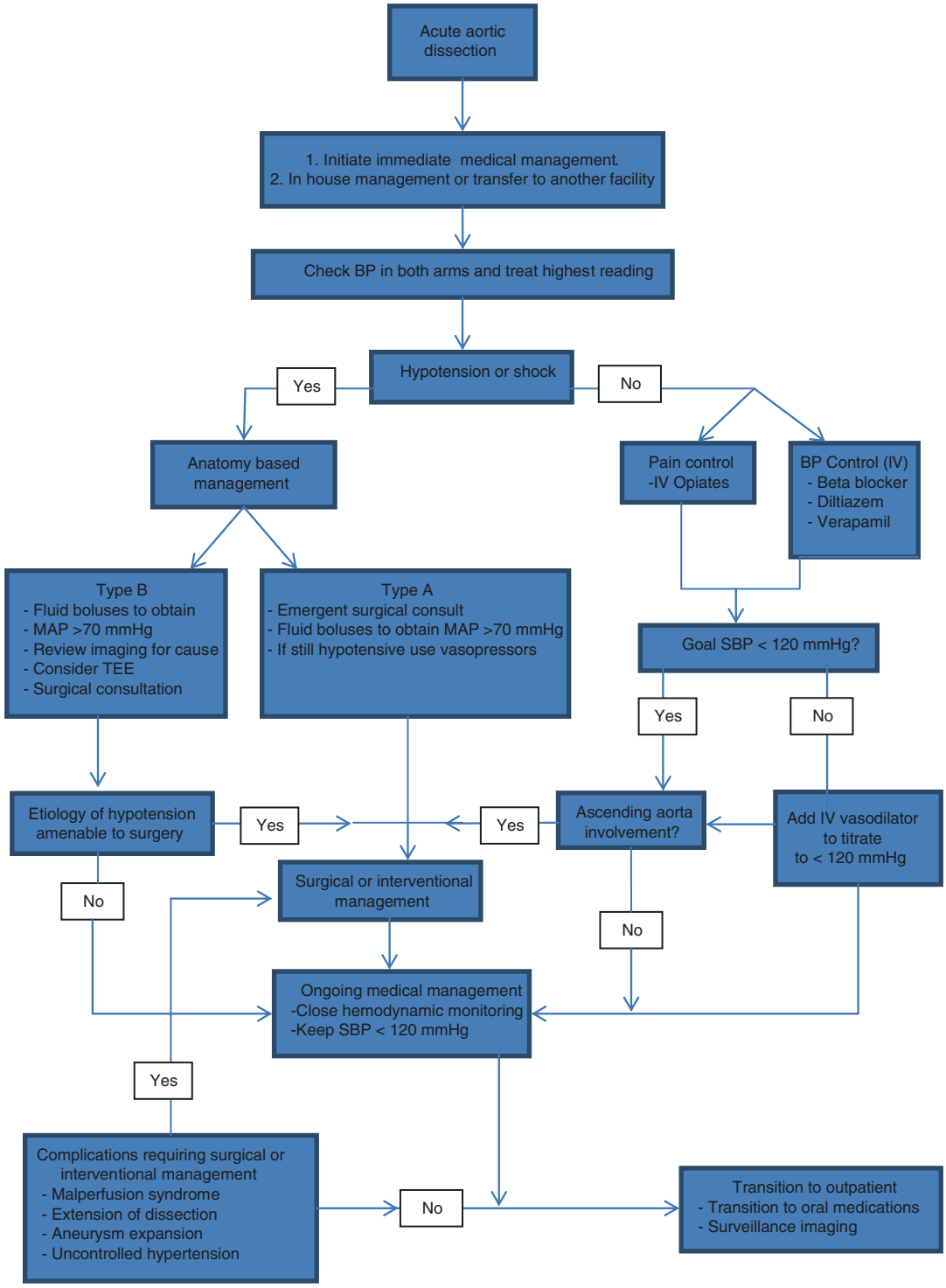


Fig. 18.7 Management of patients with aortic dissection

have evaluated whether aortic arch dissections require surgical intervention or if medical management alone is sufficient in uncomplicated cases. The initial IRAD studies showed that there was no difference in in-hospital mortality when comparing Type B dissections with or without aortic arch involvement. Additionally, it was found that aortic arch involvement was not an independent risk factor for mortality [8]. Recently, the German Registry for Acute Aortic Dissection Type A (GERAADA) study evaluated early mortality and new neurologic and malperfusion deficits among different surgical approaches for aortic arch replacement. They found that while there were more complications in the immediate post-operative period for the population treated with total arch replacement, there was no significant difference in 30-day mortality between the hemiarch and total arch groups [20]. They did not, however, compare arch replacement to medical management strategies. Nevertheless, other natural history studies suggest the risk of progression of isolated arch dissection is high and some experts argue for routine surgical management. Because of this uncertainty, we favor a team-based approach to evaluation and individualized decision-making.

References

1. De León Ayala IA, Chen Y-F. Acute aortic dissection: an update. Kaohsiung J Med Sci. 2012;28(6): 299–305.
2. Sheikh AS, Ali K, Mazhar S. Acute aortic syndrome. Circulation. 2013;128(10):1122–7.
3. Suzuki T, Isselbacher EM, Nienaber CA, et al. Type-selective benefits of medications in treatment of acute aortic dissection (from the International Registry of Acute Aortic Dissection [IRAD]). Am J Cardiol. 2012;109(1):122–7.
4. Bossone E, Suzuki T, Eagle KA, Weinsaft JW. Diagnosis of acute aortic syndromes: imaging and beyond. Herz. 2013;38(3):269–76.
5. Baliga RR, Nienaber CA, Bossone E, et al. The role of imaging in aortic dissection and related syndromes. JACC Cardiovasc Imaging. 2014;7(4):406–24.
6. Meredith EL, Masani ND. Echocardiography in the emergency assessment of acute aortic syndromes. Eur J Echocardiogr. 2009;10(1):i31–9.
7. Lempel JK, Frazier AA, Jeudy J, et al. Aortic arch dissection: a controversy of classification. Radiology. 2014;271(3):848–55.
8. Tsai TT, Isselbacher EM, Trimarchi S, et al. Acute type B aortic dissection: does aortic arch involvement affect management and outcomes? Insights from the International Registry of Acute Aortic Dissection (IRAD). Circulation. 2007;116(11 Suppl):I150–6.
9. Nienaber CA, Clough RE. Management of acute aortic dissection. Lancet. 2015;385:800–11.
10. Evangelista A, Carro A, Moral S, et al. Imaging modalities for the early diagnosis of acute aortic syndrome. Nat Rev Cardiol. 2013;10(8):477–86.
11. Nienaber CA. The role of imaging in acute aortic syndromes. Eur Heart J Cardiovasc Imaging. 2013;14(1): 15–23.
12. Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. JAMA. 2000;283(7):897–903.
13. Bonser RS, Ranasinghe AM, Loubani M, et al. Evidence, lack of evidence, controversy, and debate in the provision and performance of the surgery of acute type A aortic dissection. J Am Coll Cardiol. 2011; 58(24):2455–74.
14. Skripochnik E, Friedman P, Michler RE, Neragi-Miandoab S. The outcome of surgical management of type A aortic dissection. Asian Cardiovasc Thorac Ann. 2013;22(6):687–93.
15. Kuratani T. Best surgical option for arch extension of type B dissection: the endovascular approach. Ann Cardiothorac Surg. 2014;3(3):292–9.
16. O'Donnell S, Geotchues A, Beavers F, et al. Endovascular management of acute aortic dissections. J Vasc Surg. 2011;54(5):1283–9.
17. Suzuki T, Distante A, Zizza A, et al. Diagnosis of acute aortic dissection by D-dimer: the International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) experience. Circulation. 2009;119(20):2702–7.
18. Centofanti P, Flocco R, Ceresa F, et al. Is surgery always mandatory for type A aortic dissection? Ann Thorac Surg. 2006;82(5):1658–63; discussion 1664.
19. Feldman M, Shah M, Elefteriades JA. Medical management of acute type A aortic dissection. Ann Thorac Cardiovasc Surg. 2009;15(5):286–93.
20. Easo J, Weigang E, Hölzl PPF, et al. Influence of operative strategy for the aortic arch in DeBakey type I aortic dissection: analysis of the German Registry for Acute Aortic Dissection Type A. J Thorac Cardiovasc Surg. 2012;144(3):617–23.

Management of Endocarditis

19

Janek Manoj Senaratne and Sean van Diepen

Case Presentation

A 56 year old male with a history of hypertension presented with a 2 month history of fevers, chills, anorexia, and weight loss with a 2 week history of worsening dyspnea and pedal edema. At the time of presentation, he had a blood pressure of 90/27 mmHg, with a heart rate of 80 beats per min, temperature of 38.0 °C, and required 8 L/min of oxygen to maintain saturations of 94 %. On exam, his jugular venous pressure was 7 cm above the sternal angle. He had bilateral lung crackles, a grade III/VI decrescendo diastolic murmur along the left lower sternal border, and bilateral pitting edema. His white blood cell count was 14,000 cells/μL. Two sets of blood cultures were drawn and empiric vancomycin, gentamicin, and ciprofloxacin were initiated. At 9 h, blood cultures were positive for pansensitive Streptococcus oralis and his antimicrobial therapy was changed to ceftriaxone. A transthoracic echocardiogram reported a mildly dilated left ventricle with normal systolic function, a trileaflet aortic valve with severe aortic insufficiency, and a large 15 mm aortic valve vegetation (Fig. 19.1, Videos 19.1 and 19.2). A computed tomography (CT) scan of his head reported a left frontal subacute infarction with associated petechial hemorrhage.

Question How should this patient's native valve infective endocarditis (IE) be managed?

Answer Antimicrobial therapy and aortic valve replacement.

All patients with IE should be initiated on early empiric guideline-recommended antibiotic therapy, and antimicrobials should be further guided by culture and sensitivities. Patients with severe mitral or aortic insufficiency causing congestive heart failure should be referred for early cardiac surgery to repair or replace the incompetent valve. Prior to surgery, this patient underwent a coronary CT scan, which reported a calcium score of 0. This test was done instead of a coronary angiogram to reduce the risk of dislodging the vegetation. A dental consultation excluded an oral abscess source. On post-admission day 2, he developed shock (blood pressure 70/20 mmHg) and flash pulmonary edema (Fig. 19.2). The patient was stabilized with non-invasive mechanical ventilation and vasopressors. Dopamine was selected to increase

Electronic supplementary material The online version of this chapter (doi:10.1007/978-3-319-43341-7_19) contains supplementary material, which is available to authorized users.

J.M. Senaratne
Department of Critical Care Medicine, University of Alberta, Edmonton, AB, Canada

S. van Diepen (✉)
Department of Critical Care Medicine, Division of Cardiology, University of Alberta, Edmonton, AB, Canada
e-mail: sv9@ualberta.ca

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_19

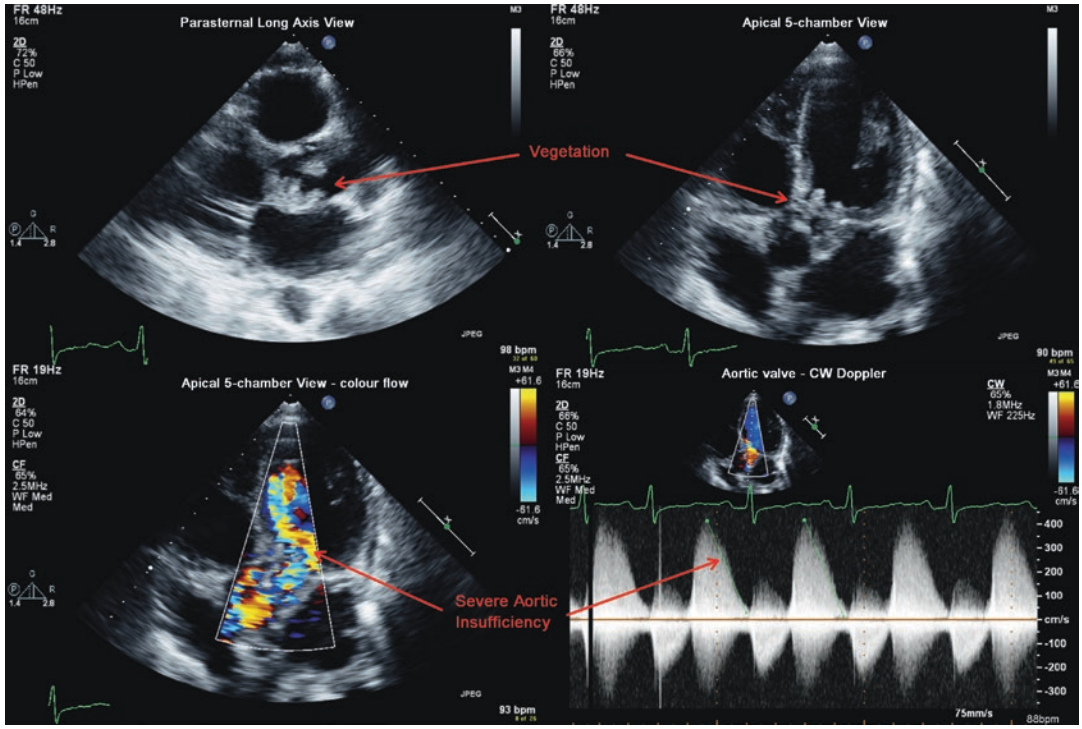


Fig. 19.1 Transthoracic echocardiogram documenting an aortic valve vegetation and severe aortic insufficiency in the parasternal long axis view and the 5-chamber apical view. Continuous wave Doppler signal of the aortic valve with a very short pressure half time suggestive of severe aortic insufficiency

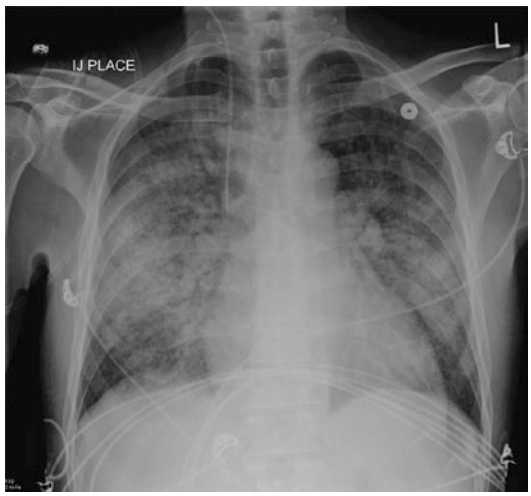


Fig. 19.2 Chest x-ray on post-admission day 2 showing severe pulmonary edema

his blood pressure and his heart rate, with the intent of shortening diastolic filling time [1]. He underwent an emergent aortic valve replacement with a bioprosthetic valve. He was extubated and transferred to the surgical ward on post-operative day 2, and discharged home on post-operative day 6. An echocardiogram prior to discharge showed a normally functioning aortic bioprosthesis with no signs of infective endocarditis. Ceftriaxone was continued for a total of 6 weeks.

Principles of Management

Epidemiology

The incidence of infective endocarditis is between 3 and 10 episodes per 100,000 person-years with a peak incidence during the ages of 70–80 of 14.5 episodes per 100,000 person-years [2–5]. Risk factors for IE include advanced age, poor dentition, injection drug use, structural heart disease (specifically valvular and congenital heart disease), the presence of prosthetic heart valves, and the presence of an intravascular catheter [6–10]. The

most common micro-organisms responsible for native valve IE in order of likelihood are listed in Table 19.1 [11].

Diagnosis

Modified Duke criteria incorporate patient risk factors, physical exam findings, laboratory studies, and echocardiographic imaging to diagnose IE (Table 19.2) [12]. Importantly, three sets of peripheral venous blood cultures (aerobic and anaerobic) should be obtained from two sites (spatial separation) at 30 min intervals (temporal separation) prior to initiating antimicrobial therapy [1, 2]. Cultures should be investigated for typical and fastidious (e.g. HACEK organisms) pathogens. A transthoracic echocardiogram (TTE) is the first recommended imaging test in IE [1, 2]. Recognizing the TTE sensitivity of 40–63 % and specificity of 98 % [13, 14], a follow-up transesophageal echocardiogram (TEE)

Table 19.1 Common causative microorganisms in infective endocarditis [11]

Microorganism	Frequency (%)
Staphylococcus aureus	31
Coagulase-negative staphylococcus	11
Viridans group streptococci	17
Streptococcus bovis	6
Other streptococci	6
Enterococcus species	10
HACEK organisms	2
Fungi/yeast	2
Polymicrobial	1
Negative cultures	10
Other	4

Abbreviation: *HACEK* organisms include *Haemophilus* species, *Aggregatibacter/Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella species*
Data from Murdoch et al. [11]

Table 19.2 Modified Duke criteria for infective endocarditis

Major criteria
1. Blood cultures positive for IE
a. Typical IE microorganism from two separate blood cultures
– Viridans streptococci
– *Streptococcus bovis*
– HACEK group
– Community-acquired enterococci
b. Microorganism consistent with IE from persistently positive blood cultures
– Two blood cultures drawn > 12 h apart
– All of three or a majority of ≥ 4 separate blood cultures (with first and last sample drawn at least 1 h apart)
c. Single positive blood culture for *Coxiella burnetii* or phase 1 IgG antibody titer > 1:800
2. Evidence of endocardial involvement
a. Echocardiography positive for IE
– Vegetation
– Abscess
– New partial dehiscence of prosthetic valve
b. New valvular regurgitation
Minor criteria
1. Predisposition
– Predisposing heart condition
– Injection drug use
2. Fever – temperature > 38° Celsius
3. Vascular phenomena
– Major arterial emboli
– Septic pulmonary infarcts
– Mycotic aneurysm
– Intracranial haemorrhages
– Conjunctival haemorrhages
– Janeway lesions
4. Immunologic phenomena
– Glomerulonephritis
– Osler's nodes
– Roth's spots
– Rheumatoid factor
5. Microbiological evidence
– Positive blood culture but does not meet a major criterion
– Serological evidence of active infection with microorganism consistent with IE

Diagnosis	
Definite IE	Possible IE
2 major criteria	1 major and 1 minor criteria
1 major and 3 minor criteria	3 minor criteria
5 minor criteria	

Data from Li et al. [12]

is recommended when: the TTE is non-diagnostic, the TTE is negative with a high index of suspicion of IE, structural cardiac complications are suspected, the patient has a prosthetic heart valve or an intra-cardiac device, or there is Staphylococcus aureus bacteremia [1, 2]. The reported sensitivity of TEE is 90–100 % [14, 15]. The reported negative predictive value of the original Duke Criteria is 92 % [16].

Antimicrobial Therapy

For acutely ill patients, an empiric antibiotic regimen of intravenous vancomycin, gentamicin, and ciprofloxacin or amoxicillin-clavulanate and gentamicin has been recommended [2]. However, initial empiric therapy should take into account local patterns of antibiotic resistance. In patients with prosthetic valves within 1 year of surgery, empiric therapy with vancomycin, gentamicin, and rifampin is recommended; rifampin should be initiated once cultures have cleared so as to reduce development of resistance [2]. Antimicrobial therapy and duration should be tailored to the specific organism and sensitivity according to published guidelines. The duration of therapy consists of a minimum of 4–6 weeks of intravenous antibiotics; the duration should be guided by guideline organism-specific recommendations [2].

Indications for Surgery

Cardiac surgery is recommended in the treatment of IE in the following situations [1, 17]: (1) aortic or mitral valve obstruction or regurgitation with heart failure, shock, severe regurgitation, or echocardiographic evidence of hemodynamic deterioration (early mitral valve closure or pulmonary hypertension); (2) locally uncontrolled infection or extension (abscess, fistula, aneurysm, heart block, or enlarging vegetation); (3) fungal, multidrug resistant, or highly resistant organisms; (4) Persistent bacteremia > 5–10 days despite appropriate antimicrobial therapy; (5) recurrent embolization with persistent vegetations; (6) vegetation > 15 mm; (7) prosthetic valves with relapsing infections.

Follow-Up Evaluation

Daily blood cultures should be drawn until the resolution of bacteremia. New infectious signs (e.g. fever) or clinical evidence of structural complications (e.g. heart failure or valvular regurgitation) merits re-initiating blood culture surveillance as described in the diagnosis section. Electrocardiographic surveillance is particularly important in patients at risk for new atrioventricular block including those with aortic valve endocarditis, microorganisms prone to peri-valvular abscess formation (e.g. *Staphylococcus aureus*), and patients with new atrioventricular block. We recommend routine electrocardiographic surveillance until blood cultures are negative and intermittently throughout the course of antimicrobial therapy – particularly in patients at high risk of new atrioventricular block including those with aortic valve endocarditis and microorganisms prone to peri-valvular abscess. Serial echocardiographic imaging has been recommended for both diagnosis and follow-up. A study in 2004 reported that in patients with a clinical suspicion of IE and a negative first TTE or TEE echocardiogram, a second or third TTE diagnosed an additional 26.7 % of patients with IE, while a second or third TEE diagnosed an additional 19.7 % [18]. Repeat imaging is also recommended when a new complication of IE is suspected (e.g. recurrent fever, new murmur, new embolus). At the completion of therapy, current guidelines, based largely on expert opinion, recommend follow-up echocardiography to detect any new silent complication or any residual vegetation [1, 2].

Evidence Contour

Although antimicrobial therapy and cardiac surgery are well established in the management of IE, there are several aspects of IE management that remain controversial or less well defined.

Timing of Non-emergent Surgery in IE

In patients without an emergent or urgent indication for cardiac surgery, there is little evidence to guide the timing of non-urgent surgery for IE. Early surgery may reduce the risk of systemic embolization of vegetations, whereas later surgery may facilitate the resolution of bacteremia and reduce the risk of infecting new bioprosthetic material. A recent small randomized study of patients with left sided valvular IE with severe mitral or aortic valve disease, and a vegetation >10 mm but no other indications for surgery were randomized to early-surgery within 48 h versus conventional care. Early surgery significantly reduced the composite end point of death and embolic events (3 % versus 23 %, p =0.03) and no differences in prosthetic valve IE recurrence was observed suggesting a possible benefit with early cardiac surgery [19].

Neuroimaging in IE

A reported 22–50 % of IE cases are complicated by a systemic embolization, with 65 % of these events involving the central nervous system [20, 21]. Cerebral emboli can cause strokes, mycotic aneurysms, and lead to hemorrhagic transformation. There are no guidelines for neuroimaging test selection; however we recommend the following approach: (1) All patients with new neurologic signs or symptoms should initially be evaluated with a non-contrast CT scan of the head. (2) Magnetic resonance imaging can be considered in symptomatic patients with a normal CT scan or to better define CT findings. (3) CT or magnetic resonance angiography can be used to evaluate mycotic aneurysms. Their role, however, in patients with early stroke symptoms to guide endovascular therapy is unclear in this population and should be made in conjunction with a neurologist [22, 23]. In neurologically asymptomatic IE patients, a small case series has reported that 79 % of patients had cerebral magnetic resonance imaging abnormalities and these findings upgraded the diagnosis of IE from possible to definite in 34 % of patients [24]. Pending further outcome based studies, we do not recommend routine neuroimaging in neurologically asymptomatic patients.

Timing of Surgery in IE with Septic Cerebral Embolic Strokes

Embolic events from IE are associated with an increase in-hospital mortality [25]. Patients who require cardiac surgery after an embolic stroke have a potential risk of hemorrhagic transformation with coronary artery bypass pump anticoagulation. Given this additional risk, the optimal timing for surgery in patients with embolic complications remains unclear. An observational study compared early surgery (1–7 days after ischemic stroke) to late surgery (>7 days after ischemic stroke) and found no difference in in-hospital or 1 year mortality [26]. Other studies, however, have reported higher in-hospital mortality and cerebral exacerbation rates associated with early surgery [27]. Until adequately powered randomized trials are performed, the appropriate timing of surgery will remain uncertain and treatment timing decisions should be individualized.

Valve Repair Versus Valve Replacement

There is very little high quality evidence to guide the choice of valve repair versus valve replacement in the setting of IE. Valve repair is theoretically more appealing given that the lack of prosthetic material reduces the risk of recurrence of IE [28–30]. A systematic review and meta-analysis of 24 observational studies compared a total of 470 patients who underwent mitral valve repair while 724 patients underwent valve replacement. Patients who underwent mitral valve repair had lower in-hospital (2.3 % versus 14.4 %) and long-term (7.8 % versus 40.5 %) mortality [31]. However, this evidence is limited by the potential

for residual confounding in observational studies and the lack of randomized studies.

Cardiac Device Related IE

The risk of IE in patients with pacemakers or implantable cardioverter defibrillators ranges from 1.82 to 1.90 per 1000-device years [32, 33]. The diagnosis of IE is more difficult in this population because blood cultures are negative in 23 %, the sensitivity of the Duke criteria is lower, and TEEs have a higher false negative rate [33]. Medical therapy alone has been associated with increased morbidity and mortality [34]. Accordingly, guidelines recommend that all patients with IE should have their devices removed and/or replaced; preferably percutaneous laser lead extraction techniques should be performed followed by a 4–6 week course of antibiotics [1, 2]. The optimal timing of both device removal and re-implantation remains unclear.

References

1. Nishimura R, Otto C, Bonow R, Carabello B, Erwin III J, Guyton R, O'Gara P, Ruiz C, Skubas N, Sorajja P, Sundt T, Thomas J. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. Circulation. 2014;129:e521–643.
2. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, Moreillon P, de Jesus Antunes M, Thilen U, Lekakis J, Lengyel M, Muller L, Naber CK, Nihoyannopoulos P, Moritz A, Zamorano JL, ESC Committee for Practice Guidelines. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J. 2009;30:2369–413.
3. Hoen B, Alla F, Selton-Suty C, Beguinot I, Bouvet A, Briancon S, Casalta JP, Danchin N, Delahaye F, Etienne J, Le Moing V, Leport C, Mainardi J, Ruimy R, Vandenesch F. Changing profile of infective endocarditis: results of a 1-year survey in France. JAMA. 2002;288:75–81.
4. Berlin J, Abrutyn E, Strom B, Kinman J, Levison M, Korzeniowski O, Feldoman R, Kaye D. Incidence of infective endocarditis in the Delaware Valley, 1988–1990. Am J Cardiol. 1995;76:933–6.
5. van der Meer J, Thompson J, Valkenburg H, Michel M. Epidemiology of bacterial endocarditis in the Netherlands. 1. Patient characteristics. Arch Intern Med. 1992;152:1863–8.
6. Griffin MR, Wilson WR, Edwards WD, O'Fallon WM, Kurland LT. Infective endocarditis. Olmsted County, Minnesota, 1950 through 1981. JAMA. 1985;254:1199–202.
7. McKinsey DS, Ratts TE, Bisno AL. Underlying cardiac lesions in adults with infective endocarditis. The changing spectrum. Am J Med. 1987;82:681–8.
8. Grover FL, Cohen DJ, Oprian C, Henderson WG, Sethi G, Hammermeister KE. Determinants of the occurrence of and survival from prosthetic valve endocarditis. Experience of the Veterans Affairs Cooperative Study on Valvular Heart Disease. J Thorac Cardiovasc Surg. 1994;108:207–14.
9. Fernandez-Hidalgo N, Almirante B, Tornos P, Pigrau C, Sambola A, Igual A, Pahissa A. Contemporary epidemiology and prognosis of health care-associated infective endocarditis. Clin Infect Dis. 2008;47:1287–97.
10. Hill EE, Herjgers P, Claus P, Vanderschueren S, Herregods MC, Peetermans WE. Infective endocarditis: changing epidemiology and predictors of 6-month mortality: a prospective cohort study. Eur Heart J. 2007;28:196–203.
11. Murdoch D, Corey G, Hoen B, Miro J, Fowler Jr V, Bayer A, Karchmer A, Olaison L, Pappas P, Moreillon P, Chambers S, Chu V, Falco V, Holland D, Jones P, Klein K, Raymond N, Read K, Tripodi M, Utili R, Wang A, Woods C, Cabell C. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the international collaboration on endocarditis-prospective cohort study. Arch Intern Med. 2009;169:463–73.
12. Li JS, Sexton DJ, Mick N, Nettles R, Fowler Jr VG, Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30:633–8.
13. Shively BK, Gurule FT, Roldan CA, Leggett JH, Schiller NB. Diagnostic value of transesophageal compared with transthoracic echocardiography in infective endocarditis. J Am Coll Cardiol. 1991;18:391–7.
14. Evangelista A, Gonzalez-Alujas M. Echocardiography in infective endocarditis. Heart. 2004;90:614–7.
15. Reynold HR, Jagen MA, Tunick PA, Kronzon I. Sensitivity of transthoracic versus transesophageal echocardiography for the detection of native valve vegetations in the modern era. J Am Soc Echocardiogr. 2003;16:67–70.
16. Dodds G, Sexton D, Durack D, Bashore T, Corey G, Kisslo J. Negative predictive value of the Duke criteria for infective endocarditis. Am J Cardiol. 1996;15:403–7.
17. Hoen B, Duval X. Clinical practice. Infective endocarditis. N Engl J Med. 2013;368:1425–33.
18. Vieira M, Grinberg M, Pomerantzeff P, Andrade J, Mansur A. Repeated echocardiographic examinations

of patients with suspected infective endocarditis. Heart. 2004;90:1020–4.
19. Kang D, Kim Y, Kim S, Sun BJ, Kim D, Yun S, Song J, Choo SJ, Chung C, Song J, Lee J, Sohn D. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med. 2012;366:2466–73.
20. Prendergast B, Tornos P. Surgery for infective endocarditis: who and when? Circulation. 2010;121:1141–52.
21. Ruttmann E, Willeit J, Ulmer H, Chevtchik O, Hofer D, Poewe W, Laufer G, Muller L. Neurological outcome of septic cardioembolic stroke after infective endocarditis. Stroke. 2006;37:2094–9.
22. Jovin T, Chamorro A, Cobo E, de Miquel M, Molina C, Rovira A, Román L, Serena J, Abilleira S, Ribó M, Millán M, Urra X, Cardona P, López-Cancio E, Tomasello A, Castaño C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Pérez M, Goyal M, Demchuk A, von Kummer R, Gallofré M, Dávalos A; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015. doi:10.1056/NEJMoa1503780.
23. Campbell B, Mitchell P, Kleinig T, Dewey H, Churilov L, Yassi N, Yan B, Dowling R, Parsons M, Oxley T, Wu T, Brooks M, Simpson M, Miteff F, Levi C, Krause M, Harrington T, Faulder K, Steinfort B, Priglinger M, Ang T, Scroop R, Barber P, McGuinness B, Wijeratne T, Phan T, Chong W, Chandra R, Bladin C, Badve M, Rice H, de Villiers L, Ma H, Desmond P, Donnan G, Davis S; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372:1009–18.
24. Duval X, Iung B, Klein I, Brochet E, Thabut G, Arnoult F, Lepage L, Laissy J, Wolff M, Leport C, IMAGE (Resonance Magnetic Imaging at the Acute Phase of Endocarditis) Study Group. Effect of early cerebral magnetic resonance imaging on clinical decisions in infective endocarditis: a prospective study. Ann Intern Med. 2010;152:497–504.
25. Chu V, Cabell C, Benjamin Jr D, Kuniholm E, Fowler Jr V, Engemann J, Sexton D, Corey G, Wang A. Early predictors of in-hospital death in infective endocarditis. Circulation. 2004;109:1745–9.
26. Barsic B, Dickerman S, Krajinovic V, Pappas P, Altclas J, Carosi G, Casabe JH, Chu VH, Delahaye F, Edathodu J, Fortes CQ, Olaison L, Pangercic A, Patel M, Rudez I, Tamin SS, Vincelk J, Bayer AS, Wang A. Influence of the timing of cardiac surgery on the outcome of patients with infective endocarditis and stroke. Clin Infect Dis. 2013;56:209–17.
27. Eishi K, Kawazoe K, Kuriyama Y, Kitoh Y, Kawashima Y, Omae T. Surgical management of infective endocarditis associated with cerebral complications. Multi-center retrospective study in Japan. J Thorac Cardiovasc Surg. 1995;110:1745–55.
28. Zegdi R, Debieche M, Latremouille C, Lebied D, Chardigny C, Grinda JM, Chauvaud S, Deloche A, Carpentier A, Fabiani JN. Long-term results of mitral valve repair in active endocarditis. Circulation. 2005;111:2532–6.
29. Iung B, Rousseau-Paziaud J, Cormier B, Garbarz E, Fondard O, Brochet E, Acar C, Couetil JP, Hvass U, Vahanian A. Contemporary results of mitral valve repair for infective endocarditis. J Am Coll Cardiol. 2004;43:386–92.
30. Delay D, Pellerin M, Carrier M, Marchand R, Auger P, Perrault LP, Hebert Y, Cartier R, Page P, Pelletier LC. Immediate and long-term results of valve replacement for native and prosthetic valve endocarditis. Ann Thorac Surg. 2000;70:1219–23.
31. Feringa H, Shaw L, Poldermans D, Hoeks S, van der Wall E, Dion R, Bax J. Mitral valve repair and replacement in endocarditis: a systematic review of literature. Ann Thorac Surg. 2007;83:564–70.
32. Johansen J, Jørgensen O, Møller M, Arnsbo P, Mortensen P, Nielsen J. Infection after pacemaker implantation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. Eur Heart J. 2011;32:991–8.
33. Uslan D, Sohail M, St Sauver J, Friedman P, Hayes D, Stoner S, Wilson W, Steckelberg J, Baddour L. Permanent pacemaker and implantable cardioverter defibrillator infection: a population-based study. Arch Intern Med. 2007;167:669–75.
34. Sohail M, Uslan D, Khan A, Friedman P, Hayes D, Wilson W, Steckelberg J, Jenkins S, Baddour L. Infective endocarditis complicating permanent pacemaker and implantable cardioverter-defibrillator infection. Mayo Clin Proc. 2008;83:46–53.

Part III

Respiratory Disease

Robert C. Hyzy

Community Acquired Pneumonia

20

Richard G. Wunderink and Mark W. Landmeier

Case Presentation

A 31 year old male with a history of diabetes mellitus type 1 and recent skin infection of the neck (for which he underwent incision and drainage and levofloxacin treatment) presented to the emergency department with a three day history of fever, cough productive of bloody sputum, and shortness of breath. He had recently returned from a trip to Asia. He was tachycardic but normotensive and had an oxygen saturation of 93 % on 3 L nasal cannula. WBC count was 21.8 K/UL with 90 % neutrophils, BUN and creatinine were 8 mg/dL and 1.0 mg/dL, respectively, and glucose >350 mg/dL. Suspicion of cavitary pneumonia on chest radiograph was confirmed by computed tomography (Fig. 20.1).

Question What would be the best empirical therapy for this patient?

Answer Ceftriaxone, azithromycin, and linezolid.

Because of additional concern for meliodosis, the patient was started on ceftazidime, azithromycin, and vancomycin. He developed progressive hypoxemia and agitation, at which time he was intubated and started on mechanical ventilation. Bronchoscopic bronchoalveolar lavage (BAL) of the right lower lobe revealed 240 WBCs with 81 % neutrophils. Sampling of a rapidly progressing pleural effusion showed a pleural fluid pH 6.95, glucose 44 mg/dL and LDH 1842 IU/L. Gram stain of both fluids revealed clusters of gram positive cocci. Chest tube drainage of the right pleural space was performed. Urinary antigen testing for S*treptocococcus pneumoniae* and fungal serologies were negative. He was empirically switched from vancomycin to linezolid. BAL and pleural fluid cultures grew methicillin-resistant *Staphylococcus aureus* (MRSA). Serum immunoglobulins (IGs) were subsequently found to be very low and he was given IVIG. After a prolonged ICU course, he was ultimately discharged to an acute rehabilitation facility and subsequently returned to full functional status. He continues to receive intermittent outpatient IVIG.

Principles of Management

Site-of-Care Decisions

Patients admitted to the ICU with severe community-acquired pneumonia (CAP) generally fall into one of two categories: (1) those whose

R.G. Wunderink (✉) • M.W. Landmeier
Department of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: r-wunderink@northwestern.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_20

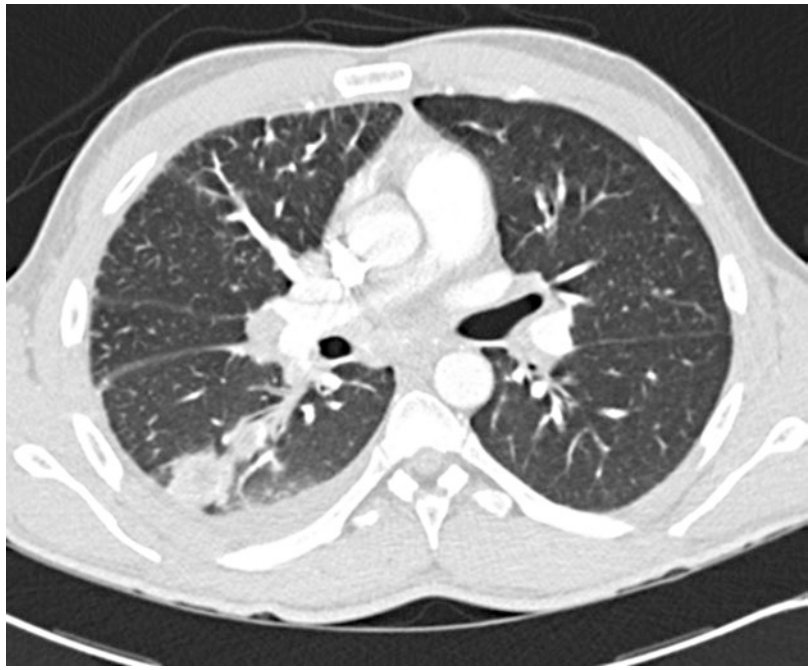


Fig. 20.1 Representative image of the CT chest upon admission

symptom severity or co-morbid conditions require ICU admission at presentation and (2) those who transfer to the ICU later because of progressive decline despite receiving inpatient therapy.

Patients in need of mechanical ventilation or vasopressor support because of septic shock automatically require intensive care. However, the decision to admit to the ICU is more difficult when such obvious needs are not present. Early identification of patients likely to deteriorate is important as increased mortality is associated with ICU transfer for delayed respiratory failure or onset of septic shock. Pooled analysis of four prospective CAP studies, of which 138 had delayed-transfer compared to 315 direct Emergency Department (ED) to ICU admissions, demonstrated that the delayed-transfer group had higher 28-day mortality (23.4 % vs. 11.7 %, $p<0.02$) and hospital length of stay (13 days vs. 7 days, $p<0.001$) in propensity-matched analysis [1].

While some delayed transfers to the ICU represent progressive pneumonia despite appropriate treatment, many patients have subtle clinical findings upon presentation that predict a more aggressive approach will lead to improved outcomes. Using the presence of ≥3 IDSA/ATS minor criteria (Table 20.1) [2] in the ED, a before/after quality improvement project demonstrated decreased mortality (adjusted odds ratio [OR] 0.24, 95 % confidence interval [CI] 0.09–0.670, $p=0.006$), fewer delayed ICU transfers (14.8 % vs. 32 %, $p<0.001$), and minimal increase in direct admissions to the ICU when an aggressive pre-ICU assessment and resuscitation protocol was utilized [3].

The Pneumonia Severity Index (PSI) and CURB-65 Score, while useful in predicting 30-day mortality and need for hospital admission, have limited ability to predict the need for intensive respiratory monitoring or vasopressor support initially. In addition to the IDSA/ATS minor criteria, several other scores such as SMART-COP [4] generally have very good sensitivity if the threshold is set optimally. However, such scoring tools will lead to a significant increase in ICU admissions if followed rigorously, and they require prospective validation.

Table 20.1 IDSA/ATS minor[a] criteria for severe community acquired pneumonia

Respiratory rate[b] ≥ 30 breaths/min
PaO_2/FiO_2 ratio[b] ≤ 250
Multilobar infiltrates
Confusion/disorientation
Uremia (BUN level, ≥20 mg/dL)
Leukopenia[c] (WBC count, <4000 cells/mm^3)
Thrombocytopenia (platelet count, <100,000 cells/mm^3)
Hypothermia (core temperature, <36 °C)
Hypotension requiring aggressive fluid resuscitation

Modified and reproduced with permission from Oxford University Press on behalf of the Infectious Disease Society of America. Mandell et al. [2]

[a]Other considerations include hypoglycemia (in a non-diabetic patient), acute alcoholism/withdrawal, hyponatremia, unexplained metabolic acidosis, elevated lactate level, cirrhosis and asplenia

[b]Need for noninvasive ventilation can substitute for a respiratory rate >30 breaths/min or $PaO_2/FiO_2 < 250$

[c]As a result of infection alone

Diagnostic Testing

Aggressive diagnostic testing is most useful in those with severe CAP requiring ICU admission and in those with risk factors for healthcare-associated pneumonia (HCAP). In such patients, the probability of finding a pathogen resistant to usual CAP empirical therapy (e.g. *Staphylococcus aureus* or *Pseudomonas aeruginosa*) is increased, and identification of a specific pathogen can lead to tailored antimicrobials, thus decreasing cost and exposure to unnecessary medications [5].

In a patient invasively ventilated, direct access to the lower respiratory tract provides the opportunity to perform an endotracheal aspirate or bronchoalveolar lavage (BAL). Moreover, bronchoscopic BAL can be useful in those where sputum or blood cultures do not yield a pathogen. In a prospective study of 262 patients admitted with CAP, fiberoptic bronchoscopic BAL provided additional diagnostic value in 49 % of patients who could not expectorate sputum and 52 % who had treatment failure 72 h after admission [6].

Blood and sputum cultures generally have low sensitivity but should still be performed upon transfer to the ICU, even in the non-intubated patient. Growth inhibition by antibiotics decreases the diagnostic yield of both tests but less so when *S. aureus* or gram-negative bacilli are the predominant pathogen [2]. Pleural fluid sampling is necessary in a CAP patient with a large pleural effusion (either upon admission or one which develops after empirical treatment for CAP), as a complicated pleural space requires adequate drainage.

Urinary antigen testing has reasonable sensitivity and excellent specificity for detecting *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1. The test can stay positive for over 3 days in patients with *S. pneumoniae* and for weeks with *L. pneumophila* [2]. Although antibiotic sensitivity data cannot be obtained, the test is qualitatively important to verify that an antibiotic regimen adequately covers such pathogens.

Viral testing is important, especially in the appropriate season. A positive influenza test in a critically-ill patient should be an impetus for antiviral therapy, which can hasten disease resolution and decrease spread.

Microbial Culprits

Microorganisms responsible for CAP in the ICU mirror those of the outpatient setting, with the addition of gram-negative pathogens and MRSA. A review of 9 studies of patients with CAP admitted to the ICU showed that the most common typical bacterial pathogens were *S. pneumoniae*, *L. pneumophila*, *Haemophilus influenzae*, aerobic gram-negative bacilli, and *S. aureus* [7]. The relative frequency of atypical pathogens in the ICU setting is unclear because of heterogeneity in diagnostic technique but is approximately 20 % [2]. Respiratory viruses, either as a pure or co-infection, can be detected in up to 49 % of severe pneumonias. Common culprits include parainfluenza virus, human metapneumovirus, influenza A and B, respiratory syncytial virus, and adenovirus [8, 9]. Much less common viral pathogens include coronaviruses, such as the SARS virus and Middle East respiratory syndrome coronavirus (MERS-CoV), parechoviruses, and enteroviruses.

Epidemiologic risk factors are helpful to suggest less common etiologies (Table 20.2). Structural lung disease (e.g. COPD with repeated exacerbations or bronchiectasis), prior hospitalization and healthcare exposure pose an increased risk of *Pseudomonas*, chronic alcoholism is a risk for other gram-negative pathogens (*Klebsiella pneumoniae* or *Acinetobacter* species), and end-stage renal disease, injection drug use, prior influenza infection, and prior treatment with fluoroquinolones pose an increased risk of *S. aureus* [2].

Empirical Versus Pathogen-Directed Therapy

With severe CAP, timely diagnosis and adequate empirical antimicrobial therapy are paramount. Retrospective analysis of 2731 adult patients with septic shock, the majority of whom had a pulmonary primary site of infection, demonstrated that each hour delay in initiation of appropriate antibiotic therapy after the onset of hypotension was associated with a mean decrease in survival of 7.6% [10]. Consideration of the

Table 20.2 Epidemiologic conditions and/or risk factors related to specific pathogens in community-acquired pneumonia

Condition	Commonly encountered pathogen(s)
Alcoholism	*Streptococcus pneumoniae*, oral anaerobes, *Klebsiella pneumoniae*, *Acinetobacter* species, *Mycobacterium tuberculosis*
COPD and/or smoking	*Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Legionella* species, *S. pneumoniae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*
Aspiration	Gram-negative enteric pathogens, oral anaerobes
Lung abscess	CA-MRSA, oral anaerobes, endemic fungal pneumonia, *M. tuberculosis*, atypical mycobacteria
Exposure to bat or bird droppings	*Histoplasma capsulatum*
Exposure to birds	*Chlamydophila psittaci* (if poultry: avian influenza)
Exposure to rabbits	*Francisella tularensis*
Exposure to farm animals or parturient cats	*Coxiella burnetti* (Q fever)
HIV infection (CD4 > 200)	*S. pneumoniae*, *H. influenzae*, *M. tuberculosis*
HIV infection (CD4 < 200)	The pathogens listed for early infection plus *Pneumocystis jirovecii*, *Cryptococcus*, *Histoplasma*, *Aspergillus*, atypical mycobacteria (especially *Mycobacterium kansasii*), *P. aeruginosa*, *H. influenzae*
Hotel or cruise ship stay in previous 2 weeks	*Legionella* species
Travel to/residence in southwestern United States	*Coccidioides* species, *Hantavirus*
Travel to/residence in Southeast and East Asia	*Burkholderia pseudomallei*, avian influenza, SARS
Influenza active in community	Influenza, *S. pneumoniae*, *Staphylococcus aureus*, *H. influenzae*
Cough >2 weeks with whoop or post tussive vomiting	*Bordetella pertussis*
Structural lung disease (e.g., bronchiectasis)	*Pseudomonas aeruginosa*, *Burkholderia cepacia*, *S. aureus*
Injection drug use	*S. aureus*, anaerobes, *M. tuberculosis*, *S. pneumoniae*
Endobronchial obstruction	Anaerobes, *S. pneumoniae*, *H. influenzae*, *S. aureus*

Modified and reproduced with permission from Oxford University Press on behalf of the Infectious Disease Society of America. Mandell et al. [2]
CA-MRSA community-acquired methicillin-resistant *Staphylococcus aureus*, *COPD* chronic obstructive pulmonary disease, *SARS* severe acute respiratory syndrome

need to alter an empirical regimen to cover specific (and perhaps drug-resistant) organisms is a major consideration when a patient is transferred to the ICU while already on standard empirical antimicrobial coverage for CAP.

In the absence of risk factors for HCAP or drug-resistant pathogens, adequate coverage of *S. pneumoniae* and *L. pneumophila* is crucial. Combination antibiotics with a beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) and either a macrolide or fluoroquinolone is recommended. A recent prospective randomized trial demonstrated improved clinical outcomes for combination therapy compared to beta-lactam monotherapy, confirming multiple observational studies showing better clinical outcomes and decreased mortality with combination therapy, especially for bacteremic pneumococcal pneumonia [2].

For suspected *Pseudomonas* CAP, dual therapy is required and can take the form of one of three initial combinations:

1. anti-pneumococcal anti-pseudomonas beta-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus fluoroquinolone (ciprofloxacin or levofloxacin), or
2. beta-lactam plus an aminoglycoside and azithromycin, or
3. beta-lactam plus an aminoglycoside and an anti-pneumococcal fluoroquinolone

For MRSA pneumonia linezolid is superior to vancomycin, particularly if a toxin-secreting community-acquired strain is the culprit [2]. A randomized double-blind trial comparing linezolid to dose-adjusted vancomycin for treatment of MRSA-proven HAP or HCAP demonstrated eradication of MRSA and clinical cure were statistically better with linezolid, and linezolid had less incidence of nephrotoxicity [11]. In the setting of methicillin-susceptible S. *aureus*, beta-lactam therapy is still the treatment of choice.

Parapneumonic Effusions

In the presence of a CAP-related pleural effusion, thoracentesis can distinguish between uncomplicated parapneumonic effusion (UPPE), complicated parapneumonic effusion (CPPE) or empyema [12]. Frank pus or a positive pleural fluid gram stain or culture indicate an infected pleural space and need for immediate drainage. However, pleural fluid gram stain and culture can be negative in CPPE or empyema. In such situations, pleural fluid chemistry is the most efficient way to assess the effusion [12]. A meta-analysis showed pleural fluid pH to have the highest diagnostic accuracy in detecting a complicated effusion, followed by glucose and lactate dehydrogenase (LDH) [13]. While optimal thresholds are still a matter of debate, a pH <7.28, glucose <40 mg/dL and/or LDH level >1000 IU/L suggests CPPE or empyema and the necessity for pleural drainage to achieve a good outcome [12, 14].

If the pleural space is not evacuated in CPPE, fibrinous adhesions develop, and neutrophils and bacteria accumulate leading to empyema. Optimal therapy for CPPE and empyema hinges on adequate antibiotic coverage and pleural drainage [15]. If pleural loculations develop, multiple thoracostomy tubes may be needed along with intrapleural instillation of fibrinolytic agents [12]. A randomized controlled trial of intrapleural DNase with concomitant tissue plasminogen activator (TPA) in patients with empyema showed a lower rate of surgical referral and hospital length of stay compared with placebo and individual agents alone [16]. Lysis of adhesions or decortication via video-assisted thoracoscopic surgery (VATS) or thoracotomy may be necessary if less invasive measures fail. The timing of surgical referral and type of surgical maneuver, though, largely depend on the patient and severity of illness.

In contrast, uncomplicated parapneumonic effusions are usually exudates with pleural fluid pH >7.28 and normal glucose. As these effusions are reactive, they should resolve with continued antibiotic therapy.

Evidence Contour

Several aspects of severe CAP management remain without consensus, including the assessment of risk for multidrug resistant (MDR) pathogens, adjuvant assessment tools, and treatments.

Risk of Multidrug Resistant (MDR) Pathogens

Empirical antibiotic therapy for severe CAP hinges on the risk for drug resistant organisms. Over the last decade HCAP has been used to describe the entity wherein patients develop pneumonia outside the hospital yet have pathogens usually associated with HAP or VAP, such as MDR gram-negative bacilli and MRSA. Criteria for HCAP and the resultant number of patients who should get broad-spectrum empirical therapy remain subject to debate. Using any risk factor for drug-resistant pathogens (DRP) leads to antibiotic overtreatment, while ignoring risk factors is associated with undertreatment and adverse outcomes [5]. In a prospective observational study, Shindo et al. found six independent risk factors for pathogens resistant to the usual CAP antibiotics: (1) hospitalization ≥ 2 days during the previous 90 days, (2) antibiotic use during the previous 90 days, (3) non-ambulatory status, (4) tube feedings, (5) immunocompromised status, and (6) use of gastric acid suppression medications [17]. Presence of three or more risk factors should prompt a physician to consider broad-spectrum antibiotic therapy, as the frequency of drug resistant pathogens may be as high as 43 %. These criteria work equally well as the previous definition of HCAP, and a strategy for initial antibiotic selection based on these risk factors may result in far less empirical broad-spectrum therapy while still identifying the majority who need it.

Drugs to Suppress Toxin with MRSA

A community-acquired MRSA (CA-MRSA) clone, distinct from that usually causing HCAP, HAP or VAP, has emerged as a cause of pneumonia with striking necrotizing features. Methicillin resistance results from a different staphylococcal cassette chromosome type (SCCmec type IV), which also includes a gene encoding Panton-Valentine leukocidin (PVL) and other exotoxins. Presence of PVL may explain the associated neutropenia while other exotoxins, such as alpha-hemolysin, may result in the characteristic severe pulmonary hemorrhage of both the MRSA and MSSA infections [18]. Antibiotic therapy that also suppresses toxin production provides better outcomes and improved survival, as illustrated in a retrospective study of PVL-positive CAP [19]. Clindamycin and linezolid have been shown to suppress in-vitro formation of PVL, alpha-hemolysin, and toxic shock syndrome toxin 1, whereas vancomycin and beta-lactams have no effect [18]. The benefit of clindamycin combined with a beta-lactam for MSSA CAP is unclear, with a recent prospective analysis demonstrating that nearly 18 % of CA-MRSA isolates were clindamycin resistant; whether antibiotic growth inhibition detected by MIC-susceptibility tests correlates with toxin-suppression activity, though, is unclear [20, 21]. While the preferred treatment for PVL-positive MSSA CAP is still unclear, linezolid appears the most reasonable choice for CA-MRSA CAP in light of its potential to suppress exotoxin and offer faster eradication of other MRSA clones. The rapid bactericidal activity of ceftaroline, a cephalosporin with MRSA activity, may obviate the need to suppress exotoxin production, but data are still very limited.

Procalcitonin

Procalcitonin (PCT), a peptide released in response to bacterial infection but suppressed by interferons induced by viral infections, has the potential to distinguish between bacterial and viral causes of pneumonia and potentially guide antibiotic decisions. In a prospective study of CAP, clinicians were encouraged (PCT level >0.25 mcg/L) or discouraged (PCT level <0.1 mcg/L) from using antibiotics based on procalcitonin cutoffs. PCT guidance reduced total antibiotic exposure, antibiotic prescriptions on admission, and antibiotic treatment duration without adversely affecting clinical outcomes [22]. Further analysis has shown that persistently elevated PCT levels are associated with adverse outcomes such as the development of pneumonia complications and death [23]. A similar benefit on shortening antibiotic duration with a PCT-driven protocol has been found

in several studies of severe sepsis. Despite these studies, PCT has not been FDA approved for this indication in the US.

Corticosteroids

Death in CAP may result from either failure to eradicate the microorganism or from inappropriate (and perhaps exaggerated) host response to the infection. This has led investigators to attempt modulation of the inflammatory response in severe CAP with corticosteroids.

While a small prospective study [24] and several retrospective studies [25] support corticosteroid administration in severe CAP, a larger randomized double-blinded trial evaluating the efficacy of prednisolone to placebo in patients with severe CAP (PSI IV or V) failed to show a beneficial effect of corticosteroids [26]. Conversely, in a highly selected group of patients with very high C-reactive protein levels on admission, use of corticosteroids was associated with less treatment failure [27].

References

1. Renaud B, Santin A, Coma E, et al. Association between timing of intensive care unit admission and outcomes for emergency department patients with community-acquired pneumonia. Crit Care Med. 2009;37(11):2867–74.
2. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM, Musher DM, Niederman MS, Torres A, Whitney CG. Infectious Disease Society of America/American Thoracic Society Consensus Guidelines on the management of community-acquired pneumonia in adults. Clin Inf Dis. 2007;44:S27–72.
3. Lim HF, Phua J, Mukhopadhyay A, et al. IDSA/ATS minor criteria aid pre-intensive care unit resuscitation in severe community-acquired pneumonia. Eur Respir J. 2014;43:852–62.
4. Charles PGP, Wolfe R, Whitby M, et al. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. Clin Inf Dis. 2008;47:375–84.
5. Wunderink RG, Waterer GW. Community-acquired pneumonia. N Engl J Med. 2014;370:543–51.
6. van der Eerden MM, Vlaspolder F, de Graaf CS, et al. Value of intensive diagnostic microbiological investigation in low- and high-risk patients with community-acquired pneumonia. Eur J Microbiol Infect Dis. 2005;24:241–9.
7. File TM. Community-acquired pneumonia. Lancet. 2003;362:1991–2001.
8. Karhu J, Ala-Kokko TI, Vuorinen T, et al. Lower respiratory tract virus findings in mechanically ventilated patients with severe community-acquired pneumonia. Clin Inf Dis. 2014;59(1):62–70.
9. Choi SH, Hong SB, Ko GB, et al. Viral infection in patients with severe pneumonia requiring intensive care unit admission. Am J Respir Crit Care Med. 2012;186:325–32.
10. Kumar A, Roberts D, Wood K, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34(6):1589–96.
11. Wunderink RG, Niederman MS, Kollef M, et al. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. Clin Inf Dis. 2012;54(5):621–9.
12. Sahn SA. Diagnosis and management of parapneumonic effusions and empyema. Clin Inf Dis. 2007;45:1480–6.
13. Heffner JE, Brown LK, Barbieri C, et al. Pleural fluid chemical analysis in parapneumonic effusions. Am J Respir Crit Care Med. 1995;151:1700–8.
14. Porcel JM, Vives M, Cao G, et al. Biomarkers of infection for the differential diagnosis of pleural effusions. Eur Respir J. 2009;34:1383–9.
15. Brook I, Frazier EH. Aerobic and anaerobic microbiology of empyema. Chest. 1993;103:1502–7.
16. Rahman NM, Maskell NA, West A, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. N Engl J Med. 2011;365:518–26.
17. Shindo Y, Ito R, Kobayashi D, et al. Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2013;188:985–95.
18. Rubinstein E, Kollef M, Nathwani D. Pneumonia caused by methicillin-resistant *Staphylococcus aureus*. Clin Inf Dis. 2008;46:S378–85.
19. Sicot N, Khanafer N, Meyssonnier V, et al. Methicillin resistance is not a predictor of severity in community-acquired Staphylococcus aureus necrotizing pneumonia--results of a prospective observational study. Clin Microbiol Infect. 2013;19:E142–8.
20. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Prevalence of methicillin-resistant *Staphylococcus aureus* as an etiology of community-acquired pneumonia. Clin Inf Dis. 2012;54(8):1126–33.
21. Mandell LA, Wunderink R. Methicillin-resistant *Staphylococcus aureus* and community-acquired pneumonia: an evolving relationship. Clin Inf Dis. 2012;54(8):1134–6.
22. Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia, a randomized trial. Am J Respir Crit Care Med. 2006;174:84–93.

23. Masia M, Gutierrez F, Shum C, et al. Usefulness of procalcitonin levels in community-acquired pneumonia according to the patient's outcome research team pneumonia severity index. Chest. 2005;128:2223–9.
24. Confalonieri M, Ubrino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia, a preliminary randomized study. Am J Respir Crit Care Med. 2005;171:242–8.
25. Garcia-Vidal C, Calbo E, Pascual V, et al. Effects of systemic steroids in patients with severe community-acquired pneumonia. Eur Respir J. 2007;30:951–6.
26. Snijders D, Daniels J, de Graaff CS, et al. Efficacy of corticosteroids in community-acquired pneumonia, a randomized double-blinded clinical trial. Am J Respir Crit Care Med. 2010;181:975–82.
27. Torres A, Sibila O, Ferrer M, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized controlled trial. JAMA. 2015;333(7):677–86.

Management of Acute Respiratory Distress Syndrome

21

Robert C. Hyzy

Case Presentation

A 53 year old woman with a history of alcohol abuse, pancreatitis, hypertension and COPD presented with 3 days epigastric pain, nausea, vomiting and decreased oral intake in addition to respiratory symptoms which included a week of cough with white sputum. At the time of presentation to the hospital her alcohol level was 207, lipase was 838, white blood cell count was 12.8 K. She was started on IV hydration and received benzodiazepines for incipient alcohol withdrawal when her mental status became delirious. Over the course of the next 12 h her oxygenation progressively deteriorated and she was intubated. Post intubation chest x-ray and a representative image from the CT scan performed are below (Figs. 21.1 and 21.2).

Question What approach should guide this patient's ventilator management?

Answer Lung Protective Ventilation

All patients with the acute respiratory distress syndrome should be treated with lung protective ventilation in order to avoid ventilator associated lung injury (VALI). This patient was started on assist control mechanical ventilation with a tidal volume of 350 ml and 100 % FiO_2. Neuromuscular blockade with cisatracurium was initiated. The depth of paralysis was monitored with train of four nerve stimulation and the depth of sedation with midazolam and fentanyl was assessed via bispectral analysis. Over the next 12 h her PEEP was increased to 16 cm H_2O and her FiO_2 was decreased to 40 %. During this time the patients plateau airway pressure ranged between 26 and 28 cm H_2O. She was treated with broad spectrum antibiotics, vancomycin, pip-tazo and azithromycin. Results of a culture obtained from a mini-BAL specimen failed to grow any pathogenic organisms. Cisatracurium was discontinued after 48 h. At that time, solu-medrol was begun at a dose of 1 mg/kg body weight. The patient had had already been on an insulin drip but the glucose target range was changed to less than 110 mg/dL from the usual less than 150 mg/dL at that time. Daily sedation holidays were instituted to assess mental functioning and a physical therapy consult was initiated to promote mobility. The patient remained hemodynamically stable with good renal function and diuresis with furosemide was initiated, resulting in a negative fluid balance of 2400 ml on the third ICU day and about 1–2 L/day subsequently. Gas exchange remained satisfactory such that on the fourth ICU day PEEP was decreased to 5 cm H_2O. By that time the patient was able to march in place at the bedside and take

R.C. Hyzy
Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA
e-mail: rhyzy@umich.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_21

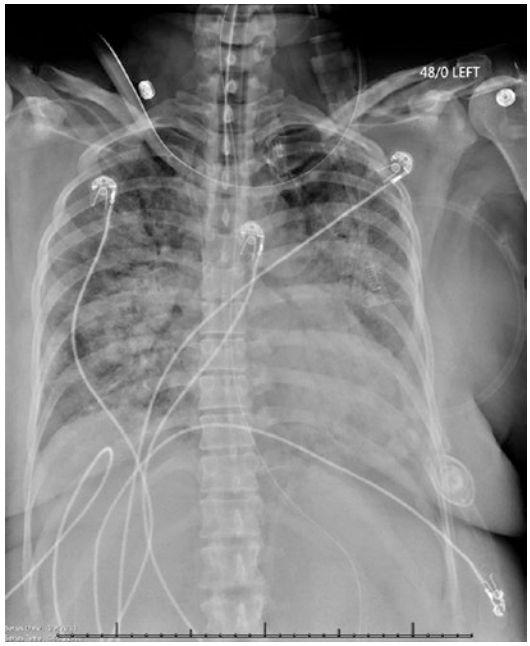


Fig. 21.1 Chest x-ray of patient with ARDS from case study showing bilateral alveolar infiltrates

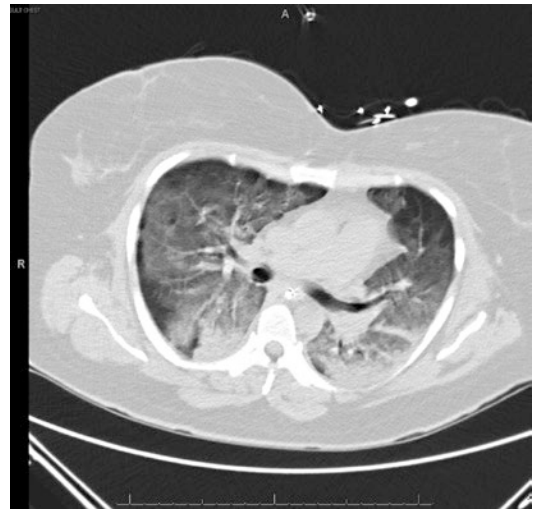


Fig. 21.2 Representative section of chest CT from patient in case study demonstrating bilateral alveolar infiltrates with mild compressive atelectasis in the dependent lung zones

a brief walk into the hall outside of her room. Later that day the patient was weaned and extubated. She was transferred out of the ICU to the general medical ward the following day.

Principles of Management

Risk Factors for ARDS and Diagnosis

Several risk factors for the development of ARDS have been identified. The lung injury prediction score (LIPS) is a model which incorporates know risk factors and predicts the likelihood of developing ARDS accordingly [1] (Table 21.1). Many patients with multiple risk factors do not develop ARDS as even patients with a LIPS score of more than 7 only develop ARDS less than half of the time. In the case presentation above the patient's history of chronic alcohol ingestion was a predisposing risk factor for the development of ARDS in what was likely to have been an aspiration pneumonia, which itself in another risk factor.

The PaO_2 to FiO_2 (P/F) ratio, a measure of oxygenation impairment was part of the old American European Consensus Conference diagnostic criteria for acute lung injury and ARDS. Although easily calculated the P/F ratio did not account for the effect of mean airway pressure on oxygenation. The Berlin criteria for ARDS, published in 2012 [2], did away with the concept of acute lung injury (ALI) in favor of classifying ARDS as mild, moderate or severe. ARDS severity is based on oxygenation criteria which also accounts to some extent, for the application of positive airway pressure. The diagnosis of ARDS is based on clinical presentation and physiology. Diffuse alveolar damage is usually seen histopathologically, but may be absent even in cases of severe ARDS [3].

Berlin Definition of ARDS

Timing

- Within 1 week of a known clinical insult or new or worsening respiratory symptoms

Chest Imaging

- Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules

Origin of Edema

- Respiratory failure not fully explained by cardiac failure or fluid overload
- Need objective assessment (e.g. echocardiography) to exclude hydrostatic edema if no risk factor present

Table 21.1 Lung injury prediction score (LIPS)

	LIPS points	Examples
Predisposing conditions		(*1*) Patient with history of alcohol abuse with septic shock from pneumonia requiring $FI_{O2} > 0.35$ in the emergency room: Sepsis + shock + pneumonia + alcohol abuse + $FI_{O2} > 0.35$ 1 + 2 + 1.5 + 1 + 2 = 7.5
Shock	2	
Aspiration	2	
Sepsis	1	
Pneumonia	1.5	
High-risk surgery[a]		
Orthopedic spine	1	
Acute abdomen	2	
Cardiac	2.5	
Aortic vascular	3.5	
High-risk trauma		(*2*) Motor vehicle accident with traumatic brain injury, lung contusion, and shock requiring $FI_{O2} > 0.35$ Traumatic brain injury + lung contusion + shock + $FI_{O2} > 0.35$ 2 + 1.5 + 2 + 2 = 7.5
Traumatic brain injury	2	
Smoke inhalation	2	
Near drowning	2	
Lung contusion	1.5	
Multiple fractures	1.5	
Risk modifiers		
Alcohol abuse	1	
Obesity (BMI > 30)	1	(*3*) Patient with history of diabetes mellitus and urosepsis with shock Sepsis + shock + diabetes 1 + 2–1 = 2
Hypoalbuminemia	1	
Chemotherapy	1	
$FI_{O2} > 0.35$ (>4 L/min)	2	
Tachypnea (RR > 30)	1.5	
$Sp_{O2} < 95\%$	1	
Acidosis (pH < 7.35)	1.5	
Diabetes mellitus[b]	−1	

Reprinted with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society
From Gajic et al. [1]
The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society
Definition of abbreviations: *BMI* body mass index, *RR* respiratory rate, Sp_{O2} oxygen saturation by pulse oximetry
[a]Add 1.5 points if emergency surgery
[b]Only if sepsis

Oxygenation

- Mild ARDS – The PaO_2/FiO_2 is >200 mmHg, but ≤300 mmHg, on ventilator settings that include positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥5 cm H_2O.
- Moderate ARDS – The PaO_2/FiO_2 is >100 mmHg, but ≤200 mmHg, on ventilator settings that include PEEP ≥5 cm H_2O.
- Severe ARDS – The PaO_2/FiO_2 is ≤100 mmHg on ventilators setting that include PEEP ≥5 cm H_2O

Lung Protective Ventilation

Avoiding over distension of the lung during mechanical ventilation of ARDS patients is called lung protective ventilation (LPV). LPV reduces

hospital and 28 day mortality [4], presumably by decreasing lung inflammation and avoiding the fibrinoproliferative phase of this condition. The largest trial to date demonstrating this was done by the NIH sponsored ARDS Network, whose results were published in 2000 [5]. The approach undertaken in this trial, the utilization of a tidal volume of less than 6.5 cc/kg of ideal body weight (IBW) (but at least 4 cc/kg) and maintaining a plateau pressure of less than 30 cm of H_2O has become the standard treatment to provide mechanical ventilation to patients with ARDS. The calculation of ideal body weight is based on height:

$$\text{Male IBW}\,(\text{kg}) = 50 + 0.91(\text{cm height} - 152.4)$$
$$\text{Female IBW}\,(\text{kg}) = 45.5 + 0.91(\text{cm height} - 152.4)$$

Plateau airway pressure is not a threshold variable [6] and it should be maintained as low as realistically possible, even though in the ARDSNet trial tidal volume was allowed to increase up to 8 cc/kg as long as plateau pressure remained under 30 cm H_2O. The ARDS Network approach is the standard approach to lung protective ventilation. However, multiple other approaches have been championed, each ostensibly offering a refinement of the basic lung protective ventilation approach of the ARDSNet. In a retrospective analysis of several of the large trials, a low driving pressure (ΔP) was found to be better correlated with ARDS mortality than tidal volume or plateau pressure [7]. Driving pressure is the pressure being applied by the ventilator to distribute gas to the recruited portion of the lungs which are not collapsed from compressive atelectasis caused by the weight of the lung in the dependent lung zones. In a patient not making spontaneous respiratory efforts ΔP can be estimated as plateau pressure minus PEEP in cm H_2O.

Open Lung Ventilation

Avoiding alveolar overdistension with a low tidal volume is the established mechanism of avoiding ventilator-associated lung injury. In the supine ARDS patient delivered gas is distributed to non-dependent lung zones. Dependent lung zones are not ventilated due to the weight of the lung, i.e. compressive atelectasis. In between the two zones is an area of lung which distends and collapses with each delivered ventilator breath, a phenomenon termed cyclic atelectasis. In animal models cyclic atelectasis produces lung injury. Optimizing the recruitment of additional areas of collapsed lung with PEEP in order to mitigate the effect of cyclic atelectasis is the rationale behind open lung ventilation. Meta-analysis of several large clinical trials demonstrated a mortality benefit to open lung ventilation [8]. However, each of the three large trials used for this analysis individually failed to demonstrate a mortality benefit. To the extent that the large clinical trials did not demonstrate harm with higher levels of PEEP, such as an increased rate of pneumothorax, clinicians may choose to use the open lung approach in their patients. Several approaches to performing open lung ventilation are available. A study evaluating the effect of PEEP on lung recruitment, as evaluated by CT scan, suggested the best tradeoff between lung recruitment while simultaneously avoiding lung overdistension was obtained via a high PEEP strategy similar to that utilized in the Lung Open Ventilation Study (LOVS) [9] (Table 21.2).

Prone Ventilation

A large randomized, multi-center trial, PROSEVA, demonstrated an impressive mortality benefit to patients who underwent prone ventilation 18 h per day [10]. Prone ventilation can be considered to be a form of open lung ventilation. This trial addressed criticisms of earlier, negative trials of prone ventilation in that the study subjects with ARDS had a severe oxygenation defect, were proned for long periods of time daily and a protocolized lung protective approach was used in the control group, the original ARDS network approach [11]. Using the low PEEP ARDS Network approach in the control group, while appropriate, leaves open the question as to whether proning adds incremental benefit to patients who are already receiving higher levels

Table 21.2 Example of open-lung high positive end-expiratory pressure (PEEP) strategy

FIO_2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
PEEP	5–10	10–18	18–20	20	20	20–22	22	22–24

of PEEP (see open lung ventilation, below). In addition, patients underwent neuromuscular blockade, which itself may have a beneficial effect on outcome. Despite these concerns, prone ventilation has assumed an important place as a rescue modality in the treatment of severe ARDS patients who have not responded to a conventional lung protective strategy.

Fluid Management

Volume removal via diuretic administration can shorten the duration of mechanical ventilation in patients who are recovering from ARDS. The Fluid and Catheter Therapy Trial of the ARDS Network demonstrated an average of 2.5 day increase in ventilator free days with a fluid conservative approach [12]. In addition, in patients in whom the total protein is less than 6.0 g/dL, the addition of albumin for 72 h helped promote fluid loss in ARDS patients and improved oxygenation [13].

Supportive Care

Other important aspects of care pertain more generally to the care of all patients receiving invasive mechanical ventilation. These include the early and successful use of enteral alimentation, a daily sedation awakening trial, delirium screening and management, early mobility, and treating the underlying illness such as pneumonia.

Evidence Contour

Several aspects of management in the patient with ARDS remain without consensus in the face of available clinical trials. Several of these are extensions of basic lung protective ventilation and essentially are attempts to find the optimal approach.

Additional Risk Factors

Vitamin D supplementation in critically ill patients who are severely deficient has been shown to decrease hospital mortality [14]. Low prehospital levels of vitamin D are associated with an increased risk of respiratory failure [15], and may be common in patients at risk for or having ARDS [16]. The NIH PETAL Network in conducting a randomized trial of high dose vitamin D in deficient patients at risk for ARDS.

Cytomegalovirus reactivation (CMV) is common in critically ill immunocompetent patients and portends a worse outcome in patients compared to CMV negative patients [17]. In one series, immunocompetent patients with ARDS were found to have a histologic evidence of CMV pneumonia on open lung biopsy in 18 of 37 cases of ARDS [18]. A NIH sponsored trial is examining whether the administration of ganciclovir improves outcomes in CMV antibody positive patients with acute respiratory failure and ARDS [19].

Subgroups and Subphenotypes

Because ARDS is a clinical syndrome, with an array of risk factors, and not a disease per se, attempts have been made to evaluate ARDS subgroups from several standpoints. Sepsis induced ARDS has a worse outcome than that due to other causes [20]. As is evident from lung biopsy and autopsy series clinical classification as either pneumonia or ARDS is frequently at odds with tissue findings [3, 21]. In addition the histopathology likely evolves over time, with pneumonia and/or diffuse alveolar damage yielding to fibrotic changes. Rather than determining which subcategory of ARDS a patient manifests on the basis of causal risk, more relevant to treatment and outcome may be subclassification based on clinical manifestations. ARDS patients demon-

strate different amounts of recruitable lung with administered PEEP [22]. Patients showing improvements in oxygenation due to lung recruitment with PEEP may have a lower mortality than those who do not [23]. Additionally, ARDS patients with a hyperinflammatory subphenotype have a higher mortality regardless of the ascribed cause for ARDS [24]. It remains to be determined identification of subgroups based on recruitability or hyperinflammatory subphenotypes represent different histopathologies (pneumonia versus diffuse alveolar damage versus fibrosis) or will lead to improved outcomes by varying the approach to therapy on that basis.

Helmet Ventilation

Noninvasive ventilation with a helmet interface, rather than the more conventional face mask, was shown in a pilot randomized trial of ARDS patients to decrease the rate of intubation. This observation awaits confirmation in a larger trial [24a].

Transpulmonary Pressure

Plateau airway pressure, measured after a delivered tidal volume, reflects lung and chest wall compliance. The contribution of the chest wall, which includes the abdominal compartment, can confound the utilization of plateau pressure as a guide to lung protective ventilation by suggesting the lung is being overdistended when in fact this is not the case. By subtracting an estimation of pleural pressure made by readings taken by an esophageal balloon (P_{es}) from the measured plateau pressure (P_{plat}) an estimate of transpulmonary pressure (P_L) may be determined and used to guide lung protective ventilation.

$$P_L = P_{plat} - P_{es}$$

A mortality benefit was observed in a single center randomized trial which used this approach [25]. The results may have been influenced by the enrollment of more than 60 % post abdominal surgery patients, a population in whom the abdominal compartment is likely to make a significant contribution to the chest wall and thereby P_{plat}. An accompanying editorial suggested, in reality, this approach was a means to justify the use of higher PEEP levels than customarily employed (i.e. > 22 cm H_2O). Also, the validity of using esophageal pressure as an estimate of pleural pressure has been questioned [26]. A larger, multi-center trial is being conducted to confirm these results [27]. This approach can be considered in patients in whom the chest wall is likely contributing to alveolar pressure, such as patients who are post-operative from abdominal surgery, are morbidly obese, have ascites or have a chest wall deformity such as scoliosis, provided the necessary equipment and expertise are available.

Pressure Limited Mechanical Ventilation

Pressure-limited modes of mechanical ventilation, including airway pressure release ventilation (APRV), bi-level, and pressure-controlled inverse ratio ventilation are all ways of providing lung protective ventilation. Ostensibly, pressure limited modes offer an advantage of less variation in transpulmonary pressure and a lower tidal volume to functional residual capacity alveolar strain ratio, which would be offer a salutary effect on VALI [28]. Additionally, APRV and bi-level ventilation offer the additional putative benefit of allowing spontaneous breathing, which might help prevent ventilator-induced respiratory muscle weakness [29] and more completely ventilate lung zones near the diaphragm. Despite adherents, to date, the superiority of this approach to volume cycled ventilation has not been demonstrated [30].

Neuromuscular Blockade

A large, multicenter randomized trial demonstrated a mortality benefit in patients who received 48 h of neuromuscular blockade following the onset of ARDS [31]. Less barotrauma was observed in the paralysis group, whereas a greater incidence of neuromuscular weakness was not. Because the Kaplan-Meier

survival curves did not separate until 14 days, the mechanistic benefit of this approach has been challenged. In addition this study has been criticized for lacking a more rigorous approach to the assessment of neuromuscular weakness. Some support is given to this study by a database analysis study which demonstrated a mortality benefit in patients with a pulmonary source of sepsis and respiratory failure who underwent neuromuscular blockade within the first 48 h for reasons other than intubation [32]. Additionally, in an animal model spontaneous breathing caused regional alveolar overdistension near the diaphragm due to Pendelluft ventilation which did not occur in paralyzed animals [33]. Hence the notion that spontaneous breathing provides "better" ventilation to lung zones near the diaphragm may not be valid. The NIH sponsored PETAL (Prevention and early treatment of acute lung injury) Network is conducting a clinical trial to re-evaluate whether neuromuscular blockade benefits patients with severe ARDS.

High Frequency Oscillatory Ventilation (HFOV)

Two large, randomized multi-center trials published in 2012, OSCILLATE and OSCAR, failed to show benefit to this clearly open-lung approach [34, 35]. Critics suggested that concerns regarding volume status and effects on the right ventricle may have contributed adversely to the findings. To the extent that the OSCILLATE trial showed an increased mortality in the HFOV group this approach cannot be recommended at present for adults with ARDS.

Extra Corporeal Membrane Oxygenation (ECMO)

A mortality benefit was observed in the British CESAR trial among patients randomized to be transported to the specialty center to receive ECMO on an intent-to-treat basis [36]. As the mortality benefit was accounted for by patients randomized to ECMO who did not receive ECMO, concerns regarding whether the benefit seen in this study represents the modality itself or the benefit of regionalization of care to a specialty hospital is a concern. Use of ECMO has been prevalent during recent H1N1 outbreaks, when young patients with few if any comorbidities developed ARDS refractory to more commonplace ventilator approaches to oxygenation [37]. Another randomized trial of ECMO in ARDS patients is currently underway in Europe [38].

Corticosteroids

Most meta-analyses have not suggested confirmed a mortality benefit to the use of corticosteroids in patients with ARDS. The LaSRS study performed by the ARDS Network is the largest trial to date examining whether corticosteroids benefit ARDS patients [39]. No mortality benefit was ultimately observed although a significantly greater of patient days alive and off assisted breathing ("ventilator-free days"). An initial mortality benefit in favor of the steroids may have been lost among the 20 patients who returned to assisted breathing, as opposed to 6 in the control group. Whether this was due to tapering steroids after weaning or the development of neuromuscular weakness is unclear. Although an increased morality was seen in LaSRS among patients who were started on corticosteroids beyond 14 days of mechanical ventilation for ARDS the confidence intervals were large. This has resulted in some authors warning against starting corticosteroids beyond 14 days. If given, corticosteroids should be administered at a dose of 1 mg per kg body weight twice per day with a taper over 28 days. Tight glycemic control may play a role in minimizing the risk of neuromuscular weakness [40]. Corticosteroid administration may result in prolonged viral replication in patients with ARDS due to H1N1 influenza. A higher mortality has been reported in observational series in these patients and corticosteroid administration is best avoided early on in the care of influenza patients with ARDS [41].

Inhaled Vasodilators

Trials of inhaled nitric oxide have failed to yield positive results. Meta-analyses have suggested that while oxygenation improves not mortality benefit accrues from the use of this agent [42]. Iloprost (synthetic PGI2) also increases pO_2. However, no large clinical trials have been performed to determine if improvements are also seen in a clinically meaningful outcome such as mortality or ventilator-free days [43].

References

1. Gajic O, Dabbagh O, Park PK, Adesanya A, Chang SY, Hou P, Anderson H 3rd, Hoth JJ, Mikkelsen ME, Gentile NT, Gong MN, Talmor D, Bajwa E, Watkins TR, Festic E, Yilmaz M, Iscimen R, Kaufman DA, Esper AM, Sadikot R, Douglas I, Sevransky J, Malinchoc M, U.S. Critical Illness and Injury Trials Group: Lung Injury Prevention Study Investigators (USCIITG-LIPS): early identification of patients at risk of acute lung injury: Evaluation of lung injury prediction score in a multicenter cohort study. Am J Respir Crit Care Med. 2011;183:462–70.
2. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307:2526–33.
3. Thille AW, Esteban A, Fernandez-Segoviano P, Maria Rodriguez J-M, Aramburu JA, Penuelas O, Cortes-Puch I, Cardinal-Fernandez P, Lorente JA, Frutos-Vivar F. Comparison of the Berlin definition for acute respiratory distress syndrome with autopsy. Am J Respir Crit Care Med. 2013;187:761–7.
4. Petrucci N, Iacovelli W. Lung protective ventilation strategy for the acute respiratory distress syndrome. Cochrane Database Syst Rev. 2013;2, CD003844.
5. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
6. Hager DN, Krishnan JA, Hayden DL, Bower RG. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med. 2005;172:1241–5.
7. Amato MBP, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372:747–55.
8. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, Brochard L, Richard JC, Lamontagne F, Bhatnagar N, Stewart TE, Guyatt G. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA. 2010;303:865.
9. Chiumello D, Cressoni M, Carlesso E, et al. Bedside selection of positive end-expiratory pressure in mild, moderate and severe acute respiratory distress syndrome. Crit Care Med. 2014;42:252.
10. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M, Hilbert G, Bengler C, Richecoeur J, Gainnier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L, PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome .N Engl J Med. 2013;368:2159.
11. Gattinoni L, Taccone T, Carlesso E, Marini JJ. Prone position in acute respiratory distress syndrome. Rationale, indications, and limits. Am J Respir Crit Care Med. 2013;188:1286–93.
12. Weidemann HP, Wheeler AP, Bernard GR et al. for the NHLBI Acute Respiratory Distress Sndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354:2564–75.
13. Martin GS, Moss M, Wheeler AP, et al. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. Crit Care Med. 2005;33:1681–7.
14. Amrein K, Schnedl HA, et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency. JAMA. 2014;312:1520.
15. Thickett DR, Moromizato T, Litonjua AA, et al. Association between prehospital vitamin D status and incident acute respiratory failure in critically ill patients: a retrospective cohort study. BMJ Open Resp Res. 2015;2, e000074.
16. Dancer RC, Parekh D, Lax S, et al. Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). Thorax. 2015.
17. Limaye AP, Kirby KA, Rubenfeld GD, et al. Cytomegalovirus reactivation in critically ill immunocompetent patients. JAMA. 2008;300:413–22.
18. Papazian L, Thomas L, Bregeon F, et al. Open-lung biopsy in patients with acute respiratory distress syndrome. Anesthesiology. 1998;88:935–44.
19. NIH Clinical Trials. Sponsor: Fred Hutchinson Cancer Research Center. Study of ganciclovir/valganciclovir for prevention of cytomegalovirus reactivation in acute injury of the lung and respiratory failure (GRAIL). https://clinicaltrials.gov/ct2/show/NCT01335932.
20. Sheu C-C, Gong M, Zhai R, et al. Clinical characteristics and outcomes of sepsis-related vs Non-sepsis-related ARDS. Chest. 2010;138:559–67.
21. Guerin C, Bayle F, Leray V, et al. Open lung biopsy in nonresolving ARDS frequently identifies diffuse alveolar damage regardless of the severity of stage and may have implications for patient management. Int Care Med. 2015;41:222–30.
22. Gattinoni L, Caroni P, Cressoni M, et al. Lung recruitment in patients with acute respiratory distress syndrome. N Engl J Med. 2006;354:1775–85.

23. Golighter EC, Kavanagh BP, Rubenfeld GD, et al. Oxygenation response to positive end-expiratory pressure predicts mortality in acute respiratory distress syndrome. A secondary analysis of the LOVS and ExPress trials. Am J Respir Crit Care Med. 2014;190:70–6.
24. Calfee CS, Delucchi K, Parsons P, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomized controlled trials. Lancet Resp Dis. 2014;2:611–20.

24a. Patel BK, Wolfe KS, Pohlman AS. et al. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with Acute Respiratory Distress Syndrome: A randomized clinical trial. JAMA 2016:315: 2435–41.

25. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, Novack V, Loring SH. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med. 2008;359:2095.
26. Chiumello D, Guerin C. Understanding the setting of PEEP from esophageal pressure in patients with ARDS. Int Care Med. 2015;41:1465–7.
27. NIH Clinical Trials. Sponsor: Beth Israel Deaconess Medical Center. EPVent 2 – a phase II study of mechanical ventilation directed by transpulmonary pressures (EPVent2). https://clinicaltrials.gov/ct2/show/NCT01681225.
28. Marini JJ. Point: Is pressure assist-control preferred over volume assist-control mode for lung protective ventilation in patients with ARDS? Yes. Chest. 2011;140:286.
29. Tobin MJ, Franco Laghi F, Jubran A. Narrative review: ventilator-induced respiratory muscle weakness. Ann Intern Med. 2010;153:240–5.
30. Rittayami N, Katsios CM, Beloncle F, et al. Pressure-controlled vs volume-controlled ventilation in acute respiratory failure: a physiology-based narrative and systematic review. Chest. 2015;142:340–55.
31. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guérin C, Prat G, Morange S, Roch A. Neuromuscular blockers in early acute respiratory distress syndrome. ACURASYS Study Investigators. N Engl J Med. 2010;363:1107.
32. Steingrub JS, Lagu T, Rothberg MB, Nathanson BH, Raghunathan K, Lindenauer PK. Treatment with neuromuscular blocking agents and the risk of in-hospital mortality among mechanically ventilated patients with severe sepsis. Crit Care Med. 2014;42:90–6.
33. Yoshida T, Torsani V, Gomes S, De Santis RR, Beraldo MA, Costa EL, Tucci MR, Zin WA, Kavanagh BP, Amato MB. Spontaneous effort causes occult pendelluft during mechanical ventilation. Am J Respir Crit Care Med. 2013;188:1420–7.
34. Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med. 2013;368:795.
35. Young D, Lamb SE, Shah S, et al. High-frequency oscillation for acute respiratory distress syndrome. N Engl J Med. 2013;368:806.
36. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D, CESAR Trial collaboration. Lancet efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009;374(9698):1351.
37. Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, Forrest P, Gattas D, Granger E, Herkes R, Jackson A, McGuinness S, Nair P, Pellegrino V, Pettilä V, Plunkett B, Pye R, Torzillo P, Webb S, Wilson M, Ziegenfuss M. Extracorporeal membrane oxygenation for 2009 influenza a(H1N1) acute respiratory distress syndrome. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators. JAMA. 2009;302:1888–95.
38. ClinicalTrials.gov Identifier: NCT01470703. https://clinicaltrials.gov/ct2/show/NCT01470703.
39. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, Thompson BT, Ancukiewicz M. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med. 2006;354:1671.
40. Hermans G, Wilmer A, Meersseman W, Milants I, Wouters PJ, Bobbaers H, Bruyninckx F, Greet Van den Berghe G. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. Am J Respir Crit Care Med. 2007;175:480–5.
41. Kim S-H, Hong S-B, Yun S-C, Choi W-I, Ahn J-J, Lee YJ, Lee H-B, Lim C-M, Koh Y. Corticosteroid treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. Am J Respir Crit Care Med. 2011;183:1207–14.
42. Adhikiari NKJ, Dellinger RP, Lundin S, et al. Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis. Crit Care Med. 2014;42:404–12.
43. Fuller BM, Mohr NM, Skrupky L, et al. The use of inhaled prostaglandins in patients with ARDS: a systemic review and meta-analysis. Chest. 2015;147:1510–22.

Acute Exacerbation of COPD: Non-invasive Positive Pressure Ventilation

22

Kristy A. Bauman

Case Presentation

A 73-year old male smoker with a past medical history of coronary artery disease, congestive heart failure and COPD on home oxygen arrived in the emergency department with difficulty breathing. He complained of gradually increasing shortness of breath on exertion for 1 week and cough with thick yellow sputum. He denied fever, chills, chest pain, orthopnea or paroxysmal nocturnal dyspnea. He had increased the use of his bronchodilators as directed by his primary care physician. This did not improve his symptoms. The morning of admission, he woke up and was unable to catch his breath. He called EMS. Upon arrival, he was afebrile with BP 160/80, HR 130, RR 36, sPO_2 85 % on 4 L/min O_2. Arterial blood gas (ABG) pH 7.24, pCO_2 60, PO_2 55, spO_2 85 %. He was awake, yet lethargic, tachypneic and using accessory muscles of respiration. Chest auscultation revealed regular tachycardia, poor air movement, end-expiratory wheeze and no crackles. Chest x-ray demonstrated hyperinflation with no infiltrates.

Question What is the immediate approach to this patient with acute respiratory failure?

Answer Non-invasive positive pressure ventilation.

In the absence of absolute contraindication, all patients with acute hypercapnic respiratory failure due to an exacerbation of COPD should be treated with non-invasive positive pressure ventilation (NIPPV). This patient was initiated on NIPPV with pressure support of 12 cm H_2O, PEEP 5 cm H_2O, and FIO_2 of 0.5 via a full face mask. Oxygen was titrated to maintain saturations of greater than 90 %. He was given two albuterol/ipratropium nebulized treatments in the first 30 min of his arrival, azithromycin 500 mg PO once, and solu-medrol 60 mg IV once. After 1 h, his respiratory rate decreased to 22 and he was no longer using accessory muscles. ABG on NIPPV demonstrated pH 7.33, pCO_2 46, pO_2 80, spO_2 95 %. He was admitted to the intensive care unit for continued management. By hospital day 2, respiratory failure resolved and he was transferred to general care.

Principals of Management

Diagnosis

Acute exacerbations of COPD are characterized by sub-acute or acute worsening of chronic respiratory symptoms. Typical symptoms are dyspnea, cough, and increased sputum purulence and volume [1]. Severity of symptoms ranges from mild, which may improve without additional medical

K.A. Bauman
Pulmonary and Critical Care Medicine, University of Michigan Health System, Ann Arbor, MI, USA
e-mail: krisbaum76@gmail.com

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_22

treatment, to severe resulting in respiratory failure or death. The hallmark of COPD exacerbations is airflow obstruction, dynamic hyperinflation and airways inflammation, often provoked by viral or bacterial infections or environmental triggers. COPD exacerbations are associated with reductions in quality of life, progression of lung disease, and increased risk of death. In a longitudinal study of 2138 COPD patients; mortality during follow-up was significantly higher in those with one or more hospitalized exacerbations during the first year of follow-up (15 %), as compared to 5 % in those without an event [2]. The predicted in hospital mortality of a COPD exacerbation is 10 % [3]. A severe exacerbation resulting in hypercapnic respiratory failure portends a 2-year mortality rate approaching 50 % [3]. Indications for ICU admission of a COPD exacerbation are given below [4]. The approach to treatment of an acute exacerbation of COPD with hypercapnic respiratory failure requiring intensive care unit admission follows.

Indications for ICU Admission

- Severe dyspnea that responds inadequately to initial emergency therapy
- Changes in mental status (confusion, lethargy, coma)
- Persistent or worsening hypoxemia ($PaO_2 < 5.3$ kPa, 40 mmHg) and/or severe/worsening respiratory acidosis (pH < 7.25) despite supplemental oxygen and noninvasive ventilation
- Need for invasive mechanical ventilation
- Hemodynamic instability—need for vasopressors

Bronchodilators

Short-acting beta adrenergic agonists (albuterol, levalbuterol) are potent bronchodilators with rapid onset of action and are first line therapy for acute exacerbation of COPD [5]. Typically, these are combined with short acting anticholinergic agents such as ipratropium bromide. Both drugs can be administered with equal efficacy via metered dose inhaler or nebulizer; however nebulized delivery is often preferred during an acute exacerbation of COPD due to ease of administration for persons in respiratory distress. Albuterol should be dosed at 2.5 mg/3 mL via nebulizer every 1–4 h or 4–8 puffs (90 mcg per puff) via MDI. Ipratropium bromide is dosed at 500 mcg by nebulizer every 4 h or 2–4 puffs (18 mcg per puff) via MDI every 4 h. There is no advantage to increasing the dose of nebulized albuterol to 5 mg and continuous nebulized beta-agonists are not recommended [6]. Side effects of beta-adrenergic agonists include tachycardia, anxiety, tremors, hypokalemia, and rarely lactic acidosis. Side effects of short acting anti-cholinergic agents include dry mouth, urinary retention and exacerbation of narrow-angle glaucoma. There is no role for methylxanthines such as aminophylline for treatment of hospitalized patients with COPD exacerbations [7, 8].

Systemic Corticosteroids

When added to bronchodilator therapy, systemic corticosteroids improve lung function, decrease treatment failure rates, prevent relapse, and decrease length of hospitalization [9–11]. There is no significant difference in clinical outcomes in hospitalized patients with a COPD exacerbation treated with oral versus intravenous corticosteroids [12]. The dose of corticosteroids and length of treatment varies widely in clinical trials. A randomized controlled trial (RCT) in patients with acute exacerbation of COPD treated in the emergency department randomized patients to either a 5 day course or a 14 day course of prednisone 40 mg daily. The study concluded that patients randomized to 5 days of treatment had similar rates of relapse within 6 months and this was noninferior to a longer course [13]. Given the short and long term side effects of systemic corticosteroids, a reasonable approach to treatment is a 5 day course of 40 mg of prednisone for most patients [5]. In critically ill patients clinicians often prescribe higher doses with little evidence to support this practice. In an observational study of ICU patients with COPD exacerbations, doses of methylprednisolone <240 mg daily compared

to >240 mg daily resulted in a slightly shorter hospital and ICU length of stay and duration of mechanical ventilation [14]. There was no mortality difference. There is not enough data to recommend an optimal dose of corticosteroids in the ICU setting.

Antibiotics

The majority of COPD exacerbations are due to bacterial or viral infections. There is evidence that viruses and bacteria act synergistically to provoke airways inflammation and exacerbation [15]. Additionally, new strains of airway bacteria have been shown to trigger a significant inflammatory response and resultant exacerbation [16]. GOLD and European Respiratory Society guidelines recommend antibiotics for all patients with a moderate to severe COPD exacerbation and for those requiring hospitalization [5, 17]. Antibiotics reduce the risk of treatment failure and length of hospital stay in persons with severe exacerbations [18]. For example, in a RCT of patients requiring intubation and mechanical ventilation, ofloxacin was compared to placebo and was found to decrease mortality (4 % vs 22 %), duration of mechanical ventilation and length of hospital stay [19]. The antibiotic regimen prescribed should target common bacterial pathogens, local patterns of resistance and risk factors for P. aeruginosa infection should be considered [20, 21]. Treatment courses of 3–7 days are appropriate in most cases. A meta-analysis comparing 5 days to greater than 7 of antibiotics (beta-lactams, macrolides, and fluoroquinolones) demonstrated no difference in outcomes and fewer drug related adverse events in those with 5 day course [22].

Non-invasive Positive Pressure Ventilation (NIPPV)

NIPPV refers to positive pressure ventilation through a nasal or oral interface as opposed to endotracheal tube or tracheostomy tube. NIPPV can be delivered through standard ICU ventilators or a variety of portable devices. Indications for NIPPV in COPD exacerbations are given below [4]. The most commonly used mode of ventilation employed in acute hypercapnic respiratory failure associated with COPD exacerbation is bilevel positive airway pressure (BPAP) where an inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) is set. Pressure support, assist control and proportional assist ventilation are other options depending on the available device. There are few studies directly comparing NIPPV modes in acute hypercapnic respiratory failure. The goals of NIPPV are to reduce work of breathing, improve minute ventilation, correct hypercapnia and avoid endotracheal intubation while maximizing patient comfort. There are several available patient interfaces, full face mask, oronasal mask, nasal mask, and nasal pillows [23]. In a randomized trial of 26 patients with COPD exacerbations, NIPPV via full face mask, nasal mask or nasal pillows were compared [24]. The nasal mask was best tolerated while the full face mask provided the greatest physiologic improvement. A larger study comparing the nasal to orofacial mask found that more than half of patients with the nasal mask needed to be changed to the face mask most often due to air leak [25]. Based upon these studies, when initiating NIPPV for acute hypercapnic respiratory failure, full face mask or oronasal mask are the preferred approach. NIPPV should be initiated as soon as possible as delays may increase the likelihood of failure and need for endotracheal intubation [26]. Indications for invasive mechanical ventilation are shown below and include: cardiac/respiratory arrest, altered mental status, inability to clear secretions and protect the airway, non-respiratory organ failure, facial deformity or trauma, high risk of aspiration, recent esophageal surgery, anticipation of prolonged need for mechanical ventilation [4, 27]. Need for emergent intubation is an absolute contra-indication to NIPPV. Altered mental status due to hypercapnia is an exception. These patients should be closely monitored. Improved pH and $PaCO_2$ within 30 min to 2 h predicts NIPPV success [28, 29]. If there is no improvement in mental status or physiologic variables within this time frame, the patient should be intubated or consider withdrawing NIPPV to oxygen therapy alone. There is high quality evidence that NIPPV for the

treatment of acute hypercapnic respiratory failure in COPD improves important clinical outcomes. A meta-analysis including 14 randomized controlled trials and greater than 700 patients comparing standard therapy to NIPPV plus standard therapy in acute COPD exacerbation concluded that NPPV decreased mortality (11 % vs. 21 %), intubation rate (16 % vs. 33 %) and reduced hospital length of stay and complications related to treatment [30].

Indications for Noninvasive Mechanical Ventilation

At least one of the following:

- Respiratory acidosis (arterial pH < 7.35 and/or $PaCO_2$ > 6.0 kPa, 45 mmHg)
- Severe dyspnea with clinical signs suggestive of respiratory muscle fatigue, increased work of breathing, or both, such as use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces

Indications for Invasive Mechanical Ventilation

- Unable to tolerate NIV or NIV failure
- Respiratory or cardiac arrest
- Respiratory pauses with loss of consciousness or gasping for air
- Diminished consciousness, psychomotor agitation inadequately controlled by sedation
- Massive aspiration
- Persistent inability to remove respiratory secretions
- Heart rate, 50 min 21 with loss of alertness
- Severe hemodynamic instability without response to fluids and vasoactive drugs
- Severe ventricular arrhythmias
- Life-threatening hypoxemia in patients unable to tolerate NIV

Evidence Contour

NIPPV Use in Individuals with Do-Not-Intubate Orders

A majority of the randomized controlled trials demonstrating efficacy of NIPPV in acute respiratory failure excluded persons with do-not-intubate (DNI) orders. In clinical practice, NIPPV is routinely used in such individuals. Typically, this requires treatment in a high level care area such as an intensive care unit utilizing resources in persons where this therapy has unclear benefit. Observational studies have concluded however that many individuals with acute respiratory failure and DNI orders do survive hospitalization when treated with NIPPV, particularly in those with a primary diagnosis of COPD or cardiogenic pulmonary edema. Hospital survival rates vary from 35 to 43 % in published studies [31, 32]. One prospective, observational study of 37 patients with acute hypercapnic respiratory failure due to acute exacerbation of COPD, DNI orders, and NIPPV use demonstrated a 1-year survival of 30 % [33].

NIPPV After Extubation

In an unselected patient population, the use of NIPPV after extubation as a rescue therapy for respiratory failure did not prevent the need for re-intubation or reduce mortality [34]. Individuals with high risk of extubation failure, such as those with COPD and hypercapnia during spontaneous breathing trials do benefit from early use of NIPPV after extubation [35–37]. Compared to standard medical therapy, those receiving NIPPV at the time of extubation were less likely to require re-intubation and 90 day survival was greater. NIPPV should be applied routinely and immediately after extubation of COPD patients with hypercapnia. The benefits of NIPPV after extubation or as a weaning strategy have not been replicated in other conditions.

References

1. Anthonisen NR, Manfreda J, Warren CPW, Hershfield ES, Harding GKM, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med. 1987;106:196–204.
2. Müllerova H, Maselli DJ, Locantore N, Vestbo J, Hurst JR, Wedzicha J, Bakke P, Agusti A, Anzueto A; for the ECLIPSE investigators. Hospitalized exacerbations of chronic obstructive pulmonary disease: risk factors and outcomes in the ECLIPSE cohort. Chest. 2014. doi:10.1378/chest.14-0655.
3. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbations of chronic obstructive pulmonary disease. JAMA. 1995;274:1852–7.
4. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347–65.
5. Global strategy for the diagnosis, management, and prevention of COPD: Revised 2014. Global initiative for Chronic obstructive lung disease (GOLD). http://www.goldcopd.org. Accessed 11 Apr 2014.
6. Nair S, Thomas E, Pearson SB, Henry MT. A randomized controlled trial to assess the optimal dose and effect of nebulized albuterol in acute exacerbations of COPD. Chest. 2005;128:48.
7. Rice KL, Leatherman JW, Duane PG, et al. Aminophylline for acute exacerbations of chronic obstructive pulmonary disease. A controlled trial. Ann Intern Med. 1987;107(3):305–9.
8. Duffy N, Walker P, Diamantea F, et al. Intravenous aminophylline in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Thorax. 2005;60(9):713–7.
9. Aaron SD, Vandemheen K, Hebert P, Dales R, Stiell IG, Ahuja J, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. N Engl J Med. 2003;348:2618–25.
10. Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1999;340:1941–7.
11. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. N Engl J Med. 1999;340:1941.
12. de Jong YP, Uil SM, Grotjohan HP, et al. Oral or IV prednisolone in the treatment of COPD exacerbations: a randomized, controlled, double-blind study. Chest. 2007;132:1741.
13. Leuppi JD, Schuetz P, Bingisser R. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. JAMA. 2013;309:2223–31.
14. Kiser TH, Allen RR, Valuck RJ, et al. Outcomes associated with corticosteroid dosage in critically ill patients with acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2014;189:1052.
15. Molyneaux PL, Mallia P, Cox MJ, Footitt J, Willis-Owen SAG, Homola D, et al. Outgrowth of the bacterial airway microbiome after rhinovirus exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;188:1224.
16. Sethi S, Evans N, Brydon JB, Murphy TF. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 2002;347:465–71.
17. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, et al. Guidelines for the management of adult lower respiratory tract infections—full version. Clin Microbiol Infect. 2011;17:E1–59.
18. Vollenweider DJ, Jarrett H, Steurer-Stey CA, et al. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012;12, CD010257.
19. Nouira S, Marghli S, Belghith M, et al. Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo-controlled trial. Lancet. 2001;358:2020.
20. Garcia-Vidal C, Almagro P, Romaní V, et al. Pseudomonas aeruginosa in patients hospitalised for COPD exacerbation: a prospective study. Eur Respir J. 2009;34:1072.
21. Stoller JK. Clinical practice. Acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 2002;346:988.
22. Falagas ME, Avgeri SG, Matthaiou DK, et al. Short- versus long-duration antimicrobial treatment for exacerbations of chronic bronchitis: a meta-analysis. J Antimicrob Chemother. 2008;62:442.
23. Van Rooyen F, Soltesz K. Non-invasive ventilation – a century of experience. Drager Medical, Inc., Germany; 2011. Drägerwerk AG & Co. KGaA.
24. Navalesi P, Fanfulla F, Frigerio P, et al. Physiologic evaluation of noninvasive mechanical ventilation delivered with three types of masks in patients with chronic hypercapnic respiratory failure. Crit Care Med. 2000;28:1785.
25. Girault C, Briel A, Benichou J, et al. Interface strategy during noninvasive positive pressure ventilation for hypercapnic acute respiratory failure. Crit Care Med. 2009;37:124.
26. Collaborative Research Group of Noninvasive Mechanical Ventilation for Chronic Obstructive Pulmonary Disease. Early use of non-invasive positive pressure ventilation for acute exacerbations of chronic obstructive pulmonary disease: a multicentre randomized controlled trial. Chin Med J (Engl). 2005;118:2034.

27. Organized jointly by the American Thoracic Society, the European Respiratory Society, the European Society of Intensive Care Medicine, and the Société de Réanimation de Langue Française, and approved by ATS Board of Directors, December 2000. International Consensus Conferences in Intensive Care Medicine: noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med. 2001;163:283.
28. Soo Hoo GW, Santiago S, Williams AJ. Nasal mechanical ventilation for hypercapnic respiratory failure in chronic obstructive pulmonary disease: determinants of success and failure. Crit Care Med. 1994;22:1253.
29. Antón A, Güell R, Gómez J, et al. Predicting the result of noninvasive ventilation in severe acute exacerbations of patients with chronic airflow limitation. Chest. 2000;117:828.
30. Ram FS, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2004;(1):CD004104.
31. Schettino G, Altobelli N, Kacmarek RM. Noninvasive positive pressure ventilation reverses acute respiratory failure in select "do-not-intubate" patients. Crit Care Med. 2005;33:1976.
32. Levy M, Tanios MA, Nelson D, et al. Outcomes of patients with do-not-intubate orders treated with non-invasive ventilation. Crit Care Med. 2004;32:2002.
33. Chu CM, Chan VL, Wong IW, et al. Noninvasive ventilation in patients with acute hypercapnic exacerbation of chronic obstructive pulmonary disease who refused endotracheal intubation. Crit Care Med. 2004;32:372.
34. Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med. 2004;350:2452.
35. Ferrer M, Sellarés J, Valencia M, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. Lancet. 2009;374:1082.
36. Nava S, Gregoretti C, Fanfulla F, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med. 2005;33:2465.
37. Ferrer M, Valencia M, Nicolas JM, et al. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med. 2006;173:164.

Management of Status Asthmaticus

23

Jacob Scott and Ryan Hadley

Case Presentation

A 25-year-old woman with a history of well controlled asthma presented to the emergency department with shortness of breath, wheezing, and sore throat over 4 days. Her wheezing and shortness of breath had worsened despite the use of inhaled short acting beta agonist every 1–2 h. Typically, she had been maintained on high dose inhaled corticosteroids and a long acting beta agonist with good control. She had a history of exacerbations with upper respiratory tract infections. She was evaluated in pulmonary clinic where she was noted to have tachypnea and increased work of breathing despite administration of a nebulized short acting beta agonist. She was subsequently sent to the emergency department.

In the emergency department, she was found to be in respiratory distress. Continuous albuterol and intravenous corticosteroids were administered. Arterial blood pH measured 7.5 and partial pressure of carbon dioxide and oxygen while breathing ambient air were 30 and 65, respectively. Despite the above treatment, the patient's respiratory status continued to worsen, and she required endotracheal intubation and mechanical ventilation. Initial ventilator settings were: tidal volume of 450 ml, respiratory rate of 20, fraction of inspired oxygen (FIO_2) of 0.40 and a positive end expiratory pressure (PEEP) of 5 cm of water. Peak airway pressure during a passive breath measured at 65 cm of water; with a pressure during an end expiratory hold (plateau pressure) of 15 cm of water. Continuous infusion of benzodiazepines and opiates provided sedation. She was admitted to the intensive care unit for further management.

In the evening, the intensivist received a call regarding hemodynamic instability. The patient's pulse rate was 150 beats per minute with a systolic blood pressure measuring 70 mm of Hg. Chest x-ray and thoracic ultrasound show no evidence of pneumothorax. Breath sounds were diminished but equal bilaterally with expiratory wheezing. Pressure measured at airway opening during end inspiratory and end expiratory holds are 45 and 25, respectively.

Question What is the next step in the management of this patient?

Answer Disconnect the ventilator to allow exhalation of trapped air.

The patient has life-threatening accumulation of air within the thorax, commonly referred to as "air trapping" or "auto-PEEP". Pneumothorax would have a similar presentation, but it was excluded by chest x-ray and bedside ultrasound.

Electronic supplementary material The online version of this chapter (doi:10.1007/978-3-319-43341-7_23) contains supplementary material, which is available to authorized users.

J. Scott • R. Hadley (✉)
Pulmonary and Critical Care Medicine,
Spectrum Health, Grand Rapids, MI, USA
e-mail: ryan.hadley@spectrumhealth.org

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_23

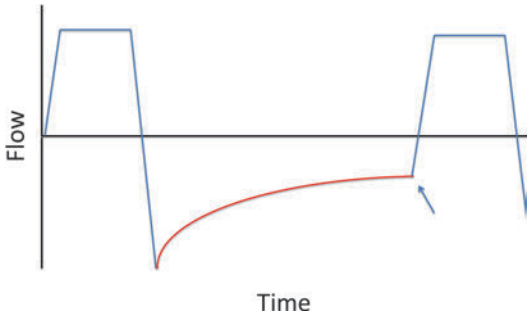


Fig. 23.1 Incomplete exhalation of delivered tidal volume. Above is a flow volume curve of an asthmatic patient on volume cycled mechanical ventilation. The patient is still exhaling the prior tidal volume at the time of the delivery of the next breath (see *arrow*). Ideally, the exhalation phase flow rate would return to 0 (complete emptying of tidal volume) prior to delivery of the next breath. The entrapped volume remains in the thorax and can accumulate and cause sequela of air trapping

Due to the patient's bronchospasm, she has an extremely prolonged expiratory phase, which leads to premature delivery of mechanical breaths prior to full exhalation of the previous breath (Fig. 23.1).

Over time, air accumulates and becomes "trapped" within the relatively fixed thoracic cage volume. Eventually, residual air increases the intrathoracic pressure (see ideal gas law below for pathophysiologic explanation).

Ideal Gas Law

$$PV = nRT$$

P = pressure, V = Volume, n = gas amount (moles), R = constant, T = temperature.

From this relationship, if the amount of gas is increased (n) in a fixed volume (V, in this case the thoracic cage) at a constant temperature, pressure will increase. If left uninterrupted, the increase in thoracic pressure will overcome the venous return pressures in the superior and inferior vena cava. Preload insufficiency and decrease in cardiac output ensue, leading to a state of obstructive shock. This trapped air cannot be discharged while mechanical breaths continue to be administered; such as in this case with the timed volume supported setting of mechanical ventilation. Thus, disconnection of the ventilator tubing from the endotracheal tube and allowing the trapped air to passively escape via an open endotracheal tube remedies this emergency.

The presence of clinically significant air trapping can be determined by measuring the pressure at airway opening (i.e. the pressure detected in the ventilator) at the end of exhalation. The total positive end expiratory pressure, or PEEP, which is composed of the PEEP set on the mechanical ventilator in combination with the pressure exerted by trapped air, or "auto-PEEP".

$$\text{Total PEEP} = \text{Ventilator PEEP} + \text{auto-PEEP}$$

Any pressure measured above the ventilator set PEEP is evidence for some degree of air trapping.

Auto peep also elevates the pressure at airway opening during an end inspiratory hold (plateau pressure) by the below formula (simplified from Truwit et al. [1]).

$$\text{Peak airway pressure} = (F \times R) + (TV / C) + \text{set PEEP} + \text{auto-PEEP}$$

Furthermore, the volume of trapped air can be directly measured and is a sensitive indicator for risk of hypotension from air trapping [2] (see section "Monitoring for Hyperinflation" and Fig. 23.2).

Air trapping can be avoided by minimizing the tidal volume and/or increasing the gas flow rate from the ventilator. Additionally, minute ventilation can be further decreased by reducing the delivered respiratory rate, which may require heavy sedation or neuromuscular blockade. Any decrease in the amount of air that needs to be exhaled, or increase in the amount of time available for exhalation, is useful. When resuming mechanical ventilation in this patient after discharge of the trapped air, she should be treated

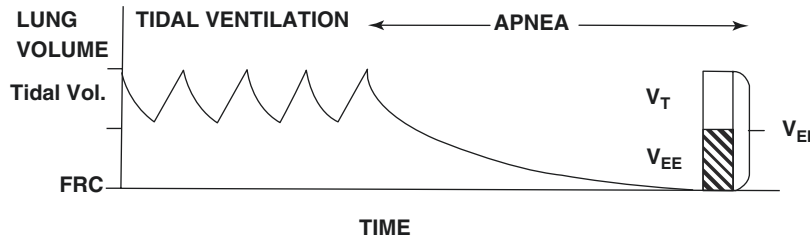


Fig. 23.2 Air trapping during mechanical ventilation in an asthmatic patient. During tidal ventilation, the lung volume never returns its physiologic starting point, the FRC. Measurement of the volume of trapped air (V_{EE}) has been studied in asthmatic patients while receiving mechanical ventilation and pharmacologic paralysis. At the end of a mechanical tidal breath, the respiratory rate is set to zero and the volume of expired air is measured until flow reaches zero. Williams and colleagues have shown that neither barotrauma nor hypotension occur when the volume of trapped air is less than 1.4 L or 15 cc/kg [2]. Note this has only been verified in the paralyzed patient. *FRC* functional residual capacity, V_{EE} end-expiratory lung volume above FRC (i.e. the volume of trapped gas), V_{EI} end inspiratory lung volume, V_T tidal volume (Reprinted with permission of the American Thoracic Society. Copyright © 2015 American Thoracic Society. Williams et al. [2]. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society)

with substantially lower minute ventilation either by a decreased respiratory rate and/or tidal volume.

Principles of Management

Inhaled Bronchodilators

Inhaled short acting bronchodilators are the mainstay of treatment of an asthma exacerbation. Most commonly, inhaled short acting beta-2 agonists such as albuterol, levalbuterol, or salbutamol are employed. These medications target the underlying physiologic cause of respiratory failure, bronchospasm. They do not, however, treat the underlying inflammatory insult which causes bronchospasm. Albuterol is the most commonly used short acting bronchodilator in the United States. In the most serious cases, it can be used as a continuous nebulized inhaled solution. No data exists in regards to withholding short acting bronchodilators during an asthma exacerbation and equipoise does not exist for such study given the presumed obvious benefit. A meta-analysis showed no advantage of continuous administration of beta agonists, as compared to intermittent administration, in acute asthma [3]. Likewise, a controlled trial in the subset of severe asthma failed to show benefit of continuous beta agonists as compared to treatments every 20 min followed by treatments every hour [4]. For the even smaller subset of life threatening asthma, no prospective data exists in adults to our knowledge.

Addition of inhaled short acting anticholinergic medications to administration of short acting beta agonists improve pulmonary mechanics [5] as well as decrease admission rates [6] in patients with severe asthma, and are recommended by a panel of experts [7]. No data exists in patients receiving mechanical ventilation, though use of anticholinergic may theoretically decrease hypersecretion of mucus and mucus plugging, a finding common in fatal asthma [8].

Corticosteroids

Corticosteroids are administered during an asthma exacerbation to decrease the inflammation that leads to bronchospasm. Meta-analysis has shown a benefit of steroid therapy in adults with acute asthma [9]. No good data exist for the optimal dose of corticosteroids, but 2 mg/kg of methylprednisolone or †he equivalent is recommended by an expert panel [7]. In a randomized trial, no benefit was demonstrated with high dose (500 mg methylprednisolone) versus standard dose (100 mg methylprednisolone) corticosteroids [10].

Monitoring of Arterial Blood Gases

Arterial blood gases are monitored during status asthmaticus in the spontaneously breathing patient. In a patient with adequate respiratory reserve during an asthma exacerbation, an arterial blood gas typically shows respiratory alkalosis. A normal pH and partial pressure of carbon dioxide with a high work of breathing, respiratory acidosis, or normalization of the pH after an initial respiratory alkalosis are all harbingers of impending respiratory embarrassment, and escalation of support with adjunctive treatments and/or invasive mechanical ventilation should be initiated.

Ventilator Strategies

Strategies for asthmatic patients on mechanical ventilation hinge on the avoidance of hyperventilation, or air trapping, as illustrated in our case. Indeed, hypotensive and mechanical complications are related to the volume of gas enclosed in the thorax above functional residual capacity (FRC) at end exhalation [2] (please see section "Monitoring for Hyperinflation"). Entrapment of supra-physiologic gas volumes is best avoided by allowing for full exhalation of tidal volumes and return to FRC. Unfortunately, with severe airway obstruction the exhalation time required to fully empty the lung to FRC can be extremely prolonged. To allow full exhalation, clinicians can either decrease the tidal volume of the inspired breath, or allow additional time for exhalation. In other words, maximization of expiratory time is key. Whatever isn't inspiratory time is expiratory time.

To this end, clinicians can decrease tidal volume in order to decrease the air volume that needs to be exhaled, or decrease the respiratory rate, which increases the time of exhalation. Adjustment of the ratio of inspiratory time to expiratory time by adjusting the flow rate (i.e. 60–100 L/min) or shape (accelerating to square) also increase the amount of exhalation time, however the incremental benefit as compared to decreasing the respiratory rate is minimal at low tidal volumes [11]. Increased flows can also increase spontaneous respiratory rates in some mechanically ventilated patients, which would outweigh any incremental benefit [12]. As a starting setting, a minute ventilation of 10 L per minute or less and a respiratory rate of 10–14 breaths/minute are reasonable [13]. Vigilant monitoring for the efficacy of ventilator settings is needed and is discussed in the section "Monitoring for Hyperinflation".

$$\text{Single breath inspiratory time} = \text{Tidal volume} / \text{Ventilator flow rate}$$

$$\text{Minute ventilation} = \text{Tidal volume} \times \text{Respiratory rate}$$

Permissive Hypercapnia/Hypoventilation

During permissive hypoventilation, hypercarbia often develops as the minute ventilation provided is not adequate to eliminate the produced carbon dioxide. In a patient with spontaneous respiration on the ventilator, hypercarbia will often lead to an increased respiratory rate, which may be detrimental (see ventilator strategies). Often, deep sedation or paralysis is needed to allow for permissive hypercapnia (or permissive hypoventilation). Elevation in carbon dioxide on arterial blood gas should be tolerated; with a goal arterial blood pH above 7.15 [14]. If the pH drops below 7.15, sodium bicarbonate or THAM infusions can be utilized. Minute ventilation can be increased cautiously if there is no significant hyperinflation. If life-threatening changes in pH continue, further strategies include deeper sedation or paralysis to minimize carbon dioxide production by muscular tissues. In the rare case that these treatments are inadequate, extracorporeal life

support (ECLS) can be utilized for CO_2 removal (see evidence contour).

Monitoring for Hyperinflation

A thorough understanding of respiratory pressures generated during mechanical ventilation is requisite to understand the pathophysiology of asthma during mechanical ventilation. Peak airway pressure is the combination of several components, as discussed below. These pressures can **ONLY** be measured in a mode with constant tidal volumes (i.e. not a pressure mode).

Respiratory causes of death from status asthmaticus often stem from circulatory collapse or mechanical complications of invasive mechanical ventilation, which are typically caused by air trapping and pneumothorax respectively. Avoidance of these complications requires monitoring for hyperinflation. Indeed, the volume of trapped air above functional residual capacity (FRC) at end exhalation correlates with risk for pneumothorax and hypotension (see Fig. 23.1) [2]. However, measuring this volume in clinical practice is difficult due to lack of familiarity with the technique needed (see Fig. 23.2 for full discussion).

Plateau pressure, Auto-PEEP, and analysis of flow volume curves are used as surrogates to directly measuring the entrapped air volume above FRC. Interestingly, plateau pressure and Auto-

Determination of Components of Peak and Plateau Airway Pressure in the Absence of Patient Effort [1]

$$\text{Peak pressure} = \text{Pressure to overcome airways resistance} + \text{Pressure to inflate lungs} + \text{total PEEP}$$

Ohm's law, or Pressure needed to overcome airways resistance

$$P_{\text{resistace}} = \text{Flow} \times \text{Resistance of airways}$$

$$\text{Compliance}\left(\text{definition}\right) = \text{Volume} / \text{Pressure}$$

(Note compliance is of respiratory system, which includes the lungs as well as external compliance from abdomen and chest wall)

$$P_{\text{compliance}} = \text{Tidal volume} / \text{Compliance}_{(\text{lugs} + \text{soft tissues})}$$

From previous PEEP discussion

$$\text{Total PEEP} = \text{Set PEEP} + \text{ Auto-PEEP}$$

$$\text{Peak airway pressure} = \left(\text{F} \times \text{R}\right) + \left(\text{TV} / \text{C}\right) + \text{set PEEP} + \text{ auto-PEEP } *$$

Plateau Pressures

During an inspiratory hold at the end of a full tidal volume (plateau pressure), the flow is zero, eliminating the first term in the equation so

$$\text{Plateau pressure} = \text{TV} / \text{C} + \text{set PEEP} + \text{ auto-PEEP } **$$

Thus

Peak airway pressure – Plateau pressure = pressure needed to overcome airways resistance; and plateau pressure is an indicator of compliance and total PEEP

PEEP did not correlate with barotrauma or hypotensive complications in a single study of mechanically ventilated asthmatic patients [2], despite having some correlation with end inspiratory lung volume (VEi) [15]. However, monitoring of these parameters is advocated by experts as a surrogate for direct measurement of trapped air volume, with goals being auto-PEEP as low as possible and plateau pressures less than 30 cm H_2O [11, 16].

Plateau pressure is reflective of the pressure "seen", collectively as an average, by the alveoli and it is this increased pressure that causes alveolar rupture and pneumothorax. In pure asthma in the non-obese patient, lung and thoracic cage compliance is normal; therefore if plateau pressure is elevated it is likely secondary to air trapping and auto-PEEP or pneumothorax.

Auto-PEEP is the difference of the measured end-expiratory pressure and the set PEEP on the ventilator, which is measured with an end expiratory hold. Exhalation is usually passive, although a mechanically ventilated patient with asthma who is not paralyzed may attempt active exhalation and thereby falsely elevate auto-PEEP. If there is air trapped within the thorax, it will increase pressure due to the increased amount of gas within a fixed thoracic cage (see previous discussion of ideal gas law in case answer). Should this complication develop and cause hemodynamic deterioration, the best solution is transient disconnection of the mechanical ventilator to eliminate further inspired air and allow for full exhalation of the trapped air. Alternatively, these emergent complications are avoided by permissive hypoventilation and diligent monitoring for air trapping by regularly measurement of auto-PEEP and plateau pressures. Air trapping can be seen on a breath to breath basis when a mechanical breath is delivered without the expiratory flow returning to zero on a flow time curve (Fig. 23.1).

Peak airway pressures are often extremely elevated in patients with asthma during mechanical ventilation due to the resistive force of constricted airways (Ohm's law: Pressure = Flow × Resistance). If increased flows are used to extend exhalation time, this will likewise raise peak airway pressure (see equation above).

However, this pressure is merely the pressure needed to overcome the airway resistance and is **NOT** transmitted to the alveolus. It is the plateau pressure, not the peak airway pressure, that is a marker of alveolar pressure and hence an indicator of risk for pneumothorax. Note that elevated plateau pressure will, by default, cause an elevated peak airway pressure. An elevated peak airway pressure with a normal plateau pressure in a patient with asthma is not worrisome and does not require specific intervention.

Recognizing Barotrauma

Pneumothorax can occur and will create similar hemodynamic instability and increased plateau airway pressures as an air trapping emergency such as seen in the clinical case above. A low threshold is needed for investigation or treatment of pneumothorax especially in an abrupt decline in clinical status or exam signs of pneumothorax (crepitus, deviated trachea, asymmetric breath sounds) develop. Pleural ultrasound can yield rapid bedside evaluation of suspected pneumothorax. Lung sliding, when seen at all intercostal spaces examined, essentially rules out pneumothorax [17]. Absence of lung sliding, while consistent with pneumothorax, is only 78 % specific for pneumothorax due to multiple false positives [17]. When seen, lung point is nearly 100 % specific, and therefore the most reliable confirmatory ultrasonographic sign for pneumothorax [17] (Video 23.1).

At the beginning of the video lung sliding is seen. When lung sliding is visualized, it rules out pneumothorax at the interspace examined. Absence of lung sliding does not confirm pneumothorax with acceptable specificity for intervention. Midway through the video, sliding can be seen to continue on the left-most part of the screen where it vanishes on the right of the screen. The point of transition of normal sliding lung (normal pleura opposing chest well) to that of no lung sliding (lack of pleural contact with chest wall) is referred to as a "lung point". This ultrasonographic sign, when seen, is nearly

100 % specific [17] and a reliable bedside sign to justify tube thoracostomy if indicated.

Evidence Contour

Adjuvant Pharmacologic Treatments

Adjuvant pharmacologic treatments are used to stave off mechanical ventilation or salvage someone failing ventilator support such that they cannot be successfully oxygenated or hypercapnic acidosis has become profound.

Magnesium

Intravenous magnesium sulfate has been promoted for patients with life-threatening asthma. Meta-analyses have demonstrated an improvement in air flow [19, 20] and hospitalization rates in adults with acute asthma [19]. A recent randomized controlled trial in the subset of severe, acute asthma showed no significant clinical benefit for magnesium sulfate infusion or nebulized inhalation [21]. Trials for the even smaller subset of life threatening asthma or impending respiratory failure do not exist. It is noted nearly all trials involve a single administered dose in the emergency room. We advocate for the adjunctive use of intravenous infusion of 2 g magnesium sulfate given the supportive meta-analyses of airflow improvement in patients with impending or current respiratory failure because even small improvements in airflow can improve air-trapping and respiratory reserve in patients with extremely impaired obstructive physiology.

Intravenous Bronchodilators

Terbutaline and isoproterenol can be used as infusions for refractory asthma unresponsive to typical measures, if tolerated by the heart rate. Limited data exists for the use of these agents [22].

Lactic Acidosis from Beta Agonist

Type B lactic acidosis from inhaled beta agonists does occur, is common, and is related to serum albuterol level, and is **NOT** a predictor of worse clinical outcomes [23, 24]

Due to their efficacy, in patients with life-threatening asthma beta agonist medications cannot be avoided and the lactic acidosis this is simply tolerated.

Heliox

Helium decreases viscosity of air allowing it to travel more efficiently through small, constricted airways [25]. Heliox is a mixture of helium and oxygen which can be inhaled as a salvage maneuver for impending respiratory failure to prevent intubation as a temporizing measure. Routine use in adult asthma exacerbations is not supported by meta-analysis [26, 27]. In the subset of patients with status asthmatics, heliox has been shown to improve oxygenation presumably by improved V/Q matching [28], It is noted if there is concomitant hypoxemia such as from pneumonia, there is a limitation in the amount fraction of inspired oxygen (FiO_2) which can be provided as the remaining fraction is needed for helium to exert is effect on the viscosity of ambient air. In a patient with impending respiratory failure, a short trial of heliox with frequent clinical monitoring can be attempted given the difficulties and potential complications of asthmatic patients during mechanical ventilation.

Noninvasive Positive Pressure Ventilation (NIV)

Noninvasive positive pressure ventilation in an asthmatic patient at risk of intubation may be useful to allow acute pharmacologic therapies to take effect, although data for this approach is limited [29]. Any asthma patient on NIV should be monitored in the intensive care unit with close clinical monitoring including serial measures of arterial blood gases. Trials of NIV should be short (1–2 h)

and a low threshold for endotracheal intubation and mechanical ventilation is needed among patients who deteriorate or fail to improve.

Avoidance of mechanical ventilation, while desirable, must be balanced with the risk of waiting too long and developing an emergent airway, which ultimately may be more dangerous for the patient.

Anesthetics

Some inhaled and infusion anesthetics, such as halothane, isoflurane, enflurane, and sevoflurane, have bronchodilatory properties and have been used in refractory status asthmaticus [30, 31]. Intravenous ketamine may be useful if the patient is also mechanically ventilated as it can be used concomitantly as a sedative [32–34]. Familiarization with the contraindications and side effects of these medications are required if the Intensivist intends to use this medication, and may require local credentialing.

Inhaled anesthetics can be used as a salvage technique; however, the logistics needed for continuous delivery are not trivial; though in refractory cases this may be preferable to extracorporeal life-support (ECLS) especially if this technology is not available at the treating center. Consultation with an anesthesia provider is requisite if inhaled anesthetics are utilized in the ICU.

Bronchoscopy

Plugging of airways by mucus and cellular debris is a common finding in autopsy of fatal asthma [8]. Use of bronchoscopy for refractory asthma patients receiving mechanical ventilation has been described in case reports with favorable outcomes [35]. Creation of a one-way valve by mucus, such as a check valve phenomenon that can be seen in COPD, to our knowledge has not been reported in asthma. One case of unilateral asthma has been described, however it was not felt to be due to check valve mechanism [36]. Regardless, if regional air trapping is seen on a radiograph (such as seen in Fig. 23.3) bronchoscopy is indicated for secretion clearance.

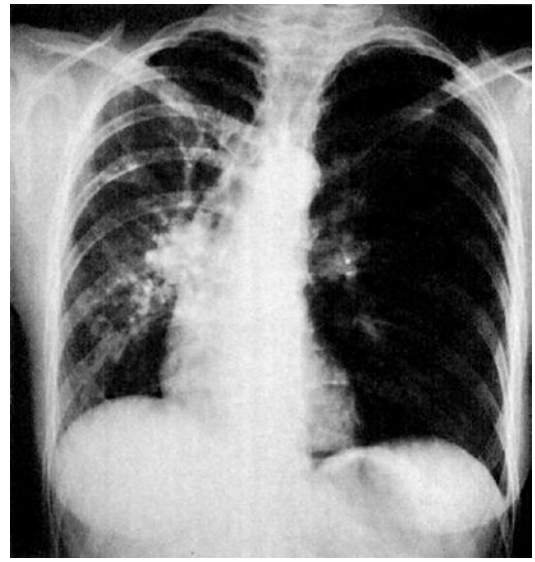


Fig. 23.3 Unilateral left lung asthma. If regional asthma or air trapping is seen, such as on the above radiograph, bronchoscopy is indicated for secretion clearance (From DiFrancia et al. [36]. Reprinted with permission from Elsevier Limited)

Extracorporeal Life Support (ECLS)

ECLS efficiently eliminates carbon dioxide from the blood. In patients failing mechanical ventilation with hypercarbia, ECLS can be a salvage technique for asthmatic patients with life threatening hypercarbia [37, 38]. Given the efficiency of extracorporeal carbon dioxide removal, new pumpless techniques of gas elimination have been developed [39] and have been used successfully in status asthmaticus [40, 41].

A myriad of complications can develop during ECLS and avoidance, if possible, is advised by maximizing adjuvant pharmacological treatments and ventilator strategies.

References

1. Truwit JD, Marini JJ. Evaluation of thoracic mechanics in the ventilated patient part II: applied mechanics. J Crit Care. 1988;3(3):199–213.
2. Williams TJ, et al. Risk factors for morbidity in mechanically ventilated patients with acute severe asthma. Am Rev Respir Dis. 1992;146(3):607–15.
3. Rodrigo GJ, Rodrigo C. Continuous vs intermittent beta-agonists in the treatment of acute adult asthma: a systematic review with meta-analysis. Chest. 2002;122(1):160–5.

4. Besbes-Ouanes L, et al. Continuous versus intermittent nebulization of salbutamol in acute severe asthma: a randomized, controlled trial. Ann Emerg Med. 2000;36(3):198–203.
5. Stoodley RG, Aaron SD, Dales RE. The role of ipratropium bromide in the emergency management of acute asthma exacerbation: a metaanalysis of randomized clinical trials. Ann Emerg Med. 1999;34(1):8–18.
6. Rodrigo GJ, Rodrigo C. The role of anticholinergics in acute asthma treatment: an evidence-based evaluation. Chest. 2002;121(6):1977–87.
7. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol. 2007;120(5 Suppl):S94–138.
8. Kuyper LM, et al. Characterization of airway plugging in fatal asthma. Am J Med. 2003;115(1):6–11.
9. Rowe BH, Keller JL, Oxman AD. Effectiveness of steroid therapy in acute exacerbations of asthma: a meta-analysis. Am J Emerg Med. 1992;10(4):301–10.
10. Emerman CL, Cydulka RK. A randomized comparison of 100-mg vs 500-mg dose of methylprednisolone in the treatment of acute asthma. Chest. 1995;107(6):1559–63.
11. Leatherman J. Mechanical ventilation for severe asthma. Chest. 2015;147(6):1671–80.
12. Corne S, et al. Effect of inspiratory flow rate on respiratory rate in intubated ventilated patients. Am J Respir Crit Care Med. 1997;156(1):304–8.
13. Leatherman JW, McArthur C, Shapiro RS. Effect of prolongation of expiratory time on dynamic hyperinflation in mechanically ventilated patients with severe asthma. Crit Care Med. 2004;32(7):1542–5.
14. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000;342(18):1301–8.
15. Tuxen DV, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. Am Rev Respir Dis. 1987;136(4):872–9.
16. Brenner B, Corbridge T, Kazzi A. Intubation and mechanical ventilation of the asthmatic patient in respiratory failure. Proc Am Thorac Soc. 2009;6(4):371–9.
17. Lichtenstein DA, et al. Ultrasound diagnosis of occult pneumothorax. Crit Care Med. 2005;33(6):1231–8.
18. Doerschug KC, Schmidt GA. Intensive care ultrasound: III. Lung and pleural ultrasound for the intensivist. Ann Am Thorac Soc. 2013;10(6):708–12.
19. Kew KM, Kirtchuk L, Michell CI. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. Cochrane Database Syst Rev. 2014;5, CD010909.
20. Alter HJ, Koepsell TD, Hilty WM. Intravenous magnesium as an adjuvant in acute bronchospasm: a meta-analysis. Ann Emerg Med. 2000;36(3):191–7.
21. Goodacre S, et al. The 3 Mg trial: a randomised controlled trial of intravenous or nebulised magnesium sulphate versus placebo in adults with acute severe asthma. Health Technol Assess. 2014;18(22):1–168.
22. Travers AH, et al. Addition of intravenous beta(2)-agonists to inhaled beta(2)-agonists for acute asthma. Cochrane Database Syst Rev. 2012;12, CD010179.
23. Lewis L, et al. Albuterol administration is commonly associated with increases in serum lactate in patients with asthma treated for acute exacerbation of asthma. Chest. 2014;145(1):53–9.
24. Rodrigo GJ, Rodrigo C. Elevated plasma lactate level associated with high dose inhaled albuterol therapy in acute severe asthma. Emerg Med J. 2005;22(6):404–8.
25. Hashemian SM, Fallahian F. The use of heliox in critical care. Int J Crit Illn Inj Sci. 2014;4(2):138–42.
26. Rodrigo GJ, et al. Use of helium-oxygen mixtures in the treatment of acute asthma: a systematic review. Chest. 2003;123(3):891–6.
27. Rodrigo G, et al. Heliox for nonintubated acute asthma patients. Cochrane Database Syst Rev. 2006;4, CD002884.
28. Schaeffer EM, et al. Oxygenation in status asthmaticus improves during ventilation with helium-oxygen. Crit Care Med. 1999;27(12):2666–70.
29. Lim WJ, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. Cochrane Database Syst Rev. 2012;12, CD004360.
30. Rosseel P, Lauwers LF, Baute L. Halothane treatment in life-threatening asthma. Intensive Care Med. 1985;11(5):241–6.
31. Bierman MI, et al. Prolonged isoflurane anesthesia in status asthmaticus. Crit Care Med. 1986;14(9):832–3.
32. Hemming A, MacKenzie I, Finfer S. Response to ketamine in status asthmaticus resistant to maximal medical treatment. Thorax. 1994;49(1):90–1.
33. Hemmingsen C, Nielsen PK, Odorico J. Ketamine in the treatment of bronchospasm during mechanical ventilation. Am J Emerg Med. 1994;12(4):417–20.
34. Strube PJ, Hallam PL. Ketamine by continuous infusion in status asthmaticus. Anaesthesia. 1986;41(10):1017–9.
35. Khan MF, et al. Bronchoscopy as a rescue therapy in patients with status asthmaticus: two case reports and review of literature. Saudi J Anaesth. 2013;7(3):327–30.
36. DiFrancia M, Barbier D, Orehek J. Left lung asthma. Chest. 1993;104(6):1919–20.
37. Mikkelsen ME, et al. Outcomes using extracorporeal life support for adult respiratory failure due to status asthmaticus. ASAIO J. 2009;55(1):47–52.
38. Mikkelsen ME, et al. Emergency extracorporeal life support for asphyxic status asthmaticus. Respir Care. 2007;52(11):1525–9.
39. Bein T, et al. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. Crit Care Med. 2006;34(5):1372–7.
40. Jung C, et al. Pumpless extracorporeal lung assist for the treatment of severe, refractory status asthmaticus. J Asthma. 2011;48(1):111–3.
41. Elliot SC, et al. Pumpless extracorporeal carbon dioxide removal for life-threatening asthma. Crit Care Med. 2007;35(3):945–8.

Immunocompromised Pneumonia

24

Robert P. Dickson

Case Presentation

A 67 year-old man with no recent hospitalizations presents to the Emergency Department with shortness of breath. He has a history of ulcerative colitis and is currently treated with cyclosporine and prednisone 10 mg/day. He denies fevers, chills or sputum production. Pulse oximetry is 82% on room air. Initial chest x-ray and high-resolution CT scan of the chest are shown (Figs. 24.1 and 24.2). Over the next 24 h, he experiences progressive hypoxemia and respiratory distress despite supplemental oxygen and empiric antibiotic therapy for community-acquired pneumonia (ceftriaxone and azithromycin). The patient undergoes endotracheal intubation and mechanical ventilation is initiated.

Question Should the patient's antimicrobial regimen be changed? What diagnostic test should be performed?

Answer The patient's antimicrobial regimen should be expanded empirically to cover *Pneumocystis jirovecii* (e.g. trimethoprim-sulfamethoxazole) given (1) his risk factors (cyclosporine and corticosteroids), (2) his consistent CT scan (interstitial infiltrate with cystic changes), (3) his hypoxemia disproportionate to radiographic infiltrate, (4) his lack of clinical response to an empiric regimen adequate for community-acquired pneumonia, and (5) the fact that empiric therapy does not compromise the diagnostic yield of subsequent bronchoscopy in the diagnosis of *Pneumocystis* pneumonia [1]. A lower respiratory tract specimen should be acquired, via bronchoscopy or mini- bronchoalveolar lavage (BAL); lavage fluid should be tested for gram stain and culture, respiratory virus polymerase chain reaction (PCR), fungal culture, galactomannan, acid-fast stain and culture, and *Pneumocystis* PCR.

The patient underwent flexible bronchoscopy, and a positive *Pneumocystis* PCR assay confirmed the diagnosis. The patient received intravenous trimethoprim-sulfamethoxazole, and oxygenation gradually improved over the next 5 days. The patient was ultimately extubated and recovered full lung function. After 21 days of treatment, the patient's trimethoprim-sulfamethoxazole was changed to the prophylactic dose (1 double-strength tablet [160/800] once daily) for the duration of his immunosuppression.

Principles of Management

Presentation

Pneumonia is a common and morbid complication of immunosuppression, whether due to primary immunodeficiency or, more commonly, secondary

R.P. Dickson
Medicine (Pulmonary and Critical Care), University of Michigan Health System, Ann Arbor, MI, USA
e-mail: rodickso@med.umich.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_24

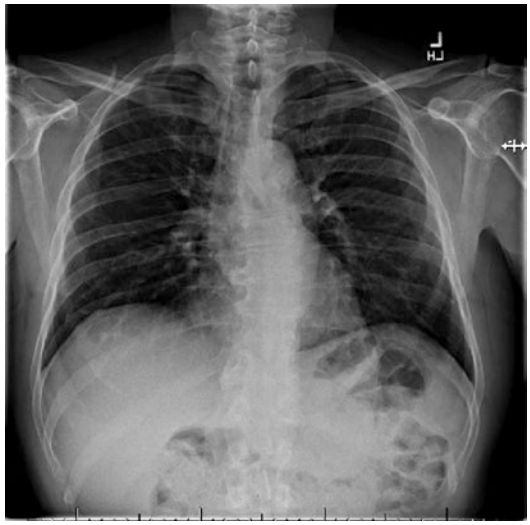


Fig. 24.1 Chest X-ray

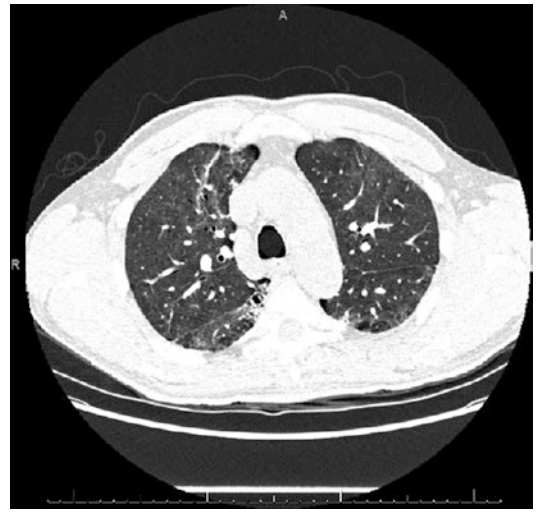


Fig. 24.2 High-resolution CT scan

to a systemic disease process or its treatment. The presentation of pneumonia among immunosuppressed patients is often more subtle, indolent and atypical than among immunocompetent patients [2]; the same immune deficits that permit microbial reproduction in the lower respiratory tract can decrease the intensity of fever, sputum production, or radiographic infiltrates. Immunosuppressed patients are often vulnerable to competing or concurrent non-infectious lung processes such as cardiogenic edema (e.g. among patients receiving cardiotoxic chemotherapy or aggressive hydration with chemotherapeutic regimens), medication toxicity (e.g. among patients receiving bleomycin or methotrexate), radiation pneumonitis, or malignancy (e.g. Kaposi's Sarcoma among patients with Human Immunodeficiency Virus [HIV]/Acquired Immunodeficiency Syndrome [AIDS]).

Etiology

The presence and persistence of microbes in the respiratory tract are determined by the balance of microbial immigration, elimination and local microbial growth conditions [3, 4], all of which are altered in immunosuppressed patients. The microbiota of the upper respiratory tract (the primary source community for migration of microbes to the lungs [4, 5]) are altered by systemic immunosuppression, whether by underlying disease (e.g. HIV/AIDS) [6] or immune-suppressing medications [7]. Impairment of innate and adaptive immunity decreases the elimination rate of transient microbes, increasing the likelihood of persistent reproduction, and makes the microbial growth conditions of the lung environment more hospitable to dysregulated reproduction [3]. Each patient's specific constellation of immune deficits predisposes him/her to a select number of opportunistic pathogens (Table 24.1). Consideration of each patient's candidate pathogen profile is critical to the appropriate selection of empiric antimicrobial therapy. Despite the wide breadth of potential pathogens in this population, the most common culprits remain the bacteria and viruses responsible for community-acquired pneumonia (e.g. *Streptococcus pneumoniae*) [9], which should be covered by any empiric regimen. Coverage for atypical organisms (*Mycoplasma* spp., *L. pneumophila* and *C. pneumoniae*) is warranted in community-dwelling patients until a specific pathogen is identified.

Diagnosis

Chest x-rays are of notoriously poor sensitivity in identifying pneumonia among immunocompromised patients; in one large series, the major-

Table 24.1 Correspondence of immunodeficiency and susceptibility to respiratory pathogens

Immune defect		Disease examples	Iatrogenic examples	Organisms to suspect
Innate immunity	Neutrophil abundance	Leukemia Parvovirus infection Agranulocytosis	Chemotherapy Methotrexate Clozapine	Gram-negative bacilli *Staphylococcus* spp. Fungi (e.g. *Aspergillus* spp.)
	Neutrophil function	Chronic granulomatous disease Cirrhosis Uremia	Anti-TNF agents [8]	*Staphylococcus aureus* Fungi (e.g. *Aspergillus* spp.)
Adaptive immunity	T-cell abundance and function	HIV/AIDS Lymphoma Primary immunodeficiency	Chemotherapy Corticosteroids Calcineurin inhibitors Anti-T-cell antibodies	*Pneumocystis jirovecci* *Cryptococcus* spp. Intracellular bacteria (e.g. *Legionella* spp.) *M. tuberculosis* Viruses (*CMV, HSV, VZV)*
	B-cell abundance and function	Multiple myeloma Primary immunodeficiency	Rituxumab	Encapsulated bacteria: *S. pneumoniae, H. influenzae*

ity of neutropenic patients with infiltrates on thin-sliced CT scans had no detectable abnormality on chest radiograph [10]. High-resolution CT scan is often helpful for confirming the presence of infection, guiding site selection for bronchoalveolar lavage, and directing empiric therapy based on imaging characteristics. The presence of cavitation is associated with *Mycobacterium* spp., *Nocardia* spp., *Aspergillus* spp. and *P. jirovecci*.; interstitial infiltrates suggest viral (e.g. Cytomegalovirus [CMV]) pneumonia or *Pneumocystis;* dense consolidation implies either bacterial pathogens or *Aspergillus* spp.. Serologic tests are of decreased utility in immunocompromised patients, especially in patients with impaired T-cell and B-cell immunity (Table 24.1), whereas antigen-based testing (e.g. *Streptococcus* and *Legionella* urinary antigens, *Cryptococcus* serum antigen testing) can be useful. An aggressive approach to sampling the lower respiratory tract (via bronchoscopy or miniature bronchoalveolar lavage ["mini-BAL"]) is warranted, as the spectrum of potential pathogens usually exceeds any reasonable empiric antimicrobial regimen. Depending on the patient's degree and type of immunosuppression, lower respiratory tract specimens should be tested for gram stain and bacterial culture, fungal culture, acid fast stain and culture, respiratory viral PCR, CMV antigen, galactomannan, *Pneumocystis* PCR. Recommended diagnostic tests by specimen site are listed in Table 24.2.

Empiric Treatment

Antimicrobial therapy should be given promptly in patients with suspected pneumonia. Unless lower respiratory tract specimens can be acquired immediately, therapy should not be delayed for the sake of increasing diagnostic yield. Empiric treatment of *Pneumocystis* does not compromise the yield of lower respiratory tract testing [1]. No single empiric regimen exists for immunocompromised pneumonia, given the diversity of immunocompromised conditions and associated infections (Table 24.1). A reasonable approach is to start with a regimen for community-acquired or healthcare-associated pneumonia as appropriate [11, 12], then expand according to the patient's specific immune deficits and past microbiological data. This regimen should then be routinely reassessed for effectiveness based on the patient's clinical response and the results of invasive microbiological testing. Empiric treatment of fungal pneumonia is rarely indicated for initial regimens but should be strongly considered in patients with clinical risk factors (e.g. prolonged neutropenia), consistent imaging (Fig. 24.3, a CT scan of a patient with aspergillosis) and lack of response to antibacterial therapy.

Table 24.2 Diagnostic testing in immunocompromised patients with suspected pneumonia

Specimen	Diagnostic tests
Bronchoalveolar lavage fluid	Cell count and differential
	Gram stain and bacterial culture
	Fungal stain and culture
	Acid-fast bacteria stain and culture
	Respiratory virus PCR
	Pneumocystis jirovecci PCR
	CMV antigen
	Galactomannan
Serum	Bacterial culture
	Fungal culture
	Acid-fast bacteria culture
	Cryptococcus antigen
	Galactomannan
	β-D-glucan
Urine	*Streptococcus* antigen
	Legionella antigen

Supportive Care

Unless otherwise contraindicated, immunocompromised patients with hypoxemic respiratory failure should be given a trial of noninvasive positive pressure ventilation (NIPPV) [13–15]. Corticosteroids are indicated for patients with HIV/AIDS and *P. jirovecci* pneumonia with room air PaO_2 under 70 or A-a gradient over 30 [16, 17], though data supporting their use in non-HIV patients with the same infection is weaker [18, 19]. Competing non-infectious diagnoses should be explored and potentially treated empirically (e.g. diuresis for infiltrates suggestive of cardiogenic edema).

Evidence Contour

Utility of Invasive Testing

Invasive sampling of the lower respiratory tract (by bronchoscopy with and without transbronchial biopsy, mini-BAL or open lung biopsy) is common in the diagnosis of pneumonia in immunocompromised patients, and wide practice variation

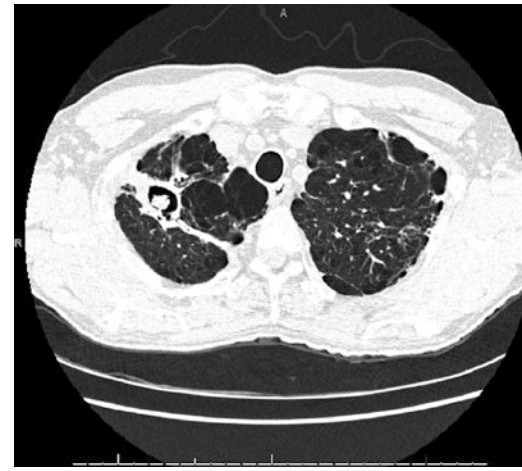


Fig. 24.3 CT scan – aspergillosis

exists among modalities used. Among intubated patients, mini-BAL performs comparably to flexible bronchoscopy with lavage [20]. Transbronchial biopsy increases the yield of bronchoalveolar lavage, generally by distinguishing invasive fungal disease from colonization [21, 22]. Transbronchial biopsy is associated with elevated rates of pneumothorax when performed on mechanically ventilated patients (14–24 %) [23, 24], though this risk must be weighed against those of alternative diagnostic maneuvers (e.g. open lung biopsy). BAL galactomannan has excellent sensitivity and specificity in the diagnosis of invasive aspergillosis [25], and it is undetermined what effect its adoption has had on the marginal yield of transbronchial biopsy. In one series of patients with hematologic malignancies and pulmonary infiltrates, open lung biopsy identified a diagnosis in 62 % of cases and changed management in 57 % of cases [26], though only 55 % of these patients had previously undergone bronchoscopy and only 13 % had undergone transbronchial biopsy.

Serum Indices of Infection

Serum tests for pneumonia in immunocompromised patients are an attractive arena for investigation, but no consensus exists regarding their utility, and in practice they rarely preclude invasive lung sampling. A serum galactomannan test is relatively specific (89 %) for invasive aspergillosis

among immunocompromised patients but has poor sensitivity (71 %) [25]; a negative result does not exclude the diagnosis. By contrast, a commercially available beta-D-glucan assay is more sensitive than serum galactomannan but less specific [27]. A serum procalcitonin level below 0.5 ng/ml effectively excludes the presence of a bacterial infection in critically ill immunocompromised patients [28].

Noninvasive Ventilation

Though noninvasive positive pressure ventilation (NIPPV) is infrequently indicated for immunocompetent patients with pneumonia given the difficulty of managing secretions and the lack of rapid reversibility, two randomized controlled trials have demonstrated a clinical benefit to its use among immunocompromised patients. In a large (238 patient) study of patients immunosuppressed for solid organ transplantation with acute respiratory failure, patients who received NIPPV (as compared to standard treatment with supplemental oxygen) were less frequently intubated and experienced lower Intensive Care Unit (ICU) mortality [13]. In a second study of more broadly immunosuppressed patients with respiratory failure and clinical evidence of pneumonia, treatment with NIPPV resulted in less frequent endotracheal intubation and lower ICU mortality and overall mortality [15].

References

1. O'Donnell WJ, Pieciak W, Chertow GM, Sanabria J, Lahive KC. Clearance of Pneumocystis carinii cysts in acute P carinii pneumonia: assessment by serial sputum induction. Chest. 1998;114(5):1264–8.
2. Sickles EA, Greene WH, Wiernik PH. Clinical presentation of infection in granulocytopenic patients. Arch Intern Med. 1975;135(5):715–9.
3. Dickson RP, Erb-Downward JR, Huffnagle GB. Towards an ecology of the lung: new conceptual models of pulmonary microbiology and pneumonia pathogenesis. Lancet Respir Med. 2014;2(3):238–46. Pubmed Central PMCID: 4004084.
4. Dickson RP, Martinez FJ, Huffnagle GB. The role of the microbiome in exacerbations of chronic lung diseases. Lancet. 2014;384(9944):691–702. Pubmed Central PMCID: 4166502.
5. Venkataraman A, Bassis CM, Beck JM, Young VB, Curtis JL, Huffnagle GB, et al. Application of a neutral community model to assess structuring of the human lung microbiome. MBio. 2015;6(1). Pubmed Central PMCID: PMC4324308.
6. Iwai S, Fei M, Huang D, Fong S, Subramanian A, Grieco K, et al. Oral and airway microbiota in HIV-infected pneumonia patients. J Clin Microbiol. 2012;50(9):2995–3002. Pubmed Central PMCID: PMC3421777.
7. Diaz PI, Hong BY, Frias-Lopez J, Dupuy AK, Angeloni M, Abusleme L, et al. Transplantation-associated long-term immunosuppression promotes oral colonization by potentially opportunistic pathogens without impacting other members of the salivary bacteriome. Clin Vaccine Immunol. 2013;20(6):920–30. Pubmed Central PMCID: PMC3675961.
8. Wright HL, Moots RJ, Bucknall RC, Edwards SW. Neutrophil function in inflammation and inflammatory diseases. Rheumatology (Oxford). 2010;49(9):1618–31.
9. Camps Serra M, Cervera C, Pumarola T, Moreno A, Perello R, Torres A, et al. Virological diagnosis in community-acquired pneumonia in immunocompromised patients. Eur Respir J. 2008;31(3):618–24.
10. Heussel CP, Kauczor HU, Heussel G, Fischer B, Mildenberger P, Thelen M. Early detection of pneumonia in febrile neutropenic patients: use of thin-section CT. AJR Am J Roentgenol. 1997;169(5):1347–53.
11. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171(4):388–416.
12. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44 Suppl 2:S27–72.
13. Antonelli M, Conti G, Bufi M, Costa MG, Lappa A, Rocco M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. JAMA. 2000;283(2):235–41.
14. Girou E, Schortgen F, Delclaux C, Brun-Buisson C, Blot F, Lefort Y, et al. Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. JAMA. 2000;284(18):2361–7.
15. Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med. 2001;344(7):481–7.
16. Consensus statement on the use of corticosteroids as adjunctive therapy for pneumocystis pneumonia in the acquired immunodeficiency syndrome. The National Institutes of Health-University of California Expert Panel for Corticosteroids as Adjunctive Therapy for Pneumocystis Pneumonia. N Engl J Med. 1990;323(21):1500–4.
17. Briel M, Bucher HC, Boscacci R, Furrer H. Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia

in patients with HIV-infection. Cochrane Database Syst Rev. 2006;3, CD006150.
18. Delclaux C, Zahar JR, Amraoui G, Leleu G, Lebargy F, Brochard L, et al. Corticosteroids as adjunctive therapy for severe Pneumocystis carinii pneumonia in non-human immunodeficiency virus-infected patients: retrospective study of 31 patients. Clin Infect Dis. 1999;29(3):670–2.
19. Pareja JG, Garland R, Koziel H. Use of adjunctive corticosteroids in severe adult non-HIV Pneumocystis carinii pneumonia. Chest. 1998;113(5):1215–24.
20. Tasbakan MS, Gurgun A, Basoglu OK, Ekren PK, Pullukcu H, Bacakoglu F. Comparison of bronchoalveolar lavage and mini-bronchoalveolar lavage in the diagnosis of pneumonia in immunocompromised patients. Respiration. 2011;81(3):229–35.
21. Cazzadori A, Di Perri G, Todeschini G, Luzzati R, Boschiero L, Perona G, et al. Transbronchial biopsy in the diagnosis of pulmonary infiltrates in immunocompromised patients. Chest. 1995;107(1):101–6.
22. Jain P, Sandur S, Meli Y, Arroliga AC, Stoller JK, Mehta AC. Role of flexible bronchoscopy in immunocompromised patients with lung infiltrates. Chest. 2004;125(2):712–22.
23. Bulpa PA, Dive AM, Mertens L, Delos MA, Jamart J, Evrard PA, et al. Combined bronchoalveolar lavage and transbronchial lung biopsy: safety and yield in ventilated patients. Eur Respir J. 2003;21(3):489–94.
24. O'Brien JD, Ettinger NA, Shevlin D, Kollef MH. Safety and yield of transbronchial biopsy in mechanically ventilated patients. Crit Care Med. 1997;25(3):440–6.
25. Guo YL, Chen YQ, Wang K, Qin SM, Wu C, Kong JL. Accuracy of BAL galactomannan in diagnosing invasive aspergillosis: a bivariate metaanalysis and systematic review. Chest. 2010;138(4):817–24.
26. White DA, Wong PW, Downey R. The utility of open lung biopsy in patients with hematologic malignancies. Am J Respir Crit Care Med. 2000;161(3 Pt 1):723–9.
27. Sulahian A, Porcher R, Bergeron A, Touratier S, Raffoux E, Menotti J, et al. Use and limits of (1–3)-beta-d-glucan assay (Fungitell), compared to galactomannan determination (Platelia Aspergillus), for diagnosis of invasive aspergillosis. J Clin Microbiol. 2014;52(7):2328–33. Pubmed Central PMCID: PMC4097729.
28. Bele N, Darmon M, Coquet I, Feugeas JP, Legriel S, Adaoui N, et al. Diagnostic accuracy of procalcitonin in critically ill immunocompromised patients. BMC Infect Dis. 2011;11:224. Pubmed Central PMCID: PMC3170614.

Venous Thromboembolism in the Intensive Care Unit

25

Scott J. Denstaedt and Thomas H. Sisson

Case Presentation

Case Scenario

A 72 year-old retired family physician with a history of hypertension and prostate cancer was admitted to the hospital with complaints of worsening dyspnea over 48 h. On presentation, he was tachycardic with a heart rate 112, tachypneic with a respiratory rate of 22, normotensive with a blood pressure of 110/70 and his pulse oximetry revealed an O_2 saturation of 88 % on room air. He had 2+ left lower extremity edema (with trace edema on the right). A chest x-ray showed no acute cardiopulmonary disease, and his EKG revealed sinus tachycardia with non-specific T wave changes. Laboratory studies were within normal limits with the exception of a troponin I which was elevated to 1.5 ng/ml (reference < 0.30 ng/ml). A CT-pulmonary angiogram revealed bilateral central pulmonary artery emboli (Fig. 25.1) and an enlarged right ventricle. The patient was admitted to the intensive care unit and started on an intravenous (IV) heparin drip.

Question If the decision is made to administer thrombolytic therapy, how would this treatment alter the patient's overall outcome? His survival?

Answer Treatment with thrombolytic therapy would likely prevent hemodynamic collapse but would not affect his chances of survival.

In the PEITHO trial, 1005 patients with submassive pulmonary embolism, defined by right ventricular enlargement or dysfunction and myocardial injury as indicated by an elevated troponin I or troponin T, were randomized to receive IV heparin and placebo versus IV heparin and recombinant Tissue plasminogen activator (t-PA) [1]. The primary endpoint was a clinical composite of death or hemodynamic decompensation within 7 days after randomization. The investigators also assessed a safety endpoint of bleeding complications. The results of this study revealed that treatment with t-PA significantly reduced the primary endpoint of death or hemodynamic decompensation within 7 days after randomization (2.6 % versus 5.6 %, p = 0.02). The difference in the primary endpoint was driven by a reduction in hemodynamic collapse as mortality was not different between the two treatment groups. The benefit of a reduction in the primary outcome with t-PA treatment came with the expense of an

S.J. Denstaedt
Pulmonary and Critical Care Medicine, University of Michigan Health System, Ann Arbor, MI, USA

T.H. Sisson (✉)
Pulmonary and Critical Care Medicine, University of Michigan Hospital and Health Systems, Ann Arbor, MI, USA
e-mail: tsisson@med.umich.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_25

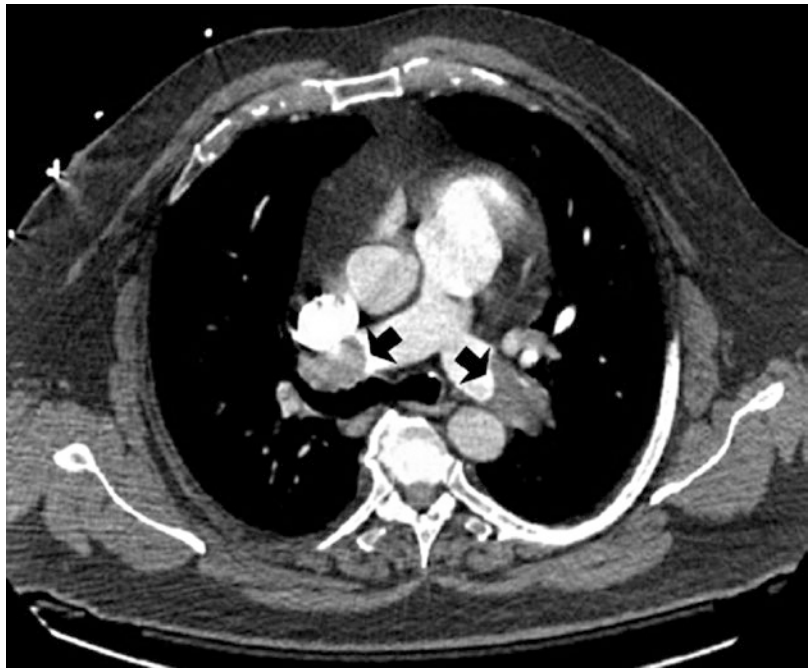


Fig. 25.1 Large central thrombi in the main bilateral pulmonary arteries (*arrows*) in a 72-year-old man who presented with submassive pulmonary embolism

increased risk of major bleeding events including extracranial bleeding ($p < 0.001$) and strokes ($p = 0.003$).

Standard Approach to Diagnosis and Management

Risk Factors

Pulmonary embolism is a consequence of thrombosis in the deeps veins of the lower extremities, pelvis, and less commonly, the upper extremities. The classic triad of risk factors for the development of deep venous thrombosis, known as Virchow's triad, includes stasis of blood flow, hypercoagulability, and endothelial injury. Patients admitted to the intensive care unit frequently experience all of these risk factors and are therefore at a heightened risk for deep venous thrombosis (DVT) and, in turn, pulmonary embolism (PE). Specifically, mechanical ventilation, sedation, and the use of paralytic agents accentuate the immobility of critical illness and thereby contribute to stasis of blood flow. In addition, central lines inserted into the upper and/or lower extremity deep veins serve as a nidus for thrombosis secondary to local endothelium disruption. Central lines placed in the femoral and internal jugular veins are associated with a particularly high risk, and the likelihood of this complication increases with the duration of catheter placement [2, 3]. Finally, the clinical diagnosis that necessitates ICU admission can modify the risk of venous thromboembolism (VTE). For example, immobility secondary to infection was associated with a shorter duration until the onset of thromboembolism as compared to patients whose immobility was due to dementia (less than 4 weeks in 94.2 vs. 25.9 % of cases; $p < 0.001$) [4]. The clinical presentations of severe sepsis and septic shock are also associated with a high rate of VTE [5]. The mechanistic connection between infection and venous thrombosis is in part explained by inflammation-induced: (1) elaboration of tissue factor, (2) impairment of anticoagu-

lant pathways, and (3) suppression of fibrinolysis secondary to the overproduction of plasminogen activator inhibitor-1 [6].

Epidemiology of VTE in the ICU

The presence of multiple risk factors for VTE in ICU patients confers a high risk of disease. Clinical studies demonstrate that both unfractionated heparin and low molecular weight heparin decrease the risk of DVT in the critical care unit [4, 7]. As a result of this evidence, current practice guidelines recommend the administration of thromboprophylaxis in the critical care setting. Therefore, it is not surprising that, in a multivariate analysis of risk factors for PE in a Tunisian ICU, the absence of pharmacologic prevention was identified as a significant predictor for PE [8]. However, even in the presence of prophylactic heparin treatment, the risk of VTE is significant. In the PROTECT study, the efficacy of low molecular weight heparin (LMWH) and unfractionated heparin (UFH) were compared in the prevention of DVT in critically ill patients [9]. Evidence for new DVT formation was determined by the performance of twice-weekly compression ultrasonography. Despite the administration of prophylactic anticoagulation, the rates of DVT were 5.1 % in patients treated with LMWH and 5.8 % in patients treated with UFH. The risk of DVT appears to be even greater in patients with acute decompensated COPD who undergo mechanical ventilation [10]. In this population, treatment with weight-adjusted LMWH was associated with a DVT incidence of 15.5 % while patients receiving placebo experienced a 28.2 % incidence of clot.

Although evidence indicates that the incidence of DVT in the ICU is high, it is less clear how often this complication results in pulmonary embolism. In the PROTECT trial, PE was evaluated when clinically indicated, and in patients treated with LMWH, there was a 1.2 % incidence of definite or probable PE as compared to a 2.1 % incidence in the group treated with UFH. While these incidences are low and reassuring, results from a 2012 study suggests that the diagnosis of PE may be frequently missed in the ICU [11]. In this investigation, 176 consecutive mechanically ventilated patients who required a CT scan for any indication underwent the standard imaging protocol for pulmonary embolism detection. The investigators discovered that the incidence of PE was 18.7 %, and in 61 % of these patients, there was no clinical suspicion of disease. Importantly, the study protocol called for the performance of lower extremity compression ultrasonography in all patients within 48 h of their CT scan, and only 33 % of individuals with a PE were found to have a concurrent DVT. Collectively, these studies demonstrate that both DVT and PE are relatively common in the ICU despite thromboprophylaxis. Perhaps even more concerning is the observation that the majority of patients diagnosed with a PE lacked clinical features of the disease.

Clinical Presentation

The clinical presentation in the accompanying case scenario is highly suggestive of pulmonary embolism. However, in the ambulatory population, the clinical features of venous thromboembolic disease are largely non-specific. The lack of specificity in both symptoms and signs of pulmonary embolism was highlighted in PIOPED II, a study in which patients with suspected PE were enrolled to evaluate the predictive value of Computed-tomography pulmonary angiography (CT-PA) [12]. As part of this study, the frequency of symptoms and signs in patients with confirmed PE were compared to enrolled patients who ultimately ruled out for thromboembolism. Surprisingly, this investigation revealed that the presentation of hemoptysis or pleuritic chest pain was more common in PE-negative patients than in the PE-positive group (56 vs 44 %, $p < 0.01$). Furthermore, there was no difference between the two groups in the frequency of presenting with circulatory collapse. The presence of uncomplicated dyspnea (i.e. dyspnea without accompanying symptoms of chest pain, hemoptysis or circulatory collapse) was more common in patients diagnosed with PE than the PE-negative group but the overall percentages

were similar (36 % versus 26 %, P < 0.01). With respect to specific symptoms or signs, the complaint or clinical detection of calf or thigh swelling or pain was most discerning for those who did versus those who did not have a PE.

In the critical care patient, co-morbid conditions that are associated with hypotension and hypoxemia make it even more challenging to identify patients with VTE. In a single center study of 4408 ICU patients, 87 (1.9 %) were diagnosed with pulmonary embolism [8]. Abnormalities in this group that led to the evaluation and diagnosis of PE included hypotension (57.5 %), positive SIRS criteria (72.4 %), respiratory distress requiring mechanical ventilation (81.6 %), and clinical manifestations of DVT (17.2 %). These derangements, perhaps with the exception of clinical manifestation of DVT, are not specific for PE and can be observed in other conditions that commonly lead to ICU admission including septic or hemorrhagic shock, congestive heart failure, and pneumonia.

The low sensitivity and specificity of symptoms and signs for VTE motivated the development of clinical prediction tools including the Wells Criteria (Table 25.1) and the Geneva Scoring System (Table 25.2) to aid clinicians in the evaluation of VTE. The Wells criteria either dichotomizes or trichotomizes patients into VTE risk categories [13]. This prediction tool has been well validated in the outpatient setting, but in hospitalized patients, it was found to perform less well for the diagnosis of DVT [14]. The Wells Criteria and the Geneva Score have not been explicitly evaluated in the critical care setting. However, based on the challenge of evaluating symptoms in the ICU patient who may be intubated, sedated, and/or delirious and in the presence of concurrent critical illnesses that commonly result in tachycardia and lower extremity edema, it is likely that the predictive value of this tool, like the inpatient setting, is weak in the critical care population. The limitation of these tools in the ICU setting is supported by the findings of Bahloul and colleagues who calculated both the Wells and Geneva scores in 87 patients who were diagnosed with PE in the critical care setting [8]. In this study, only 5 (5.7 %) patients had a high

Table 25.1 Wells criteria for pulmonary embolism risk

Variable	Points
Clinical signs and symptoms of DVT	3
Alternative diagnosis less likely than PE	3
Heart rate >100/min	1.5
Immobilization (>3d) or surgery in the prior 4 wk	1.5
Prior PE or DVT	1.5
Hemoptysis	1
Malignancy (receiving treatment, treated in last 6 mo, palliative)	1

Score	Clinical probability	PE incidence
Trichotomized score		
0–1	Low	0.2–7.0 %
2–6	Moderate	12.4–26.6 %
≥6	High	27.2–72.8 %
Dichotomized score		
≤4	Unlikely	2.3–9.4 %
≥4	Likely	27.6–51.6 %

From Wells et al. [13]

Table 25.2 Revised Geneva Score for pulmonary embolism risk

Variable	Points
Risk factors	
Age > 65 y	1
Prior PE or DVT	3
Surgery (under general anesthesia) or fracture of the lower limbs within 1 mo	2
Active malignant condition (solid or hematologic, currently active or considered cured < 1 y)	2
Symptoms	
Unilateral lower-limb pain	3
Hemoptysis	2
Clinical signs	
Heart rate	
75–94 beats/min	3
≥95 beats/min	5
Pain on lower-limb deep venous palpation and unilateral edema	4

Score	Clinical probability	PE incidence
0–3	Low	5.0–12.0 %
4–10	Intermediate	24.6–32.8 %
≥11	High	61.0–83.4 %

From Le Gal et al. [39]

probability score using Wells Criteria and only 6 (6.9 %) patients were classified as high probability according to Geneva Score. Based on these findings, it is crucial to maintain a high index of suspicion for VTE as a potential etiology of subtle (and not so subtle) physiologic changes in an ICU population.

Pulmonary Embolism Severity

Patients with pulmonary embolism can be categorized into low, intermediate, and high risk groups. Stratifying individuals into risk categories can be useful in decisions about disposition and treatment. The presence of hemodynamic collapse, which results from an acute increase in pulmonary artery pressure and associated right heart failure, readily classifies patients into a high-risk group with an estimated mortality of 30–50 % and mandates a treatment strategy that includes vascular reperfusion (see section "Treatment"). Hemodynamic stability in the presence of right ventricular (RV) dysfunction defines an intermediate risk category. Evidence of RV dysfunction can be detected on imaging studies including echocardiography (Fig. 25.2) and CT-PA and with elevated biochemical markers such as brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), troponin-I, and troponin-T levels. Several systematic reviews reveal an increased risk of death in patients with pulmonary embolism who also have evidence of abnormal RV function by imaging or elevated biomarkers. For example, in a recent meta-analysis, CT-PA evidence of right heart dysfunction carried an odds ratio of death from PE of 7.4 (95 % confidence interval 1.4–39.5) [15]. A separate study found that either CT-PA or echocardiographic evidence of RV dysfunction was associated with an unadjusted risk ratio for death of 2.4 (95 % confidence interval 1.3–4.4) [16]. In this same systematic review, elevations in brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and troponin also predicted an increased risk of death, but the threshold values for these biomarkers varied considerably between studies. Because of the higher rate of death, patients in this intermediate risk group may hypothetically benefit from aggressive treatment to reestablish vascular reperfusion (see section "Treatment").

Beyond categorizing patients based on the presence/absence of hemodynamic instability or RV dysfunction, several prognostic scoring systems have been developed to estimate the 30-day mortality in patients with PE. These tools primarily aid clinicians in their decisions about patient disposition. Individuals with low scores may be safely managed as outpatients while patients with high scores require hospitalization in an acute

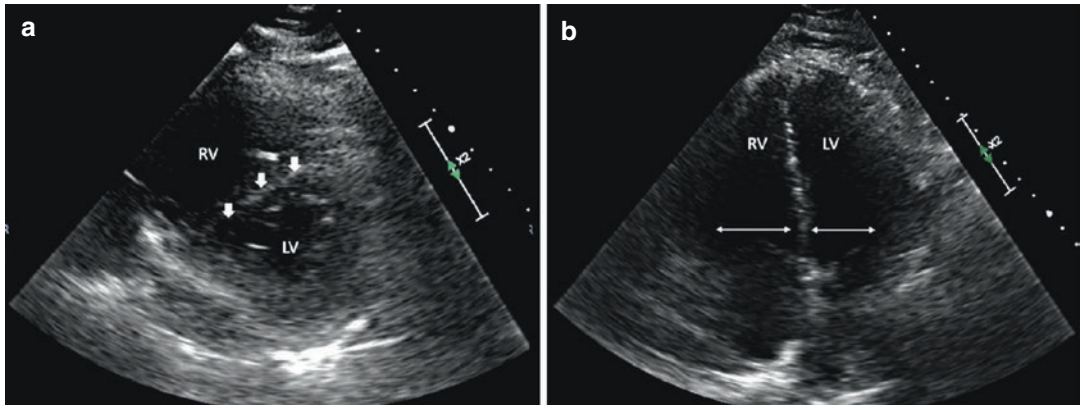


Fig. 25.2 (**a**) Right ventricular (*RV*) strain seen on parasternal short axis view with the intraventricular septum (*arrows*) bowing into the left ventricle (*LV*). The result is known as a "D-sign". (**b**) Increased RV/LV ratio seen on apical four chamber view

Table 25.3 Pulmonary embolism severity index

Predictors	Points
Demographics	
Age, per year	Age in year
Male sex	+10
Comorbid illnesses	
Cancer	+30
Heart failure	+10
Chronic lung disease	+10
Clinical findings	
Pulse ≥ 100/min	+20
Systolic blood pressure < 100 mmHg	+30
Respiratory rate ≥ 30/min	+20
Temperature < 36 °C	+20
Altered mental status	+60
Arterial oxygen saturation < 90 %	+20

Score	Risk class	30-day mortality
≤65	I, very low	0–1.6 %
66–85	II, low	1.7–3.5 %
86–105	III, intermediate	3.2–7.1 %
106–125	IV, high	4.0–11.4 %
>125	V, very high	10.0–24.5 %

From Aujesky et al. [17]

care bed or in the intensive care unit. The Pulmonary Embolism Severity Index (PESI) and the simplified PESI are examples of these risk predictor tools (Table 25.3). The PESI is comprised of 11 simple patient variables that are each independently associated with PE mortality [17]. The composite score assigns individuals to one of five risk categories. In class I and II, the lowest risk categories, 30-day mortality rates were between 0 and 3.5 % in the derivation and validation groups. In contrast, patients in the highest risk category (Class V) exhibited 30-day mortality rates ranging between 10.0 and 24.5 %. More recent data suggests that combining the PESI with echocardiographic and biomarker data can further refine risk stratification [18]. Whether these tools of risk prediction play any role in an ICU patient with VTE is unclear. However, for those individuals diagnosed with PE outside of the intensive care unit, it may be prudent to consider admission to a higher level of care such as a critical care unit if a patient is determined to be in the highest risk category for mortality.

Diagnosis

With a few exceptions, the diagnostic approach to VTE in the ICU should not be fundamentally different than in the emergency department or on the general care wards. The initial step in evaluating an ambulatory patient (i.e. presenting to the emergency department or clinic) with suspected pulmonary embolism is to assess the clinical probability of disease. The implementation of a clinical probability tool such as Wells Criteria greatly facilitates this assessment. Those individuals determined to have a low likelihood of PE (Table 25.1) should be initially evaluated with a d-dimer. Patients with a high clinical likelihood of disease (or low clinical likelihood and a positive d-dimer) should undergo a diagnostic study for PE such as a ventilation-perfusion scan or a CT-PA. The latter imaging approach is often the preferred modality because it also allows for the detection of other abnormalities that might explain a patient's clinical syndrome, and it can provide information about the status of the right ventricle. Based on the results of PIOPED I and PIOPED II, additional diagnostic studies such as pulmonary angiography should be entertained when the results of the CT-PA or ventilation/perfusion scan are discordant with the clinical probability of disease.

When evaluating a patient in the ICU with suspected PE, the clinical likelihood tools, as detailed previously, are not well validated. In addition, d-dimer levels are elevated by a variety of ICU conditions and, as a result, lack predictive value. Therefore, patients with suspected PE should preferably undergo a PE-CT (or possibly a ventilation-perfusion scan) to evaluate for disease. However, this imaging study necessitates patient transfer from the ICU to the radiology department, which may be challenging in the setting of clinical instability. In such a case, an alternative approach to the diagnosis is required. Compression ultrasonography to evaluate for the presence of DVT is one consideration, as a positive test would warrant treatment for VTE. However, as previously noted, DVT is only identified in approximately one-third of patients in the ICU with PE, so a negative test does not exclude the diagnosis and additional work-up is then required.

Echocardiography, either transthoracic or transesophageal, offers alternative bed-side modalities for PE evaluation. In a prospective study, the sensitivity and specificity of an abnormal transthoracic echocardiography (TTE) (defined by two of the following criteria: RV hypokinesis, RV dilation, or tricuspid regurgitation) was compared to pulmonary angiography for the diagnosis of PE. This study determined that the sensitivity of TTE was only 56 % (with a specificity of 90 %), indicating that this study is useful only if abnormal [19]. In comparison, transesophageal echocardiography (TEE) offers the advantage of central pulmonary artery visualization and can thereby detect proximal PE. In a study of 49 consecutive patients with clinical suspicion of PE and unexplained right ventricular overload on transthoracic echocardiography, TEE detected pulmonary arterial emboli in 32/40 patients (80 %) who had centrally located disease (i.e. main or lobar arteries) [20]. Unfortunately, this test is not useful for peripheral emboli. A final diagnostic consideration for the patient who is too unstable for transfer is a bedside perfusion scan. A normal scan would provide reassurance that a PE is not responsible for a patient's clinical instability. An abnormal scan, in the absence of a concurrent ventilation scan, will not define a probability of PE and should be interpreted with caution.

Treatment

Once the diagnosis of PE is made, the principles of treatment do not differ significantly between the ICU, emergency department, and general ward. In patients with an acceptable bleeding risk, anticoagulation should be administered promptly with the goal of achieving therapeutic dosing within 24 h. A failure to achieve therapeutic anticoagulation within this time period resulted in a much higher recurrence rate of VTE (23.3% vs 4 %) for those whose activated partial thromboplastin time exceeded the therapeutic threshold by 24 h (P = .02) [21]. Delays in instituting anticoagulation are also associated with an increased in-hospital (1.5 % vs 5.6 %; P = .093) and 30 day (5.6 % vs 14.8 %; P = .037) mortality [22]. Heparin is the preferred agent for initial anticoagulation. Based on more predictable dosing (usually without the need for monitoring), lower risk of drug-induced thrombocytopenia, and equivalent (if not superior) efficacy, low molecular weight preparations are often preferred over the intravenous administration of unfractionated heparin [23]. However, in the ICU, unfractionated heparin with utilization of weight-based dosing protocols (Tables 25.4a and 25.4b), is considered a better choice particularly in an unstable patient due in large part to its

Table 25.4a Unfractionated heparin nomogram for VTE using aPTT

Initial dose	80 units/kg, followed by 18 units/kg/h
aPTT, <35 s	80 units/kg bolus, then increase rate 4 units/kg/h
aPTT, 35–45 s	40 units/kg bolus, then increase rate 2 units/kg/h
aPTT, 36–70 s[a]	No change
aPTT, 71–90 s	Decrease rate by 2 units/kg/h
aPTT, > 90 s	Hold 1 h, then decrease rate by 3 units/kg/h

Adapted from Garcia et al. [40]
Testing is repeated every 6 h until therapeutic range is reached for two consecutive tests, and then daily
[a]Therapeutic aPTT range is considered 46–70s and corresponds with an anti-Xa activity of 0.3–0.7 units/mL. Target range at institutions may vary depending on reagents/equipment used to perform assay

Table 25.4b Unfractionated heparin nomogram for VTE using anti-Xa

Initial dose	80 units/kg, followed by 18 units/kg/h
Xa, < 0.2	80 units/kg bolus, then increase rate 1.5 units/kg/h
Xa, 0.2–0.29	40 units/kg bolus, then increase rate 1 units/kg/h
Xa, 0.3–0.7	No change
Xa, 0.71–0.8	Decrease rate by 1 units/kg/h
Xa, 0.81–0.99	Decrease rate by 1.5 units/kg/h
Xa Greater than or equal to 1	Decrease rate by 3 units/kg/h

Adapted from University of Michigan Health Systems Heparin Dosing Nomogram
Testing is repeated every 6 h until therapeutic range is reached for two consecutive tests, and then daily

shorter half-life (45 min versus 4–5 h for LMWH). This shorter half-life is advantageous in the critical care patient population that may require invasive procedures and/or is at increased risk of bleeding. Also, close monitoring of the aPTT/anti-Xa is less of an issue in the ICU setting. In non-ICU patients, heparin is typically used as a bridge to long-term anticoagulation, and warfarin is started within the first 24 h of therapy after the patient is therapeutic on heparin. In the ICU, because of the bleeding risk and procedural requirements, it is prudent to delay the initiation of warfarin until the patient is ready to transition to a lower level of care.

Patients with hemodynamically unstable disease (defined by a systolic blood pressure < 90 mmHg for greater than 15 min) require reperfusion therapy in addition to anticoagulation. Options include systemic thrombolysis, catheter-directed thrombolysis and embolectomy (surgical versus mechanical). Systemic administration of a thrombolytic does not require mobilization of the interventional radiology team and therefore avoids delays in treatment. Catheter directed thrombolysis, on the other hand, allows for the administration of a lower thrombolytic dose, which carries the potential to reduce bleeding complications. Otherwise, the decision should be dictated by local availability/expertise as there have been few head to head comparisons of the different modalities, and what data exists suggest equivalency. For example, in patients with acute massive pulmonary embolus (n = 25), a retrospective analysis of catheter-directed thrombolysis versus mechanical embolectomy with ultrasound-accelerated thrombolysis found no difference in mortality between the two approaches (9.1 % in the mechanical embolectomy group and 14.2 % in the catheter-directed thrombolysis group, p = NS). Notably, mechanical embolectomy did result in improved embolus removal (p < .02), more rapid thrombolysis (17.4 ± 5.23 versus 25.3 ± 7.35 h, p = .03), and fewer treatment-related hemorrhagic complication (0 % versus 21.4 %, p = .02) [24]. Therefore, if mechanical embolectomy is available, one could make the argument to use this modality preferentially, especially in patients at increased bleeding risk.

In patients with active bleeding (or deemed to be at a high risk of bleeding complications as a result of an intracranial neoplasm, recent (i.e., <2 months) intracranial or spinal surgery or trauma, hemorrhagic stroke, or a bleeding diathesis) anticoagulation is contraindicated. As a result, an inferior vena cava is required in these individuals to prevent further episodes of embolism.

Evidence Contour

Reperfusion Therapy in Patients with Hemodynamically Stable Pulmonary Embolism

Hemodynamically stable PE patients with evidence of right heart dysfunction (based on abnormal imaging or elevated biomarkers) are at increased risk of death (see section "Pulmonary Embolism Severity"). The worse prognosis in this subgroup has motivated several investigations to assess the efficacy of reperfusion strategies. As detailed in the section "Case Presentation", in the PEITHO trial, patients with sub-massive pulmonary embolism as defined by RV enlargement or elevated cardiac biomarkers were randomized to receive IV heparin and placebo versus IV heparin and recombinant t-PA (as a reperfusion strategy). The results of this study revealed that t-PA significantly reduced the primary composite outcome of death or hemodynamic decompensation within the first week after randomization. However, there was no difference in survival between groups. The findings of this study are similar to two previous randomized controlled trials in which systemic thrombolysis was found to improve hemodynamic endpoints (as assessed by echocardiography or need for secondary thrombolysis) [25, 26]. Mortality was a component of the composite endpoint in only one of the two study protocols and, as was the case in the PEITHO trial, was not different between the two treatment arms. The failure of the hemodynamic benefits of thrombolysis treatment to translate into a survival benefit in these studies is at least in part due to the low event rates. Furthermore, in PEITHO, hemorrhagic

complications led to four deaths in the t-PA group, and this complication offset any potential mortality benefit of reperfusion therapy. Subgroup analysis in the PEITHO trial suggests that patients less than 75 years of age have fewer bleeding complications, suggesting a more favorable benefit to risk ratio in these individuals.

Ultrasound-assisted catheter-directed thrombolysis in conjunction with low dose t-PA has also been evaluated as a reperfusion strategy in intermediate risk PE patients (n = 59) [27]. The primary outcome in this study was echocardiographic assessment of the right ventricle/left ventricle ratio from baseline to 24 h. Safety outcomes including death, and major and minor bleeding were also assessed. Catheter-mediated thrombolysis successfully reduced the mean right ventricle/left ventricle ratio by 0.30 ± 0.20 versus a minimal improvement (0.03 ± 0.16) in the heparin alone control group (P < 0.001). With respect to safety, there were no major bleeding events in this trial and only four episodes of minor bleeding (three in the catheter-mediated thrombolysis group; P = 0.61). Also, there was only a single death (in the placebo group). Several additional safety and efficacy trials have since been published demonstrating minimal major bleeding rates with significant improvement in pulmonary artery systolic pressure [28, 29]. Catheter-directed therapy may therefore be an option at capable centers for the patient with increased risk of bleeding, although long-term and comparative data are lacking.

A recent meta-analysis of thrombolytic therapy in submassive PE concluded that treatment did not significantly reduce the risk of mortality or recurrent PE, but does prevent clinical deterioration requiring escalation of care [30]. The failure to achieve a survival benefit may be a byproduct of inadequate power for this endpoint alone. As such, guidelines around this issue are nebulous but generally recommend therapy for the decompensating patient [31–33] (Table 25.5).

Table 25.5 Guideline recommendations for systemic thrombolysis in hemodynamically stable acute PE

	ACCP 2016[a]	ESC 2014[b]	AHA 2011[c]
Low bleeding risk	Routine use of systemic thrombolysis not recommended (Grade 1B). Close monitoring in patients with severe symptoms and marked cardiopulmonary involvement (Grade 2C). Systemic thrombolysis suggested if cardiopulmonary deterioration[d] occurs (Grade s2C)	Routine use of systemic thrombolysis not recommended (Class III, level B). Close monitoring in intermediate-high-risk[e] PE. (Class I, level B). Systemic thrombolysis should be considered in intermediate-high-risk PE if clinical signs of hemodynamic decompensation (Class IIa, level B)	Routine use of systemic thrombolysis not recommended for low risk or stable submassive PE. (Class III, level B) Consider for patients who have clinical evidence of adverse prognosis[f] (Class IIb, level C).
High bleeding risk	Mechanical catheter directed therapy with or without catheter directed thrombolysis recommended if hypotension (Grade 2C)	Surgical embolectomy (Class IIb, level C) or catheter-directed treatment (Class IIb, level B) may be considered in intermediate-high-risk patients	Surgical embolectomy or catheter embolectomy may be considered in those who have clinical evidence of adverse prognosis (Class II, level C)

[a]Kearon et al. [32]
[b]Kostantinides et al. [2]
[c]Jaff et al. [33]
[d]Cardiopulmonary deterioration includes shock, impending shock, progressive increase in heart rate, worsening gas exchange, progressive right heart dysfunction on echocardiography, increase in cardiac biomarkers
[e]Intermediate-high-risk PE defined as absence of shock or hypotension, PESI class III-V, signs of RV dysfunction on imaging test (Echocardiography: RV-LV diameter >0.9 or 1.0, hypokinesis of the RV free wall, increased velocity of the tricuspid regurgitant jet; Computed tomographic angiography: increased end diastolic RV/LV ratio > 0.9 or 1.0), positive cardiac biomarkers (troponin, natriuretic peptide)
[f]Adverse clinical prognosis includes new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis

Table 25.6 Considerations for bleeding following systemic thrombolytic therapy

Absolute contraindications[a]
Prior intracranial hemorrhage
Known intracranial neoplasm, arteriovenous malformation, or aneurysm
Ischemic stroke < 3 mo
Recent surgery in proximity to brain or spinal canal
Recent closed-head or facial trauma with radiographic evidence of fracture or brain injury
Active bleeding or bleeding diathesis
Suspected aortic dissection
Relative contraindications[a]
Age >75
Ischemic stroke > 3 mo
Current use of anticoagulation
History of poorly controlled hypertension
Uncontrolled hypertension (systolic blood pressure > 180 or diastolic blood pressure > 110)
Dementia
Pregnancy
Major surgery within 3 weeks
Non-compressible vascular punctures
Cardiopulmonary resuscitation for > 10 min
Internal bleeding within 2–4 weeks
Other risk factors
INR > 1.7[b]
Female gender[c]
Age > 65[d]
Renal disease[d]

[a]Jaff et al. [33]
[b]Curtis et al. [34]
[c]Meyer et al. [1]
[d]Stein et al. [35]

Certainly, significant bleeding complications have countered the benefit of thrombolysis. In addition, we lack the ability to predict major bleeding with thrombolysis in patients with acute PE. Historically, contraindications to thrombolysis for patients with PE have been drawn from data collected in patients with myocardial infarction [33]. Several recent studies have identified bleeding risk factors specific to patients with PE, including age > 65–75, renal failure, INR > 1.7 and female gender which may contribute directly to bleeding risk [1, 34, 35] (Table 25.6). However, it is unclear how these risk factors should modify clinical practice. Therefore, until further data is available, it remains at the clinician's discretion to determine whether the potential benefits of reperfusion treatment outweigh the risks of hemorrhagic complications in the individual patient.

IVC Filter Placement

Beyond using IVC filters for patients who cannot be anti-coagulated due to a heightened bleeding risk, it has been hypothesized that the employment of these devices in conjunction with heparin might improve outcomes in high risk PE patients. This hypothesis was best addressed in a recent trial in which patients with acute pulmonary embolism, lower-extremity venous thrombosis, and at least 1 additional risk factor were randomized to treatment with a retrievable inferior vena cava filter plus anticoagulation (n = 200) or anticoagulation alone (n = 199) [36]. Retrievable filters were used in light of previous evidence demonstrating an increased risk of DVT in patients with permanent devices, and the study protocol called for removal at 3 months post-deployment (which occurred successfully in 153 of 164 attempts). The primary endpoint of this study was symptomatic recurrent PE at 3 months, and this event occurred rarely. Furthermore, there was no difference in this outcome between the two groups. Specifically, six patients who had received a filter experienced a recurrent PE (3.0 %, all fatal) while three patients (1.5 %, two fatal) in the control group received this diagnosis (p = .50). The results of this study are consistent with an investigation in cancer patients in which filter placement had no effect on the incidence of PE, but again the event rates were low (3 %) [37]. Whether temporary filter placement in hemodynamically unstable PE patients, particularly those individuals already undergoing catheter-directed thrombolysis in Interventional Radiology, is beneficial has not been adequately studied, and this approach is at the preference of the treating physician.

Direct Factor Xa and Thrombin Inhibitors

Recent studies indicate that direct factor Xa and thrombin inhibitors have equivalent efficacy to standard anticoagulation in stable patients with

VTE (reviewed in [38]). These agents are attractive because they are administered at a fixed dose and do not require monitoring. However, to our knowledge, they have not been evaluated in hemodynamically unstable individuals and should therefore not be used in this population. In addition, the inability to reverse these agents renders them less attractive in the ICU, even in the individual who is diagnosed with a hemodynamically stable PE. With the advent of a monoclonal antibody to reverse dabigatran (one of the direct thrombin inhibitors), the comfort level with using these particular agents in the critical care unit may increase in the future. However, until more data is available in the ICU population, we recommend using these agents with extreme caution.

References

1. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, Bluhmki E, Bouvaist H, Brenner B, Couturaud F, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014;370:1402–11.
2. Minet C, Potton L, Bonadona A, Hamidfar-Roy R, Somohano CA, Lugosi M, Cartier JC, Ferretti G, Schwebel C, Timsit JF. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. Crit Care. 2015;19:287.
3. Ibrahim EH, Iregui M, Prentice D, Sherman G, Kollef MH, Shannon W. Deep vein thrombosis during prolonged mechanical ventilation despite prophylaxis. Crit Care Med. 2002;30:771–4.
4. Frasson S, Gussoni G, Di Micco P, Barba R, Bertoletti L, Nunez MJ, Valero B, Samperiz AL, Rivas A, Monreal M, et al. Infection as cause of immobility and occurrence of venous thromboembolism: analysis of 1635 medical cases from the RIETE registry. J Thromb Thrombolysis. 2016;41(3):404–12.
5. Kaplan D, Casper TC, Elliott CG, Men S, Pendleton RC, Kraiss LW, Weyrich AS, Grissom CK, Zimmerman GA, Rondina MT. VTE incidence and risk factors in patients with severe sepsis and septic shock. Chest. 2015;148:1224–30.
6. Semeraro N, Ammollo CT, Semeraro F, Colucci M. Sepsis, thrombosis and organ dysfunction. Thromb Res. 2012;129:290–5.
7. Cade JF. High risk of the critically ill for venous thromboembolism. Crit Care Med. 1982;10:448–50.
8. Bahloul M, Chaari A, Kallel H, Abid L, Hamida CB, Dammak H, Rekik N, Mnif J, Chelly H, Bouaziz M. Pulmonary embolism in intensive care unit: Predictive factors, clinical manifestations and outcome. Ann Thorac Med. 2010;5:97–103.
9. PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group, Cook D, Meade M, Guyatt G, Walter S, Heels-Ansdell D, Warkentin TE, Zytaruk N, et al. Dalteparin versus unfractionated heparin in critically ill patients. N Engl J Med. 2011;364:1305–14.
10. Fraisse F, Holzapfel L, Couland JM, Simonneau G, Bedock B, Feissel M, Herbecq P, Pordes R, Poussel JF, Roux L. Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. Am J Respir Crit Care Med. 2000;161:1109–14.
11. Minet C, Lugosi M, Savoye PY, Menez C, Ruckly S, Bonadona A, Schwebel C, Hamidfar-Roy R, Dumanoir P, Ara-Somohano C, et al. Pulmonary embolism in mechanically ventilated patients requiring computed tomography: Prevalence, risk factors, and outcome. Crit Care Med. 2012;40:3202–8.
12. Stein PD, Beemath A, Matta F, Weg JG, Yusen RD, Hales CA, Hull RD, Leeper Jr KV, Sostman HD, Tapson VF, et al. Clinical characteristics of patients with acute pulmonary embolism: data from PIOPED II. Am J Med. 2007;120:871–9.
13. Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, Turpie AG, Bormanis J, Weitz J, Chamberlain M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83:416–20.
14. Silveira PC, Ip IK, Goldhaber SZ, Piazza G, Benson CB, Khorasani R. Performance of wells score for deep vein thrombosis in the inpatient setting. JAMA Intern Med. 2015;175:1112–7.
15. Trujillo-Santos J, den Exter PL, Gomez V, Del Castillo H, Moreno C, van der Hulle T, Huisman MV, Monreal M, Yusen RD, Jimenez D. Computed tomography-assessed right ventricular dysfunction and risk stratification of patients with acute non-massive pulmonary embolism: systematic review and meta-analysis. J Thromb Haemost. 2013;11:1823–32.
16. Sanchez O, Trinquart L, Colombet I, Durieux P, Huisman MV, Chatellier G, Meyer G. Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. Eur Heart J. 2008;29:1569–77.
17. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, Roy PM, Fine MJ. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. 2005;172:1041–6.
18. Sanchez O, Trinquart L, Planquette B, Couturaud F, Verschuren F, Caille V, Meneveau N, Pacouret G, Roy PM, Righini M, et al. Echocardiography and pulmonary embolism severity index have independent prognostic roles in pulmonary embolism. Eur Respir J. 2013;42:681–8.
19. Miniati M, Monti S, Pratali L, Di Ricco G, Marini C, Formichi B, Prediletto R, Michelassi C, Di Lorenzo M, Tonelli L, et al. Value of transthoracic echocar-

diography in the diagnosis of pulmonary embolism: results of a prospective study in unselected patients. Am J Med. 2001;110:528–35.
20. Pruszczyk P, Torbicki A, Pacho R, Chlebus M, Kuch-Wocial A, Pruszynski B, Gurba H. Noninvasive diagnosis of suspected severe pulmonary embolism: transesophageal echocardiography vs spiral CT. Chest. 1997;112:722–8.
21. Hull RD, Raskob GE, Brant RF, Pineo GF, Valentine KA. Relation between the time to achieve the lower limit of the APTT therapeutic range and recurrent venous thromboembolism during heparin treatment for deep vein thrombosis. Arch Intern Med. 1997;157:2562–8.
22. Smith SB, Geske JB, Maguire JM, Zane NA, Carter RE, Morgenthaler TI. Early anticoagulation is associated with reduced mortality for acute pulmonary embolism. Chest. 2010;137:1382–90.
23. Hull RD, Raskob GE, Pineo GF, Green D, Trowbridge AA, Elliott CG, Lerner RG, Hall J, Sparling T, Brettell HR, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med. 1992;326:975–82.
24. Lin PH, Annambhotla S, Bechara CF, Athamneh H, Weakley SM, Kobayashi K, Kougias P. Comparison of percutaneous ultrasound-accelerated thrombolysis versus catheter-directed thrombolysis in patients with acute massive pulmonary embolism. Vascular. 2009;17 Suppl 3:S137–47.
25. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W, Management S, Prognosis of Pulmonary Embolism-3 Trial, I. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med. 2002;347:1143–50.
26. Becattini C, Agnelli G, Salvi A, Grifoni S, Pancaldi LG, Enea I, Balsemin F, Campanini M, Ghirarduzzi A, Casazza F, et al. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thromb Res. 2010;125:e82–6.
27. Kucher N, Boekstegers P, Muller OJ, Kupatt C, Beyer-Westendorf J, Heitzer T, Tebbe U, Horstkotte J, Muller R, Blessing E, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014;129:479–86.
28. Piazza G, Hohlfelder B, Jaff MR, Ouriel K, Engelhardt TC, Sterling KM, Jones NJ, Gurley JC, Bhatheja R, Kennedy RJ, et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. JACC Cardiovasc Interv. 2015;8:1382–92.
29. Kuo WT, Banerjee A, Kim PS, DeMarco Jr FJ, Levy JR, Facchini FR, Unver K, Bertini MJ, Sista AK, Hall MJ, et al. Pulmonary embolism response to fragmentation, embolectomy, and catheter thrombolysis (PERFECT): initial results from a prospective multicenter registry. Chest. 2015;148:667–73.
30. Nakamura S, Takano H, Kubota Y, Asai K, Shimizu W. Impact of the efficacy of thrombolytic therapy on the mortality of patients with acute submassive pulmonary embolism: a meta-analysis. J Thromb Haemost. 2014;12:1086–95.
31. Konstantinides SV. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35:3145–6.
32. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149:315–52.
33. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, Jenkins JS, Kline JA, Michaels AD, Thistlethwaite P, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011;123:1788–830.
34. Curtis GM, Lam SW, Reddy AJ, Bauer SR. Risk factors associated with bleeding after alteplase administration for pulmonary embolism: a case–control study. Pharmacotherapy. 2014;34:818–25.
35. Stein PD, Matta F, Steinberger DS, Keyes DC. Intracerebral hemorrhage with thrombolytic therapy for acute pulmonary embolism. Am J Med. 2012;125:50–6.
36. Mismetti P, Laporte S, Pellerin O, Ennezat PV, Couturaud F, Elias A, Falvo N, Meneveau N, Quere I, Roy PM, et al. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. JAMA. 2015;313:1627–35.
37. Barginear MF, Gralla RJ, Bradley TP, Ali SS, Shapira I, Greben C, Nier-Shoulson N, Akerman M, Lesser M, Budman DR. Investigating the benefit of adding a vena cava filter to anticoagulation with fondaparinux sodium in patients with cancer and venous thromboembolism in a prospective randomized clinical trial. Support Care Cancer. 2012;20:2865–72.
38. Wells PS, Forgie MA, Rodger MA. Treatment of venous thromboembolism. JAMA. 2014;311:717–28.
39. Le Gal G, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med. 2006;144:165–71.
40. Garcia DA, et al. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest. 2012;141(2_suppl):e24S–43S.

Massive Hemoptysis

26

Andrew M. Namen, Norman E. Adair, and David L. Bowton

Case Presentation

A 61 year old man presented to the emergency department reportedly vomiting blood. He was unable to speak due to blood flooding his oropharynx and severe respiratory distress. The airway was secured with tracheal intubation. Gastric lavage showed no active bleeding. The patient then coughed and filled the ventilator circuit with bright red blood. Laboratory testing revealed hemoglobin of 8 mg/dl, platelet count 260×10^3/μl, INR of 1.1 and PTT of 35 s. Chest X-ray revealed an area suspicious for bronchiectasis in the Left Lower Lobe (LLL) and infiltrates in the Right Lower Lobe (RLL) and Right Upper Lobe (RUL) (Fig. 26.1).

The patient was transferred to intensive care. Flexible bronchoscopy showed no active bleeding but blood was seen in the superior segment of the RLL. Another episode of hemoptysis estimated at 500 ml occurred. The patient was positioned with his right side down and aggressively suctioned through the endotracheal tube. Selective intubation of the left mainstem bronchus was unsuccessful because of poor visibility due to blood in the airway and endotracheal tube.

Multi-detector computed tomography with contrast demonstrated right lower lobe consolidation and associated atelectasis. There was narrowing of the right upper lobe bronchus by soft tissue density (Fig. 26.2).

Bronchial angiography was undertaken. The right and left bronchial arteries both arose from a single trunk. The left bronchial artery was relatively small with no abnormal vessels. On the right, the vessel divided into a branch to the upper lobe and a major lower lobe branch which was moderately enlarged with hyperemia in the lower lobe, associated with the area of consolidated lung. The right lower lobe bronchial artery was embolized and post embolization no flow in the right lower lobe bronchial artery was observed (Fig. 26.3).

Soon thereafter, there was another episode of massive hemoptysis, which filled the ventilator circuit. This was associated with vasopressor-dependent hypotension, worsening hypoxemia and bradycardia.

A dual lumen endotracheal tube was placed, and both right and left sides were ventilated. The patient became more stable with decreasing vasopressor need. A right lower lobectomy was performed.

A.M. Namen (✉)
Pulmonary, Critical Care, Allergy & Immunology, Wake Forest University/Wake Forest Baptist Health, Winston-Salem, NC, USA
e-mail: Anamen@wakehealth.edu

N.E. Adair
Pulmonary, Allergy and Critical Care Medicine, Wake Forest University/Wake Forest Baptist Health, Winston-Salem, NC, USA

D.L. Bowton
Department of Anesthesiology, Section of Critical Care, Wake Forest University/Wake Forest Baptist Health, Winston-Salem, NC, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_26

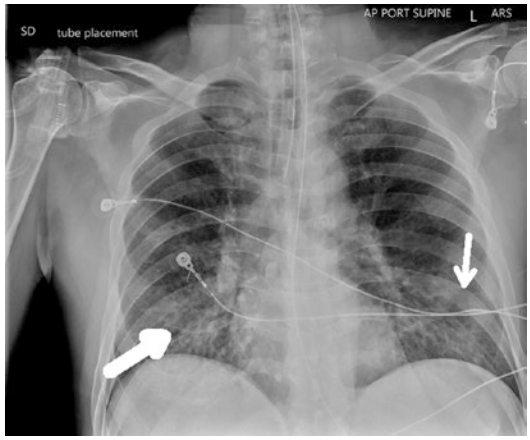


Fig. 26.1 Arrows demonstrate Right lower lobe consolidation (*wide arrow*) and Left Lower Lobe bronchiectasis (*thin arrow*)

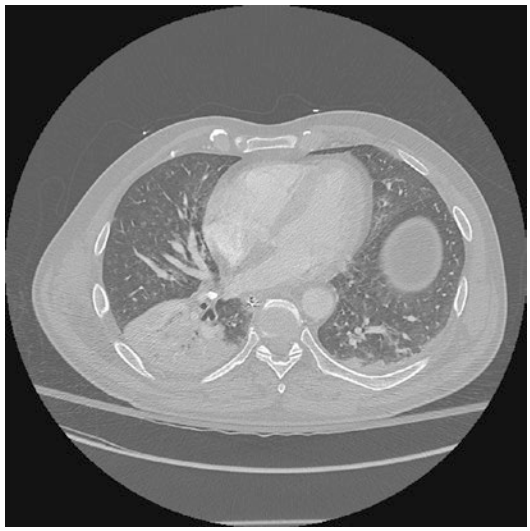


Fig. 26.2 Computed tomography image demonstrates dense right lower lobe infiltrate with broncholithiasis

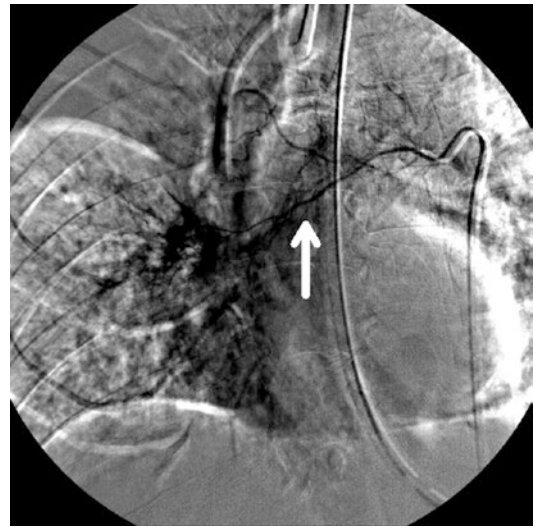


Fig. 26.3 Right Bronchial artery arteriogram demonstrates both upper lobe and lower lobe branch (*arrow*)

Principles of Management

Epidemiology

Massive hemoptysis occurs in about 5–15 % of all admissions for hemoptysis [1, 2]. Mortality was 7 % in a single center retrospective review of 1,087 patients [2] but has been reported as high as 75 % when the volume of hemoptysis exceeds 600 ml in 24 h. The wide range of mortality likely reflects the lack of a standard definition of massive hemoptysis as well as the variability in underlying etiology [3–5].

A scoring system to identify risk for mortality was derived from a 14 year experience of 1,087 patients admitted for hemoptysis, 717 of whom were admitted to the Intensive Care Unit (ICU), and 10 % of whom demonstrated massive hemoptysis with a mean cumulative volume of >200 ml. Risk factors include chronic alcoholism, ≥2 chest x-ray quadrants involved, pulmonary artery involvement, cancer, aspergillus infection or mycetoma, and initial mechanical ventilation. Two or more risk factors demonstrated a higher mortality [2]. (These risk factors are noted in the clinical algorithm, Fig. 26.4).

Sources of Hemorrhage

Hemoptysis, including massive hemoptysis, usually originates from pathology that involves the high pressure bronchial arterial supply (90 %) [6, 7]. The bronchial artery or arteries originate from the descending thoracic aorta (DTA) at thoracic vertebral level T3-8 most often T5-6. While the most common pattern is a right and left bronchial artery arising from the DTA, variability is extensive, and commonly involves a right bronchial

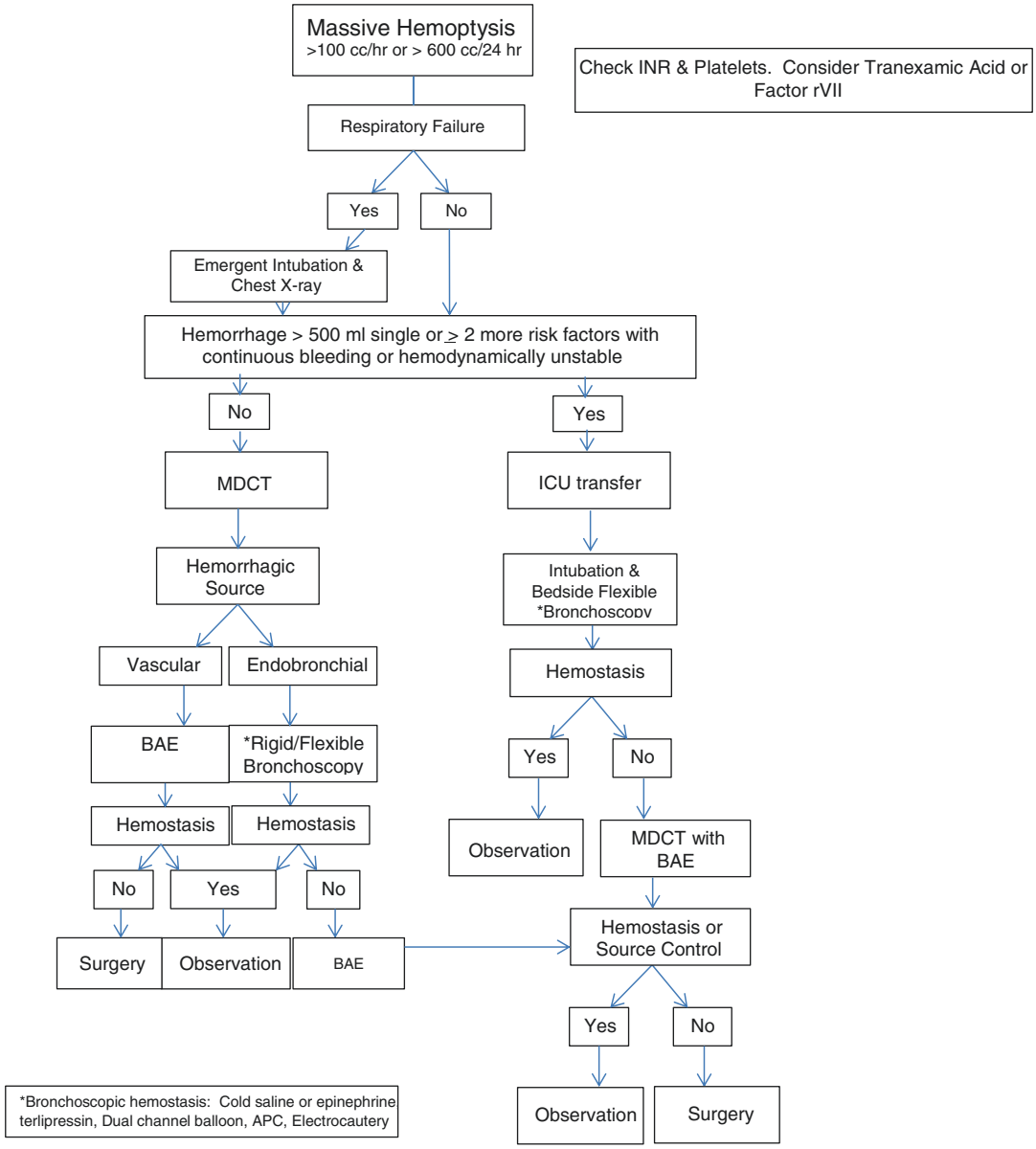


Fig. 26.4 Clinical algorithm to massive hemoptysis

artery arising from an intercostal artery (also-called intercostobronchial trunk) or 2 right bronchial arteries arising from the DTA and/or intercostobronchial trunk. Left bronchial arteries can also arise from intercostobronchial trunks [7]. The spinal artery of Adamkiewicz supplies the distal thoracic and lumbar spinal cord and originates from an intercostal artery at thoracic vertebral level T9-12 in 75% of patients. However, it infrequently originates between T5-T8 and may be occluded during embolization of the bronchial artery resulting in spinal cord ischemia or infarction [8].

The pulmonary artery infrequently is the source of hemoptysis. Infection, malignant disease, traumatic injuries (e.g. Swan Ganz catheter balloon rupture of PA) and arteriovenous malformations are the most common causes for pulmonary arterial

bleeding [6, 9–11]. Rarely hemoptysis may involve non-bronchial or pulmonary arteries. Non-bronchopulmonary arteries may enter the lung via transpleural adhesions as a result of chronic inflammation or congenital anomalies and may anastomose with the pulmonary artery circulation [9, 10]. Other potential nonbronchial arterial sources include the aorta (ruptured aneurysm), intercostal arteries, coronary, thyrocervical, pericardiodiaphragmatic, musculophrenic, and inferior phrenic arteries. Diffuse alveolar hemorrhage syndromes are rarely a cause of massive hemoptysis.

Diseases Associated with Massive Hemoptysis

Many diseases have been associated with massive hemoptysis and vary by geographic region. Tuberculosis continues to be a major cause of massive hemoptysis world-wide. Bronchiectasis, malignancy, trauma, pneumonia, and mycetoma are the most causes of massive hemoptysis in the USA [12, 13] (Table 26.1).

The etiology for hemoptysis will direct treatment decisions. Systemic diseases such as vasculitis will require anti-inflammatory or immunosuppression whereas coagulopathies will require reversal of coagulation abnormalities [13–19]. Focal lung or bronchial conditions causing massive hemoptysis may require either bronchoscopic intervention or bronchial artery embolization (BAE) as a first approach.

Imaging

Plain radiographs will not permit localization of bleeding site in upwards of 35 % of patients [20]. Multidetector CT angiography is capable of ascertaining the site of bleeding and/or suggesting a diagnosis in more than 80 % of patients and the yield may be higher with the use of reformatted image techniques [21]. Further, CT angiography is helpful to guide bronchial artery embolization [6, 7, 9, 20].

An Approach to Managing Life Threatening Hemoptysis (Algorithm, Fig. 26.4)

Several algorithms have been developed to provide guidance for an approach to severe or massive hemoptysis and most agree that an initial multidisciplinary approach is indicated with immediate evaluation by pulmonology, interventional radiology and thoracic surgery [22–25]. We propose the following:

The initial survey should include a simple "ABC" assessment: Airway, Blood loss, and Clinical condition.

Table 26.1 Causes of massive hemoptysis

Infectious	Mycobacterial (TB), Fungal (mycetoma), Necrotizing Bacterial Pneumonia (Klebsiella, Streptococcus, Staphylcoccus, Actinomyces)
Neoplastic	Bronchogenic, Renal cell, melanoma, carcinoid, adenocystic, etc.
Vascular	Bronchial artery aneurysm, Pulmonary artery aneurysm, Cardiac and Pulmonary Malformations, Arteriovenous malformations, Airway vascular fistula, Dieulofoy's Disease, etc.
Pulmonary	Bronchiectasis, Broncholithiasis, Diffuse alveolar hemorrhage, Crytogenic, Inhalation: crackcocaine, etc.
Diffuse Alveolar Hemorrhage Syndromes	Granulomatosis with Polyangitis, Microscopic polyangitis, Anti-GBM (Goodpastures), Isolated pulmonary capillaritis, SLE, Eosinophilic granulomatosis with polyangitis, Antiphospholipid antibody, toxin and drug induced lung injury, IgA deposition vasculitis, etc.
Trauma	High dose brachytherapy, Pulmonary artery rupture, Biopsy and Trauma
Hematologic	Coagulopathy and Platelet disorders

Airway: Does the volume of bleeding into the airway require emergent airway management?

Blood: Has there been a single bleeding event of large volume >100 cc or is the bleeding recurrent? Is the bleeding in excess of 100 per hour for >2 h?

Clinical Condition: Is there hemodynamic instability (signs of hypoperfusion, tachycardia, or hypotension)?

The decision regarding immediate airway management should be determined. Adequate intravenous access should be established with at least two large bore IV lines. Fluid resuscitation should be initiated, if indicated. A complete blood count, testing for coagulopathies, and cross match for transfusion should be obtained. In addition, perform electrocardiogram and obtain cardiac biomarkers.

Intubation: Options are dual lumen or single lumen endotracheal tube with the intent to protect the lung on the non-bleeding side. Single lumen endotracheal intubation is preferred when airway visibility is poor (see discussion of dual lumen endotracheal tubes below).

Position: The patient should be positioned with the presumed side of bleeding dependent (lateral decubitus) to reduce the likelihood of flooding of the unaffected lung with blood. However, lateral decubitus position with the bleeding side down may worsen hypoxemia (due to increased perfusion to poorly aerated lung) [26].

Assessment

- *Active Hemorrhage and unstable:* If transport is not considered safe, the initial evaluation to localize and treat would be with rigid and/or flexible bronchoscope. This may allow therapeutic endoscopic intervention (Cold Saline/epinephrine [EPI], anti-diuretic hormone [ADH], argon plasma coagulation [APC], tamponade endobronchial blocker). (Table 26.2) [27, 30–33].
- *Active Hemorrhage and stable:* In this setting bronchoscopy is limited due to poor visibility and proceeding to radiologic investigation maybe more informative.
- *Non-active hemorrhage and the unstable patient*: ICU setting to stabilize the patient with possible bronchoscopic approach for localization and treatment.
- *Non-active hemorrhage and the stable patient*: Multidetector Computed Tomography (MDCT) and 3D volume averaging provides the best detail for localization and selection of treatment options [11, 21, 23] (Table 26.2).

No localization of a culprit lesion via bronchoscopy is an indication for immediate multidetector CT. This may indicate that embolization is needed.

If hemostasis cannot be achieved then urgent resectional surgery [34, 35] should be considered.

Evidence Contour

Rigid Versus Flexible Bronchoscopy

In massive hemoptysis, rigid bronchoscopy has several advantages: the large inner diameter and more effective suctioning capability improve clearance of blood from airways (especially in voluminous flooding); the ability to ventilate; and ancillary devices that are not available with flexible bronchoscopy e.g. laser. Disadvantages include the lack of availability and/or expertise for rigid bronchoscopy [24]. Flexible bronchoscopy has the advantages of ease of access, and wide availability of skilled individuals plus it may allow specialized techniques to control airway bleeding (i.e. APC, cryotherapy, electro cautery).

Dual Lumen Versus Unilateral Airway Intubation: Benefits and Limitations

Consideration should be given to placing a dual lumen endotracheal tube to isolate the side of hemorrhage and protect the contralateral lung from blood. Dual-lumen endotracheal tubes have various designs but all have two lumens,

Table 26.2 Bronchoscopic and systemic treatments for massive hemoptysis

Treatment	Mechanism of action	Procedure	Complications
Cold Saline	Vasoconstriction with localized thrombosis	50 cc aliquots at 4 °C	Bradycardia [22, 27]
Topical Epinephrine (Epi), terlipressin or ornipressin	Epi, Terlipressin (5iu), Ornipressin (0.5 mg), vasoconstriction	1:20000 Epi in cold saline	Tachyarrhythmias [27]
Balloon Tamponade	Tamponade	Double lumen occluding balloon with saline	Post-obstructive Pneumonia
Fibrinogen –thrombin	Fibrinogen, fibronectin, factor III, plasminogen and aprotinin/ thrombin		[28, 29]
Argon Plasma Coagulation	High frequency electric current with dessication of surface	Direct visualization	Gas embolism [30–32]
Tranexamic Acid	*Endobronchial or Systemic*. antifibrinolytic	Endobronchial 500–1,000 mg or oral for chronic bleed	Clotting disorders. i.e. PE [17–19]
Factor rVII	*Systemic*: coagulation in tissue damage. Activates IX then Xa then fibrin thrombin	60–90 ug/kg	CVA [14–16]

each of which can be ventilated, permitting both isolation of each lung and instillation of vasoactive agents or saline into the airway. Disadvantages: the lumens are small, potentially limiting flexible bronchoscopy and the removal of blood and secretions. During patient transport or turning, dual-lumen tubes can easily become displaced. Placement of dual lumen ET tubes can be difficult and requires considerable expertise and the ability to visualize the airway. If visualization of the airway is limited due to airway flooding then a single lumen ET tube may be directed into the main bronchus of the unaffected lung.

One Transport or Two?

The unpredictability of repeat hemorrhage heightens the need to quickly identify location and cause. In the stable patient (per Algorithm), multidetector CT with 3D volume rendering is the first choice. MDCT allows a noninvasive approach to arterial and pulmonary anatomy for potential identification of both the site and cause of hemorrhage in 77 % and 73 % of patients, respectively [20]. The stable patient could transfer to radiology for diagnostic CT followed by Interventional Radiology (IR) for possible BAE if a significant vascular pathology is identified (control of hemorrhage in 66–90 %). In the unstable patient, ICU transfer and immediate bedside bronchoscopy with control of the source when possible and supportive care [36] has been evaluated and is considered standard of care. ICU care limits diagnostic testing to bedside bronchoscopy and portable chest x-ray. Bronchoscopy may localize disease but frequently does not achieve hemostasis (up to 60 %) and a second transport to IR for BAE is required [37].

Recurrent Bleeding; Repeat Embolization or Surgery?

Recurrent bleeding or persistent bleeding occurs in 5–44 % of patients after initial BAE. For recurrent hemoptysis, a second BAE may be effective and avoid surgery; surgery for massive hemoptysis has a high risk of morbidity (25 %) and mortality (7–40 %) [38]. Generally, second attempt at embolization is favored if the anatomy

suggests an amenable lesion but the uniqueness of each patient and pathology requires multidisciplinary decision making [37].

References

1. Croco JA, Rooney JJ, Fankushen DS, DiBenedetto RJ, Lyons HA. Massive hemoptysis. Arch Intern Med. 1968;121:495–8.
2. Fartoukh M, Khoshnood B, Parrot A, Khalil A, Carette M, Stoclin A, Mayaud C, Cadranel J, Ancel P. Early prediction of in-hospital mortality of patients with hemoptysis: an approach to defining severe hemoptysis. Respiration. 2012;83:106–14.
3. Dwelk RA, Stoller JK. Role of bronchoscopy in massive hemoptysis. Clin Chest Med. 1999;20:89–105.
4. Ibrahim WH. Massive hemoptysis: the definition should be revised. Eur Respir J. 2008;32:1131–2.
5. Jean-Baptiste E. Clinical assessment and management of massive hemoptysis. Crit Care Med. 2000;28:1642–7.
6. Remy-Jardin M, Bouaziz N, Dumont P, Brillet P-Y, Remy J. Bronchial and non bronchial systemic arteries at multi-detector row CT angiography: comparison with conventional angiography. Radiology. 2004;233:741–9.
7. Yoon W, Kim JK, Kim YH, Chung TW, Kang HK. Bronchial and nonbronchial systemic artery embolization for life-threatening hemoptysis: a comprehensive review. Radiographics. 2002;22(6):1395–409.
8. Shamji MF, Maziak DE, Shamji FM, Ginsberg RJ, Pon R. Circulation of the spinal cord: an important consideration for thoracic surgeons. Ann Thorac Surg. 2003;76:315–21.
9. Khalil A, Fartoukh M, Tassart M, Parrot A, Marsault C, Carette MF. Role of MDCT in identification of the bleeding site and the vessels causing hemoptysis. Am J Roentgenol. 2007;188:117–25.
10. Noe GD, Jaffe SM, Molan MP. CT and CT angiography in massive hemoptysis with emphasis on preembolization assessment. Clin Radiol. 2011;66:869–75.
11. Yoon YC, Lee KS, Jeong YJ, Shin SW, Chung MJ, Kwon OJ. Hemoptysis: bronchial and nonbronchial systemic arteries at 16-detector row CT. Radiology. 2005;234:292–8.
12. Düpree HJ, Lewejohann JC, Gleiss J, Muhl E, Bruch HP. Fiberoptic bronchoscopy of intubated patients with life-threatening hemoptysis. World J Surg. 2001;25(1):104–7.
13. Cho AH, Khosla R. A case of massive airway clotting after use of activated factor VII for massive hemoptysis: management with flexible bronchoscopy and cryoadhesion. J Bronchol Interv Pulmonol. 2013;20(3):276–7.
14. Lau EM, Yozghatlian V, Kosky C, Moriarty C, Dentice R, Waugh R, Torzillo PJ, Bye PT. Recombinant activated factor VII for massive hemoptysis in patients with cystic fibrosis. Chest. 2009;136(1):277–81.
15. Estella A, Jareño A, Perez-Bello Fontaiña L. Intrapulmonary administration of recombinant activated factor VII in diffuse alveolar hemorrhage: a report of two case stories. Cases J. 2008;1(1):150.
16. Yildirim H, Ucgun I, Yalcin AU, Gulbaş Z, Sahin G, Acikalin MF, Metintas M, Ak G. Recombinant factor VIIa treatment for life-threatening haemoptysis. Respirology. 2006;11(5):652–4.
17. Moen CA, Burrell A, Dunnig J. Does tranexamic acid stop haemoptysis. Interact Cardiovasc Thoracic Surg. 2013;17(6):991–4.
18. Binesh F, Samet M, Bovanlu TR. A case of pulmonary carcinoid tumour in a pregnant woman successfully treated with bronchoscopic (electrocautery) therapy. BMJ Case Rep. 2013.
19. Prutsky G, Domecq JP, Salazar CA, Accinelli R. Antifibrinolytic therapy to reduce hemoptysis from any cause. Cochrane Database Syst Rev. 2012:1–20.
20. Revel MP, Fournier LS, Hennebicque AS, Cuenod CA, Meyer G, Reynaud P, Frija G. Can CT replace bronchoscopy in the detection of the site and cause of bleeding in patients with large or massive hemoptysis? Am J Roentgenol. 2002;179(5):1217–24.
21. Morita Y, Takase K, Ichikawa H, Yamada T, Sato A, Higano S, Takahashi S. Bronchial artery anatomy: preoperative 3D simulation with multidetector CT. Radiology. 2010;255(3):934–43.
22. Sakr L, Dutau H. Massive hemoptysis: an update on the role of bronchoscopy in diagnosis and management. Respiration. 2010;80:38–58.
23. Larici AR, Franchi P, Occhipinti M, Contegiacomo A, del Ciello A, Calandriello L, Storto ML, Marano R, Bonomo L. Diagnosis and management of hemoptysis. Diagn Interv Radiol. 2014;20(4):299–309.
24. Haponik EF, Fein A, Chin R. Managing life-threatening hemoptysis: has anything really changed? Chest. 2000;118:1431–5.
25. Johnson JL. Manifestations of hemoptysis. How to manage minor, moderate, and massive bleeding. Postgrad Med. 2002;112(4):101–6. 108–109, 113.
26. Bahk JH, Lim YJ, Kim CS. Positioning of a double-lumen endobronchial tube without the aid of any instruments: an implication for emergency management. J Trauma. 2000;49(5):899–902.
27. Tüller C, Tüller D, Tamm M, Brutsche MH. Hemodynamic effects of endobronchial application of ornipressin versus terlipressin. Respiration. 2004;71(4):397–401.
28. de Gracia J, de la Rosa D, Catalán E, Alvarez A, Bravo C, Morell F. Use of endoscopic fibrinogen-thrombin in the treatment of severe hemoptysis. Respir Med. 2003;97(7):790–5.
29. Lorusso R, De Cicco G, Vizzardi E, Gelsomino S. Human fibrinogen/thrombin-coated collagen patch to control intraoperative severe pulmonary hemorrhage and air leakage after correction of a ruptured thoracic aortic aneurysm. Ann Thorac Surg. 2011;91(3):917–9.

30. Reddy C, Majid A, Michaud G, Feller-Kopman D, Eberhardt R, Herth F, Ernst A. Gas embolism following bronchoscopic argon plasma coagulation: a case series. Chest. 2008;134(5):1066–9.
31. Dalar L, Sökücü SN, Özdemir C, Büyükkale S, Altın S. Endobronchial argon plasma coagulation for treatment of dieulafoy disease. Respir Care. 2015;60(1): e11–3.
32. Ernst A, Anantham D. Update on interventional bronchoscopy for the thoracic radiologist. J Thorac Imaging. 2011;26(4):263–77.
33. Colchen A, Fischler M. Emergency interventional bronchoscopies. Rev Pneumol Clin. 2011;67(4): 209–13.
34. Alexander GR. A retrospective review comparing treatment outcomes of emergency lung resection for massive hemoptysis with and without preoperative bronchial artery embolization. Eur J Cardiothoracic Surg. 2014;45:251–5.
35. Harrison M, Cowan S, Cavarocchi N, Hirose H. Massive haemoptysis on veno-arterial extracorporeal membrane oxygenation. Eur J Cardiothorac Surg. 2012;42(3):587–9.
36. Ong TH, Eng P. Massive hemoptysis requiring intensive care. Intensive Care Med. 2003;29(2):317–20.
37. Ketai LH, Mohammed TL, Kirsch J, Kanne JP, Chung JH, Donnelly EF, Ginsburg ME, Heitkamp DE, Henry TS, Kazerooni EA, Lorenz JM, McComb BL, Ravenel JG, Saleh AG, Shah RD, Steiner RM, Suh RD, Expert Panel on Thoracic Imaging. ACR appropriateness criteria for hemoptysis. J Thorac Imaging. 2014;29(3):W19–22.
38. Kiral H, Evman S, Tezel C, Alpay L, Lacin T, Baysungur V, Yalcinkaya I. Pulmonary resection in the treatment of life-threatening hemoptysis. Ann Thorac Cardiovasc Surg. 2015;21:125–31.
39. Lin CS, Becker WH. Broncholith as a cause of fatal hemoptysis. JAMA. 1978;239(20):2153.

Sedation and Delirium

27

Timothy D. Girard

Case Presentation

A 74-year-old man with a history of coronary artery disease, congestive heart failure, hypertension, and atrial fibrillation presented with 12 h of progressive shortness of breath, chest pressure, and cough. At the time of presentation, he was tachycardic (HR 148), tachyneac (RR 38), hypoxemic (SaO_2 initially 78 % on room air), and struggling to breathe (demonstrated by use of accessory muscles and shallow breaths). Chest x-ray was consistent with bilateral pulmonary edema, B-type natriuretic peptide (BNP) was 8 times the upper limit of normal, and ECG showed rapid atrial fibrillation without ST segment changes. In addition to supplemental oxygen, furosemide, morphine, and aspirin, continuous positive airway pressure (CPAP) was initiated and SaO_2 improved to 89 % on 100 % FiO_2. The patient, however, became confused and agitated, which progressed after receipt of additional doses of morphine. In his confused state, the patient removed the CPAP mask on multiple occasions, with each event causing declines in SaO_2, so the patient was intubated and invasively mechanically ventilated while being sedated with a continuous midazolam infusion. He was transferred from the Emergency Department to the ICU.

Question What is the best approach to managing this patient's sedation and delirium?

Answer Close monitoring, minimizing sedation, and eliminating risk factors for delirium.

Critically ill patients, especially those who are mechanically ventilated, frequently experience pain, anxiety, and/or agitation, prompting treatment with analgesics and sedatives. Care should be taken when administering these medications since oversedation and delirium are common in the ICU, where they are associated with poor outcomes. After transfer to the ICU, midazolam was discontinued, and intermittent fentanyl boluses were used to treat pain in lieu of morphine after labs revealed acute kidney injury. Depth of sedation was monitored every 2 h (and when sedating medications were given) using the Richmond Agitation-Sedation Scale (RASS), and the patient was assessed for delirium every 8 h with the Confusion Assessment Method for the ICU (CAM-ICU). During the first 6 h after transfer to the ICU, the fentanyl dose and frequency were increased due to ongoing pain and agitation, and propofol was started and titrated with a goal of achieving a target RASS of −1 (drowsy) or 0 (alert and calm). By the next morning, RASS was consistently either −2 (light seda-

T.D. Girard
Clinical Research, Investigation, and Systems Modeling of Acute illness (CRISMA) Center in the Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
e-mail: timothy.girard@upmc.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_27

tion) or −1 (drowsy), but the patient remained delirious (CAM-ICU positive). Ongoing treatment for acute exacerbation of congestive heart failure included volume control ventilation with low tidal volumes (6 mL/kg ideal body weight) and FiO_2 and PEEP titrated to maintain $SaO_2 > 89\%$. Intermittent furosemide was continued, leading to significant diuresis and improved oxygenation. Daily spontaneous awakening trials (SATs) were paired with spontaneous breathing trials (SBTs) each morning that safety screens were passed, and physical and occupational therapy were initiated early. One hour into an SAT on the first full ICU day, propofol was restarted at 1/2 the previous dose due to recurrence of agitation. Propofol was held again during an SAT on the second ICU day and was not subsequently restarted. Similarly, intermittent fentanyl boluses were held and no longer needed by the second ICU day. The patient remained comfortable without sedation through the third ICU day, when he passed an SBT, was alert, non-delirious (CAM-ICU negative), had a strong cough and minimal secretions, and was successfully extubated. The next day, he was transferred out of the ICU to the general medical ward.

Principles of Management

Monitoring Sedation and Delirium

Two sedation scales—the RASS [1, 2] (Fig. 27.1; used in this case) and the Sedation-Agitation Scale (SAS) [3]—are well-validated for use in the ICU and are therefore recommended in the 2013 Society of Critical Care Medicine (SCCM) guidelines for the management of pain, agitation, and delirium in the ICU [4] (Table 27.1). By giving ICU practitioners a reliable means by which to assess, describe, and document a patient's level of consciousness, these tools can improve patient care. Multiple randomized trials have shown that a protocol guided by a validated sedation scale improves outcomes, including duration of mechanical ventilation [5, 6].

The SCCM guidelines (Table 27.1) also recommend monitoring ICU patients for delirium using one of two validated tools: the CAM-ICU [7] (Fig. 27.2; used in this case) or the Intensive Care Delirium Screening Checklist (ICDSC) [8]. Delirium, which is frequently hypoactive (i.e., characterized by somnolence rather than agitation) in the ICU, is easily overlooked when a validated assessment tool is not used. Use of the CAM-ICU or ICDSC, therefore, can improve detection and management of delirium.

Minimizing Sedation

Oversedation is common and harmful in the ICU, where heavily sedated patients remain on the ventilator longer and have higher mortality rates than their less sedated counterparts [9]. Patients who require sedatives during critical illness should therefore be managed with light rather than heavy sedation (barring a specific, time-limited indication for the latter, e.g., neuromuscular blockade, open abdomen, etc.). Use of a validated sedation scale (see section on "Sedative Choice") is an important part of efforts to maintain light sedation, since frequent, reliable data regarding actual vs. targeted level of sedation can prompt changes in sedative choice, dose, and/or frequency. In addition to use of sedation scales, strategies that can improve outcomes by minimizing sedation include treating pain adequately before using sedatives [10], avoiding benzodiazepines in favor of other sedatives (e.g., propofol, dexmedetomidine, and/or an opioid) [11], using a sedation protocol [5], and interrupting sedatives on a daily basis with SATs [12, 13].

Risk Factors for Delirium

Though questions remain regarding the most effective strategies to prevent and treat delirium (see Prevention of Delirium and Antipsychotics sections), studies have identified a number of modifiable risk factors for delirium that should be addressed whenever possible when managing patients who are high

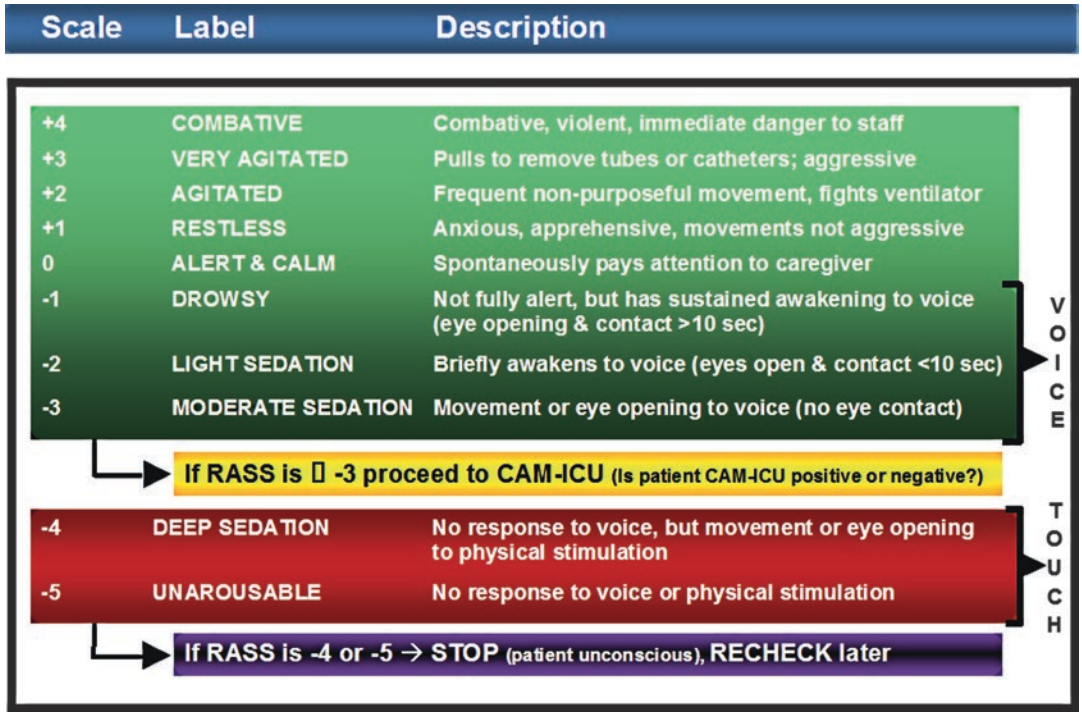


Fig. 27.1 Richmond Agitation-Sedation Scale (© Vanderbilt University)

Table 27.1 The ICU pain, agitation, and delirium care bundle

Component	Pain	Agitation	Delirium
Assess	Assess ≥4×/shift and prn NRS if patient can report pain BPS or CPOT if patient cannot report	Assess ≥4×/shift and prn RASS or SAS if not paralyzed Brain function monitor if paralyzed	Assess delirium each shift and prn CAM-ICU or ICDSC
Treat	Treat pain then reassess Non-pharmacologic (relaxation) IV opioids +/– non-opioids for non-neuropathic pain Gabapentin or carbamazepine for neuropathic pain	Targeted sedation and/or daily SATs to achieve goal of RASS −1 to 0 or SAS 3 to 4 If undersedated, use non-benzodiazepine sedatives as needed If oversedated, hold sedatives	Treat pain as needed Reorient patients; provide eyeglasses, hearing aids as needed Avoid benzodiazepines unless alcohol or benzodiazepine withdrawal Avoid rivastigmine Avoid antipsychotics if QTc is high
Prevent	Preprocedural analgesia Relaxation therapy	Treat pain before using sedation Consider daily SBTs and early mobility unless contraindicated EEG if high ICP warrants burst suppression or high risk for seizures	Identify delirium risk factors Avoid benzodiazepines Early mobility Promote sleep Restart baseline psychiatric medications if indicated

This table modifies and summarizes the full bundle described in Barr et al. [4]
Abbreviations: *BPS* Behavioral Pain Scale, *CAM-ICU* Confusion Assessment Method for the Intensive Care Unit, *CPOT* Critical-Care Pain Observation Tool, *EEG* electroencephalogram, *ICDSC* Intensive Care Delirium Screening Checklist, *ICP* intracranial pressure, *IV* intravenous, *NRS* numeric rating scale, *RASS* Richmond Agitation-Sedation Scale, *SAS* Sedation Agitation Scale, *SATs* spontaneous awakening trials, *SBTs* spontaneous breathing trials

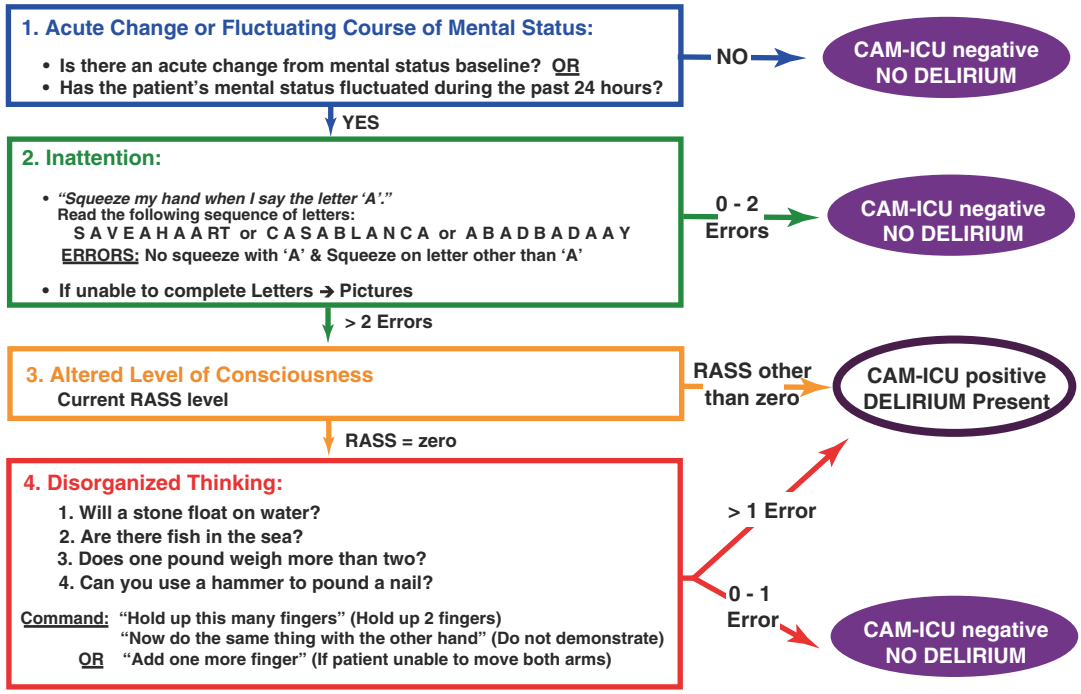


Fig. 27.2 CAM-ICU (© 2002 Vanderbilt University)

risk as well as those already delirious. Numerous observational and interventional studies have found benzodiazepines (used initially in this case) increase delirium risk [14, 15], whereas dexmedetomidine does not [16, 17]. This may be because benzodiazepine pharmacokinetics make them prone to cause oversedation—drug-induced coma, regardless of which medication is the culprit, is a delirium risk factor—or because of their mechanism of action in the brain (GABA agonism). Infection, acute kidney injury, metabolic acidosis, mechanical ventilation, and high severity of illness are also risk factors for delirium that, in many cases, can be addressed [18].

In addition to the modifiable risk factors listed herein, many risk factors for delirium are not modifiable but an awareness of these factors may prompt clinicians to monitor high-risk patients more closely for delirium. These include advanced age and hypertension (both present in this case) as well as preexisting cognitive impairment, emergency surgery, and trauma.

Evidence Contour

This case highlights a number of evidence gaps and areas of controversy that remain despite the growing body of evidence regarding sedation and delirium in the ICU.

Sedative Choice

Dozens of randomized controlled trials have examined whether sedative choice affects outcomes in the ICU. Most compared a benzodiazepine (typically midazolam), the class of sedatives used most frequently in the ICU for several decades, with a non-benzodiazepine sedative, and the large majority of these trials found non-benzodiazepine sedation resulted in better outcomes (Table 27.2). A recent meta-analysis, in fact, found that benzodiazepine sedation (compared with sedation using propofol or dexmedetomidine) delays extubation and discharge from the ICU [11]. These data led the SCCM guidelines [4]

Table 27.2 Randomized trials comparing benzodiazepines with alternative sedatives in the ICU

First author	Year	Population	Outcome(s) improved
Benzodiazepines vs. propofol			
Trials finding better outcomes with propofol			
Grounds RM	1987	Cardiac surgery	Faster awakening
Aitkenhead AR	1989	General ICU	More consistent awakening, faster weaning
McMurray TJ	1990	Cardiac surgery	Faster awakening
Carrasco G	1993	General ICU	More accurate sedation, faster awakening, lower costs
Roekaerts PM	1993	Cardiac surgery	Faster awakening, earlier extubation
Ronan KP	1995	Surgical ICU	Faster awakening
Sherry KM	1996	Cardiac surgery	Lower costs
Chamorro C	1996	General ICU	Better ventilator synchrony, faster awakening
Barrientos-Vega R	1997	General ICU	Earlier extubation
Weinbroum AA	1997	General ICU	Faster awakening
Sanchez-Izquierdo-Riera JA	1998	Trauma ICU	Faster awakening
McCollam JS	1999	Trauma ICU	Less oversedation
Hall RI	2001	Mixed ICU	More accurate sedation, earlier extubation
Carson SS	2006	Medical ICU	Fewer ventilator days
Trials finding no differences in outcomes			
Searle NR	1997	Cardiac surgery	None
Kress JP	2000	Medical ICU	None
Huey-Ling L	2008	Cardiac surgery	None
Trials finding better outcomes with the benzodiazepine			
None			
Benzodiazepines vs. remifentanil			
Trials finding better outcomes with remifentanil			
Breen D	2005	Mixed ICU	Shorter duration of mechanical ventilation
Muellejans B	2006	Cardiac surgery	Earlier extubation and ICU discharge
Rozendaal FW	2009	Mixed ICU	Lighter sedation, shorter weaning time
Trials finding no differences in outcomes			
None			
Trials finding better outcomes with the benzodiazepine			
None			
Benzodiazepines vs. dexmedetomidine			
Trials finding better outcomes with dexmedetomidine			
Pandharipande PP	2007	Mixed ICU	More accurate sedation, more delirium/coma-free days
Riker RR	2009	Mixed ICU	Lower prevalence of delirium, earlier extubation
Ruokonen E	2009	Mixed ICU	Shorter duration of mechanical ventilation[a]

(continued)

Table 27.2 (continued)

First author	Year	Population	Outcome(s) improved
Maldonado JR	2009	Cardiac surgery	Lower incidence and duration of delirium
Esmaoglu A	2009	Eclampsia	Shorter ICU length of stay
Dasta JF	2010	Mixed ICU	Lower ICU costs
Jakob SM	2012	General ICU	Lighter sedation, fewer ventilation days
Trials finding no differences in outcomes			
None			
Trials finding better outcomes with the benzodiazepine			
None			

From Ely et al. [35]. Reprinted with permission from Elsevier Limited
Abbreviations: *ICU* intensive care unit
[a]According to post-hoc analysis adjusting for study center, sedative agent before randomization, and target sedation level

to recommend non-benzodiazepines for sedation in the ICU, but questions remain regarding which drug(s) should be preferred. Dexmedetomidine has the benefit of facilitating light sedation and reducing delirium risk [16, 17], but costs remain high and the patient population that benefits the most from this agent has not yet been clearly defined. Propofol is less expensive than dexmedetomidine and less prone to cause oversedation than benzodiazepines but its use in some patients is limited by hemodynamic effects. Other drugs, including opioids, clonidine, haloperidol, and atypical antipsychotics are sometimes used to manage agitation in the ICU, but evidence of benefit in randomized trials is needed before use of these agents can be widely recommended.

Spontaneous Awakening Trials (SATs)

Protocolized daily SATs (also known as daily interruption of sedatives), which were used in this case, were shown in two randomized controlled trials [12, 13] to improve outcomes, including long-term survival, but these trials were conducted at a time when heavy sedation was common so controversy exists regarding whether SATs are beneficial in ICUs that target light sedation. A recent multicenter randomized trial [19] sought to address this question by comparing a light sedation protocol alone vs. the light sedation protocol plus SATs and found no difference in outcomes. This trial, however, did not use a safety screen to identify patients likely to tolerate an SAT, and significantly higher sedative doses were delivered to patients in the SAT group. Whereas many ICUs continue to employ SATs and others do not, one thing is clear—SATs are most beneficial when they result in an overall reduction of sedative exposure.

Sedative-Related Delirium

Delirium can be caused by a variety of insults (e.g., both respiratory failure and sedatives were implicated in this case), but most studies to date showing that delirium is associated with adverse outcomes—including delayed extubation, prolonged hospitalization, increase mortality, and long-term cognitive impairment (see Delirium and Long-Term Outcomes section)—have not distinguished one type of delirium from another. Thus, it is not known if certain phenotypes of delirium are more injurious (or benign) than others. Sedative-related delirium has recently received attention because one study [20] found that patients whose delirium resolved within 2 h of sedative discontinuation (so called rapidly reversible, sedation-related delirium) had better outcomes than those whose delirium did not resolve quickly. More data on the effects of sedative-related delirium are needed before it can be concluded that this form of delirium is not harmful given that this study's results were

based on a very small number (N = 12) of patients who had rapidly reversible, sedation-related delirium.

Prevention of Delirium

Critically ill patients often develop delirium early during the course of their illness, so prevention of delirium in the ICU is a major challenge. In light of evidence from the geriatrics literature [21] suggesting that non-pharmacological prevention strategies, such as frequent orientation, sleep protocols, and early mobilization, are effective in some settings, similar strategies have been recommended in the ICU. One study, for example, found that ICU patients using earplugs to promote sleep had less confusion than those without earplugs [22], and another found that mechanically ventilated ICU patients managed with early physical and occupational therapy spent fewer days delirious than those in the control group [23]. No randomized trial to date, however, has examined whether a multicomponent prevention protocol, widely considered beneficial outside the ICU, can prevent delirium in the ICU. Though the risk of implementing such protocols is likely low, the cost may be high so evidence is needed to guide use of prevention protocols.

Antipsychotics

Though not used in the current case, antipsychotics (whether the typical agent, haloperidol, or any one of a number of atypical antipsychotics) are frequently used to treat delirium in the ICU despite a lack of evidence from randomized trials. Two placebo-controlled, randomized trials [24, 25] have now reported that haloperidol was no better than placebo in reducing delirium in the ICU, and one of these also found no benefit with ziprasidone, an atypical antipsychotic [24]. One small trial (N = 36) did suggest that quetiapine hastened resolution of delirium compared with placebo [26], but neither atypical nor typical antipsychotics were recommended in the recent SCCM guidelines [4] given the need for more evidence and the association between these drugs and adverse events in other settings. If used to treat delirium in the ICU, clinicians should consider discontinuing antipsychotics prior to ICU discharge to reduce the likelihood that patients will be unnecessarily discharged from the hospital with a new prescription for one of these medications [27].

Delirium and Long-Term Outcomes

Several observational studies have examined the relationship between delirium in the ICU and long-term outcomes in survivors of critical illness. Initially these studies focused on long-term mortality, finding that (compared with non-delirious patients) those with delirium in the ICU are more likely to die in the months to years after critical illness [28–30]. Though one recent negative study [31] generated some controversy regarding the relationship between delirium and mortality, studies examining delirium as a predictor of long-term cognitive impairment have been consistent—patients with delirium, especially over a prolonged period of time, are at highest risk for long-term cognitive impairment after critical illness [32–34], a poor outcome that is now recognized to affect up the one-third of survivors. It remains unclear whether delirium itself is injurious or is a marker of underlying brain injury, and the mechanisms of brain injury leading to delirium and long-term cognitive impairment have yet to be firmly elucidated. The answers to these questions are critically important given that the most effective prevention and treatment strategies are likely to be those directed at the mechanisms of injury.

References

1. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10):1338–44.
2. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the

Richmond Agitation-Sedation Scale (RASS). JAMA. 2003;289(22):2983–91.
3. Riker RR, Fraser GL, Cox PM. Continuous infusion of haloperidol controls agitation in critically ill patients. Crit Care Med. 1994;22(3):433–40.
4. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263–306.
5. Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med. 1999;27(12):2609–15.
6. Treggiari MM, Romand JA, Yanez ND, Deem SA, Goldberg J, Hudson L, et al. Randomized trial of light versus deep sedation on mental health after critical illness. Crit Care Med. 2009;37(9):2527–34.
7. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286(21):2703–10.
8. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med. 2001;27(5):859–64.
9. Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. Am J Respir Crit Care Med. 2012;186(8):724–31.
10. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet. 2010;375(9713):475–80.
11. Fraser GL, Devlin JW, Worby CP, Alhazzani W, Barr J, Dasta JF, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. Crit Care Med. 2013;41(9 Suppl 1):S30–8.
12. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med. 2000;342(20):1471–7.
13. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet. 2008;371(9607):126–34.
14. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006;104(1):21–6.
15. Pisani MA, Murphy TE, Araujo KLB, Slattum P, Van Ness PH, Inouye SK. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. Crit Care Med. 2009;37(1):177–83.
16. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA. 2007;298(22):2644–53.
17. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301(5):489–99.
18. Zaal IJ, Devlin JW, Peelen LM, Slooter AJ. A systematic review of risk factors for delirium in the ICU*. Crit Care Med. 2015;43(1):40–7.
19. Mehta S, Burry L, Cook D, Fergusson D, Steinberg M, Granton J, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA. 2012;308(19):1985–92.
20. Patel SB, Poston JT, Pohlman A, Hall JB, Kress JP. Rapidly reversible, sedation-related delirium versus persistent delirium in the intensive care unit. Am J Respir Crit Care Med. 2014;189(6):658–65.
21. Inouye SK, Bogardus Jr ST, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med. 1999;340(9):669–76.
22. Van Rompaey B, Elseviers MM, Van Drom W, Fromont V, Jorens PG. The effect of earplugs during the night on the onset of delirium and sleep perception: a randomized controlled trial in intensive care patients. Crit Care. 2012;16(3):R73.
23. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373(9678):1874–82.
24. Girard TD, Pandharipande PP, Carson SS, Schmidt GA, Wright PE, Canonico AE, et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med. 2010;38(2):428–37.
25. Page VJ, Ely EW, Gates S, Zhao XB, Alce T, Shintani A, et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2013;1(7):515–23.
26. Devlin JW, Roberts RJ, Fong JJ, Skrobik Y, Riker RR, Hill NS, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med. 2010;38(2):419–27.
27. Rowe AS, Hamilton LA, Curtis RA, Davis CR, Smith LN, Peek GK, et al. Risk factors for discharge on a new antipsychotic medication after admission to an intensive care unit. J Crit Care. 2015;30(6):1283–6.
28. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell Jr FE, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004;291(14):1753–62.
29. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated

with 1-year mortality in an older intensive care unit population. Am J Respir Crit Care Med. 2009;180(11):1092–7.
30. Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW, et al. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. Crit Care Med. 2010;38(12):2311–8.
31. Klein Klouwenberg PM, Zaal IJ, Spitoni C, Ong DS, van der Kooi AW, Bonten MJ, et al. The attributable mortality of delirium in critically ill patients: prospective cohort study. BMJ. 2014;349:g6652.
32. Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med. 2010;38(7):1513–20.
33. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369(14):1306–16.
34. Wolters AE, van Dijk D, Pasma W, Cremer OL, Looije MF, de Lange DW, et al. Long-term outcome of delirium during intensive care unit stay in survivors of critical illness: a prospective cohort study. Crit Care. 2014;18(3):R125.
35. Ely EW, Dittus RS, Girard TD. Point: should benzodiazepines be avoided in mechanically ventilated patients? Yes. Chest. 2012;142(2):281–4; discussion 9–90.

Prolonged Mechanical Ventilation

28

Thomas Bice and Shannon S. Carson

Case Presentation

A 55 year-old woman with a history of type II diabetes mellitus and hypertension was admitted for acute hypoxemic respiratory failure from acute respiratory distress syndrome (ARDS) secondary to pneumonia and septic shock. She was managed with lung protective ventilation, antibiotics, vasopressors, and supportive care. Her clinical course was complicated by delirium and shock, both of which subsequently resolved, and acute renal failure requiring hemodialysis. On day 14 of mechanical ventilation she followed commands on intermittent analgesic for comfort, but she continued to fail all spontaneous breathing trials. She was scheduled to undergo tracheostomy the next day to facilitate prolonged mechanical ventilation.

Question What approach should guide this patient's ventilator management?

Answer Daily tracheostomy collar trials as long as tolerated

T. Bice (✉) • S.S. Carson
Pulmonary and Critical Care Medicine, University of North Carolina Chapel Hill, Chapel Hill, NC, USA
e-mail: thomas_bice@med.unc.edu

Principles of Management

Diagnosis

Prolonged mechanical ventilation (PMV) is defined as requiring mechanical ventilation for greater than 14–21 days for acute illness or injury. This population comprises 5–10 % of mechanically ventilated patients; their long-term mortality, hospital lengths of stay, and resource utilization are significantly higher than for other mechanically ventilated patients [1–3]. By definition, PMV patients have failed to be weaned from mechanical ventilation in a timely manner using standard approaches. They are often weak with skeletal muscle atrophy, prone to delirium and recurrent infections, and can develop metabolic complications and skin breakdown. Therefore, special consideration to the management of PMV patients is required.

Assess Expected Survival

Because PMV patients have survived the immediate phase of critical illness but often have poor long-term survival, the Provent14 score was developed to predict 1-year mortality in patients requiring PMV [4]. Using 5 simple clinical variables measured on day 14 of ventilation, the Provent14 score can accurately predict the 1-year mortality for this population (Table 28.1). The case patient would receive a score of 3 – 1 point for non-trauma, 1 point for hemodialysis, and 1

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_28

Table 28.1 ProVent14 score and associated mortality

Patient characteristics	Points	Total score	1-year mortality % (95 % CI)
Non-trauma	1	0	4 (0, 9)
Requiring vasopressors	1	1	28 (19, 37)
Requiring hemodialysis	1	2	43 (35, 51)
Platelet count ≤100	1	3	61 (52, 70)
Age 50–64	1	4–6	92 (84, 100)
Age ≥65	2		

Data from Hough et al. [4]

point for her age – and would have an expected 1-year mortality of 61 % (95 % CI 52–70). These data can help inform discussions with the patient or their surrogates about the patient's values and preferences for care.

Place Tracheostomy

If it is consistent with the patient's goals of care, placement of a tracheostomy is suggested for several potential benefits:

(a) Improve patient comfort
(b) Reduce need for sedation or analgesia
(c) Allow for easier oral care and suctioning
(d) Improve weaning from mechanical ventilation
(e) Facilitate earlier rehabilitation, communication, and oral nutrition
(f) Facilitate transfer to lower level of care

Only one small study has addressed the impact of tracheostomy on patient comfort [5]. Among 13 responders, 100 % felt the tracheostomy was more comfortable than an endotracheal tube. Tracheostomy use is increasing over time, likely as a result of accepted consensus recommendations and more convenient bedside approaches [6]. Despite this increase, the best approach to performing a tracheostomy remains unclear. The two most common approaches are percutaneous dilational tracheostomy, using a wire and a series of dilators (Fig. **28.1**), and open surgical tracheostomy. There is little convincing data for the superiority of either approach, but a recent meta-analysis suggests that most outcomes favor percutaneous placement [7].

Daily Tracheostomy Collar Trials

In the only randomized clinical trial of weaning approaches in PMV patients, patients admitted to a long-term acute care hospital (LTAC) were evaluated for readiness for weaning or liberation from mechanical ventilation [8]. On arrival, patients were placed on tracheostomy collar for up to 120 h. The 316 who developed respiratory distress during this screening time were randomized to either daily tracheostomy collar for up to 12 h with assist-control ventilation at night, or gradual reduction of pressure support ventilation. The group randomized to daily tracheostomy trials was liberated from mechanical ventilation 4 days faster than the daily pressure support reduction group (15 days vs 19 days, respectively). Based on this evidence, the best approach to ventilator management for PMV patients is to perform daily tracheostomy trials for as long as the patient can tolerate, with full ventilator support at night, until the patient remains off for 12 h for 2 consecutive days. Then, proceeding with longer tracheostomy collar trials is appropriate.

Early Mobility

All mechanically ventilated patients benefit from efforts to limit sedatives and facilitate early mobility during mechanical ventilation [9, 10]. Implementing protocols to institute early physical therapy is critical to improving outcomes for PMV patients. The ABCDEF bundle, supported by The Society of Critical Care Medicine's ICU Liberation Collaborative, is an example of an approach to bundling evidence-based interventions for limiting sedation, preventing pain and delirium, and facilitating early mobility and communication with patient's families [11–13].

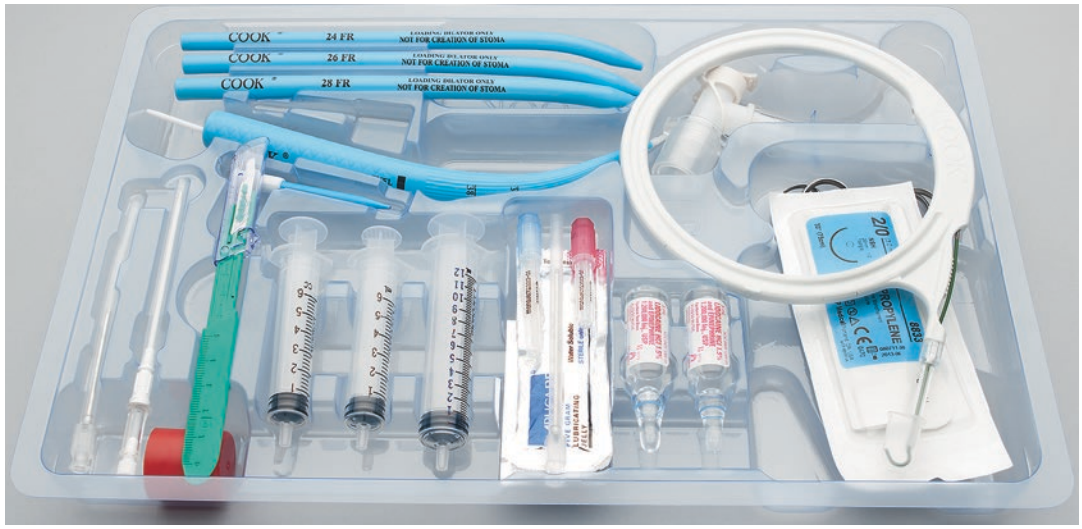


Fig. 28.1 Components of a percutaneous dilational tracheostomy kit (Permission for use granted by Cook Medical, Bloomington, Indiana)

Speaking Valve Trials

One of the most frustrating symptoms for PMV patients is difficulty with communication [14]. Lack of verbal communication causes frustration, powerlessness, and apathy. The design of some speaking valves (Fig. 28.2) permits them to be used in-line with mechanical ventilation, allowing for earlier initiation of communication. In the first study to date, the safety of in-line speaking valves was assessed compared to historical use of speaking valves after weaning from mechanical ventilation [15]. Patients were able to resume verbal communication an average of 9 days earlier, with no impact on duration of mechanical ventilation and no deleterious effects on patient care. Consideration should be given to earlier adoption of speaking valve placement with in-line compatible valves and ventilators.

Tracheostomy Removal

No data exists on the safest process of tracheostomy decannulation, so timing and methods vary by institution. Common techniques include gradual downsizing and use of fenestrated tracheostomy tubes (Fig. **28.3**). In the gradual downsizing method, after the patient is successfully weaned from mechanical ventilation, the tracheostomy tube is downsized to a size 4 or 6 cuffless tube, and the tube is then capped with a speaking valve or other cover. Using a fenestrated tracheostomy tube, one can proceed directly from the initial tracheostomy tube to a fenestrated tube, and then proceed with capping trials. However, the fenestrations can become obstructed, either by secretions or against the posterior wall of the trachea. In this case, one would need to proceed as with a non-fenestrated tube.

Evidence Contour

Timing of Tracheostomy

One of the most controversial topics in caring for the critically ill is the timing of tracheostomy placement. Given the proposed benefits, clinicians might favor placing the tracheostomy as early as possible, but this should be balanced by limiting unnecessary tracheostomy placement. Despite more than 20 randomized controlled trials, there has yet to be a demonstrated benefit of early tracheostomy on mortality, and minimal to no benefit on duration of mechanical ventilation,

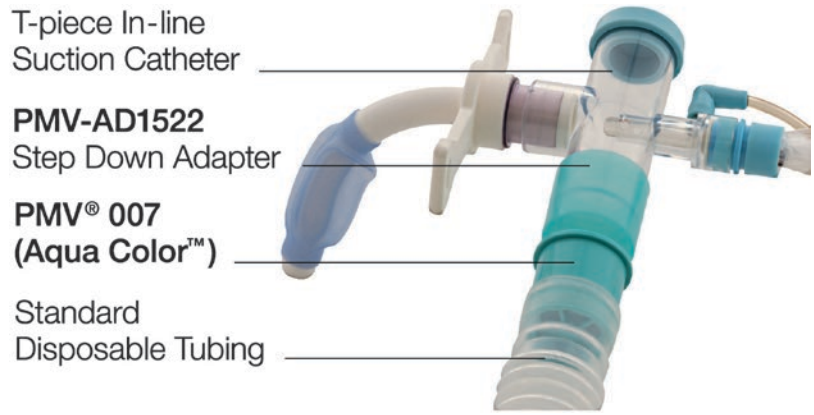


Fig. 28.2 The Passy-Muir® speaking valve for use with tracheostomy, either in-line with the ventilator, or with an aerosol tracheostomy collar (Image courtesy of Passy-Muir, Inc. Irvine, CA)

ICU length of stay, or sedation use. In the largest clinical trial to date, nearly 1000 patients were randomized to either tracheostomy in the first 4 days, or after 10 days. While there was no difference in mortality in the study, the most remarkable outcome was that less than half of patients randomized to late tracheostomy ever received a tracheostomy. This suggests that half the tracheostomies placed in the early group were potentially unnecessary. The available evidence suggests that, despite our inclinations, there is little to no benefit to tracheostomy prior to 10 days of mechanical ventilation. Therefore, we suggest evaluation of the patient's prognosis by the ProVent14 score at day 14, followed by a discussion with the patient and/or their surrogates regarding the expected outcome and the patient's preferences and goals. That sets the appropriate stage for discussions of whether a tracheostomy is indicated.

Benefit of Transfer to LTAC

The use of LTACs has increased dramatically over the last two decades; nationally nearly 5 % of PMV patients are transferred to an LTAC [16, 17]. This practice can lead to a significant reduction in costs and length of stay for the hospital, but it is unclear whether LTAC transfer yields significant savings for the healthcare system as a whole [18, 19]. In one observational study, the costs of an episode of illness — counting time in the referring hospital and referral LTAC — was nearly 50 % higher for patients referred to LTACs compared to those not referred. Total hospital length of stay was also increased by at least 20 days for those referred to an LTAC. In another study that also included time in skilled nursing facilities, LTAC referral resulted in lower actual healthcare costs due to fewer acute hospital readmissions [20]. However Medicare payments were higher for patients referred to LTACs because of the different payment systems. While appealing to hospitals, discharge to LTAC can result in cost-shifting rather than cost reduction, with little change in patient outcome. Yet the goals of LTAC care for this patient population are appropriate. Through coordination of aggressive physical therapy, weaning of mechanical ventilation, nutrition, and nursing care, many LTACs demonstrate a broad patient-centered strategy that should be utilized in all acute care hospitals.

Survivorship Clinics and Symptom Burden

Over the last few years, there has been increased focus on the long-term physical, cognitive, and mental health effects after critical illness – the post-intensive care syndrome (PICS) [21]. Given the longer period of critical illness for PMV patients and their known poor long-term functional outcomes, the impact of PICS is significant and warrants consideration of post-ICU clinics. Some recommendations exist for organization of these clinics, as well as their potential for

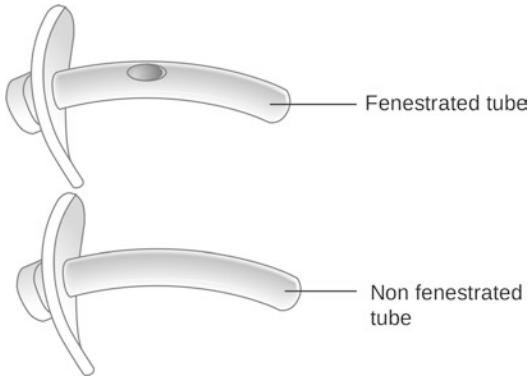


Fig. 28.3 Fenestrated tracheostomy tube This image has been released as part of an open knowledge project by Cancer Research UK. If re-used, attribute to Cancer Research UK/Wikimedia Commons

improvement of posttraumatic stress disorder symptoms. However there are as yet limited data on how they impact clinical outcomes and they are currently not widely utilized [22, 23]. There remains great potential for research into the organization, structure and effectiveness of post-ICU clinics.

References

1. Carson SS. Outcomes of prolonged mechanical ventilation. Curr Opin Crit Care. 2006;12(5):405–11. Epub 2006/09/01.
2. Cox CE, Martinu T, Sathy SJ, Clay AS, Chia J, Gray AL, et al. Expectations and outcomes of prolonged mechanical ventilation. Crit Care Med. 2009;37(11):2888–94; quiz 904. Epub 2009/09/23.
3. Unroe M, Kahn JM, Carson SS, Govert JA, Martinu T, Sathy SJ, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. Ann Intern Med. 2010;153(3):167–75. Epub 2010/08/04.
4. Hough CL, Caldwell ES, Cox CE, Douglas IS, Kahn JM, White DB, et al. Development and validation of a mortality prediction model for patients receiving 14 days of mechanical ventilation. Crit Care Med. 2015;43(11):2339–45. Epub 2015/08/08.
5. Blot F, Similowski T, Trouillet JL, Chardon P, Korach JM, Costa MA, et al. Early tracheotomy versus prolonged endotracheal intubation in unselected severely ill ICU patients. Intensive Care Med. 2008;34(10):1779–87.
6. Mehta AB, Syeda SN, Bajpayee L, Cooke CR, Walkey AJ, Wiener RS. Trends in tracheostomy for mechanically ventilated patients in the United States, 1993–2012. Am J Respir Crit Care Med. 2015;192:446–54.
7. Higgins KM, Punthakee X. Meta-analysis comparison of open versus percutaneous tracheostomy. Laryngoscope. 2007;117(3):447–54. Epub 2007/03/06.
8. Jubran A, Grant BJB, Duffner LA, Collins EG, Lanuza DM, Hoffman LA, et al. Effect of pressure support vs unassisted breathing through a tracheostomy collar on weaning duration in patients requiring prolonged mechanical ventilation: a randomized trial. JAMA J Am Med Assoc. 2013;309(7):671–7.
9. Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med. 2008;36(8):2238–43.
10. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373(9678):1874–82.
11. ICU Liberation. Society of Critical Care Medicine; [cited 2015 5/8/2015]; Available from: http://www.iculiberation.org/Pages/default.aspx.
12. Balas MC, Burke WJ, Gannon D, Cohen MZ, Colburn L, Bevil C, et al. Implementing the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle into everyday care: opportunities, challenges, and lessons learned for implementing the ICU Pain, Agitation, and Delirium Guidelines. Crit Care Med. 2013;41(9 Suppl 1):S116–27. Epub 2013/10/18.
13. Balas MC, Devlin JW, Verceles AC, Morris P, Ely EW. Adapting the ABCDEF bundle to meet the needs of patients requiring prolonged mechanical ventilation in the long-term acute care hospital setting: historical perspectives and practical implications. Semin Respir Crit Care Med. 2016;37(1):119–35. Epub 2016/01/29.
14. Carroll SM. Silent, slow lifeworld: the communication experience of nonvocal ventilated patients. Qual Health Res. 2007;17(9):1165–77. Epub 2007/10/31.
15. Sutt AL, Cornwell P, Mullany D, Kinneally T, Fraser JF. The use of tracheostomy speaking valves in mechanically ventilated patients results in improved communication and does not prolong ventilation time in cardiothoracic intensive care unit patients. J Crit Care. 2015;30(3):491–4. Epub 2015/01/21.
16. Kahn JM, Benson NM, Appleby D, Carson SS, Iwashyna TJ. Long-term acute care hospital utilization after critical illness. JAMA. 2010;303(22):2253–9. Epub 2010/06/10.
17. Kahn JM, Le T, Angus DC, Cox CE, Hough CL, White DB, et al. The epidemiology of chronic critical illness in the United States*. Crit Care Med. 2015;43(2):282–7. Epub 2014/11/08.
18. Hall WB, Willis LE, Medvedev S, Carson SS. The implications of long-term acute care hospital transfer practices for measures of in-hospital mortality and length of stay. Am J Respir Crit Care Med. 2012;185(1):53–7. Epub 2011/09/24.
19. Kandilov AMG, Dalton K. Utilization and payment effects of medicare referrals to long-term care hospitals. 2011; Available from: http://www.rti.org/reports/cms/kennell/CMS_LTCH_Referral_Effects.pdf.

20. Kahn JM, Werner RM, David G, Ten Have TR, Benson NM, Asch DA. Effectiveness of long-term acute care hospitalization in elderly patients with chronic critical illness. Med Care. 2013;51(1):4–10. Epub 2012/08/10.
21. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40(2):502–9. Epub 2011/09/29.
22. Mehlhorn J, Freytag A, Schmidt K, Brunkhorst FM, Graf J, Troitzsch U, et al. Rehabilitation interventions for postintensive care syndrome: a systematic review. Crit Care Med. 2014;42(5):1263–71. Epub 2014/01/15.
23. Van Der Schaaf M, Bakhshi-Raiez F, Van Der Steen M, Dongelmans DA, De Keizer NF. Recommendations for intensive care follow-up clinics; report from a survey and conference of Dutch intensive cares. Minerva Anestesiol. 2015;81(2):135–44. Epub 2014/05/16.

Ventilator-Associated Pneumonia and Other Complications

29

Jennifer P. Stevens and Michael D. Howell

Case Presentation

A 55-year-old woman with a history of type 2 diabetes mellitus, chronic obstructive pulmonary disease, obesity hypoventilation syndrome, and sleep apnea, along with coronary artery disease with a 3-vessel bypass five years prior, developed new onset shortness of breath and fever after babysitting her 3-year-old grandchild. She arrived at the emergency room with worsening respiratory status. Her ventilation rapidly deteriorated despite the use of noninvasive positive pressure ventilation and she became minimally responsive, prompting endotracheal intubation and admission to the medical intensive care unit. A chest x-ray at that time showed a lobar infiltrate. Cultures from endotracheal aspirates were negative. After three days of management of her COPD with intravenous steroids, antibiotic coverage with levofloxacin, and inhaled bronchodilator therapy, her oxygenation continued to improve. She continued to fail her spontaneous breathing trial, however, and remained intubated. On ICU day 5, however, she developed a new fever and her oxygenation worsened. Having previously been down to an FiO_2 of 0.3, this fraction was increased to 0.5, and her PEEP was increased to 10 cm from 5 cm of water to maintain adequate oxygenation. A chest xray now shows diffuse, bilateral infiltrates (Fig. 29.1).

Question What is this patient's diagnosis?

Answer Ventilator-Associated Pneumonia (VAP)

Despite aggressive and supportive management, pneumonias that arise from hospital settings remain a challenging and enduring clinical entity. Ventilator-associated pneumonia is defined as pneumonia in those patients who have been intubated for at least two to three days, with worsening radiographic features, increasing secretions, bronchospasm, or hemoptysis, or with worsening status on the ventilator. While early treatment is essential, rapid de-escalation of antibiotics in the face of negative culture results is also important. Sampling of the respiratory tract is necessary to further guide management and noninvasive sampling is preferred [1]. Samples may be obtained either through tracheobronchial aspiration, bronchoalveolar lavage, mini-BAL, or protected specimen brush (PSB). Careful observation of individual hospitals' bacterial antibiogram is essential to provide treatment targeted to the resistance profile of each institution. The most common MDR pathogens include *P. aeruginosa, Escheriochia coli, Klebsiella pneumonia,* and *Acinetobacter* species as well as methicillin-resistant *S. aureus* [2].

J.P. Stevens
Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

M.D. Howell (✉)
Center for Healthcare Delivery Science and Innovation, University of Chicago Medicine, Chicago, IL, USA
e-mail: mdh@uchicago.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_29

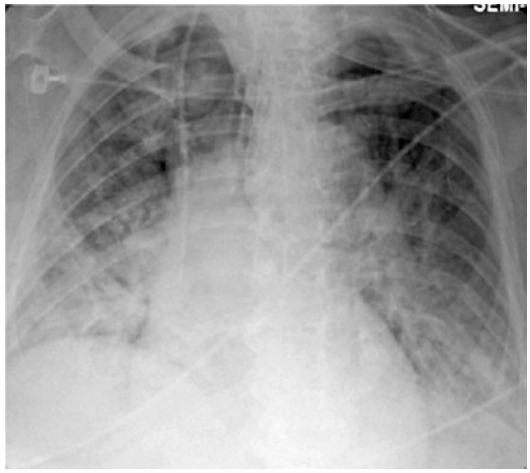


Fig. 29.1 Chest xray on ICU day 5

Principles of Management

Rapid Identification and Empiric Treatment of VAP Is Essential

A high suspicion for VAP followed by rapid diagnosis and treatment is critically important. Zilberberg and colleagues found that among nearly 400 patients alive at 48 h with HCAP, inappropriate empiric antibiotic therapy was associated with a significant increase in mortality (30 % versus 18.3 %, p = 0.013; OR 2.88 95 % CI 1.46–5.67 in multivariable logistic regression). Treatment escalation did not change the risk of death in this single-center study [3]. Unfortunately, treatment is often delayed. In one study among 107 patients, 30.7 % of patients had their therapy for VAP inappropriately delayed, defined as ≥ 24 h passing between VAP onset and providing the appropriate antimicrobial treatment. A delay in writing the antibiotic orders was the primary reason for delay in therapy in 75 % of cases [4].

Treat Patients with VAP Broadly for Multidrug Resistant Organisms

Patients with VAP should universally initiated on therapy for (1) MRSA (for example, with vancomycin or linezolid) and for (2) resistant gram-negatives, such as *Pseudomonas aeruginosa, Klebsiella pneumoniase,* and *Acinetobacter* species. Treatment options could include: antipseudomonal cephalosporins (cefepime or ceftazidime), antipseudomonal carbapenems (imipenem or meropenem), β-Lactam/β-lactamase inhibitor (piperacillin-tazobactam). For patients for whom combination therapy is considered (see Evidence Contour below), addition of an antipseudomonal flouroquinolone or an aminoglycoside should be considered. The dominant pathogens in one's local ICU should also contribute to decision making for appropriate choices of therapy but should be guided by the overall principles of the ATS/IDSA guidelines, as demonstrated by the IMPACT HAP collaboration [5, 6].

In addition to MDR risk factors, appropriate antimicrobial therapy should consider the patient's risk factors for: (1) extended-spectrum beta-lactamase-producing *Enterobactereriaceae*; (2) *Legionella*; and (3) anaerobes. If ESBL *Enterobactereiaceae* is suspected, a carbapenem should be used. Concerns about *Legionella* should prompt use of a macrolide or fluroquinolone over an aminoglycoside. Some providers would treat patients with recent aspiration events for anaerobes, using clindamycin, β-Lactam/β--lactamase inhibitors, or a carbapenem.

For all other patients for whom the suspicion of VAP is low, appropriate therapy should be guided by the patient's risk factors for multidrug resistant organisms. In the absence of risk factors for MDR organisms, the ATS/IDSA guidelines recommend antibiotic therapy that targets *Streptococcus pneumonia, Haemophilus influenza,* Methicillin-sensitive *Staphylococcus aureus*, and antibiotic-sensitive enteric gram negatives: ceftriaxone or levofloxacin, moxifloxacin, or ciprofloxacin, ampicillin/sulbactam or ertapenem [2]. While not all patients with HCAP have MDR organisms, distinguishing between the two may be difficult with recent residence in a nursing home or hospitalization for more than 48 h in the past 3 months appearing to increase the patient's risk the most [7, 8].

Duration of Therapy – 8 or 15 Days

Patients with ventilator-associated pneumonia should have the duration of antimicrobial therapy

guided by type of organism. In a study of 401 patients using a randomized controlled design, there was no difference in mortality in the arm treated for 8 days versus 15 days, although patients with *Pseudomonas* spp. had higher rates of recurrence [9]. A subsequent meta-analysis demonstrated patients with lactose non-fermenting gram-negative bacilli had nearly a 2-fold increased odds of recurrence with shorter therapy courses [10]. However, more recent systematic reviews and the ATS/IDSA 2016 guideline [2] has challenged this distinction. The current recommendation for all VAP, including non-fermenting gram-negative bacilli, is to treat for a short course (7 or 8 days) [11].

Rapidly De-Escalate Antimicrobial Therapy

It is critical to de-escalate antimicrobial therapy when a specific pathogen has been identified, or when cultures are negative at around 72 h. This helps prevent over-use of antibiotics and the development of resistance. Observational data provide a strong safety signal. In a study of surgical patients, neither mortality (34 % versus 42 %) nor recurrent pneumonias (27 % versus 35 %) differed between patients with VAP who underwent de-escalation versus those who did not [12]. Among 398 patients with VAP in Kollef et al., de-escalation of therapy occurred for 22 % of patients. These patients had a lower mortality rate (17 %) than those patients who underwent escalation (43 %) or who had not change to their regimens (24 %) [13].

Another possible guide to safely de-escalate antibiotic therapy may be procalcitonin levels. In subgroup analyses of the PRORATA trial, investigators found that patients with ventilator-associated pneumonia assigned to the study arm (where antibiotics were discontinued after procalcitonin levels reached <0.5 μg) had 3.1 fewer days (95 % CI 0.7 days – 5.6 days) than those patients assigned to the control arm, without a difference in mortality found in the overall study [14]. Other studies that have looked at procalcitonin to guide therapy for undifferentiated septic shock or in broader settings have replicated that mortality does not appear to be affected when procalcitonin is used to guide therapy, although the findings on duration of antibiotics is more heterogeneous [15, 16]. Current recommendations, however, are to continue to use clinical evidence rather than biomarkers [2].

Clinicians Should Remain Vigilant for Other Causes of Fever in the ICU

Not all fevers are pneumonia, even in ICU patients with radiographic infiltrates. If patients are not improving at 48–72 h and respiratory cultures taken before antibiotics are negative, be vigilant for other causes of fever (such as central line infections, etc.) and for complications of pneumonia (such as empyema). This scenario should also prompt reconsideration of the potential presence of resistant pathogens, and it may warrant consultation with infectious disease specialists.

Evidence Contour

Invasive Versus Noninvasive Sampling Strategies

In all patients with suspected VAP, obtain an endotracheal aspirate for culture at minimum. Whether to pursue bronchoscopic sampling (or other invasive techniques) is more controversial. Endotracheal aspirates are very sensitive – a negative result is quite helpful because it has a high negative predictive value. Positive results can be harder to interpret. In one study, in 52 episodes of pneumonia, endotracheal aspirate was found to have a sensitivity of 97.7 % and specificity of 50 % as compared with protected brush specimen [17]. Other studies have employed the Clinical Pulmonary Infection Score (CPIS) with a cut-off of 6 as a noninvasive method of identifying patients with VAP, using autopsy findings of pneumonia as the gold standard (Table 29.1) [18]. Fabregas et al. found a score of greater than 6 had a sensitivity of 77 % but a specificity of 42 % [19]. Conversely, bronchoscopic sampling may be less sensitive but is more specific for pneumonia. Randomized

Table 29.1 Calculation of the clinical pulmonary infection score (CPIS)

Parameter		Points
Temperature	36.5–38.4	0
	38.5–38.9	1
	≥39.0 and ≤36.0	2
Blood leukocytes/mm^3	4000–11,000	0
	<4000 or >11,000	1
	Above + band forms ≥500	2
Tracheal secretions	<14+	0
	≥14+	1
	Above plus purulence	2
Oxygenation, PaO_2:FiO_2, mmHg	>240 or ARDS	0
	≤240 and no ARDS	2
Pulmonary radiograph finding	No infiltrate	0
	Diffuse or patchy infiltrate	1
	Localized infilitrate	2
Culture of tracheal aspirate specimen	Pathogenic bacteria cultured ≤1 or growth	0
	Pathogenic bacteria culture >1+	1
	Above plus same bacteria on gram stain >1+	2

The score may be calculated as a noninvasive method of determining whether a patient is a low-risk for pneumonia. A score of more than 6 has a 77 % sensitivity and 42 % specificity to identify VAP [19]

controlled trials are mixed. An RCT of 413 patients found no benefit to invasive sampling in unadjusted analyses, but did after adjustment for baseline factors [20]. A more recent RCT of 740 patients found no benefit to bronchoalveolar lavage over endotracheal aspirate [21]. Our practice is to perform immediate endotracheal aspirate in all patients with suspected VAP, but to reserve bronchoalveolar lavage or protected brush for selected cases.

Effective Treatment Strategies for MRSA VAP

The current recommendation from the ATS/IDSA is for coverage with either (1) 15 mg/kg of vancomycin every 12 h with a target serum trough between 15 and 20 mg/kg OR (2) 600 mg of linezolid. One major prospective trial of 1184 patients, however suggested that linezolid may be superior to vancomycin. In this study, 46 % of patients treated with vancomycin had cultures persistently positive for MRSA, while only 17 % of patients treated with linezolid did. At 60 days, however, there was no difference in mortality rates, although nephrotoxicity did occur at greater rates with vancomycin [22]. As research in this space continues to evolve, linezolid may be a particularly good option among patients with renal failure, although current guidelines suggest either therapy for treatment.

Utility of ATS/IDSA Recommendations for Dual Gram-Negative Coverage

Coverage with a second agent for gram-negative bacilli may be warranted based on local microbiologic patterns and was recommended by the 2005 recommendations for VAP treatment by the ATS/IDSA [2]. Current recommendations from the 2016 update are to prescribe 2 antipseudomonal antibiotics when patients have risk factors for antimicrobial resistance, when the prevalence of gram-negative isolates resistant to the proposed monotherapeutic agent exceds 10 %, and when antimicrobial susceptibaility rates are unavailable [2]. However, it is worth noting that synergy of medications has only been demonstrated *in vitro* and in neutropenic or bacteremic patients and one randomized controlled trial did not demonstrate differences in clinical outcomes between monotherapy and combination therapy groups [6, 23, 24]. An observational cohort study in *Lancet* suggested combination therapy may be harmful, as the cohort of patients with ATS/IDSA-compliant antimicrobial therapy had a higher risk of death at 28 days than the noncompliant group [25]. This remains controversial, whether these individuals were at higher risk of death from the medications, the infections, or misidentification of them as at higher risk for MDR infection. Further research will be necessary to identify who, if anyone, should be receiving such broad antibiotic coverage from the outset.

Evolving Surveillance Definitions

While clinical suspicion and identification of ventilator-associated pneumonia should remain high, significant controversy has revolved around establishing a reliable epidemiological surveillance definition. Prior to January 2013 the Centers for Disease Control's surveillance reporting definition the included several subjective components, including the change in the "character of sputum" and in radiographs [26–30]. As a result, several studies identified little agreement either across infection control experts at a single institution [31] or across multiple institutions [32]. Other definitions that sought to identify episodes of VAP either through greater invasive strategies or through other scoring mechanisms fared equally poorly [33].

In response, an effort of many professional societies and the CDC generated an alternative approach with the creation of the entity Ventilator Associated Event (VAE) [34]. Intended to cast a broader net, this newly-defined condition is intended to identify the majority of iatrogenic harm from mechanical ventilation, including but not limited to pneumonia [35, 36]. Further, it is designed to be reliable as it is solely based on any changes made to the ventilator that would indicate worsening oxygenation after a period of stability and at least three days into the course of mechanical ventilation. Review of radiology has been removed from the definition. There are subsequent sub-categories of harm, including probably or possible pneumonia, which are based on antibiotic changes and evidence of positive qualitative or quantitative cultures. (Table 29.2) [34].

While several studies have shown that this definition does lead to a reliable identification of individuals at higher risk of in-hospital mortality, it remains unclear the breadth of true disease states captured by definition [37, 38]. Lilly and colleagues found that the new VAE definition captured neither pneumonias nor hospital-acquired complications 93% of the time [39]. In contrast, Boudma and colleagues found ventilator-associated condition to be reasonably sensitive at identifying episodes of VAP (0.92) but not specific (0.28) [40]. Further, Adult Respiratory Distress Syndrome is likely to be captured alongside VAP under the larger label of VAE [39, 41]. The first major intervention study to date designed to attempt to reduce rates of VAE demonstrated found spontaneous awakening trials and spontaneous breathing trials

Table 29.2 National Health Safety Network definition of Ventilator-Associated Event

Type of ventilator-associated event	Definition
Ventilator-associated condition (VAC)	Either: 1. An increase in daily minimum $FiO_2 \geq 0.20$ OR 2. An increase in daily minimum PEEP values of ≥3 cm H_2O Either must be sustained for 2 or more calendar days
Infection-related ventilator-associated condition (iVAC)	VAC PLUS 1. Temperature >38° or <36° OR WBC ≥12,000 cells/mm^3 or ≤4,000 cells/mm^3 AND 2. A new antimicrobial started and continued for 4 or more days
Possible ventilator associated pneumonia	iVAC PLUS 1. Purulent respiratory secretions OR 2. A positive qualitative, semi-qualitative, or quantitative culture of sputum, endotracheal aspirate, bronchoalveolar lavage, lung tissue or protected specimen brushing
Probable ventilator associated pneumonia	iVAC PLUS 1. Purulent respiratory secretions AND a positive semi-quantitative, or qualitative culture of sputum, endotracheal aspirate, bronchoalveolar lavage, lung tissue or protected specimen brushing OR 2. A positive pleural fluid culture, positive lung histopathology, a positive diagnostic test for Legionella spp., a positive test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus

A patient must be intubated with stable ventilator settings for 2 or more days before this may be applied

Table 29.3 Recommendations from the Society of Healthcare Epidemiology of America and the Infectious Disease Society of America's 2014 updated recommendations for VAP prevention [36]

Recommendation	Level of recommendation
Minimizing sedation and assessing readiness to extubate daily through pairing spontaneous breathing trials and spontaneous awakening trials, which have been shown in two randomized control trials and one meta-analysis to reduce length of stay and duration of mechanical ventilation [43–46]	HIGH
Instituting early mobilization and physical therapy, which has been shown to decrease length of stay and improve earlier return to independent function [47]	MODERATE
Implementing strategies to reduce pooling of secretions above the endotracheal tube cuff, such as using endotracheal tubes with subglottic suctioning for patients requiring mechanical ventilation of 48 h or more [48–50]. A meta-analysis demonstrated reduction in VAP rates and length of mechanical ventilation [51]	MODERATE
Changing ventilator circuits only when needed rather than on a schedule, which does little to decrease VAPs but does reduce costs [52]	HIGH
Making use of noninvasive positive pressure ventilation (NIPPV) whenever possible, but only in the populations which have been shown to have some benefit (*e.g.* in chronic obstructive pulmonary disease or cardiogenic pulmonary edema) [53]. This recommendation, however, cautions use of NIPPV that may delay intubation, such as profound hypoxemia, acute respiratory distress syndrome or impaired consciousness [54]	HIGH
Keeping the head of the bed elevated to at least 30°, which has only been shown to decrease VAP rates in one of three randomized control trials, but has little downside [55–57]	LOW

to be effective [42]. However, this remains a significant area of evolving science.

New and Old Strategies to Prevent VAP

Other modifiable risk factors for patients with VAP should be considered, in an effort to minimize the likelihood of developing VAP at the outset. These were described in a recent update on preventing ventilator associated pneumonia by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Disease Society of America (IDSA) and are summarized in Table 29.3 [36].

References

1. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, et al. Management of adults with hospital-acquired and ventilator-assocated pneumonia: 2016 clinical practice guidelines by the infectious disease Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63:1–51.
2. American Thoracic S, Infectious Diseases Society of A. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171(4):388–416.
3. Zilberberg MD, Shorr AF, Micek ST, Mody SH, Kollef MH. Antimicrobial therapy escalation and hospital mortality among patients with health-care-associated pneumonia: a single-center experience. Chest. 2008;134(5):963–8.
4. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest. 2002;122(1):262–8.
5. Mangino JE, Peyrani P, Ford KD, et al. Development and implementation of a performance improvement project in adult intensive care units: overview of the Improving Medicine Through Pathway Assessment of Critical Therapy in Hospital-Acquired Pneumonia (IMPACT-HAP) study. Crit Care. 2011;15(1):R38.
6. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society, November 1995. Am J Respir Crit Care Med. 1996;153(5):1711–25.
7. Shorr AF, Zilberberg MD, Reichley R, et al. Validation of a clinical score for assessing the risk of resistant pathogens in patients with pneumonia presenting to

the emergency department. Clin Infect Dis. 2012;54(2):193–8.
8. Aliberti S, Di Pasquale M, Zanaboni AM, et al. Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia. Clin Infect Dis. 2012;54(4):470–8.
9. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA. 2003;290(19):2588–98.
10. Pugh R, Grant C, Cooke RP, Dempsey G. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. Cochrane Database Syst Rev. 2011;(10):CD007577.
11. Dimopoulos G, Poulakou G, Pneumatikos IA, Armaganidis A, Kollef MH, Matthaiou DK. Short- vs long-duration antibiotic regimens for ventilator-associated pneumonia: a systematic review and meta-analysis. Chest. 2013;144:1759–67.
12. Eachempati SR, Hydo LJ, Shou J, Barie PS. Does de-escalation of antibiotic therapy for ventilator-associated pneumonia affect the likelihood of recurrent pneumonia or mortality in critically ill surgical patients? J Trauma. 2009;66(5):1343–8.
13. Kollef MH, Morrow LE, Niederman MS, et al. Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. Chest. 2006;129(5):1210–8.
14. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet. 2010;375(9713):463–74.
15. Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med. 2011;171(15):1322–31.
16. Shehabi Y, Sterba M, Garrett PM, et al. Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. Am J Respir Crit Care Med. 2014;190(10):1102–10.
17. Rumbak MJ, Bass RL. Tracheal aspirate correlates with protected specimen brush in long-term ventilated patients who have clinical pneumonia. Chest. 1994;106(2):531–4.
18. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med. 2000;162(2 Pt 1):505–11.
19. Fabregas N, Ewig S, Torres A, et al. Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. Thorax. 1999;54(10):867–73.
20. Fagon JY, Chastre J, Wolff M, et al. Invasive and non-invasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. Ann Intern Med. 2000;132(8):621–30.
21. The Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med. 2006;355(25):2619–30.
22. Wunderink RG, Niederman MS, Kollef MH, et al. Linezolid in methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a randomized, controlled study. Clin Infect Dis. 2012;54(5):621–9.
23. Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for Pseudomonas aeruginosa bacteremia: outcome correlations in a prospective study of 200 patients. Am J Med. 1989;87(5):540–6.
24. Heyland DK, Dodek P, Muscedere J, Day A, Cook D, Canadian Critical Care Trials G. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. Crit Care Med. 2008;36(3):737–44.
25. Kett DH, Cano E, Quartin AA, et al. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. Lancet Infect Dis. 2011;11(3):181–9.
26. Klompas M. Does this patient have ventilator-associated pneumonia? JAMA. 2007;297(14):1583–93.
27. Klompas M. Ventilator-associated pneumonia: is zero possible? Clin Infect Dis. 2010;51(10):1123–6.
28. Klompas M. The paradox of ventilator-associated pneumonia prevention measures. Crit Care. 2009;13(5):315.
29. Klompas M. Eight initiatives that misleadingly lower ventilator-associated pneumonia rates. Am J Infect Control. 2012;40(5):408–10.
30. CDC. Ventilator-Associated Pneumonia (VAP) Event. 2009; PNEU definitions from CDC. 2011. Available at: http://www.cdc.gov/nhsn/PDFs/pscManual/6pscVAPcurrent.pdf. Accessed 24 May 2011.
31. Klompas M. Interobserver variability in ventilator-associated pneumonia surveillance. Am J Infect Control. 2010;38(3):237–9.
32. Stevens JP, Kachniarz B, Wright SB, et al. When policy gets it right: variability in U.S. Hospitals' diagnosis of ventilator-associated pneumonia*. Crit Care Med. 2014;42(3):497–503.
33. Minei JP, Hawkins K, Moody B, et al. Alternative case definitions of ventilator-associated pneumonia identify different patients in a surgical intensive care unit. Shock. 2000;14(3):331–6; discussion 336–7.
34. CDC. Improving surveillance for ventilator-associated events in adults. 2013. http://www.cdc.gov/nhsn/PDFs/vae/CDC_VAE_CommunicationsSummary-for-compliance_20120313.pdf. Accessed 26 March 2013.
35. Klompas M. Ventilator-associated conditions versus ventilator-associated pneumonia: different by design. Curr Infect Dis Rep. 2014;16(10):430.
36. Klompas M, Branson R, Eichenwald EC, et al. Strategies to prevent ventilator-associated pneumonia

in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35(8):915–36.
37. Stevens JP, Silva G, Gillis J, et al. Automated surveillance for ventilator-associated events. Chest. 2014;146(6):1612–8.
38. Klompas M, Kleinman K, Murphy MV. Descriptive epidemiology and attributable morbidity of ventilator-associated events. Infect Control Hosp Epidemiol. 2014;35(5):502–10.
39. Lilly CM, Landry KE, Sood RN, et al. Prevalence and test characteristics of national health safety network ventilator-associated events. Crit Care Med. 2014;42(9):2019–28.
40. Bouadma L, Sonneville R, Garrouste-Orgeas M, et al. Ventilator-associated events: prevalence, outcome, and relationship with ventilator-associated pneumonia. Crit Care Med. 2015;43:1798–806.
41. Magill SS, Rhodes B, Klompas M. Improving ventilator-associated event surveillance in the National Healthcare Safety Network and addressing knowledge gaps: update and review. Curr Opin Infect Dis. 2014;27(4):394–400.
42. Klompas M, Anderson D, Trick W, et al. The preventability of ventilator-associated events. The CDC Prevention Epicenters Wake Up and Breathe Collaborative. Am J Respir Crit Care Med. 2015; 191(3):292–301.
43. Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA. 2012;308(19): 1985–92.
44. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet. 2008;371(9607): 126–34.
45. Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med. 1996;335(25):1864–9.
46. Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Engl J Med. 1995;332(6):345–50.
47. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373(9678):1874–82.
48. Lacherade JC, De Jonghe B, Guezennec P, et al. Intermittent subglottic secretion drainage and ventilator-associated pneumonia: a multicenter trial. Am J Respir Crit Care Med. 2010;182(7):910–7.
49. Shorr AF, O'Malley PG. Continuous subglottic suctioning for the prevention of ventilator-associated pneumonia : potential economic implications. Chest. 2001;119(1):228–35.
50. Hallais C, Merle V, Guitard PG, et al. Is continuous subglottic suctioning cost-effective for the prevention of ventilator-associated pneumonia? Infect Control Hosp Epidemiol. 2011;32(2):131–5.
51. Muscedere J, Rewa O, McKechnie K, Jiang X, Laporta D, Heyland DK. Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: a systematic review and meta-analysis. Crit Care Med. 2011;39(8):1985–91.
52. Dreyfuss D, Djedaini K, Weber P, et al. Prospective study of nosocomial pneumonia and of patient and circuit colonization during mechanical ventilation with circuit changes every 48 hours versus no change. Am Rev Respir Dis. 1991;143(4 Pt 1):738–43.
53. Hess DR. Noninvasive positive-pressure ventilation and ventilator-associated pneumonia. Respir Care. 2005;50(7):924–9; discussion 929–31.
54. Carron M, Freo U, BaHammam AS, et al. Complications of non-invasive ventilation techniques: a comprehensive qualitative review of randomized trials. Br J Anaesth. 2013;110(6):896–914.
55. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet. 1999; 354(9193):1851–8.
56. van Nieuwenhoven CA, Vandenbroucke-Grauls C, van Tiel FH, et al. Feasibility and effects of the semi-recumbent position to prevent ventilator-associated pneumonia: a randomized study. Crit Care Med. 2006;34(2):396–402.
57. Keeley L. Reducing the risk of ventilator-acquired pneumonia through head of bed elevation. Nurs Crit Care. 2007;12(6):287–94.

Respiratory Failure in a Patient with Idiopathic Pulmonary Fibrosis

30

Ryan Hadley

Case Presentation

A 65 year old gentleman with Idiopathic Pulmonary Fibrosis (IPF) diagnosed 2 years prior by imaging and surgical lung biopsy is evaluated for acute on chronic shortness of breath. Previously he was able to take care of his activities of daily living with supplemental oxygen administered by nasal cannula at 4 l/min. One day prior to presentation his breathlessness rapidly escalated over the course of a day, with inability to ambulate or bathe, prompting evaluation. He had no fevers, sick exposures, change in his baseline cough, or lower extremity edema. He is on no treatment other than oxygen for his condition.

Upon evaluation in the emergency room he is noted to require 100 % oxygen to maintain his oxygen saturation, although saturation continued to fall with minimal movement. Arterial blood gas showed a pH of 7.5, PCO2 of 44, PaO2 of 65 with saturation of 91 % on 100 % oxygen by face mask. His hypoxemia continued to worsen and he required invasive mechanical ventilation. He was admitted to the intensive care unit (ICU).

On evaluation, beta naturetic peptide and echocardiogram were normal and he was without signs of volume overload. White blood cell count was elevated to 14,000 per mm^3 (normal 4,000–10,000 per mm^3). A computed tomography of the chest was completed and lung windows are shown in Fig. 30.1 alongside his baseline CT scan. Contrast to enhance the pulmonary vasculature showed no evidence of venothromboembolism. Bronchoscopy is completed and alveolar lavage was negative for infectious organisms including respiratory virus polymerase chain reaction (PCR).

Question What is the likely diagnosis?

Answer The patient has most likely suffered an acute exacerbation of IPF (AE-IPF).

The triggers as well as etiologies for AE-IPF are not known. The cardinal features are acute clinical worsening (<30 days) in a patient with known or newly diagnosed IPF with acceleration of dyspnea and/or hypoxemia and new radiologic changes, typically ground glass opacities, on a background of fibrotic disease (example Fig. 30.1) [1, 2]. The underlying pathologic insult is classically described as diffuse alveolar damage [3], the histologic finding of ARDS, which has been superimposed on usual interstitial pneumonia. Common concomitant symptoms mimic a viral lower respiratory tract infection with fever, malaise, flu like symptoms and cough; though these symptoms are not needed to make the diagnosis [1, 2]. Infection is the chief differential diagnosis. Ideally, infection is excluded by bronchoalveolar lavage (BAL) as in the case presentation; how-

R. Hadley
Pulmonary and Critical Care Medicine, Spectrum Health, Grand Rapids, MI, USA
e-mail: ryan.hadley@spectrumhealth.org

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_30

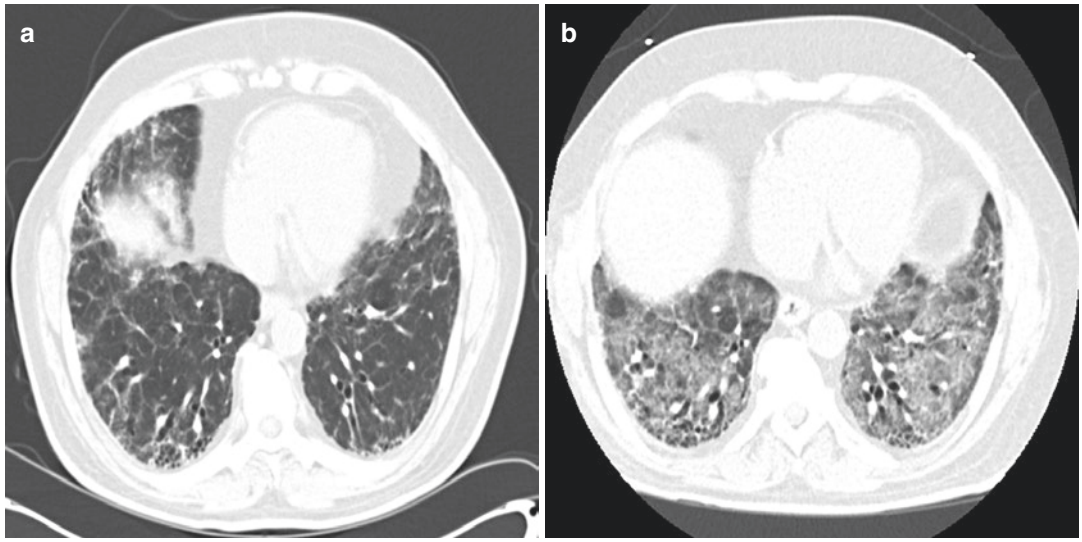


Fig. 30.1 (**a**) Baseline CT scan of patient with basal predominant interlobular septal thickening and traction bronchiechtasis and mild (lower right lung) honeycombing typical of IPF. (**b**) CT scan of the same patient after presentation for acute on chronic dyspnea and worsened hypoxemia

ever given the worsening hypoxemia in addition to typical poor baseline pulmonary health a BAL may precipitate a life-threatening impairment in gas exchange. If the lower airways cannot be sampled by BAL, treatment for typical bacterial organisms or hospital acquired organisms if applicable are employed presumptively. If structural lung disease exists (as most patients usually have traction bronchiectasis) it may be worthwhile to treat *Pseudomonas* on an empiric basis. Other conditions that need to be excluded are pneumothorax, pulmonary hypertension, left ventricular failure from systolic or diastolic dysfunction, pulmonary embolism, or acute respiratory distress syndrome of other known causes (i.e. sepsis, pancreatitis, trauma, pneumonia. For more detail see Chap. 21). Cross-sectional imaging is used to rule out small pneumothorax not seen as well as to confirm radiologic changes, which usually are ground glass in appearance, but dense infiltrates can also be seen. A CT pulmonary angiogram has the advantage of evaluating for pulmonary embolus in patients without renal failure.

In sum, AE-IPF is diagnosed when a patient with IPF has acute worsening of dyspnea and/or hypoxemia as well as new ground glass opacities on CT after exclusion of the conditions below. Diffuse alveolar damage is the typical underlying histopathology.

Principles of Management

Incidence and Prognosis

Based on prospective trials of IPF the incidence of AE-IPF can be estimated. The incidence of acute exacerbation and IPF is approximately 2–14 % per year [4–6]. Acute exacerbations are often devastating. If patients require mechanical ventilation, mortality has been reported to be 78–86 % [7, 8]. Some authors have proposed that this condition is futile and these patients should not receive critical care intervention such as mechanical ventilation [9, 10]. Others have argued and shown that even short term survival allows a window for pulmonary transplantation [8]. An accurate diagnosis is of utmost importance to exclude reversible causes.

Pathologic insult: The classical description of pathologic insult due to acute exacerbation of IPF is diffuse alveolar damage [3], which is the same as ARDS, but here is superimposed on the pathological findings of idiopathic pulmonary fibrosis: usual interstitial pneumonia.

Corticosteroids

As idiopathic pulmonary fibrosis is a rare condition, and acute exacerbations occur spontaneously and abruptly, large prospective randomized trials evaluating treatment are lacking. Expert consensus recommends treatment with corticosteroids though recommended dosage has not been established [11]. Dosing ranges from Solu-Medrol of 1 mg/kg up to "pulse" doses of 1000 mg per day [1]. It is our practice to use 2 mg/kg/day of Solu-Medrol in divided doses similar to what has been used in ARDS [12], given the similar underlying histopathologic insult.

Supportive Care

Supportive care is essential for treatment of idiopathic pulmonary fibrosis given the lack of evidence-based therapies. Mechanical intubation is typically needed but, noninvasive ventilation can be attempted (see below). While evaluation for conditions listed in Table 30.1 is suggested, this is not always possible in a given patient. Presumptive treatment with antibacterial agents and diuretics in conjunction with systemic corticosteroids are typically administered unless significant contraindications exist. Heparin can also be considered if pulmonary embolism cannot be adequately excluded.

Palliative Care

Acute exacerbation of idiopathic pulmonary fibrosis is often in terminal event. Patients and family should be made aware of this poor prognosis to allow appropriate decisions about possibly limiting intensive care interventions. Ideally, goals of care planning would occur in the outpatient setting prior to clinical worsening. In patients who are not transplant candidates, palliative care is often a valid choice [9].

Table 30.1 Conditions to be excluded in the diagnosis of AE-IPF

Pneumothorax
Cardiogenic pulmonary edema
Pulmonary embolus
Identifiable cause of acute lung injury or ARDS
Lower respiratory tract infection
Pulmonary hypertension

Ensure Correct Diagnosis

The diagnosis of acute exacerbation of IPF is in the domain of the intensivist. However diagnosis and management of idiopathic pulmonary fibrosis is usually the realm of the pulmonologist. Ensuring that the patient has an accurate diagnosis of idiopathic pulmonary fibrosis is critical to determining prognosis for the underlying condition. Fibrotic lung disease associated with collagen-vascular disease, such as polymyositis, has also been associated with acute exacerbations, and may have a better prognosis [13]. Many pulmonologists who are less familiar with interstitial lung diseases often incorrectly attribute all types of lung fibrosis to idiopathic pulmonary fibrosis [14]. Given the disparate outcomes, accurate discrimination of IPF from other fibrotic lung diseases is critical. Clues on CT scan suggesting the diagnosis of IPF are lower lung, subpleural predominance of interlobular septal thickening with honeycombing and traction bronchiectasis (see Fig. 30.1) [11]. In IPF patients without an acute exacerbation, ground glass infiltrates should be minimal [11]. Clinical findings should include a conspicuous absence of inhalational exposures and rheumatologic conditions as well as presence of "velcro" rales. If the diagnosis is in doubt, consultation with a pulmonary specialist with experience in interstitial lung disease is recommended.

Exacerbation During Surgical Procedures

Often, patients with undergo a biopsy to establish a diagnosis of IPF. Additionally, patients with IPF are at higher risk of lung cancer which may require surgical treatment. Thoracic surgery for lung cancer resection or surgical lung biopsy can precipitate an acute exacerbation of IPF [15–18]. Interestingly the insult is often radiologically worse in the

nonoperative lung [17]. This may be due to the ventilator-associated lung injury from excessive stretch from single lung ventilation during the operation to de-gas the operative lung. Some have suggested restrictive intraoperative fluid management may minimize post-operative AE-IPF risk (see evidence contour) [15]. AE-IPF after non-pulmonary operation has only been reported once [19].

Evidence Contour

Noninvasive Ventilation

Given the poor prognosis of patients who require mechanical ventilation, some have suggested that noninvasive ventilation would be a good strategy for patients with clinical deterioration and idiopathic pulmonary fibrosis. Small, retrospective studies have shown improved outcomes in patients supported with noninvasive positive pressure ventilation (NIPPV) [20–22], however a selection bias may account for the better prognosis as patients who can be successfully supported with NIPPV are likely less ill. Of the patients in these studies who failed NIPPV, mortality was reported as 85–100 % [20–22].

High Flow Nasal Cannula

High flow nasal cannula has been shown to have salutatory affects in idiopathic pulmonary fibrosis patients without an acute exacerbation, specifically decreased minute ventilation, respiratory rate, capillary carbon dioxide were seen [23]. Additionally, small increases in airway pressure were reported, suggesting a partial "PEEP" affect [23]. Use of high flow nasal cannula in AE-IPF has not been reported. Anecdotally, we have used high cannula with great success in patients with IPF and clinical worsening.

Ventilator Settings

Higher levels of PEEP have been associated with higher mortality in single retrospective analysis [24]. A selection bias for patients with worse hypoxemia requiring higher levels of mean airway pressure is one explanation; however multiple variables were accounted for in the analysis. It may be true that patients with acute exacerbation of IPF have a different physiology and those with ARDS where higher levels of PEEP are felt to be beneficial. The optimal ventilator settings for acute exacerbation of IPF are not known, however to the extent possible we adhere to lung protective ventilation similar to ARDS (see ARDS Chap. 21).

Anticoagulation

A single, unblinded prospective study has shown a benefit in patients admitted with clinical worsening of idiopathic pulmonary fibrosis treated with anticoagulation [25]. Anticoagulation was initiated at the time of clinical worsening, which may or may not have been an acute exacerbation. Coumadin was used in the outpatient setting and low molecular weight heparin was used if the patient was admitted, such as with AE-IPF. All patients were treated with corticosteroid as well. In the subset of patients who had AE-IPF, anticoagulated patients had a lower mortality (18 % vs 71 %). However, 30 % of patients randomized to the treatment arm dropped out of the study, in this unblinded study. Additionally, pulmonary embolism was not excluded as a cause of clinical worsening, and may have played a role in some patients [11].

A large, double blind prospective trial of coumadin in the treatment of IPF was stopped early due to increased mortality in coumadin arm [26]. No difference in incidence of AE-IPF observed.

Use of anticoagulation in IPF patients without thromboembolic disease was recommended against by a panel of experts [11]. Anticoagulation specifically used to treat AE-IPF does not have sufficient data to support its use.

Cyclophosphamide

Cyclophosphamide has been used in case series for treatment of AE-IPF. Morawiec and colleagues described 10 patients who were treated with cyclophosphamide and pulse dose solu-medrol

during acute exacerbations with 100 % and 72 % 1 month and 3 months survival rates, respectively [27]. Patients were treated with a methylprednisolone pulse (1,000 mg) at days 1–3 and on day 4 placed on an escalating regimen of cyclophosphamide with an initial dose of 500 mg intravenously. The dose of cyclophosphamide was increased by 200 mg every 2 weeks, provided the total white blood cell count remained at >3,000 cells · mm^{-3}. The maximum single administered dose was 1,500 mg of cyclophosphamide. Lack of randomization significantly limits the utility of this study. In patients who do not respond to corticosteroids, we consider a trial of cyclophosphamide 2 mg/ kg IV daily on a patient by patient basis.

Cyclosporin A

Inase and coworkers retrospectively analyzed 13 patients after AE-IPF. All patients received pulse solu-medrol followed by oral prednisone, and 7 received cyclosporine A titrated to serum levels of 100–150 in addition to steroids [28]. In the patients treated with cyclosporine A none experienced a re-exacerbation of IPF. All patients with steroids alone died of respiratory failure within 66 weeks, whereas four out of the seven treated with cyclosporine A survived for over 2 years after their exacerbation.

Sakamoto also evaluated the use of cyclosporine A in AE-IPF retrospectively [29]. Similar to Inase, all patients were treated with pulse solu-medrol followed by prednisone. Two out of 11 patients treated with cyclosporine A died during their initial exacerbation, compared to 6 out of 11 patients who were treated with steroids alone. Prevention of re-exacerbation was not observed with five patients experiencing repeat exacerbations while on cyclosporine A.

Similar to cyclophosphamide, lack of randomized prospective trials limit widespread adoption of cyclosporine for treatment of AE-IPF

Restrictive Operative Fluid Balance

Mizuno retrospectively evaluated 52 patients with IPF after pulmonary resection of non-small cell lung cancer and found that higher positive intraoperative fluid balance was associated with AE-IPF after multivariate analysis [15]. Prospective use of restrictive fluid practices towards the prevention of postoperative AE-IPF has not been established.

Pulmonary Transplantation

In patients without other medical comorbidities or of advanced age, pulmonary transplantation can be performed in patients with idiopathic pulmonary fibrosis. In patients who are already listed for transplant and develop acute exacerbation, extracorporeal life-support or mechanical ventilation are not contraindications to pulmonary transplant; though vigilance and of maintaining a robust functional status and avoiding critical care weakness are major challenges.

De Novo evaluation of patients with acute exacerbation for pulmonary transplantation is difficult as the typical pre-operative studies, such as colonoscopy, heart catheterization etc. become much more perilous in a patient with severe respiratory failure or on extracorporeal life-support. However, this has been reported successfully [30].

Extracorporeal Life Support

To our knowledge, extracorporeal life-support has not been used to support patients with acute exacerbation of idiopathic pulmonary fibrosis other than to provide a bridge to transplant. In patients who are not candidates for pulmonary transplantation, we suggest against extracorporeal life support given the overall poor prognosis of the condition. In patients whom ECLS is used as a bridge to transplant (IPF and non-IPF patients), ECLS longer than 14 days has been associated with worse post-transplant survival [31].

Anti-fibrotic Medications

Early studies suggested use of pirfenidone lowered the rate of acute exacerbation of idiopathic

pulmonary fibrosis [4], though this was not seen on subsequent studies [32]. Nintedanib did not reduce the incidence of AE-IPF [6]. Both pirfenidone and nintedanib were both recently approved for treatment of IPF. The initiation of pirfenidone or nintedanib as a treatment specifically for AE-IPF has not been an established and is not recommended.

References

1. Hyzy R et al. Acute exacerbation of idiopathic pulmonary fibrosis. Chest. 2007;132(5):1652–8.
2. Collard HR et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2007;176(7):636–43.
3. Kondoh Y et al. Acute exacerbation in idiopathic pulmonary fibrosis. Analysis of clinical and pathologic findings in three cases. Chest. 1993;103(6): 1808–12.
4. Azuma A et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2005;171(9): 1040–7.
5. Martinez FJ et al. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med. 2014; 370(22):2093–101.
6. Richeldi L et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014; 370(22):2071–82.
7. Kim DS et al. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. Eur Respir J. 2006;27(1):143–50.
8. Gaudry S et al. Invasive mechanical ventilation in patients with fibrosing interstitial pneumonia. J Thorac Cardiovasc Surg. 2014;147(1):47–53.
9. Mallick S. Outcome of patients with idiopathic pulmonary fibrosis (IPF) ventilated in intensive care unit. Respir Med. 2008;102(10):1355–9.
10. Al-Hameed FM, Sharma S. Outcome of patients admitted to the intensive care unit for acute exacerbation of idiopathic pulmonary fibrosis. Can Respir J. 2004;11(2):117–22.
11. Raghu G et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788–824.
12. Steinberg KP et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med. 2006;354(16):1671–84.
13. Tachikawa R et al. Clinical features and outcome of acute exacerbation of interstitial pneumonia: collagen vascular diseases-related versus idiopathic. Respiration. 2012;83(1):20–7.
14. Flaherty KR et al. Idiopathic interstitial pneumonia: do community and academic physicians agree on diagnosis? Am J Respir Crit Care Med. 2007;175(10): 1054–60.
15. Mizuno Y et al. The importance of intraoperative fluid balance for the prevention of postoperative acute exacerbation of idiopathic pulmonary fibrosis after pulmonary resection for primary lung cancer. Eur J Cardiothorac Surg. 2012;41(6): e161–5.
16. Shintani Y et al. Predictive factors for postoperative acute exacerbation of interstitial pneumonia combined with lung cancer. Gen Thorac Cardiovasc Surg. 2010;58(4):182–5.
17. Kondoh Y et al. Acute exacerbation of interstitial pneumonia following surgical lung biopsy. Respir Med. 2006;100(10):1753–9.
18. Park JH et al. Mortality and risk factors for surgical lung biopsy in patients with idiopathic interstitial pneumonia. Eur J Cardiothorac Surg. 2007;31(6): 1115–9.
19. Ghatol A, Ruhl AP, Danoff SK. Exacerbations in idiopathic pulmonary fibrosis triggered by pulmonary and nonpulmonary surgery: a case series and comprehensive review of the literature. Lung. 2012;190(4): 373–80.
20. Tomii K et al. Role of non-invasive ventilation in managing life-threatening acute exacerbation of interstitial pneumonia. Intern Med. 2010;49(14): 1341–7.
21. Yokoyama T et al. Noninvasive ventilation in acute exacerbation of idiopathic pulmonary fibrosis. Intern Med. 2010;49(15):1509–14.
22. Gungor G et al. Why do patients with interstitial lung diseases fail in the ICU? A 2-center cohort study. Respir Care. 2013;58(3):525–31.
23. Braunlich J et al. Effects of nasal high flow on ventilation in volunteers, COPD and idiopathic pulmonary fibrosis patients. Respiration. 2013;85(4):3 19–25.
24. Fernandez-Perez ER et al. Ventilator settings and outcome of respiratory failure in chronic interstitial lung disease. Chest. 2008;133(5):1113–9.
25. Kubo H et al. Anticoagulant therapy for idiopathic pulmonary fibrosis. Chest. 2005;128(3):1475–82.
26. Noth I et al. A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2012;186(1):88–95.
27. Morawiec E et al. Exacerbations of idiopathic pulmonary fibrosis treated with corticosteroids and cyclophosphamide pulses. Eur Respir J. 2011;38(6): 1487–9.
28. Inase N et al. Cyclosporin A followed by the treatment of acute exacerbation of idiopathic pulmonary fibrosis

with corticosteroid. Intern Med. 2003;42(7):565–70.
29. Sakamoto S et al. Cyclosporin A in the treatment of acute exacerbation of idiopathic pulmonary fibrosis. Intern Med. 2010;49(2):109–15.
30. Hoopes CW et al. Extracorporeal membrane oxygenation as a bridge to pulmonary transplantation. J Thorac Cardiovasc Surg. 2013;145(3):862–7; discussion 867–8.
31. Crotti S et al. Organ allocation waiting time during extracorporeal bridge to lung transplant affects outcomes. Chest. 2013;144(3):1018–25.
32. Taniguchi H et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35(4):821–9.

Weaning from Mechanical Ventilation

31

Ayodeji Adegunsoye and John P. Kress

Case Presentation

A 68 year old woman with a history of hypertension, diabetes, asthma, congestive heart failure (CHF) and end stage renal disease was intubated and admitted to the ICU for respiratory failure and hypotension following a one week history of fever, dyspnea, anorexia and cough productive of yellowish-green sputum. At initial presentation to the ICU, she received a bolus of intravenous crystalloid, and was commenced on vasoactive support with norepinephrine, vasopressin and phenylephrine infusions. White blood cell count was 15K and she was commenced on broad-spectrum IV antibiotics. Respiratory and blood cultures subsequently grew *Pseudomonas aeruginosa* and antibiotics were narrowed to IV cefepime. Over the next 72 h she became afebrile, her white blood cell count dropped to 8.5K and her vasoactive support was weaned off. Her most recent CXR, vital signs and mechanical ventilator settings are shown in Fig. 31.1.

Question What approach would best determine her readiness for liberation from the mechanical ventilator?

Answer Spontaneous breathing trial (SBT)

All intubated patients should be assessed with a SBT to determine their readiness for liberation from the mechanical ventilator after the underlying cause for intubation has been addressed and is improving. The patient had been ventilated on small tidal volumes (6 ml/kg ideal body weight) and her plateau airway pressures ranged between 20 and 24 cmH_2O. Her PaO_2/FiO_2 ratio remained >200 with a PEEP of 5cmH_2O and FiO_2 of 40%. Her hemodynamic status remained stable with no requirement for vasopressor support. She received an analgesic infusion of fentanyl, which was interrupted on a daily basis to assess her mental function. Physical and occupational therapy were commenced within 24 h of her ICU admission and she was maintained on a daily negative fluid balance of 1–2 L per day. Her most recent arterial blood gas was 7.32/42/75/98 and she had minimal airway secretions. Continuous sedation was discontinued and while she was awake, a 30-min spontaneous-breathing trial was performed with CPAP of 5 cm of water and her observed vital signs afterwards are depicted in Fig. 31.2.

A. Adegunsoye (✉)
Section of Pulmonary & Critical Care,
Department of Medicine,
University of Chicago Medicine,
Chicago, IL, USA
e-mail: deji@uchicago.edu

J.P. Kress
Medical Intensive Care Unit,
Section of Pulmonary & Critical Care,
Department of Medicine,
University of Chicago Medicine,
Chicago, IL, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_31

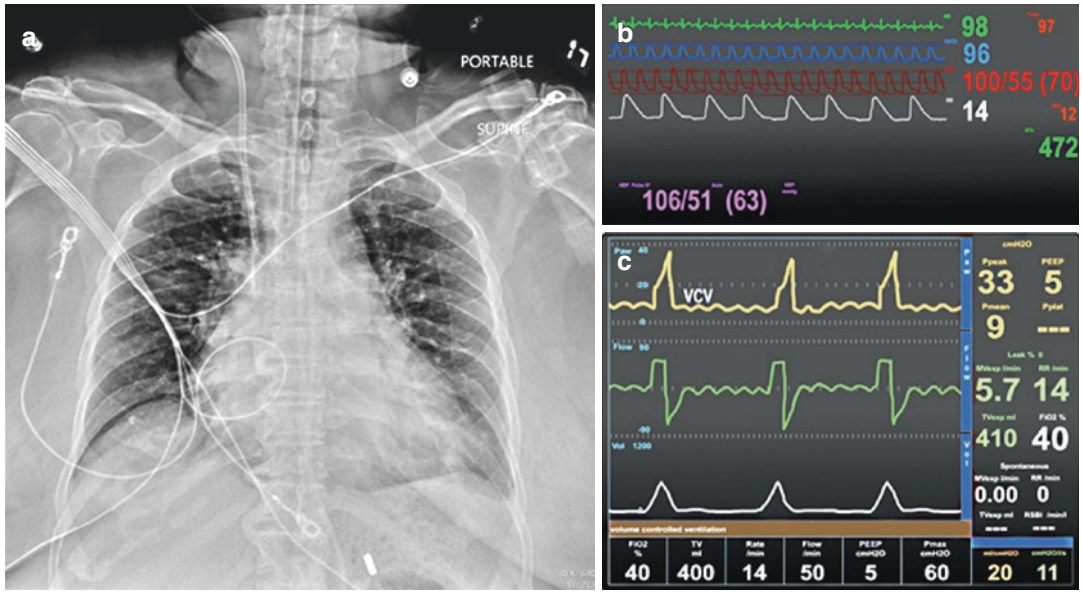


Fig. 31.1 (**a**) Chest x-ray of index patient on admission day 3. (**b**) Telemetry monitor showing the patient's vital signs on admission day 3. (**c**) Mechanical ventilator parameters of the index patient on admission day 3

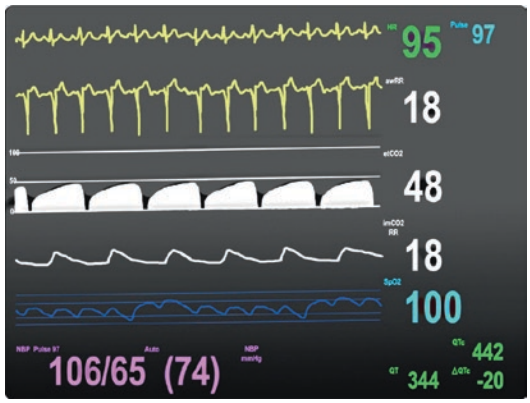


Fig. 31.2 Telemetry monitor showing the patient's vital signs after a 30-min spontaneous breathing trial

Principles of Management

Strategies to Minimize the Requirement for Mechanical Ventilation

Various disease states predispose patients to respiratory failure ultimately requiring mechanical ventilation for respiratory support. In patients with sepsis, the need for mechanical ventilation may be prevented by instituting early aggressive resuscitative measures [1]; however, this protocol-based care may not result in improved outcomes [2, 3]. Similarly, instituting non-invasive ventilation in patients with acute cardiogenic pulmonary edema or acute exacerbation of chronic obstructive pulmonary disease could reduce the need for intubation and mechanical ventilation in these patients [4–7].

Strategies to Reduce the Duration of Mechanical Ventilation

Once a patient has been intubated, several strategies which could speed up readiness for liberation from mechanical ventilation include the use of lung protective ventilation in ARDS [8], interruption of sedatives on a daily basis [9], implementing physical and occupational therapy early [10], conservative fluid management in ARDS [11] and the prevention of ventilator-associated pneumonia [12].

Evaluation of Patient's Readiness for Spontaneous Breathing

Patients determined to be ready for a trial of spontaneous breathing should exhibit improvement in the underlying factors that led to respiratory failure and be hemodynamically stable with a ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) that exceeds 200 on a positive end-expiratory pressure (PEEP) of 5 cmH_2O or less [13].

Perform a Spontaneous Breathing Trial in Patients Deemed Ready

An SBT is performed to demonstrate the patient's ability to breathe on minimal or no ventilator support for at least 30 min. Usually, this is performed on continuous positive airway pressure, low-level pressure support or utilizing a T-piece. The occurrence of oxygen saturation ≤90 %, heart rate >140/min, respiratory rate >35/min for more than 5 min, a sustained variation of 20 % or more in the heart rate, systolic blood pressure below 90 mmHg or exceeding 180 mmHg, increase in anxiety or diaphoresis all portend failure [13].

Assess Patient's Ability to Protect the Airway

A successful trial of spontaneous breathing will lead to an evaluation of the patient's ability to effect airway protection upon removal of the endotracheal tube. This assesses the patient's mentation, strength of cough and quantity of airway secretions. Demonstration of adequate unassisted breathing and airway protection should prompt immediate removal of the endotracheal tube. Otherwise, if SBT is unsuccessful, re-initiation of mechanical ventilation at the prior support level should be ensured while a careful investigation is performed to determine and treat the underlying reason for failure before repeating an evaluation for a trial of spontaneous breathing again [13].

Evidence Contour

Assessing the Need for an Artificial Airway

Demonstration of some capability to interact with the health care team is required prior to removal of the patient's endotracheal tube. However, the exact significance and the degree to which it plays a role in successful extubation remain controversial [14]. It has been suggested that in patients capable of protecting their airway, a Glasgow coma scale score of ≥8 predicts successful extubation [15]. Prolonged mechanical ventilation, female sex and traumatic or repeated intubation have all been associated with post-extubation upper airway obstruction [16] leading to suggestions for the use of the cuff leak test (air leak detection during mechanical ventilation with a deflated endotracheal tube balloon) in these patients to assess the patency of the upper airway prior to extubation [17]. Patients at high risk of post-extubation stridor were identified in a single study of intubated medical patients using a cuff leak of <110 ml within 24 h of extubation [18]. Steroids and/or epinephrine may be used during this period to reduce the risk or for treatment in those patients who develop stridor afterwards [19]. The use of NIPPV and/or heliox has also been advocated [19].

Weaning Protocols

The use of weaning protocols enforces daily evaluation of readiness for extubation by using pre-specified criteria and implementing trial of spontaneous breathing in a structured form. The WEAN study, a multicenter, randomized controlled trial which compared automated weaning with the use of a standardized protocol demonstrated significantly faster liberation from mechanical ventilation and fewer cases of protracted ventilation or tracheostomies [20]. Similarly, a large Cochrane meta-analysis of ten trials compared automated weaning protocols and non-automated weaning strategies and

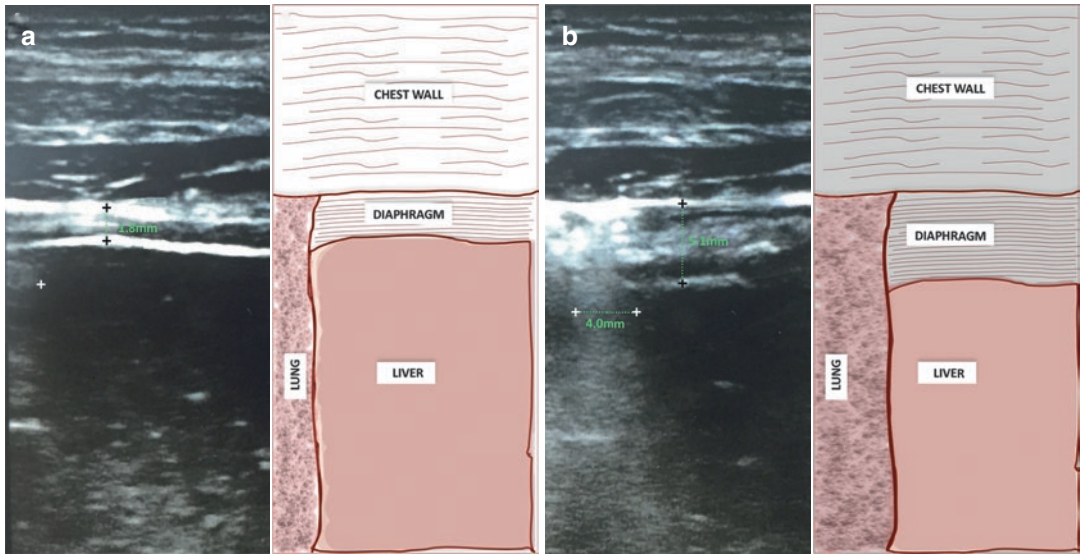


Fig. 31.3 A high resolution 13–6 MHz ultrasound linear probe (SonoSite Edge, SonoSite, Inc., Washington USA) held perpendicular to the chest was used to evaluate real-time movement of the diaphragm in the zone of apposition. Measurements obtained were recorded in B mode (two dimensional) ultrasonography by placing the transducer along the line of an intercostal space between the right anteroaxillary and midaxillary lines to ensure the zone of apposition is visualized ~0.5–2 cm below the right costophrenic sinus. Air in the lungs facilitates easy detection of the inferior border of the sinus and the two bright parallel lines of its peritoneal and pleural membranes identify the diaphragm with an intervening muscular layer during maximal expiratory effort (**a**) and maximal inspiratory effort (**b**). Ultrasonographic measurements of diaphragmatic thickening (*black crosses*) and hepatic displacement (*white crosses*) during spontaneous breathing trials have been demonstrated to be useful in predicting extubation outcomes [22–24]

demonstrated a decrease in the duration of mechanical ventilation, time to successful extubation, ICU length of stay and proportion of patients on mechanical ventilation for more than 7 days in patients on a protocolized weaning strategy [21]. Though yet to be widely adopted, this automated strategy possibly ensures all mechanically ventilated patients are given a fair chance to demonstrate their ability for spontaneous breathing at the earliest time (Figs. 31.3 and 31.4).

Sample Ventilator Liberation Pathway

Procedure to be implemented by physician or appropriately certified healthcare professional after eligibility has been determined following collaborative daily assessment by nursing and respiratory therapist. Necessary equipment and personnel confirmed to be available and responsible physician notified.

1. Initiate FiO_2 Wean Protocol:
   - Monitor pulse oximetry (SpO_2) during FiO_2 weaning (once determined to correlate with arterial blood gas)
   - Post-intubation, decrease FiO_2 by 10–20 % every 30 min till $FiO_2 < 0.5$ while $SpO_2 > 95$ % and/or $PaO_2 > 75$ mmHg
   - At target SpO_2, obtain ABG to confirm adequate oxygen saturation
   - PEEP may be increased (after discussion with the physician) to ensure $FiO_2 \leq 0.7$
2. Daily Assessment for Eligibility for Liberation:
   - Respiratory therapist screens all ventilated patients daily by asking these questions between 5:00–7:00 am. Assessment per-

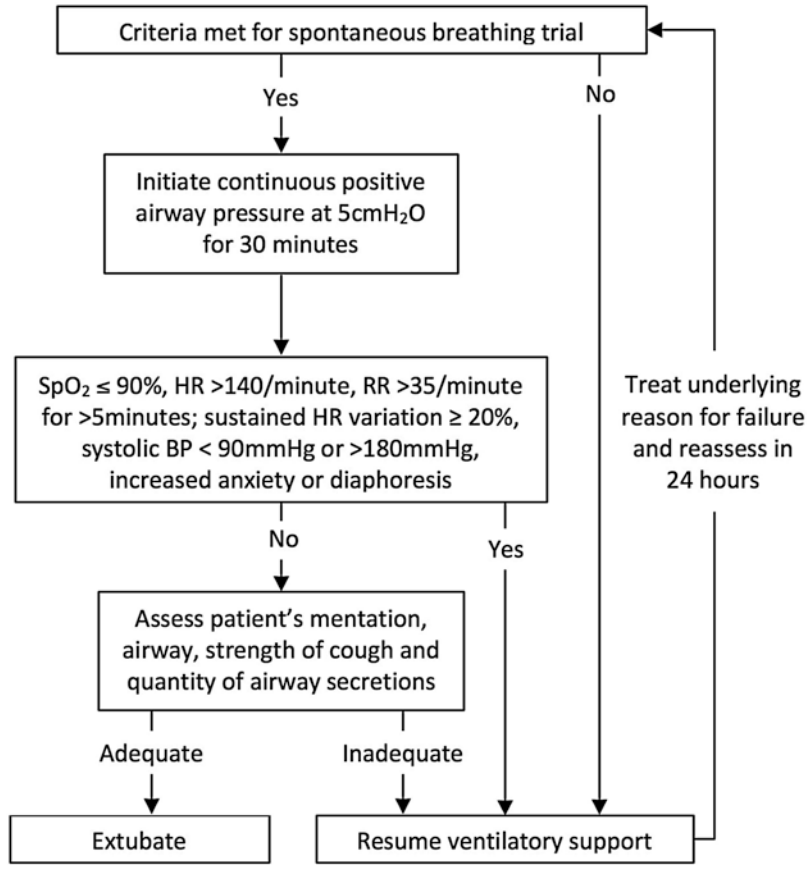


Fig. 31.4 Sample weaning protocol. Readiness for spontaneous breathing evaluated and patient meets the following criteria: (1) Demonstrates hemodynamic stability. (2) Sedative infusion discontinued. (3) Tube feedings stopped. (4) $PaO_2/FiO_2 > 200$; PEEP $\leq 5cmH_2O$

formed on all post-operative/post-procedure patients as needed upon awakening from sedation.

- Response must be "yes" for 'a – c'; or "yes" for 'a – d' in the presence of neuromuscular disease.

(a) $PaO_2 \geq 60$ mmHg on $FIO_2 \leq 0.5$, PEEP ≤ 7.5, $SpO_2 \geq 88\,\%$
(b) Hemodynamically stable, absence of vasoactive support except for Dopamine/Dobutamine ≤5 mcg/kg/min or norepinephrine ≤2 mcg/kg/min
(c) Patient triggers ventilator spontaneously
(d) Vital capacity >15 ml/kg; maximum expiratory pressure >40 & negative inspiratory force >25

3. Spontaneous Breathing Trial (Fig. 31.4):
   - Patient to be placed in semi-fowlers position.
   - Switch ventilator to spontaneous mode with pressure support of 8–10 or CPAP of 5 for 30 min on the same FiO_2.
   - If patient does not tolerate SBT, resume full ventilator support immediately and reassess daily or every 4 h for post-op/post-procedure patients; if patient tolerates SBT, screen for extubation readiness.
4. Screen for Extubation Readiness:
   - Awake & responsive to verbal commands?
   - Can Patient protect his/her airway? (Intact & adequate cough reflex)
   - Cough strength: (Weak/Satisfactory/Strong)

- No concerns about frequency of suctioning
- No concerns about upper airway patency?
- For patients with neuromuscular disease – can sustain head lift against moderate resistance?

  (If patient passes, extubation can be performed and new supplemental oxygen modality instituted; else go to Step 2. If repeated failure and intubated for >10–14 days – consider tracheostomy).

5. Extubation Procedure:
   - Request anesthesiologist or senior critical care physician for 'difficult to intubate patients' or 'prior airway trauma' prior to extubation
   - Ensure gastric feeds have been held for ≥2 h
   - Place mask for non-invasive ventilation at bedside
   - Perform oropharyngeal and ETT suctioning
   - Encourage patient to breathe in maximally
   - Extubate to nasal cannula at 4–6 l/min with close observation for at least 30 min
   - Ensure $SpO_2 \geq 92\%$ by titrating FIO_2 accordingly
   - For impending respiratory failure, expedite management of stridor with racemic epinephrine (0.5 q20 min up to 3× prn); humidified O_2±dexamethasone. Consider non-Invasive ventilation prior to reintubation
   - Deep breathing and cough maneuvers every 1–2 h
   - Maintain NPO for 4 h; evaluate for aspiration risk – if high: consult speech therapy; if minimal: resume tube feeds
   - Assessment by patients nurse every 4 h for signs of respiratory distress during ICU stay

Diaphragmatic Ultrasound as an Index for Discontinuation of Mechanical Ventilation

Ventilator induced diaphragm atrophy has been shown to occur even with short periods of mechanical ventilation and may delay liberation from the ventilator. Diaphragm dome motion as visualized by ultrasonography has limited utility and success in predicting extubation outcomes [25]. A recent prospective study of 63 subjects demonstrated that ultrasonographic measurement of diaphragm muscle thickening (Δtdi%) ≥30 % in the zone of apposition using a 7–10 Mhz ultrasound transducer is an effective predictor of extubation success or failure with a sensitivity and specificity of 88 % and 71 % respectively; a positive predictive value (PPV) of 91 % and a negative predictive value (NPV) of 63 % (area under the receiver operating characteristic curve for Δtdi% was 0.79) [26]. A similar prospective study of 43 subjects and Δtdi% >36 % had a PPV of 93 % and a NPV of 88 % [27]. The increasing use of ultrasonography in intensive care and the non-invasive approach with no special effort required of the patient makes it appealing in the evaluation of extubation outcomes.

Pressure Support Versus T-Tube for Weaning from Mechanical Ventilation

Low-level pressure support and spontaneous breathing through a T-Tube are optional modes of ventilator support used in liberation from mechanical ventilation. It was recently shown in a small prospective study of 28 patients undergoing cardiac surgery that either method did not confer a significant difference in the lung function or post-operative hospital course [28]. However, a large Cochrane review of >1200 patients suggests that pressure support ventilation may be more effective than a T-tube in facilitating successful spontaneous breathing trial. The evidence was insufficient to demonstrate superiority to T-tube in successful weaning, rapid shallow breathing index, reintubation risk, ICU mortality and length of stay [29].

Tracheostomy for Prolonged Transition

Patients who require prolonged weaning are increasingly being subjected to tracheostomy

[30]. The optimal time for performing tracheostomies in these patients remains controversial. Multiple studies have reported conflicting results on the effect of early tracheostomy on short-term mortality, incidence of pneumonia and ICU length of stay [31–34]. A meta-analysis of the available studies concluded that the evidence remains insufficient to recommend the early performance of tracheostomy in mechanically ventilated patients [35].

References

1. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative G. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368–77.
2. Pro CI, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F, Filbin MR, Shapiro NI, Angus DC. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370:1683–93.
3. Investigators A, Group ACT, Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ, Higgins AM, Holdgate A, Howe BD, Webb SA, Williams P. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371:1496–506.
4. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, Simonneau G, Benito S, Gasparetto A, Lemaire F, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1995;333:817–22.
5. Ram FS, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2004;(1):CD004104.
6. Masip J, Roque M, Sanchez B, Fernandez R, Subirana M, Exposito JA. Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. JAMA. 2005;294:3124–30.
7. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J, Trialists CPO. Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med. 2008;359:142–51.
8. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
9. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med. 2000;342:1471–7.
10. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister KE, Hall JB, Kress JP. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373:1874–82.
11. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, DeBoisblanc B, Connors Jr AF, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354:2564–75.
12. Dezfulian C, Shojania K, Collard HR, Kim HM, Matthay MA, Saint S. Subglottic secretion drainage for preventing ventilator-associated pneumonia: a meta-analysis. Am J Med. 2005;118:11–8.
13. McConville JF, Kress JP. Weaning patients from the ventilator. N Engl J Med. 2012;367:2233–9.
14. Coplin WM, Pierson DJ, Cooley KD, Newell DW, Rubenfeld GD. Implications of extubation delay in brain-injured patients meeting standard weaning criteria. Am J Respir Crit Care Med. 2000;161:1530–6.
15. King CS, Moores LK, Epstein SK. Should patients be able to follow commands prior to extubation? Respir Care. 2010;55:56–65.
16. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. Am J Med. 1993;94:281–8.
17. Fisher MM, Raper RF. The 'cuff-leak' test for extubation. Anaesthesia. 1992;47:10–2.
18. Miller RL, Cole RP. Association between reduced cuff leak volume and postextubation stridor. Chest. 1996;110:1035–40.
19. Macintyre NR. Evidence-based assessments in the ventilator discontinuation process. Respir Care. 2012;57:1611–8.
20. Burns KE, Meade MO, Lessard MR, Hand L, Zhou Q, Keenan SP, Lellouche F. Wean earlier and automatically with new technology (the WEAN study). A multicenter, pilot randomized controlled trial. Am J Respir Crit Care Med. 2013;187:1203–11.
21. Burns KE, Lellouche F, Nisenbaum R, Lessard MR, Friedrich JO. Automated weaning and SBT systems versus non-automated weaning strategies for weaning time in invasively ventilated critically ill adults. Cochrane Database Syst Rev. 2014;(9):CD008638.
22. Matamis D, Soilemezi E, Tsagourias M, Akoumianaki E, Dimassi S, Boroli F, Richard JC, Brochard L. Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. Intensive Care Med. 2013;39:801–10.
23. Vivier E, Mekontso Dessap A, Dimassi S, Vargas F, Lyazidi A, Thille AW, Brochard L. Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. Intensive Care Med. 2012;38:796–803.

24. Ueki J, De Bruin PF, Pride NB. In vivo assessment of diaphragm contraction by ultrasound in normal subjects. Thorax. 1995;50:1157–61.
25. Kim WY, Suh HJ, Hong SB, Koh Y, Lim CM. Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. Crit Care Med. 2011;39:2627–30.
26. DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. Thorax. 2014;69:423–7.
27. Ferrari G, De Filippi G, Elia F, Panero F, Volpicelli G, Apra F. Diaphragm ultrasound as a new index of discontinuation from mechanical ventilation. Crit Ultrasound J. 2014;6:8.
28. Lourenco IS, Franco AM, Bassetto S, Rodrigues AJ. Pressure support-ventilation versus spontaneous breathing with "T-tube" for interrupting the ventilation after cardiac operations. Rev Bras Cir Cardiovasc orgao oficial da Sociedade Brasileira de Cirurgia Cardiovascular. 2013;28:455–61.
29. Ladeira MT, Vital FM, Andriolo RB, Andriolo BN, Atallah AN, Peccin MS. Pressure support versus T-tube for weaning from mechanical ventilation in adults. Cochrane Database Syst Rev. 2014;(5):CD006056.
30. Cox CE, Carson SS, Holmes GM, Howard A, Carey TS. Increase in tracheostomy for prolonged mechanical ventilation in North Carolina, 1993–2002. Crit Care Med. 2004;32:2219–26.
31. Arabi Y, Haddad S, Shirawi N, Al Shimemeri A. Early tracheostomy in intensive care trauma patients improves resource utilization: a cohort study and literature review. Crit Care. 2004;8:R347–52.
32. Rumbak MJ, Newton M, Truncale T, Schwartz SW, Adams JW, Hazard PB. A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients. Crit Care Med. 2004;32:1689–94.
33. Trouillet JL, Luyt CE, Guiguet M, Ouattara A, Vaissier E, Makri R, Nieszkowska A, Leprince P, Pavie A, Chastre J, Combes A. Early percutaneous tracheotomy versus prolonged intubation of mechanically ventilated patients after cardiac surgery: a randomized trial. Ann Intern Med. 2011;154:373–83.
34. Patel SB, Kress JP. Early tracheotomy after cardiac surgery: not ready for prime time. Ann Intern Med. 2011;154:434–5.
35. Gomes Silva BN, Andriolo RB, Saconato H, Atallah AN, Valente O. Early versus late tracheostomy for critically ill patients. Cochrane Database Syst Rev. 2012;(3):CD007271.

The Post-intensive Care Syndrome

32

Jason H. Maley and Mark E. Mikkelsen

Case Presentation

A 60 year-old man with a history of tobacco use and diabetes mellitus was admitted to the hospital with community acquired pneumonia. His course was complicated by hypoxemic respiratory failure requiring 5 days of mechanical ventilation in the Intensive Care Unit (ICU). After 13 days in the hospital, including 5 days of delirium, he was discharged to an acute rehabilitation facility. Upon returning home to live with his wife, he described a frequent fear that his breathing will worsen and that he may have to return to the hospital. He kept a bag of his possessions ready for an emergency return to the hospital. His wife reported that his thinking "isn't quite the same" as prior to the acute illness. He slept on the first floor as he had difficulty climbing the flight of stairs to his bedroom. He also reported developing depression secondary to his dependence on others' for his activities of daily living and his inability to return to work as an accountant.

Question Which features are characteristic of the Post-Intensive Care Syndrome?

Answer The Post-Intensive Care Syndrome (PICS) describes a constellation of symptoms, which includes impairment in neuropsychological and physical well-being that occurs following an episode of critical illness [1, 2].

This recently recognized entity lies at the core of critical care survivorship. Patients who have experienced shock, respiratory failure, and prolonged sedation and mechanical ventilation are most at risk for development of PICS. Furthermore, pre-existing impairment in one or more of these domains may worsen after critical illness, a fact that warrants obtaining a history that captures physical function, mental health and cognitive function pre-illness. A longitudinal, coordinated effort is required to mitigate the risk of PICS development and rehabilitate new or more severe impairments (Table 32.1).

Principles of Management

Diagnosis

Survivors of critical illness are at risk for PICS development, and in particular those who experience shock and respiratory failure requiring mechanical ventilation. Risk factors associated with long-term physical and/or neuropsychological impairment include sepsis, acute respiratory distress syndrome (ARDS), multi-system organ failure, prolonged ICU length of stay, duration of delirium, glucose dysregulation, and the use of corticosteroids [2, 5–9].

J.H. Maley • M.E. Mikkelsen (✉)
Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA
e-mail: mark.mikkelsen@uphs.upenn.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_32

Table 32.1 Post-intensive care syndrome: diagnosis, prevention, and rehabilitation strategies that can be paired with educational efforts to prepare out-patient providers, survivors, and their caregivers about the potential long-term consequences of critical illness

Domain	Diagnosis	Prevention	Rehabilitation
Cognition	Use a validated, screening test at time of discharge or initial follow-up (e.g., Montreal Cognitive Assessment)	ABCDEF bundle to minimize delirium and preserve physical function	1. Compensation and rehabilitation therapy through consultation with expert providers 2. Cognitive exercises 3. Prioritize early occupational and physical therapy
Mental health	Use validated screening tests to identify symptoms of depression, anxiety (Hospital Anxiety and Depression Scale), or post-traumatic stress disorder (PTSS-10) [3, 4]	1. ABCDEF bundle 2. ICU diary 3. Avoid hypoglycemia and sustained, severe hypoxemia as potential strategies to prevent long-term psychological distress	1. Consultation with psychologists and/or psychiatrists based on symptoms 2. Consideration of pharmacologic treatment
Physical function	Physical examination, including use of standardized scoring systems, and ancillary testing if necessary	ABCDEF bundle, with a focus on early occupational and physical therapy	1. Continued occupational and physical therapy

Abbreviations: *PTSS-10* post-traumatic Stress Syndrome 10-Questions Inventory

Physical and neuropsychological impairment should be screened for at the time of hospital discharge to guide the procurement of post-acute care services (Table 32.2). Physical impairment is common following critical illness, can be measured using a standardized scale, and frequently contributes to the need for skilled care or acute rehabilitation facility placement. Several validated options exist to examine functional status, and specific areas of functional abilities, clinically. Cognitive impairment is an under-recognized consequence of critical illness. In a prospective study of survivors of shock and respiratory failure, Pandharipande et al. revealed that 40 % of survivors performed at a level consistent with moderate traumatic brain injury at 3 months, 26 % performed at a level consistent with mild Alzheimer's disease, and these impairments frequently persisted [8]. Given its prevalence, providers should screen for cognitive impairment in ICU survivors with suspected PICS. A number of validated screening tools exist to identify cognitive impairment, including the Mini Mental Status Exam, the Mini-Cog, and the Montreal Cognitive Assessment (MoCA). As a simple, highly sensitive, and validated test, the MoCA is arguably the best screening tool to detect mild cognitive impairment in ICU survivors [10]. Psychiatric illness seen in PICS manifests as symptoms of anxiety, depression, or post-traumatic stress disorder (PTSD) [14].

Prevention and Rehabilitation

A growing body of literature supports the use of the "ABCDEF" bundle as a potential means to mitigate the risk of PICS [15]. The components of the ABCDE bundle include the coordination of sedation minimization and standardized ventilator weaning [16], delirium monitoring, prevention, and management, and early occupational and physical therapy [17]. When coupled with family engagement and empowerment, the bundle is transformed to the ABCDEF bundle. The benefits of an ABCDE bundle include reduced duration of delirium, reduced incidence of ventilator-associated events, increased ventilator-free days, and improved functional outcomes at discharge with increased likelihood of return to functional independence [16–20].

Table 32.2 Clinical strategies to screen for neuropsychological and physical impairment after critical illness

Domain	Test	Range	Score interpretation
Cognition	Montreal Cognitive Assessment (MoCA) [10]	0–30	Normal (>25) Impairment: Mild (18–25) Moderate (10–17) Severe (<10)
Depression	Hospital Anxiety and Depression Scale [3]	0–21	Normal (0–7) Abnormal (≥8)
Anxiety	Hospital Anxiety and Depression Scale [3]	0–21	Normal (0–7) Abnormal (≥8)
Post-traumatic stress disorder	Post-Traumatic Stress Syndrome 10-Questions Inventory (PTSS-10) [4]	0–70	Normal (0–34) Impaired (≥35)
Physical function	Activities of Daily Living [11]	0–6	Independence for activities of bathing, dressing, toileting, transferring, continence, and feeding would sum to 6
Physical function, strength	Medical Research Council examination [12]	0–60	ICU-acquired paresis defined as sum score less than 48
Physical function	Timed Up and Go Test [13]	Time required to stand, walk 3 m, return, and sit	Longer times (>14 s) associated with adverse outcomes, including falls

Abbreviations: *PTSS-10* post-traumatic Stress Syndrome 10-Questions Inventory

Components of the ABCDEF Bundle

A Recommended Strategy to Mitigate the Risk of Post-intensive Care Syndrome

Assess, Prevent, and Manage Pain
- Daily assessment with validated scales, such as the behavioral pain scale
- Prevention and management with goal-directed treatment for pain

Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT)
- Daily safety screen
- Daily sedation interruption and/or minimization of sedation use to target
- Use of sedation scales in goal-directed delivery of medications
- Daily ventilator weaning attempt

Choice of Analgesia and Sedation
- Choice of agent and delivery modality, continuous versus intermittent

Delirium: Assess, Prevent, and Manage
- Daily assessment in all ICU patients
- Avoidance or minimization of medications that exacerbated delirium
- Active management with non-pharmacologic and appropriate pharmacologic treatment

Early Mobility and **E**xercise
- Daily exercise regimens, including ambulation as tolerated

Family Engagement and Empowerment
- Engage and communicate with families on rounds as active participants in patient care
- Facilitate family participation with care tasks in the ICU (e.g. cleaning, feeding)

To complement the ABCDEF bundle, an effective strategy to reduce psychological distress in survivors is the use of the ICU diary [21]. The ICU diary has been shown to reduce post-ICU PTSD symptoms. Used widely throughout Europe (www.icu-diary.org), yet with limited use in the United States given traditionally uncoordinated care between acute care and post-discharge care, an ICU diary is a notebook within which doctors, nurses, family members, and patient visitors can record, in patient-friendly language, information about the patient's hospital course and messages from friends and family. The ICU diary may also include pictures of the patient during the course of

their illness. Post-discharge, patients review the content of the diary with a health care provider as a strategy to fill gaps in their memory regarding the hospitalization and to realign delusional memories with an accurate depiction of the illness narrative. Beyond the positive effect that the ICU diary can have on the patient's psychological condition, its use also appears beneficial to family members. Because it is increasingly recognized that family members of survivors also experience lasting psychological effects, known as Post-Intensive Care Syndrome- Family (PICS-F) [1], the ability to mitigate long-term psychological distress in caregivers is an important one.

Evidence Contour

Effective strategies for use in the ICU and post-discharge are urgently needed to reduce the burden of PICS.

ICU Follow Up Clinic

While conceptually appealing, the benefits of an ICU follow-up clinic have yet to be demonstrated [22]. Following discharge from the ICU, primary care physicians were historically responsible for all follow-up care. Increasingly, however, ICU follow-up clinics staffed by pulmonary and critical care specialists are being established to screen for and address symptoms related to PICS. These specialized clinics employ a multidisciplinary approach with extensive care coordination between physical and occupational therapists, psychologist and psychiatrists, physical medicine and rehabilitation physicians, pulmonary physicians and neurologists. Given the resources required to staff such a clinic, systematic research is required to identify the optimal staffing structure and processes that lead to better patient-centered outcomes.

In the absence of compelling data regarding the optimal approach to longitudinally follow survivors after critical illness, the following "best practice" principles can be applied. First, to address the informational needs of survivors and their caregivers [23], it is critical to increase awareness of PICS so as to inform providers of the anticipated challenges faced by many patients after a critical illness. Second, this knowledge should facilitate discussions between health care providers and the patient and their family regarding what they may encounter following discharge from an ICU. The patient described in the above case may have followed up in an intensive care follow-up clinic or with his primary care physician. Regardless, during clinic visits, a manual to guide and chart the progress made during recovery should be developed and consultations placed with experts to attend to the symptoms and impairments identified (e.g., physical and occupational therapy, psychologists and/or psychiatrists, etc.) (Table 32.1).

Cognitive Rehabilitation

The potential for cognitive rehabilitation as a means to improve the lives of survivors of critical illness exists, yet requires further study. In a small randomized trial of ICU survivors with cognitive or physical impairment at discharge, subjects randomized to receive cognitive and physical rehabilitation in their homes experienced improved executive function at three month follow-up compared to control subjects [24]. More proximally, cognitive rehabilitation initiated in the ICU appears to be feasible [25]. In addition to timely referral to rehabilitation experts, strategies during the ICU stay and beyond should consider incorporating cognitive exercise, given the potential for neural plasticity, and coping and compensation strategies (e.g. memory aids) as means to potentially prevent and remediate neuropsychological impairment. Last, given the relationship between physical and cognitive function [26, 27], physical therapy has the potential to be the most effective means to preserve cognitive function and/or rehabilitate cognitive impairment.

Because long-term impairment may be challenging to effectively rehabilitate, urgent investigation is also needed to understand how ICU

practice can impact long-term health. For example, traditional ventilator strategies in ARDS protocolize oxygenation targets far below normal levels. Because hypoxemia has been associated with long-term cognitive impairment [6], it is plausible that targeting normoxemia in ARDS could result in improved long-term outcomes [28]. Through careful design of future clinical trials, the opportunity exists to better understand the long-term effects of critical care interventions so as to optimize both short- and long-term outcomes and reduce the burden of PICS.

References

1. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40(2):502–9.
2. Mikkelsen ME, Netzer G, Iwashyna TJ. Post-intensive care syndrome (PICS) and post-intensive care syndrome – family (PICS-F). In: UpToDate, Basow DS, editors. UpToDate. Waltham;2014.
3. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983; 67:361–70.
4. Weisaeth L. Torture of a Norwegian ship's crew. The torture, stress reactions and psychiatric after-effects. Acta Psychiatr Scand Suppl. 1989;355:63–72.
5. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010; 304(16):1787–94.
6. Mikkelsen ME, Christie JD, Lanken PN, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. Am J Respir Crit Care Med. 2012;185(12):1307–15.
7. Hopkins RO, Suchyta MR, Snow GL, et al. Blood glucose dysregulation and cognitive outcome in ARDS survivors. Brain Inj. 2010;24(12):1478.
8. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369(14):1306–16.
9. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, Jones RN. Cognitive trajectories after postoperative delirium. N Engl J Med. 2012;3 67:30–9.
10. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695–9.
11. Katz S. Assessing self-maintenance: activities of daily living, mobility and instrumental activities of daily living. J Am Geriatr Soc. 1983;31(12): 721–6.
12. Kleyweg RP, van der Meche FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barre syndrome. Muscle Nerve. 1991;14:1103–9.
13. Bohannon RW. Reference values for the Timed Up and Go Test: a descriptive meta-analysis. J Geriatr Phys Ther. 2006;29(2):64–8.
14. Jackson JC, Pandharipande PP, Girard TD, et al. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. Lancet Resp Med. 2014;2(5):369–79.
15. Pandharipande P, Banerjee A, McGrane S, Ely EW. Liberation and animation for ventilated ICU patients: the ABCDE bundle for the back-end of critical care. Crit Care. 2010;14(3):157.
16. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet. 2008;371(9607):126–34.
17. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomized, controlled trial. Lancet. 2009;373:1874–82.
18. Balas MC, Vasilevskis EE, Olsen KM, et al. Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. Crit Care Med. 2014;42(5):1024–36.
19. Klompas M, Anderson D, Trick W, et al. The preventability of ventilator-associated events: the CDC Prevention Epicenters' Wake Up and Breathe Collaborative. Am J Resp Crit Care Med. 2015; 191:292–301. Epub Nov 4.
20. Calvo-Ayala E, Khan BA, Farber MO, et al. Interventions to improve the physical function of ICU survivors: a systematic review. Chest. 2013;144(5):1469–80.
21. Mehlhorn J, Freytag A, Schmidt K, et al. Rehabilitation interventions for postintensive care syndrome: a systematic review. Crit Care Med. 2014;42(5):1263–71.
22. Jensen JF, Thomsen T, Overgaard D, et al. Impact of follow-up consultations for ICU survivors on post-ICU syndrome: a systematic review and meta-analysis. Int Care Med. 2015;41:763–75.
23. Lee CM, Herridge MS, Matte A, et al. Education and support needs during recovery in acute respiratory distress syndrome. Crit Care. 2009;13:R153.
24. Jackson JC, Ely EW, et al. Cognitive and physical rehabilitation of intensive care unit survivors: results of the RETURN randomized controlled pilot investigation. Crit Care Med. 2012;40(4):1088–197.
25. Brummel NE, Girard TD, Ely EW, et al. Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients:

the Activity and Cognitive Therapy in ICU (ACT-ICU) trial. Intensive Care Med. 2014;40(3): 370–9.
26. Hopkins RO, Suchyta MR, Farrer TJ, Needham D. Improving post-intensive care unit neuropsychiatric outcomes: understanding cognitive effects of physical activity. Am J Respir Crit Care Med. 2012;186(12): 1220–8.
27. Cohen D, Anderson B, Christie JD, et al. Cognitive function, mental health, and health-related quality of life after lung transplantation. Ann Am Thor Soc. 2014;11(4):522–30.
28. Mikkelsen ME, Anderson B, Christie JD, et al. Can we optimize long-term outcomes in acute respiratory distress syndrome by targeting normoxemia? Ann Am Thorac Soc. 2014;11(4):613–8.

33 Management of Decompensated Right Ventricular Failure in the Intensive Care Unit

Rana Lee Adawi Awdish and Michael P. Mendez

Case Presentation

A 64 year old woman with a history of COPD (FEV1 of 1.1 L, 35 % predicted) on supplemental oxygen of 2 L/min by nasal cannula, obesity hypoventilation syndrome, and hypertension, was admitted with a 3-day history of worsening shortness of breath, increased productive cough, and pleuritic chest pain. On admission the patient had an increased white blood cell count (14.5 K), increased oxygen requirement to 6 L/min, and evidence of right lower lobe consolidation on computed tomographic pulmonary angiography (CTPA) (Fig. 33.1). No evidence of pulmonary embolism was seen. Twenty-four hours after admission, the patient developed increased work of breathing, worsening hypoxemia, and bilateral infiltrates on chest radiograph. She was intubated and transferred to the intensive care unit for mechanical ventilation and hemodynamic monitoring.

In the intensive care unit, a central venous catheter was placed which demonstrated central venous pressure (CVP) of 3 cm H_2O and a mixed venous oxygen saturation ($ScvO_2$) of 65 %. She was begun on intermittent sedation, and initial ventilator settings of FiO_2 60 %, tidal volume 450 cc (8 cc/kg ideal body weight), respiratory rate of 16 breaths per minute, and PEEP of 5 mmHg. At these settings, plateau pressure was 24 mmHg and there was no detectable autopeep. A point-of-care ultrasound performed by the intensivist demonstrated preserved left ventricular systolic function, however enlarged right ventricle and septal flattening were noted (Video 33.1). A plethoric inferior vena cava was noted to be discordant with the low CVP.

Question What approach should guide this patient's fluid management?

Answer Proper fluid management is critical for successful management of RV failure.

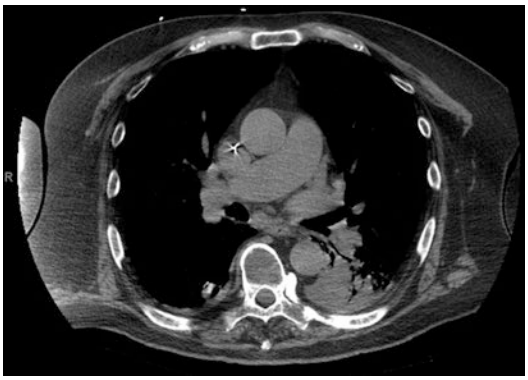


Fig. 33.1 CT scan demonstrating pneumonia in the left lower lobe a Pulmonary to Aorta ratio greater than 1

Electronic supplementary material The online version of this chapter (doi:10.1007/978-3-319-43341-7_33) contains supplementary material, which is available to authorized users.

R.L.A. Awdish
Department of Pulmonary and Critical Care Medicine, Henry Ford Health System, Detroit, MI, USA

M.P. Mendez (✉)
Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA
e-mail: mpmendez@umich.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_33

In this case, given the ongoing infection, vigilance for a decreased intravascular volume must be maintained. With the increased vascular permeability, decreased oral intake and insensible losses related to fever, our patient is at high risk of hypovolemia and ensuing shock. This is accentuated by use of analgesics and sedative medications that are utilized for ventilator synchrony, which contribute to decreased venous tone and reduced right-sided preload [1]. Adequate right-sided filling pressure is a prerequisite for adequate cardiac output and in this patient volume resuscitation should be instituted as quickly as possible, with strict attention to RV parameters and end-organ perfusion.

Review of the patient's outpatient records revealed that she had undergone a work-up for pulmonary hypertension the year prior to presentation, when an echocardiogram performed in the evaluation of worsening lower extremity edema revealed a pulmonary artery systolic pressure (PASP) of 55 mmHg and dilated right ventricle. She subsequently underwent a V/Q scan, which was negative for chronic thromboembolic disease. Screening autoimmune serology was negative. Following diuresis, a right heart catheterization in euvolemic state was reported as: mean right atrial pressure (mRAP) of 14 mmHg, pulmonary artery pressure (systolic/diastolic/mean) 65/22/32 mmHg, PCWP 15 mmHg, cardiac output/cardiac index by Fick of 4.2 Lmin/1.8 L/min/m^2. The patient's pulmonary hypertension was judged to be primarily Group 3 in nature, related to chronic lung disease and hypoxemia and efforts focused on optimizing underlying comorbid conditions. Her baseline hemodynamics were useful in establishing her mRAP or right-sided filling pressures as being elevated. This gave a target for resuscitation, namely a CVP > 14 mmHg. Given the addition of positive pressure mechanical ventilation, an increased right-ventricular afterload, a target filling pressure of 16–18 mmHg would be an appropriate initial target, though multiple endpoints of perfusion should still be monitored.

Principles of Management

Diagnosis

This patient is manifested clinical and echocardiographic evidence of right ventricular dysfunction, which given the patient's history and negative CTPA is likely acute on chronic. Determining the causes of RV failure, specifically whether it is the result of established pulmonary vascular disease and secondary to concomitant disease states or a result of an acute increase in RV afterload versus RV ischemia is a critical step for patients presenting to the ICU with evidence of RV dysfunction. Also critical, though often difficult, is differentiating pressure overload from volume overload. If echocardiographic and CT imaging indicate an acute pulmonary embolism as a cause, relieving the increase in pressure/afterload attributed by the PE is the first and most critical treatment. If RV ischemia is identified, the treatment algorithm similarly shifts to reperfusion strategies. In situations where RV failure is acute on chronic as is the case with this patient, the conditions responsible for the chronic RV failure cannot be readily reversed and management options are limited to optimizing RV function.

In order to optimize RV function, it is necessary to first have accurate assessment of filling pressures and baseline hemodynamics. The utility of invasive monitoring for this purpose is controversial and will be addressed below. In addition to bedside echocardiography performed by the intensivist [2], formal assessment with transthoracic echocardiography (TTE) offers added utility [3]. In addition to assessing filling pressures, TTE can contribute to the quantification of degree of contribution of LV dysfunction and valvular heart disease. Estimates of pulmonary artery systolic pressure PASP on TTE are not indicative of severity of dysfunction as PASP falls with fall in cardiac output and attention is best directed at other surrogates of severity. RV systolic function can be assessed via the tricuspid annular plane systolic excursion (TAPSE) by measuring the systolic displacement of the RV base toward the

RV apex [4]. This has been shown to correlate well with RV ejection fraction, and values below 1.8 cm indicate a low RV stroke volume index with high sensitivity, though utility in acute settings is not well validated [5]. In addition to low TAPSE, prognostic indicators of poor prognosis in pulmonary hypertension are right atrial enlargement, pericardial effusion [6], and septal displacement, but this is not well studied in critically ill patients [7]. Though TTE estimates of PASP generally correlates with invasive measurements, the frequency of variance increases in patients with chronic lung disease [8], and similarly positive pressure ventilation can contribute to inaccurate assessment of pressure.

CTPA, though often obtained to exclude other causes of respiratory failure, may suggest the presence of right ventricular dysfunction. A ratio of main pulmonary artery to aortic diameter of greater than 1 correlates with elevated pulmonary artery pressure generally (Fig. 33.1) [9]. Alternatively, a pulmonary artery with a diameter greater than 2.9 cm has a high specificity for the presence of PH [9]. Other radiographic signs include increased right ventricular wall thickness (>4 mm), right ventricular dilation defined as right ventricle ventricle–to–left ventricle diameter ratio of more than 1:1 at the midventricular level on axial images, dilatation of the inferior vena cava and hepatic veins; and pericardial effusion [10, 11].

Monitoring of End-Organ Perfusion

Monitoring of endpoints of perfusion in patients with RV failure is critical, as acidemia that results from hypoperfusion and elevated lactate can worsen hypoxemic vasoconstriction in the pulmonary vascular bed, thus increasing afterload [12]. That said, monitoring for these patients can be accomplished by modalities utilized in the care of any critically ill patient. A central venous catheter that allows serial measurement of $ScvO_2$ and CVP is a valuable tool. By accurately assessing $ScvO_2$ and monitoring for values lower than 70%, the SvO_2 can be both an indicator of reduced cardiac output and provide a measure of current filling pressure. Superior vena cava central access is favored for this, as it is felt to be a more reliable surrogate of SvO_2 if well-positioned [13]. Similarly, serum lactate and urine output remain important indicators of tissue perfusion.

Serial point-of-care ultrasound may also be helpful, both for assessing hypovolemic states as well as identifying optimal timing to offload the RV [14]. For example, if TTE reveals RV dilation and impingement on LV filling this would suggest reduction in preload through diuresis may be needed. However, with hypovolemia, the inferior vena cava may not collapse, as pressure overload can predominate, even in settings of low intravascular volume (Video 33.2).

Pulse pressure variation (PPV) and stroke volume variation (SVV) are well-established modalities in the ICU, however the utility in pulmonary hypertension is not well established [15]. Small studies have demonstrated that PPV is in fact not predictive of increased stroke volume in patients with pulmonary hypertension [16, 17]. This is likely because in pulmonary hypertension, PPV and SVV are related to an inspiratory increase in RV afterload rather than a decrease in RV preload, and thus do not reliably indicate fluid responsiveness. Conceptually, lack of response to a volume challenge in the setting of high PPV or SVV may actually serve as an indicator of RV dysfunction.

Optimization of Right-Sided Filling Pressures

The CVP is a reliable surrogate of right atrial pressure [18]. The CVP pressure tracing consists of three positive waves (a, c, and v) and two descents (termed x and y) (Fig. 33.2). The CVP is measured immediately prior to the c wave when there is continuity with the right ventricle and gives an accurate estimate of preload. Optimally, the CVP is measured at end-expiration, when there is a net neutral pleural pressure and respiratory effect on central pulmonary vasculature is minimized [19]. Patients with chronic

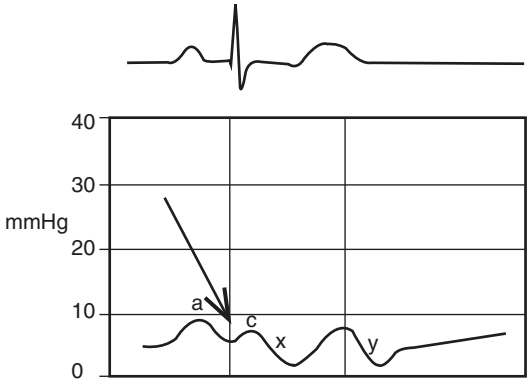


Fig. 33.2 The CVP is measured directly before the c wave (*arrow*)

compensated RV dysfunction generally have higher CVP at baseline and tend to be dependent on higher right-sided preload. Though there is considerable variation not only between individual patients, but also in varying states of afterload, in general preload goals should be targeted to maintain a moderately elevated filling pressure. Initial targets of 8–12 mmHg, with adjustment for observations of surrogates of low cardiac output or hypoperfusion are prudent. Should one have access to baseline hemodynamics for any individual patient, whether mRAP from right heart catheterization or estimate of CVP from TTE in a steady-state, these values can guide fluid management in a far more individualized way, allowing of course for variability and progression over time.

Reversal of Conditions that Heighten Pulmonary Vascular Tone

Many of the diseases that affect patients in the intensive care unit can worsen pulmonary vascular resistance (PVR). These conditions must be aggressively addressed in the setting of acute on chronic RV failure as they have a deleterious effect on the RV by increasing afterload. Perhaps most commonly implicated is hypoxic pulmonary vasoconstriction that occurs as a response to decreased oxygen saturation. Though the vasoconstriction is most pronounced in the setting of low alveolar oxygen tension, it is also affected by hypoxemia in the pulmonary and bronchial artery beds. Standard intensive care monitoring adequately assesses systemic oxygenation, but pulmonary arterial oxygenation is less easy to assess without invasive monitoring device. Measuring $ScvO_2$ can be a useful surrogate. Situations that worsen the vasoconstrictive response and PVR include hypercapnea and acidemia, and efforts to avoid each must be made [20, 21]. This is difficult when patients progress to ARDS and standard of care would mandate low-tidal volume ventilation and permissive hypercapnea. This unique situation will be elaborated upon below.

Ventilation Strategy

In general, when faced with RV dysfunction, attention to avoiding exposure to hypoxemia primarily and secondarily to hypercapnea and ensuing acidosis is prioritized [22]. As high lung volumes and associated distending pressures can worsen RV afterload, ventilating near functional residual capacity is favored [23, 24]. Though respiratory therapist driven ventilator liberation protocol is still relevant in this group, the presence of higher degrees of hypoxemia may be tolerated as many will have right to left shunting through patent foramen ovale (PFO). Should worsening hypoxemia be noted with increasing levels of PEEP, a dedicated bubble study for identification of occult PFO should be obtained for confirmation. Generally, high levels of PEEP should be avoided as autopsy studies suggest greater than 30 % of the population has PFO [25] and in the setting of right ventricular dysfunction and increased afterload there may be increased right to left shunting. APRV is discussed below.

Supportive Care

Early, broad-spectrum antibiotics, adherence to proven ventilator bundle strategies to minimize risk of ventilator associated events and complications are of equal importance in patients with RV dysfunction. Additionally, compliance with ABCDE protocol to ensure timely liberation of patients from mechanical ventilator support is essential [26].

Evidence Contour

Several aspects of management in the patient with acute decompensated RV failure remain without consensus in the face of available clinical trials. There are theoretical benefits to certain therapeutic options, and animal models support pathophysiologic rationale behind these choices.

Pulmonary Artery Catheter Use in Decompensated RV Failure

When reliable measurement of pulmonary hemodynamics is needed, pulmonary artery catheterization (PAC) provides valuable information on cardiac output, pulmonary artery pressure and filling pressures. Although the routine use of a PAC has not been well studied in the management of RV failure in the intensive care unit, serial measurement of hemodynamics can add value particularly in complex cases [24]. For example, in situations in which RV function is highly variable and dependent on small changes in volume or preload, then having serial measurements of cardiac output as fluid resuscitation is effected can be critical. Should the patient progress to require inotropic support, a PAC may be of value in titration of effect. Because of the complexity and small but real risk of complications such as pulmonary artery rupture, the benefit of PAC placement should be felt to outweigh the risks when used [27].

Choice of Vasopressor

Patients with chronic RV dysfunction often tolerate infection poorly, as systemic vasodilation and decreased preload impair already compromised RV function [28]. As such, even with appropriate fluid management and optimization of filling pressures, they may progress to shock and require vasopressor support. There is no ideal vasopressor, as none increases systemic pressure and RV contractility without increasing PVR [18]. However, norepinephrine is favored for patients with RV dysfunction who require pressor support [29]. Norepinephrine has predominantly α1 effects, with limited β1 receptor stimulation. In a small study of patients with sepsis with right heart failure, norepinephrine use was associated with improved RV myocardial oxygen delivery. Phenylephrine is not favored as it can cause reflex bradycardia, which is especially troubling for patients in whom tachycardia may be their sole means of increasing cardiac output, when stroke volume is relatively fixed [30]. Epinephrine is a mixed α/β receptor agonist that can induce vasoconstriction and increase inotropy [31]. Vasopressin at high doses causes pulmonary and coronary artery vasoconstriction [32]. Taken in aggregate, norepinephrine is a reasonable choice in these difficult clinical scenarios.

Selective Use of Inotropic Agents

Inotropic agents should be considered only when there is clear evidence of inadequate tissue perfusion despite optimization of volume status, preload and afterload. The risk of all inotropes is the incidence of tachyarrhythmias. Low-dose dopamine is a reasonable option to improve cardiac output without increasing PVR in patients with RV failure [33]. Dobutamine acts via β1 receptor, but can cause vasodilatation due to β2 effects and as such, higher doses should be avoided [34]. Milrinone is often the agent of choice, as it is the only non-adrenergic inotrope, and can improve inotropy while promoting pulmonary arterial vasodilatation [35].

Use of Selective Pulmonary Vasodilators

There are situations in which a patient has met endpoints in terms of preload, volume status, and oxygenation but there is not an appreciable improvement in RV function. Though vasodilating agents are an appealing choice, it is important to remember that no pulmonary vasodilator has been approved for the treatment of RV failure in critically ill patients [18]. In the setting of associated lung disease, administration can worsen gas exchange by blunting hypoxic pulmonary vasoconstriction and impairing V/Q matching. In the

setting of left heart disease, the influx of volume accomplished through pulmonary vasodilation may be poorly tolerated by the LV and result in worsening of hypoxemic respiratory failure [36].

Despite the inherent risks, there are times when attempting to offload the RV is the last best option. There is variability in the risks of each vasodilating agent. Inhaled nitric oxide (iNO) is a potent pulmonary vasodilator with an extremely short half-life, making it an appealing option. Importantly, because it preferentially affects the areas of the lung that are well ventilated, it can improve oxygenation by decreasing shunt fraction. There is evidence that iNO improves RV function and mixed venous oxygen saturation in patients with acute RV failure, though again it is difficult to extrapolate to acute on chronic RV failure [37]. Similarly, there are prostacyclin derivatives available by inhalation, but little is known about their use in critical illness.

Phosphodiesterase 5 (PDE5) inhibitors reduce PVR and may improve RV contractility, but little is known about their use in critical illness. These agents increase pulmonary vasodilation via the nitric oxide pathway. There is evidence in animal models that these agents may improve RV function in patients with chronic pulmonary hypertension who develop acute RV failure [38]. In contrast to the inhaled agents, PDE5 inhibitors can cause systemic hypotension and must be used cautiously in patients who are hemodynamically unstable [39]. This combined with their longer half-life makes their use particularly best suited for a pulmonary hypertension specialist. And this is true of the remainder of the available agents including intravenous prostacyclin analogues.

Ventilatory Considerations in the Face of ARDS

Principles surrounding the ventilator management of these patients are confounded in the face of ARDS. Acute hypoxia as a cause of pulmonary vasoconstriction is well described and is worsened by many factors, including acidosis and hypercapnia [40]. The evidence for benefit for a low tidal volume strategy is sound, and should be undertaken in a manner so as to avoid permissive hypercapnia, which will worsen pulmonary vasoconstriction. More straightforward perhaps is the recommendation that in refractory hypoxemia, a high PEEP strategy should be avoided. First, high PEEP leads to RV dilatation and reduced cardiac output in severe ARDS. Second, as many patients have occult PFO, which in the setting of chronic RV dysfunction manifest right to left shunting, increasing levels of PEEP can worsen shunting. Both atelectasis and ventilation at high lung volumes should therefore be avoided in patients with RV dysfunction as both worsen RV afterload. Prone ventilation may also reduce plateau pressures and pCO_2 sufficiently to improve acute RV failure, but evidence is limited [41, 42].

Airway pressure release ventilation (APRV) is sometimes employed for refractory hypoxemic respiratory failure [43]. As such, the setting required to successfully oxygenate a patient who has been refractory to conventional mechanical ventilation involve relatively high pressure settings. In patients with PH, APRV can increase PVR by prolonging the time exposed to high distending pressures. This increases afterload through compression of the alveolar vessels and likely outweighs the benefits conferred by reversing hypoxemia.

Extra Corporeal Membrane Oxygenation (ECMO)

Patients with refractory RV failure may benefit from support with ECMO as a bridge to transplantation. At centers with the expertise in this modality of support, the decision to proceed hinges upon whether the patient has been optimized with medical therapy and whether the patient is a reasonable candidate for lung or heart-lung transplantation. In order to provide hemodynamic and ventilatory support veno-arterial ECMO is preferred [44]. Use of this modality is contingent upon the patient's ability to tolerate intense anticoagulation and the possibility to achieve transplant within a reasonable amount of time.

References

1. Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med. 2002;30(1): 119–41.
2. Beaulieu Y. Bedside echocardiography in the assessment of the critically ill. Crit Care Med. 2007;35(5 Suppl):S235–49.
3. Romero-Bermejo FJ, Ruiz-Bailen M, Guerrero-De-Mier M, Lopez-Alvaro J. Echocardiographic hemodynamic monitoring in the critically ill patient. Curr Cardiol Rev. 2011;7(3):146–56.
4. Sato T, Tsujino I, Ohira H, Oyama-Manabe N, Yamada A, Ito YM, et al. Validation study on the accuracy of echocardiographic measurements of right ventricular systolic function in pulmonary hypertension. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr. 2012; 25(3):280–6.
5. Forfia PR, Fisher MR, Mathai SC, Housten-Harris T, Hemnes AR, Borlaug BA, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med. 2006;174(9): 1034–41.
6. Batal O, Dardari Z, Costabile C, Gorcsan J, Arena VC, Mathier MA. Prognostic value of pericardial effusion on serial echocardiograms in pulmonary arterial hypertension. Echocardiography. 2015;32:1471–6.
7. Raymond RJ, Hinderliter AL, Willis PW, Ralph D, Caldwell EJ, Williams W, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. J Am Coll Cardiol. 2002;39(7):1214–9.
8. Arcasoy SM, Christie JD, Ferrari VA, Sutton MS, Zisman DA, Blumenthal NP, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med. 2003;167(5):735–40.
9. Corson N, Armato 3rd SG, Labby ZE, Straus C, Starkey A, Gomberg-Maitland M. CT-based pulmonary artery measurements for the assessment of pulmonary hypertension. Acad Radiol. 2014;21(4):523–30.
10. Frazier AA, Burke AP. The imaging of pulmonary hypertension. Semin Ultrasound CT MR. 2012;33(6): 535–51.
11. Tan RT, Kuzo R, Goodman LR, Siegel R, Haasler GB, Presberg KW. Utility of CT scan evaluation for predicting pulmonary hypertension in patients with parenchymal lung disease. Medical College of Wisconsin Lung Transplant Group. Chest. 1998;113(5):1250–6.
12. Rudolph AM, Yuan S. Response of the pulmonary vasculature to hypoxia and H+ ion concentration changes. J Clin Invest. 1966;45(3):399–411.
13. Walley KR. Use of central venous oxygen saturation to guide therapy. Am J Respir Crit Care Med. 2011;184(5):514–20.
14. Beaulieu Y. Specific skill set and goals of focused echocardiography for critical care clinicians. Crit Care Med. 2007;35(5 Suppl):S144–9.
15. Pinsky MR. Functional haemodynamic monitoring. Curr Opin Crit Care. 2014;20(3):288–93.
16. Wyler von Ballmoos M, Takala J, Roeck M, Porta F, Tueller D, Ganter CC, et al. Pulse-pressure variation and hemodynamic response in patients with elevated pulmonary artery pressure: a clinical study. Crit Care. 2010;14(3):R111.
17. Mahjoub Y, Pila C, Friggeri A, Zogheib E, Lobjoie E, Tinturier F, et al. Assessing fluid responsiveness in critically ill patients: false-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle. Crit Care Med. 2009;37(9):2570–5.
18. Ventetuolo CE, Klinger JR. Management of acute right ventricular failure in the intensive care unit. Ann Am Thorac Soc. 2014;11(5):811–22.
19. Gore JA, Alpert JS, Benntti JR, Kotilainen PR. Handbook of hemodynamic monitoring. Little Brown and Company, Boston, MA, USA; 1985.
20. Harvey RM, Enson Y, Betti R, Lewis ML, Rochester DF, Ferrer MI. Further observations on the effect of hydrogen ion on the pulmonary circulation. Circulation. 1967;35(6):1019–27.
21. Viitanen A, Salmenpera M, Heinonen J. Right ventricular response to hypercarbia after cardiac surgery. Anesthesiology. 1990;73(3):393–400.
22. Viitanen A, Salmenpera M, Heinonen J, Hynynen M. Pulmonary vascular resistance before and after cardiopulmonary bypass. The effect of PaCO2. Chest. 1989;95(4):773–8.
23. Dambrosio M, Fiore G, Brienza N, Cinnella G, Marucci M, Ranieri VM, et al. Right ventricular myocardial function in ARF patients. PEEP as a challenge for the right heart. Intensive Care Med. 1996;22(8):772–80.
24. Hoeper MM, Granton J. Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. Am J Respir Crit Care Med. 2011;184(10):1114–24.
25. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc. 1984;59(1):17–20.
26. Pandharipande P, Banerjee A, McGrane S, Ely EW. Liberation and animation for ventilated ICU patients: the ABCDE bundle for the back-end of critical care. Crit Care. 2010;14(3):157.
27. Hadian M, Pinsky MR. Evidence-based review of the use of the pulmonary artery catheter: impact data and complications. Crit Care. 2006;10 Suppl 3:S8.
28. Chan CM, Klinger JR. The right ventricle in sepsis. Clin Chest Med. 2008;29(4):661–76. ix.
29. Schreuder WO, Schneider AJ, Groeneveld AB, Thijs LG. Effect of dopamine vs norepinephrine on hemodynamics in septic shock. Emphasis on right ventricular performance. Chest. 1989;95(6):1282–8.
30. Rich S, Gubin S, Hart K. The effects of phenylephrine on right ventricular performance in patients with pulmonary hypertension. Chest. 1990;98(5):1102–6.
31. Le Tulzo Y, Seguin P, Gacouin A, Camus C, Suprin E, Jouannic I, et al. Effects of epinephrine on right ven-

tricular function in patients with severe septic shock and right ventricular failure: a preliminary descriptive study. Intensive Care Med. 1997;23(6):664–70.
32. Leather HA, Segers P, Berends N, Vandermeersch E, Wouters PF. Effects of vasopressin on right ventricular function in an experimental model of acute pulmonary hypertension. Crit Care Med. 2002;30(11): 2548–52.
33. Holloway EL, Polumbo RA, Harrison DC. Acute circulatory effects of dopamine in patients with pulmonary hypertension. Br Heart J. 1975;37(5):482–5.
34. Acosta F, Sansano T, Palenciano CG, Falcon L, Domenech P, Robles R, et al. Effects of dobutamine on right ventricular function and pulmonary circulation in pulmonary hypertension during liver transplantation. Transplant Proc. 2005;37(9):3869–70.
35. Chen EP, Bittner HB, Davis Jr RD, Van Trigt 3rd P. Milrinone improves pulmonary hemodynamics and right ventricular function in chronic pulmonary hypertension. Ann Thorac Surg. 1997;63(3):814–21.
36. Vachiery JL, Adir Y, Barbera JA, Champion H, Coghlan JG, Cottin V, et al. Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol. 2013; 62(25 Suppl):D100–8.
37. Bhorade S, Christenson J, O'Connor M, Lavoie A, Pohlman A, Hall JB. Response to inhaled nitric oxide in patients with acute right heart syndrome. Am J Respir Crit Care Med. 1999;159(2):571–9.
38. Nagendran J, Archer SL, Soliman D, Gurtu V, Moudgil R, Haromy A, et al. Phosphodiesterase type 5 is highly expressed in the hypertrophied human right ventricle, and acute inhibition of phosphodiesterase type 5 improves contractility. Circulation. 2007;116(3):238–48.
39. Vachiery JL, Huez S, Gillies H, Layton G, Hayashi N, Gao X, et al. Safety, tolerability and pharmacokinetics of an intravenous bolus of sildenafil in patients with pulmonary arterial hypertension. Br J Clin Pharmacol. 2011;71(2):289–92.
40. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000;342(18):1301–8.
41. Repesse X, Charron C, Vieillard-Baron A. Acute cor pulmonale in ARDS: rationale for protecting the right ventricle. Chest. 2015;147(1):259–65.
42. Jozwiak M, Teboul JL, Anguel N, Persichini R, Silva S, Chemla D, et al. Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2013;188(12):1428–33.
43. Varpula T, Valta P, Niemi R, Takkunen O, Hynynen M, Pettila VV. Airway pressure release ventilation as a primary ventilatory mode in acute respiratory distress syndrome. Acta Anaesthesiol Scand. 2004;48(6): 722–31.
44. Olsson KM, Simon A, Strueber M, Hadem J, Wiesner O, Gottlieb J, et al. Extracorporeal membrane oxygenation in nonintubated patients as bridge to lung transplantation. Am J Transpl Off J Am Soc Transpl Am Soc Transpl Surg. 2010;10(9):2173–8.

Diffuse Alveolar Hemorrhage

34

Joshua Smith and Mark Daren Williams

Case Presentation

A 43-year-old Hispanic male originally from Honduras presented to the Emergency room with cough producing yellow sputum for 1 month, with recent change to blood tinged over the previous days. His past medical history was pertinent for hypertension and end stage renal disease requiring thrice weekly hemodialysis. He had missed dialysis for the previous week prior to presentation due to bad weather. He also reported fever, chills, and sore throat with the onset of hemoptysis. Of note, the patient had presented to another local hospital 2 months prior with similar symptoms of hemoptysis. He was evaluated by gastroenterology and otolaryngology and an endoscopy and laryngoscopy were performed. There were no obvious signs of bleeding but endoscopy did note blood emanating from the larynx. At presentation, his physical exam was notable for bilateral inspiratory rales with normal vital signs including oxygen saturation of 98 % on room air.

J. Smith, MD
Internal Medicine – Division of Pulmonary and Critical Care Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

M.D. Williams, MD, FCCP (✉)
Pulmonary/Critical Care Medicine, Indiana University School of Medicine, Indianapolis, IN, USA
e-mail: drmarkdwilliams@gmail.com

He was initially diagnosed with end-stage renal failure 18 months prior following a motor vehicle accident. The patient was uninjured but was noted to have a serum creatinine of 21 mg/dl. A renal ultrasound showed moderate to marked cortical hyperechoic texture suggesting renal parenchymal disease attributed to long-standing hypertension. He was started on hemodialysis and remained compliant despite some logistical challenges regarding his immigrant status. The patient had lived in the United States for the previous 10 years with no recent travel or sick contacts. He denied any use of tobacco, alcohol, or illicit drug use. He previously worked as a roofer, but was currently unemployed due to his dialysis dependence.

At the time of presentation, his laboratory data was notable for anemia with hemoglobin of 5.9 g/dl, Potassium 6.6 mmol/L, BNP 2092 pg/ml and serum creatinine 23 mg/dl. A chest x-ray showed multifocal bilateral alveolar opacities (Figs. 34.1 and 34.2). The patient was initially treated with hemodialysis, broad spectrum antibiotics, and placed in respiratory isolation for evaluation of tuberculosis. The patient reported that his hemoptysis improved significantly following serial sessions of dialysis, yet chest imaging remained unchanged. Sputum culture, respiratory viral antigen panel, and AFB smears were negative. A bronchoscopy was performed 4 days after admission and revealed a progressively bloody bronchoalveolar lavage (Fig. 34.3) consistent with a diagno-

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_34

sis of diffuse alveolar hemorrhage. Serologic analysis confirmed the diagnosis.

Question What is the diagnosis?

Answer Capillaritis with diffuse alveolar hemorrhage

This patient presented with hemoptysis confirmed to be diffuse alveolar hemorrhage and chronic renal failure. The initial suspected etiology was volume overload due to missed dialysis sessions due to the elevated BNP level. The patient was treated conservatively with dialysis and while his reported hemoptysis improved, his chest x-ray showed persistent alveolar infiltrates. The serologic analysis that confirmed the diagnosis included Antinuclear Antibody of 1:360, P-ANCA positivity, and antibody to Myeloperoxidase of greater than 8.0 units. The constellation of diffuse alveolar hemorrhage, renal involvement, and p-ANCA/MPO positivity confirmed a diagnosis of Microscopic Polyangiitis. Imaging of the sinuses showed no signs of inflammation of the upper respiratory tract. The patient was treated with prednisone and cyclophosphamide pulse dosing for six doses. He had one subsequent episode of hemoptysis requiring hospitalization 1 month after initial presentation. In general, he responded well to treatment and was weaned from corticosteroids over the next 3 months after completion of cyclophosphamide with improvement on chest imaging (Fig. 34.4).

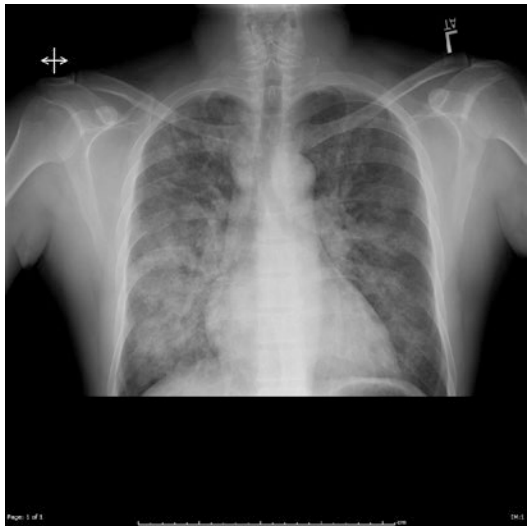


Fig. 34.1 Chest X-ray at initial presentation showing multifocal bilateral alveolar opacities

Principles of Management

Differential Diagnosis

The differential diagnosis for diffuse alveolar hemorrhage can be quite extensive ranging from autoimmune to coagulopathy to medications. Three

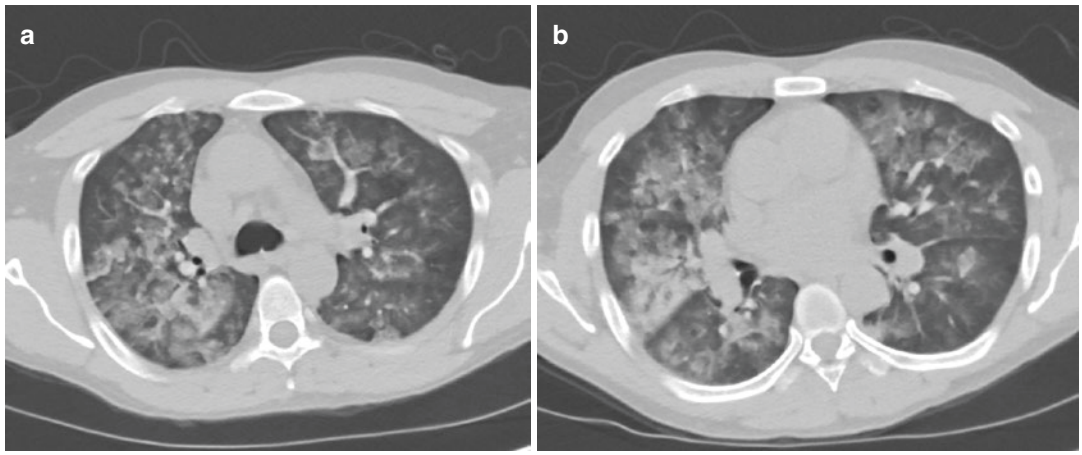


Fig. 34.2 (**a**, **b**) Chest CT images performed after hemodialysis showing diffuse bilateral alveolar opacities

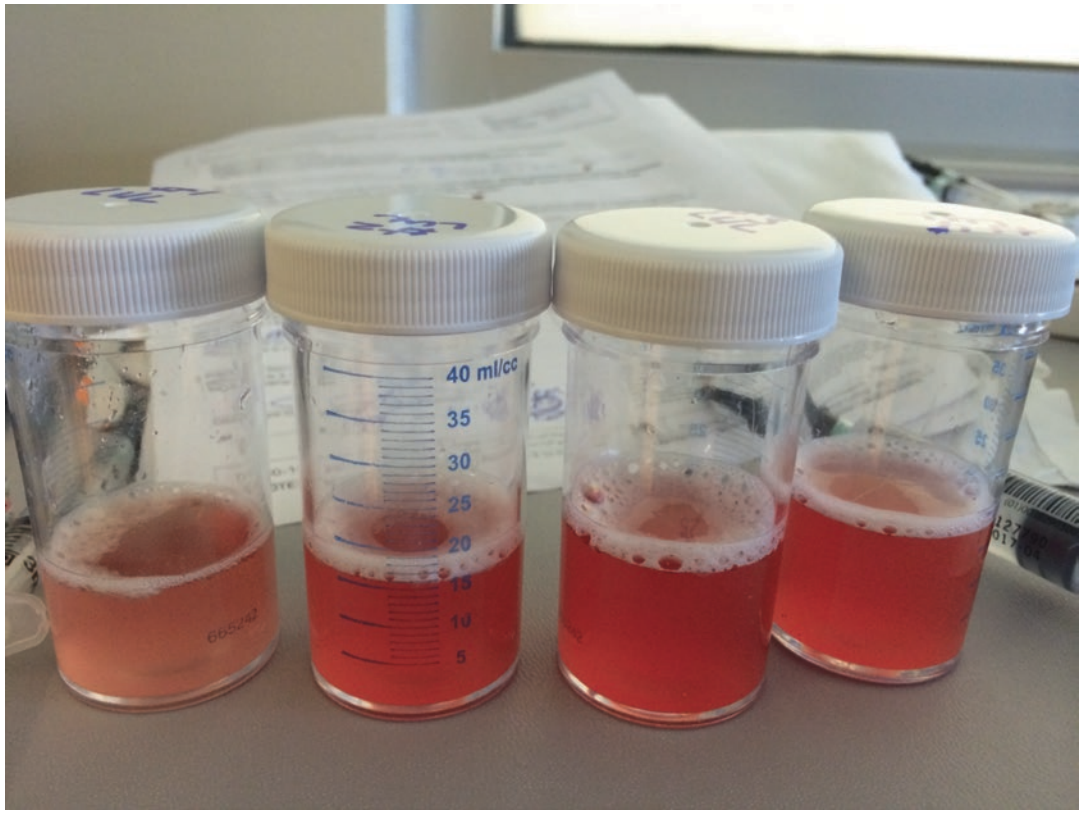


Fig. 34.3 Sequential bronchoalveolar lavages starting left to right showing progressively bloody return

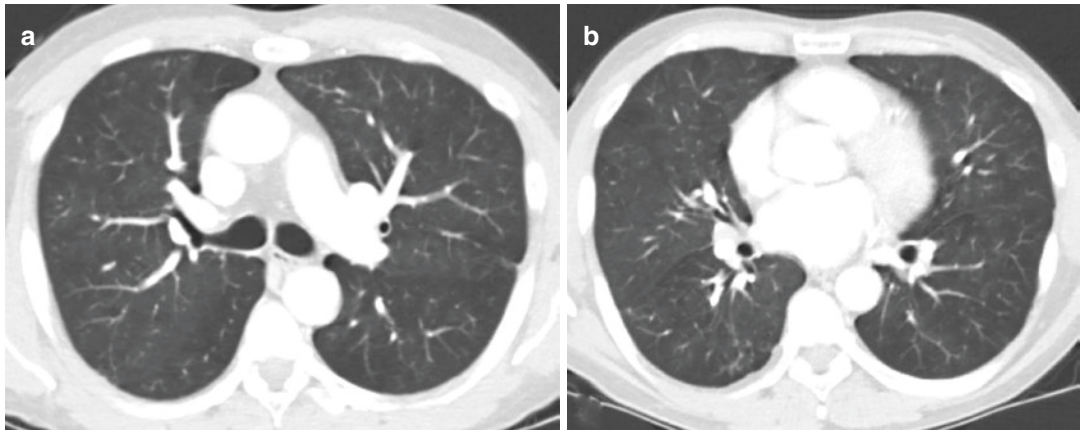


Fig. 34.4 (**a**, **b**) Chest CT images performed after 1 year of immunosuppressive treatment showing resolution of alveolar opacities

characteristic patterns have been identified: Capillaritis, 'Bland' pulmonary hemorrhage, and alveolar bleeding due to another process [1, 2]. Capillaritis is the most common cause of DAH and is typically a result of antibody-mediated cell damage. Autoimmune conditions associated with DAH include antineutrophil cytoplasmic antibody (ANCA) associated vasculitides,

Goodpasture Syndrome, Systemic Lupus Erythematosus (Table 34.1). Initial evaluation of a patient with hemoptysis and suspected diffuse alveolar hemorrhage typically includes fiberoptic bronchoscopy to identify a source of bleeding, identification of potential infectious etiologies, and serologic workup for autoimmune conditions.

Classification

Microscopic Polyangiitis (MPA) is a member of the group of ANCA-associated vasculitides. This group also includes granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA or Churg-Strauss Syndrome). These diseases are characterized by pauci-immune necrotizing inflammation of small vessels [3]. MPA has previously been described as a subgroup of Polyarteritis Nodosa (small vessel form) and is distinguished from GPA by the absence of granuloma formation. MPA is most commonly associated with rapidly progressive glomerulonephritis, although alveolar hemorrhage has been reported in up to 12–29 % of cases [4].

Diagnosis

The diagnosis of ANCA-associated vasculitides is usually based upon findings of pulmonary and/or renal abnormalities with small-vessel necrotizing inflammation with the presence of autoantibodies directed against neutrophilic antigens. Previously, ANCA directed antibodies were classified as cytoplasmic-pattern and perinuclear-patter, c-ANCA and p-ANCA, respectively. The two ANCA antigens commonly identified are proteinase 3 (PR3) and myeloperoxidase (MPO). MPO is more commonly associated with microscopic polyangiitis with a sensitivity of 50–70 %, although PR3 has been identified in cases of MPA with a sensitivity of 26 % [5–7]. Specificity of the combination of P-ANCA and MPO for ANCA-associated vasculitides is significantly greater at 99.8 % [8]. In a review of patients with MPA and alveolar hemorrhage, 14

Table 34.1 Causes of diffuse alveolar hemorrhage

Capillaritis
Granulomatosis with polyangiitis (GPA)
Churg-Strauss syndrome
Microscopic polyangiitis (MPA)
Isolated pauci-immune pulmonary capillaritis
Idiopathic pauci-immune glomerulonephritis
Primary immune complex-mediated vasculitis
Goodpasture's syndrome
Henoch-Schonlein purpura
Systemic lupus erythematosus
Rheumatoid arthritis
Antiphospholipid antibody syndrome
Mixed connective tissue disease
Polymyositis/dermatomyositis
Essential cryoglobulinemia
Behcet's disease
Acute lung transplantation rejection
Autologous bone marrow transplantation
Bland Pulmonary Hemorrhage
Idiopathic pulmonary hemosiderosis
Coagulopathy: anticoagulants, anti-platelet, thrombolytics, DIC
Mitral stenosis, pulmonary veno-occlusive disease
Infection: human immunodeficiency virus infection, infective endocarditis
Toxin or inhalation injury: isocyanates, crack cocaine, retinoic acid
Drug-associated disease: propylthiouracil, diphenylhydantoin, amiodarone, mitomycin,
D-penicillamine, sirolimus, methotrexate, haloperidol, nitrofurantoin, gold,
all-trans-retinoic acid (ATRA), bleomycin, montelukast, zafirlukast, infliximab
Alveolar bleeding due to another condition
Diffuse alveolar damage
Pulmonary embolism
Sarcoidosis
High-altitude pulmonary edema, barotrauma
Infection: invasive aspergillosis, cytomegalovirus infection, legionellosis, herpes simplex virus infection,
mycoplasma, hantavirus infection, leptospirosis, other bacterial pneumoniae
Malignant conditions
Lymphangioleiomyomatosis
Tuberous sclerosis
Pulmonary capillary hemangiomatosis
Lymphangiography

out of 27 patients revealed p-ANCA positivity while 11 out of 27 patients were c-ANCA positive [4]. Among those with p-ANCA antibodies, 12 out of 12 patients were positive for MPO specific antibodies. The requirement of biopsy for the diagnosis of ANCA associated vasculitides remains controversial. In the correct clinical setting with rapidly progressive glomerulonephritis, radiographic abnormalities, and serologic confirmation of antibody, the diagnosis of ANCA-associated vasculitis can be determined. Given the relapsing nature of disease and requirements for prolonged immunosuppression, it is suggested that confirmation of diagnosis by histopathology be determined whenever possible.

Treatment

Historically, initial management of ANCA-associated vasculitides has centered on immunosuppression with corticosteroids and cyclophosphamide. The goal of treatment is induction of remission and maintenance of disease suppression. Therapy is typically tailored to severity of disease, notably mild vs. moderate to severe. These determinations are based upon organ-threatening or life-threatening manifestations. Pulmonary involvement, and specifically alveolar hemorrhage, is considered moderate to severe disease. Plasmapheresis has been shown to be beneficial in patients with diffuse alveolar hemorrhage and ANCA-associated vasculitis [9].

Evidence Contour

Rituximab

Recently, there have been alternative treatment options identified in the treatment of ANCA-associated vasculitides. Cyclophosphamide carries several adverse reactions including cytopenias, infertility, bladder injury, and risk of malignancy. It has been identified that B lymphocytes play an integral in role in the pathogenicity of auto-immunity [10]. Rituximab, an anti-CD20 monoclonal antibody, has been successfully used to reduce B-lymphocyte populations. Since 2010, there has been growing evidence that Rituximab can be used as an alternative to cyclophosphamide in the treatment of ANCA-associated vasculitides. When compared with cyclophosphamide, Rituximab was found to be non-inferior at induction of remission and maintenance of remission [11, 12]. In fact, Rituximab was found to be more effective for inducing remission of relapsing disease (67 % vs. 42) [11]. Rituximab has been found to be superior to azathioprine in disease remission over 2 years [13]. Thus, rituximab has been shown to be a viable option for treatment of ANCA-associated vasculitides. While the patient in the case report was treated with cyclophosphamide, the use of rituximab could have been entertained.

Recombinant Factor VII

Refractory diffuse alveolar hemorrhage can present a therapeutic dilemma. Systemic recombinant Factor VII has been successfully used in a case of massive hemoptysis due to community acquired pneumonia [14]. Case reports and observational studies have shown a beneficial effect of intrapulmonary administration of activated recombinant factor VII in cases of refractory diffuse alveolar hemorrhage [15, 16]. Primarily, this practice has been shown to be beneficial in cases of DAH in allogeneic hematopoetic stem cell transplant recipients. Limited case reports, however, have reported successful cessation of bleeding in cases of ANCA-associated vasculitis [15, 17]. At this time, use of recombinant Factor VII is considered "off-label" but further study is warranted for general use in cases of diffuse alveolar hemorrhage refractory to standard therapy.

References

1. Ioachimescu OC, Stoller JK. Diffuse alveolar hemorrhage: diagnosing it and finding the cause. Cleve Clin J Med. 2008;75(4):258–80.
2. Park MS. Diffuse alveolar hemorrhage. Tuberculosis Respir Dis. 2013;74(4):151–62.

3. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65(1):1–11.
4. Lauque D, Cadranel J, Lazor R, Pourrat J, Ronco P, Guillevin L, et al. Microscopic polyangiitis with alveolar hemorrhage. A study of 29 cases and review of the literature. Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). Medicine. 2000;79(4):222–33.
5. Kallenberg CG. Pathogenesis of ANCA-associated vasculitides. Ann Rheum Dis. 2011;70 Suppl 1:i59–63.
6. Frankel SK, Schwarz MI. The pulmonary vasculitides. Am J Respir Crit Care Med. 2012;186(3):216–24.
7. Brown KK. Pulmonary vasculitis. Proc Am Thorac Soc. 2006;3(1):48–57.
8. Choi HK, Liu S, Merkel PA, Colditz GA, Niles JL. Diagnostic performance of antineutrophil cytoplasmic antibody tests for idiopathic vasculitides: metaanalysis with a focus on antimyeloperoxidase antibodies. J Rheumatol. 2001;28(7):1584–90.
9. Klemmer PJ, Chalermskulrat W, Reif MS, Hogan SL, Henke DC, Falk RJ. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. Am J Kidney Dis. 2003;42(6):1149–53.
10. Martin F, Chan AC. Pathogenic roles of B cells in human autoimmunity; insights from the clinic. Immunity. 2004;20(5):517–27.
11. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363(3):221–32.
12. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med. 2013;369(5):417–27.
13. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014;371(19):1771–80.
14. Macdonald JA, Fraser JF, Foot CL, Tran K. Successful use of recombinant factor VII in massive hemoptysis due to community-acquired pneumonia. Chest J. 2006;130(2):577–9.
15. Heslet L, Nielsen JD, Levi M, Sengeløv H, Johansson PI. Successful pulmonary administration of activated recombinant factor VII in diffuse alveolar hemorrhage. Crit Care. 2006;10(6):R177.
16. Heslet L, Nielsen JD, Nepper-Christensen S. Local pulmonary administration of factor VIIa (rFVIIa) in diffuse alveolar hemorrhage (DAH)–a review of a new treatment paradigm. Biolog Targ Ther. 2012;6:37.
17. Dabar G, Harmouche C, Jammal M. Efficacy of recombinant activated factor VII in diffuse alveolar haemorrhage. Rev Mal Respir. 2011;28(1):106–11.

Part IV

Neurologic Disease

Romergryko G. Geocadin

Acute Stroke Emergency Management

35

Pravin George and Lucia Rivera Lara

Case Presentation

A 53-year-old woman with a history of atrial fibrillation, smoking, arterial hypertension, diabetes mellitus, and previous transient ischemic attack (TIA) with left lower extremity weakness; presented within 30 min of a sudden loss of right-sided motor function of both the upper and lower extremity, a profound global aphasia, a right facial droop and a gaze deviation to the left. Her presenting National Institutes of Health Stroke Scale (NIHSS) score was 18. At the time of presentation to the hospital her platelet count was 250 k, white blood cell count was 8.8 K, and coagulation factors (aPTT, PT/INR) were within normal limits. Her blood pressure was 170/90, heart rate was 110 and irregularly irregular and respiratory rate was 17. She was protecting her airway while in the emergency department. Her home medications were listed as lisinopril 20 mg and aspirin 81 mg, both of which her husband stated, "she hadn't filled in years." She was immediately taken for head computed tomography (CT) which was unrevealing except for a small hyperdensity at the location of the left middle cerebral artery origin (Fig. 35.1). She then underwent a CT angiography of the neck and brain vessels that revealed a cut off of the left middle cerebral artery (Fig. 35.2). She was immediately dosed with intravenous tissue plasminogen activator (IV tPA).

Question What approach should guide the remainder of this patient's acute stroke management?

Answer Emergent endovascular thrombectomy

All patients with acute ischemic stroke (AIS) who present within 6 h of symptoms onset should be evaluated for IV tPA and/or acute endovascular therapy. IV tPA ideally should be dosed within 3 h of symptoms onset, with better outcomes directly correlated to shorter door to thrombolytic times. This patient, following a head CT that revealed no hemorrhage and not having any other contraindication, was started on IV tPA. The stroke and neuroradiology teams reviewed her imaging and calculated an Alberta Stroke Program Early CT Score (ASPECTS) of greater than 7. She was taken expeditiously to the angiography suite where an NIHSS score by the stroke team was repeated, revealing little to no clinical improvement, and was

P. George (✉)
Neurocritical Care, Anesthesia Critical Care Medicine, The Johns Hopkins Hospital, Phipps 455, 1800 Orleans Street, Baltimore 21287, MD, USA

Neurocritical Care, The Cleveland Clinic, Cerebrovascular Center, Mailcode S-80, 9500 Euclid Avenue, Cleveland 44195, OH, USA
e-mail: ccf.georgep2@gmail.com; DoctorPGeorge@gmail.com

L.R. Lara
Neurocritical Care, Anesthesia Critical Care Medicine, The Johns Hopkins Hospital, Phipps 455, 1800 Orleans Street, Baltimore 21287, MD, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_35

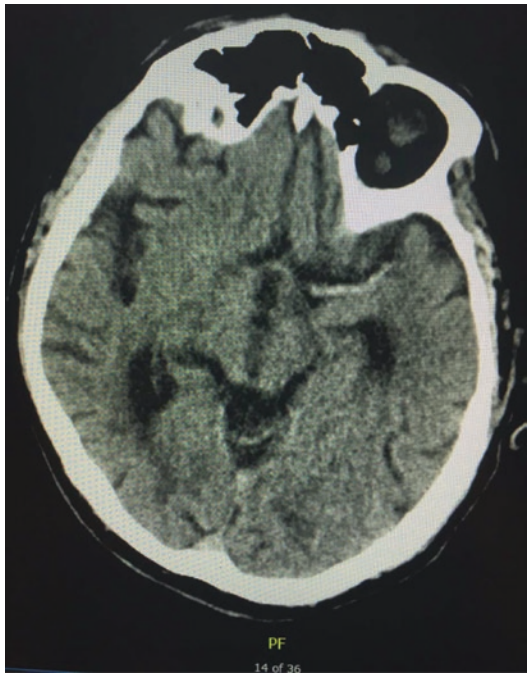


Fig. 35.1 Hyperdense LMCA sign

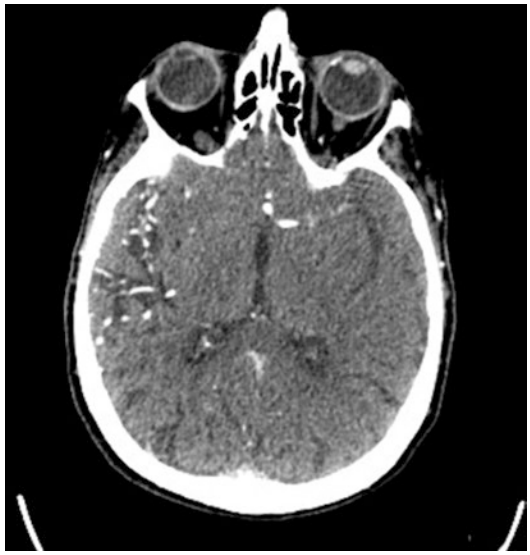


Fig. 35.2 Acute LMCA cut-off

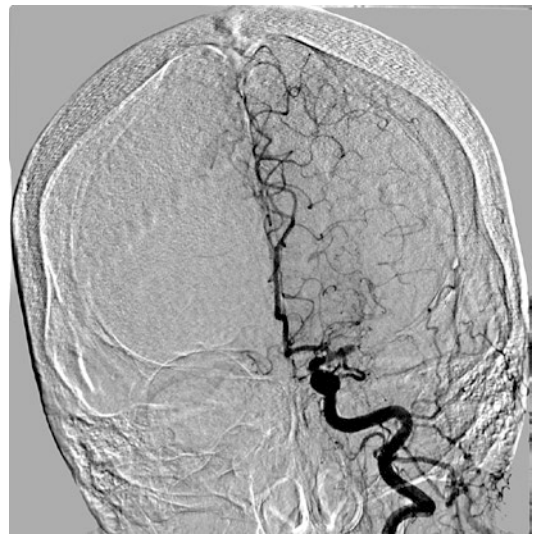


Fig. 35.3 Acute LEFT middle cerebral artery cut-off seen on digital subtraction angiogram

subsequently started on conscious sedation with midazolam and fentanyl in preparation for endovascular thrombectomy. Neuro-endovascular specialists performed an emergent cerebral diagnostic angiogram (Fig. 35.3), which revealed a persistent left middle cerebral artery occlusion. A stent-retriever device was deployed in the area of occlusion for roughly 2–3 min (Fig. 35.4). Following the single pass attempt, the stent-retriever was pulled with intact clot noted, which was integrated within the stent mesh upon device removal. A confirmatory angiogram was shot immediately following the thrombectomy procedure showing complete recanalization of the left middle cerebral artery with no distal artery cut-off (Fig. 35.5). The patient was then brought to the neurological critical care unit where vital signs and comprehensive neurological assessments were completed every hour for 24 h. Her systolic blood pressure was kept below 180 mmHg and glucose checks were instituted every 4 h with a goal to maintain euglycemia (glucose 80–200 mg/dL). Within a few hours, the patient was able to move her right upper and lower extremity against gravity, her forced gaze deviation was resolved and she was able to follow simple commands. One day later, the patient began speaking more fluently and was able to sit in a chair and tolerate a regular diet. An MRI was completed within 48 h of the endovascular procedure that showed a very small ischemic stroke core on diffusion-weighted imaging and T2 fluid attenuated (FLAIR) imaging. She also underwent an echocardiogram that revealed a 65% ejection fraction,

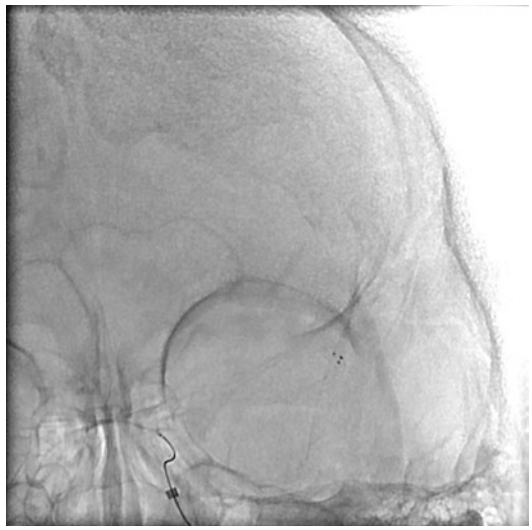


Fig. 35.4 Deployment of stent-retriever into the area of occlusion for roughly 2–3 min

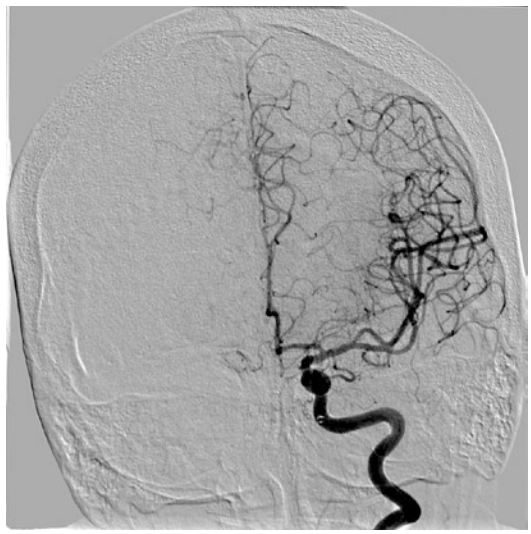


Fig. 35.5 Confirmatory angiogram showing recanalization of the LEFT middle cerebral artery

moderate left atrial enlargement and no apical thrombus. Her CHA_2DS_2 -VASc was calculated as a 5, and she was started on a regimen of enoxaparin (1 mg/kg) twice daily for secondary stroke prevention as a bridge to the novel anticoagulant apixaban during an outpatient follow-up stroke appointment. The patient continued to make improvements in neurological status and was transferred out of the ICU 2 days after the endovascular therapy with full strength on the right side of her body and only minimal word finding difficulties.

Principles of Management

Diagnosis

Acute ischemic stroke remains a clinical diagnosis that should be made within the first minutes of a patient entering the emergency department. Tools such as the NIHSS (Table 35.1) help to assess and communicate stroke symptom severity, however in the presence of an acute, focal neurological change, stroke should always be strongly considered. Ideally an initial head CT should be completed as soon as possible and within 25 min of patient arrival to assess for acute intracranial pathology, such as intracranial hemorrhage [1, 2]. If the CT scan is negative for pathology, the patient meets time criteria, does not have a contraindication, and continues to have a neurological deficit suggestive of acute ischemic stroke, IV tPA should be administered [1]. A CT angiogram of the head and neck to assess vessel status, perfusion status and possible vessel occlusion can be completed at the time of the initial CT scan so long as it does not delay the delivery time of IV tPA [1]. An MRI with diffusion-weighted imaging (MRI-DWI) in the stroke patient can be used to show areas of restricted diffusion of water that correspond to areas of acute ischemia. Unlike the head CT for acute stroke imaging, findings on MRI-DWI generally appear within minutes of ischemia.

Acute Stroke Management, tPA Administration

The goal for AIS therapy focuses on revascularization with IV tPA ideally within 45 min of arrival and no later than 1 h after arrival [1, 2]. Once a negative CT result is obtained, the threshold for starting tPA falls to the treating clinician, taking into account the severity of stroke symptoms by NIHSS, the bleed risk of the patient and any known contraindications such as recent

Table 35.1 NIHSS scoring

1A – Level of consciousness
Alert; keenly responsive (score 0)
Arouses to minor stimulation (score 1)
Requires repeated stimulation to arouse or painful stimulation (score 2)
Unresponsive, only reflexic posturing (score 3)
1B – Communication – Ask "What Month is it? How old are you?"
Both questions correct (score 0)
Only 1 question answered correctly or if the patients is intubated or has a language barrier (score 1)
No questions answered correctly/aphasic (score 2)
1C – Command following – Ask patient to "Blink eyes" and "Squeeze Hands"
Performs both tasks correctly (score 0)
Performs one task correctly (score 1)
Performs none correctly (score 2)
2 – Horizontal eye movements
No gaze deviation, palsy (Score 0)
Partial Gaze Palsy: Can be overcome (Score 1)
Forced Gaze Palsy: Cannot be overcome, even with oculocephalic reflex (Score 2)
3 – Visual fields
No Visual Loss (Score 0)
Partial Hemianopia (Score 1)
Complete Hemianopia (Score 2)
Blind or Bilateral Hemianopia (Score 3)
4 – Facial weakness
Normal symmetry (Score 0)
Minor paralysis, flattened nasolabial fold, smile asymmetry (Score 1)
Partial paralysis, Lower Face only (Score 2)
Complete paralysis, upper and lower face (Score 3)
5a – Left arm: Ask patient to hold LEFT arm up for 10 s
No drift 10 s, or amputee (score 0)
Drift, but doesn't hit the bed (score 1)
Drift, but it does hit the bed (score 2)
Is not able to effort against gravity (score 3)
No movement at all (score 4)
5B – Right arm: Ask patient to hold RIGHT arm up for 10 s
No drift 10 s, or amputee (score 0)
Drift, but doesn't hit the bed (score 1)
Drift, but it does hit the bed (score 2)
Is not able to effort against gravity (score 3)
No movement at all (score 4)
6A – Left leg: Ask patient to hold LEFT leg up for 5 s
No drift for 5 s, or amputee (score 0)
Drift, but doesn't hit the bed (score 1)
Drift, but it does hit the bed (score 2)
Is not able to lift against gravity (score 3)
No movement at all (Score 4)
6B – Right leg: Ask patient to hold LEFT leg up for 5 s
No drift for 5 s, or amputee (score 0)
Drift, but doesn't hit the bed (score 1)
Drift, but it does hit the bed (score 2)
Is not able to lift against gravity (score 3)
No movement at all (score 4)
7 – Ataxia: finger to nose and heel to shin testing
No ataxia noted, patient aphasic, patient paralyzed (score 0)
Ataxia noted in 1 limb (score 1)
Ataxia noted in 2 limbs (score 2)
8 – Sensation: testing pain, light touch, vibration sensation bilaterally
Normal sensation bilaterally (score 0)
Mild-moderate unilateral loss of sensation (score 1)
Complete unilateral loss of sensation or unresponsive (score 2)
9 – Language: testing naming of objects, reading simple sentences, describing a scene
Normal (score 0)
Mild – moderate aphasia, decreased ability to communicate but is able to get most ideas out (score 1)
Severe aphasia – very difficult to communicate, unable to have effective communication (score 2)
Mute/global aphasia or coma – no speech or auditory comprehension (score 3)
10 – Dysarthria: repeat or read words testing different parts of the tongue
Normal speech (score 0)
Mild-moderate dysarthria – slurred words, but understandable (score 1)
Mute or severe dysarthria – unable to comprehend speech (score 2)
11 – Extinction: visual, tactile, auditory, or personal inattention to one side
No extinction noted (score 0)
Extinction to one extremity (score 1)
Profound unilateral extinction, more than one extremity or more than one modality (score 2)
Score is total out of 41 points

From Daniel Runde, MD. NIH Stroke Scale/Score (NIHSS) [Internet] 2016 [Accessed 2016 Mar 02]. Available at http://www.mdcalc.com/nih-stroke-scale-score-nihss/

major surgery at a non-compressible site, recent myocardial infarction or stroke, or recent or active major gastrointestinal or brain hemorrhage. All patients suspected of AIS above the age of 18 who present within 3 h of known symptoms onset (or last known well time) and have no bleeding or allergic contraindication should receive IV tPA, if feasible to give under that time target [1]. Systemic tPA is dosed at 0.9 mg/kg with 10 % of the dose given as an IV bolus and the remaining 90 % given over the course of an hour [1, 3]. A select group of AIS patients (those not on anticoagulation, younger than 80 years of age and without a previous diagnosis of both stroke and diabetes) continue to have a higher benefit/risk ratio from IV tPA to a 4.5 h time target [1, 4]. Patients taking the novel anticoagulants (Apixaban, Rivaroxiban, Dabigatran, Edoxaban) within the previous 2 days, patients on warfarin with an INR > 1.7 and patients on a therapeutic dose of IV heparin or subcutaneous low-molecular weight heparin should not receive IV tPA [1].

Table 35.2 Modified Rankin Score (can utilize the mRS-9Q scale [http://www.modifiedrankin.com/] for easy score determination)

Patient has no symptoms of any disease process at all (score 0)
Patient has mild symptoms of a disease, no disability, is independent (score 1)
Patient has mild – moderate symptoms of a disease, some disability, is independent (score 2)
Patient has moderate – severe symptoms of a disease, moderate disability, requires help with some activities of daily living, but is able to walk without assistance (score 3)
Patient has severe symptoms of a disease, with moderately severe disability and is unable to walk without assistance and is unable to attend to bodily needs without assistance (score 4)
Patient has severe symptoms of a disease, with severe disability, remains bedridden, incontinent and requires constant nursing care and attention (score 5)
Patient has died (score 6)

Acute Stroke Management, Endovascular Thrombectomy

Immediately following IV tPA administration, all AIS patients with known large cerebral vessel occlusion per imaging (CTA or MRA) should be considered for endovascular recanalization therapy [1, 5–7]. Several randomized controlled trials published in 2014 and 2015 (i.e. MR CLEAN, SWIFT PRIME, EXTEND IA, ESCAPE, REVASCAT) showed that endovascular therapy is indicated for select patients suffering acute ischemic stroke who present within 6 h of stroke onset (or last known well time) and meet certain imaging and clinical criteria [8–13]. Each of the studies showed a high likelihood of favorable outcome with a number needed to treat of 4 or less. The ideal patients considered for endovascular therapy should have an NIHSS score of greater than 6 and/or a severe deficit such as hemianopsia or aphasia, a CT ASPECTS of greater than 6 [14], a baseline independence of function (modified Rankin score of less than 2 (Table 35.2), show an acute perfusion abnormality to a brain territory, and have no contraindication to contrast-dye administration [6, 13]. Patients who benefited from endovascular therapy in the recent trials were those with a large anterior territory (anterior cerebral artery/middle cerebral artery/carotid terminus) artery occlusion who presented within the first hours of deficit, had an NIHSS score of >6, and were less than 80 years of age (Table 35.1) [8–12]. Patients with posterior territory strokes were not studied. The CT ASPECTS is calculated off of CT source images comparing the stroke-affected side with the unaffected side in 10 separate brain regions [15]. For each region noticeably affected, the ASPECTS is decreased from total score of 10 (no regions affected) to a score of zero (all regions affected).

Supportive Care

All AIS patients should ideally be monitored closely in a dedicated neurosciences ICU or in a stroke unit with continuous monitored telemetry and neurologic expertise for at least the first few days following an event. Patients under 60 years of age with large AIS (greater than 1/3 of a supratentorial hemisphere or a large cerebellar infarct) should be offered decompressive craniectomy within 48 h for definitive malignant cerebral

edema management before cerebral herniation occurs and without taking into account which hemisphere (dominant or non-dominant) has infarcted [1]. The DECIMAL, DESTINY and HAMLET studies show strong evidence for an improvement in outcome for patients under 60 years of age with large anterior circulation AIS who undergo early hemicraniectomy [16–18]. Outcomes of "medical optimization" of intracranial pressure with hyperosmolar agents (e.g. mannitol) prior to hemicraniectomy have not been readily studied, and delay of surgery while utilizing these therapies is not recommended [1]. At the time of this manuscript, there are ongoing studies examining whether medications such as IV glyburide for the management of malignant cerebral edema is efficacious in preventing the need for hemicraniectomy [19]. Physical, occupational and speech therapies should be offered to patients as soon as feasible [1]. All AIS patients should undergo a swallowing function examination upon admission and enteral access should be placed if the patient is unable to cooperate [1]. Daily delirium and depression screening and complication management (deep vein thrombosis prophylaxis, secondary pneumonia prevention, urinary tract infection reduction, etc.) is essential for successful outcome [1].

Atrial Fibrillation, Heart Failure and Anticoagulation

Several risk factors for the development of AIS have been identified. Although hypertension, hyperlipidemia, diabetes, vascular diseases and smoking history contribute significantly to one's stroke risk, atrial fibrillation is one of the most ubiquitous and greatest risk factors for stroke [20–22]. Recently, the CHA_2DS_2 -VASc scoring system was created and validated to stratify the yearly stroke risk in a patient with atrial fibrillation and compare it to the risk of bleeding from systemic anticoagulation (Table 35.3) [23]. Patients with a score higher than 2 are encouraged to start systemic anticoagulation so long as there are no additional contraindications or increased bleeding risks. Recently, novel anticoagulants (apixaban, edoxaban, dabigatran and rivaroxaban) have been FDA approved for use in patients with non-valvular atrial fibrillation. These novel oral anticoagulants (NOAC) were found to be superior to warfarin for stroke prevention in patients with atrial fibrillation with atrial fibrillation and in some cases (i.e. apixaban) with lower hemorrhage risk [24–27]. Patients with heart failure and an ejection fraction (EF) of <15 % are also at a higher risk for ischemic stroke. The WARCEF trial was completed which compared the efficacy of aspirin to warfarin in the prevention of heart failure related strokes [28, 29]. Among WARCEF patients with heart failure and EF of <15 % who were in sinus rhythm, there was no significant overall difference in the primary outcome between treatment with warfarin and treatment with aspirin.

Table 35.3 CHA_2DS_2 – VASc Score calculation for atrial fibrillation stroke risk

Congestive Heart Failure (score 1)
Hypertension - >140/90 (score 1)
Age > 75 years (score 2)
Diabetes mellitus (score 1)
Stroke, TIA or thromboembolism history (score 2)
Vascular disease (score 1)
Age 65 to 74 (score 1)
Sex **C**ategory– female gender (score 1)
Stroke risk/year in relation to score (off anticoagulation) is as follows:
Score 1: 1.3 % chance of stroke per year
Score 2: 2.2 % chance of stroke per year
Score 3: 3.2 % chance of stroke per year
Score 4: 4.0 % chance of stroke per year
Score 5: 6.7 % chance of stroke per year
Score 6: 9.8 % chance of stroke per year
Score 7: 9.6 % chance of stroke per year
Score 8: 6.7 % chance of stroke per year
Score 9: 15.2 % chance of stroke per year

Secondary Stroke Prevention in the Acute Stroke Setting

The SPARCL and JUPITER trials both found that certain HMG-CoA reductase inhibitors ("statins") reduce the risk of strokes and cardio-

vascular events in patients with recent stroke or transient ischemic attack [30–32]. The conclusion of the SPARCL trial was that high-dose atorvastatin 80 mg should be used; however there was a slight increase in the incidence of hemorrhagic stroke. Current recommendations state that patients with a concerning lipid panel (increased LDL, increased cholesterol, decreased HDL) should at least be started on a statin and the dose titrated to an improvement in lipid numbers over time. Regarding blood pressure, the long-term management strategy is to maintain systolic blood pressures less than 130 mmHg, however as is further described below, acute blood pressure management is as of yet controversial [1, 33–35]. Diabetes also should be controlled in a patient's long-term stroke management strategy, but clinicians should be careful to prevent hypoglycemia (glucose <60 mg/dL) and severe hyperglycemia (glucose >200 mg/dL) in the acute stroke setting [1, 36, 37]. ASA 81 mg with a single loading dose of 325 mg should also be started within 24–48 h of acute stroke as this was found to reduce rates of secondary stroke in both the CAST and IST studies [1, 38, 39]. Other antiplatelet agents such as clopidogrel and agents such as glycoprotein IIb/IIIa receptor antagonists have not been studied in acute secondary prevention of stroke, and their use is not currently recommended outside of clinical trials [1].

Evidence Contour

Several aspects of management in the patient with acute ischemic stroke remain without consensus in the face of available clinical trials.

"Wake-Up" Strokes

A number of patients (~25 % of all strokes) present to the emergency department with AIS symptoms noted only after awakening without knowledge of the exact time of onset [40]. In many of these patients the official "last-known well" time may have been several hours. There is some evidence to suggest that "wake-up strokes" may occur close to awakening and that these patients may also be tPA candidates, however the bleeding risk has not been assessed in this population. Clinical trials including WAKE-UP, SAIL-ON and EXTEND are ongoing to test the safety and efficacy of IV tPA on the wake-up stroke population.

Acute Cerebral Artery Dissection, Antiplatelets Versus Anticoagulation

Several studies have tried to address the question of whether anticoagulation or antiplatelet therapies are superior in the treatment of acute cerebral artery dissection. CADISS, a randomized controlled trial of 250 dissection patients (118 carotid, 132 vertebral) recently published in 2015 showed that there was no difference of efficacy between antiplatelet and anticoagulant medications at preventing the endpoints of stroke and death in those with symptomatic arterial dissection [41]. It should be noted however, that anticoagulant medications are associated with higher rates of both systemic and intracranial bleeding complications.

Blood Pressure Management in Acute Stroke Patients

Following AIS, the optimal blood pressure strategy was initially theorized to allow for permissive hypertension with a systolic goal of less than 180 to avoid countering the body's natural autoregulatory compensation of ischemia while minimizing secondary hemorrhagic complications. The large, randomized 2014 CATIS trial did not show a significant difference in patients who underwent aggressive blood pressure reduction (10–25 % within the first 24 h) to a goal of 140/90 within 7 days from the control group of patients in which they discontinued all antihypertensive medications [42]. Many stroke clinicians now opt for a lower target blood pressure as long as there are no symptomatic changes in the patient's neurological examination. Regarding exceptional conditions in which patients have symptomatic

hypotension that leads to neurological worsening ("perfusion dependence") there is some limited evidence that pharmacologically induced hypertension may be utilized for a short period under close monitoring [1]. There is however insufficient evidence to recommend volume expansion, prolonged pharmacologically induced hypertension, albumin infusions, and hemodilution for stroke patients.

Hemicraniectomy in Patients Older than 60 Years Old with Large Hemispheric Stroke

As previously discussed, several randomized control trials have shown a definite benefit in morbidity and mortality end-points to early hemicraniectomy for the reduction of malignant cerebral edema in patients under the age of 60 with large territory strokes within 24–48 h after onset of symptoms. DESTINY II a recent randomized trial showed that in patients over the age of 60, morbidity was marginally reduced by hemicraniectomy; however outcomes were complicated by significant morbidity [43]. Many of the patients who underwent hemicraniectomy in the trial improved only from a modified Rankin scale score of 6 (dead) to 5 (bed-bound with constant nursing care) and none of the patients in either arm became functionally independent. In the therapy of patients over the age of 60 with large stroke, the strategy to avoid mortality should largely center on medical therapy (osmotherapy) with family discussions on goals of care.

Early Rehabilitation in Stroke Patients

A number of hospital based studies, both in the ICU as well as on floor units have found that the early rehabilitation of patients is generally associated with better outcomes for patients across several pathologic processes, lower complication rates and fewer days spent in the hospital. The recent AVERT randomized controlled trial however showed that very early mobilization of AIS patients was associated with a reduction in the odds of a favorable outcome at 3 months and that early mobilization did not lead to fewer immobility related complications in these patients [44]. There was little to no harm caused by early mobilization and the study did not specifically speculate as to why there was a reduction in the favorable outcomes at 3 months. A number of stroke clinicians still advocate for early mobilization of stroke patients, as ongoing studies are pending. There is a randomized study published in 2011 utilizing Fluoxetine for motor recovery after acute ischemic stroke (FLAME study), which showed modest improvements in functional outcomes at 3 months post stroke in the Fluoxetine arm [45]. The mechanism for this improvement is unknown and it is speculated the medication may stimulate some degree of brain plasticity.

Basilar Artery Thrombosis, Therapy After 4.5 Hours

As with other strokes, if a patient arrives within the appropriate time window (<4.5 h) IV tPA should be initiated, if eligible, and the patient should be considered a candidate for endovascular therapy [1]. Basilar artery thrombosis is however an uncommon form of AIS and its consequences are often fatal [46]. There are a number of studies and case reports revealing improved outcomes following successful recanalization of the basilar artery even out to several hours post traditional timelines for anterior artery strokes, however due to the differences in management style and nature of these studies, recommendations regarding therapy are lacking. The prospectively collected BASICS registry indicates that about 1/3 of patients post recanalization with either IV tPA or intra-arterial therapy die, 1/3 lose functional independence and 1/3 regain function [47]. In general, for patients with limited symptomatology and suspected acute basilar occlusion, endovascular intervention may be warranted to limit the sequelae of the disease. The intra-arterial therapy can take place in some cases even up to 48 h post initial stroke symptoms with the potential for improved outcomes

[47]. Studies are ongoing to determine safety and efficacy of endovascular recanalization in posterior circulation large vessel strokes.

Endovascular Therapy Without IV tPA, After 4.5 Hours

IV tPA is limited in its utility after 4.5 h as the statistical risk of hemorrhage becomes greater than the potential benefit [48]. Endovascular therapy alone has not been shown to be inferior to IV tPA for the recanalization of vessels, and utilizing the newer stent-retriever devices has shown a greater than 90 % success rate in some studies [12, 13]. Due to the success rate of these devices and the lack of necessity to utilize tPA, some stroke clinicians and endovascular specialists offer intervention to 6 h or longer based on imaging criterion and clinical expertise. Some newer trials are utilizing the CT ASPECTS score and/or CT perfusion studies to calculate the risk and benefits of the procedure while others utilize MRI-DWI and penumbra characteristics to guide the decision for intra-arterial therapy [15]. The current recommendation for intra-arterial therapy without tPA is based on clinical examination and should be reserved for patients that either have a small ischemic core on MRI-DWI or an ASPECTS score >7 at the time of intervention [13].

Stenting in Acute Stroke Therapy

Intracranial arterial stenosis (ICAS) is generally caused by a buildup of plaques on the vessel walls and occurs in patients with atherosclerosis. When the stenosis becomes severe enough, it can lead to stroke either through plaque rupture or by occlusion of the vessel. The mainstay of therapy for patients with ICAS has been a combination of antiplatelet medications, anti-hypertensives, lipid-lowering agents, smoking cessation, lifestyle modification and diabetic glucose management. The SAMMPRIS trial, published in 2012 studied stenting versus aggressive medical therapy for ICAS [49]. Patients in both groups received dual anti-platelet medication with aspirin and clopidogrel for 90 days in addition to the modifications as listed above. The experimental arm additionally included endovascular stenting of a symptomatic cerebral artery. The study was halted early due to the high risk of stroke following stenting and because the risk of stroke with aggressive medical therapy alone was lower than expected. Patients with recurrent stroke due to ICAS despite aggressive medical therapy are now rarely offered intracranial stenting and it is recommended that these patients enroll in medical device trials.

Patients with extracranial arterial stenosis (ECAS) in the carotid arteries are candidates for either stenting or carotid endarterectomy [50–52]. The CREST trial published in 2010 addressed which therapeutic management was recommended for patients with ECAS [53]. It was found that patients had a higher risk of stroke with stenting and a higher risk of myocardial infarction with endarterectomy, and the composite primary outcome of stroke, myocardial infarction or death did not significantly differ between groups. Carotid artery stenting tended to show greater efficacy in patients under 70 years old, while carotid endarterectomy showed greater efficacy in those greater than 70 years old. CREST-2 is now currently in progress to assess the efficacy of stenting in asymptomatic patients [54].

Stenting for acute dissection has not been readily studied however can potentially provide some benefit in select patients who can tolerate a short course of dual-antiplatelet therapy.

Dual Anti-platelet Therapy, Aspirin plus Clopidogrel for Secondary Stroke Prevention

In 1996, the CAPRIE study, in 2005, the CARESS trial and in 2010 the CLAIR study showed that in patients with symptomatic carotid stenosis, combination therapy with clopidogrel and aspirin was more effective than aspirin alone in reducing asymptomatic embolization [55–57]. The MATCH trial, a 2004 study of 7599 patients, found that adding aspirin to clopidogrel in high risk patients with recent ischemic stroke or TIA

lead to greater bleeding risk than clopidogrel alone, and the combination was not associated with fewer ischemic events [58]. CHARISMA, a large 2006 study (15,603 patients), found that clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke or death, and in 2012 the SPS3 study showed that the combination did not reduce the rate of lacunar stroke [59, 60]. A 2013 systematic review and meta-analysis later also found that dual-antiplatelet therapy lasting for more than 1 year did not reduce recurrent stroke risk and increased the risk for intracranial hemorrhage over clopidogrel monotherapy [61]. The CHANCE trial, also released in 2013, showed that among patients with TIA or minor stroke the treatment for the first 90 days with combination aspirin and clopidogrel followed by monotherapy reduced the risk of stroke and did not increase the risk of hemorrhage in the Chinese population [62]. A larger scale trial, POINT, is currently in progress to assess the efficacy and safety of short-term (90 day) dual-antiplatelet therapy [63]. In light of these studies, there is insufficient evidence to recommend long-term (>3 month) dual-antiplatelet therapy, however clinicians can consider short-term combination therapy for the treatment of recurrent stroke and micro-embolic events.

References

1. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke. Stroke. 2013;44:870–947.
2. Fonarow GC, Zhao X, et al. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. JAMA. 2014; 311(16):1632–40.
3. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–7.
4. Hacke W, Kaste M, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke (ECASS III). N Engl J Med. 2008;359:1317–29.
5. Furlan AJ, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. JAMA. 1999;282:2003–11.
6. Powers WJ, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients with Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2015;46(10):3020–35.
7. Addition of stent thrombectomy in treatment of acute ischemic stroke patients reduces disability in global studies [Internet] 2015. [Accessed 2 Mar 2016]. Available from http://www.businesswire.com/news/home/20150211006099/en/Addition-Stent-Thrombectomy-Treatment-Acute-Ischemic-Stroke.
8. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke (MR CLEAN). N Engl J Med. 2015; 372(1):11–20.
9. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke (ESCAPE). N Engl J Med. 2015;372(11):1019–30.
10. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection (EXTEND IA). N Engl J Med. 2015;372(11):1009–18.
11. Saver JL, Goyal M, Bonafe A, et al. Solitaire™ with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial: protocol for a randomized, controlled, multicenter study comparing the Solitaire revascularization device with IV tPA with IV tPA alone in acute ischemic stroke. Int J Stroke. 2015;10(3):439–48.
12. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke (REVASCAT). N Engl J Med. 2015;372(24):2296–306.
13. Broderick JP, Berkhemer OA, Palesch YY, et al. Endovascular therapy is effective and safe for patients with severe ischemic stroke: pooled analysis of interventional management of stroke III and multicenter randomized clinical trial of endovascular therapy for acute ischemic stroke in the Netherlands data. IMS III investigators; MR CLEAN Investigators. Stroke. 2015;46(12):3416–22.
14. Faculty of Medicine, University of Calgary. Understanding Alberta Stroke Program Early CT score (ASPECTS) [Internet] 2015 [Accessed 2 Mar 2016]. Available from: http://www.aspectsinstroke.com/aspects/what-is-aspects.
15. Hill MD, Demchuk AM, Goyal M. Alberta Stroke Program early computed tomography score to select patients for endovascular treatment: Interventional Management of Stroke (IMS)-III Trial. Stroke. 2014;45(2):444–9.
16. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB, HAMLET investigators. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. Lancet Neurol. 2009;8(4):326–33.
17. Jüttler E, Schwab S, Schmiedek P, Unterberg A, Hennerici M, Woitzik J, Witte S, Jenetzky E, Hacke W,

DESTINY Study Group. Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial. Stroke. 2007;38(9):2518–25.
18. Vahedi K, Vicaut E, Mateo J, Kurtz A, Orabi M, Guichard JP, Boutron C, Couvreur G, Rouanet F, Touzé E, Guillon B, Carpentier A, Yelnik A, George B, Payen D, Bousser MG, DECIMAL Investigators. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). Stroke. 2007;38(9):2506–17.
19. Sheth KN, Elm JJ, Beslow LA, et al. Glyburide Advantage in Malignant Edema and Stroke (GAMES-RP) Trial: rationale and design. Neurocrit Care. 2016;24:132–9.
20. Paciaroni M, Agnelli G, Falocci N, et al. Prognostic value of trans-thoracic echocardiography in patients with acute stroke and atrial fibrillation: findings from the RAF study. J Neurol. 2016;263:231–7.
21. Mozaffarian D,Benjamin EJ, Go AS, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29–e322.
22. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial brillation after transient ischaemic attack or minor stroke. Lancet. 1993;342(8882):1255–62.
23. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263–72.
24. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51.
25. Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Commit- tees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92.
26. Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.
27. Giugliano RP, Ruff CT, Braunwald E, et al; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093–104.
28. Homma S, Thompson JL, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm (WARCEF). N Engl J Med. 2012;366(20):1859–69.
29. Pullicino PM, Qian M, Sacco RL, et al. Recurrent stroke in the warfarin versus aspirin in reduced cardiac ejection fraction (WARCEF) trial. Cerebrovasc Dis. 2014;38(3):176–81.
30. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355(6):549–59.
31. Amarenco P, Benavente O, Goldstein LB, et al; Stroke Prevention by Aggressive Reduction in Cholesterol Levels Investiga- tors. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial by stroke subtypes. Stroke. 2009;40(4):1405–9.
32. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein (JUPITER). N Engl J Med. 2008;359:2195–207.
33. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358(9287):1033–41.
34. Arauz-Pacheco C, Parrott MA, Raskin P, American Diabetes Association. Treatment of hypertension in adults with diabetes. Diabetes Care. 2003;26 Suppl 1:S80–2.
35. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.
36. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577–89.
37. Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009;373(9677):1765–72.
38. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet. 1997;349(9066):1641–9.
39. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet. 1997;349(9065):1569–81.
40. Rimmele DL, Thomalla G. Wake-up stroke: clinical characteristics, imaging findings, and treatment option – an update. Front Neurol. 2014;5:35.
41. Markus HS, Hayter E, Levi C, et al. Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS): a randomised trial. Lancet Neurol. 2015;14(4):361–7.
42. He J, Zhang Y, Xu T, et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. JAMA. 2014;311(5):479–89.
43. Jüttler E, Unterberg A, Woitzik J, et al. DESTINY II Investigators. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. N Engl J Med. 2014;370(12):1091–100.
44. Bernhardt J, Langhorne P, Lindley RI, et al. Efficacy and safety of very early mobilisation within 24 h of

stroke onset (AVERT): a randomised controlled trial. Lancet. 2015;386(9988):46–55.
45. Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011;10(2):123–30.
46. Baird TA, Muir KW, Bone I. Basilar artery occlusion. Neurocrit Care. 2004;1:319–29.
47. Schonewille WJ, Wijman CA, Michel P, et al. The basilar artery international cooperation study (BASICS). Int J Stroke. 2007;2(3):220–3.
48. The IST-3 Collaborative Group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 hours of acute ischemic stroke (the third international stroke trial IST-3): a randomized controlled trial. Lancet. 2012;379(9834): 2352–63.
49. Derdeyn CP, Chimowitz MI, Lynn MJ, et al; Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Trial Investigators. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the Final results of a randomised trial. Lancet. 2014;383(9914):333–41.
50. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis (NASCET). N Engl J Med. 1991;325(7):445–53.
51. Ferguson GG, Eliasziw M, Barr HW, et al. The North American Symptomatic Carotid Endarterectomy Trial: surgical results in 1415 patients. (NASCET). Stroke. 1999;30(9):1751–8.
52. International Carotid Stenting Study Investigators, Ederle J, Dobson J, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet. 2010;375(9719):985–97.
53. Mantese VA, Timaran CH, Chiu D, et al. The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). Stroke. 2010;41:S31–4.
54. Brott TG. Carotid revascularization and medical management for asymptomatic carotid stenosis trial (CREST-2). In: ClinicalTrials.gov [website on the Internet]. Bethseda: US National Library of Medicine; 2014.
55. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet. 1996;348(9038):1329–39.
56. Markus HS, Droste DW, Kaps M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation. 2005;111(17):2233–40.
57. Wong KS, Chen C, Fu J, et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. Lancet Neurol. 2010;9(5):489–97.
58. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. 2004;364(9431):331–7.
59. Bhatt DL, Fox KAA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events (CHARISMA). N Engl J Med. 2006;354:1706–17.
60. SPS3 Investigators, Benavente OR, Hart RG, et al. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. N Engl J Med. 2012; 367(9):817–25.
61. Lee M, Saver JL, Hong KS, et al. Risk-benefit profile of long-term dual- versus single-antiplatelet therapy among patients with ischemic stroke: a systematic review and meta-analysis. Ann Intern Med. 2013;159(7):463.
62. Wang Y, Wang Y, Zhao X, et al; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013;369(1):11–9.
63. Johnston SC, Easton JD, Farrant M, et al. Platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trial: rationale and design. Int J Stroke. 2013;8(6):479–83.

Bacterial Meningitis in the ICU

36

Jennifer S. Hughes and Indhu M. Subramanian

Case Presentation

A 55 year old man with a history of recurrent bacterial sinusitis was brought to the emergency department for 1 day of progressive confusion. The patient complained of a severe, generalized headache and light sensitivity. On exam he was febrile to 102.1 °F, agitated and oriented to name only. Severe nuchal rigidity was present, but no obvious focal neurologic deficits were observed on exam. Papilledema was not visualized on fundoscopy although the exam was limited due to the patient's significant photosensitivity.

Blood cultures were sent immediately and the patient was initiated on empiric IV antibiotic therapy with vancomycin, ampicillin, and ceftriaxone. A computed tomography (CT) of the brain without contrast did not reveal any mass lesions or obvious signs of increased intracranial pressure. A lumbar puncture (LP) was significant for an elevated opening pressure of 32 cmH_2O and CSF analysis revealed a white blood cell (WBC) count of 3000 cells/μL with 88 % neutrophils, glucose of 30 mg/dL and protein of 250 mg/dL. A gram stain showed gram positive cocci in pairs and chains (Fig. 36.1).

During transfer of the patient from the ED, the patient developed a generalized tonic-clonic seizure and was urgently given IV lorazepam. Due to decreased level of consciousness after the seizure, the patient was intubated for airway protection and was admitted to the ICU.

Question What additional inpatient precautions should be taken for the most likely diagnosis?

Answer Droplet precautions for presumed acute community acquired bacterial meningitis.

This patient presented with the 'classic triad' for bacterial meningitis of fever, neck stiffness and altered mental status (AMS). Although the

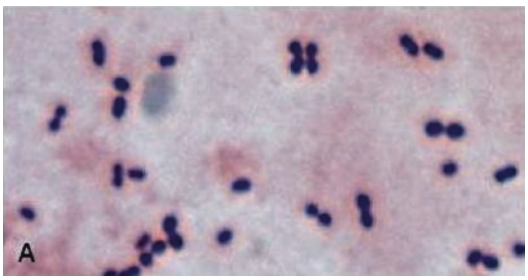


Fig. 36.1 Gram positive lancet shaped diplococcic confirming *Streptococcus pneumonia* (Image courtesy of Dr. Valerie Ng at Alameda Health System)

J.S. Hughes
Department of Internal Medicine,
Highland Hospital, Alameda Health System,
Oakland, CA, USA

I.M. Subramanian (✉)
Pulmonary and Critical Care Faculty,
Department of Internal Medicine, Highland Hospital,
Alameda Health System, Oakland, CA, USA
e-mail: isubramanian@alamedahealthsystem.org;
isubramanian@acmedctr.org

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_36

complete triad is present only 44 % of the time [1], nearly all patients with bacterial meningitis will present with one of the three findings [2]. The absence of all three of these signs in the classic triad essentially eliminates bacterial meningitis from the differential [2]. The classic physical exams for evaluation of meningeal irritation, Kernig's and Brudzinski's signs are not that useful as these only have 61 % sensitivity for bacterial meningitis compared to nuchal rigidity (difficulty with chin to chest or flexion of the cervical spine) which has 84 % sensitivity for bacterial meningitis [3]. While these physical exam signs may provide support in establishing the diagnosis, a lumbar puncture is still required for definitive diagnosis.

Until the specific pathogen responsible for community acquired bacterial meningitis has been identified, strong consideration should be given for initiating droplet precautions. Droplet precautions are recommended by the CDC to decrease the spread of infection caused by *Neisseria meningitides* and *Haemophilus influenzae* type b. A definitive diagnosis may be delayed for several days [4]. In addition, depending on the quality of the gram stain, differentiating between gram positive cocci and gram negative cocci may be difficult. For these reasons, a general recommendation is to keep patients with presumed community acquired bacterial meningitis in droplet precautions for at least the first 24 h of therapy and until the etiology has been determined.

Although appropriate empiric antibiotics to cover the usual organisms implicated in community acquired bacterial meningitis were initiated, all adult patients with suspected or confirmed bacterial meningitis by lumbar puncture should also be treated with IV dexamethasone prior to or at the time of their first dose of antibiotics [1]. In our case, this patient should have be started on the standard dose of dexamethasone at 10 mg IV q6h, 15 min prior to initiation of his antibiotics to complete a 4 day course [1, 5]. The efficacy of steroids in bacterial meningitis is discussed further in the management section of this chapter.

It is critical to initiate empiric antibiotics promptly and without delay while awaiting CSF gram stain results or imaging of the brain. In this case, the patient did meet criteria for imaging prior to LP due to altered level of consciousness, (see below), still empiric antibiotics were given promptly. Initially, during selection of the antibiotics it is important to assume a high likelihood of antimicrobial resistance and select broad coverage. In this case, our patient's empiric antibiotics included vancomycin and ceftriaxone to cover for the most common pathogens, *Streptococcus pneumoniae* and *Neisseria meningitides.* Because this patient was over age 50 years, ampicillin was also appropriately added to cover for *Listeria monocytogenes.*

Although the gram positive diplococci were seen on gram stain, suggestive of *Streptococcus pneumoniae*, the patient was continued on the recommended empiric antibiotics vancomycin 15 mg/kg IV q8h (15–20 ug/mL trough target) and ceftriaxone 2 g IV q12h until definitive culture results and sensitivities are available. See Fig. 36.1.

Our patient was also started on anti-epileptic therapy and had no additional seizure activity. Over the next few days the CSF cultures grew pansensitive *Streptococcus pneumoniae* and the patient was continued on ceftriaxone for a 14 day course. By the third day the patient was alert and able to follow commands and was extubated. Seizure medications were discontinued and no further seizures occurred.

Principles of Management

Early recognition and treatment is critical to survival from bacterial meningitis. The host inflammatory response to this infection can be devastating. Several host and pathogen related factors ultimately lead to this condition. Virulence factors allow bacteria to colonize host epithelium with seeding of the bloodstream, crossing of the blood brain barrier and subsequent multiplication in the CSF due to the relative paucity of humoral immunity in the CSF. This cascade of events can lead to both systemic and neurologic complications. Here we will discuss the basic epidemiology, diagnosis, and treatment of community acquired bacterial meningitis.

Epidemiology

In recent decades there has been a shift in the pathogens responsible for bacterial meningitis. With the development and standardization of childhood vaccines against H. influenza type b (Hib) in 1985, pneumococcal vaccines (pneumococcal conjugate vaccine [PCV13] and pneumococcal polysaccharide vaccine [PPSV23]) in 2000 and meningococcal conjugate vaccine (MCV4) in 2005 the burden of bacterial meningitis has shifted to predominately older populations [6, 7]. Despite vaccines, *Streptococcus pneumoniae* and *Neisseria meningitidis* still account for over 80 % of bacterial meningitis cases [7, 8]. Less common pathogens, *Group B Streptococcus* (GBS), *Haemophilus influenzae Listeria monocytogenes* make up the remaining approximately 17 % of cases [7]. Patients' ages 16–50 are at greatest risk for *Neisseria meningitidis* or *Streptococcus pneumoniae,* however, patients over the age of 50 or immunocompromised patients have an increased risk for *Listeria monocytogenes,* GBS, and aerobic gram negative bacilli [7, 8].

Diagnosis

All patients with suspected bacterial meningitis should receive an LP unless contraindicated. See Fig. 36.2 for a management algorithm in all patients with suspected bacterial meningitis. Relative contraindications include elevated intracranial pressure, thrombocytopenia/bleeding diathesis or spinal epidural abscess [10]. If collection of CSF is delayed for imaging or other reasons, blood cultures should be collected prior to antimicrobial administration but antibiotics should not be delayed. Positivity of blood cultures for bacterial meningitis range from 50 to 90 % [1].

CSF results consistent with the diagnosis of bacterial meningitis include (1) elevated opening pressure (normal 20cmH2O), (2) pleocytosis of 1000 to 5000 μL with a >80 % neutrophil predominance, (3) glucose below 40 mg/dL (in adults glucose ratio CSF: serum ≤0.4), (4) mildly elevated protein level 100–500 mg/dL and (5) cloudy or turbid appearance.

Sensitivity for a positive gram stain ranges from 60 to 90 % with a >97 % specificity; greater likelihood of positive gram stains are seen in streptococcus pneumoniae, H. flu and Neisseria as opposed to gram negative bacilli [11]. See Table 36.1. CSF cultures identify an organism 70 to 85 % of the time [13]. Serum and urine bacterial antigens are not routinely helpful.

Notably, a traumatic tap, intracerebral or subarachnoid hemorrhage or recent seizure can all result in a falsely elevated WBC in the CSF. To correct WBC for a traumatic tap, subtract 1 WBC for every 500 to 1500 red blood cells (RBCs) in CSF to give the 'Adjusted CSF WBC' [14].

Select patients may be at risk for undergoing an LP and should receive imaging prior to LP. Antibiotic administration, however, should not be delayed [15]. See Fig. 36.2.

Repeat LPs are not indicated in patients with bacterial meningitis unless there has been no clinical improvement after 48 h of appropriate antibiotics. This is especially important if there is concern for pneumococcal meningitis with penicillin or cephalosporin resistance or when the patient has been treated with dexamethasone [1].

Antibiotics

A delay in administration of antibiotics of greater than 3 h from admission in bacterial meningitis has been associated with increased morbidity and mortality. Antibiotics should target the presumed pathogen identified by gram stain, or empirically started if the LP is delayed [1]. Antibiotics should be bactericidal and cross the blood brain barrier [16].

Empiric antibiotics for adults are vancomycin and a third generation cephalosporin (ceftriaxone or cefotaxime). In patients with risk factors for listeria (>50 years old, immunocompromised or alcoholism) the addition of ampicillin or penicillin G should be included. If there is a beta-lactam allergy: Vancomycin and moxifloxacin are considered empiric coverage with trimethoprim-sulfamethoxazole added for listeria. Consider the use of a fourth generation cephalosporin such as cefepime or a carbapenem such as meropenem in

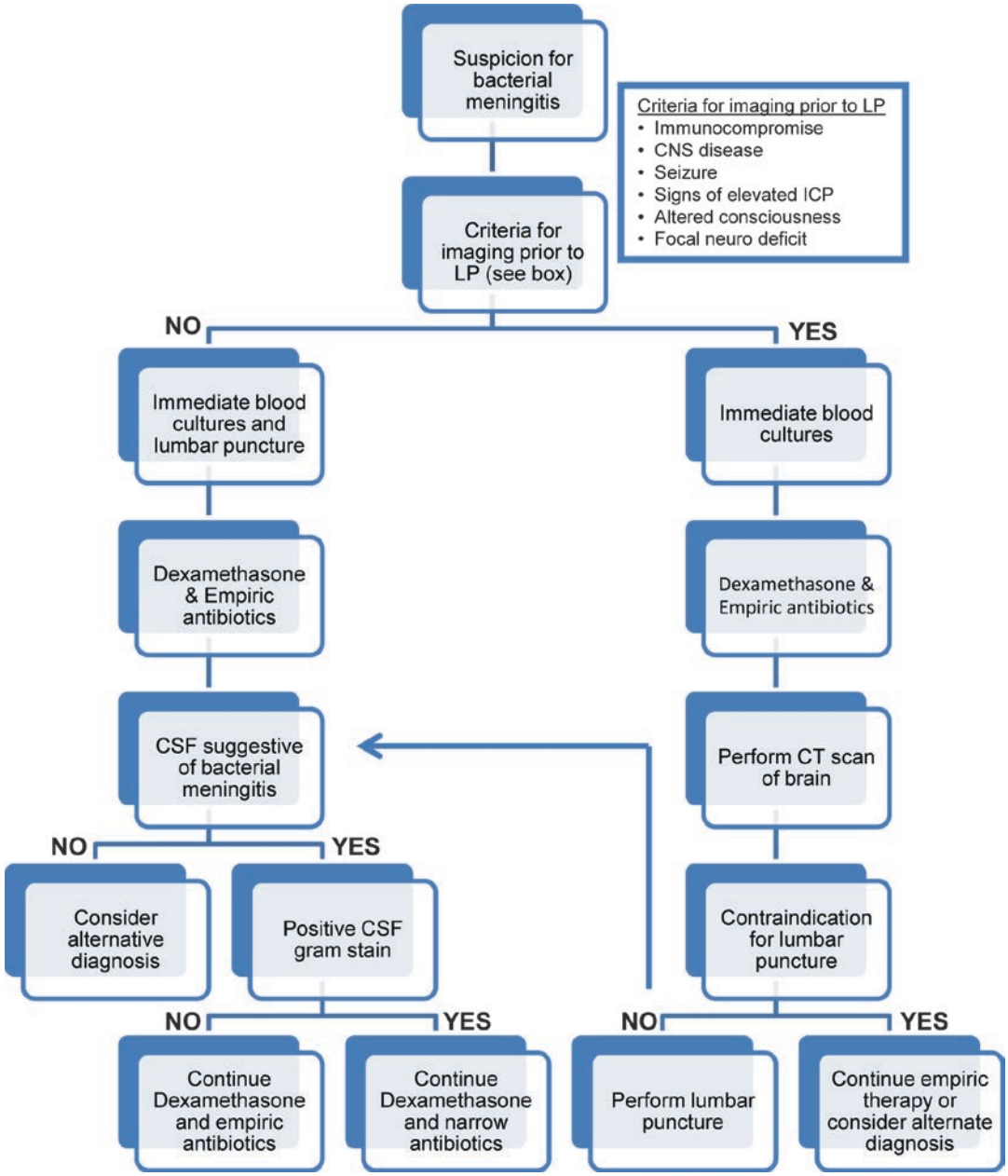


Fig. 36.2 Management algorithm for adults with suspected bacterial meningitis [9] (From Tunkel et al. [9]. Reprinted with permission from Oxford University Press)

severely immunocompromised patients to cover for additional gram negative pathogens.

The duration of antibiotic therapy is usually from 7 to 14 days but should be guided by the specific pathogen identified, disease severity and antimicrobial agent selected [9, 17, 18] See Table 36.2.

Steroids

Dexamethasone works via two routes: (1) reduction in meningeal inflammation (2) blunting a secondary inflammatory response to the bacterial products released from the first dose of antibiotics

[17]. Optimal initiation of dexamethasone is 15 to 20 min prior the first dose of antibiotics, or alongside their first dose of antibiotics. The recommended dose of dexamethasone is 0.15 mg/kg IV every 6 h [4]. The administration of dexamethasone in patients with bacterial meningitis reduces unfavorable neurological outcomes. Notably, the reduction in mortality was only statistically significant in patients presenting with a moderate level of neurological impairment at admission (Glasgow Coma Scale [GCS] score of 8 to 11). No benefit to mortality was seen if the patients with GCS scores > 11. No proven benefit and a higher likelihood of poor outcomes have been identified if dexamethasone is given after antibiotics have been started [4].

Table 36.1 Gram stain appearance for specific bacterial meningitis pathogens [12].

Gram stain appearance	Specific pathogen
Gram positive diplococci 'lancet-shaped'	***Streptococcus pneumoniae***
Gram positive cocci in clusters or tetrads	***Staphylococcus aureus***
Gram positive cocci	***Streptococcus agalactiae***
Gram positive rods	***Listeria monocytogenes***
Gram negative diplococci	***Neisseria meningitidis***
Pleomorphic gram negative rods (cocco-bacilli)	***Haemophilus influenzae***
Gram negative rods	***E. Coli* or other *Enterobacteriaceae***
Gram negative rods (bacilli)	***Pseudomonas aeruginosa***

The reduction in neurologic sequelae and mortality with adjunctive steroids are clearly seen with pneumococcal meningitis. Unfortunately these findings have not been proven in meningitis caused by other pathogens. Nevertheless, the Infectious Diseases Society of America (IDSA) recommends adjunctive dexamethasone in all adult patients with suspected or proven bacterial meningitis.

Long Term Neurologic Complications

The risk of developing any neurologic complications has been sited to be as high as 28 % overall in community acquired bacterial meningitis and depends on the pathogen involved,

Table 36.2 Recommended antibiotic duration for specific bacterial meningitis pathogens [1]

Specific pathogen	Antibiotics	Duration
Strep pneumoniae		
PCN		
MIC < 0.06 mcg/mL	Penicillin G (monotherapy)	10–14 days
MIC ≥ 0.12[a]	3rd generation cephalosporin[b]	
If Ceftriaxone MIC > 1 mcg/mL	Add Vancomycin	
Neisseria meningitidis	3rd generation cephalosporin[b]	7 days
Haemophilus influenzae		7 days
Beta-lactamase NEG	Ampicillin	
Beta-lactamase POS	3rd generation cephalosporin[b]	
Listeria monocytogenes	Ampicillin or Penicillin G	21 days
Streptococcus agalactiae	Ampicillin or Penicillin G	14–21 days
	Plus aminoglycoside	
***E. Coli* or other Enterobacteriaceae**[a]	3rd generation cephalosporin[b]	14–21 days
Pseudomonas aeruginosa[a]	Cefepime or ceftazidime	21 days
Staphylococcus aureus		
Methicillin susceptible	Nafcillin or oxacillin	10–14 days
Methicillin resistant	Vancomycin	

MIC minimum inhibitory concentration
[a]Add rifampin if MIC >2 mcg/mL for 3rd generation cephalosporin to maximize CSF penetration.
[b]Ceftriaxone or cefotaxime

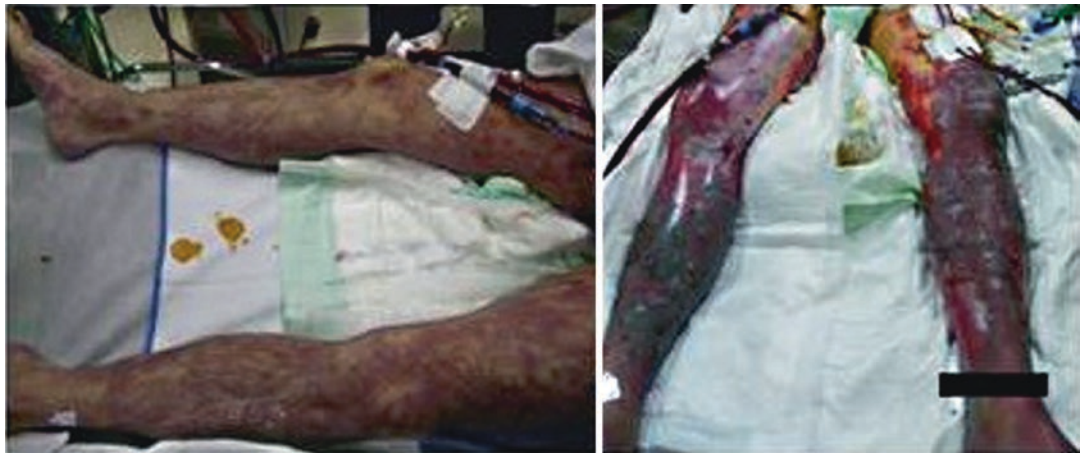


Fig. 36.3 Examples of purpura fulminans (From Endo et al. [24]. Courtesy of Biomed Central (Open Access))

time to antibiotic administration, severity at presentation, and whether steroids were administered [19]. Neurologic complications include both early onset (altered mental status, elevated ICP, seizures, focal neurologic deficits) and more long term sequelae (permanent neurologic deficits, hearing loss, or cognitive impairment). One study examined a model for prediction for neurologic complications or death at discharge using hypotension, altered mental status, and seizures as criteria. The presence of 2 of the 3 criteria predicted a 56 % chance of adverse outcome, while the presence of only 1 of the 3 criteria predicted a 9 % chance of adverse outcome. It was also noted that neurologic events were seen more in pneumococcal meningitis [17].

Meningococcemia

It is important to briefly discuss additional specific details related to *N. meningitidis* and the development of meningococcemia. *N. meningitidis* can cause three major syndromes: meningitis alone; meningitis accompanied by meningococcemia (sepsis); or meningococcemia without meningitis. In these disease states caused by *N. meningitidis,* mortality is higher and timely antibiotics are crucial with an antibiotic delay of even 30 min considered unacceptable [20].

Meningeal signs and symptoms along with fever and petechial rash should immediately prompt a suspicion for *N. meningitidis* and the possibility of meningococcemia. An additional nonspecific clue includes the presence of myalgias which are not often seen with pneumococcal meningitis and are typically more severe than the myalgias seen with influenza. Neisseria infections often occur in outbreaks in the late winter and can present similarly to the flu with nonspecific URI symptoms preceding more serious symptoms which can develop within a matter of hours. A key clinical feature to be aware of with meningococcal infection is a rash which can be petechial or hemorrhagic and is seen in about half of all cases [21]. This rash usually is more prominent in the trunk and lower extremities and at sites where pressure is applied to the skin such as belts or elastic bands [22]. Mucous membranes of the soft palate and eye must also be examined for signs of hemorrhage. The lesions are usually 1 to 2 mm in diameter and can coalesce into larger patches. The severity of the rash is directly proportional to the overall severity of illness including the presence of shock and disseminated intravascular coagulation (DIC). The devastating complication of purpura fulminans is seen in 15–25 % cases [23]. See Fig. 36.3. The cascade of organ dysfunction seen in meningococcemia – coagulopathy, DIC, acute respiratory distress syndrome (ARDS), sepsis, purpura fulminans

and adrenal shock (Waterhouse-Friderichsen syndrome) are initiated in large part by the lipooligosaccharide, a potent toxin in the bacterial meningococcal membrane [25].

A key management principle in meningococcal infections is the prevention of spread to others. Importantly, droplet precautions should be started as soon as possible in all cases of community acquired bacterial meningitis and should be continued until meningococcal and/or haemophilus infection has been ruled out. In cases with confirmed meningococcal infection consideration for post-exposure prophylaxis should be given (see evidence contour section).

Evidence Contour

ICP Management

Elevations in intracranial pressure (ICP) are commonly seen in bacterial meningitis and are thought to be related to the development of permanent neurological problems such as deafness, epilepsy and poor cognition [26]. Reducing infection-induced swelling (vasogenic edema) is a goal to improve outcomes. In addition to antimicrobial therapy, initial medical management of elevated ICP from meningitis includes general measures (1) elevating head of bed >30° with head in neutral position to avoid jugular vein compression, (2) maintenance of normothermia, (3) avoidance of hypotension/hypovolemia (4) hyperventilation, and (5) mannitol [26]. While monitoring of ICP is not standard of care in bacterial meningitis, it may be considered in patients with a GCS < 8 and the gold standard for monitoring ICP involves the placement of an intraventicular catheter. Other osmotic therapies such as the use of glycerol have been evaluated for ICP management in bacterial meningitis but have not shown benefit in adults [27, 28].

Hypothermia

Therapeutic hypothermia has known neuroprotective benefits following cardiac arrest. Hypothermia as adjunctive therapy in the management of bacterial meningitis has yielded inconsistent and potentially harmful results in regard to both mortality and neurologic outcomes [29, 30]. The exclusion of patients who received dexamethasone in some of the studies leads to an unclear conclusion regarding the addition of therapeutic hypothermia in bacterial meningitis patients [29]. At this time we do not recommend therapeutic hypothermia in the setting of bacterial meningitis.

Gram-Negative Bacilli Meningitis

Gram negative bacilli (GNB) meningitis occurs most frequently in neonates and infants, however, there are two additional patterns of infection: nosocomial GNB meningitis (in the setting of head trauma or neurosurgery) and spontaneous, community acquired GNB meningitis, (typically from another source of infection, such as a urinary tract infection). The incidence of nosocomial GNB meningitis is on the rise secondary to more complex neurosurgical operations and routine prophylactic antibiotics given to prevent surgical site infections [31].

Patients who present with spontaneous GNB meningitis are typically elderly or have comorbidities including cancer, diabetes, cirrhosis, immunosuppression, or splenectomy [32]. The most common pathogens are Escherichia coli (38%) and Pseudomonas species [32]. GNB meningitis presents less often with the classic meningitis triad and is associated with more neurological and systemic complications than other causes of bacterial meningitis and carries a higher mortality rate [32].

Shunts and Other Intracranial Devices

CSF shunts increase a patients risk for bacterial meningitis. Internalized shunts (draining to the peritoneum, commonly ventriculoperitoneal or VP shunt) have an infection rate of 5–15%, with an infection most common in the first month of placement. External devices such as a ventriculostomy catheter or an Ommaya reservoir (access for

administration of chemotherapy or antibiotics) may also develop infections [33]. Clinical presentation may be subtle and result from obstruction of the shunt with symptoms consistent with elevated intracranial pressure (headache, nausea and vomiting, somnolence and altered mental status). In contrast to community acquired bacterial meningitis, nuchal rigidity tends to be absent, as there is no communication between the infected ventricles and the meninges.

Evaluation still requires blood cultures, CSF cultures and imaging. However, interpretation of the CSF is more complex and cannot be made on a single parameter. Repeated positive CSF cultures over several days will help confirm the diagnosis [34]. Shunt removal is indicated to ensure treatment success [9].

Post Exposure Prophylaxis

Not all bacterial meningitis pathogens require post exposure prophylaxis for contacts to minimize spread, however both *Neisseria meningitidis* and *Haemophilus influenzae* do.

Individuals who require prophylaxis for meningitis are (1) close contacts (household members, daycare workers, military), (2) travelers in direct contact with respiratory secretions or close proximity to index patient for >8 h flight, and (3) individuals in close contact with respiratory secretions (including kissing, mouth to mouth resuscitation and endotracheal intubation). Prophylaxis should occur in a timely manner, ideally within <24 h of exposure. Prophylaxis should be given to appropriate individuals several days after exposure, however the CDC does not recommend prophylaxis >14 days after exposure [35]. Eradication of nasopharyngeal carriage is performed in outbreak settings and for the index patient (if they did not receive ceftriaxone), prior to discharge to prevent further transmission [36].

References

1. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma J, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med. 2004;351(18):1849–59.
2. Attia J, Hatala R, Cook D, Wong J. Does this adult patient have acute meningitis? JAMA. 1999;281(2):175–81.
3. McGee S. Evidence-based physical diagnosis. 2nd ed. St. Louis: Saunders Elsevier; 2007.
4. Siegel JD, Rhinehart E, Jackson M, Chiarello L, and the Healthcare infection control practices advisory committee. 2007 Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings. Am J Infect Control. 2007; 35: 1–226.
5. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. N Engl J Med. 2002; 347(20):1549–56.
6. Prevention CfDCa [Internet]. Atlanta: Haemophilus influenzae type b.; 2012 [updated 2014 April 4; cited 2015 May 10]. Available from: http://www.cdc.gov/hi-disease/.
7. Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, et al. Bacterial Meningitis in the United States, 1998–2007. N Engl J Med. 2011; 364(21):2016–25.
8. van de Beek D, de Gans J, Tunkel AR, Wijdicks EFM. Community-acquired bacterial meningitis in adults. N Engl J Med. 2006;354(1):44–52.
9. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld M, et al. Practice guidelines for management of bacterial meningitis. Clin Infect Dis. 2004;39:1267–84.
10. Johnson KS, Sexton DJ, Aminoff MJ, Wilterdink JL. Lumbar puncture: technique, indications, contraindications, and complications in adults [Internet]. Waltham: UpToDate: 2013 [cited 2015 Feb 18]. Available from: UpToDate.
11. Tunkel AR, Calderwood SB, Thorner AR. Initial therapy and prognosis of bacterial meningitis in adults [Internet]. Waltham: UpToDate; 2013 [cited 2014 Nov 18]. Available from: UpToDate.
12. Barenfanger J, Drake CA. Interpretation of gram stains for the nonmicrobiologist. Lab Med. 2001; 32(7):368–75.
13. Tunkel AR, Calderwood SB, Thorner AR. Clinical features and diagnosis of acute bacterial meningitis in adults [Internet]. Waltham: UpToDate; 2014 [cited 2014 Nov 18]. Available from: UpToDate.
14. Tunkel AR. Approach to the patient with central nervous system infection. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 7th ed. Philadelphia: Churchill Livingstone Elsevier; 2010. p. 1183.
15. Auburtin M, Wolff M, Charpentier J, Varon E, Le Tulzo Y, Girault C, et al. Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: the PNEUMOREA prospective multicenter study. Crit Care Med. 2006;34(11):2758–65.
16. Sinner SW, Tunkel AR. Antimicrobial agents in the treatment of bacterial meningitis. Infect Dis Clin North Am. 2004;18(3):581–602.
17. Aronin SI. Bacterial Meningitis: principles and practical aspects of therapy. Curr Infect Dis Rep. 2000; 2(4):337–44.

18. van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. Bacterial meningitis 2: advances in treatment of bacterial meningitis. Lancet. 2012;380:1693–702.
19. Durand M, Calderwood SB, Weber DJ, Miller SI, Southwick FS, Caviness VS, et al. Acute Bacterial Meningitis in Adults: a review of 493 episodes. N Engl J Med. 1993;328(1):21–8.
20. Tunkel AR, van de Beek D, Scheld WM. Acute meningitis. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 7th ed. Philadelphia: Churchill Livingstone; 2010. p. 1189.
21. Carpenter RR, Petersdorf RG. The clinical spectrum of bacterial meningitis. Am J Med. 1962;33(2):262–75.
22. Apicella M, Calderwood SB, Edwards MS, Baron EL. Clinical manifestations of meningococcal infection [Internet]. Waltham; 2014 [cited 2015 May 16]. Available from: UpToDate.
23. Algren JT, Lal S, Cutliff SA, Richman BJ. Predictors of outcome in acute meningococcal infection in children. Crit Care Med. 1993;21(3):447.
24. Endo A, Shiraishi A, Aiboshi J, Hayashi Y, Otomo Y. A case of purpura fulminans caused by hemophilus influenza complicated by reversible cardiomyopathy. J Intens Care. 2010;2(13):1–4.
25. Kahler CM, Stephens DS. Genetic basis for biosynthesis, structure, and function of meningococcal lipooligosaccharide (endotoxin). Crit Rev Microbiol. 1998;24(4):281.
26. Raslan A, Bhardwaj A. Medical management of Cerebral edema. Neurosurg Focus. 2007;22(5):1–12.
27. Ajdukiewicz KM, Cartwright KE, Scarborough M, Mwambene JB, Goodson P, Molyneux ME, et al. Glycerol adjuvant therapy in adults with bacterial meningitis in a high HIV seroprevalence setting in Malawi: a double-blind, randomised controlled trial. Lancet. 2011;11:293–300.
28. Peltola H, Roine I, Fernandez J, Zavala I, Gonzalez Ayala S, Gonzalez Mata A, et al. Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. Clin Infect Dis. 2007;45:1277–86.
29. Kutlesa M, Lepur D, Barsic B. Therapeutic hypothermia for adult community-acquired bacterial meningitis – historical control study. Clin Neurol Neurosurg. 2014;123:181–6.
30. Mourvillier B, Tubach F, van de Beek D, Garot D, Pichon N, Georges H, et al. Induced hypothermia in severe bacterial meningitis: a randomized clinical trial. JAMA. 2013;310(20):2174–83.
31. Korinek A-M, Baugnon T, Golmard J-L, van Effenterre R, Coriat P, Puybasset L. Risk factors for adult nosocomial meningitis after craniotomy role of antibiotic prophylaxis. Neurosurgery. 2006;59(1):126–33.
32. Pomar V, Benito N, Lopez-Contreras J, Coll P, Gurgui M, Domingo P. Spontaneous gram-negative bacillary meningitis in adult patients: characteristics and outcome. BMC Infect Dis. 2013;13:451–60.
33. Simon TD, Hall M, Riva-Cambrin J, Albert JE, Jeffries HE, Lafleur B, et al. Infection rates following initial cerebrospinal fluid shunt placement across pediatric hospitals in the United States. Clinical article. Hydrocephalus Clinical Research Network. J Neurosurg Pediatr. 2009;4(2):156.
34. Meredith FT, Phillips HK, Reller LB. Clinical utility of broth cultures of cerebrospinal fluid from patients at risk for shunt infections. J Clin Microbiol. 1997;35(12):3109.
35. Gardner P. Prevention of meningococcal disease. N Engl J Med. 2006;355:1466–73.
36. Andersen J, Berthelsen L, Bech Jensen B, Lind I. Dynamics of the meningococcal carrier state and characteristics of the carrier strains: a longitudinal study within three cohorts of military recruits. Epidemiol Infect. 1998;121(1):85–94.

Management of Intracerebral Hemorrhage

37

Shamir Haji and Neeraj Naval

Case Presentation

A 67-year-old female with a history of uncontrolled hypertension and hyperlipidemia presents after sudden onset of headache followed by vomiting and progressive left hemiparesis over 2 hours. Vital signs were notable for a systolic blood pressure of 230 mmHg. Laboratory values upon arrival, including coagulation parameters and toxicology screen, were unrevealing. CT head imaging was performed on arrival and the pertinent images are shown below (Fig. 37.1).

Question Would early surgical intervention be appropriate in the initial management of this patient?

Answer Certain patients may benefit from early neurosurgical intervention in the setting of intracerebral hemorrhage [2].

S. Haji (✉)
Division of Neurosciences Critical Care, Anesthesia and Critical Care Medicine, Johns Hopkins Hospital, Baltimore, MD, USA
e-mail: shaji2@jhmi.edu

N. Naval
Inpatient Neurosciences & Neurocritical Care, Lyerly Neurosurgery, Baptist Neurological Institute, Jacksonville, FL, USA

However, the International Surgical Trial in Intracerebral Haemorrahage (STICH) did not demonstrate improved 6-month functional outcome or mortality with the early evacuation of supratentorial hematomas [3]. Furthermore, STICH II did not demonstrate any significant difference in combined death or disability in patients undergoing evacuation of supratentorial hematoma volumes of 10 to 100 cc without intraventricular hemorrhage (IVH) when compared with the maximal medical management group [4]. However, patients with cerebellar hemorrhages > 3 cm with 4th ventricular effacement and/or hydrocephalus should undergo urgent surgical intervention given elevated morbidity and mortality with conservative management in this group [2, 4, 5]. Younger patients with rapid neurological decompensation secondary to hematoma expansion, or with underlying lesions such as aneurysms, AVMs and tumors may also be surgical candidates [2, 4, 5]. The Minimally Invasive Surgery Plus Recombinant Tissue-Type Plasminogen Activator for Intracerebral Hemorrhage Evacuation II (MISTIE II) trial demonstrated a reduction in perihematomal edema and a trend towards improved outcomes in the hematoma evacuation group [6]. The MISTIE III trial is currently in progress. Phase 3 of Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) IVH trial is a randomized control study, which aims to evaluate clearance of clot and outcome in patients with large intraventricular hemorrhage receiving

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_37

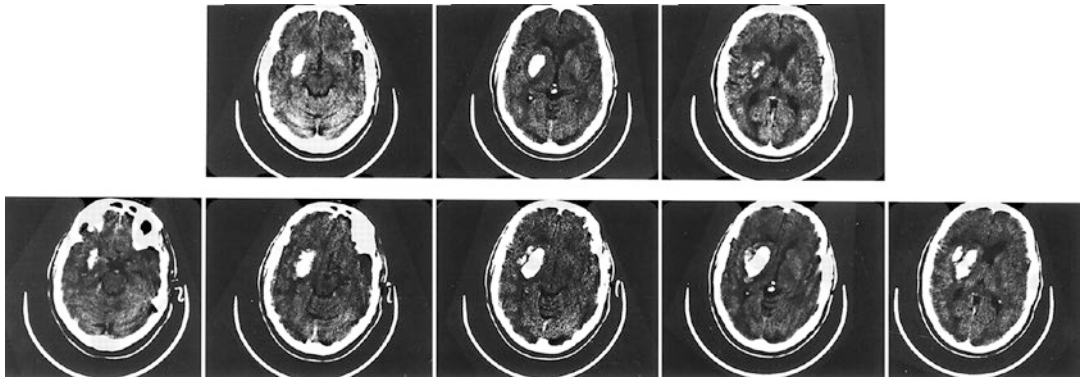


Fig. 37.1 Axial CT brain demonstrating right putaminal hemorrhage (From Brott et al. [1]. Reprinted with permission from Wolters Kluwer Health, Inc.)

scheduled injections of rt-PA through EVD [7]. Study results are expected in the near future.

This patient's CT scan demonstrates a large right basal ganglia hemorrhage without intraventicular extension. Current guidelines would advocate for maximal medical management [2, 5].

Principles of Management

Clinical Presentation

The onset of acute severe headache, vomiting, seizure, significant hypertension (often > 220 mmHg), and rapid deterioration in consciousness with possible accompanying pupillary dilatation, posturing and abnormal respiratory pattern should provoke a high suspicion for intracerebral hemorrhage (ICH) [2].

Diagnosis

The rapid onset of focal neurological symptoms warrants brain imaging on an emergent basis [2, 5]. CT scans provide a rapid method of evaluating the head for acute pathology, including intracerebral hemorrhage (ICH). Brain CT imaging in the latter often demonstrates intra-axial, focal area(s) of hyperdensity with mass effect and effacement of the surrounding parenchyma [2]. Hemorrhage location(s) provide clues to the underlying pathology. In addition to trauma, multiple etiologies of non-traumatic ICH exist, and include hypertension, vascular malformations, trauma, cerebral amyloid angiopathy, brain neoplasm, infarction, vasculitis, illicit drug-related, bleeding diathesis, and anticoagulation [2, 5]. Hypertension is the most common cause of non-traumatic ICH. Typical locations suggestive of a hypertensive bleed include the basal ganglia (most commonly putamen) and thalamus, as well as the pons and cerebellum [2, 5]. Hematoma volume can be estimated using the ABC/2 method (Fig. 37.2) [9]. Large hematoma volumes and evidence of heterogeneous attenuation are predictive of subsequent hematoma expansion [1, 2, 5, 10].

Acute Management

In addition to emergent brain imaging, initial laboratory assessments should include coagulation parameters and toxicology screen, with elevations in the former requiring rapid normalization with appropriate reversal agents. Contrast-enhanced head imaging, often CT angiography, can provide additional information about the presence of underlying vascular malformations, aneurysms, as well as the presence of contrast extravasation within the hematoma [1, 10, 11]. The latter "spot sign" is suggestive of active bleeding and predicts hematoma expansion, as well as likely higher morbidity and mortality [1, 10, 11]. Demchuk et al. found a positive predictive

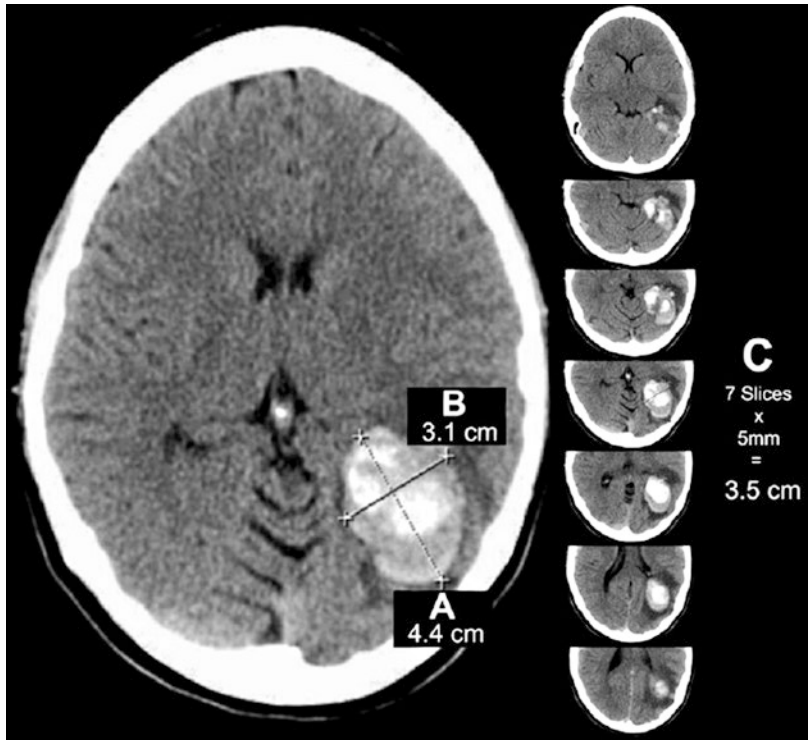


Fig. 37.2 Example of ICH calculation using ABC/2 formula. (**a**) Greatest hemorrhage diameter by CT. (**b**) Diameter 90° to A. (**c**) The approximate number of CT slices with hemorrhage multiplied by slice thickness (From Beslow et al. [8]. Reprinted with permission from Wolters Kluwer Health, Inc.)

value of 61 % for hematoma expansion in the presence of the spot sign [10]. Exacerbating factors for expansion also include antithrombotic and anticoagulation therapy, as well as persistent hypertension, and therefore aggressive management with anticoagulation reversal and antihypertensive therapy is warranted [1, 2, 5, 10].

Serial CT head imaging, usually within 4–6-h, is critical for the evaluation of hematoma expansion and obstructive hydrocephalus. Brott and Broderick found 38 % of hematomas expand by 33 % of original volume or at least 6 cc within 24-h of symptom onset, with most reaching significant expansion within 4 h [1]. Intraventricular hemorrhage is a risk factor for development of the hydrocephalus [12]. The initial presence or subsequent development of ventricular system enlargement warrants rapid neurosurgical intervention with external ventricular drain (EVD) placement and drainage of cerebral spinal fluid (CSF) [2, 5, 12].

Airway patency should be monitored carefully. Large or rapidly expanding hematomas, particularly with evidence of obstructive hydrocephalus, often result in depressed mental status and compromised airway protection [2]. Emergent intubation is warranted in these circumstances with utilization of agents such as propofol and lidocaine to blunt potential intraprocedural intracranial pressure crises [2].

Brain herniation is the most dreaded outcome of ICH, leading to increased morbidity and mortality, particularly in the absence of rapid intervention and reversal. Clinical manifestations include the development of new or worsening neurological deficits, including depressed mental status and pupillary abnormalities, thus mandating frequent monitoring of the patient's neurological exam in acute setting [2, 5]. Rapid intervention is critical and includes elevating the head to 30°, hyperventilation (with rapid sequence intubation in the setting of an unsecured

airway), and administration of hyperosmolar therapy [2, 5, 13]. Repeat head imaging is warranted when the patient is stabilized with insertion of an EVD if obstructive hydrocephalus is present [1–5, 11]. Ultimately the patient may require decompressive hemicraniectomy to improve odds of survival, even though the data for functional outcome amelioration amongst survivors is not nearly as robust as for large hemispheric ischemic strokes [2–6].

Natural History

The ICH score is a risk stratification scale using the Glasgow Coma Score (GCS), age, ICH volume, infratentorial location, and presence of IVH to predict 30-day mortality (Table 37.1 and Fig. 37.3) [14]. The tissue at the epicenter of the hematoma undergoes rapid destruction causing clinical neurological insult and is unlikely to be salvaged [15]. Hematoma expansion and perihematomal edema can worsen mass effect and may contribute to further injury and higher mortality. Edema develops early after ICH and peaks up to 2 weeks after onset, although the most rapid increase occurs in first 2 days on MRI imaging [16]. The degree of edema is predictive of poor outcome. Secondary injury as a consequence of blood–brain-barrier damage, inflammation, and reticulocyte lysis can further worsen injury to the surrounding parenchyma [15, 16].

Table 37.1 ICH score for predicting 30-day mortality

Component	ICH score points
GCS	
3–4	2
5–12	1
13–15	0
ICH volume (mL)	
≥30	1
<30	0
Intraventricular hemorrhage	
Yes	1
No	0
Infratentorial origin of ICH	
Yes	1
No	0
Age (y)	
≥80	1
<80	0
Total ICH score	**0–6**

From Hemphill et al. [14]. Reprinted with permission from Wolters Kluwer Health, Inc.

Complications

Damage or irritability of the cerebral cortex in the setting of ICH can manifest as seizures. Although occasionally a presenting symptom, seizures can develop at any point after the inciting event and therefore antiepileptic drugs are a mainstay in the initial treatment [2, 5, 17, 18].

ICP can be measured via an EVD or a dedicated ICP monitor. Persistent ICP elevations can further complicate the management of ICH, often manifesting as herniation events. ICP crises are treated algorithmically, as noted above, often beginning with raising the head of the bed, hyperventilation with a goal PCO2 of 30–35, and hyperosmolar therapy [2]. Additional iatrogenic interventions include the use intravenous agents to drive down the ICP, such as propofol and pentobarbital, as well as systemic body temperature cooling [2, 5].

Evidence Contour

Hyperosmolar Therapy

Urgent intervention is warranted in the setting of increased intracranial pressure as assessed by invasive monitoring techniques or changes in the neurological examination, such as the rapid development of pupillary dilation and absent reactivity. In addition to head elevation and hyperventilation, hyperosmotic agents are often utilized for rapid ICP reduction, effectively removing free water and dehydrating the brain parenchyma [2, 5, 13]. Mannitol and hypertonic saline are two commonly utilized agents. Mannitol, typically administered in 1 g per kilogram boluses, increases serum osmolality and induces an osmotic gradient between the serum and brain parenchyma,

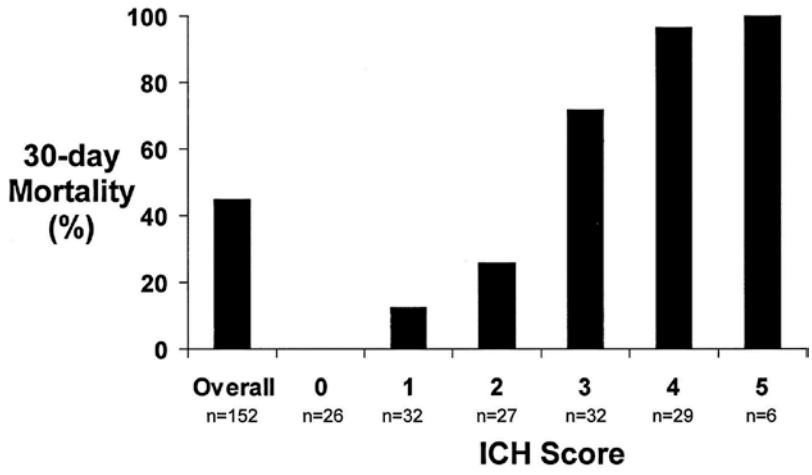


Fig. 37.3 ICH score and 30-day mortality (From Hemphill et al. [14]. Reprinted with permission from Wolters Kluwer Health, Inc.)

resulting in osmotic diuresis. Despite being widely available and easily administered through a peripheral line, caution should be used given the potential for hypotension, volume depletion and electrolyte disturbances [13]. Serum osmolality >320–340 mOsm/kg or poor renal function may be limiting factors. Mannitol can cross the blood–brain-barrier and extravasate into the damaged parenchyma especially given the lower reflection coefficient than hypertonic saline (0.9 and 1.0, respectively), posing the theoretical risk of "rebound" elevations in ICP secondary to a reversal of the osmotic gradient in the setting of recurrent use [13].

Alternatively, hypertonic saline, used in widely varying volume and tonicity, is also utilized for urgent ICP reduction [13]. The mechanism of action is similar to mannitol although without the accompanying diuresis and subsequent hypovolemia [13]. Hypertonic saline is less likely to cross the damaged BBB and cause worsening mass effect and shift with recurrent use. Given the risk of thrombophlebitis, solutions of 3% or greater should be administered via central IV access [13].

Several randomized control trials evaluating various etiologies of increased ICP have compared the efficacy of hypertonic saline and mannitol, with a meta-analysis of these trials demonstrating marginally greater efficacy of hypertonic saline (16% more likely to decrease ICP < 20 1 h post administration) in the management of elevated ICP, although clinical outcomes were not measured [13]. Current guidelines advise clinician discretion in the utilization of either agent and do not recommend one over the other [5, 13].

Seizure Prophylaxis

Brain injury involving the cortex increases the risk of epileptogenic activity. The incidence of electrographic seizures may be as high as nearly 1/3 of patients with ICH, with most occurring within 24-h of the inciting event [2, 5, 17, 18]. Vespa et al. reported a relatively high frequency of seizures after lobar (28%) and deep (21%) ICH [18]. Lobar location and small hematomas may be early predictors of early seizures. Although management often involves the use of seizure prophylaxis, current guidelines recommend otherwise [5]. Furthermore the agent of choice and duration of treatment remain areas of debate. One prospective review found phenytoin to be associated with a higher incidence of fever and worse outcomes [17]. The association of seizures with clinical outcomes remains unclear, however. Alterations in mental status incongruent with the degree of cerebral injury certainly warrant continuous EEG monitoring [2, 5, 18]. Seizures should be managed with anticonvulsant therapy, although the choice of anticonvulsant remains debatable. Prophylactic anti-epileptic medication is not recommended by current AHA guidelines [2, 5].

Hypothermia

Fever has been strongly associated with poorer neurological outcomes in patients with brain injury [2, 5, 19, 20]. Investigation into temperature reduction as a neuroprotective treatment began in the 1950s and has subsequently been most studied in the context of traumatic brain injury. Multiple studies have postulated the beneficial effects of mild to moderate hypothermia to be secondary to the reduction of cerebral metabolism and potential reduction of ICP and CBF [19, 20]. The attenuation of several secondary injury mechanisms, including free radical generation, excitotoxicity, and inflammation, may also be contributory [15, 19, 20]. However, limiting side effects of systemic cooling have included coagulopathy and cardiac arrhythmias [19, 20]. Furthermore, an optimal method of cooling, target core temperature, and duration of cooling has not been established [19, 20].

In comparison to standard medical or surgical treatment, hypothermia has not been shown to improve outcomes in patients with traumatic brain injury. The National Acute Brain Injury Study: Hypothermia II, a randomized control trial comparing normothermia and hypothermia in patients with traumatic brain injury, did not demonstrate a difference in functional outcome between the two groups at 6-months [20]. In 2015, the Hypothermia for Intracranial Hypertension after Traumatic Brain Injury study, a randomized control trial of elevated ICP management comparing standard care to hypothermia plus standard care, did not find better outcomes in the hypothermia group [19]. At this time, ensuring strict normothermia remains the standard in this patient population [5].

Hypertension Management

Elevated blood pressure, defined as SBP > 140 mmHg, is present in approximately 75 % of patients with acute ICH. Proposed mechanisms include stress activation of neuro-endocrine systems and damage to central autonomic centers, including the insular cortex. Hypertension is a strong predictor of early mortality in ICH [2, 5, 21]. However, the intensity of blood pressure control in this setting has remained a topic of debate. Proponents for aggressive control cite hematomal expansion, early neurological deterioration and higher mortality as the basis for targeting systolic blood pressures of < 140 mmHg. Conversely, rapid reduction and aggressive targeting of blood pressure may run the theoretical risk of perihematomal and perhaps more global ischemia [21]. The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT2) compared early intensive blood pressure lowering with SBP < 140 mmHg to target SBP < 180 mmHg and did not demonstrate any significant difference in death or major disability at 90-days between groups, but did demonstrate better 90-day modified Rankin scores [21]. Aggressive blood pressure strategies have not been found to reduce hematoma volumes or perihematoma cerebral blood flow [21, 22]. Furthermore, the Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial (ICH-ADAPT) study, did not find that intensive blood pressure reduction precipitated perihematomal ischemia [22]. The results of the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH II) trial, which will randomize participants to target blood pressure goals of SBP <140 mmHg or SBP < 180 mmHg, are pending. Current AHA guidelines suggest that early aggressive blood pressure management strategies with target SBP < 140 mmHg appear to be safe and may maximize patient outcomes, especially in patients with smaller ICH volumes (<20 cc), admission GCS 12–15, and initial SBP < 220 [5]. In others, a more conservative approach may be reasonable.

References

1. Brott T, Broderick J, Kothari R, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke. 1997;28:1–5.
2. Chan S, Hemphill 3rd JC. Critical care management of intracerebral hemorrhage. Crit Care Clin. 2014; 30:699–717.
3. Morgenstern LB, Frankowski RF, Shedden P, et al. Surgical treatment of intracerebral hemorrhage

(STICH): a single-center, randomized clinical trial. Neurology. 1998;51:1359–63.
4. Mendelow AD, Gregson BA, Rowan EN, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematoma (STICH II): a randomised trial. Lancet. 2013;382(9890):397–408.
5. Hemphill 3rd JC, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46:2032–60.
6. Abdu E, Hanley DF, Newell DW. Minimally invasive treatment for intracerebral hemorrhage. Neurosurg Focus. 2012;32(4):1–7.
7. Naff N, Williams NA, Keyl PM, et al. Low dose recombinant tissue-type plasminogen activator enhances clot resolution in brain hemorrhage: the intraventricular hemorrhage thrombolysis trial. Stroke. 2011;42:3009–16.
8. Beslow LA, Ichord RN, Kasner SE et al. ABC/XYZ estimates intracerebral hemorrhage volume as a percentage of total brain volume in children. Stroke. 2010;41(4):691–4.
9. Kothari RU, Brott T, Broderick JP. The ABCs of measuring intracerebral hemorrhage volume. Stroke. 1996;27:1304–5.
10. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. Lancet Neurology. 2012;11(4): 307–14.
11. Goldstein JN, Fazen LE, Snider R, et al. Contrast extravasation on CT angiography predicts hematoma expansion in intracerebral hemorrhage. Neurology. 2007;68:889–94.
12. Bhattathiri PS, Gregson B, Prasad KS, et al. Intraventricular hemorrhage and hydrocephalus after spontaneous intracerebral hemorrhage: results from the STICH trial. Acta Neurochir Suppl. 2006;96:65–8.
13. Kamel H, Navi BB, Nakagawa K, et al. Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: a meta-analysis of randomized clinical trials. Crit Care Med. 2001;39(3):554–9.
14. Hemphill JC, Bonovich DC, Besmertis L, et al. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001;32:891–97.
15. Ziai WC. Hemorrhagic stroke: hematology and inflammatory signaling of intracerebral hemorrhage. Stroke. 2013;44:574–78.
16. Venkatasubramanian C, Mlynash M, Finley-Caulfield A, et al. Natural history of perihematomal edema after intracerebral hemorrhage measured by serial magnetic resonance imaging. Stroke. 2011;42:73–80.
17. Naidech AM, Garg RK, Liebling S, et al. Anticonvulsant use and outcomes after intracerebral hemorrhage. Stroke. 2009;40(12):3810–5.
18. Vespa PM, O'Phelan K, Shah M, et al. Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. Neurology. 2003;60(9):1441–6.
19. Andrews PJD, Sinclair HL, Rodriguez A, et al. Hypothermia for intracranial hypertension after traumatic brain injury. N Engl J Med. 2015;373:2403–12.
20. Clifton GL, Valadka A, Zygun D, et al. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomized trial. Lancet Neurol. 2011;10(2):131–9.
21. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368(25):2355–65. INTERACT-2
22. Butcher K, Jeerakathil T, Emery D, et al. The intracerebral hemorrhage acutely decreasing arterial blood pressure trial: ICH ADAPT. Int J Stroke. 2010;5: 227–33.

Status Epilepticus

38

Jharna N. Shah and Christa O'Hana V. San Luis

Case Presentation

A 35 year-old woman with a history of thyroid nodules, thyroidectomy and migraines presented with a feeling of chills and headaches in the primary care clinic and was diagnosed with a viral illness. She developed a fever up to 103 °F and then presented to the emergency department (ED) where she received antibiotics and underwent a Computed Tomography (CT) scan of the head which was normal. She continued to have headaches and was treated with antibiotics for presumed sinusitis. She then progressed to lethargy and developed convulsions that were witnessed by her husband. Initial management included ceftriaxone and acyclovir, a lumbar puncture (LP) and a magnetic resonance imaging (MRI) of the brain which were unremarkable. Herpes simplex virus PCR and cerebrospinal fluid (CSF) cultures were negative; hence, antibiotics and acyclovir were discontinued. She was sent home after 3 days. She returned 24 h after discharge with another convulsive episode that lasted 20 min but she did not return to her baseline mental status. Continuous electroencephalogram (EEG) was ordered and 19 subsequent electrographic seizures were recorded, four of which were associated with clinical generalized tonic-clonic seizures within the first 24 h. Figure 38.1 demonstrates electrographic status epilepticus in a different patient.

Question What is the primary goal of status epilepticus (SE) management?

Answer Emergent control of both clinical and electrographic seizure activity with simultaneous patient stabilization and prompt work up of etiology.

The primary focus of SE management is stopping the seizures, clinical and electrographic (seen only on EEG). The Neurocritical Care Society (NCS) consensus statement defines SE as seizures that continue for more than 5 min or recurrent seizure activity without return to baseline level of consciousness between seizures [1]. The patient's airway, breathing and circulation should be assessed initially along with simultaneous administration of abortive treatment for SE. Neurology consult must be initiated at the same time for timely identification of non-convulsive SE (NCSE), SE mimics as well as guidance on further management should abortive treatment fail. In the ED, the evaluation of seizures usually is clinical, unless EEG is available.

J.N. Shah (✉)
Division of Neurosciences Critical Care,
The Johns Hopkins University School of Medicine,
Baltimore, MD, USA
e-mail: jharnashah@gmail.com

C.O.V. San Luis
Neurology, Division of Neurocritical Care,
University of Mississippi Medical Center,
Jackson, MS, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_38

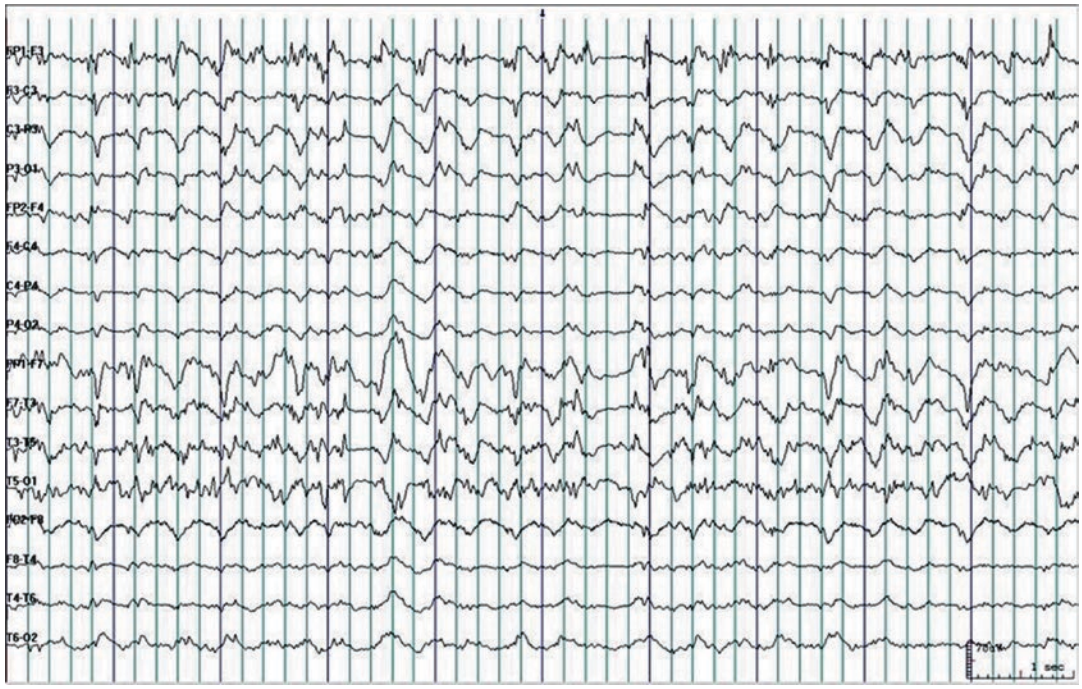


Fig. 38.1 EEG of a different patient showing ongoing polymorphic, rhythmic, left-sided spike, polyspike and slow wave activity, waxing and waning consistent with focal status epilepticus (Figure courtesy of Dr Peter W Kaplan, Johns Hopkins University)

The patient's convulsions stopped; however, she was confused, able to follow simple commands but remained lethargic, secondary to either post-ictal effect of seizures, sedative effect of the benzodiazepine or NCSE. EEG was performed when she was admitted to the ward, which showed multiple electrographic seizures along with recurrence of clinical seizures. She was started on intravenous (IV) fosphenytoin. Phenytoin peak level must be measured 2–4 h after the loading dose with a target free level of 1.5–2.5. An additional bolus may be given. As she continued to have electrographic SE, she was started on IV levetiracetam. Valproic acid was avoided due to competitive plasma protein binding with and subsequent decrease in protein binding of phenytoin. IV lacosamide was added the following day due to continuation of SE. She was then transferred to the neurointensive care unit for refractory SE, was intubated for airway protection, and started on continuous EEG monitoring and intravenous midazolam drip to achieve burst suppression pattern of 2–3 bursts per 10-s page. She was then in super-refractory SE (SRSE) and was transitioned to Pentobarbital infusion titrated to burst suppression pattern for 72 h with concomitant initiation of phenobarbital, which was titrated up to a level of 200 μg/mL. Ketogenic diet and other anti-epileptic drugs (AEDs) such as clonazepam, topamax and valproic acid were initiated while the pentobarbital infusion was weaned off.

The work-up for the etiology of her SRSE was continued simultaneously during the titration of her AEDs. Blood chemistries, CSF studies, viral PCRs and cultures, CSF and serum paraneoplastic studies, MRI brain, whole body CT and PET scan survey were all unrevealing. Her seizures are presumed to be likely autoimmune in etiology and she received a trial of empiric pulse steroids (1 g of IV methylprednisolone sodium succinate for 5 days) followed by plasmapheresis with improvement in electrographic seizures. However, the patient remained comatose, likely due to the high phenobarbital levels. Gradual downtitration of phenobarbital resulted in improvement in

mental status with no recurrence of seizures. She was ambulatory but required some assistance and was discharged to a rehabilitation facility after 52 days of hospitalization.

Principles of Management

Diagnosis of SE and Underlying Etiology

SE is diagnosed when a clinical and/or electrographic seizure lasts more than 5 min or two or more seizures occur without return to baseline level of consciousness [1–3]. SE can be classified into convulsive (CSE) or nonconvulsive (NCSE) status epilepticus. CSE involves visually evident tonic, tonic-clonic, clonic or clonic activity of one limb, one side or the whole body with or without impairment of consciousness [6]. NCSE involves ongoing electrographic seizures without clinical convulsions [1, 4]. Most common causes of SE include subtherapeutic AED levels, stroke and remote brain injury/ congenital malformations [5]. The initial work-up should include glucose, complete blood count, toxicology testing, liver function tests, basic metabolic panel, urinalysis and AED levels (if applicable). Brain imaging, usually a CT scan of the head, should be done to rule out a structural lesion. Magnetic Resonance Imaging (MRI) of the brain with and without contrast and lumbar puncture should be pursued once patient has been stabilized. CSF studies should include cell count, cytopathology, gram stain, bacterial culture, viral titers, HSV PCR, and VDRL testing. Additional testing such as paraneoplastic or autoimmune panel, fungal and mycobacterial cultures can be sent depending on exposure and history (Table 38.1). An emergent EEG should be performed, especially for suspicion of NCSE, although it is not required for the early management of CSE [4]. A detailed history regarding the side and location of seizure onset, eye or head deviation, urinary or stool incontinence, recent sickness or behavioral changes, travel, illicit substance exposure, head trauma, past or family history of seizures must be elicited. If initial work-up is unrevealing, then additional testing to evaluate for occult malignancy must be pursued as SE can often be a presenting feature of a paraneoplastic or autoimmune condition. In spite of extensive evaluation, the etiology of SE is often not found.

Table 38.1 Cerebrospinal fluid studies to be sent for status epilepticus work-up

Basic	Other infectious	Paraneoplastic or autoimmune anti-bodies
Cell count Differential count Glucose Protein Gram stain Viral culture Bacterial culture VDRL HSV PCR	Fungal culture Acid fast bacillus stain Acid fast bacillus culture	Anti-NMDA Anti-VGKC Anti-Hu Anti-CRMP5 Anti-Ma2 Anti-Ampiphysin

Pharmacologic Therapy of SE

SE is a neurologic emergency. The primary goal is rapid detection and early termination. The secondary goal is to achieve therapeutic level of an IV medication that will control the seizures as soon as possible. First line therapy for emergent SE treatment is benzodiazepines such as lorazepam and diazepam [6–8]. A recent randomized, controlled trial (RCT) in 2011 showed that intramuscular (IM) midazolam had a higher rate of seizure control as compared to IV lorazepam when used in the prehospital setting [9], which is important when IV access is unavailable. If the patient is still convulsing upon arrival in the ED, second-line treatment should be initiated for seizure cessation and maintenance of antiepileptic action [1, 4]. Second-line therapy includes valproate sodium [10], fosphenytoin [7], phenobarbital and levetiracetam. IV lacosamide has been increasingly used and was found to be as effective as phenytoin with lesser adverse effects [11]. Choice of agent is guided by patient factors such as hemodynamic stability, drug-drug interactions, side effect profile and prior AED. If seizures continue, another second-line medication can be considered; however, the use of a third-line agent

Table 38.2 Medications used for the management of Status epilepticus

Medications	Dosages	Significant adverse effects
Intermittent dosing		
Diazepam	L: 0.15 mg/kg IV up to 10 mg/dose (max rate 5 mg/min)	IV contains propylene glycol
Lorazepam	L: 0.1 mg/kg IV up to 4 mg/dose (max rate 2 mg/min)	IV contains propylene glycol
Midazolam	L: 0.2 mg/kg IM up to maximum 10 mg	Respiratory depression, hypotension
Fosphenytoin	L: 20 mg PE/kg IV, may give additional 5 mg/kg (max rate 150 mg/min) M: 100 mg Q8h (goal free level 1.0–2.0)	Hypotension, arrhythmias
Lacosamide	L: 200–400 mg IV M: 100–200 mg Q12h	PR prolongation, hypotension
Levetiracetam	L: 1000–3000 mg IV (max rate 2–5 mg/kg/min) M: 250–1500 mg Q12h	
Phenobarbital	L: 20 mg/kg IV, may give additional 5–10 mg/kg (max rate 50–100 mg/min) M: 50–100 mg Q8h	Hypotension, respiratory depression
Phenytoin	L: 20 mg/kg, may give additional 5–10 mg/kg, (max rate 50 mg/min)	Arrhythmias, respiratory depression, purple glove syndrome, IV contains propylene glycol
Topiramate	L: 200–400 mg NG/PO M: 300–1600 mg/day PO (divided 2–4 times daily)	Metabolic acidosis
Valproate sodium	L: 20–40 mg/kg IV, may give additional 20 mg/kg (max rate 3–6 mg/kg/min) M: Up to 60 mg/kg/day	Hyperammonemia, pancreatitis, thrombocytopenia, hepatotoxicity
Continuous dosing		
Midazolam	L: 0.2 mg/kg (max rate 2 mg/min) M: 0.05–2 mg/kg/h	Respiratory depression, hypotension
Pentobarbital	L: 5–15 mg/kg (max rate ≤50 mg/min) M: 0.5–5 mg/kg/h	Hypotension, respiratory and cardiac depression, paralytic ileus, propylene glycol toxicity
Propofol	L: 1–2 mg/kg M: 20–200 mcg/kg/min	Respiratory and cardiac depression, (Propofol infusion syndrome: rhabdomyolysis, metabolic acidosis, renal failure)
Thiopental	L: 2–7 mg/kg (max rate ≤50 mg/min) M: 0.5–5 mg/kg/h	Hypotension, respiratory and cardiac depression

Adapted from Brophy et al. [1], with permission from Springer Science + Business Media LLC
L loading, *M* maintenance, *IM* intramuscular, *IV* intravenous, *PO* oral, *NG* nasogastric

such as continuous infusion of AEDs and IV anesthetics is strongly recommended. Table 38.2 provides a list of medications used in the management of SE.

Refractory SE (RSE)

RSE has been defined variably as SE requiring general anesthesia [12], persistent SE due to failure of emergent and urgent AED to control SE [1], or the failure of two or three AEDs [13–15] over a span of different time durations [15–18]. I V midazolam, propofol, pentobarbital or thiopental (not available in the US) can be used [19, 20]. Dosage and rate of infusion are titrated to achieve a therapeutic goal of either suppression of seizures or burst suppression on EEG. If a patient is on anesthetic therapy for 24 h and SE either continues, recurs or recurs as the anesthetic is weaned or stopped, the condition is termed malignant or **super-refractory status epilepticus (SRSE)**.

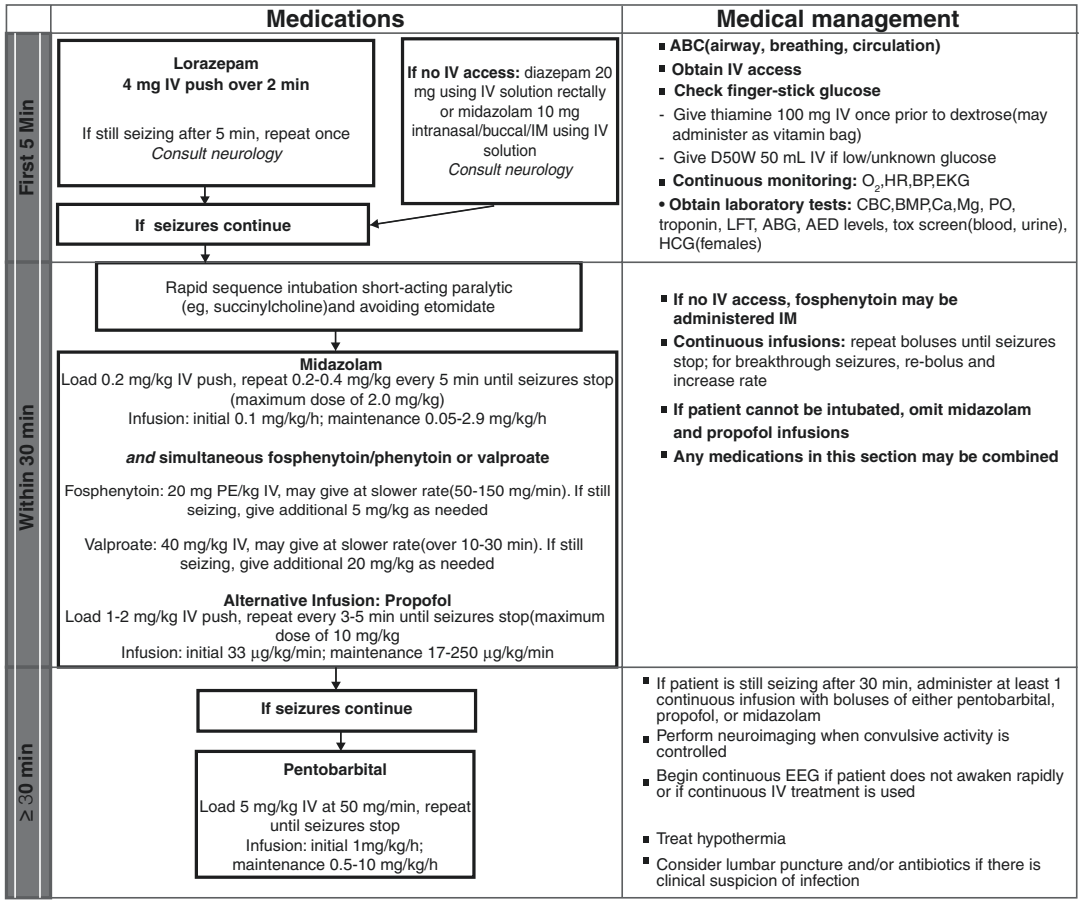


Fig. 38.2 Status epilepticus treatment algorithm from Yale University showing simultaneous status epilepticus and medical management (With permission: Amber Castle, PharmD, BCPS Yale-New Haven Hospital, New Haven, CT)

There are no RCTs evaluating the management of SRSE [18]. An example of an algorithmic approach to SE is presented in Fig. 38.2 [4].

Medical Management of SE

Rapid assessment of medical stability of a patient in SE is important to prevent complications as pharmacologic therapy may compromise the airway and cause cardiac and hemodynamic abnormalities. Use of non-invasive ventilation during the administration of first-line therapy can be pursued. However, intubation and mechanical ventilation are often needed once second- and third-line therapies are instituted. Frequent monitoring of vital signs is mandatory as hypotension and arrhythmias are common, especially with phenytoin (infusion rate-dependent) and lacosamide. Common medical issues arising during the management of SE are presented in Table 38.3.

Multidisciplinary Care

A multidisciplinary approach to the management of patients with SE must be pursued and must involve not only the neurologist, epileptologist, and neurointensivist but also include the nurses, respiratory therapists, pharmacists, therapists, nutritionist and if applicable, neurosurgeons and palliative care specialists. The prolonged ICU and hospital stay for patients with SE is often complicated by infections, hemodynamic instability, ventilator dependence, venous thromboembolism, skin ulcers, malnutrition and delirium.

Table 38.3 Medical issues encountered among patients with status epilepticus

Systemic complication	Mechanism	Management
Acid–base disorder[a,b]	Respiratory acidosis from hypoventilation Metabolic acidosis from recurrent muscular contraction	Close monitoring Fluid resuscitation for lactic acidosis Endotracheal intubation if unable to compensate for respiratory acidosis
Pulmonary[a,b]		
Hypoxia Atelectasis Pneumonia Pleural effusions	Aspiration, obstruction, apnea, mucus plugging, pulmonary edema	Endotracheal intubation for airway protection Bronchoscopy Thoracentesis Antibiotics
Cardiac		
Stress Cardiomyopathy[a,b,c] Arrhythmias	Sudden catecholamine hyperactivity Electrolyte imbalances	Supportive care, hemodynamic monitoring, vasopressors; typically reversible. Electrolyte replacement Serial ECG, troponin monitoring and echocardiogram
Musculoskeletal injuries		
Cervical spine, skull and extremity fractures Dislocations Tongue lacerations	Falls Violent extremity movements	Surveillance imaging High index of suspicion Orthopedic referral
Drug related **See medications table**		
Long-term complications of prolonged ICU stay [a,b]		
Thromboembolic disease Recurrent pneumonia, atelectasis Ventilator-dependence requiring tracheostomy Dysphagia requiring feeding tube placement Health-care associated infections such as UTI, clostridium difficile, blood stream infections Critical illness myopathy and neuropathy	Prolonged immobilization and sedation causes atelectasis, myopathy and neuropathy Prolonged mechanical ventilator use can cause recurrent pneumonia Prolonged urinary catheter use can cause UTI Use of multiple antibiotics can contribute to development of clostridium difficile infection and other drug resistant bacteria	Involvement of the rehabilitation team while in the ICU Daily SBT (if possible) Early discontinuation of urinary catheters Rational use of antibiotics

ECG electrocardiogram, *SBT* spontaneous breathing trials, *UTI* urinary tract infection
[a]Hocker [37]
[b]Wijdicks [38]
[c]Belcour et al. [39]

Evidence Contour

Randomized controlled trials are lacking to support consensus statements or guidelines [1, 7, 9, 21] regarding the treatment of SE including newer AEDs beyond the use of benzodiazepine as the first-line therapy; and the same is true for RSE and SRSE. Although there is some agreement among experts regarding second-line therapy, there is a lack of consensus regarding subsequent management options, goals of treatment and the aggressiveness in management of NCSE.

Goals of Treatment

The control of SE is based on cessation of clinical as well as electrographic seizures, which

requires several considerations. The goal of therapy can be cessation of electrographic seizures, burst-suppression or complete background suppression to an isoelectric pattern. There is no consensus on the electrographic end-point to guide addition of new agents and titration of medication dosages. In a systematic review comparing propofol, midazolam and pentobarbital for RSE, patients treated with EEG background suppression were less likely to have breakthrough seizures as compared to patients treated with seizure suppression goal (4 vs 53 %; $p < 0.001$) [20]. However, another study involving 47 patients in RSE did not show any difference in outcomes in patients achieving burst-suppression on EEG as compared to those who did not achieve burst suppression [22] . There is also lack of consensus on the intensity and duration of suppression. Bursts of less than 1 s with a suppression period of 10 s have been recommended; however, variable durations of bursts and suppressions have been tested, with some advocating isoelectric EEG as a therapeutic target [23]. Intensivists using anesthetics or barbiturates often maintain burst suppression for 24–48 h before attempting to withdraw the anesthetic agent. Recurrence of seizures during the withdrawal of an agent will prompt uptitration of the agent as well as addition of newer agents. Withdrawal of anesthetic agents should be done with EEG monitoring and initiation of other maintenance AEDs.

Non-convulsive Status Epilepticus (NCSE)

NCSE is a state of ongoing or intermittent clinical epileptic activity without convulsions for at least 30 min, with electrographic evidence of seizures [24]. It is classified into absence (generalized) and focal NCSE. NCSE constitutes about 20-25 % of SE cases. The incidence of NCS and NCSE is reported to be 8–56 % and 13–37 %, respectively [24–27] in patients with coma or altered mental status. NCSE may be underreported as it is usually diagnosed with EEG that is performed in the setting of high suspicion for NCSE. NCS has been noted in 48 % of patients after termination of generalized convulsive SE [27], 22 % with severe traumatic brain injury, 6 % with ischemic stroke, 28 % with intracerebral hemorrhage, and 17 % with CNS infections [26].

Patients may demonstrate confusion or varying degrees of alteration of consciousness and occasionally be noted to have subtle findings of eyelid blinking, ocular movements or facial twitching. Diagnosis of NCSE is made with prolonged EEG monitoring, often up to 24–48 h. EEG patterns can range from frequent or continuous, focal or generalized spike and wave discharges, periodic lateralized epileptiform discharges (PLEDs), bilateral periodic epileptiform discharges (BIPEDs), generalized periodic epileptiform discharges (GPEDs), or triphasic waves [28]. There is significant controversy regarding the occurrence of neuronal brain damage with NCSE [29, 30]. NCSE may be associated with neuronal loss, chronic atrophy and cognitive and behavioral consequences, although the evidence is based on animal studies or small case series [30]. Hence, there is debate about the level of aggressiveness in treatment of NCSE in comatose patients. Some experts recommend treating NCSE along the same algorithm as GCSE, while some others are reluctant to advocate for intravenous anesthetics for NCSE alone, reserving it for unusual cases [29, 31].

Mortality rates in NCSE range from 18 to 36 % [26, 32]. Death is usually secondary to underlying etiology and acute medical complications and rarely due to NCSE itself. Prognosis in NCSE depends on the etiology of the SE, complications of treatment, level of consciousness and EEG patterns [31].

Other Treatment Options in SE

There are several novel therapies used for RSE and SRSE that are gaining popularity but their use is not guided by large studies or randomized controlled trials. Therapies aiming a variety of treatment targets are now available [1, 18].

Ketamine is an intravenous anesthetic agent that binds to GABA(A) receptor as well as has antagonistic action at the N-methyl-D-aspartate receptor, with theoretical neurotoxic risk. Inhaled anesthetics such as isoflurane and desflurane can

be used but are limited by their complications such as hypotension, infections, paralytic ileus and deep venous thrombosis. Corticosteroids and immunotherapy with intravenous immunoglobulins and plasmapheresis are being increasingly used based on the rationale of an occult immunological disease with yet unidentified antibodies and the role of inflammation in epileptogenesis. Ketogenic diet is gaining popularity in SRSE due to anti-epileptic as well as possible anti-inflammatory actions. It alters the primary cerebral energy metabolism from glucose to ketones and with possibly multiple mechanisms of anti-epileptic action [32, 33]. Hypothermia is known to reduce cerebral metabolic rate, oxygen utilization, ATP consumption, glutaminergic drive, mitochondrial dysfunction, calcium overload, free radical production, oxidative stress, permeability of blood–brain barrier and pro-inflammatory reactions [34]. Case reports have attempted to achieve hypothermia to 31–35 °C. Complications include acid–base disturbances, coagulation disorders, disseminated intravascular coagulation, thrombosis, infection, cardiac arrhythmia, bowel ischemia and paralytic ileus. Electroconvulsive therapy is a form of cerebral stimulation that increases presynaptic release of GABA and prolongs the refractory period after a seizure [35]. It is recommended as a daily treatment for 5–8 day course. Neurosurgical resection of the culprit lesion that is well-defined on radiologic and electrographic monitoring has been attempted. Other options such as corpus callosotomy and multiple subpial transactions have also been described. Other treatment options that have been explored are transcranial magnetic stimulation, vagus nerve stimulator, deep brain stimulation, cerebrospinal fluid drainage, intravenous magnesium sulfate, pyridoxine, and newer AEDs such as lacosamide, topiramate, and neurosteroid such as allopregnanolone [36].

References

1. Brophy G, Bell R, Claassen J, Alldredge B, Bleck T, Glauser T et al. Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17:3–23.
2. Lowenstein DH, Bleck T, Macdonald R. It's time to revise the definition of status epilepticus. Epilepsia. 1999;40(i):120–2.
3. Meierkord H, Boon P, Engelsen B, Gocke K, Shorvon S, Tinuper P, et al. EFNS guideline on the management of status epilepticus in adults. Eur J Neurol. 2010;17:348–55.
4. Hirsch L, Gaspard N. Status epilepticus. Continuum. 2013;19(3):767–94.
5. DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology. 1996;46:1029–35.
6. Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of lorazepam and diazepam in status epilepticus. JAMA. 1983;249(11):1452–4.
7. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med. 1998;339(12):792–8.
8. Alldredge B, Gelb A, Isaacs SM, Corry M, Allen F, Urich S, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med. 2001;345:631–7.
9. Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y et al; NETT Investigators. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med. 2012; 366(7): 591–600.
10. Agarwal P, Kumar N, Chandra R, Gupta G, Antony AR, Garg N. Randomized study of intravenous valproate and phenytoin in status epilepticus. Seizure. 2007;16(6):527–32.
11. Kellinghaus C, Berning S, Stögbauer F. Intravenous lacosamide or phenytoin for treatment of refractory status epilepticus. Acta Neurol Scand. 2014;129(5):294–9.
12. Shorvon S, Ferlisi M. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain. 2012;135:2314–28.
13. Jagoda A, Riggio S. Refractory status epilepticus in adults. Ann Emerg Med. 1993;22:1337–48.
14. Bleck T. Advances in the management of refractory status epilepticus. Crit Care Med. 1993;21:955–7.
15. Hanley D, Kross J. Use of Midazolam in the treatment of refractory status epilepticus. Clin Ther. 1998;20: 1093–105.
16. Stecker MM, Kramer TH, Raps EC, O'Meeghan R, Dulaney E, Skaar DJ. Treatment of refractory status epilepticus with propofol. Epilepsia. 1998;39:18–26.
17. Mayer SA, Claassen J, Lokin J, Mendelsohn F, Dennis LJ, Fitzsimmons BF. Refractory status epilepticus: frequency, risk factors and impact on outcome. Arch Neurol. 2002;59:205–10.
18. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain. 2011;134:2802–18.

19. Prasad A, Worrall B, Bertram E, Bleck T. Propofol and Midazolam in the treatment of refractory status epilepticus. Epilepsia. 2001;42(3):380–6.
20. Claassen J, Hirsch L, Emerson R, Mayer S. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia. 2002;43(2):146–53.
21. Huff JS, Melnick E, TOmaszewski C, Thiessen M, Jagoda A, Fesmire F. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with seizures. Ann Emerg Med. 2014;63:437–47.
22. Rossetti AO, Logroscino G, Bromfield EB. Refractory status epilepticus: effect of treatment aggressiveness on prognosis. Arch Neurol. 2005;62(11):1698–702.
23. Mirsattari SM, Sharpe MD, Young GB. Treatment of refractory status epilepticus with inhalational anesthetic agents: isoflurane and desflurane. Arch Neurol. 2004;61(8):1254–9.
24. Kaplan PW. The clinical features, diagnosis, and prognosis of nonconvulsive status epilepticus. Neurologist. 2005;11(6):348–61. Review.
25. Bleck TP. Management approaches to prolonged seizures and status epilepticus. Epilepsia. 1999;40 Suppl 1:S59–63; discussion S64–6.
26. Shneker BF, Fountain NB. Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. Neurology. 2003;61(8):1066–73.
27. Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. 2004;62(10):1743–8.
28. Beniczky S, Hirsch LJ, Kaplan PW, Pressler R, Bauer G, Aurlien H et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia. 2013;54 Suppl 6:28–9.
29. Kaplan PW. Nonconvulsive status epilepticus. Neurology. 2003;61(8):1035–6.
30. Wasterlain CG, Chen JW. Mechanistic and pharmacologic aspects of status epilepticus and its treatment with new antiepileptic drugs. Epilepsia. 2008;49 Suppl 9:63–73.
31. Maganti R, Gerber P, Drees C, Chung S. Nonconvulsive status epilepticus. Epilepsy Behav. 2008;12(4):572–86.
32. Caraballo RH, Vining E. Ketogenic diet. HandbClin Neurol. 2012;108:783–93.
33. Thakur K, Probasco J, Hocker S, Roehl K, Henry B, Kossoff E, et al. Ketogenic diet for adults in super-refractory status epilepticus. Neurology. 2014;82: 665–70.
34. Corry JJ, Dhar R, Murphy T, Diringer MN. Hypothermia for refracotyr status epilepticus. Neurocrit Care. 2008;9:189–97.
35. Kamel H, Cornes SB, Hegde M, Hall SE, Josephson SA. Electroconvulsive therapy for refractory status epilepticus: a case series. Neurocrit Care. 2010;12: 204–10.
36. Broomall E, Natale JE, Grimason M, Goldstein J, Smith CM, Chang C, et al. Pediatric super-refractory status epilepticus treated with allopregnanolone. Ann Neurol. 2014;76(6):911–5.
37. Hocker S. Systemic complications of status epilepticus- an update. Epilepsy & Behavior. 2015;49:83–7.
38. Wijdicks E. The multifaceted care of status epilepticus. Epilepsia. 2013;54 Suppl 6:61–3.
39. Belcour D, et al. Prevalence and risk factors of stress cardiomyopathy after convulsive status epilepticus in ICU patients. Crit Care Med. 2015;43(10):2164–70.

Neuroleptic Malignant Syndrome

39

Kathryn Rosenblatt

Introduction

Neuroleptic malignant syndrome (NMS) is a rare and potentially life-threatening drug-induced neurologic emergency characterized by fever, muscle rigidity, altered mental status, and autonomic dysfunction [1]. NMS is believed to be a result of dopamine deficiency from excessive dopaminergic blockade by antipsychotic medication and several anti-emetics, and less often by withdrawal of dopamine agonist therapy [2, 3]. Successful treatment requires prompt recognition, cessation of offending agents, aggressive supportive care, and administration of certain pharmacotherapies and interventions, such as dantrolene, bromocriptine and electroconvulsive therapy (ECT). While NMS is easily recognized in its severe form, early identification can be challenging because it is heterogeneous in onset and progression and several medical conditions exhibit similar symptoms [4–8]. The variability in NMS presentation makes controlled trials and collection of data difficult, and consequently, many aspects remain controversial, including pathophysiological mechanisms, risk factors, diagnostic criteria, prognosis and treatment [9].

K. Rosenblatt
Anesthesiology & Critical Care Medicine, Division of Neuroanesthesia and Neurosciences Critical Care, Johns Hopkins Hospital, Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: krosenb3@jhmi.edu

Case Presentation

An 87-year-old man with atrial fibrillation on rivaroxaban (Xarelto) and mild dementia was admitted from the medical-behavioral unit (MBU) to the intensive care unit (ICU) with hypoxemia, fever and muscle rigidity. Six days prior, he presented to the emergency department (ED) with a scalp hematoma after an unwitnessed fall at home. Physical exam in the ED was otherwise normal and computed tomography (CT) scans of his head and cervical spine were negative for acute injury or pathological process. An episode of agitation in the ED was treated a 5 mg intramuscular (IM) injection of haloperidol and the patient was admitted for observation. Of note, the patient's wife reported an acceleration in his dementia over the past few months and he was recently made DNR/DNI; he has been increasingly confused, with episodes of agitated behavior mostly at night, with restless legs while sleeping and periodic falls out of bed. The day after admission, the patient was appropriate and cooperative but in the evening, he became acutely agitated, confused and combative, grabbing and hitting staff. He ripped out his intravenous catheter and haloperidol, 3 mg, was again administered intramuscularly. The following day, the patient was admitted to the MBU under the care of a geriatric psychiatrist. He exhibited impulsive behavior and confusion with periods of restlessness and fidgety movements. At times, he was combative, requiring quetiapine (Seroquel) 12.5 mg every 6 h and olanzapine

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_39

(Zyprexa) 1.25 mg IM daily over the course of three days. On the morning of the sixth day after his fall, the patient was noted to have poor appetite and was less interactive than previously. He appeared withdrawn and was not responding to verbal cues over the course of the day. In the afternoon he was noted to have increasing tremor in his arms and legs and diffuse muscle rigidity with new-onset coughing spasms. His blood pressure (BP) was 122/95 but his previously rate-controlled atrial fibrillation was now 171 beats per minute (bpm). His respirations at 20 breaths per minute were associated with a gurgling noise and his oxygen (O_2) saturation was 86 % on room air. His axillary temperature was 98.9 °F. Repeat vital signs on 2 l per minute of O_2 by nasal cannula improved saturation to 90–92 %, but BP had decreased to 82/33, and his temperature measured rectally was 103.2 °F. The patient was placed on a non-rebreather (NRB) face mask and transferred to the ICU. In the ICU, the patient was nonverbal, febrile to 104.1 °F and displayed lead-pipe rigidity. He remained with an O_2 saturation above 95 % on NRB. Repeat CT head showed no new bleed or other intracranial process. A cooling blanket and ice packs were applied and 4 l of normal saline were given for hypotension and decreased urine output. Laboratory studies were remarkable for a white blood cell count of 9.2×10^3 μL, with 90 % neutrophils and creatine kinase (CK) level of 1273 U/L (Normal, 35–232 U/L). Urinalysis, electrolytes, thyroid function tests, liver enzymes and coagulation studies were normal. A lumbar puncture was performed with a normal CSF profile and all cultures and serologies were negative. EEG was within broad limits of normal.

Question How do you make this diagnosis?

Answer By exclusion. Neuroleptic Malignant Syndrome is diagnosed by eliminating other potential causal explanations for the typical clinical findings

After the exclusion of CNS infection, cerebrovascular abnormality, status epilepticus, and systemic conditions, a diagnosis of neuroleptic malignant syndrome (NMS) was made based on altered mental status, muscle rigidity, hyperthermia, hemodynamic instability and elevated creatine kinase in the setting of recent exposure to haloperidol, quetiapine and olanzapine. All antipsychotics were stopped. Benzodiazepines were considered to control the rigidity but were avoided given concerns for respiratory failure in this DNI patient. A nasogastric tube was inserted and the patient was given bromocriptine 2.5 mg every six hours. Strict volume status assessments and serial electrolyte and renal function laboratory testing were performed to guide IV hydration for a goal of euvolemia. Heart rate improved to the low 90s with fluid administration. Piperacillin/tazobactam was given for 3 days but was stopped once cultures were finalized. After four doses, bromocriptine was increased to 5 mg every 6 h. The patient's symptoms slowly improved over the following week, with rigidity, hyperthermia and autonomic dysfunction resolving before his mental status returned to baseline.

Principles of Management

Diagnosis

In 2011, an international multispecialty expert panel published consensus recommendations for diagnostic criteria of NMS using a set of quantitative critical values and priority-scored clinical features [10]. While this criteria system has yet to be independently validated, it may help guide diagnosis. Clinical features were given a priority score by the panel for their relative importance in contributing to the diagnosis. The following features are listed in order of higher to lower scored values: recent dopamine antagonist exposure, or dopamine agonist withdrawal; hyperthermia; rigidity; mental status alteration; CK elevation; sympathetic nervous system lability; tachycardia plus tachypnea; and a negative work-up for other causes. The critical values were defined as hyperthermia > 100.4 °F or > 38.0 °C on at least 2 occasions, CK level at least 4 times the upper limit of normal, blood pressure elevation of ≥ 25 % above baseline, blood pressure fluctuation ≥ 20 mmHg diastolic

or ≥ 25 mmHg systolic change within 24 h; tachycardia ≥ 25 % above baseline, and tachypnea ≥ 50 % above baseline.

This distinct set of clinical features and laboratory abnormalities are all highly associated with NMS yet no single test is specific to the diagnosis. A workup to rule out other serious neurological or medical conditions, including central nervous system (CNS) infections, toxic or metabolic etiologies, inflammatory or autoimmune conditions, status epilepticus and systemic conditions is an essential first step. The diagnosis of NMS is subsequently made based on positive clinical and laboratory findings after the exclusion of alternative causes [10]. In a clinical review of 153 published case reports of NMS, mental status change or muscle rigidity was the initial manifestation in 82.3 % of cases [11]. These early symptoms should prompt brain imaging studies and lumbar puncture to exclude intracranial pathology such as subarachnoid hemorrhage (SAH) and CNS infection [12], and electroencephalography can rule out status epilepticus. However, it may be difficult to distinguish NMS from other medication-induced movement disorders, toxin-induced hyperthermias and acute dysautonomias such as serotonin syndrome (SS), malignant hyperthermia (MH), malignant catatonia, and central anticholinergic syndrome (CAS).

Medication History and Temporal Clues

The patient's medication history along with the temporal progression of signs and symptoms provide the most valuable clues to diagnosis (Table 39.1). Most cases of NMS present gradually within the first week of drug administration, and all usually within 30 days [13]. In contrast, malignant hyperthermia, anticholinergic syndrome and serotonin toxicity tend to present rapidly after exposure to causative agents [14, 15]. Nearly all dopamine antagonists have been implicated in NMS. Withdrawal of dopamine agonists has also been associated with a less severe form. Conventional, "typical," or first-generation antipsychotic (FGA) agents pose greater risk than newer "atypical" or second-generation antipsychotic (SGA) drugs and certain antiemetic medications [6, 16–22]. NMS occurs within the therapeutic dosage range of antipsychotics and is not a dose-dependent phenomenon. Though recent or rapid dose escalation, higher doses, parenteral administration and a switch from one agent to another have been implicated as risk factors in case–control studies [5, 23–27]. Additional factors associated with a heightened risk of neuroleptic malignant syndrome include exhaustion, dehydration, and iron deficiency [24, 27, 28].

Drugs with anticholinergic activity, such as tricyclic antidepressants, antihistamines, phenothiazines, and antiparkinson agents can cause fever by disturbing central hypothalamic function and decreasing peripheral heat dissipation [29–32]. Marked hyperthermia and CAS can occur when these drugs are taken in combination. Anticholinergic medications are a common treatment for FGA extrapyramidal side effects; distinguishing between NMS and CAS by medication history can be difficult in these patients. Direct or indirect serotonin agonists lead to SS and diagnosis of NMS may be also be challenging in patients taking both serotonergic and neuroleptic agents [33]. On the other hand, exposure history is helpful in distinguishing between NMS and MH, a hypermetabolic crisis that occurs when a MH-susceptible individual is administered potent halogenated inhalational anesthetics or succinylcholine. When the history uncovers several possible offending drugs from multiple categories or in the absence of a reliable history, a detailed examination of clinical features can also be useful in differentiating among disorders [34] (Table 39.1).

The Clinical Tetrad of NMS: Clues to Diagnosis and Management Concerns

A review of 222 published cases revealed a common sequence of symptom development in 70.5 % of NMS patients, beginning with mental status changes, followed by muscle rigidity, then

Table 39.1 Differential diagnosis for neuroleptic malignant syndrome

		Disorder	Onset time	Muscular symptom	Other features	Postulated mechanism	Causative agents	Possible treatments
Medication-induced movement disorder		Medication-induced acute dystonia	Hours to a few days	Sustained, involuntary muscle contraction, torticollis, retrocollis, oculogyric crisis, blepharospasm	–	Imbalance of dopaminergic/cholinergic transmission	Neuroleptic dosage increase or decrease in dosage of medication to treat EPS	Anticholinergics, benzodiazepines
		Medication-induced acute akathisia	Hours to days	Fidgety movements of the legs, rocking from foot to foot, pacing	Complaints of restlessness and unease	Mesocortical D_2 antagonism		Dose reduction, propranolol, benzodiazepines, anticholinergics
		Neuroleptic-induced parkinsonims	Weeks	Akinesia, bradykinesia, rigidity, shuffling gait, resting tremor	Masklike facies, postural instability	Postsynaptic striatal D_2 antagonism		Dose reduction, anticholinergics, dopamine agonists
		Tardive dyskinesia	3 months to years	Late onset involuntary athetoid or choreiform movements, buccolinguomasticatory movements	–	Excess dopaminergic activity	Neuroleptic use for at least a few months	Early recognition, stop offending antipsychotic, cholinergics
	Toxin-induced hyperthermia	Neuroleptic malignant syndrome	2–10 days	Lead-pipe rigidity, bradyreflexia	Altered mental status, hyperthermia, autonomic instability, catatonia, mutism	D_2 antagonism in striatum, hypothalamus and mesocortex	FGAs (chlorpromazine, haloperidol, fluphenazine), SGAs (clozapine, risperidone, olanzapine, quetiapine), antiemetics (prochlorperazine, promethazine, trimethobenzamide, thiethylperazine, metoclopramide), amoxapine	Early recognition, stop offending drug, cooling, fluid resuscitation, cardiopulmonary support, benzodiazepines, dantrolene, bromocriptine, amantadine, or other direct-acting dopamine agonist, ECT

(continued)

		Disorder	Onset time	Muscular symptom	Other features	Postulated mechanism	Causative agents	Possible treatments
		Serotonin syndrome	Hours (<24)	Clonus, hyperreflexia, fasciculation, tremor	Anxiety, disorientation, psychomotor agitation, hyperalertness, hyperthermia, autonomic hyperactivity, gastrointestinal symptoms	Excessive stimulation of serotoninergic receptors in the peripheral and central nervous system	MAOIs, SSRIs, meperidine, dextromethorphan, TCAs, L-tryptophan, lithium, linezolid, valproate, ondansetron	Cyproheptadine, active cooling
		Central anticholinergic syndrome	1 to 2 h	Myoclonus, choreoathetosis	Hypervigilance, agitation, hallucinations, delirium, coma, mydriasis, hyperthermia, tachycardia, hypertension, tachypnea, dry flushed skin, dry mucous membranes, decreased bowel sounds, urinary retention	Central cortical and subcortical muscarinic receptor antagonism	Antihistamines, TCAs, cyclobenzaprine, orphenadrine, antiparkinson agents, antispasmodics, phenothiazines, atropine, scopolamine	Physostigmine, supportive care
		Malinant hyperthermia	Minutes to hours (<12 h)	Rigor mortis-like rigidity	Hypercarbia, tachycardia, tachypnea, mixed respiratory and metabolic acidemia, hyperthermia, rhabdomyolysis	AD gene disorder of ryanodine receptor Ca^{+} channel, uncontrolled release of Ca^{+} with elevation of intracytyoplasmic Ca+ levels, continuous muscle activation, and ATP breakdown. SR Ca^{+} pump unable to re-sequester Ca^{+}. ATP breakdown further aggravates heat production	Volatile anesthetic agents (halothane, isoflurane, sevoflurane, desflurane), depolarizing neuromuscular blocker (succinylcholine)	Dantrolene, active cooling

D_2 dopamine type-2 receptor, *AD* autosomal dominant, *Ca^{+}* calcium, *SR* sarcoplasmic reticulum, *ATP* adenosine triphosphate, *EPS* extrapyramidal signs, *FGA* first-generation antipsychotic, *SGA* second-generation antipsychotic, *MAOI* monoamine oxidase inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant, *ECT* electro-convulsive therapy

hyperthermia, and finally autonomic dysfunction [11]. Appearance of any of these four cardinal signs should prompt early initiation of supportive care with a low threshold for suspicion since NMS complications are severe and occur frequently. A recent analysis of the nationwide inpatient sample (NIS) database was performed, identifying rates of complications, mortality, and outcomes in 1346 patients with NMS from 2002 to 2011 [35]. In-hospital death occurred in 75 (5.6%) patients and the most prevalent complication was rhabdomyolysis (30.1%). Universal management of NMS includes immediate discontinuation of the offending drug, or reinstitution in the case of abrupt discontinuation of dopaminergic therapy, correction of dehydration and electrolyte imbalance, controlling the hyperthermia and rigidity, and preventing complications. The need for monitoring in an intensive care unit with expert and robust supportive care is undisputed.

Hyperthermia

Abrupt reduction in dopaminergic transmission in the hypothalamus alters the core temperature set point, leading to impaired thermoregulation in NMS [36]. Blockade of dopamine receptors in the corpus striatum causes muscular rigidity and secondary heat production. While fever is a defining symptom in NMS, many conditions in critically ill patients result in inflammation, tissue injury and a febrile reaction and it may be difficult to determine the etiology of a fever early in the clinical course. Leukocytosis, ranging from 10,000 to 40,000/μL, with or without a "left shift" is a consistent laboratory finding in NMS [37]. Obtaining appropriate cultures should not be avoided although approximately half of febrile patients in the intensive care unit (ICU) will have a non-infectious cause of fever, with most no greater than 38.9 °C (102 °F) [38]. A fever in excess of 38.9 °C (102 °F) is usually of an infectious etiology, though a transfusion reaction or a drug fever may also trigger temperatures exceeding 102 °F [39]. In patients with a temperature greater than 104 °F, however, NMS, SS, MH and SAH should always be considered. Hyperthermia should be aggressively treated with cooling blankets, ice packs and fans. The role of NSAIDs and acetaminophen in toxin-induced hyperthermia is not established but antipyretic agents can be helpful if an infection is a comorbid factor.

Altered Mental Status

A reduced or fluctuating level of consciousness typically precedes systemic signs in patients with NMS [11] but the onset of symptoms may be underappreciated given the psychiatric comorbidity of susceptible patients. Altered mental status is multifactorial and may reflect hypothalamic and spinal dopamine receptor antagonism, hyperthermia effects on the CNS, or direct effects of other drugs [40]. Individuals may appear alert but dazed and unresponsive. Catatonic signs and mutism can be prominent and patients may evolve into profound encephalopathy and eventual coma [41]. Malignant or lethal catatonia, a condition similar to NMS that some argue is on the same spectrum [42], can be distinguished by a several-week prodrome of psychosis, agitation, and catatonic excitement [43, 44]. Hyperactivity and agitation are common to SS and CAS, in contrast to the catatonic stupor more prevalent in NMS [12].

Muscular Rigidity

Interference with nigrostriatal dopamine pathways contributes to muscle rigidity and tremor in NMS, classically characterized by "lead pipe rigidity" or stable resistance through all ranges of motion when passively moving the extremities [1, 2, 45, 46]. The motor symptoms of malignant catatonia display more positive phenomena (dystonic posturing and stereotyped repetitive movements) than what is seen in NMS while the presence of myoclonus, ataxia, shivering and hyperreflexia is more indicative of serotonin syndrome [33, 47] (Table 39.1). Patients with anticholinergic syndrome have few muscular abnormalities because skeletal muscle contraction is effected by nicotinic rather than muscarinic transmission. The muscle rigidity seen in malignant hyperthermia, however, is quite similar to

NMS and must be distinguished by the clinical setting. Tremor is often associated with NMS, and dystonia, trismus, chorea, opisthotonus, and other dyskinesias are present less commonly [5, 48]. Patients can also have prominent dysarthria, sialorrhea, and dysphagia and prophylactic intubation may be required. Acute respiratory failure was the strongest independent predictor of mortality ($p<0.001$) in the NIS database analysis [35]. Creatine kinase concentration may be elevated before the onset of muscle rigidity and higher levels are consistent with a poor prognosis [48–50]. Muscle damage and necrosis from the metabolic inequality between energy consumption and production can progress quickly to rhabdomyolysis, with associated hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia and lactemia. Aggressive fluid resuscitation to maintain adequate urine output is imperative in preventing progression to acute myoglobinuric renal failure, compartment syndrome, cardiac dysrhythmias from electrolyte abnormalities, and disseminated intravascular coagulopathy [51, 52]. Sodium bicarbonate to alkalinize the urine and prevent breakdown of myoglobin into nephrotoxic metabolites is often used though it has not been shown to be superior to saline alone, and bicarbonate may worsen hypocalcemia [51].

Autonomic Dysfunction

Dysautonomia in NMS is likely due to hypothalamic dopamine type-2 (D_2) receptor blockade. Removal of normal dopamine regulation of efferent sympathetic activity leads to autonomic activation while unregulated vasomotor and sudomotor activity causes labile blood pressure and heart rate [53]. Early clues of autonomic instability are urinary incontinence, pallor and profuse diaphoresis, with increased "insensible fluid losses." Hypotension should be treated with generous isotonic crystalloid administration but vasopressors, antiarrhythmic agents or pacing may be required. Respiratory distress and tachypnea are common and result from hypermetabolism and subsequent metabolic acidosis. Chest wall restriction, autonomic dysfunction with loss of protective airway reflexes and aspiration pneumonia can lead to respiratory failure.

Evidence Contour

Treatment of NMS with pharmacological agents and electroconvulsive therapy (ECT) is controversial and large clinical trials investigating specific therapies are lacking. Recommendations for the use of single- or combination-therapy consisting of benzodiazepines, dantrolene, bromocriptine, amantadine and ECT are based upon case reports and anecdotal evidence and their benefit over good supportive care is debated [54, 55]. The lack of other proven treatments and high fatality rate of the disorder easily justifies their use in patients with severe NMS.

Benzodiazepines

Benzodiazepines are the most widely used pharmacologic adjuncts in management of NMS because of their rapid onset of action and usefulness in reversing catatonic symptoms and agitation. Benzodiazepines facilitate GABA-mediated chloride transport, producing neuronal hyperpolarization which attenuates the sympathetic hyperactivity characterized by NMS [40]. Several clinical reports suggest that lorazepam and other benzodiazepines may reduce recovery time and improve outcome [19, 56, 57] and a few cases found benzodiazepines to be effective when other medications failed [58]. A trial of lorazepam, starting with 1–2 mg parenterally, is a reasonable first-line intervention for acute NMS with difficulty in assessing mental status as the primary disadvantage.

Dantrolene

Because of its efficacy in reducing heat production, rigidity and oxygen consumption in anesthetic-induced malignant hyperthermia, dan-

trolene, a direct-acting skeletal muscle relaxant, has been used in the treatment of NMS. Dantrolene is believed to decrease skeletal muscle contraction by interfering with calcium ion release from the sarcoplasmic reticulum which uncouples the excitation-contraction process. In some meta-analyses, improvement of NMS occurred in approximately 80 % of patients treated with dantrolene monotherapy [59–61]. In contrast, a more recent meta-analysis of 271 published cases found that treatment of NMS with dantrolene as monotherapy was associated with a higher mortality, and complete time to remission was prolonged by combination therapy including dantrolene [54]. Dantrolene can be administered intravenously starting with an initial bolus dose of 1–2.5 mg/kg followed by 1 mg/kg every 6 h up to a maximum dose of 10 mg/kg/day [6, 60–63]. Effects are usually reported within minutes of administration. Due to a risk of hepatoxicity, dantrolene is typically discontinued once symptoms begin to resolve although some recommend continuing for 10 days followed by a slow taper with doses of oral dantrolene that range from 50 to 200 mg/d to minimize relapse [63].

Bromocriptine

Bromocriptine is a centrally acting synthetic dopamine agonist that stimulates D_2 receptors and antagonizes type-1 receptors (D_1) in the hypothalamus and the neostriatum of the CNS. Bromocriptine is used in NMS to reverse the hypodopaminergic state precipitated by the antipsychotic-related striatal D_2 antagonism and therefore ameliorate the manifestations of NMS [2]. In a review of 67 published cases of NMS, Bromocriptine was found to significantly shorten time to clinical response compared to supportive treatment alone [60] and a larger review of 734 cases found that bromocriptine significantly reduced mortality rate compared with supportive care (10 % versus 21 %) [61]. In contrast, a small prospective study in 20 patients showed that dantrolene and/or bromocriptine use was associated with a more prolonged course (9.9 versus 6.8 days) and a higher incidence of complications compared with those receiving supportive care alone [55]. However, patients in the treated group of this nonrandomized study were sicker than those not treated. Bromocriptine is not available in an injectable form and therefore, can be given only orally or through a feeding tube, starting with doses of 2.5 mg, 2–3 times daily, increasing doses by 2.5 mg every 24 h until a response is obtained or until reaching a maximum dose of 45 mg/day. It is recommended that bromocriptine be continued for 10 days after symptoms are controlled and then tapered slowly to minimize the likelihood of recrudescence of NMS [6, 60, 61, 63].

Amantadine

Other dopamine agonists with anecdotal evidence of success include ropinirole, levodopa [64, 65], and amantadine [6, 66, 67]. Dopaminergic agents may be associated with exacerbation of underlying psychiatric illness but is usually well tolerated in psychotic patients. Amantadine has been used to treat Parkinson disease and has been tried in neuroleptic malignant syndrome because it increases synaptic dopamine activity. Its antiparkinsonian activity results from blocking reuptake of dopamine into presynaptic neurons and causing direct stimulation of postsynaptic receptors.

Electroconvulsive Therapy

Although there are no prospective, randomized, controlled data, the efficacy of ECT in treating malignant catatonia and improving Parkinsonism provide rationale for its use in NMS, especially in patients not responding to other treatments or in whom non-pharmacologic psychotropic treatment is needed. Clinical response, presumably by enhancing central dopaminergic transmission, was seen by the third or fourth treatment in a review of 5 patients treated with ECT, and after an average of 4.1 treatments in a comprehensive literature review of 55 patients [68, 69]. A review

of published cases found a lower mortality rate in ECT treated patients compared with those receiving supportive care alone [70]. The interpretation of these results are limited by variable timing of ECT in relation to symptom onset and lack of randomization.

References

1. Velamoor VR. Neuroleptic malignant syndrome. Recognition, prevention and management. Drug Saf. 1998;19(1):73–82.
2. Henderson VW, Wooten GF. Neuroleptic malignant syndrome: a pathogenetic role for dopamine receptor blockade? Neurology. 1981;31(2):132–7.
3. Toru M, Matsuda O, Makiguchi K, Sugano K. Neuroleptic malignant syndrome-like state following a withdrawal of antiparkinsonian drugs. J Nerv Ment Dis. 1981;169(5):324–7.
4. Addonizio G, Susman VL, Roth SD. Symptoms of neuroleptic malignant syndrome in 82 consecutive inpatients. Am J Psychiatry. 1986;143(12):1587–90.
5. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Med Clin North Am. 1993;77(1):185–202.
6. Strawn JR, Keck PE, Caroff SN. Neuroleptic malignant syndrome. Am J Psychiatry. 2007;164(6):870–6.
7. Rosebush P, Stewart T. A prospective analysis of 24 episodes of neuroleptic malignant syndrome. Am J Psychiatry. 1989;146(6):717–25.
8. Caroff SN. Neuroleptic malignant syndrome. In: Mann SC, Lazarus A, editors. Neuroleptic malignant syndrome and related conditions. 2nd ed. Washington, DC: American Psychiatric Pub; 2003. p. 1–44.
9. Margetić B, Aukst-Margetić B. Neuroleptic malignant syndrome and its controversies. Pharmacoepidemiol Drug Saf. 2010;19(5):429–35.
10. Gurrera RJ, Caroff SN, Cohen A, Carroll BT, DeRoos F, Francis A, et al. An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method. J Clin Psychiatry. 2011;72(9):1222–8.
11. Velamoor VR, Norman RM, Caroff SN, Mann SC, Sullivan KA, Antelo RE. Progression of symptoms in neuroleptic malignant syndrome. J Nerv Ment Dis. 1994;182(3):168–73.
12. Carbone JR. The neuroleptic malignant and serotonin syndromes. Emerg Med Clin North Am. 2000;18(2):317–25, x.
13. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Psychopharmacol Bull. 1988;24(1):25–9.
14. Litman RS, Flood CD, Kaplan RF, Kim YL, Tobin JR. Postoperative malignant hyperthermia: an analysis of cases from the North American Malignant Hyperthermia Registry. Anesthesiology. 2008;109(5):825–9.
15. Mason PJ, Morris VA, Balcezak TJ. Serotonin syndrome. Presentation of 2 cases and review of the literature. Medicine [Baltimore]. 2000;79(4):201–9.
16. Nielsen RE, Wallenstein Jensen SO, Nielsen J. Neuroleptic malignant syndrome-an 11-year longitudinal case–control study. Can J Psychiatry Rev Can Psychiatr. 2012;57(8):512–8.
17. Chandran GJ, Mikler JR, Keegan DL. Neuroleptic malignant syndrome: case report and discussion. CMAJ Can Med Assoc J J Assoc Medicale Can. 2003;169(5):439–42.
18. Seitz DP, Gill SS. Neuroleptic malignant syndrome complicating antipsychotic treatment of delirium or agitation in medical and surgical patients: case reports and a review of the literature. Psychosomatics. 2009;50(1):8–15.
19. Yacoub A, Francis A. Neuroleptic malignant syndrome induced by atypical neuroleptics and responsive to lorazepam. Neuropsychiatr Dis Treat. 2006;2(2):235–40.
20. Ananth J, Parameswaran S, Gunatilake S, Burgoyne K, Sidhom T. Neuroleptic malignant syndrome and atypical antipsychotic drugs. J Clin Psychiatry. 2004;65(4):464–70.
21. Hasan S, Buckley P. Novel antipsychotics and the neuroleptic malignant syndrome: a review and critique. Am J Psychiatry. 1998;155(8):1113–6.
22. Stübner S, Rustenbeck E, Grohmann R, Wagner G, Engel R, Neundörfer G, et al. Severe and uncommon involuntary movement disorders due to psychotropic drugs. Pharmacopsychiatry. 2004;37 Suppl 1:S54–64.
23. Shalev A, Hermesh H, Munitz H. Mortality from neuroleptic malignant syndrome. J Clin Psychiatry. 1989;50(1):18–25.
24. Keck PE, Pope HG, Cohen BM, McElroy SL, Nierenberg AA. Risk factors for neuroleptic malignant syndrome. A case–control study. Arch Gen Psychiatry. 1989;46(10):914–8.
25. Hermesh H, Aizenberg D, Weizman A, Lapidot M, Mayor C, Munitz H. Risk for definite neuroleptic malignant syndrome. A prospective study in 223 consecutive in-patients. Br J Psychiatry J Ment Sci. 1992;161:254–7.
26. Berardi D, Amore M, Keck PE, Troia M, Dell'Atti M. Clinical and pharmacologic risk factors for neuroleptic malignant syndrome: a case–control study. Biol Psychiatry. 1998;44(8):748–54.
27. Sachdev P, Mason C, Hadzi-Pavlovic D. Case–control study of neuroleptic malignant syndrome. Am J Psychiatry. 1997;154(8):1156–8.
28. Rosebush PI, Mazurek MF. Serum iron and neuroleptic malignant syndrome. Lancet Lond Engl. 1991;338(8760):149–51.
29. Schneck HJ, Rupreht J. Central anticholinergic syndrome [CAS] in anesthesia and intensive care. Acta Anaesthesiol Belg. 1989;40(3):219–28.

30. Brown DV, Heller F, Barkin R. Anticholinergic syndrome after anesthesia: a case report and review. Am J Ther. 2004;11(2):144–53.
31. Denborough M. Malignant hyperthermia. Lancet Lond Engl. 1998;352(9134):1131–6.
32. Larach MG, Gronert GA, Allen GC, Brandom BW, Lehman EB. Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006. Anesth Analg. 2010;110(2):498–507.
33. Dosi R, Ambaliya A, Joshi H, Patell R. Serotonin syndrome versus neuroleptic malignant syndrome: a challenging clinical quandary. BMJ Case Rep. 2014 doi:10.1136/bcr-2014-204154.
34. Perry PJ, Wilborn CA. Serotonin syndrome vs neuroleptic malignant syndrome: a contrast of causes, diagnoses, and management. Ann Clin Psychiatry Off J Am Acad Clin Psychiatr. 2012;24(2):155–62.
35. Modi S, Dharaiya D, Schultz L, Varelas P. Neuroleptic malignant syndrome: complications, outcomes, and mortality. Neurocrit Care. 2016;24(1):97–103.
36. Gurrera RJ, Chang SS. Thermoregulatory dysfunction in neuroleptic malignant syndrome. Biol Psychiatry. 1996;39(3):207–12.
37. Addonizio G, Susman VL, Roth SD. Neuroleptic malignant syndrome: review and analysis of 115 cases. Biol Psychiatry. 1987;22(8):1004–20.
38. Circiumaru B, Baldock G, Cohen J. A prospective study of fever in the intensive care unit. Intensive Care Med. 1999;25(7):668–73.
39. Marik PE. Fever in the ICU. Chest. 2000;117(3):855–69.
40. Gurrera RJ, Romero JA. Sympathoadrenomedullary activity in the neuroleptic malignant syndrome. Biol Psychiatry. 1992;32(4):334–43.
41. Koch M, Chandragiri S, Rizvi S, Petrides G, Francis A. Catatonic signs in neuroleptic malignant syndrome. Compr Psychiatry. 2000;41(1):73–5.
42. Lee JWY. Neuroleptic-induced catatonia: clinical presentation, response to benzodiazepines, and relationship to neuroleptic malignant syndrome. J Clin Psychopharmacol. 2010;30(1):3–10.
43. Castillo E, Rubin RT, Holsboer-Trachsler E. Clinical differentiation between lethal catatonia and neuroleptic malignant syndrome. Am J Psychiatry. 1989;146(3):324–8.
44. Fleischhacker WW, Unterweger B, Kane JM, Hinterhuber H. The neuroleptic malignant syndrome and its differentiation from lethal catatonia. Acta Psychiatr Scand. 1990;81(1):3–5.
45. Adnet P, Lestavel P, Krivosic-Horber R. Neuroleptic malignant syndrome. Br J Anaesth. 2000;85(1):129–35.
46. Caroff SN, Mann SC, Campbell EC, Sullivan KA. Movement disorders associated with atypical antipsychotic drugs. J Clin Psychiatry. 2002;63 Suppl 4:12–9.
47. Wijemanne S, Jankovic J. Movement disorders in catatonia. J Neurol Neurosurg Psychiatry. 2015;86(8):825–32.
48. Levenson JL. Neuroleptic malignant syndrome. Am J Psychiatry. 1985;142(10):1137–45.
49. Nisijima K. Elevated creatine kinase does not necessarily correspond temporally with onset of muscle rigidity in neuroleptic malignant syndrome: a report of two cases. Neuropsychiatr Dis Treat. 2012;8:615–8.
50. Védie C, Poinso F, Hemmi F, Rivet B. Major symptoms and differential diagnosis of neuroleptic malignant syndrome: three case reports. Eur Psychiatry J Assoc Eur Psychiatr. 2000;15(5):334–7.
51. Bagley WH, Yang H, Shah KH. Rhabdomyolysis. Intern Emerg Med. 2007;2(3):210–8.
52. Lappa A, Podestà M, Capelli O, Castagna A, Di Placido G, Alampi D, et al. Successful treatment of a complicated case of neuroleptic malignant syndrome. Intensive Care Med. 2002;28(7):976–7.
53. Gurrera RJ. Sympathoadrenal hyperactivity and the etiology of neuroleptic malignant syndrome. Am J Psychiatry. 1999;156(2):169–80.
54. Reulbach U, Dütsch C, Biermann T, Sperling W, Thuerauf N, Kornhuber J, et al. Managing an effective treatment for neuroleptic malignant syndrome. Crit Care Lond Engl. 2007;11(1):R4.
55. Rosebush PI, Stewart T, Mazurek MF. The treatment of neuroleptic malignant syndrome. Are dantrolene and bromocriptine useful adjuncts to supportive care? Br J Psychiatry J Ment Sci. 1991;159:709–12.
56. Francis A, Chandragiri S, Rizvi S, Koch M, Petrides G. Is Lorazepam a treatment for neuroleptic malignant syndrome? CNS Spectr. 2000;5(7):54–7.
57. Tural U, Onder E. Clinical and pharmacologic risk factors for neuroleptic malignant syndrome and their association with death. Psychiatry Clin Neurosci. 2010;64(1):79–87.
58. Miyaoka H, Shishikura K, Otsubo T, Muramatsu D, Kamijima K. Diazepam-responsive neuroleptic malignant syndrome: a diagnostic subtype? Am J Psychiatry. 1997;154(6):882.
59. Mann SC, Lazarus A, editors. Neuroleptic malignant syndrome and related conditions. 2nd ed. Washington, DC: American Psychiatric Pub; 2003. 204 p.
60. Rosenberg MR, Green M. Neuroleptic malignant syndrome. Review of response to therapy. Arch Intern Med. 1989;149(9):1927–31.
61. Sakkas P, Davis JM, Janicak PG, Wang ZY. Drug treatment of the neuroleptic malignant syndrome. Psychopharmacol Bull. 1991;27(3):381–4.
62. Tsutsumi Y, Yamamoto K, Matsuura S, Hata S, Sakai M, Shirakura K. The treatment of neuroleptic malignant syndrome using dantrolene sodium. Psychiatry Clin Neurosci. 1998;52(4):433–8.
63. Bhanushali MJ, Tuite PJ. The evaluation and management of patients with neuroleptic malignant syndrome. Neurol Clin. 2004;22(2):389–411.
64. Shoop SA, Cernek PK. Carbidopa/levodopa in the treatment of neuroleptic malignant syndrome. Ann Pharmacother. 1997;31(1):119.

65. Nisijima K, Noguti M, Ishiguro T. Intravenous injection of levodopa is more effective than dantrolene as therapy for neuroleptic malignant syndrome. Biol Psychiatry. 1997;41(8):913–4.
66. Jee A. Amantadine in neuroleptic malignant syndrome. Postgrad Med J. 1987;63(740):508–9.
67. Gangadhar BN, Desai NG, Channabasavanna SM. Amantadine in the neuroleptic malignant syndrome. J Clin Psychiatry. 1984;45(12):526.
68. Trollor JN, Sachdev PS. Electroconvulsive treatment of neuroleptic malignant syndrome: a review and report of cases. Aust N Z J Psychiatry. 1999;33(5):650–9.
69. Nisijima K, Ishiguro T. Electroconvulsive therapy for the treatment of neuroleptic malignant syndrome with psychotic symptoms: a report of five cases. J ECT. 1999;15(2):158–63.
70. Davis JM, Janicak PG, Sakkas P, Gilmore C, Wang Z. Electroconvulsive therapy in the treatment of the neuroleptic malignant syndrome. Convuls Ther. 1991;7(2):111–20.

Traumatic Brain Injury

40

Yogesh Moradiya and Romergryko G. Geocadin

Case Presentation

Forty two year old man is brought to the emergency department after he was hit by a car while crossing a street. Upon EMS arrival, he had normal vital signs and was awake and mumbling incomprehensible words. The patient deteriorated en route to the hospital and is now unresponsive with Glasgow Coma Scale (GCS) of 4 and extensor posturing. His blood pressure now is 205/120 mmHg with heart rate of 45 beats/min. Left pupil is fixed and dilated. CT scan of the head performed after endotracheal intubation showed large left temporal epidural hematoma with midline shift of 7 mm towards right and left uncal herniation. Additionally, there is evidence of bifrontal hemorrhagic contusions and thin layer of subarachnoid hemorrhage along cortical surface. Laboratory studies revealed normal hemoglobin and hematocrit and a Focused Assessment with Sonography in Trauma (FAST) study did not show signs of major extracranial bleeding. Bedside examination and imaging studies did not show any major cervical, extremities or thoracoabdominal trauma.

Question What is the most appropriate treatment for this patient with severe traumatic brain injury at this time?

Answer Emergent surgical evacuation of epidural hematoma.

This patient has suffered severe traumatic brain injury with no evidence of other significant extracranial injury. The patient is showing signs of increased intracranial pressure as evident from decreased level of consciousness and Cushing reflex caused by evolving epidural hematoma. Patient underwent emergent left temporal craniotomy and epidural hematoma evacuation. An intraparenchymal fiberoptic intracranial pressure monitoring device and a brain tissue oxygen tension ($PbtO_2$) monitoring device were inserted in the right frontal region. A target driven protocol-based treatment of intracranial hypertension and brain tissue hypoxia was initiated with goal ICP <20 mmHg, CPP >60 mmHg and $PbtO_2 > 20$ mmHg. On postoperative day 2, neurological examination improved slightly with patient withdrawing to painful stimuli on upper extremities, however still unable to follow commands. Patient had episodes of sustained elevations in intracranial pressure above 25 mmHg lasting longer than 15 min. Patient was treated with isotonic saline bolus to treat hypotension and

Y. Moradiya (✉)
Neurosurgery, Hofstra Northwell School of Medicine, Manhasset, NY, USA
e-mail: YogeshMoradiyaMD@gmail.com

R.G. Geocadin
Neurology, Neurosurgery and Anesthesiology – Critical Care Medicine, Neurosciences Critical Care Division, Johns Hopkins University School of Medicine, Baltimore, MD, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_40

Mannitol to treat intracranial hypertension. Sustained brain tissue hypoxia in the setting of normal CPP was treated with induced systemic hyperoxia by increase in FiO_2 and blood transfusion to increase oxygen carrying capacity. Patient developed intracranial hypertension refractory to hyperosmolar therapy and propofol sedation. Patient was placed on intravenous pentobarbital coma. Continuous EEG monitoring was used to assess the depth of sedation with goal of achieving burst suppression. Patient did not respond to medical therapy for treatment of refractory intracranial hypertension and a bifrontal decompressive craniectomy was performed.

Principles of Management

Primary and Secondary Brain Injury

TBI results in two distinct phases of brain injury. The primary brain injury that occurs at time of trauma is physical tissue injury resulting in shearing or compression of brain parenchyma. Severity of primary brain injury is a major determinant of outcome; however, it is generally irreversible and non-modifiable. Secondary brain injury that occurs hours to days after the traumatic event is the result of complex interaction between various intracranial and systemic factors. Brain ischemia resulting from secondary injury caused by decreased cerebral perfusion pressure from elevated intracranial pressure or systemic hypotension, hypoxia, hypocapnia, and brain herniation can significantly impact outcome and therefore, management of TBI focuses on reducing this secondary injury.

Severity of Traumatic Brain Injury

Classification of TBI based on initial severity helps in predicting likely outcome as well as understanding natural history. Severity of TBI is defined based on findings on neuroimaging, GCS within first 24 h of presentation, presence or absence and duration of loss of consciousness, post-traumatic amnesia and change in mental status. Table 40.1.

Prehospital and Emergency Department

Two major causes of secondary brain injury after TBI are cerebral hypoperfusion and hypoxia. Studies have shown that systolic BP < 90 mmHg and PaO_2 < 60 mmHg are associated with poor outcomes after TBI [1]. The prehospital treatment is focused toward establishing and maintaining adequate circulation, patent airway and oxygenation. Securement of airway by endotracheal intubation should be considered in patients with GCS <9 while ensuring hemodynamic stability. Crystalloids are preferred over colloids for fluid resuscitation as use of albumin resulted in increased mortality in a randomized clinical trial [2]. All patients with suspected moderate to severe TBI or GCS <15 should undergo neuroimaging evaluation. Non-contrast CT of head is preferred modality due to rapidity, wide availability and high sensitivity for detection of intra- and extraparenchymal hemorrhage and fractures. Common findings on initial CT of head in severe TBI include one or more of cerebral contusion (frontal and temporal lobes are common location), subdural hematoma, epidural hematoma, subarachnoid hemorrhage, intraventricular hemorrhage, diffuse cerebral edema, skull fracture and extracranial hematoma. Frequently, initial CT scan in comatose patients with severe TBI and diffuse axonal injury may be largely unremarkable. A follow up CT done 6–12 h after the initial CT may show development of new lesions or expansion of previously seen contusions. Early detection and treatment of intracranial hypertension should begin in emergency department as both duration and severity of low cerebral perfusion are associated with worse outcomes. Patients with severe TBI should be transferred to a tertiary center with emergent neurosurgical services once hemodynamic stability is established [3] (Fig. 40.1).

Mechanical Ventilation

Positive end-expiratory pressure should be kept to minimum to adequately oxygenate in patients with intracranial hypertension requiring mechanical

Table 40.1 Classification of severity of traumatic brain injury

Criteria	Mild	Moderate	Severe
Neuroimaging	Normal	Normal or abnormal	Abnormal
Initial GCS	13–15	9–12	<9
Loss of consciousness	Absent or upto 30 min	30 min to 24 h	More than 24 h
Post-traumatic amnesia	Absent or upto 24 h	1–7 days	More than 7 days
Change in mental status	Absent or upto 24 h	More than 24 h	

Adapted from VA/DoD clinical practice guideline for management of concussion/mild traumatic brain injury

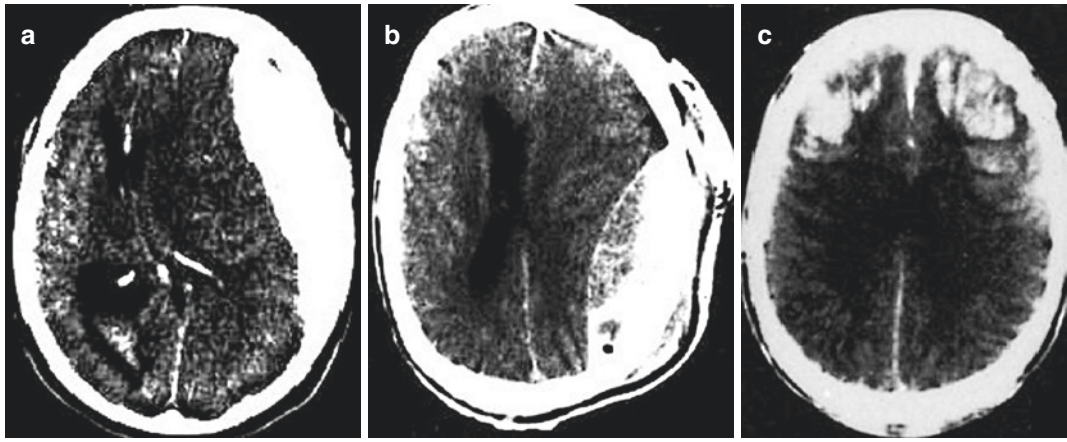


Fig. 40.1 CT scan of the head showing different findings in severe traumatic brain injury. (**a**) Crescent shaped hyperdensity in the suggestive of left sided acute subdural hematoma with mass effect and left to right midline shift. (**b**) Lenticular hyperdensity suggestive of acute epidural hematoma with effacement of left lateral ventricle. (**c**) Bifrontal traumatic cerebral contusions

ventilatory support. Prolonged hyperventilation induced hypocapnia increases risk of ischemia by cerebral vasoconstriction while permissive hypercapnia may lead to intracranial hypertension via cerebral vasodilation.

Analgesia, Sedation and Neuromuscular Paralysis

Inadequate pain control, agitation and anxiety may increase ICP and cerebral oxygen demand while unnecessary and excessive sedation results in inability to detect change in neurological exam. Therefore, judicious use of short acting opioids such as fentanyl, ramifentanyl or morphine is warranted for pain control and propofol or short acting benzodiazepine such as midazolam may be used to provide sedation. Non-depolarizing muscle relaxants should be used for patient-ventilator dyssynchrony causing refractory hypoxia and to treat intracranial hypertension caused by excessive coughing or straining.

Surgical Treatment

Epidural Hematoma

Patients with EDH and GCS score <9 should undergo surgical evacuation. Surgery is also recommended for patients with EDH volume ≥30 cc, thickness ≥15 mm or midline shift of ≥5 mm regardless of GCS. Patients managed nonoperatively should undergo serial CT imaging and frequent neurological monitoring where emergent neurosurgical treatment is available. Temporal location increases the risk of deterioration and therefore, threshold for surgery should be kept lower for patients with temporal EDH. Time from neurological worsening to EDH evacuation correlates more with outcomes than time from injury to evacuation. Therefore, in patients undergoing initial non-surgical treatment,

neurological deterioration as defined by worsening level of consciousness, abnormal papillary reflex, and appearance of new focality or worsening of existing focal deficits should prompt urgent surgical evacuation.

Subdural Hematoma

The indications for surgery in acute traumatic SDH include clot thickness >10 mm or midline shift >5 mm on initial CT imaging regardless of GCS. In patients with smaller SDH, GCS <9 or decrease in GCS by 2 points or more since presentation, presence of papillary abnormality or persistent elevation of ICP >20 mmHg should prompt surgical evacuation.

Intraparenchymal Hematoma/ Traumatic Cerebral Contusion

Patients with GCS of <9 with frontal or temporal hematoma of >20 cc with midline shift of ≥5 mm or cisternal compression and those with any hematoma of >50 cc should undergo evacuation. Also, patients with neurological deterioration thought to be related to intraparenchymal hematoma should also be treated surgically [4]. Neurologically stable patients with parenchymal contusion showing no significant mass effect on CT scan can be managed nonoperatively with close monitoring and serial imaging. Patients with medically refractory intracranial hypertension from diffuse cerebral edema may be treated with bifrontal or hemispheric decompressivecraniectomy.

Evidence Contour

Indication of Intracranial Pressure Monitoring and Pressure Threshold

Invasive ICP monitoring is not routinely indicated in all cases of TBI and the risks of monitoring such as infection and bleeding must be weighed against the benefit of additional information obtained by such monitoring. Patients with severe TBI with abnormal CT scan and GCS <9 should undergo ICP monitoring as they have high likelihood of transient or persistent elevation in ICP resulting in compromise in cerebral perfusion pressure and inability of serial clinical examinations to identify subtle changes related to intracranial hypertension due to poor baseline neurological status. Normal neuroimaging especially during early hours of TBI does not rule out intracranial hypertension. Patients with two or more of the following factors should undergo ICP monitoring in the absence of abnormal findings on CT scan of the head: age above 40 years, motor posturing, systolic blood pressure <90 mmHg. The ICP threshold above which interventions aimed at lowering the ICP should be implemented is unclear at this time. ICP of above 20 mmHg is generally recommended as the treatment threshold by several guidelines. Cerebral perfusion pressure (CPP = MAP-ICP) based threshold may provide for a more physiologically rational parameter and should be used in conjunction with ICP parameter with goal CPP >60–65 mmHg. Different devices used for ICP monitoring use any of available technologies such as fiberoptic sensor, microchip with internal strain gauge, air pouch or fluid filled catheter connected to pressure transducer. Devices also differ in terms of location of tip such as subdural, epidural, subarachnoid, intraparenchymal and intraventricular. Of these, fluid-filled transduced ventriculostomy catheter provides the most accurate ICP value and also allows for therapeutic CSF drainage and is therefore, preferred over other modalities.

Post-traumatic Seizures

Patients with moderate to severe TBI often have convulsive episode immediately after the impact. The issue of whether these 'impact seizures' represent true epileptic convulsion or convulsive concussion is not settled. Either way, these post-traumatic early seizures which can occur up to a week after the injury represent symptomatic events and have low likelihood of recurrence. Risk factors for early seizures are younger age, subdural hematoma, cortical contusions and penetrating head injury. Prophylactic use of AEDs in TBI is controversial. A pooled analysis of controlled trials showed that the use of prophylactic AEDs in selected TBI patients resulted in lower

incidence of early posttraumatic seizures [5]. However, in a placebo controlled randomized trial, phenytoin did not reduce the rate of early posttraumatic seizures in young patients with blunt head injuries [6]. Early seizures may degenerate in to status epilepticus with associated high mortality and both convulsive and non-convulsive seizures can worsen intracranial hypertension. Therefore, use of AEDs for 1 week to prevent seizures in patients at high risk for early seizures is recommended. Phenytoin is preferred agent because of stronger evidence and availability of IV formulation. However, Levetiracetam is an acceptable alternative to phenytoin based on similar outcomes in a large prospective study [7]. Long term prophylaxis is ineffective in preventing late posttraumatic epilepsy and later treatment should be started or continued on occurrence basis.

Therapeutic Hypothermia

High quality randomized trials have failed to show benefit of induced hypothermia after TBI [8, 9]. Use of therapeutic hypothermia was associated with risk of medical complications and its routine use to improve neurological outcomes in TBI is not recommended.

Advanced Neuromonitoring

Brain Tissue Oxygen ($PbtO_2$)

Partial pressure of oxygen in brain tissue can be monitored by an electrode placed in the brain region at risk for tissue hypoxia. Persistent brain tissue hypoxia defined as $PbtO_2 < 20$ mmHg has been shown to be associated with worse outcomes after TBI. It is unclear whether this association is an indicator of severity of injury or a potentially modifiable parameter to change the outcomes. Several non-randomized studies have shown that a protocol based $PbtO_2$ monitoring and interventions to minimize brain tissue hypoxia such as normobaric hyperoxia, elevation of CPP by reduction in ICP or hemodynamic augmentation and blood transfusion to increase O_2 carrying capacity is associated with better outcomes [10, 11]. A phase II randomized trial (BOOST-2) also showed that $PbtO_2$ monitoring and protocol based interventions are feasible, safe and associated with trend toward better outcomes compared to ICP monitoring based intervention alone [12].

Cerebral Microdialysis

Microdialysis consists of continuous sampling of the small molecules in the interstitial fluid via a small catheter placed within the tissue at risk for secondary injury. Analysis of various biochemical markers provides important information regarding metabolic milieu of the cerebral tissue. Tissue hypoxia leads to increased lactate production via anaerobic metabolism resulting in high lactate/pyruvate ratio and increase in glutamate due to decreased glial uptake as a result of ATP depletion. Advanced ischemia leads to increase in glycerol from decomposition of cell membrane. Tissue glucose concentration without parallel decrease in blood glucose may indicate a state of ischemia. These metabolic markers in microdialysis can aide in prognostication. Their role in interventions aimed at improving outcomes by affecting cerebral oxygenation, perfusion and glycemic state has not been established yet.

Jugular Bulb Oximetry

A popular monitoring technique in the past, Jugular bulb oximetry ($SjvO_2$) helps in determining the balance between cerebral blood flow and metabolic demand. Reduction in $SjvO_2$ indicates increase in oxygen extraction or decrease in cerebral blood flow as a result of decrease in CPP. The duration and the degree of abnormal $SjvO_2$ are associated with worsened outcomes after TBI.

Prophylactic Antibiotics

Penetrating brain injury has high risk of intracranial infection. Presence of CSF fistulae, transventricular injury and air sinus wounds increases the risk of infection further. Therefore, broad spectrum prophylactic antibiotics are recommended in all cases of penetrating brain injury [13].

Antibiotic prophylaxis is not indicated in non-penetrating basilar skull fractures with or without CSF leak [14].

Steroids and Neuroprotective Agents

Use of high dose intravenous corticosteroids following moderate to severe TBI was associated with increased risk of death within 2 weeks and is contraindicated [15]. A variety of neuroprotective agents have been studied in animals and humans for TBI. The results from early studies on use of Magnesium, Citicoline, progesterone and erythropoietin after TBI were promising, however, randomized clinical trials failed to show effectiveness of these strategies in TBI [16–21]. Effectiveness of routine use of hyperbaric oxygen and cyclosporine after TBI requires further confirmation by randomized clinical trials [22, 23].

References

1. McHugh GS, Engel DC, Butcher I, Steyerberg EW, Lu J, Mushkudiani N, et al. Prognostic value of secondary insults in traumatic brain injury: results from the IMPACT study. J Neurotrauma. 2007;24(2):287–93.
2. Investigators SS, Australian, New Zealand Intensive Care Society Clinical Trials G, Australian Red Cross Blood S, George Institute for International H, Myburgh J. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med. 2007;357(9):874–84.
3. Suarez JI, Zaidat OO, Suri MF, Feen ES, Lynch G, Hickman J, et al. Length of stay and mortality in neurocritically ill patients: impact of a specialized neurocritical care team. Crit Care Med. 2004;32(11):2311–7.
4. Bullock MR, Chesnut R, Ghajar J, Gordon D, Hartl R, Newell DW, et al. Surgical management of traumatic parenchymal lesions. Neurosurgery. 2006;58(3 Suppl):S25–46; discussion Si–iv.
5. Chang BS, Lowenstein DH, Quality Standards Subcommittee of the American Academy of N. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2003;60(1):10–6.
6. Young KD, Okada PJ, Sokolove PE, Palchak MJ, Panacek EA, Baren JM, et al. A randomized, double-blinded, placebo-controlled trial of phenytoin for the prevention of early posttraumatic seizures in children with moderate to severe blunt head injury. Ann Emerg Med. 2004;43(4):435–46.
7. Inaba K, Menaker J, Branco BC, Gooch J, Okoye OT, Herrold J, et al. A prospective multicenter comparison of levetiracetam versus phenytoin for early posttraumatic seizure prophylaxis. J Trauma Acute Care Surg. 2013;74(3):766–71; discussion 71–3.
8. Sydenham E, Roberts I, Alderson P. Hypothermia for traumatic head injury. Cochrane Database Syst Rev. 2009;(2):CD001048.
9. Andrews PJ, Sinclair HL, Rodriguez A, Harris BA, Battison CG, Rhodes JK, et al. Hypothermia for intracranial hypertension after traumatic brain injury. N Engl J Med. 2015;373(25):2403–12.
10. Spiotta AM, Stiefel MF, Gracias VH, Garuffe AM, Kofke WA, Maloney-Wilensky E, et al. Brain tissue oxygen-directed management and outcome in patients with severe traumatic brain injury. J Neurosurg. 2010;113(3):571–80.
11. Narotam PK, Morrison JF, Nathoo N. Brain tissue oxygen monitoring in traumatic brain injury and major trauma: outcome analysis of a brain tissue oxygen-directed therapy. J Neurosurg. 2009;111(4):672–82.
12. Neurocritical Care Society 12th annual meeting. Neurocritical Care. 2014;21(1):1–285.
13. Antibiotic prophylaxis for penetrating brain injury. J Trauma. 2001;51(2 Suppl):S34–40.
14. Ratilal BO, Costa J, Pappamikail L, Sampaio C. Antibiotic prophylaxis for preventing meningitis in patients with basilar skull fractures. Cochrane Database Syst Rev. 2015;(4):CD004884.
15. Roberts I, Yates D, Sandercock P, Farrell B, Wasserberg J, Lomas G, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. Lancet. 2004;364(9442):1321–8.
16. Zafonte RD, Bagiella E, Ansel BM, Novack TA, Friedewald WT, Hesdorffer DC, et al. Effect of citicoline on functional and cognitive status among patients with traumatic brain injury: Citicoline Brain Injury Treatment Trial (COBRIT). JAMA. 2012;308(19):1993–2000.
17. Nichol A, French C, Little L, Haddad S, Presneill J, Arabi Y, et al. Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. Lancet. 2015;386(10012):2499–506.
18. Temkin NR, Anderson GD, Winn HR, Ellenbogen RG, Britz GW, Schuster J, et al. Magnesium sulfate for neuroprotection after traumatic brain injury: a randomised controlled trial. Lancet Neurol. 2007;6(1):29–38.
19. Arango MF, Bainbridge D. Magnesium for acute traumatic brain injury. Cochrane Database Syst Rev. 2008;(4):CD005400.
20. Wright DW, Yeatts SD, Silbergleit R, Palesch YY, Hertzberg VS, Frankel M, et al. Very early administration of progesterone for acute traumatic brain injury. N Engl J Med. 2014;371(26):2457–66.
21. Skolnick BE, Maas AI, Narayan RK, van der Hoop RG, MacAllister T, Ward JD, et al. A clinical trial of

progesterone for severe traumatic brain injury. N Engl J Med. 2014;371(26):2467–76.
22. Bennett MH, Trytko B, Jonker B. Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. Cochrane Database Syst Rev. 2012;(12):CD004609.
23. Mazzeo AT, Brophy GM, Gilman CB, Alves OL, Robles JR, Hayes RL, et al. Safety and tolerability of cyclosporin a in severe traumatic brain injury patients: results from a prospective randomized trial. J Neurotrauma. 2009;26(12):2195–206.

Management of Anoxic Brain Injury

41

Maximilian Mulder and Romergryko G. Geocadin

Case Presentation

A 46 year old male with a history of tobacco dependence and uncontrolled diabetes is brought in to the emergency department after a resuscitated cardiac arrest. He had been in his usual state of health and after waking up this morning collapsed at the side of the bed and was noted to be apneic by his wife. When the paramedics arrived, he had received no bystander CPR and he was in ventricular fibrillation and he ultimately regained return of spontaneous circulation (ROSC) after 7 shocks and was intubated in the field.

On arrival to the ED unresponsiveness was confirmed, he was connected to a ventilator after verifying endotracheal tube positioning and obtaining labs and 12 lead ECG. He was given a 30 mL/Kg bolus of chilled (4 °C) normal saline solution, packed in ice and rushed to the cardiac catheterization lab. There he was found to have no significant obstructive coronary artery disease but was noted to have biventricular failure with elevated filling pressures. Transthoracic echocardiography showed a severely reduced left ventricular ejection fraction of ~10 %. On his way to the Intensive Care Unit, he had a CT scan of the brain which was read as concerning for early loss of gray-white matter differentiation (Fig. 41.1). He arrives in the ICU intubated, sedated, paralyzed and ice packed.

Question What approach should guide this patient's management?

Answer Targeted Temperature Management (TTM) with initial Mild Therapeutic Hypothermia followed by Maintenance of Normothermia.

Most adult patients, with few exceptions, that suffer anoxic brain injury should be treated with targeted temperature management in order to minimize secondary brain injury. On arrival to the ICU the patient was connected to an automated closed-loop intravascular cooling system. Target temperature of 33 °C was achieved within four hours from return of spontaneous circulation (ROSC). In order to facilitate cooling to goal temperature, shivering was countered by sedation with midazolam and fentanyl infusions as well as paralysis with cis-atracurium. Target temperature was maintained for 24 h, after which controlled active rewarming of 0.25 °C per hour was undertaken with the closed loop TTM system until the patient was rewarmed to the new target temperature of 37 °C. At this point the

M. Mulder (✉)
Neurocritical Care Unit, Department of Critical Care, Abbott Northwestern Hospital, Minneapolis, MN, USA
e-mail: maximilian.mulder@allina.com

R.G. Geocadin
Neurology, Neurosurgery and Anesthesiology – Critical Care Medicine, Neurosciences Critical Care Division, Johns Hopkins University School of Medicine, Baltimore, MD, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_41

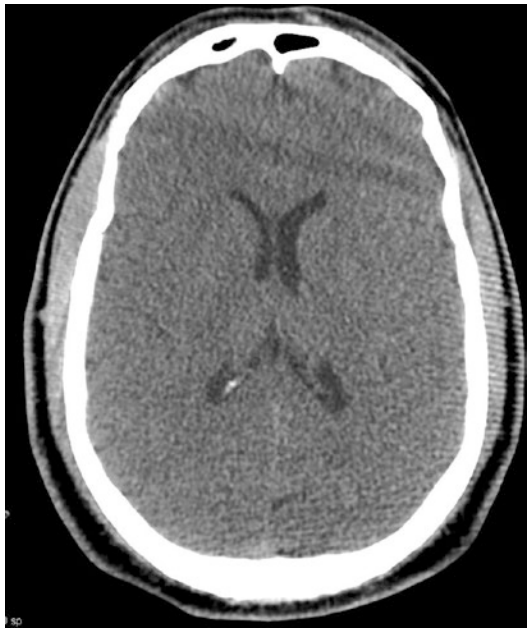


Fig. 41.1 A representative image from the CT of the brain is shown

TTM system was set to maintain normothermia, cooling the patient if necessary to maintain a temperature of 37 °C for the next 72 h. During this entire time patient was monitored with continuous EEG; he had follow up MRI of the brain which did not demonstrate evidence of focal or diffuse damage, serum neuron specific enolase levels drawn at 48 and 72 h were 26 ng/mL and 19 ng/mL respectively. He remained comatose on minimal sedation for 118 h from ROSC prior to improvement in his neurologic examination. He was extubated on hospital day 8 and was quite delirious, but had a non-focal neurologic exam and was able to participate actively with physical and occupational therapy. He was transferred out of the ICU on hospital day 10 and discharged to home on hospital day 13. Neurocognitive testing at 90 day follow up showed normal function with very mild short term memory impairment that was not impacting his performance at work (Fig. 41.2).

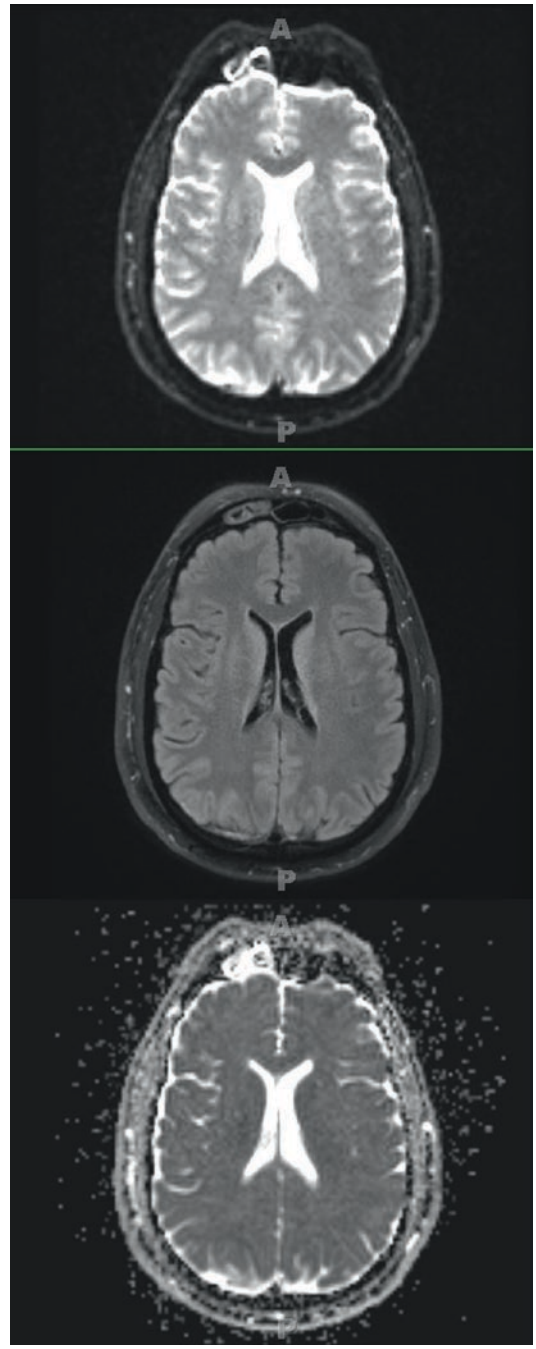


Fig. 41.2 A representative image from the MRI of the brain is shown

Principles of Management

Diagnosis

Anoxic brain injury, also known as hypoxic encephalopathy, ischemic-hypoxic encephalopathy is a fairly heterogenous entity. It best conceptualized as a spectrum of brain injury ranging from brain death, minimally conscious states, to recovery of consciousness with cognitive impairment and movement disorders to mild transient loss of consciousness with or without transient neurologic deficits. The diagnosis is made after loss of consciousness after an episode of global cerebral hypoxia or hypoperfusion. It is in essence a clinical diagnosis, as no radiological, laboratory or electrophysiologic test can fully diagnose it; these ancillary exams are often negative even in cases of severe anoxic encephalopathy.

Therapeutic Hypothermia

The use of hypothermia in the treatment of injuries dates back to antiquity, with one of the earliest applications being attributed to Hippocrates, who recommended covering wounded combatants in snow to enhance survival and recovery. In modern times, the observation that hypothermia mitigates acute neurological injury and improves outcomes was made decades ago. The first documented use of hypothermia for neuroprotection after in-hospital cardiac arrest consists of a 1958 case series of 4 patients [1]. One of the first human clinical studies on induced hypothermia for out-of hospital cardiac arrest survivors was a pilot safety and feasibility study performed by Bernard et al. in 1997 [2], this was followed in 1998, by another small study by Yanagawa et al. [3]. These two studies suggested a potential therapeutic benefit from induced hypothermia in comatose post-cardiac arrest survivors, and paved the way for subsequent definitive trials.

In the following two decades, there have been three landmark trials in TTM for hypoxic ischemic brain injury. In 2002 the two initial trials were published simultaneously, one in Australia and the other in Europe. The Australian study was Bernard et al.'s follow up study that enrolled comatose survivors of ventricular fibrillation arrests [4]. This study randomized 77 patients to receive mild therapeutic hypothermia of 33 °C or normothermia (no temperature intervention). The hypothermia arm included 43 patients while the normothermia arm had 34 patients. In this trial, cooling was initiated by paramedics prior to hospital arrival and cooling was achieved and maintained with ice packs. The target temperature was maintained for 12 h and patients were sedated and paralyzed with repeated boluses of midazolam and vecuronium as needed to prevent shivering, followed by active rewarming with a heated-air blanket beginning at 18 h after hospital arrival, with continued sedation and neuromuscular blockade to suppress shivering. Discharge to home or to a rehabilitation facility was regarded as a good outcome, whereas in-hospital mortality and discharge to a long-term nursing facility were regarded as poor outcomes. The study found that 21 of 43 patients (49 %) treated with hypothermia had good outcomes and were discharge to home or to a rehabilitation facility, compared with 9 of 34 (26 %) in the normothermia group (relative risk (RR) of good outcome, 1.85, 95 % confidence interval (CI) 0.97–3.49, number needed to treat (NNT) = 4). Mortality at discharge was 22 of 43 (51 %) in the hypothermia group and 23 of 34 (68 %) in the normothermia group (RR 0.76, 95 % CI 0.52–1.10, NNT = 6).

The second, larger trial by the European Hypothermia after Cardiac Arrest (HACA) group, randomized 273 comatose survivors of ventricular fibrillation arrests to mild therapeutic hypothermia (32–34 °C) beginning after hospital arrival versus normothermia [5]. One hundred and thirty-seven patients were randomized to the hypothermia arm, while 138 patients were randomized to the normothermia arm. Patients in the hypothermia group were cooled by via forced air mattresses and blankets, and were maintained at target temperature for 24 h. Patients were subsequently rewarmed passively over a period of 8 h. Sedation with midazolam and paralysis with vecuronium was administered to prevent shivering. Seventy-five of the 136 patients (55 %) in the

hypothermia group had a favorable neurological outcome (able to live independently and work at least part-time) at 6 months compared with 54 of 137 (39 %) in the normothermia group (RR 1.40, 95 % CI 1.08–1.81, NNT = 6). At 6 months there were 56 deaths among the 137 participants (41 %) in the hypothermia group versus 76 of 138 (55 %) in the normothermia group (RR 0.74, 95 % CI 0.58–0.95, NNT = 7).

The third, largest and most recent trial is the Therapeutic Temperature Management (TTM 33–36) trial [6]. This prospective multicenter study undertaken in Europe and Australia randomized 939 comatose OHCA survivors to cooling to 33 or 36 °C, with protocolized sedation, rewarming and prognostic evaluation. In this study the method of cooling was left at the discretion of each study site; however the intention was to reach goal temperature as quickly as possible. Rewarming was initiated at 28 h from randomization and done with controlled active rewarming of 0.5 °C per hour. Mandatory sedation was only able to be stopped or tapered at 36 h from randomization. This study found no significant difference in outcomes or complications between the two temperature groups.

Maintenance of Normothermia

Active, controlled rewarming at a rate of 0.25 °C per hour is recommended until a core temperature of 36–37 °C is achieved [7]. Once the patient has been rewarmed, the therapeutic temperature management system should remain in place for a further 48–72 h to ensure normothermia, protecting the brain from the detrimental effects of hyperthermia [8]. Rebound pyrexia is a common phenomenon occurring in about 40 % of patients post therapeutic hypothermia only temperatures >38.7 °C appear to be associated with worse neurologic outcomes in patients who survive to discharge [9]. It must be noted that current guidelines suggest preventing hyperpyrexia >37.7 °C based on data from data from focal cerebral ischemia [7]. The mechanism for this common presentation of fever after therapeutic hypothermia is not well understood, however several factor are thought to contribute to its presence: altered thermoregulation from damage to thalamic structures, rebound hyperthermia, infection and pro-inflammatory states all are likely contributors.

Supportive Care

During targeted temperature management the prevention of shivering is a crucial intervention to allow for rapid induction of therapeutic hypothermia, and to avoid the metabolic stress required to generate body heat through shivering. The use of sedation, paralysis and other adjuvant measures is necessary for adequate TTM. Factors such as age, weight, hemodynamic status, renal and hepatic function, effects of hypothermia on pharmacokinetics and dynamics and the ability to preserve the neurologic examination are factors that weigh on the choice of drugs. At this time no definitive evidence supporting a particular drug regimen exists, however short acting and rapidly cleared drugs with neutral hemodynamic profiles are ideal. Adjuvant measure to control shivering include targeting serum magnesium levels of 3–4 mg/dL, the use of buspirone and meperidine, skin counter warming and heat applied to feet and hands can also be helpful.

Cerebral edema has been reported on the initial cranial CT in approximately 30 % of patients following cardiac arrest [10], however there is no evidence supporting the use of invasive measurement of intracranial pressure to manage this patient population [11]. Basic neurocritical care nursing measures such as maintaining the head of the bed elevated to 30° and in a neutral midline position should be maintained to improve cerebral venous drainage and minimize elevations in intracranial pressure. In HE secondary to cardiac arrest, the incidence of non-convulsive status epilepticus (NCSE) is estimated to be as high as 24 % [12, 13], and is associated with worse outcomes [14, 15]. Post hypoxic myoclonus occurs in roughly 20 % of patients, and traditionally the presence of seizures or myoclonus has been regarded as predictors for poor neurologic outcomes. However, this has been shown to not

always be the case [16, 17]. There is insufficient evidence to recommend prophylactic use of antiepileptic drugs in patients with anoxic-ischemic encephalopathy; however if possible, continuous electroencephalographic monitoring provides the opportunity for early detection and aggressive treatment of NCSE which may impact outcomes and survival.

The ventilator management of patients undergoing therapeutic hypothermia for hypoxic-ischemic encephalopathy should follow a few simple parameters as outlined in current guidelines [7]: arterial partial pressure of oxygen should be approximately 100 mmHg and pulse oxymetry saturations should be equal or greater than 94 %; partial pressures of carbon dioxide should be 40–45 mmHg. The management of common respiratory problems following cardiopulmonary arrest is addressed elsewhere in this book. Cardiovascular care including management of myocardial ischemia, arrhythmias and shock are beyond the scope of this chapter. However, the following basic principles should be regarded: euvolemia should be targeted to accommodate cardiac, pulmonary and renal concerns. An adequate intravascular volume is crucial for cerebral perfusion and to allow for expected cold diuresis during hypothermia. Blood pressure goals should be individualized based on cardiac function, end organ perfusion and taking into account an approximation of the status of cerebral autoregulation. Usually a mean arterial pressure (MAP) of 65 mmHg is adequate and recommended by current guidelines [7]; however a MAP of 70–100 mmHg may be considered in particularly to augment cerebral perfusion pressure in cases of cerebral edema and elevated ICP. There is no quality data on hemodynamic parameters for this population. Empiric antibiotics are encouraged in situations when a clinical infection is suspected, as early initiation of antibiotic therapy has been associated with better outcomes following TTM for cardiopulmonary arrests [18].

Hypothermia causes alterations in endogenous insulin release as well as decreasing insulin sensitivity, therefore great care must be taken to avoid hypoglycemia during rewarming as insulin sensitivity increases back to baseline. As in other forms of brain injury, normoglycemia should be maintained with insulin infusions to avoid the potentially erratic absorption of subcutaneous insulin secondary to peripheral vasoconstriction with changes in temperature as well as the fluctuations of glycemia during therapeutic hypothermia. Current guidelines recommend keeping blood glucose levels between 144 and 180 mg/dL as well as aggressively correcting hypoglycemia <80 mg/dL [7].

Evidence Contour

The mainstay of management in patients with anoxic brain injury involves neuroprotective strategies and supportive critical care management. The only proven effective neuroprotective intervention is mild therapeutic hypothermia, though current evidence leaves questions regarding the optimal depth and duration of therapy. The prognostication of neurologic outcomes is a major area of focus for clinicians and researchers, as there is no optimal paradigm to date.

Therapeutic Hypothermia

Following the initial two landmark trials, the International Liaison Committee on Resuscitation (ILCOR), and the American Heart Association (AHA) published an interim scientific statement in 2003 with recommendations on the use of therapeutic hypothermia in comatose survivors of cardiac arrest [19]. This was followed in 2005 and updated in 2010 in the AHA Guidelines for CPR and Emergency Cardiovascular Care [7], which included the following treatment recommendations: (a) Unconscious adult patients resuscitated after in- or out-of-hospital cardiac arrest should be cooled to 32–34 °C for 12–24 h when the initial rhythm was ventricular fibrillation (Class Ib). (b) Similar therapy may be beneficial for patients with in-hospital cardiac arrest or out-of-hospital arrest associated with an initial rhythm other than ventricular fibrillation (Class IIb). To further assess the impact of hypothermia

on neurologic outcomes, a Cochrane systematic review of hypothermia for neuroprotection after cardiac arrest was published by Holzer et al. [20], and concluded that with conventional cooling methods, patients receiving TTM were more likely to reach a good neurologic outcome (RR 1.55; 95 % CI 1.22 to 1.96) and were more likely to survive to hospital discharge (RR 1.35; 95 % CI 1.10 to 1.65) compared to standard care. It also showed no difference in adverse events between hypothermia and control patients. International guidelines have not been published or updated since the publication of the TTM trial, however ILCOR did issue a statement after the publication of the TTM trial urging clinicians to continue to guide themselves with the existing recommendations pending consensus on the implications of the TTM trial [21]. Some clinicians and institutions have interpreted the results of the TTM trial as evidence against mild therapeutic hypothermia, given the lack of difference in outcomes between the two groups and the fact that 36 °C does not constitute mild therapeutic hypothermia (defined as 32–35 °C). What remains as an unanswered question is how this data applies to populations where the rate of bystander CPR is far lower than the excellent rates reported in the TTM trial, and if more severe anoxic-ischemic injury derives a greater benefit than those with milder injury. Pending clarification of this crucial question, we recommend continuing to use temperatures of 32–34 °C, and reserving the use of temperatures of 36 °C for patients that cannot tolerate lower temperatures.

It is generally accepted that prompt initiation of hypothermia and rapid achievement of target temperature is ideal [22]. Clinical evidence in humans undergoing intra-arrest therapeutic hypothermia is limited, but has been shown to be safe [23–26], improve rates of return of spontaneous circulation, neurologic outcomes and survival [27]. Most evidence indicates that the sooner TTM is initiated, the better; however animal data indicates that initiating hypothermia after 12 h has no benefit [28]. This must be tempered with the realization that the most recent (and best) evidence for induction of pre-hospital therapeutic hypothermia, has shown that despite reaching target temperature sooner, this intervention failed to translate into improved survival or neurologic outcomes [29].

Rewarming and Maintenance of Normothermia

The recommendations for the speed of rewarming and avoidance of hyperthermia after rewarming are still somewhat controversial. They are based on assumptions and observations from both laboratory research and clinical studies indicating a correlation between worse outcomes, markers of neuronal damage or dysfunction and damage in the setting of pyrexia [30–34]. However, some limited clinical data do not support the notion of slower rewarming resulting in improved neurologic outcomes [35]. The recommendation to rewarm at 0.25 °C per hour is based more on pre-clinical data and the concept that there are no significant gains from rapid rewarming and there may be some clinical benefit.

Neurologic Prognostication

The 2006 practice parameters of the American Academy of Neurology provide specific recommendations for the prognostication of neurologic outcomes for cardiac arrest survivors; however these recommendations are based mainly on dated observations from the pre-therapeutic hypothermia era. This practice parameter is endorsed by both the 2008 ILCOR [36] and the 2010 AHA guidelines for CPR and emergency cardiovascular care [7] for use in patients not treated with hypothermia. They also caution on its use in patients treated with hypothermia as available parameters are less reliable for predicting poor outcome in these cases, and waiting at least 72 h before making prognostication attempts is recommended. Delayed neurologic recovery beyond 72 h has been well documented [37, 38].

Traditionally the clinical exam was the cornerstone of neuroprognostication. An exam with absent pupillary or corneal reflexes as well as extensor or absent motor response on post arrest

day three is considered by the AAN guidelines to have a false positive rate (FPR) of zero with a 95 % confidence interval (CI) of 0–3 for predicting a poor neurologic outcome. However, in the post therapeutic hypothermia setting, several studies have challenged the reliability of clinical testing [16, 39–41]. It was also common to equate the presence of post anoxic status myoclonus in the first 24 h with a universally poor outcome; AAN guidelines assigned this finding a FPR of zero with CI of 0–8.8, however more recent studies have also questioned these values [16, 17].

Neuron specific enolase is the most commonly used and studied biomarker of brain injury for prognostication in the setting of hypoxic-ischemic encephalopathy. In the AAN guidelines, a NSE value >33 μg/L obtained within the first 72 h is assigned a FPR of zero with a CI of 0–3. Steffen et al. [42] have questioned the cutoff value in patients who have undergone hypothermia, where in order to have 100 % specificity the cutoff needed to be raised to 78.9 μg/L. They did however find a similar cutoff value to that quoted by the AAN guidelines for patients who were not treated with therapeutic hypothermia.

Electroencephalography (EEG) and SSEP are the most common electrophysiologic study modalities employed in neuroprognostication. EEG has been evaluated in the prognostication of cardiac arrest survivors [16, 43–45], and has also led to some important clinical discoveries and emerging data seems to support its growing utility [46]. The 2006 AAN practice parameters assign EEG a FPR of 3 % with a CI of 0.9–11; making it the least predictive method to predict neurologic outcomes. Abend et al. [47] pooled four existing studies [16, 43, 44, 48] on EEG in hypoxic-ischemic encephalopathy patients who had undergone therapeutic hypothermia and found that 29 % of these patients had acute electrographic non-convulsive status epilepticus (NCSE). This has important clinical repercussions and illustrates the need for continuous electroencephalographic (cEEG) monitoring of these patients until they recover consciousness, as aggressive antiepileptic treatment should be instated to avoid falling into self fulfilling prophecies equating NCSE to a poor outcome [49]. This is important, as 6 % of patients in Abend et al.'s [47] pooled sample recovered consciousness including several with minimal residual neurologic deficits.

In contrast to the established guidelines and practice where SSEP is considered the most accurate ancillary method to aid clinical diagnosis of poor neurologic outcome (FPR 0.7 % CI 0–3.7), a recent study comparing SSEP and cEEG by Cloostermans et al. [50] found EEG to be superior in terms of its sensitivity to predict poor neurologic outcomes in hypoxic-ischemic encephalopathy treated with therapeutic hypothermia. Leithner et al. [51] demonstrated that neurologic recovery is possible despite absent or minimally present median nerve N20 responses (>24 h) after cardiac arrest. In the study by Bouwes et al. [39], the absence of N20 responses on SSEP during the hypothermia therapy had a FPR of 3 %.

Imaging studies have also been employed for prognostication mainly in the form of brain computed tomography (CT) and Magnetic Resonance Imaging (MRI). The use of imaging has not yet been formally incorporated into any guidelines however, and has been used based on individual clinician practice. At this stage these tools simply can provide supporting information in an overall multi-modal prognostication strategy, no decisions should be made based on solely one modality, but particularly not based on imaging alone. With regards to a multi-modal prognostication algorithm, there is no clear international consensus regarding how to best implement such a process [52, 53]. At this time we recommend the use of a multimodal approach based on individual center experience, expertise and available resources taking into account the limitations of all existing methods.

References

1. Williams GR, Spencer FC. The clinical use of hypothermia following cardiac arrest. Ann Surg. 1958;148(3):462–8.
2. Bernard S, Jones B, Horne M. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. Ann Emerg Med. 1997;30(2):146–53.

3. Yanagawa Y, Ishihara S, Norio H, Takino M, Kawakami M, Takasu A, et al. Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. Resuscitation. 1998;39(1–2):61–6.
4. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002;346(8):557–63.
5. The Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346(8):549–56.
6. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33 °C versus 36 °C after cardiac arrest. N Engl J Med. 2013;369(23):2197–206.
7. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, et al. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122(18 Suppl 3):S768–86.
8. Bro-Jeppesen J, Hassager C, Wanscher M, Søholm H, Thomsen JH, Lippert FK, et al. Post-hypothermia fever is associated with increased mortality after out-of-hospital cardiac arrest. Resuscitation. 2013;84(12):1734–40.
9. Leary M, Grossestreuer AV, Iannacone S, Gonzalez M, Shofer FS, Povey C, et al. Pyrexia and neurologic outcomes after therapeutic hypothermia for cardiac arrest. Resuscitation. 2013;84(8):1056–61.
10. Naples R, Ellison E, Brady WJ. Cranial computed tomography in the resuscitated patient with cardiac arrest. Am J Emerg Med. 2009;27(1):63–7.
11. Nordmark J, Rubertsson S, Mörtberg E, Nilsson P, Enblad P. Intracerebral monitoring in comatose patients treated with hypothermia after a cardiac arrest. Acta Anaesthesiol Scand. 2009;53(3):289–98.
12. Rittenberger JC, Popescu A, Brenner RP, Guyette FX, Callaway CW. Frequency and timing of nonconvulsive status epilepticus in comatose post-cardiac arrest subjects treated with hypothermia. Neurocrit Care. 2012;16(1):114–22.
13. Mani R, Schmitt SE, Mazer M, Putt ME, Gaieski DF. The frequency and timing of epileptiform activity on continuous electroencephalogram in comatose post-cardiac arrest syndrome patients treated with therapeutic hypothermia. Resuscitation. 2012;83(7):840–7.
14. Rossetti AO, Urbano LA, Delodder F, Kaplan PW, Oddo M. Prognostic value of continuous EEG monitoring during therapeutic hypothermia after cardiac arrest. Crit Care. 2010;14(5):R173.
15. Nielsen N, Sunde K, Hovdenes J, Riker RR, Rubertsson S, Stammet P, et al. Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia. Crit Care Med. 2011;39(1):57–64.
16. Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. Ann Neurol. 2010;67(3):301–7.
17. Lucas JM, Cocchi MN, Salciccioli J, Stanbridge JA, Geocadin RG, Herman ST, et al. Neurologic recovery after therapeutic hypothermia in patients with post-cardiac arrest myoclonus. Resuscitation. 2012;83(2):265–9.
18. Davies KJ, Walters JH, Kerslake IM, Greenwood R, Thomas MJC. Early antibiotics improve survival following out-of hospital cardiac arrest. Resuscitation. 2012;84(5):616–9.
19. Nolan JP, Morley PT, Vanden Hoek TL, Hickey RW, Kloeck WGJ, Billi J, et al. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the international liaison committee on resuscitation. Circulation. 2003;108:118–21.
20. Arrich J, Holzer M, Havel C, Müllner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation (2012 Review). Cochrane Database Syst Rev. 2012;(9):1–40.
21. Ian J, Nadkarni V. Targeted temperature management following cardiac arrest: an update -ILCOR. 2013.
22. Sendelbach S, Hearst MO, Johnson PJ, Unger BT, Mooney MR. Effects of variation in temperature management on cerebral performance category scores in patients who received therapeutic hypothermia post cardiac arrest. Resuscitation. 2012;83(7):829–34.
23. Garrett JS, Studnek JR, Blackwell T, Vandeventer S, Pearson DA, Heffner AC, et al. The association between intra-arrest therapeutic hypothermia and return of spontaneous circulation among individuals experiencing out of hospital cardiac arrest. Resuscitation. 2011;82(1):21–5.
24. Bruel C, Parienti J-J, Marie W, Arrot X, Daubin C, Du Cheyron D, et al. Mild hypothermia during advanced life support: a preliminary study in out-of-hospital cardiac arrest. Crit Care. 2008;12(1):R31.
25. Kämäräinen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Induction of therapeutic hypothermia during prehospital CPR using ice-cold intravenous fluid. Resuscitation. 2008;79(2):205–11.
26. Scolletta S, Taccone FS, Nordberg P, Donadello K, Vincent J-L, Castren M. Intra-arrest hypothermia during cardiac arrest: a systematic review. Crit Care. 2012;16(2):R41.
27. Castrén M, Nordberg P, Svensson L, Taccone F, Vincent J-L, Desruelles D, et al. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). Circulation. 2010;122(7):729–36.
28. Kuboyama K, Safar P, Radovsky A, Tisherman SA, Stezoski SW, Alexander H. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. Crit Care Med. 1993;21(9):1348–58.
29. Kim F, Nichol G, Maynard C, Hallstrom A, Kudenchuk PJ, Rea T, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. JAMA. 2013;98104:1–8.

30. Suffoletto B, Peberdy MA, van der Hoek T, Callaway C. Body temperature changes are associated with outcomes following in-hospital cardiac arrest and return of spontaneous circulation. Resuscitation. 2009;80(12):1365–70.
31. Zeiner A, Holzer M, Sterz F, Schörkhuber W, Eisenburger P, Havel C, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med. 2001;161(16):2007–12.
32. Hata JS, Shelsky CR, Hindman BJ, Smith TC, Simmons JS, Todd MM. A prospective, observational clinical trial of fever reduction to reduce systemic oxygen consumption in the setting of acute brain injury. Neurocrit Care. 2008;9(1):37–44.
33. Badjatia N. Hyperthermia and fever control in brain injury. Crit Care Med. 2009;37(Suppl):S250–7.
34. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. Crit Care Med. 2009;37(3):1101–20.
35. Bouwes A, Robillard LBM, Binnekade JM, de Pont A-CJM, Wieske L, Den Hartog AW, et al. The influence of rewarming after therapeutic hypothermia on outcome after cardiac arrest. Resuscitation. 2012;83(8):996–1000.
36. Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Böttiger BW, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation. Circulation. 2008;118(23):2452–83.
37. Mulder M, Gibbs HG, Smith SW, Dhaliwal R, Scott NL, Sprenkle MD, et al. Awakening and withdrawal of life-sustaining treatment in cardiac arrest survivors treated with therapeutic hypothermia*. Crit Care Med. 2014;42(12):2493–9.
38. Howell K, Grill E, Klein A-M, Straube A, Bender A. Rehabilitation outcome of anoxic-ischaemic encephalopathy survivors with prolonged disorders of consciousness. Resuscitation. 2013;84(10):1409–15.
39. Bouwes A, Binnekade JM, Kuiper MA, Bosch FH, Zandstra DF, Toornvliet AC, et al. Prognosis of coma after therapeutic hypothermia: a prospective cohort study. Ann Neurol. 2012;71(2):206–12.
40. Al Thenayan E, Savard M, Sharpe M, Norton L, Young B. Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest. Neurology. 2008;71(19):1535–7.
41. Rittenberger JC, Sangl J, Wheeler M, Guyette FX, Callaway CW. Association between clinical examination and outcome after cardiac arrest. Resuscitation. 2010;81(9):1128–32.
42. Steffen IG, Hasper D, Ploner CJ, Schefold JC, Dietz E, Martens F, et al. Mild therapeutic hypothermia alters neuron specific enolase as an outcome predictor after resuscitation: 97 prospective hypothermia patients compared to 133 historical non-hypothermia patients. Crit Care. 2010;14(2):R69.
43. Legriel S, Bruneel F, Sediri H, Hilly J, Abbosh N, Lagarrigue MH, et al. Early EEG monitoring for detecting postanoxic status epilepticus during therapeutic hypothermia: a pilot study. Neurocrit Care. 2009;11(3):338–44.
44. Wennervirta JE, Ermes MJ, Tiainen SM, Salmi TK, Hynninen MS, Särkelä MOK, et al. Hypothermia-treated cardiac arrest patients with good neurological outcome differ early in quantitative variables of EEG suppression and epileptiform activity. Crit Care Med. 2009;37(8):2427–35.
45. Oh SH, Park KN, Kim YM, Kim HJ, Youn CS, Kim SCSH, et al. The prognostic value of continuous amplitude-integrated electroencephalogram applied immediately after return of spontaneous circulation in therapeutic hypothermia-treated cardiac arrest patients. Resuscitation. 2012;84(2):200–5.
46. Tjepkema-Cloostermans MC, Hofmeijer J, Trof RJ, Blans MJ, Beishuizen A, van Putten MJ. Electroencephalogram predicts outcome in patients with postanoxic coma during mild therapeutic hypothermia*. Crit Care Med. 2015;43(1):159–67.
47. Abend NS, Mani R, Tschuda TN, Chang T, Topjian AA, Donnelly M, et al. EEG monitoring during therapeutic hypothermia in neonates, children, and adults. Am J Electroneurodiagnostic Technol. 2012;51(3):1–20.
48. Rundgren M, Westhall E, Cronberg T, Rosén I, Friberg H. Continuous amplitude-integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. Crit Care Med. 2010;38(9):1838–44.
49. Geocadin RG, Ritzl EK. Seizures and status epilepticus in post cardiac arrest syndrome: therapeutic opportunities to improve outcome or basis to withhold life sustaining therapies? Resuscitation. 2012;83(7):791–2.
50. Cloostermans MC, van Meulen FB, Eertman CJ, Hom HW, van Putten MJAM. Continuous electroencephalography monitoring for early prediction of neurological outcome in postanoxic patients after cardiac arrest: a prospective cohort study. Crit Care Med. 2012;40(10):2867–75.
51. Leithner C, Ploner CJ, Hasper D, Storm C. Does hypothermia influence the predictive value of bilateral absent N20 after cardiac arrest? Neurology. 2010;74(12):965–9.
52. Oddo M, Rossetti AO. Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia. Crit Care Med. 2014;42(6):1340–7.
53. Cronberg T, Brizzi M, Liedholm LJ, Rosén I, Rubertsson S, Rylander C, et al. Neurological prognostication after cardiac arrest--recommendations from the Swedish Resuscitation Council. Resuscitation. 2013;84(7):867–72.

Part V

Renal Disease

John A. Kellum

42 Traditional and Novel Tools for Diagnosis of Acute Kidney Injury

Fadi A. Tohme and John A. Kellum

Case Presentation

A 58-year-old male with unknown past medical history was admitted to the intensive care unit after he had a witnessed seizure in a parking lot. When paramedics arrived, his blood pressure was 213/115 mmHg. He was unresponsive. CT scan of the head without IV contrast showed a large right parietal lobe hemorrhage with mild midline shift. Laboratory exam revealed a WBC count of 13.2×10^9/L, Hemoglobin 10.2 g/dL, Platelets $178{,}000 \times 10^6$/L. Serum creatinine was 1.8 mg/dL and blood urea nitrogen (BUN) 41 mg/dL. Baseline serum creatinine was unknown. BMI was 27.3. An indwelling urinary catheter was placed and yielded 50 cc of urine. He was intubated and treated with calcium channel blockers, anti-seizure medications and intravenous fluid resuscitation. Twelve hours after admission, he had produced 150 cc of urine, and his repeat labs showed a serum creatinine of 2.2 mg/dL and a BUN of 47 mg/dL. A renal ultrasound showed normal sized kidneys, with increase in echogenicity of the renal cortex compared to the liver parenchyma, but no hydronephrosis. Urinalysis and urine microscopy revealed 1+ protein, no blood or cellular casts.

Question What establishes the diagnosis of Acute Kidney Injury in this case?

Answer Increase in serum creatinine and oliguria.

Criteria for diagnosis of acute kidney injury (AKI) include a 1.5 fold increase in serum creatinine compared to baseline (within the prior 7 days), an absolute increase in serum creatinine (SCr) by 0.3 mg/dL (26.5 μmol/L) or more (within 48 h) or a decrease in urine output to less than 0.5 cc/Kg/h for 6–12 h. In this case, SCr was elevated on admission (1.8 mg/dL), but it was not clear whether this represented acute kidney injury or Chronic Kidney Disease (CKD). Low urine output through the indwelling urinary catheter initially and over the next few hours after admission was an important first clue to the diagnosis of AKI. Subsequent increase in SCr by ≥0.3 mg/dL (from 1.8 to 2.2 mg/dL) confirmed the diagnosis. When baseline creatinine is not known, both renal ultrasonography and urine sediment examination can provide useful clues on the acuity of kidney injury. In this case, the increase in renal cortex echogenicity and presence of mild proteinuria suggested the presence of some

F.A. Tohme
Renal & Electrolyte Division,
University of Pittsburgh Medical Center,
Pittsburgh, PA, USA

J.A. Kellum (✉)
Critical Care Research, Center for Critical Care Nephrology, Critical Care Medicine,
University of Pittsburgh, Pittsburgh, PA, USA
e-mail: kellum@pitt.edu; robertsondc@upmc.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_42

degree of chronic kidney dysfunction prior to admission. Therefore, this patient probably had acute kidney injury superimposed on CKD.

Principles of Management

Serum Creatinine and Urine Output

Despite having several limitations, changes in serum creatinine and urine output remain the backbone of diagnosis of acute kidney injury. In 2004, the RIFLE (Risk Injury Failure Loss End-stage renal disease) criteria were published [1], and included either change in serum creatinine (1.5 fold increase or more) or urine output (less than 0.5 mL/Kg/h for 6 h) as diagnostic criteria for AKI. Including both urine output and SCr in the definition of AKI increased the sensitivity of AKI diagnosis [2] but also recognized that AKI can be non-oliguric in 40–60 % of cases [3, 4]. Whether actual body weight or ideal body weight should be used to judge urine output is a subject of debate. Using actual body weight does increase the sensitivity of AKI diagnosis but will decrease specificity [5]. One shortcoming of the RIFLE classification was its inaccuracy in patients with preexisting CKD: a patient with a baseline SCr of 2.2 mg/dL would require an increase in SCr to 3.3 mg/dL in order to be at risk for AKI (RIFLE-R). For this reason, the AKI Network (AKIN) proposed a modification to RIFLE in 2007 that would also classify AKI when a small increase in creatinine (0.3 mg/dl or greater) is observed in a short period of time (48 h or less) [6]. The AKIN group indicated two important caveats: excluding urinary obstruction when urine output is the sole criteria used to define AKI, and application of diagnostic criteria only after volume status has been optimized [6]. In 2012, in an effort to harmonize RIFLE, AKIN and pRIFLE (a modification for pediatrics), Kidney Disease Improving Global Outcomes (KDIGO) proposed a unified version of these rules [7] (Table 42.1).

Blood Urea Nitrogen (BUN) is commonly used as a marker for AKI, despite being affected by many non-renal factors (protein intake, catabolic state, volume status etc.). The ratio of BUN to SCr, similarly to urine chemistry (fractional excretion of sodium and urea) and urine microscopy are useful tools for workup of AKI. Nonetheless, BUN, urine studies and kidney biopsy are rarely helpful in establishing the diagnosis of AKI in clinical practice.

Table 42.1 Definition of AKI per KDIGO guidelines

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥0.3 mg/dl (>26.5 μmol/l) increase	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (353.6 μmol/l) OR Initiation of renal replacement therapy *OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m²*	<0.3 ml/kg/h for ≥24 h OR Anuria for ≥12 h

Minimum criteria for Acute Kidney Injury include an Increase in SCr by ≥0.3 mg/dl (>26.5 μmol/l) observed within 48 h; or an Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or Urine volume <0.5 ml/kg/h for 6 h

Despite the usefulness of RIFLE, AKIN and KDIGO criteria, clinical judgment remains a key component of AKI diagnosis. Diagnostic criteria provide a "frame of reference" for the clinician and are essential for large epidemiological studies and quality improvement projects. Nevertheless, those criteria do not take into account the patient's clinical course and response to therapy, which are often key to establishing or refuting the diagnosis of AKI.

Relationship Between Serum Creatinine and Urine Output

Several studies have demonstrated that oliguric AKI carries a worse prognosis compared to non-oliguric AKI. In other words, the presence of the two components of the definition of AKI is

Table 42.2 Relationship between urine output and serum creatinine criteria and clinical outcomes

KDIGO Stage		Urine Output Only				
		No AKI	Stage 1	Stage 2	Stage 3	Total
Serum Creatinine Only	No AKI	8,179	3,158	5,421	440	17,198
	Dead	4.3%	5.3%	7.9%	17.7%	5.9%
	RRT	0.0%	0.0%	0.1%	1.1%	0.1%
	Stage 1	1,889	1,262	3,485	842	7,478
	Dead	8.0%	11.3%	13.0%	32.1%	13.6%
	RRT	0.3%	0.7%	0.6%	10.9%	1.7%
	Stage 2	618	476	1,533	831	3,458
	Dead	11.3%	23.9%	21.5%	44.2%	25.5%
	RRT	1.0%	1.3%	1.7%	21.7%	6.3%
	Stage 3	371	321	1,019	2,200	3,911
	Dead	11.6%	38.6%	28.0%	51.1%	40.3%
	RRT	3.2%	17.8%	14.2%	55.3%	36.6%
	Total	11,057	5,217	11,458	4,313	32,045
	Dead	5.6%	10.5%	13.0%	42.6%	14.0%
	RRT	0.3%	1.4%	1.7%	34.6%	5.6%

Source: Kellum et al. [8]
Shown are the number of patients, % hospital mortality, and % renal replacement therapy (RRT) for patients by maximum acute kidney injury (AKI) criteria (UO, SC, or both). Colors denote similar outcome patterns

associated with worse outcomes [3, 8]. Isolated oliguria without subsequent increase in SCr still appears to be associated with a decrease in 1-year survival [8]. These results further validate the role of urine output in diagnosing and staging of AKI (Table 42.2).

Differentiating Between AKI and CKD

Renal ultrasonography is a useful tool for differentiation of CKD from AKI. When no information about baseline renal function is available, findings such as a small kidney size and an

increased echogenicity of the renal cortex compared to the liver parenchyma are good surrogates of chronic irreversible kidney disease [9]. The caveat here is that one cannot rule out superimposed AKI on CKD. Nevertheless, this remains useful information in diagnosing and classifying the severity of AKI. Oliguria and anuria are suggestive of AKI. Other parameters such as serum calcium and phosphorus, intact parathyroid hormone (iPTH) levels and hemoglobin are less helpful for differentiation between AKI and CKD. A group in Turkey suggested that setting the cutoff for intact PTH as 170 pg/mL or more could be a sensitive and specific way to distinguish CKD from AKI [10].

Clinical Use of Novel Biomarkers

There is currently a multitude of well-validated biomarkers that are able to predict, diagnose early, differentiate the severity and provide information on the course and outcomes of AKI. Despite reasonable performance, these biomarkers have yet to become established in clinical practice, despite their availability in certain regions of the world [11, 12]. The 10th Acute Dialysis Quality Initiative (ADQI) meeting in 2014 examined the discrepancy between the number of biomarkers that have been validated and their limited clinical application till this moment [13]. Ideally, "damage biomarkers" should be incorporated with "functional biomarkers" (such as urine output, SCr) to improve management of AKI. Incorporation of AKI biomarkers, or possibly a combination of those biomarkers, into clinical tools (such as the incorporation of cardiac troponins in the TIMI risk score for unstable angina and non-ST elevation myocardial infarction) that will guide management of AKI is the next step for those biomarkers. Cost is also a consideration, but the costs associated with current practice, which often includes testing such as urine chemistries, must also be considered. Finally, the costs associated with delayed recognition of AKI are also likely to be considerable. In late 2014, the US Food and Drug Administration announced the clearance of the first biomarker for AKI, urine [TIMP-2] [IGFBP7] (trade name NephroCheck™). The extent to which this test changes the existing paradigm is still unknown but the test characteristics are superior to previous markers [10].

Evidence Contour

Some questions surrounding the diagnosis of AKI remain subject for debate and for further investigation.

Determining Baseline Serum Creatinine

KDIGO guidelines emphasize the use of relative changes in SCr rather than absolute numbers for diagnosis and classification of AKI. Determining baseline SCr is therefore a necessary step to the diagnosis of AKI. It is not uncommon that information about baseline renal function is not available, especially upon initial evaluation of critically ill patients. The ADQI group suggested that an estimated glomerular filtration rate (eGFR) of 75 ml/mn/1.73 m^2 be assumed for such patients and calculating their baseline SCr using the Modification of Diet in Renal Disease (MDRD) formula [6]. The problem with this method is that CKD is one of the most important risk factors for AKI [14], and assuming that patients with AKI have a near-normal baseline eGFR will under-estimate their baseline SCr and therefore over-estimate the incidence of AKI [15]. Using this method in the case example would have resulted in overestimation of the severity of AKI by assuming a normal eGFR at baseline. Thus, this method should be avoided in patients with a suspicion of CKD. Conversely, using the minimum inpatient SCr or the admission SCr tends to underdiagnose AKI and is also suboptimal [15]. Multiple imputation is a commonly used method in statistical analyses that uses known patient characteristics to estimate

missing data points. This method has shown promise in its ability to determine baseline SCr in a more accurate way [16], but is not widely used in clinical practice to this date. Currently the best method will depend on the patient in question and require clinical judgment.

Imaging Techniques for Diagnosis of AKI

Several studies have examined the utility of resistive indices (RI) through renal Doppler ultrasonography in diagnosing or predicting AKI prior to alteration of functional markers such as urine output and SCr [17–19]. Unfortunately, resistive indices are affected by a wide variety of factors [20, 21], which limits their specificity and usefulness in the clinical setting. Assessing kidney function or GFR through imaging is also an appealing idea, as information about the structure, perfusion and differential function of both kidneys may also be obtained. Functional magnetic resonance (functional MR) imaging is a promising tool for evaluation of glomerular filtration rate and renal oxygenation but is limited by need for exogenous contrast media and is still largely experimental [22]. Real-time GFR measurement using fluorescent markers is also a promising method but is still limited to animal models of AKI [23–25]. Contrast-enhanced ultrasonography (CEUS) is a new technique that can identify alterations in renal perfusion and has been applied in renal transplantation to differentiate between rejection and acute tubular necrosis. CEUS has yet to be validated for AKI in the ICU setting [26].

Emerging Role for Novel Biomarkers

Recognizing the poor sensitivity of functional markers (urine output and SCr) for early diagnosis of AKI, there has been a growing interest in identifying better biomarkers of AKI. Biomarkers can be divided into three categories: those that detect "functional changes" (SCr, urine output or serum cystatin C), those that detect "kidney damage" (urine and serum neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule 1 [KIM-1] and liver-type fatty-acid binding protein [LFABP] among others), and those that detect "kidney stress" (urinary insulin-like growth factor-binding protein 7 [IGFBP7] and tissue inhibitor of metalloproteinases-2 [TIMP-2]). Measuring "kidney damage" while urine output and SCr (functional markers) are still within normal ranges allows detection of "subclinical AKI". On the other side, "functional AKI" is when there is oliguria or elevation in SCr, but damage markers have not risen yet. This could well represent a normal adaptive mechanism by the kidneys in response to a certain stressor, such as hypotension, hypovolemia or changes in renal blood flow. Cell cycle arrest biomarkers (such as TIMP-2 and IGFBP7) have been suggested to detect "kidney stress" prior to the incurrence of "damage". Cell cycle arrest is a protective mechanism that eukaryotic cells use in response to injury and stress to halt cell division. TIMP-2 and IGFBP7 are expressed in tubular cells in response to DNA and other signals, increasing the expression of p proteins, which block the effect of cyclin-dependent protein kinase complexes, thereby resulting in G1 cycle arrest. Prediction of moderate to severe AKI (KDIGO stage 2–3) 12 h after the sample was better using the [TIMP-2] [IGFBP7] product compared to previously described markers [27]. The "ideal biomarker" would be one that will rise very shortly after the episode of AKI, improve rapidly with resolution of AKI, have a high sensitivity and specificity, be highly reproducible, easily obtainable and most importantly be able to predict severity and affect management and outcomes. Since one single biomarker is unlikely to provide all this information, a combination of biomarkers has often been used in clinical trials [27, 28]. The extent of which current and future biomarkers will improve the existing algorithm for diagnosis of AKI has yet to be determined (Fig. 42.1).

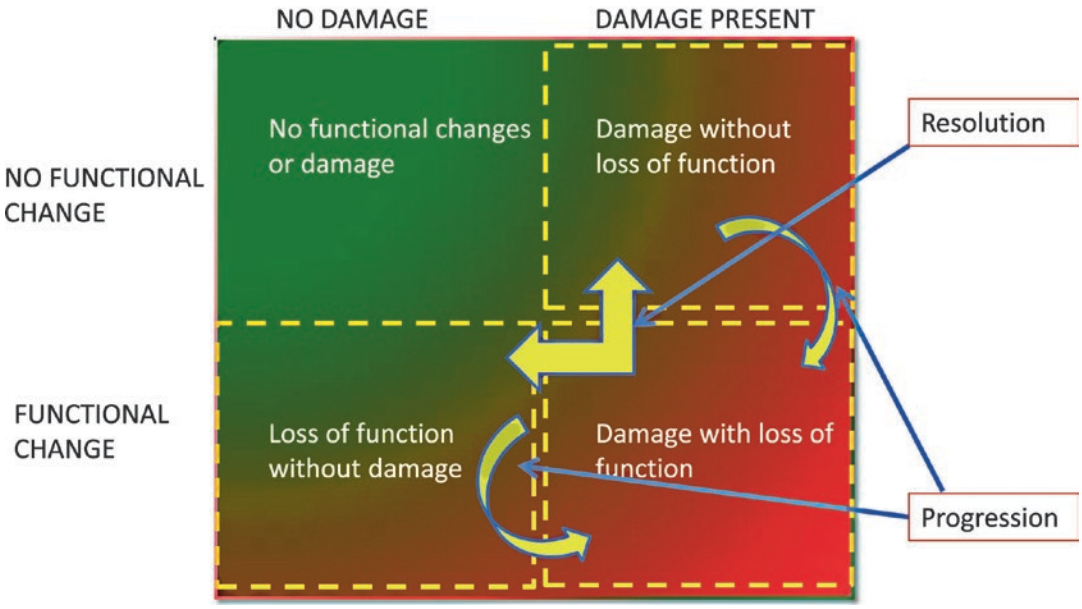


Fig. 42.1 Proposed framework for evaluating AKI based on Biomarkers. A combination of kidney functional and damage markers simultaneously provides a simple method to stratify patients with AKI. At initial presentation, patients would be evaluated in terms of these two domains, and then could be assessed over time to monitor their transitions across the domains (Adapted from the 10th ADQI meeting report)

References

1. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8:R204–12.
2. Wlodzimirow KA, et al. A comparison of RIFLE with and without urine output criteria for acute kidney injury in critically ill patients. Crit Care. 2012; 16:R200.
3. Morgan DJR, Ho KM. A comparison of nonoliguric and oliguric severe acute kidney injury according to the risk injury failure loss end-stage (RIFLE) criteria. Nephron Clin Pract. 2010;115:c59–65.
4. Ulusoy S, Arı D, Ozkan G, Cansız M, Kaynar K. The frequency and outcome of acute kidney injury in a tertiary hospital: which factors affect mortality? Artif Organs. 2015;39:n/a–n/a.
5. Thongprayoon C, Cheungpasitporn W, Akhoundi A, Ahmed AH, Kashani KB. Actual versus ideal body weight for acute kidney injury diagnosis and classification in critically ill patients. BMC Nephrol. 2014; 15:176.
6. Mehta RL, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
7. Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012; 2:1–138.
8. Kellum JA, et al. Classifying AKI by urine output versus serum creatinine level. J Am Soc Nephrol. 2015:1–8. doi:10.1681/ASN.2014070724.
9. Moghazi S, et al. Correlation of renal histopathology with sonographic findings. Kidney Int. 2005;67: 1515–20.
10. Ozmen S, Danis R, Akin D, Cil T, Yazanel O. Parathyroid hormone as a marker for the differential diagnosis of acute and chronic renal failure. Ren Fail. 2007;29:509–12.
11. Singer E, et al. Urinary neutrophil gelatinase-associated lipocalin distinguishes pre-renal from intrinsic renal failure and predicts outcomes. Kidney Int. 2011;80:405–14.
12. Vaidya VS, et al. Urinary biomarkers for sensitive and specific detection of acute kidney injury in humans. Clin Transl Sci. 2008;1:200–8.
13. Murray PT, et al. Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th Acute Dialysis Quality Initiative consensus conference. Kidney Int. 2014;85:513–21.
14. Singh P, Rifkin DE, Blantz RC. Chronic kidney disease: an inherent risk factor for acute kidney injury? Clin J Am Soc Nephrol. 2010;5:1690–5.

15. Siew ED, et al. Commonly used surrogates for baseline renal function affect the classification and prognosis of acute kidney injury. Kidney Int. 2010;77:536–42.
16. Siew ED, et al. Use of multiple imputation method to improve estimation of missing baseline serum creatinine in acute kidney injury research. Clin J Am Soc Nephrol. 2013;8:10–8.
17. Schnell D, et al. Renal resistive index better predicts the occurrence of acute kidney injury than cystatin C. Shock. 2012;38:592–7.
18. Bossard G, Bourgoin P, Corbeau JJ, Huntzinger J, Beydon L. Early detection of postoperative acute kidney injury by Doppler renal resistive index in cardiac surgery with cardiopulmonary bypass. Br J Anaesth. 2011;107:891–8.
19. Lerolle N, et al. Renal failure in septic shock: predictive value of Doppler-based renal arterial resistive index. Intensive Care Med. 2006;32:1553–9.
20. Heine GH, Gerhart MK, Ulrich C, Köhler H, Girndt M. Renal Doppler resistance indices are associated with systemic atherosclerosis in kidney transplant recipients. Kidney Int. 2005;68:878–85.
21. Thalhammer C, et al. Duplex sonography after living donor kidney transplantation: new insights in the early postoperative phase. Ultraschall Med. 2006;27:141–5.
22. Ebrahimi B, Textor SC, Lerman LO. Renal relevant radiology: renal functional magnetic resonance imaging. Clin J Am Soc Nephrol. 2014;9:395–405.
23. Schock-Kusch D, et al. Transcutaneous assessment of renal function in conscious rats with a device for measuring FITC-sinistrin disappearance curves. Kidney Int. 2011;79:1254–8.
24. Rabito CA, Chen Y, Schomacker KT, Modell MD. Optical, real-time monitoring of the glomerular filtration rate. Appl Opt. 2005;44:5956–65.
25. Wang E, et al. A portable fiberoptic ratiometric fluorescence analyzer provides rapid point-of-care determination of glomerular filtration rate in large animals. Kidney Int. 2012;81:112–7.
26. Schneider A, Johnson L, Goodwin M, Schelleman A, Bellomo R. Bench-to-bedside review: contrast enhanced ultrasonography–a promising technique to assess renal perfusion in the ICU. Crit Care. 2011;15:157.
27. Kashani K, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care. 2013;17:R25.
28. Prowle JR, et al. Combination of biomarkers for diagnosis of acute kidney injury after cardiopulmonary bypass. Ren Fail. 2015;37:408–16.

Management of Acute Kidney Injury

43

Fadi A. Tohme and John A. Kellum

Case Presentation

A 58-year-old female with a history of obesity, type 2 diabetes mellitus, essential hypertension and locally advanced uterine cancer was admitted to the intensive care unit with fevers, malaise, nausea and decreased urine output over the last 2 days. Her initial evaluation was relevant for a blood pressure of 87/48, pulse of 92/min and temperature of 101.3 F (38.5 C). She was alert, but appeared ill and confused. There was an implantable venous infusion 'port' in the right chest, no rales, costovertebral angle tenderness or lower extremity edema. Laboratory exam revealed a WBC count of 17.8 × 10^9/L, Hemoglobin of 8.8 g/dL, Platelets of 212,000 × 10^6/L. Serum sodium was 135 mEq/L, potassium 6.3 mEq/L, chloride 100 mEq/L, total carbon dioxide 12 mEq/L, blood urea nitrogen (BUN) 97 mg/dL and serum creatinine (SCr) 4.3 mg/dL. Serum glucose was 270 mg/dL and lactic acid 4.6 mEq/L. She had an indwelling urinary catheter placed which yielded 50 cc of urine. Blood and urine cultures were sent. She was started on broad-spectrum intravenous antibiotics and a continuous infusion of insulin.

Question What are the basics of management of Acute Kidney Injury (AKI) in this case?

Answer Ascertainment and treatment of the underlying cause together with prevention of further injury and supportive care including renal replacement therapy.

In this patient with septic shock the treating physician must simultaneously resuscitate and treat the source of sepsis while ruling out other treatable causes of AKI. This patient is in shock as evidenced by a low arterial blood pressure (made more profound by the history of hypertension) and hyperlactatemia which in a resting patient is evidence of cellular stress likely a function of inadequate tissue perfusion. The initial management involves the infusion of intravenous isotonic crystalloids and if necessary, vasopressors may be added to preserve tissue perfusion, if hypotension persists despite restoration of intravascular volume. Care should be taken to avoid fluid overload which is a significant risk in a patient with AKI. At the same time unresuscitated shock will injure multiple tissues including the kidneys.

Sepsis is a leading cause of AKI and the most likely etiology given the case presented. However, other etiologies need to be excluded. For example, what medications was the patient taking? In addition, timely detection and relief

F.A. Tohme
Renal & Electrolyte Division, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

J.A. Kellum (✉)
Critical Care Research, Center for Critical Care Nephrology, Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA
e-mail: kellum@pitt.edu; robertsondc@upmc.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_43

of urinary obstruction is important, especially in this patient with a history of locally advanced gynecologic cancer, which puts her at risk for ureteral obstruction.

Complications of AKI such as hyperkalemia, volume overload and metabolic acidosis are managed concomitantly. Attention must be paid to prevent further injury to the kidneys (discontinuation of angiotensin converting enzyme [ACE] inhibitors, aldosterone receptor blockers [ARBs], non-steroidal anti-inflammatory drugs (NSAIDs), avoidance of radiographic contrast media etc.) and to adjust dosage of renally excreted medications. Renal replacement therapy should be instituted when (or preferably before) complications from AKI arise despite medical management. This patient was treated with intravenous boluses of lactated Ringer's (a physiologically balanced crystalloid solution), but her mean arterial pressure (MAP) remained low despite fluid resuscitation. She was started on norepinephrine with a goal to keep her MAP above 65–70 mmHg. Insulin and isotonic fluids were used to correct hyperkalemia. Repeat potassium was 5.2 mEq/L. A renal ultrasound showed normal kidney size with no hydronephrosis. Twenty-four hours after presentation, she became hypoxic (requiring 6 l of oxygen) with chest x-ray showing pulmonary edema. She was given IV loop diuretics, but remained oliguric, and her SCr increased to 5.1 mg/dL. A temporary hemodialysis catheter was placed and she was started on continuous venovenous hemodiafiltration (CVVHDF) at a dose of 25 cc/Kg/h. Five days after admission, she was no longer requiring vasopressor support and was no longer volume overloaded. Urine output progressively increased, renal replacement therapy was discontinued, and SCr returned to her baseline value of 1.1 mg/dL.

Principles of Management

Intravenous Fluids and Vasopressors

The classic paradigm that explains acute reduction in glomerular filtration rate (AKI) in critically ill patients is centered on decreased renal perfusion that exceeds the ability of kidneys to auto-regulate in the setting of shock. Septic shock, major surgery, hypovolemia and heart failure are the leading causes of AKI in the ICU setting [1] and are all characterized by hypotension and shock. Our understanding of the pathophysiology of AKI has markedly improved over the last decade, and factors in addition to decreased renal perfusion such as inflammation and microcirculation dysfunction – to name a few – have surfaced as important contributors to AKI. Few strategies are available in clinical practice to counteract those newly recognized factors, and reversal of shock while avoiding harm from fluid overload remains the most widely accepted first step in management of AKI in such settings. This is done through administration of isotonic intravenous fluids in hypovolemic conditions or in vasoplegic shock (septic shock, severe pancreatitis, anaphylaxis, burns). Several factors should be kept in mind when administering intravenous fluids to a patient with AKI. First, that vasoplegic shock might or might not be fluid-responsive. Second, that restoration of renal tissue perfusion might or might not reverse AKI, especially in the presence of established "damage" to the kidneys. In addition, once kidneys are injured, resuscitation milestones like resolution of oliguria may be unreliable [2]. Lastly, intravenous fluids can lead to fluid overload, which is a negative prognostic factor in AKI. This is especially true for elderly individuals, or when heart failure or cardiogenic shock is suspected.

Initial concerns that the use of vasoactive medications (such as norepinephrine and vasopressin) might cause further vasoconstriction and worsening AKI by reducing renal blood flow are not valid [3]. An increase in renal blood flow was demonstrated in experimental models of sepsis when dogs were infused with norepinephrine at clinically relevant doses. This is thought to be a result of an improvement in blood pressure, which through the baroreceptor reflex decreases sympathetic tone and improves renal blood flow [4]. Norepinephrine and vasopressin have also been used in conjunction with intravenous albumin for treatment of the hepatorenal syndrome, where splanchnic vasodilation is thought to play an essential role in the development of AKI. A meta-analysis including 154 patients with type I hepatorenal syndrome showed similar rates of resolution of AKI with norepinephrine plus

albumin when compared to terlipressin (a vasopressin analogue) plus albumin, with lower cost and complication rates [5]. It is important to note that despite potential reversal of AKI, vasopressors have a questionable effect on mortality in patients with type I hepatorenal syndrome, and that liver transplantation remains the mainstay of therapy in this condition.

Consider Alternative Etiologies and Specific Treatments for AKI

While septic shock is the most likely etiology of AKI in this patient, care should be taken not to miss other important causes. Drugs and radiographic contrast media are among the most common causes of AKI, and nephrotoxicity from antimicrobial agents is an important contributor [6]. Obstructive uropathy is an uncommon cause of AKI in the ICU setting [1]. Nevertheless, it is a potentially reversible cause of AKI, and should be suspected and alleviated in the appropriate clinical setting (solitary kidney, active gynecologic, gastrointestinal or urological cancer, known nephrolithiasis). Systematic use of renal ultrasonography to detect hydronephrosis in patients with AKI is not recommended, as it is unlikely to change management or to be cost-efficient [7]. Primary or secondary glomerular diseases are also uncommon causes of AKI in the ICU. On the other hand, It is essential to suspect glomerular disease in the appropriate clinical setting (proteinuria, hematuria, multi-organ involvement), as specific treatments like immunosuppressive agents and plasma exchange can often alter the course of AKI [8]. Similarly, specific treatments may exist for other etiologies of AKI, such as the hepatorenal syndrome, cardiorenal syndrome or acute interstitial nephritis, but are beyond the scope of this chapter.

Prevention of Further Injury

The lack of effective therapies to reverse AKI makes prevention of further kidney damage an essential step in management. Radiocontrast agent use is avoided whenever possible. This can be done through use of alternate imaging modalities or use of non-nephrotoxic radiocontrast agents such as carbon dioxide if available [9]. In cases where use of radiocontrast agent is unavoidable, the dose of contrast agent administered is minimized, and isotonic intravenous fluids are given before and after radiocontrast administration. In patients with AKI, drugs such as NSAIDs, ACE inhibitors, ARBs, aminoglycosides, amphotericin B and intravenous acyclovir should be avoided whenever possible. Scleroderma renal crisis is an exception to this rule, as ACE inhibitors (captopril) are considered the treatment of choice despite the common presence of AKI. Failing to adjust dosage of renally eliminated medications in AKI is common and frequently leads to adverse drug events. Worsening AKI and hypotension appear to be the most common preventable adverse drug events [10]. Special attention to medication dosage is therefore essential in AKI, especially for certain medication classes such as antimicrobials, opiates and antithrombotics (Fig. 43.1).

Diuretics

Loop diuretics have been hypothesized to improve AKI through washing the debris blocking renal tubules and decreasing oxygen consumption at the tubular level [11]. Those theories have been disproved by randomized controlled trials, and Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommends against the use of diuretics for prevention or treatment of AKI [12]. Nevertheless, diuretics are still commonly used in patients with AKI[14], usually to help manage volume overload. Patients with both AKI and acute lung injury, for example, might benefit from loop diuretics as part of a lung-protective ventilation strategy [14]. Another possible role for loop diuretics in AKI is in patients with decompensated heart failure or the cardiorenal syndrome. Response to diuretics in this syndrome varies, as SCr might increase, stay the same or improve. Two explanations have been proposed for the improvement in SCr in patients with decompensated heart failure and AKI that receive diuretics: reduction in intra-abdominal and renal venous pressure, and

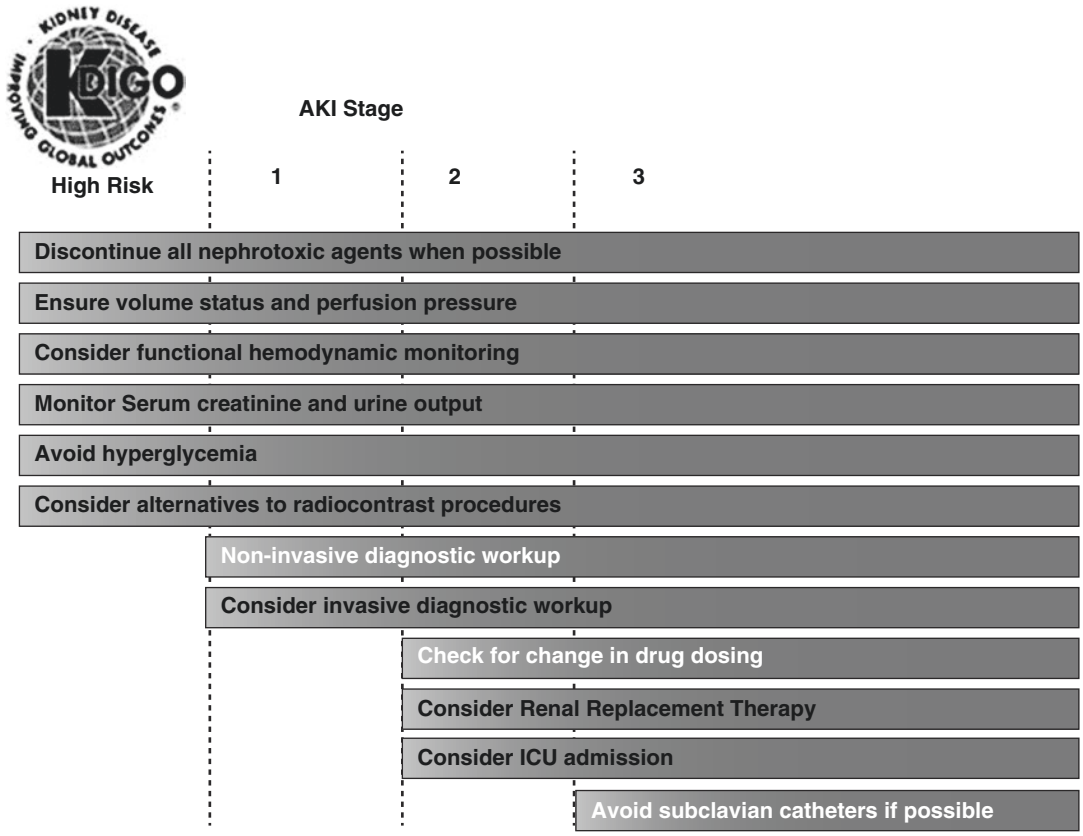


Fig. 43.1 Stage-based management of AKI (From Section 2: AKI Definition. *Kidney Int Suppl* 2012;2(1):19–36. Reprinted with permission from Elsevier)

improvement of LV filling and therefore cardiac output through reduction of RV dilation (ventricular interdependence). The effect of diuretic therapy on survival in patients with the cardiorenal syndrome is not well established and requires further exploration. It is important to remember that judicious use of intravenous fluids will often avoid the need for diuretics.

Medical Management of Complications of AKI

Volume overload, hyperkalemia, metabolic acidosis, hyperphosphatemia, hypocalcemia and bleeding disorders are the main complications of AKI. Their management is an integral part of treating AKI. Volume overload is often managed with IV loop diuretics (see "Diuretics" above). Nevertheless, a trial of diuretics should not be viewed as a mandatory prerequisite prior to the initiation of renal replacement therapy. Prompt initiation of dialysis in an anuric patient with severe volume overload would be a good example. Hyperkalemia is commonly seen in oliguric patients with active tissue breakdown, such as tumor lysis syndrome and rhabdomyolysis. Because hyperkalemia is often asymptomatic, its first manifestations can often be ventricular dysrhythmias and death, which is why it should rapidly be recognized and promptly treated. Transient and rapidly acting therapies include intravenous insulin plus glucose (if serum glucose is less than 250 mg/dL) and beta-2 agonists such as high-dose nebulized albuterol (10–20 mg). A continuous infusion of intravenous bicarbonate can lower potassium levels after 4–6 h in patients with metabolic acidosis [15]. It is

not efficacious in the first hour of infusion and is not recommended for rapid treatment of hyperkalemia [16]. A calcium infusion is administered to decrease the incidence of cardiac dysrhythmias when EKG changes such as prolonged QRS interval or absence of P waves are present. Metabolic acidosis often complicates AKI, but can also result from shock and lactic acidosis, or chloride administration, all of which are commonly present with AKI. Use of exogenous bicarbonate for the treatment of metabolic acidosis is very controversial, and is usually reserved for severe acidosis with an arterial pH < 7.1. Bicarbonate infusions can cause symptomatic hypocalcemia (decreased ionized calcium through increased binding of calcium to albumin) with potential cardiotoxicity, hypernatremia, volume overload and an increase in arterial and tissue capillary PCO_2. The rationale behind the use of bicarbonate therapy is that severe acidemia (pH < 7.1) is associated with hemodynamic instability and impaired response to catecholamines [17]. Severe hyperphosphatemia can potentially cause symptomatic hypocalcemia through precipitation of calcium and phosphate. Use of oral phosphate binders to treat hyperphosphatemia in AKI is based on expert opinion as there is no clear evidence that such treatment improves outcomes.

Renal Replacement Therapy

Dialysis is the treatment of choice for severe AKI, or when complications of AKI fail to respond to medical therapy. Commonly accepted indications for initiation of renal replacement therapy (RRT) include hyperkalemia (potassium > 6.5 mEq/L or rapidly increasing despite medical therapy), metabolic acidosis (pH < 7.1 despite bicarbonate therapy), volume overload unresponsive to diuretics, uremic symptoms and signs (pericarditis, altered mental status without an alternative explanation to uremia) and AKI in the setting of certain intoxications (such as ethylene glycol, methanol or lithium). KDIGO guidelines recommend considering the clinical context and trend of laboratory exams rather than a single cutoff for BUN and SCr when making the decision to initiate RRT [12]. The two commonly used modalities for RRT in the ICU setting are intermittent hemodialysis (iHD) and continuous renal replacement therapy (CRRT). The use of hemofiltration in CRRT offers the theoretical advantage of "convective" clearance of middleweight molecules, which is not well achieved with "diffusive" clearance of iHD. Inflammatory mediators and cytokines are examples of middle-sized molecules that are thought to have a deleterious role in septic patients. Randomized prospective trials have failed to show any superiority of CRRT to iHD in terms of survival and recovery of renal function [18, 19]. CRRT offers the potential advantages of less hypotension and more efficient volume removal in hemodynamically unstable patients [20], but this does not translate into increased survival compared to iHD. The choice of modality remains dependent on staff and equipment availability and differences in comfort level and expertise. Higher intensity hemodialysis does not seem to improve mortality or recovery of renal function and is associated with more electrolyte abnormalities such as hypophosphatemia [21]. A delivered effluent volume of 20–25 cc/Kg/h is recommended for CRRT (Fig. 43.2).

Evidence Contour

Choice of Intravenous Fluid Solution

The best type of intravenous fluids for management of AKI has been intensely investigated but remains controversial. KDIGO recommends using isotonic crystalloids rather than colloids for volume expansion, in the absence of hemorrhagic shock [12]. This is based on higher cost of intravenous albumin solutions and a randomized control trial of nearly 7000 patients that showed no difference in outcomes between resuscitation with 4 % human albumin and isotonic saline 28 days after randomization [22]. Other colloid formulations such as hydroxyethylstarch (HES) have no added benefit to isotonic crystalloids [23] and should be avoided, as there is a concern

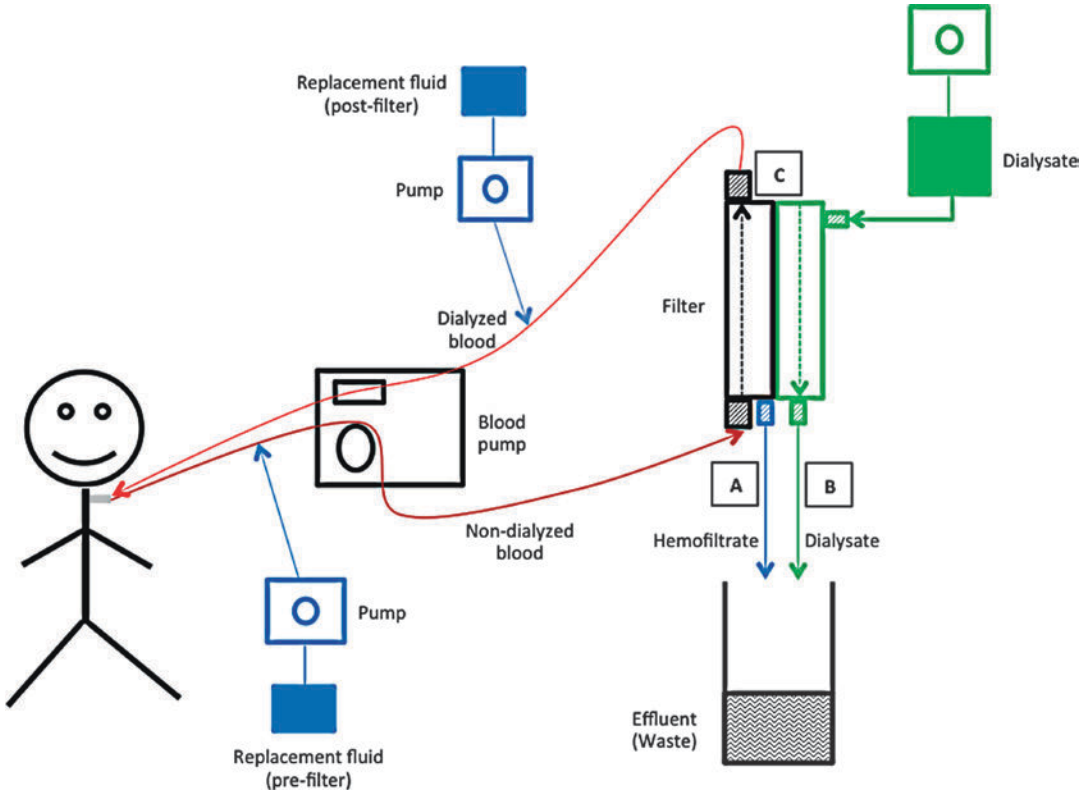


Fig. 43.2 Continuous renal replacement therapy circuits. (**a**) In continuous veno-venous hemofiltration (CVVH – *blue*), blood purification is achieved through "convection". The blood pump generates a pressure that allows passage of plasma water through the filter. Water drags toxins and electrolytes (solvent drag). Replacement fluids are given before and/or after the filter to prevent volume and electrolyte losses. (**b**) In continuous veno-venous hemodialysis (CVVHD – *green*), blood purification is achieved through "diffusion". A toxin-free fluid with appropriate amounts of electrolytes (dialysate) is pumped across the filter. Blood circulates inside the filter's hollow fibers, while dialysate circulates countercurrently outside of those fibers. Toxins and electrolyte follow a concentration gradient across this semi-permeable membrane and are eliminated through diffusion. There is no need for replacement fluids as there is no water loss or hemofiltration (**c**) Continuous veno-venous hemodiafiltration (CVVHDF – *blue* and *green*) is a combination of both methods. Both diffuse and convection are used for blood purification

for increased risk of AKI and mortality when such solutions are used in sepsis [24]. Isotonic normal saline has supra-physiologic contents of chloride: normal plasma has roughly 100 mEq/L of chloride compared to 142 mEq/L of chloride added to the plasma when 1 L of 0.9 % sodium chloride is administered (only 92 % of plasma is water). In a prospective study, a chloride-liberal strategy was associated with higher rates of AKI and need for RRT [25]. Avoidance of hyperchloremia and chloride-induced metabolic acidosis is an argument used by proponents of more physiologic or "balanced" solutions. Lactated Ringer's is a commonly used balanced solution (contains 109 mEq/L of chloride), but is slightly hypotonic, and is limited by the fact that it contains calcium, which prevents its co-administration with blood products. Non-calcium containing physiologic solutions such as plasmalyte are gaining popularity but have yet to show superiority compared to normal saline using hard outcomes such as mortality or need for RRT. A recent RCT that compared small volumes (approximately 2 L) of saline to plasmalyte in relatively low-risk patients failed to demonstrate any advantage with plasmalyte [26]. The amount of potassium that lactated Ringer's or plasmalyte contain is too small to cause clinically significant

Table 43.1 Composition of commonly used crystalloid and colloid solutions

	0.9 % saline	Lactated Ringer's	Plasmalyte	Albumin (human) 5 %
Sodium (mEq/L)	154	130	140	130–160
Chloride (mEq/L)	154	109	98	
Acetate (mEq/L)			27	
Lactate (mEq/L)		28		
Gluconate (mEq/L)			23	
Calcium (mEq/L)		3		
Potassium (mEq/L)		4	5	
Magnesium (mEq/L)			1.5	
Protein (g/L)				50

increases in serum potassium values. In kidney transplant recipients for example, normal saline was found to be associated with more hyperkalemia compared to lactated Ringer's [27]. This can be due to transcellular shifts of potassium associated with hyperchloremic acidosis (Table 43.1).

Nutrition in AKI

Initial reports suggested that early enteral nutrition (within 48 h from illness) could be beneficial in critically ill patients, at least in decreasing the rate of infections [28]. This remains controversial, especially with a recent large randomized trial showing no difference in mortality or infections between early nutrition through the enteral or parenteral routes [29]. Patients with AKI, especially those who require RRT, have protein hypercatabolism, which is driven by inflammation, stress and acidosis. They frequently have protein-calorie malnutrition [30], which is why they have been thought to be a group that might particularly benefit from early nutrition. This was confirmed by a large prospective study examining predictors of mortality in AKI patients, where patients who received enteral nutrition had an increased chance of survival [31].

Tight Glycemic Control

Hyperglycemia is associated with worse outcomes in critically ill patients, including patients with AKI [32]. Whether hyperglycemia is a contributor to those outcomes or only a marker of disease severity is unclear. Initial reports indicating less need for RRT with intensive insulin therapy in patients with AKI [33] were disproved by a large randomized controlled trial [34]. Glycemic control is probably beneficial in patients with AKI, but blood sugar values of 140–180 mg/dL should be targeted rather than 80–110 mg/dL. The latter target is associated with a higher risk of hypoglycemia and death [35].

Vasodilators and Growth Factor Interventions

Use of agents that cause renal vasodilation has been attempted to treat AKI. Low-dose dopamine has been studied in patients with AKI in different clinical settings. A placebo-controlled randomized study confirmed previous findings that low-dose dopamine offers no benefit in the treatment of AKI [36]. Other agents such as fenoldopam, atrial natriuretic peptide (ANP) and growth factors (recombinant human IGF-1) do not appear to be beneficial neither, and KDIGO recommends against their use in clinical practice [12].

Early Initiation of Dialysis

Prophylactic dialysis is the initiation of RRT in critically ill patients with AKI prior the development of "life-threatening complications" such as hyperkalemia, volume overload and acidosis. The role of such practice remains controversial and has not been validated in well-designed and adequately powered prospective randomized trials.

Retrospective analyses of large observational cohorts indicated that initiation of dialysis with a lower level of BUN (less than 76 mg/dL) provided a survival benefit [37]. Another report indicated that initiation of dialysis if urine output was less than 100 cc for 8 h after cardiac surgery was associated with better survival [38]. This contrasts to a randomized controlled trial that included 208 patients with AKI, and failed to show a survival benefit or a decrease in need for RRT after 3 months in the group that received early dialysis [39]. The small number of patients included in this trial does not make it powered enough to refute the potential benefit of early initiation of dialysis.

References

1. Uchino S et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294:813–8.
2. Srisawat N et al. Urinary biomarkers and renal recovery in critically ill patients with renal support. Clin J Am Soc Nephrol. 2011;6:1815–23.
3. Bellomo R, Wan L, May C. Vasoactive drugs and acute kidney injury. Crit Care Med. 2008;36:S179–86.
4. Bellomo R, Kellum JA, Wisniewski SR, Pinsky MR. Effects of norepinephrine on the renal vasculature in normal and endotoxemic dogs. Am J Respir Crit Care Med. 1999;159:1186–92.
5. Nassar Junior AP, Farias AQ, D' Albuquerque LAC, Carrilho FJ, Malbouisson LMS. Terlipressin versus norepinephrine in the treatment of hepatorenal syndrome: a systematic review and meta-analysis. PLoS One. 2014;9:e107466.
6. Bellomo R. The epidemiology of acute renal failure: 1975 versus 2005. Curr Opin Crit Care. 2006;12:557–60.
7. Licurse A et al. Renal ultrasonography in the evaluation of acute kidney injury: developing a risk stratification framework. Arch Intern Med. 2010;170:1900–7.
8. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. Kidney Inter Suppl. 2012;2;139–274.
9. Shaw DR, Kessel DO. The current status of the use of carbon dioxide in diagnostic and interventional angiographic procedures. Cardiovasc Intervent Radiol. 2006;29:323–31.
10. Cox ZL et al. Adverse drug events during AKI and its recovery. Clin J Am Soc Nephrol. 2013;8:1070–8.
11. Karajala V, Mansour W, Kellum JA. Diuretics in acute kidney injury. Minerva Anestesiol. 2009;75:251–7.
12. Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.
13. Mehta RL, Pascual MT, Soroko S, Chertow GM. Diuretics, mortality, and nonrecovery of renal function in acute renal failure. JAMA. 2002;288:2547–53.
14. Grams ME, Estrella MM, Coresh J, Brower RG, Liu KD. Fluid balance, diuretic use, and mortality in acute kidney injury. Clin J Am Soc Nephrol. 2011;6:966–73.
15. Blumberg A, Weidmann P, Ferrari P. Effect of prolonged bicarbonate administration on plasma potassium in terminal renal failure. Kidney Int. 1992;41:369–74.
16. Allon M, Shanklin N. Effect of bicarbonate administration on plasma potassium in dialysis patients: interactions with insulin and albuterol. Am J Kidney Dis. 1996;28:508–14.
17. Marsh JD, Margolis TI, Kim D. Mechanism of diminished contractile response to catecholamines during acidosis. Am J Physiol. 1988;254:H20–7.
18. Vinsonneau C, et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. Lancet (London, England). 2006;368:379–85.
19. Schneider AG et al. Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Med. 2013;39:987–97.
20. Augustine JJ, Sandy D, Seifert TH, Paganini EP. A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. Am J Kidney Dis. 2004;44:1000–7.
21. Palevsky PM et al. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med. 2008;359:7–20.
22. Finfer S et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247–56.
23. Brunkhorst FM et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358:125–39.
24. Wiedermann CJ. Systematic review of randomized clinical trials on the use of hydroxyethyl starch for fluid management in sepsis. BMC Emerg Med. 2008;8:1.
25. Yunos NM et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308:1566–72.
26. Young P, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit. JAMA. 2015;1. doi:10.1001/jama.2015.12334.
27. O'Malley CMN, et al. A randomized, double-blind comparison of lactated Ringer's solution and 0.9 % NaCl during renal transplantation. Anesth Analg. 2005;100;1518–24, table of contents.
28. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med. 2001;29:2264–70.

29. Harvey SE et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med. 2014;371:1673–84.
30. Fiaccadori E et al. Prevalence and clinical outcome associated with preexisting malnutrition in acute renal failure: a prospective cohort study. J Am Soc Nephrol. 1999;10:581–93.
31. Metnitz PGH et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med. 2002;30:2051–8.
32. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc. 2003;78:1471–8.
33. Van den Berghe G et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359–67.
34. Finfer S et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
35. Finfer S et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
36. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet (London, England). 2000;356:2139–43.
37. Liu KD et al. Timing of initiation of dialysis in critically ill patients with acute kidney injury. Clin J Am Soc Nephrol. 2006;1:915–9.
38. Demirkiliç U, et al. Timing of replacement therapy for acute renal failure after cardiac surgery. J Card Surg. 2004;19:17–20.
39. Jamale TE et al. Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: a randomized controlled trial. Am J Kidney Dis. 2013;62:1116–21.

Rhabdomyolysis

44

Saraswathi Gopal, Amir Kazory, and Azra Bihorac

Case Presentation

A 24-yo Hispanic female (gravida 3, para 2) was admitted to a community hospital in the 24th week of pregnancy with complaints of shortness of breath and hemoptysis for 3 days. Her past medical history was significant for hypertension, systemic lupus erythematosus (SLE), and lupus nephritis (WHO type 2). SLE was diagnosed 2 years prior to this admission and she was treated with a short course of oral prednisone and azathioprine which lead to complete remission. She did not have any history of nicotine, alcohol or illicit drug abuse. On physical exam she was found to have bilateral pleural effusions and distant heart sounds. Laboratory data were significant for hemolytic anemia with a hematocrit of 19%, increased lactate dehydrogenase (LDH) levels, leukopenia, and mild acute kidney injury with a serum creatinine of 1.3 mg/dL. Echocardiogram revealed presence of pericardial effusion without any evidence of tamponade. SLE flare was suspected and she received intravenous methylprednisolone 250 mg/day. On the third day of admission, patient presented with respiratory failure and was intubated. Sedation was maintained by propofol infusion (ranging from 5.5 to 7.1 mg/kg/h) while patient was on mechanical ventilation. The following day she was transferred to a tertiary care hospital for further evaluation and management.

At the time of transfer, the temperature was 37.0 °C, the pulse was 98, and the blood pressure was 111/49 mmHg. The patient was receiving ventilatory assistance. Urinalysis revealed turbid and amber urine, with a specific gravity of 1.014, and 3+ for protein; the sediment contained greater than 100 RBCs and 30 WBCs, with numerous granular casts per low-power field. Laboratory tests are summarized in Tables 44.1 and 44.2. An electrocardiogram showed a normal sinus rhythm at a rate of 89, with non-specific T wave alterations in the precordial leads. Arterial blood gas while the patient was receiving 70% oxygen revealed a pH of 7.41, a partial pressure of oxygen of 70 mmHg, and a partial pressure of carbon dioxide of 25 mmHg. Abdominal ultrasound was normal with an intrauterine pregnancy. Echocardiogram demonstrated moderate pericardial effusion (18 mm posterior) with no evidence of hemodynamic compromise. Left and right ventricular size and systolic function were normal. Serologic testing was positive for antinuclear antibodies, anti-native DNA antibodies, anti-ribonuclear protein

S. Gopal
Division of Nephrology Hypertension and Renal Transplantation, Department of Medicine, University of Florida, Gainesville, FL, USA

A. Kazory
Medicine/Nephrology, University of Florida, Gainesville, FL, USA

A. Bihorac (✉)
Department of Anesthesiology/Division of Critical Care Medicine, University of Florida College of Medicine, Gainesville, FL, USA
e-mail: azra.bihorac@medicine.ufl.edu; ABihorac@anest.ufl.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_44

Table 44.1 Blood chemical values

	Day 1 3:30	Day 1 18:30	Day 2 3:30	Day 2 16:15	Day 2 23:30	Day 3 1:00	Day 3 2:38
Blood Urea nitrogen (mg/dl)	49	53	55	61	65		68
Creatinine (mg/dl)	1.6	1.4	1.5	2.7	3.1		3.4
Albumin (g/dl)	1.6						
Glucose	189	193	153	151	152		192
Sodium (mmol/l)	134	135	135	134	134	140	134
Potassium (mmol/l)	4.3	3.5	3.4	5.3	7.1	5.5	7
Chloride (mmol/l)	109	100	100	100	104		100
Carbon dioxide (mmol/l)	19	26	25	19	13		19
Calcium (mg/dl)	6.1	5.7	6.6	5.8	10.3		6.2
Phosphorus (mg/dl)	7.2	5.2	5.8	9.8			14.4
Aspartate aminotransferase (U/l)	14						
Alanine aminotransferase (U/l)	19						
Lactate dehydrogenase (U/l)	732		1682				
Alkaline phosphatase (U/l)	73						
Creatinine kinase (U/l)	<25					134756	
Creatine kinase-MB (ng/mL)	1.5					545	
Troponin T (U/l)	<0.01						
PH			7.41		7.27	7.48	7.42
pCO2			36		27.8	27.9	26.4

Table 44.2 Hematologic values

	Day 1 3:30	Day 1 18:30	Day 2 3:30	Day 2 16:15	Day 2 23:30	Day 3 1:00	Day 3 2:38
Hematocrit (%)	19	23	24	40	43		43
Mean corpuscular volume (μm^3)	93	90	84	84	83		81
Haptoglobin		Normal					
White-cell count (per mm^3)	19,600	16,000	11,000	23,000	21,000		22,000
Differential count (%)							
Neutrophils Band forms Lymphocytes Monocytes Eosinophils Basophils	89 1 6 4 0 0	84 14 2 0 0 0	95 0 4 1 0 0				91 0 5 4 0 0
Platelet count (per mm^3)	175,000	134,000	119,000	250,000	227,000		251,000
Prothrombin time (s)	11.8						
Partial-thromboplastin time (s)	29						

antibodies and anti-smith antibodies. Complement CH50 was <10 U/ml and antineutrophil cytoplasmic antibodies were absent.

Based on the patient's clinical presentation, coupled with her past medical history and serological data, the diagnosis of lupus flare was made. Treatment with intravenous methylprednisolone at the dose of 1000 mg/day was then initiated. Supportive therapy included blood transfusions, empirical antibiotics (ampicillin and sulbactam), and mechanical ventilation with sedation by propofol drip at a mean rate of 6 mg/kg/h. She was

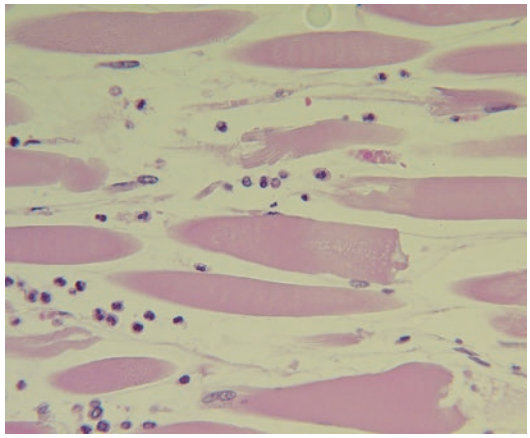


Fig. 44.1 Skeletal muscle biopsy revealed acute diffuse rhabdomyolysis with nuclear drop-out, hyaline-like myocytes with loss of striations, acute inflammation and edema

also receiving dopamine, aspirin, erythropoietin, and pantoprazole. On the third hospital day, she presented with sudden onset of hypotension and tachyarrhythmia necessitating initiation of vasopressors for hemodynamic support. Laboratory work-up revealed serum creatine kinase (CK) level rising to 134,756 U/L, severe hyperkalemia, new-onset high anion-gap metabolic acidosis, and worsening acute kidney injury (AKI) (Table 44.1).

Question What is the evidence based approach to manage this patient's acute kidney injury?

Answer In the absence of any other etiology for rhabdomyolysis, the diagnosis rhabdomyolysis due to propofol was made and propofol drip was immediately discontinued.

Due to her metabolic abnormalities (hyperkalemia, metabolic acidosis) and worsening renal failure a decision was made to initiate renal replacement therapy. However, while preparing patient for renal replacement therapy, her hyperkalemia worsened in spite of medical treatment and within 2 hours (h) she developed ventricular tachycardia rapidly followed by cardiac arrest and death. Autopsy was performed and confirmed histologic evidence of rhabdomyolysis in skeletal muscles (Fig. 44.1).

Principles of Management

There is a lack of level I evidence from which the best management plans for rhabdomyolysis may be derived. In fact, no randomized controlled trials studying treatment of rhabdomyolysis have been conducted, and most evidence is based on retrospective clinical studies, case reports and animal models.

Diagnosis

Rhabdomyolysis involves damage to the skeletal muscle fibers and the release of toxic intracellular contents into the circulation. The causes of rhabdomyolysis are summarized in Table 44.3. The clinical spectrum of Rhabdomyolysis is rather wide and variable. The classic triad of symptoms including muscle weakness, pain and reddish brown urine are present in less than 50 % of the patients [1, 2]. Most frequently, the involved muscle groups are the postural muscles of the thighs, calves and lower back [3]. Nonspecific systemic symptoms, such as malaise, fever, abdominal pain, nausea and vomiting may also be seen. Apart from history and physical examination a definitive diagnosis can be made by laboratory studies including serum creatine kinase (CK) and urine myoglobin levels. In some cases a skeletal muscle biopsy can also be used to confirm the diagnosis [4].

CK rises in rhabdomyolysis within 12 h of the onset of muscle injury, peaks in 1–3 days, and declines 3–5 days after the cessation of muscle injury. Although various values of CK have been postulated to define rhabdomyolysis, the magnitude of elevation is rather arbitrary; and there is no cut-off value that conclusively diagnoses rhabdomyolysis. Abnormal CK levels are commonly seen in injured intensive care unit patients, and a level of 5000 U/l or greater is related to renal failure [5]. Myoglobin is normally bound to plasma globulins. During muscle injury the amount of myoglobin spilled in the circulation exceeds the plasma binding capacity (>1.5 mg/dl) and is excreted in the urine [6, 7]. It is the myoglobin, which imparts the reddish brown color to the urine in rhabdomyolysis. Serum myoglobin usually increases before a rise in

CK and drops more rapidly than does the decline in CK concentration (in 1–6 h) [8]. Moreover, myoglobinuria may not be visible or may resolve early in the course of rhabdomyolysis. Due to these factors neither serum myoglobin nor urinary myoglobin levels can be used as reliable diagnostic indicators for rhabdomyolysis.

Muscle biopsy is not necessary, although it can be used to confirm the diagnosis of rhabdomyolysis. The histopathological findings usually include loss of cell nucleus and muscular stria with the absence of inflammatory cells [9].

Fluid Therapy

There is evidence to suggest early hydration is essential to prevent and limit the severity of renal failure in rhabdomyolysis [10]. There is no data to support or guide the amount of fluids that need to be administered. Most patients with rhabdomyolysis are hypovolemic, so fluid resuscitation to maintain a minimum urine output goal of 2 ml/kg/h is recommended [11]. A Foley catheter should be placed in order to monitor the urine output closely. In severe cases of crush injury,

Table 44.3 Causes of rhabdomyolysis

Trauma	Any trauma leading to muscle damage Motor vehicle accidents especially crush injuries Physical torture/abuse Prolonged immobilization Overexertion (long distance running or prolonged exercise) Delirium tremens Epilepsy
Vascular	Any vascular occlusion Thrombosis Embolism Iatrogenic-Prolonged vessel clamping during surgery
Sepsis	
Hyperthermia	Neuroleptic malignant syndrome malignant hyperthermia
Electric current	Cardioversion, high voltage electric current
Electrolyte abnormalities	Hypernatremia Hypocalcemia Hyponatremia Hypokalemia Hypophosphatemia
Metabolic diseases	Carnitine deficiency Creatinine palmitoyl transferase deficiency Myophosphorylase deficiency (McArdle disease) Mitochondrial respiratory chain enzyme deficiencies Phosphofruktokinase deficiency
Infections	Coxsackievirus Falciparum malaria Herpes viruses Human immunodeficiency virus Legionella Salmonella Streptoccocus Tularemia
Endocrine disorders	Hyperaldosteronism Hypothyroidism Ketoacidosis Hyperaldosteronism
Toxins	Heavy metals Insect venoms Snake venoms
Autoimmune diseases	Polymyositis

Table 44.3 (continued)

Drugs	Sedatives/ hypnotic drugs Benzodiazepines Diazepam Nitrazepam Flunitrazepam Lorazepam Triazolam Barbiturates Gluthetimide Drugs of addiction Heroin Cocaine Amphetamine Methadone D-lysergic acid diethylamide (LSD) Antidepressants and Antipsychotic drugs Amitriptyline Fluoxetine Fluphenazine Haloperidol Lithium Protriptyline Phenelzine Perphenazine Promethazine Chlorpromazine Loxapine Promazine Trifluoperazine Amoxapine Doxepine Antilipemic drugs Lovastatin Pravastatin Simvastatin Bezafibrate Clozafibrate Ciprofibate Clofibrate Others Alcohol Amphotericin B Azathrioprine Butyrophenones Epsilon-aminocaproic acid Halothane Moxalactam Oxprenolol Paracetamol Penicillamine Pentamidine Phencyclidine Phenylpropanolamine Propofol Quinidine Salicylates Strychnine Succinylcholine Theophyline Terbutaline Thiazides Vasopressin Diphenhydramine Doxylamine

administration of blood products and intravenous fluids simultaneously is important to correct severe hypovolemic state [12].

Treating Reversible Causes of Muscle Damage

Underlying causes of muscle damage must be identified to prevent ongoing muscle destruction. Causes such as infections, trauma, hyperthermia, electrolyte abnormalities and medication induced muscle damage should be identified and addressed appropriately. In cases of drug induced rhabdomyolysis the offending agent should be identified and stopped immediately, if necessary drugs and toxins should be eliminated (e.g., gastric lavage, antidotes and/or haemodialysis) whenever possible [4].

Management of Complications

Complications of rhabdomyolysis include acute renal failure, acidosis, compartment syndrome, hepatic dysfunction, disseminated intravascular coagulation, arrhythmias and cardiac arrest.

Acute renal failure (ARF) develops in 33 % of patients [2] with rhabdomyolysis. Factors known to contribute to rhabdomyolysis-induced acute renal failure include hypovolemic, acidosis or aciduria, tubular obstruction, and the nephrotoxic effects of myoglobin. Aggressive rehydration is considered the standard of care in preventing acute renal failure in patients with rhabdomyolysis.

Hyperkalemia and hypocalcaemia occurring after muscle damage can predispose to cardiac arrhythmias. Hyperkalemia should be managed aggressively when present. Treatment can be initiated with insulin and dextrose. Intravenous calcium can be administered but becomes less effective when hyperphosphatemia is present since calcium and phosphorus can precipitate removing both of them from circulation [13]. Dialysis should be considered as a lifesaving procedure for patients with a rising or elevated potassium level, persistent acidosis, or oliguric renal failure with fluid overload.

Disseminated intravascular coagulation (DIC) results from complement activation of clotting cascade by components released after muscle injury. This usually occurs after severe rhabdomyolysis, leading to hemorrhagic complications [3]. DIC usually resolves spontaneously after several days if the underlying cause is corrected, but if hemorrhagic complications occur, therapy with platelets, vitamin K, and fresh frozen plasma may be necessary.

Compartment syndrome is another complication of rhabdomyolysis. Most skeletal muscles are confined to compartments formed by fascia, bones and other structures. When muscle fibers are ischemic and edematous, it raises the intra compartment pressure potentiating a vicious cycle of more ischemia and damage [2, 6]. Compartment syndrome requires immediate orthopedic consultation for fasciotomy.

Evidence Contour

Bicarbonate Therapy

Alkalinization of the urine is also a common intervention in rhabdomyolysis, but evidence of a clinical benefit is lacking. The concept of urine alkalinization derives from the precipitation of myoglobin in an acidic environment, and therefore, urinary alkalinization (pH. 6.5) theoretically can decrease the deposition of myoglobin in renal tubules. Animal studies and small retrospective studies have shown that alkalinization is better than using intravenous fluids alone in patients with rhabdomyolysis [14, 15]. However, subsequent retrospective studies have failed to establish this benefit. Based on available evidence, it can be concurred that alkalinization with sodium bicarbonate is not necessary and is not superior to giving intravenous fluids alone [16, 17].

Diuretics and Mannitol

In some experimental studies Mannitol is suggested to have a protective effect due to the diuresis, which minimizes intratubular heme

deposition [11, 18, 19]. It has also been suggested that mannitol acts as a free-radical scavenger, thereby minimizing cell injury [20]. Loop diuretics have also been used to increase urine output in patients with acute renal failure secondary to rhabdomyolysis. While diuretics and mannitol have been used in preventing acute renal failure, there is little clinical evidence to support the use of these agents in rhabdomyolysis. While randomized controlled trials are lacking, the available evidence suggests that mannitol and diuretic therapy have no benefit over and above aggressive fluid resuscitation [16, 18, 21, 22].

Antioxidants and Free Radical Scavengers

Free radical scavengers have shown to reduce the ischemia reperfusion injury in rhabdomyolysis in experimental models [23]. Pentoxyphylline improves microvascular circulation, acts to decrease neutrophil adhesion and cytokine release [24]. Vitamin E (alfa tocopherol), vitamin C (ascorbic acid), lazaroids (21-aminosteroids) and minerals such as zinc, manganese and selenium all have antioxidant activity [25, 26]. These agents might have a role in the treatment of rhabdomyolysis, but further studies are needed to validate their use.

RRT for Prevention of Acute Kidney Injury

Attempts have been made to study myoglobin removal by renal replacement therapy. Based on the size of myoglobin protein, conventional hemodialysis is not effective in clearing myoglobin from the circulation. Evidence from isolated studies have shown that continuous venovenous hemofiltration or hemodialfiltration has some efficacy in removing myoglobin [27], but the effect of this removal on the outcome (acute kidney injury) is not known. Until further studies are done, renal replacement therapy cannot be recommended as a preventive method to avoid acute kidney injury in patients with rhabdomyolysis.

References

1. Warren J. Rhabdomyolysis: a review. Muscle Nerve. 2002;25:332–47.
2. Gabow PA, Kaehney WD, Kelleher SP. The spectrum of rhabdomyolysis. Medicine. 1982;61:141–9.
3. Tintinalli JE, Kelen GD, Stapczynski JS. Emergency medicine: a comprehensive study guide. 6th ed. New York: McGraw-Hill Inc; 2004.
4. Khan FY. Rhabdomyolysis: a review of the literature. Neth J Med. 2009;67(9):272–83.
5. Brochard L, Abroug F, Brenner M, et al; ATS/ERS/ESICM/ SCCM/SRLF Ad Hoc Committee on Acute Renal Failure. An official ATS/ERS/ESICM/SCCM/SRLF statement: prevention and management of acute renal failure in the ICU patient: an international consensus conference in intensive care medicine. Am J Respir Crit Care Med. 2010;181(10):1128–55.
6. Poels P, Gabreels F. Rhabdomyolysis: a review of literature. Clin Neurol Neurosurg. 1995;95:175–92.
7. Adams EC. Differentiation of myoglobin and hemoglobin in biological fluids. Ann Clin Lab Sci. 1980;10:493–9.
8. Minnema BJ, Neligan PC, Quraishi NA, Fehlings MG, Prakash S. A case of occult compartment syndrome and nonresolving rhabdomyolysis. J Gen Intern Med. 2008;23:871–4.
9. Hino I, Akama H, Furuya T. Pravastatin induced rhabdomyolysis in a patient with mixed connective tissue disease. Arthritis Rheum. 1996;39(7):1259.
10. Bonventre J, Shah S, Walker P, Humphreys M. Rhabdomyolysis-induced acute renal failure. In: Jacobson SK, editor. The principles and practice of nephrology. 2nd ed. St. Louis: Mosby; 1995. p. 564–76.
11. Curry SC, Chang D, Connor D. Drug- and toxin-induced rhabdomyolysis. Ann Emerg Med. 1989;18:1068–84.
12. Russell TA. Acute renal failure related to rhabdomyolysis: pathophysiology, diagnosis, and collaborative management. Nephrol Nurs J. 2005;32:409–17. quiz 418–419.
13. Visweswaran P, Guntupalli J. Rhabdomyolysis. Crit Care Clin. 1999;15:415–28.
14. Eneas JF, Schoenfeld PY, Humphreys MH. The effect of infusion of mannitol-sodium bicarbonate on the clinical course of myoglobinuria. Arch Intern Med. 1979;139(7):801–5.
15. Ron D, Taitelman U, Michaelson M, Bar-Joseph G, Bursztein S, Better OS. Prevention of acute renal failure in traumatic rhabdomyolysis. Arch Intern Med. 1984;144(2):277–80.
16. Brown CV, Rhee P, Chan L, Evans K, Demetriades D, Velmahos GC. Preventing renal failure in patients with rhabdomyolysis do bicarbonate and mannitol make a difference? J Trauma. 2004;56(6):1191–6.
17. De Meijer AR, Fikkers BG, de Keijzer MH, van Engelen BG, Drenth JPH. Serum creatine kinase as predictor of clinical course in rhabdomyolysis: a 5-year intensive care survey. Intensive Care Med. 2003;29(7):1121–5.

18. Zager R. Rhabdomyolysis and myohemoglobinuric acute renal failure. Kidney Int. 1996;49: 314–26.
19. Zager R. Studies of mechanisms and protective maneuvers in myoglobinuric acute renal injury. Lab Invest. 1989;60:619–29.
20. Odeh M. The role of reperfusion-induced injury in the pathogenesis of the crush syndrome. N Engl J Med. 1991;324:1417–22.
21. David WS. Myoglobinuria. Neurol Clin. 2000; 18(215–243):60.
22. Star RA. Treatment of acute renal failure. Kidney Int. 1998;54:1817–31.
23. Walker P, Lindsay T, Labbe R, Mickle D, Romaschin A. Salvage of skeletal muscle with free radical scavengers. J Vasc Surg. 1987;5:68–75.
24. Mandell G. ARDS, neutrophils, and pentoxifylline. Am Rev Resp Dis. 1988;136:1103–5.
25. Maclin L. Free radical tissue damage: protective role of anti-oxidant nutrients. FASEB J. 1987;1:441–5.
26. Braughler J, Pregenzer J, Chase R, Duncan L, Jacobsen E, McCall J. Novel 21-aminosteroids as potent inhibitors of iron dependent lipid preoxidation. J Biol Chem. 1987;262:1438–40.
27. Ronco C. Extracorporeal therapies in acute rhabdomyolysis and myoglobin clearance. Crit Care. 2005;9:141–2.

Hyponatremia

45

Christian Overgaard-Steensen and Troels Ring

Case Presentation

A 65-year-old librarian was admitted with a reduced level of consciousness (Glasgow Coma Scale (GCS) score of 7). Her husband related that 20 h previously she said she was tired and felt "strange" and went to bed early. The next morning, he could not wake her up. For 3 days she had been vomiting and drinking water/soda. On day 2 she went to an emergency department because she was feeling ill and had muscle cramps. She was advised to drink water. Her past medical history revealed intermitting bladder pains treated with nonsteroidal anti-inflammatory drugs, besides this she was healthy. At the time of presentation, pulse oximetry showed 100 % saturation (supplemental oxygen with a face mask was given), her respiratory rate was 25 per minute, blood pressure was 109/95 mmHg, with a heart rate of 77 beats/min. She had bilateral abnormal plantar responses (extension), was rigid in all extremities, with an extension/pronation pattern, and slowly reacting pupils. Arterial blood gas analysis was as follows: pH = 7.58, pCO_2 = 2.8 kPa (21 mmHg), pO_2 = 25.4 kPa (191 mmHg), Hgb = 8.7 mmol/l (14 g/dl), lactate = 1.5 mmol/l, BE = −2.2 mmol/l, P-[glucose] = 8.6 mmol/l (155 g/dl), P[Na] = 108 mmol/l and P[K] = 2.9 mmol/l. Body temperature was 37.7 ° C (99.9 ° F).

Question What approach should guide this patient's management?

Answer Bolus therapy with 3 % NaCl and avoidance of overcorrection

All patients with severe cerebral symptoms (altered level of consciousness, seizures, rigidity) and hypotonic hyponatremia should be treated with bolus 2 ml/kg weight 3 % NaCl to reduce brain edema together with treatment/diagnosis of other potential causes of the cerebral symptoms. Next, overcorrection should be avoided to reduce the risk of osmotic demyelination (OD). Treatment with a bolus of 70 mmol NaCl was immediately instituted and within 15 min repeated twice as symptoms persisted. Treatment resulted in an increase in P[Na] to 114 mmol/l. The rigidity diminished, but she was still had a GCS score of 7–8. 10 mg of diazepam was given iv without effect. On a minor suspicion of meningitis, antibiotic therapy was initiated. To secure the airway, she was intubated before a CT scan of the cerebrum (CTC) was performed. The CTC showed discrete signs of brain edema (Fig. 45.1). The patient was transferred to the ICU

C. Overgaard-Steensen (✉)
Department of Neuroanaesthesiology, Rigshospitalet, Copenhagen, Denmark
e-mail: christian.overgaard.steensen@clin.au.dk

T. Ring
Nephrology, Aalborg University Hospital, Aalborg, Denmark

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_45

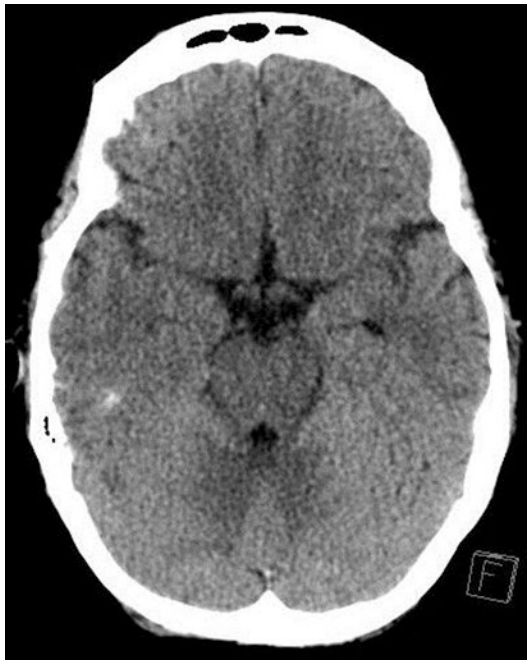


Fig. 45.1 CT scan of cerebrum after hypertonic saline bolus therapy

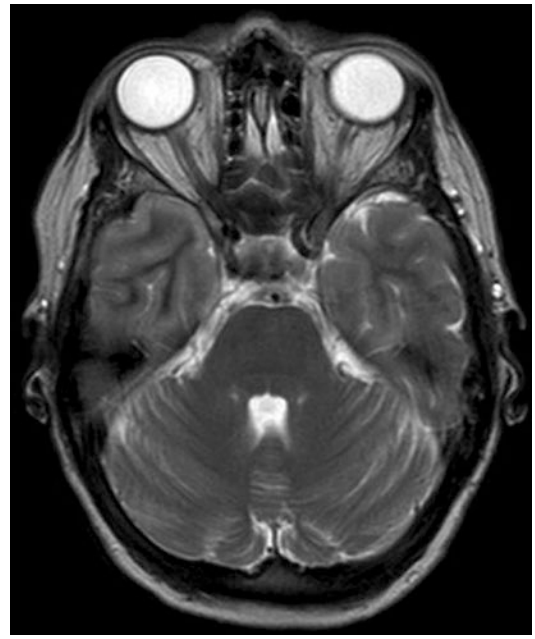


Fig. 45.2 MR imaging, T_2-weighted, 14 days after correction of hyponatremia without signs of osmotic demyelination

for propofol sedation, frequent P[Na] measurements and avoidance of overcorrection (maximal 118 mmol/l 24 h after admission). Cerebrospinal fluid showed no signs of meningitis. An electroencephalogram was without paroxysmal activity. Blood tests showed slightly elevated CRP/leucocytes and normal creatinine/urea/albumin. P[Na] and urine production were measured hourly. A large urine flow (up to 500 ml/h) resulted in a rapid increase in P[Na]. This was counteracted by infusion of 5% glucose, and desmopressin treatment was considered – but not given – to reduce the risk of OD. The next day, P[Na] was 121 mmol/l and she was extubated; the GCS score was 10. P[Na] continued to increase without sodium supplementation due to a large urine volume, with a high electrolyte-free water clearance (EFWC) (U[Na]=42 mmol/l and U[K]=15 mmol/l) (see next section for calculations). This was counteracted by giving sterile water and 5% glucose. On day 2, P[Na] was 125 mmol/l, and on day 3, 132 mmol/l. Her consciousness level increased to a GCS score of 15, and she was transferred to the neurological ward. A MR scanning 14 days later showed no signs of OD (Fig. 45.2), and she was discharged with only a slightly impaired visual performance (homonym hemianopia), which gradually improved.

Principles of Management

ABCD Followed by Diagnosis

The first step in the approach to the patient with an altered level of consciousness is to ensure a patent airway, adequate breathing and circulation together with a brief evaluation of the patient's neurological disability and measurement of blood sugar (ABCD approach). This is crucial to treat/rule out hypoxia, hypercapnia, hypotension and/or hypoglycemia as causes behind the altered consciousness level and to reduce secondary brain damage [1]. Next, swift determination of electrolytes must be prioritized in the patient with severe cerebral symptoms together with the diagnosis/treatment of other possible causes of the cerebral symptoms (e.g. meningitis). The diagnosis of hypotonic hyponatremia is based on a reduced P[Na] without hyperglycemia. In the presence of

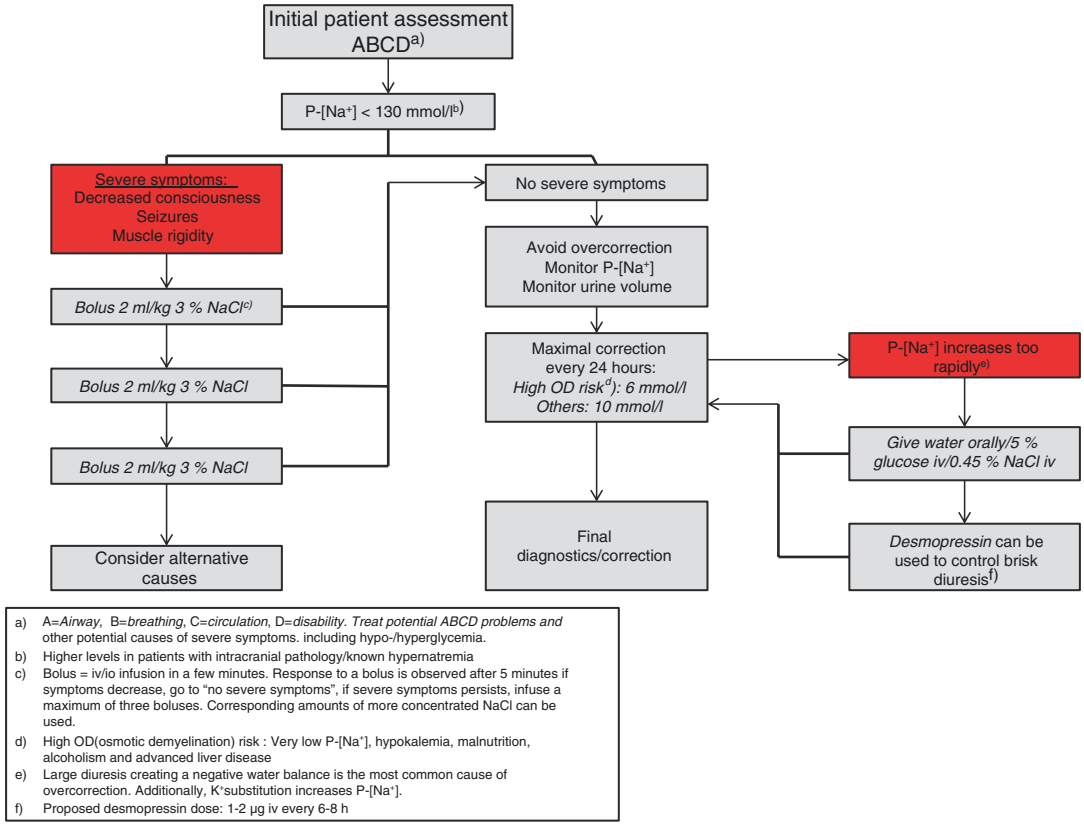


Fig. 45.3 Hyponatremia treatment algorithm. *P-[Na+]* plasma sodium concentration, *OD* osmotic demyelination

hyperglycemia, the measured P[Na] should be corrected/increased by 0.4 mmol/l per 1 mmol increase in P-[glucose] (or a correction of 2.4 meq/l per 100 mg/dl increase in P-[glucose]) [2]. Hyponatremia together with severe symptoms indicates brain edema/increased intracranial pressure (ICP). That is, ongoing brain damage and a substantial risk of herniation. Therefore acute treatment should normally not be delayed by performance of a CTC. On the other hand, if hyponatremia is present without severe symptoms, a more hesitant approach is appropriate.

Bolus Therapy

In hyponatremia with severe symptoms, immediate ICP reduction is best induced with one or more boluses of 2 ml/kg 3 % (0.5 mmol/l) NaCl (e.g. 100 ml in a patient weighing 50 kg (110 lbs) (or a corresponding amount of more hypertonic NaCl) given iv/intraosseously (Fig. 45.3) [3–5]. One 2 ml/kg 3 % NaCl bolus causes an increase in P[Na] of approximately 2 mmol/l and an immediate reduction in ICP. The bolus can be repeated at 5-min intervals. Cerebral symptoms/ICP decreases sufficiently when P[Na] increases 4–6 mmol/l, hence no more than three boluses should be given [3, 6]. Crucially, 0.9 % NaCl should not be used to acutely increase P[Na] in patients with severe symptoms. The resulting P[Na] is unpredictable, and the hyponatremia may worsen in the patient with syndrome of inappropriate antidiuretic hormone (SIADH) (see section "Mechanisms Behind the Hyponatremia/Lasting Correction") [6, 7].

Avoidance of Overcorrection

A rapid increase in P[Na] can result in osmotic brain damage and death, OD. In relation to

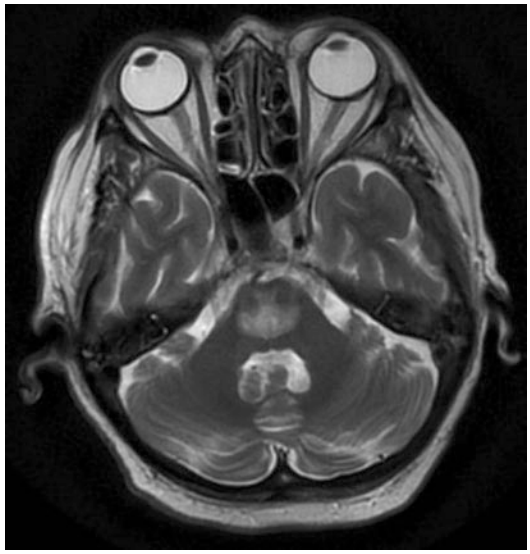


Fig. 45.4 MR imaging, T_2-weighted, demonstrating osmotic demyelination in a 63-year-old woman after rapid correction of hospital-acquired hyponatremia (developed within 48 h)

hyponatremia, the course is bi-phasic: First, a reduction in cerebral symptoms followed by a gradual neurological worsening. OD is linked to the cerebral adaption to hyponatremia over time. Cerebral symptoms wane parallel with a reduced cerebral content of potassium, organic osmolytes and water. However, OD is also seen when a rapidly developed hyponatremia (Fig. 45.4) is swiftly corrected [8, 9] and in rapidly developed hypernatremia [3, 6]. Therefore, P[Na] should be corrected slowly in all patients. The increase in P[Na] should be of no more than 10 mmol/l in the first 24 h and less than 8 mmol/l every 24 h thereafter [3, 4]. In patients with additional risk factors of OD (very low P[Na], hypokalemia, malnutrition, alcoholism, and advanced liver disease), the increase should be maximally 6 mmol/l in every 24 h [3–5].

Controlling the correction of hyponatremia can be a challenging task and needs a high level of observation. This is illustrated by the real-life case at the beginning of this chapter. First, it is crucial to state a maximal increase in P[Na]. Secondly, frequent measurements of P[Na] and urine volume are needed. Finally, practical measures should be instituted if P[Na] rises too quickly.

Understanding what determines P[Na] in the individual patient lies at the root of safe correction. Edelman demonstrated that P[Na] is determined by exchangeable sodium (eNa^+), exchangeable potassium (eK^+) and total body water (TBW) [10]. The relation is simplified in Eq. 45.1 [7]:

$$P\left[Na^+\right] = \frac{eNa^+ + eK^+}{TBW} \tag{45.1}$$

The physiological fundament for Eq. 45.1 is that sodium is the principal extracellular osmolyte, potassium is the principal intracellular osmolyte, and they do not freely cross the cell membrane in contrast to water. According to Eq. 45.1, hyponatremia develops when the proportion between cations ($eNa^+ + eK^+$) and water decreases.

Equation 45.1 is not readily useful at the bedside. However, it was recently demonstrated that it is valid in the individual and that the changes in P[Na] (changes from $P[Na]_1$ to $P[Na]_2$) are determined by changes in the external cation balances ($\Delta(Na^+ + K^+)$) and water balances (ΔTBW) according to Eq. 45.2 [7, 11]:

$$\mathrm{P}-\left[\mathrm{Na}^+\right]_2 = \frac{\mathrm{P}-\left[\mathrm{Na}^+\right]_1 \times TBW + \Delta\left(Na^+ + K^+\right)}{TBW + \Delta TBW} \tag{45.2}$$

In other words, P[Na] is influenced by the water balance and equally by the sodium and potassium balances. The primary cause of overcorrection in the hyponatremic patient (and in the case related above) is the large volume of diluted urine (diuresis) [12, 13]. Hypotonic fluids like water given orally or 5 % glucose iv can be used to counteract the effect of the diuresis. Besides monitoring P[Na], calculation of EFWC based on the urine cation concentration (U[Na] + U[K]) is useful because it quantifies the kidney's impact on P[Na] [7]:

$$EFWC = urin_{volume} x\left(1 - \frac{\mathrm{U}-\left[Na^+\right] + \mathrm{U}-\left[K^+\right]}{\mathrm{P}-\left[Na^+\right]}\right) \tag{45.3}$$

If electrolyte free water is excreted ((U[Na] + U[K]) < P[Na]), then the kidney counteracts the hyponatremia and will restore normonatremia. In this situation, a rapid increase in P[Na] may result. If the rise in P[Na] due to a large increase in urine volume (e.g. 300 ml/h)/high EFWC cannot be controlled, the V_2-receptor agonist desmopressin is effective in reducing EFWC (e.g. 1–2 µg desmopressin iv every 6–8 h). The administration of desmopressin can also be necessary if P[Na] has increased too much, and a re-lowering to the desired level is needed [3–5].

However, it is important that the individual patient represents a dynamic system and urine volume can change dramatically in hours, leading to a rapid increase in P[Na] and making an exact prediction of P[Na] based on formulas uncertain [13, 14]. The safest way is close monitoring of P[Na] and urine output, especially if urine volumes are large, and adjustment of fluid treatment according to P[Na], EFWC and Eq. 45.2.

One special situation is the hyponatremic patient in need of acute dialysis. Here, measures must be taken to avoid rapid overcorrection, e.g. reducing the blood flow or diluting the fluids given [6].

Table 45.1 Commonly prescribed drugs associated with hyponatremia

Groups	Drugs
Diuretics	Thiazides Indapamide
Antidepressant agents	Selective serotonin reuptake inhibitors
	Tricyclic antidepressants (mirtazapine)
	Selective norepinephrine reuptake inhibitors Monoamine oxidase inhibitors
Antipsychotic agents	Phenothiazines, Butyrophenones
Anti-seizure drugs	Carbamazapine, oxcarbazepine, valproate
	Lamotrigine Clofibrate
Antineoplastic agents	Alkylating agents (e.g. cyclophosphamide, ifosfamide) Platinium compounds (e.g. cisplatin) Vinca alkaloids (e.g. vincristine) Methotrexate
V_2-receptor agonist	Desmopressin, vasopressin, oxytocin
Miscellaneous	Nonsteroidal anti-inflammatory drugs Opiates Voriconazole 3,4-methylenedioxy-methamphetamine (ecstacy)
Hypotonic fluids	

Mechanisms Behind the Hyponatremia/Lasting Correction

When the initial therapy has stabilized the patient and measures to avoid overcorrection have been undertaken, mechanisms behind the hyponatremia must be identified. This can be challenging because (1) multiple combined causes are common [15, 16], (2) the initial mechanisms causing hyponatremia can be evanescent, and (3) hypovolemic and normovolemic hyponatremia (SIADH) can seldom be separated clinically but can be deduced from the response to treatment with 0.9 % NaCl [17]. Therefore, the diagnosis goes hand-in-hand with the treatment response and the causes of the hyponatremia may overlap.

To support the diagnosis, the *patient's history* is important: current disease, exploration of thirst feeling, known comorbidities (e.g. heart failure, liver failure, and renal impairment), medications (Table 45.1) and a meticulous history of fluid intake (quantity/quality) and output (diuresis, gastrointestinal loss). The *vital signs* are determined together with the stigmata of chronic illness. A *urine sample* should be obtained as soon as possible – preferably before therapy is initiated – and analyzed for U[Na], U[K], osmolality to calculate EFWC and hence the kidneys' contribution to the hyponatremia.

Hyponatremia with Reduced ECV/ Sodium

Loss of sodium (gastrointestinal, renal, blood, wounds, etc.) and thereby a reduction in extracellular volume (ECV) (sodium is the principal

osmolyte in the ECV) results in hypovolemia and reduced perfusion with non-osmotic stimulation of antidiuretic hormone (ADH) secretion. ADH reduces renal water excretion (reduces EFWC). Ingestion/infusion of hypotonic fluids (e.g. water, 5 % glucose, KNaGlucose) in this situation can result in hyponatremia. With hypoperfusion, the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system are activated [18]. This results in reduced urine sodium excretion. However, a low U[Na] is not always present in patients on diuretic therapy or those with adrenal deficiency and/or metabolic alkalosis from vomiting. When the sodium/ECV deficit is restored (e.g. with 0.9 % NaCl/ringer-lactate), the ADH stimulus is abolished, and a high EFWC can result in a rapid P[Na] increase, with impending overcorrection.

Hyponatremia with Increased Extracellular Volume/Sodium

In conditions with increased ECV (e.g. congestive heart failure, cirrhotic liver failure) hyponatremia is caused by non-osmotic stimulation of ADH secretion and thirst due to hypoperfusion. In addition, RASS and the sympathetic nervous system are activated, resulting in low U[Na]. Optimizing the hemodynamics is the cornerstone of treatment in these situations.

Hyponatremia Despite Suppressed ADH

Normally functioning kidneys have an enormous capacity to excrete water (1 l/h), so excessive water input (e.g. polydipsia) must exceed this to produce hyponatremia. Much less water intake can produce hyponatremia when the kidney's ability to excrete water is reduced. Low solute (protein, cations) intake in severe malnutrition (e.g. cancer, anorexia nervosa, beer potomania) reduces the kidney's ability to excrete water because pure water cannot be excreted. Urine osmolality is low. Reduced glomerular filtration rate with increasing age puts the elderly at risk of hyponatremia [19]. Treatment should take into account any polydipsia, malnutrition and/or reduced renal function.

Syndrome of Inappropriate Antidiuretic Hormone

In SIADH, non-osmotic ADH secretion and thirst are present despite normal perfusion. The combination of non-osmotic ADH secretion and no hemodynamic activation of RASS/sympathetic nervous system can result in very low/negative EFWC (U[Na] + U[K]) >> P[Na]). This puts the patient at high risk of hyponatremia when hypotonic fluids (e.g. 5 % glucose, Darrow-glucose) are prescribed or ingested [20]. When U[Na] is high, infusion of 0.9 % NaCl can result in worsening of the hyponatremia because the sodium is excreted in a smaller volume than infused, with electrolyte-free water being retained ("desalination"). Failure to increase P[Na] with 0.9 % NaCl therapy is a practical way to distinguish SIADH from hyponatremia with reduced ECV.

In the critically ill, SIADH may be due to various drugs (Table 45.1), malignant disease, central nervous system disorders (infection, bleeding, thrombosis, space occupying disorders, psychosis and generalized disorders), pulmonary disorders (infection, asthma, respirator treatment) or other more non-specific causes (general anesthesia, postoperative nausea, pain and stress) [21]. SIADH may be divided into (1) *self-limiting mechanisms* (common in the hospitalized patient), with an inherent risk of overcorrection when ADH stimulus is abolished (e.g. nausea stops) and (2) *persistent conditions* (e.g. paraneoplastic phenomenon) that, in the absence of V_2-receptor antagonist treatment, will rarely be overcorrected.

The conventional criteria for SIADH are plasma hypo-osmolality (P-Osm <275 mOsm/kg) without maximally diluted urine (U-Osm >100 mOsm/kg), high U[Na] (>40 mmol/l), normal circulation, normal renal, thyroid and adrenal function [21]. However, in the critically ill patient, other hyponatremia mechanisms are likely to co-exist (renal impairment, use of diuretics, low solute intake) and must be determined and corrected. When persistent SIADH is the likely diagnosis, the cornerstone is investigation and treatment of its underlying causes (e.g. cancer). In critical illness, correction of the hyponatremia is achieved primarily by restriction

of hypotonic water and infusion of hypertonic saline (e.g. 0.1–0.4 mmol/kg/h). In the persistent form of SIADH, V_2-receptor antagonist treatment may be the most effective option; however, treatment most be monitored to avoid overcorrection and dehydration. V_2-receptor antagonists should not be used routinely in the victim of critical neurosurgical illness (e.g. subarachnoid hemorrhage, traumatic brain injury) because its use can result in dehydration and thereby secondary brain damage (e.g. delayed cerebral ischemia) [22].

Adrenal Deficiency

Adrenal deficiency can induce hyponatremia [23]. In the critically ill patient, a random plasma cortisol level above 700 nmol/l (25 μg/dl) virtually excludes adrenal deficiency [23]. If this value is inconclusive, low-dose adrenocorticotropic hormone stimulation should be performed. Treatment is hormone substitution.

Evidence Contour

Several aspects of management of the patient with hyponatremia are based on small studies (case studies/retrospective studies) and physiological extrapolations. Despite a growing consensus, controversies still exist and are partly explained by the fact that the hyponatremia patient population is very heterogenic with regard to time frame, co-morbidities and mechanisms behind the hyponatremia.

Rate of Correction/Risk of Osmotic Demyelination

Avoiding overcorrection is pivotal to diminish the risk of OD. However, no prospective randomized studies have established an absolutely safe and definitive speed for correction of hyponatremia. In a small clinical MRI study, OD lesions were observed in patients corrected with more than 10 mmol/l/day [8]. In retrospective studies, OD has been seen in patients corrected more than 12 mmol/l/day [24–26]. Therefore, one group advocates slow correction [24]. On the other hand, hesitation in the acute correction of hyponatremia with severe symptoms can be fatal, and one group found no correlation with OD [27]. Therefore, this group advocates rapid correction [27]. It appears that the conflict between these opposing standpoints is gradually giving way to an emerging consensus: Treatment of hyponatremia with severe symptoms should involve prompt, but small increase in P[Na] followed by slow correction [12, 28], a consensus which is also reflected in current guidelines [4, 5].

Acute Versus Chronic Hyponatremia

The distinction between "acute" hyponatremia (developed within 48 h) and "chronic" hyponatremia lies at the root of former treatment guidelines. Acutely developed hyponatremia could/should be corrected to normonatremia acutely to treat or prevent brain edema, and chronic hyponatremia should be corrected slowly to avoid OD. This is based on the brain's adaption to hyponatremia [1]. However, the distinction is arbitrary and difficult to use in practice. First, the time-frame for development is often not known. Second, pre-existing hyponatremia is the greatest risk factor for the development of severe cerebral symptoms – acute worsening of chronic hyponatremia [29]. Third, rapid correction of acute hyponatremia just as the rapid development of hypernatremia from normonatremia [3] can result in OD (Fig. 45.4) [8, 9]. Therefore, the safest approach may be based on prompt bolus therapy with hypertonic saline in patients with severe cerebral symptoms combined with cautious correction in all patients [3, 4].

Hyponatremia and Association with Mortality?

Retrospective studies have documented that patients with hyponatremia have higher over-all mortality than patients with normonatremia [30–32]. Whether

hyponatremia is the cause of death in these patients or merely an indicator of underlying illness has yet to be determined. Correction of hyponatremia with a V_2-receptor antagonist in patients with heart failure showed no effect on mortality/morbidity [33]. However, it seems rational to aim for normonatremia in the critically ill with the use of appropriate fluid therapy.

References

1. Overgaard-Steensen C. Initial approach to the hyponatremic patient. Acta Anaesthesiol Scand. 2011;55(2):139–48.
2. Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med. 1999;106(4):399–403.
3. Sterns RH. Disorders of plasma sodium–causes, consequences, and correction. N Engl J Med. 2015; 372(1):55–65.
4. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Eur J Endocrinol. 2014;170(3):G1–47.
5. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126(10 Suppl 1): S1–42.
6. Overgaard-Steensen C, Ring T. Clinical review: practical approach to hyponatraemia and hypernatraemia in critically ill patients. Crit Care. 2013;17(1):206.
7. Rose BD. New approach to disturbances in the plasma sodium concentration. Am J Med. 1986;81(6):1033–40.
8. Brunner JE, Redmond JM, Haggar AM, Kruger DF, Elias SB. Central pontine myelinolysis and pontine lesions after rapid correction of hyponatremia: a prospective magnetic resonance imaging study. Ann Neurol. 1990;27(1):61–6.
9. Lin CM, Po HL. Extrapontine myelinolysis after correction of hyponatremia presenting as generalized tonic seizures. Am J Emerg Med. 2008;26(5):632–6.
10. Edelman IS, Leibman J, O'Meara MP, Birkenfeld LW. Interrelations between serum sodium concentration, serum osmolarity and total exchangeable sodium, total exchangeable potassium and total body water. J Clin Invest. 1958;37(9):1236–56.
11. Overgaard-Steensen C, Larsson A, Bluhme H, Tonnesen E, Frokiaer J, Ring T. Edelman's equation is valid in acute hyponatremia in a porcine model: plasma sodium concentration is determined by external balances of water and cations. Am J Physiol Regul Integr Comp Physiol. 2010;298(1):R120–9.
12. Sterns RH, Nigwekar SU, Hix JK. The treatment of hyponatremia. Semin Nephrol. 2009;29(3):282–99.
13. Liamis G, Kalogirou M, Saugos V, Elisaf M. Therapeutic approach in patients with dysnatraemias. Nephrol Dial Transplant. 2006;21(6):1564–9.
14. Lindner G, Schwarz C, Kneidinger N, Kramer L, Oberbauer R, Druml W. Can we really predict the change in serum sodium levels? An analysis of currently proposed formulae in hypernatraemic patients. Nephrol Dial Transplant. 2008;23(11):3501–8.
15. Clayton JA, Le Jeune IR, Hall IP. Severe hyponatraemia in medical in-patients: aetiology, assessment and outcome. QJM. 2006;99(8):505–11.
16. Shapiro DS, Sonnenblick M, Galperin I, Melkonyan L, Munter G. Severe hyponatraemia in elderly hospitalized patients: prevalence, aetiology and outcome. Intern Med J. 2010;40(8):574–80.
17. Chung HM, Kluge R, Schrier RW, Anderson RJ. Clinical assessment of extracellular fluid volume in hyponatremia. Am J Med. 1987;83(5):905–8.
18. Schrier RW. Use of diuretics in heart failure and cirrhosis. Semin Nephrol. 2011;31(6):503–12.
19. Cowen LE, Hodak SP, Verbalis JG. Age-associated abnormalities of water homeostasis. Endocrinol Metab Clin North Am. 2013;42(2):349–70.
20. Anderson RJ, Chung HM, Kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. Ann Intern Med. 1985;102(2):164–8.
21. Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. N Engl J Med. 2007;356(20):2064–72.
22. Connolly Jr ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43(6):1711–37.
23. Liamis G, Milionis HJ, Elisaf M. Endocrine disorders: causes of hyponatremia not to neglect. Ann Med. 2011;43(3):179–87.
24. Sterns RH, Riggs JE, Schochet Jr SS. Osmotic demyelination syndrome following correction of hyponatremia. N Engl J Med. 1986;314(24):1535–42.
25. Sterns RH, Cappuccio JD, Silver SM, Cohen EP. Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective. J Am Soc Nephrol. 1994;4(8):1522–30.
26. Vu T, Wong RF, Hamblin PS, Zajac JF, Grossmann MF. Patients presenting with severe hypotonic hyponatremia: etiological factors, assessment, and outcomes. Hosp Pract (Minneap). 2009;37(1):128–36.
27. Ayus JC, Krothapalli RK, Arieff AI. Changing concepts in treatment of severe symptomatic hyponatremia. Rapid correction and possible relation to central pontine myelinolysis. Am J Med. 1985;78(6 Pt 1): 897–902.
28. Moritz ML, Ayus JC. 100 cc 3% sodium chloride bolus: a novel treatment for hyponatremic encephalopathy. Metab Brain Dis. 2010;25(1):91–6.
29. Bissram M, Scott FD, Liu L, Rosner MH. Risk factors for symptomatic hyponatraemia: the role of pre-existing

asymptomatic hyponatraemia. Intern Med J. 2007; 37(3):149–55.
30. Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. Am J Med. 2009;122(9):857–65.
31. Wald R, Jaber BL, Price LL, Upadhyay A, Madias NE. Impact of hospital-associated hyponatremia on selected outcomes. Arch Intern Med. 2010;170(3): 294–302.
32. Funk GC, Lindner G, Druml W, Metnitz B, Schwarz C, Bauer P, et al. Incidence and prognosis of dysnatremias present on ICU admission. Intensive Care Med. 2010;36(2):304–11.
33. Konstam MA, Gheorghiade M, Burnett Jr JC, Grinfeld L, Maggioni AP, Swedberg K, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 2007; 297(12):1319–31.

Part VI

Endocrine Disease

Jonathan M. Fine and Robyn Scatena

Management of Severe Hyponatremia and SIADH

46

Robyn Scatena

Case Presentation

A 51 year old woman with hypothyroidism, diabetes and hypertension presented with two weeks of progressive fatigue, weakness, and difficulty walking. In the emergency department she complained of lightheadedness and dizziness. Her initial blood pressure was 70/42. She was awake and alert, with 4/5 strength throughout. Her son had recently passed away and she reported decreased appetite, decreased oral intake, and weight loss. She had been smoking one pack of cigarettes per day since age 11. Initial serum sodium was 117 mmol/L, urine sodium 69 mmol/L, and urine osmolality 576 mOsm/kg. She was treated with 2 liters (L) of intravenous (IV) 0.9 % saline, and blood pressure improved to her baseline, 117/74.

Question What is the cause of this patient's severe hyponatremia, and with what urgency should it be corrected?

R. Scatena
Yale University School of Medicine,
New Haven, CT, USA

Department of Medicine, Section of Pulmonary, Critical and Sleep, Norwalk Hospital,
Norwalk, CT, USA
e-mail: robyn.scatena@norwalkhealth.org

Answer Evaluate volume status and sodium balance, and correct slowly.

Most patients with severe hyponatremia do not need urgent correction. Time should be taken to evaluate for underlying cause, treating slowly and monitoring sodium levels frequently. This patient was admitted with symptoms attributable to hyponatremia but no critical neurologic findings, so rapid sodium correction was not necessary. Initial IV fluids corrected blood pressure. At that point, the patient was euvolemic and still hyponatremic at 119 mmol/L. Urine sodium and osmolality were consistent with the syndrome of inappropriate antidiuretic hormone activity (SIADH), though measured serum osmolality results were not available. With SIADH the most likely diagnosis, fluids were restricted to 1 L per day and oral sodium chloride (NaCl) tablets begun. Serum sodium increased to 121 mmol/L by day 4 and the patient was transferred to the medical wards. Thereafter, she was found to be orthostatic and treated with IV normal saline. Serum sodium initially remained stable on IV fluids, and repeat studies demonstrated urine sodium 140 mmol/L, urine osmolality 389 mOsm/kg, and serum osmolality 256 mOsm/kg, consistent with SIADH. By hospital day 10, despite resuming fluid restriction and escalating oral NaCl doses, serum sodium had decreased to 113 mmol/L, and the patient remained neurologically intact. Tolvaptan was begun and serum sodium increased to 120 mmol/L within 24 h, remaining stable in the mid-120s. Chest imaging

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_46

demonstrated a 2.5 cm left upper lobe nodule concerning for malignancy which proved to be the cause of her SIADH.

Principles of Management

Risk Stratification

Severely depressed mental status or seizures in acute onset hyponatremia (<48 h) suggest cerebral edema and mandate intensive care unit (ICU) admission and urgent correction of serum sodium concentration. All patients with acute onset severe hyponatremia (serum sodium concentration <120 meq/L), even those without symptoms, are at risk for cerebral edema and should receive urgent serum sodium correction in the ICU [1]. In most cases, asymptomatic patients with severe chronic hyponatremia benefit from ICU admission for monitoring of symptoms and rate of correction during initial management.

Evaluation

In patients not requiring emergent correction, the first step is clinical determination of volume status using history and physical exam. Physical exam findings for volume status are listed in Table 46.1. Table 46.2 presents common hyponatremia syndromes in the ICU by volume status. Serum osmolality less than 275 mOsm/kg water and urine osmolality greater than 100 in a hyponatremic patient with normal salt intake suggests renal free water retention which may be considered "inappropriate" if the patient is euvolemic. Spot urine sodium ≥40 mmol/L is further evidence of free water retention [2]. Once SIADH is diagnosed workup should begin for underlying cause. The most common causes of SIADH in the ICU are summarized in Table 46.3. Evidence of antidiuretic hormone (ADH) activity in a hypovolemic or hemodynamically unstable patient should be expected as a compensatory mechanism and *not* taken to represent SIADH. In cases of indeterminate volume status, it is acceptable to infuse 500 mL to one liter of 0.9 % sodium chloride. Improvement in serum sodium suggests an element of hypovolemia, whereas further reduction in serum sodium with increased urine sodium and urinary osmolality ≥100 suggest SIADH [3]. The discrimination between SIADH and cerebral salt wasting (CSW) is difficult. CSW occurs after brain injury or neurosurgical procedures. Urinary salt and chloride losses cause diuresis and hypovolemia which drives ADH secretion and free water retention. Diagnosis requires proof that urinary sodium losses and volume depletion preceded the development of hyponatremia [1].

Table 46.1 Physical exam findings for volume status

Hypovolemic	Euvolemic	Hypervolemic
Orthostasis Poor skin turgor Dry mucous membranes	Normal heart rate and blood pressure Normal skin turgor Moist mucus membranes	Lower extremity or sacral edema Ascites

Correcting Serum Sodium

If hypovolemia is present or suspected, 0.9 % saline infusion should be administered. For patients with severe acute or symptomatic hyponatremia, hypertonic (3 %) saline should be infused at a rate of 1–2 ml/kg actual body weight [2]. Correction of serum sodium concentration by 4–6 meq/L in the first 2–3 h is sufficient to significantly reduce intracranial pressure and increase cerebral perfusion pressure [4]. Serum sodium should be monitored hourly and infusion stopped when symptoms resolve. For patients who do not require emergent rapid correction of serum sodium concentration, management should be tailored to the underlying condition. Management of the hypervolemic hyponatremias requires addressing underlying organ dysfunction (Table 46.2). Glucocorticoid or thyroid hormone deficiency, discussed elsewhere, can be treated by supplementing these hormones. Severe hyponatremia from CSW may initially require hypertonic saline, though in most cases volume expansion

Table 46.2 Common causes of hyponatremia in the ICU, by volume status

Hypovolemic	Euvolemic	Hypervolemic
Cerebral salt wasting Excessive diuretic therapy GI fluid losses Hemorrhage Burn Adrenal insufficiency Hyperglycemia	SIADH Large volume hypotonic fluid infusion during surgery Primary polydipsia Endurance exercise Ecstasy use Hypothyroidism Adrenal insufficiency Low solute diet	Congestive heart failure Cirrhosis Nephrotic syndrome Renal failure

Table 46.3 Common causes of SIADH in the ICU

ICU care-associated	Malignant	Pulmonary	Neurologic	Pharmacologic
Anesthesia Pain Positive pressure ventilation Nausea	Small cell lung cancer Head and neck cancer Prostate cancer Lymphoma Brain tumor	Cystic fibrosis Pneumonia	Head trauma Intracranial hemorrhage CNS infection Stroke Guillain Barré Delirium Tremens	Narcotics Methylenedioxy-N-methamphetamine (Ecstasy) Nicotine Antipsychotics NSAIDs Vasopressin Cyclophosphamide

with isotonic saline is sufficient [2]. SIADH is managed with fluid restriction and ensuring adequate dietary sodium and protein intake. In the ICU, total fluid intake should be limited to 500 mL less than daily urinary output, and should account for oral fluids, solid foods, and IV medications [5].

Monitoring Correction Rate

In patients with asymptomatic chronic hyponatremia, there is virtually no risk of death from cerebral edema. Accordingly, guidelines and expert opinion recommend that correction be limited to 6–8 meq/L per day, with serum sodium checks every 2–4 h. During correction of hypovolemic hyponatremia, urinary output must be monitored closely, for which a urinary catheter is helpful. Once the hypovolemic stimulus for ADH secretion has been relieved, ADH levels will drop, urinary output will increase, and serum sodium concentration will increase rapidly. At this point the isotonic saline solution should be stopped and serum sodium monitored carefully. If correction proceeds at a rate greater than 0.5 meq/L/h for more than 4 h, rate of rise can be slowed by administering hypotonic fluids or IV desmopressin 2–4 micrograms [5].

Osmotic Demyelination Syndrome (ODS)

In the setting of serum hyponatremia, brain cells extrude organic solutes, which prevents cerebral swelling. This process takes about 2 days, but when hyponatremia is corrected, it can take up to a week for cells to recapture lost osmolytes. If serum sodium correction outpaces solute recapture, central pontine or extrapontine myelinolysis results. ODS classically has a biphasic presentation: the patient's neurologic status initially improves with serum sodium correction, but days later, pseudobulbar palsy and quadriparesis develop. Most described cases of ODS resulted from serum sodium correction greater than 10–12 mmol/L in 24 h or 18 mmol/L in 48 h, though slower rates of correction have been associated with this syndrome in high-risk patients including those with alcoholism, cirrhosis and severe malnutrition [5].

Evidence Contour

Diagnostics

Spot urine sodium concentration is used to support a diagnosis of SIADH but is less useful in patients on diuretics due to natriuretic effect. One study demonstrated that for patients on diuretics, **the fractional excretion of uric acid** performed just as well as urine sodium concentration in patients not on diuretics, with values over 12 % consistent with SIADH [6].

Spot urine sodium concentration is a fairly good stand-alone test for SIADH, with one study demonstrating a diagnostic accuracy of 0.82 for urine sodium 50 meq/L or greater [7].

Novel Treatments

Vasopressor receptor antagonists (**vaptans**) bind the vasopressin type 2 (V_2) receptor in the distal nephron to cause excretion of free water. Four large studies of vaptans (conivaptan and tolvaptan) in patients with euvolemic or hypervolemic hyponatremia demonstrated significant short-term and lasting improvement in serum sodium concentration. In the SALT-1 and SALT-2 trials, average sodium levels increased from 129 to approximately 135 at days 4 and days 30. Adverse events included dehydration, renal dysfunction, hypernatremia, and overly rapid serum sodium correction [8–10]. Concerns regarding safety of vaptans in the ICU center on their ability to cause significant aquaresis and hypovolemia and the potential for overly rapid correction of serum sodium. Hyponatremia in ICU patients is often multifactorial, and patients with SIADH may have concomitant intravascular hypovolemia. For this reason, many experts recommend withholding vaptans even for strongly suspected SIADH until euvolemia is certain [5].

Urea has been described as a treatment for SIADH. It causes renal sodium retention and free water excretion but tastes very bad [11]. Excellent results have been reported for the administration of urea via enteric tubes along with moderate amounts of isotonic saline in ICU patients with hyponatremia [11–13].

Osmotic Demyelination Syndrome

Outcomes

Outcomes for ODS have historically been presumed to be very poor, but in a 2012 study of 36 patients with ODS, 14 patients survived without significant disability at one year. Patients with alcoholism were more likely to have poor outcomes [14].

Prevention

In animal models of chronic hyponatremia, **rapid relowering of the serum sodium concentration** after excessive correction can prevent ODS [15]. Two case reports have demonstrated success of this approach in patients who developed neurological symptoms after overly rapid correction [16, 17].

Patients with chronic renal failure rarely develop ODS despite large and rapid corrections of hyponatremia with hemodialysis [18, 19]. Induced renal failure and exogenous **urea** administration increase the rate of brain osmolyte reaccumulation and prevent ODS during rapid sodium correction in rats; no human studies of urea for ODS prevention exist [20, 21].

References

1. Sterns RH, Hix JK, Silver SM. Management of hyponatremia in the ICU. Chest. 2013;144:672–9.
2. Ellison DH, Berl T. The syndrome of inappropriate antidiuresis. N Engl J Med. 2007;356:2064–72.
3. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. Am J Med. 2007;120:S1–S21.
4. Sterns RH, Nigwekar SU, Hix JK. The treatment of hyponatremia. Semin Nephrol. 2009;29:196–215.
5. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier R, Sterns RH, Thompson CJ. Diagnosis, evaluation and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126:S1–S42.
6. Fenske W, Störk S, Koschker A, Blechschmidt A, Lorenz D, Wortmann S, Allolio B. Value of fractional uric acid excretion in differential diagnosis of hyponatremic patients on diuretics. J Clin Endocrinol Metab. 2008;93:2991–7.
7. Hato T, Ng R. Diagnostic value of urine sodium concentration in hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion versus hypovolemia. Hawaii Med J. 2010;69:264–7.

8. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec F, Orlandi C. Tolvaptan, a selective oral vasopressin V_2-receptor antagonist, for hyponatremia. N Engl J Med. 2006;355:2099–112.
9. Ghali JK, Koren MJ, Taylor JR, Brooks-Asplund E, Fan K, Long WA, Smith N. Efficacy and safety of oral conivaptan: a V1/V2a vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. J Clin Endocrinol Metab. 2006;91:2145–52.
10. Annane D, Decaux G, Smith N, Conivaptan Study Group. Efficacy and safety of oral conivaptan, a vasopressin-receptor antagonist, evaluated in a randomized, controlled trial in patients with euvolemic or hypervolemic hyponatremia. Am J Med Sci. 2009;337:28–36.
11. Decaux G, Andres C, Kengge FG, Soupart A. Treatment of euvolemic hyponatremia in the intensive care unit by urea. Crit Care. 2010;14:R184.
12. Decaux G, Brimioulle S, Genette F, Mockel J. Treatment of the syndrome of inappropriate secretion of antidiuretic hormone by urea. Am J Nephrol. 1980;69:99–106.
13. Coussement J, Danguy C, Zouaoui-Boudjeltia K, Defrance P, Bankir L, Biston P, Piagnerelli M. Treatment of the syndrome of inappropriate secretion of antidiuretic hormone with urea in critically Ill patients. Am J Nephrol. 2012;35:265–70.
14. Louis G, Megarbane B, Lavoué S, Lassalle V, Argaud L, Poussel JF, Georges H, Bollaert P. Long-term outcome of patients hospitalized in intensive care units with central or extrapontine myelinolysis. Crit Care Med. 2012;40:970–2.
15. Gankam KF, Soupart A, Pochet R, et al. Re-induction of hyponatremia after rapid overcorrection of hyponatremia reduces mortality in rats. Kidney Int. 2009;76:614–21.
16. Soupart A, Ngassa M, Decaux G. Therapeutic relowering of the serum sodium in a patient after excessive correction of hyponatremia. Clin Nephrol. 1999;51:383–6.
17. Oya S, Tsutsumi K, Ueki K, Kirino T. Reinduction of hyponatremia to treat central pontine myelinolysis. Neurology. 2001;57:1931–2.
18. Sterns RH, Silver SM. Hemodialysis in hyponatremia: is there a risk? Semin Dial Transplant. 1990;3:3–4.
19. Dhrolia MF, Akhtar SF, Ahmed E, Naqvi A, Rizvi A. Azotemia protects the brain from osmotic demyelination on rapid correction of hyponatremia. Saudi J Kidney Dis Transpl. 2014;25(3):558–66.
20. Soupart A, Silver S, Schröeder B, Sterns R, Decaux G. Rapid (24-hour) reaccumulation of brain organic osmolytes (particularly myo-inositol in azotemic rats after correction of chronic hyponatremia. J Am Soc Nephrol. 2002;13:1433–41.
21. Soupart A, Stenuit A, Perier O, Decaux G. Limits of brain tolerance to daily increment in serum sodium in chronically hyponatremic rats treated by hypertonic saline or urea: advantage of urea. Clin Sci. 1991;80:77–84.

Diabetic Ketoacidosis

47

Neal Hakimi and Jonathan M. Fine

Case Presentation

A 30 year old male with a past medical history of diabetes mellitus, hyperlipidemia, and alcohol abuse presented with 3 days of nausea, vomiting, diffuse abdominal pain and low urine output. He admitted to using his insulin inconsistently over the past week. His serum glucose was 796 mg/dL, sodium 124 meq/L, potassium 5.4 meq/L, chloride 80 meq/L, and bicarbonate 2 meq/L. An arterial blood gas obtained in the emergency department demonstrated a pH of 6.92, pCO_2 9.8, and pO_2 134 with the patient inspiring room air. His leukocyte count was 19,600, with 73 % neutrophils and 16 % bands. His chest X-ray was normal. His electrocardiogram showed sinus tachycardia. Urinalysis revealed 3+ ketones and was positive for leukocyte esterase.

On physical exam he was afebrile, his heart rate was 106 beats/min, respiratory rate 28 breaths/min, blood pressure 139/95 mmHg, and oxygen saturation 99 % while breathing room air. He weighed 74 kg. He was slightly cachectic, but alert and oriented to person, place, and time. His mucous membranes were dry. There was no lymphadenopathy or jugular venous distention. He was tachycardic with a regular rhythm and tachypneic with clear lung sounds bilaterally. His abdomen was diffusely tender to palpation without distention, guarding, or rebound tenderness. His skin was warm and dry.

Question What is the most important initial intervention in treating this patient?

Answer Fluid Resuscitation

After establishing that there is a patent airway and adequate oxygenation, the first intervention is to provide a 15–20 mL/kg fluid bolus of normal saline. Patients with diabetic ketoacidosis (DKA) are profoundly hypovolemic and often have a free water deficit as well. Administering intravenous (IV) fluids decreases the plasma osmolality thereby improving insulin responsiveness. After fluid resuscitation is initiated, insulin replacement therapy should be given.

The patient was given a 2 l fluid bolus of 0.9 % sodium chloride (NaCl) then placed on maintenance infusion of 0.45 % NaCl at a rate of 300 mL/h. After the initial fluid bolus, he was given 10 units of IV insulin then started on an infusion at 7 units/h. Once his serum potassium dropped below 5 mEq/L, potassium was added to his maintenance fluid. After several hours his serum glucose decreased to 204 mg/dl, however

N. Hakimi
Section of Pulmonary, Critical Care and Sleep Medicine, Yale University School of Medicine, New Haven, CT, USA

J.M. Fine (✉)
Internal Medicine, Pulmonary and Critical Section, Norwalk Hospital, Norwalk, CT, USA
e-mail: jonathan.fine@wchn.org

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_47

his serum bicarbonate was still low and the anion gap remained elevated. As a result 5 % dextrose was added to his IV fluids and the insulin infusion was continued until his serum bicarbonate and anion gap normalized. He was then transitioned to daily insulin glargine and pre-meal insulin lispro, with 4 h of overlap time between the first dose of insulin glargine and the discontinuation of the regular insulin infusion.

Broad spectrum antibiotics were begun empirically on admission. At 48 h, urine culture grew Group B Streptococcus and antibiotic coverage was narrowed. The patient was discharged home after 3 days in the hospital.

Principles of Management

Diagnosis

The diagnosis of DKA is made based on the triad of hyperglycemia (serum glucose > 250), metabolic acidosis (pH < 7.3, $HCO_3 < 18$), and the presence of ketones either in the blood or urine [1, 2]. The anion gap = $[Na^+] - [Cl^- + HCO3^-]$ and is elevated (>10). In DKA, the increased anion gap reflects unmeasured keto-acids in the blood, although additional etiologies for elevated anion gap should always be considered.

Causes of Anion Gap Metabolic Acidosis
Methanol
Renal Failure
Ketoacidosis (diabetic, starvation, alcoholic)
Glycols (ethylene, propylene)
Lactic acidosis (L-lactate, D-lactate)
Salicylates
Oxoproline (pyroglutamic acid)

The measured serum sodium level is often low, due to dilutional hyponatremia from a shift in fluids from the intracellular to the extracellular space. A normal or elevated serum sodium level results from a severe free water deficit. Serum potassium level may also be elevated, normal, or low depending on the degree of acidosis, the amount of osmotic diuresis, baseline kidney function, and the duration of the disease process. Despite a normal or high serum potassium level, patients with DKA almost always have substantial depletion of total body potassium due to extracellular shifts related to acidemia and urinary losses.

Initial evaluation of a patient with suspected DKA should include complete blood count with differential, electrolytes, blood urea nitrogen, creatinine, phosphorus, magnesium, urinalysis, and electrocardiogram [1, 3]. Amylase and lipase are often elevated in DKA despite the absence of any radiographic evidence of pancreatitis [4, 5]. A thorough search for infection should be made in all patients presenting with DKA, as moderate to severe infection is often a precipitating factor [6]. Other acute medical conditions which may precipitate DKA include myocardial infarction, cerebrovascular accident, pancreatitis, and arterial thromboembolism. In the developed world most deaths from DKA are seen in patients with concurrent illness, mainly myocardial infarction and serious infection [7, 8].

Fluid Replacement

The average fluid deficit in patients with DKA ranges from 6 to 10 l [9]. The free water deficit can be calculated using the patient's total body water based on lean body weight times the gender based dosing factor and measured sodium:

$$\text{Free Water Deficit} = \text{Dosing Factor} \times \text{weight}(\text{Kg}) \times \left[\left(\text{Serum Na}^+ / 140\right) - 1\right]$$

$$\text{Dosing Factor} = 0.6(\text{Male}) \text{ and } 0.5(\text{Female})$$

Fluid replacement therapy is usually initiated with isotonic saline. The initial infusion rate should be 15–20 ml/kg/h for the first 3–4 h (approximately 1.0 to 1.5 l/h for average sized adults), with a maximum of 50 ml/kg within the first 4 h.

After the initial fluid resuscitation, the choice of fluid replacement depends on the serum electrolytes, the serum glucose, and urine output. The sodium level should be adjusted for the serum glucose concentration [10].

$$\text{Corrected Sodium} = \text{Measured sodium} + 0.024 \times (\text{Serum glucose} \quad 100)$$

If the corrected serum sodium level is normal or elevated, then 0.45 % NaCl should be used in place on 0.9 % NaCl to better correct the free water deficit. However, if the corrected serum sodium is low or the urine output is suboptimal, a persistent intravascular volume deficit is likely and 0.9 % NaCl should be continued. Once the serum glucose reaches 250 mg/dl, 5 % dextrose should be added to the IV fluids to maintain a serum glucose between 150–200 mg/dl until metabolic acidosis resolves.

Insulin

Insulin is typically administered as an IV bolus of 0.1-0.15 units/kg followed by an infusion of 0.1 units/kg/h. Prior to initiating insulin therapy, potassium must be repleted to at least 3.3 mEq/L, as insulin will shift potassium intracellularly, worsening hypokalemia and potentially causing cardiac arrhythmias. The target reduction in glucose levels is 50–70 mg/dL each hour. If the glucose does not fall by at least 50 mg/dL in the first hour, the insulin infusion should be doubled every hour until the desired rate of glucose decline is achieved. Insulin therapy should not be discontinued until metabolic acidosis resolves and the anion gap normalizes.

Electrolyte Repletion

If the initial serum potassium is 3.3–5.0 mEq/L, 20–30 mEq of potassium should be added to each liter of fluid. If the initial serum potassium is elevated, supplemental potassium should not be given and the serum potassium should be monitored every 2–3 h. The serum potassium should be maintained between 4–5 mEq/L.

Routine phosphate repletion is not recommended given the absence of clear benefit and its association with hypocalcemia and other electrolyte disturbances [11–13]. Most experts, however, recommend repletion when serum phosphate concentration falls below 1.0 mg/dl to prevent skeletal muscle weakness and respiratory failure.

Magnesium deficiency can result in cardiac dysrhythmias, seizures, muscle spasm, and paresthesia. Magnesium should be replaced when serum magnesium levels fall below 1.2 mg/dl.

Treatment of Precipitating Condition

While non-adherence to insulin therapy is often the precipitating factor in DKA, other causes such as infections and additional acute medical conditions (e.g., pancreatitis, myocardial infarction, etc.) should be actively considered [6, 14]. If a source of infection is suspected, concurrent treatment with appropriate antimicrobial therapy should not be delayed, especially if signs of shock are present.

Most patients with DKA will have a leukocytosis corresponding to the degree of acidosis; therefore the white blood cell count alone may not be a reliable predictor of infection. In one study of patients presenting to the emergency department with DKA, the presence of a significant number of immature band forms of leukocytes (i.e., bandemia) on the cell differential had a high sensitivity and specificity for the

presence of serious infection [15]. Patients with significant bandemia should be considered to have a clinically relevant infection until proven otherwise.

Complications

The most feared complication of DKA is cerebral edema; however the vast majority of cases are seen in children. There have been case reports of adults developing cerebral edema after aggressive fluid resuscitation [16, 17]. Typical features include headache and lethargy followed by altered mental status, respiratory depression, seizures, and coma. Treatment is generally supportive. Mannitol and hypertonic saline have been used successfully to treat cerebral edema in DKA [18], although there are no controlled trials to support this practice.

Non-cardiogenic pulmonary edema is another potential complication of DKA treatment [19]. The pathophysiology may be related to decreased oncotic pressure and increased pulmonary capillary permeability [20–22]. Appropriate fluid resuscitation should not be withheld in patients with pulmonary edema as their intravascular volume may still be low (Fig. 47.1).

Evidence Contour

Bicarbonate Infusion

Use of bicarbonate in DKA remains controversial [22]. Prospective trials have not demonstrated any benefit or harm with bicarbonate therapy in patients with moderate metabolic acidosis (pH > 6.9) [23, 24]. Nonetheless, severe metabolic acidosis can impair cardiac contractility, reduce oxygen delivery by shifting the oxyhemoglobin dissociation curve, and cause organ dysfunction. Although there are no controlled trials supporting bicarbonate administration, most experts recommend initiating bicarbonate therapy when the pH is less than 6.9. Bicarbonate should be given as an infusion of 100 mmol sodium bicarbonate in 400 ml sterile water with 20 mEq of potassium over 2 h. The pH should be monitored and bicarbonate stopped once pH is greater than 7.0 [1].

Site of Care

Classically DKA has been treated with intravenous insulin, often in an intensive care unit setting. With current pressures to reduce costs and lengths of stay while maintaining optimal outcomes, much attention has been focused on alternative sites of care for DKA. Several studies have demonstrated the safety and feasibility of treating mild to moderate DKA with subcutaneous insulin analogues. One randomized, prospective trial demonstrated a significant reduction in hospital charges with the use of hourly subcutaneous insulin lispro administered on the general medical floor when compared to the use of an insulin infusion in the ICU, without an increase in adverse outcomes [25]. Other trials have also demonstrated the safety and efficacy of this approach [26].

Form of Insulin Administered

American Diabetes Association (ADA) guidelines now allow for the use of subcutaneous (SC) or intramuscular (IM) insulin as an alternative to intravenous insulin for the treatment of DKA [1]. If SC or IM insulin is to be used, the initial dose of insulin should be 0.4 units/kg with half given as an IV bolus and half given SC or IM. Subsequent doses should be 0.1 units/kg SC or IM every hour. If the blood glucose does not fall by 50–70 mg/dL every hour, then additional IV insulin boluses (10 units) can be given hourly.

Euglycemic DKA

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, a new class of oral hypoglycemic agents approved by the FDA for use in patients with type 2 diabetes, have been associated with an increased risk of DKA with unusually mild

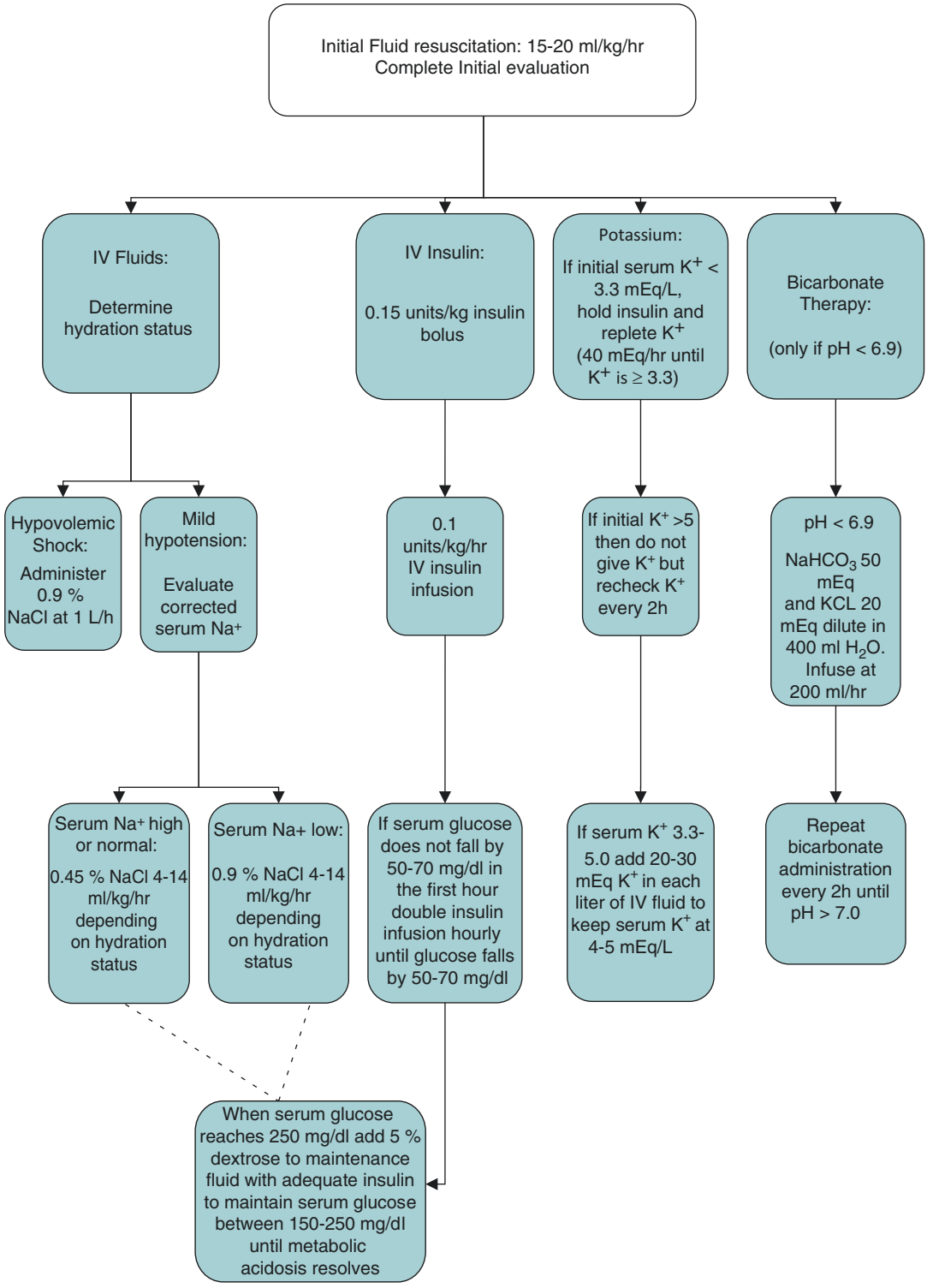


Fig. 47.1 Algorithm of DKA management (Data from: Kitabchi et al. [1])

glucose elevations. These drugs act by increasing urinary glucose excretion, thereby keeping serum glucose low. Since glucose is the main stimulus for endogenous insulin release, plasma insulin levels decrease. Plasma glucagon levels increase due to the inhibition of SGLT2-mediated glucose transport into α-cells, leading to lipolysis and lipid oxidation. The result is a relatively "euglycemic DKA." A high index of suspicion for this condition is warranted in patients who are taking SGLT2 inhibitors. Treatment remains the same with the caveat that early addition of dextrose to maintenance fluids may be necessary.

References

1. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Hyperglycemic crises in diabetes. Diabetes Care. 2004;27 Suppl 1:S94–102.
2. Arora S, Henderson SO, Long T, Menchine M. Diagnostic accuracy of point-of-care testing for diabetic ketoacidosis at emergency-department triage: {beta}-hydroxybutyrate versus the urine dipstick. Diabetes Care. 2011;34(4):852–4.
3. Westerberg DP. Diabetic ketoacidosis: evaluation and treatment. Am Fam Physician. 2013;87(5):337–46.
4. Nair S, Yadav D, Pitchumoni CS. Association of diabetic ketoacidosis and acute pancreatitis: observations in 100 consecutive episodes of DKA. Am J Gastroenterol. 2000;95(10):2795–800.
5. Yadav D, Nair S, Norkus EP, Pitchumoni CS. Nonspecific hyperamylasemia and hyperlipasemia in diabetic ketoacidosis: incidence and correlation with biochemical abnormalities. Am J Gastroenterol. 2000;95(11):3123–8.
6. Newton C, Raskin P. Diabetic ketoacidosis in type 1 and type 2 diabetes mellitus. Arch Intern Med. 2004;164(17):1925.
7. Basu A, Close C, Jenkins D, Krentz A, Nattrass M, Wright A. Persisting mortality in diabetic ketoacidosis. Diabet Med. 1993;10(3):282–4.
8. Spears B. Deaths associated with diabetic ketoacidosis and hyperosmolar coma. Ann Emerg Med. 1990; 19(6):726.
9. Hillman K. Fluid resuscitation in diabetic emergencies – a reappraisal. Intensive Care Med. 1987;13(1): 4–8.
10. Hillier T, Abbott R, Barrett E. Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med. 1999;106(4):399–403.
11. Wilson H. Phosphate therapy in diabetic ketoacidosis. Arch Intern Med. 1982;142(3):517–20.
12. Fisher J, Kitabchi A. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis*. J Clin Endocrinol Metabol. 1983;57(1):177–80.
13. Diabetic ketoacidosis. Induction of hypocalcemia and hypomagnesemia by phosphate therapy. Am J Med. 1979;67(5):A63.
14. Musey V, Lee J, Crawford R, Klatka M, McAdams D, Phillips L. Diabetes in urban African-Americans. I. Cessation of insulin therapy is the major precipitating cause of diabetic ketoacidosis. Diabetes Care. 1995; 18(4):483–9.
15. Diabetic ketoacidosis and infection: Leukocyte count and differential as early predictors of serious infection. J Emerg Med. 1988;6(3):257–8.
16. Chan N, Manchanda S, Feher M, Morgan D. Fatal cerebral oedema associated with hyponatraemia in adult diabetic ketoacidosis. Pract Diabet Int. 1998; 15(7):209–11.
17. Troy P, Clark R, Kakarala S, Burns J, Silverman I, Shore E. Cerebral edema during treatment of diabetic ketoacidosis in an adult with new onset diabetes. Neurocrit Care. 2005;2(1):055–8.
18. Curtis J, Bohn D, Daneman D. Use of hypertonic saline in the treatment of cerebral edema in diabetic ketoacidosis (DKA). Pediatr Diabetes. 2001;2(4): 191–4.
19. Sprung C. Pulmonary edema; a complication of diabetic ketoacidosis. Chest. 1980;77(5):687.
20. Powner D. Altered pulmonary capillary permeability complicating recovery from diabetic ketoacidosis. Chest. 1975;68(2):253.
21. Brun-Buisson C, Bonnet F, Bergeret S, Lemaire F, Rapin M. Recurrent high-permeability pulmonary edema associated with diabetic ketoacidosis. Crit Care Med. 1985;13(1):55–6.
22. Viallon A, Zeni F, Lafond P, et al. Does bicarbonate therapy improve the management of severe diabetic ketoacidosis? Crit Care Med. 1999;27(12):2690–3.
23. Morris LR, Murphy MB, Kitabchi AE. Bicarbonate therapy in severe diabetic ketoacidosis. Ann Intern Med. 1986;105(6):836–40.
24. Chua HR, Schneider A, Bellomo R. Bicarbonate in diabetic ketoacidosis – a systematic review. Ann Intensive Care. 2011;1(1):23.
25. Umpierrez G, Latif K, Stoever J, et al. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. Am J Med. 2004;117(5): 291–6.
26. Umpierrez G, Cuervo R, Karabell A, Latif K, Freire A, Kitabchi A. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. Diabetes Care. 2004;27(8):1873–8.

Thyroid Storm

48

Matthew E. Schmitt and Robyn Scatena

Case Presentation

A 48 year old male with a history of chronic low back pain after involvement in a motor vehicle collision, tobacco dependence, and chronic obstructive pulmonary disease presented with a four day history of worsening respiratory symptoms. The patient complained of increasing shortness of breath, productive cough without hemoptysis, subjective fever and chills, nausea, and decreased oral intake. At the time of presentation the patient was cooperative, but disoriented to time and place, tachycardic and without pedal edema. Labored, coarse breath sounds were heard bilaterally. It was also noted on exam that the patient appeared to have bulging eyes or proptosis. Chest radiograph showed patchy interstitial opacities in the lingula. He was started on IV hydration and received empiric antibiotics for community acquired pneumonia. Over the course of the next 4 h his respiratory status progressively deteriorated and he was intubated. An EKG showed sinus tachycardia with a heart rate of 160 bpm with no ST-T wave changes. Initial laboratory values included a thyroid stimulating hormone (TSH) < 0.01 uIU/mL, free thyroxine (T4) 3.74 ng/dL, free triiodothyronine (T3) 5.71 pg/mL, venous lactic acid of 2.0 mmol/L, and pro brain natriuretic peptide (pro BNP) 1,583 pg/mL.

Question What diagnosis best explains the patient's laboratory abnormalities, EKG findings, and proptosis on exam?

Answer Thyroid Storm

The patient's presentation is most consistent with thyroid storm with an underlying respiratory infection as a triggering factor. This patient was started on IV corticosteroids along with oral methimazole and propranolol via a small bore feeding tube. He was also continued on IV hydration and antibiotics for community acquired pneumonia. Results of a sputum culture failed to grow any pathogenic organisms and rapid influenza A and B antigen testing was negative. Further laboratory testing revealed an elevated thyroid stimulating immunoglobulin level approximately four times the upper limit of normal. Ultrasound of the thyroid showed normal size and vascularity with no discrete nodules seen. Within 72 h the patient's heart rate, respiratory status, and encephalopathy improved and the patient was successfully extubated. The patient was weaned off IV corticosteroids and

M.E. Schmitt (✉)
Department of Medicine, Section of Pulmonary, Critical Care and Sleep Medicine, Norwalk Hospital, Norwalk, CT, USA
e-mail: matthew.schmitt@wchn.org

R. Scatena
Yale University School of Medicine, New Haven, CT, USA

Department of Medicine, Section of Pulmonary, Critical Care and Sleep Medicine, Norwalk Hospital, Norwalk, CT, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_48

maintained on lower doses of propranolol and methimazole. Repeat laboratory testing revealed improved levels of free T4 and free T3. He was able to be transferred out of the medical ICU on the fourth day, and discharged home on medical therapy one week later.

Principles of Management

Incidence

In patients with critical illness, thyroid function plays a significant role in maintaining the normal physiologic environment and any disturbance can adversely affect the outcome and prognosis in these patients [1]. Thyroid storm is defined as a rare, life-threatening augmentation of the manifestations of severe thyrotoxicosis.

Prevalence estimates for the condition are roughly 1 % of hospitalized subjects with hyperthyroidism, and less than 10 % of patients hospitalized for thyrotoxicosis [2]. The condition is more frequent in the female gender, with a female to male ratio of about 3 to 1 [3].

Prompt identification and adequate treatment is essential as prognosis is unfavorable in many cases [4]. Support of the patient in an intensive care unit is crucial, given the mortality rate of approximately 10–30 % [3, 5]. Death is attributed to multi-organ failure in about 25 % of patients and because of congestive heart failure in about 20 % of patients [3].

Etiology

The factors contributing to the development of thyroid storm have not been completely elucidated. Levels of serum free T4, the prohormone, and free T3, the active thyroid hormone, are approximately as high as in patients with uncomplicated thyrotoxicosis. The severity of presentation is not correlated with hormone levels [3]. The most agreed upon hypotheses concerning the development of thyroid storm include increased responsiveness to catecholamines, a rapid rate of increase in serum thyroid hormone levels, or enhanced cellular responses to thyroid hormone [5]. There are numerous known triggers of thyrotoxic storm, and the most common triggers are listed below in Table 48.1 [6].

Presentation

In many cases thyroid storm presents as multi-organ failure with the constellation of symptoms resembling an exaggeration of the usual symptoms of hyperthyroidism [7, 8]. The organs mainly affected by excess thyroid hormone are the heart, nervous system, gastrointestinal tract, and the liver [9–12]. Cardiovascular symptoms include atrial tachycardia to rates that can exceed 140 beats/min, congestive heart failure, and atrial fibrillation. Hypotension, ventricular tachycardia, arrhythmia, and death from cardiovascular collapse can also occur [13]. Fever is a frequent event, and hyperpyrexia of 104 °F to 106 °F is common. Altered mental status with agitation, anxiety, delirium, psychosis, stupor, or coma is often encountered and considered by many experts to be integral to the diagnosis [14]. Severe nausea, abdominal pain, vomiting, diarrhea, or hepatic failure with jaundice may occur [15]. Physical examination may show warm and moist

Table 48.1 Triggers of thyroid storm

Common Known Triggers of Thyroid Storm:
Withdrawal of anti-thyroid drug therapy
Iodide compound intake or radioiodine (I^{131} or I^{123}) therapy in patients with Graves' disease or autonomously functioning thyroid nodules
Major surgery, particularly thyroidectomy
Trauma, especially in the neck area
Systemic infections
Pregnancy/parturition
Diabetic ketoacidosis
Severe emotional stress
Cerebrovascular disease
Pulmonary thromboembolism
Intense exercise
Use of tyrosine-kinase inhibitors (particularly sorafenib)
Minor surgery (such as extraction of teeth)

Papi et al. [6]

skin, hand tremor, lid lag, goiter, and ophthalmopathy (in the occurrence of Graves' disease) [15]. Clinicians should be aware that clinical symptomatology can pose difficulties in distinguishing thyroid storm from other medical emergencies, such as neuroleptic malignant syndrome, malignant hyperthermia, and pheochromocytoma [7].

Diagnosis

In critically ill patients the diagnosis of thyroid storm is essentially a clinical one with laboratory tests of thyroid function being confirmatory in the appropriate setting [14]. Clinicians may base the diagnosis of thyroid storm on several factors, which include a history of thyroid disease and potential triggering factors, typical signs and symptoms, and serum free T3 and free T4 concentrations exceeding the normal reference range and suppression of TSH levels [16]. In all patients with suspected thyroid storm, thyroid function tests (TSH, free T4, and free T3) should be assessed. Because hormone levels in thyroid storm patients are generally not higher than in patients with uncomplicated overt hyperthyroidism, the degree of hyperthyroidism is not a diagnostic criterion [17]. The clinical findings in suspected patients are frequently associated with elevation of serum bilirubin and transaminase levels, hyperglycemia, low total cholesterol values, leukocytosis or leukopenia, and electrolyte imbalances [18]. Hyperglycemia is due to a catecholamine-induced inhibition of insulin release and increased glycogenolysis. Hypercalcemia may be secondary to hemoconcentration and enhanced bone resorption [17]. Radioiodine uptake is not necessary for the diagnosis in suspected patients, and treatment should not be delayed for scanning in patients with clinical manifestations compatible with thyroid storm [15].

Treatment

Treating thyroid storm generally follows the same principles as treating those with uncomplicated hyperthyroidism, except that the medications are given more frequently and in higher doses [15]. Because the mortality rate of thyroid storm can be substantial, full support of the patient in an intensive care unit is considered essential [3, 5]. The specific principles of thyroid storm treatment are based upon case studies and clinical experience [15]. In addition to specific therapy directed against the thyroid, supportive therapy (e.g., supplemental oxygen, intubation and mechanical ventilation, fluid resuscitation, electrolyte correction) and recognition and treatment of precipitating factors are crucial components in optimizing the final outcome [15].

In general the therapeutic regimen typically relies on the following medications, with a recommended medication dosing guide shown below in Table 48.2.

Table 48.2 Medication dosing guide

*Principles of medication dosing outlined below are based upon clinical experience and case studies
Beta-Blockers
Propranolol: 60–80 mg PO every 4–6 h; 1–2 mg IV every 4–8 h
Esmolol: Loading dose of 250–500 mcg/kg followed by infusion at 50–100 mcg/kg per minute
Thionamides
Propylthiouracil (PTU): 200 mg PO every 4 h; PTU enema (eight 50 mg tablets of PTU dissolved in 90 mL of sterile water); PTU suppository (200 mg of PTU dissolved in polyethylene glycol base)
Methimazole: 15–20 mg PO every 4–6 h
Iodine Solutions
Potassium iodide-iodine (Lugol's) solution: 10 drops (8 mg iodide/iodine per drop [0.05 mL] every 6 h
Saturated solution of potassium iodide (SSKI): 5 drops (50 mg iodide/drop [0.05 mL] every 6 h
*Iodine solutions can be irritating and should be diluted in 240 mL or more of beverage
Iodinated radiocontrast agents
Sodium ipodate: 500–1000 mg/day PO
Iopanoic acid: 500–1000 mg/day PO
Glucocorticoids
Hydrocortisone: 100 mg IV every 8 h
Lithium
Lithium carbonate: 300 mg PO every 6–8 h
*Renal and neurologic toxicity limit lithium utility

Ross [15]
Papi et al. [6]
*No universally agreed upon doses and routes of administration for the medications used to treat thyroid storm

Beta-Blockers

These medications are cornerstones of treatment in most patients with severe hyperthyroidism. Caution is advised when using these medications in patients with heart failure; however it is important to note that improvement in cardiac function may be seen with control of tachycardia. Propranolol is often the drug of choice because it antagonizes the increased binding of catecholamines to beta-adrenergic receptors and it reduces the peripheral deiodination of T4 to T3, the process by which the majority of T3 is created [6]. An alternative to propranolol is to utilize the short-acting beta-blocker esmolol. Esmolol use permits rapid titration of the drug to achieve the desired effect while minimizing adverse reactions [19]. In patients with severe reactive airways disease, cardioselective beta-blockers may be considered, but should be used with caution [15].

Thionamides

Thionamides block de novo thyroid hormone synthesis roughly within 1–2 h after administration. However, it is noted that these medications have no effect on the release of preformed hormone from the thyroid gland. In the United States the thionamide drugs available are propylthiouracil (PTU) and methimazole.

No consensus data exist that show patients do better clinically with one thionamide over another. Some sources suggest starting treatment for life-threatening thyroid storm with PTU since it can be administered regularly every four hours in an intensive care unit, and because PTU, but not methimazole, blocks T4 to T3 conversion [20]. However, because methimazole has a longer duration of action and is less hepatotoxic than PTU it may be preferred for severe but not life-threatening hyperthyroidism. Patients who are started on PTU in the intensive care unit should be transitioned to methimazole before discharge from the hospital.

Both propylthiouracil and methimazole can be given orally via tablets or suspended in liquid. Both drugs can also be made up as a suppository or enema for rectal administration [17, 21, 22]. There are also case reports of PTU being given intravenously in order to attain euthyroidism [21].

Iodine Containing Solutions

These medications help block the release of T4 and T3 from the thyroid gland within hours and are traditionally used in the treatment of thyroid storm. Importantly, the administration of iodine should be delayed for at least one hour after thionamide administration in order to prevent the iodine from acting as substrate for new hormone synthesis [17]. Oral doses are potassium iodide-iodine (Lugol's) solution or saturated solution of potassium iodide (SSKI). Iodine containing solutions can also be given rectally [21, 22]. Because these solutions may irritate the gastrointestinal tract, they should be diluted in 240 mL or more of beverage and taken with food. Local esophageal or duodenal mucosal injury and hemorrhage have been reported after oral administration of potassium iodide-iodine solution [23].

Glucocorticoids

Glucocorticoids reduce T4 to T3 conversion. They may also treat potentially associated adrenal insufficiency and have a direct effect on any underlying thyroid related autoimmune process [24]. Limited data suggest improved outcomes with the use of glucocorticoids for the treatment of thyroid storm [25]. Therefore, it is reasonable to consider administering hydrocortisone in patients with thyroid storm.

Patients Unable to Take a Thionamide

Some patients must discontinue thionamides because of side effects such as agranulocytosis, hepatotoxicity, or allergic reaction. In such patients who require urgent treatment of hyperthyroidism, thyroidectomy is the treatment of choice. Preoperative treatment of thyrotoxicosis is required in patients who are to undergo surgery, and this typically involves medications such as beta-blockers, glucocorticoids, and iodine containing solutions [26].

Evidence Contour

Several aspects involving the diagnosis and management in patients with suspected thyroid storm remain without clear consensus given limited

data and clinical trials. These approaches should be considered attempts to find the optimal diagnosis and treatment for these patients in the face of the available medical literature. As such, caution should be taken when applying these approaches as novel risks and benefits may be revealed by the evolving medical literature.

Diagnostic Clinical Tools

Definitively diagnosing thyroid storm can be difficult as there are no universally accepted criteria or validated clinical tools for diagnosis [15]. However, in an effort to standardize and objectify thyroid storm Mazzaferri et al. introduced diagnostic criteria for thyroid storm in 1969 [25]. In 1993 Burch and Wartofsky delineated a point system assessing degrees of dysfunction in various systems to identify thyroid storm patients more definitively [17], as shown in Table 48.3. While the scoring system is likely sensitive, it is not very specific [15]. Alternative diagnostic criteria based upon clinical findings similar to that of the Burch and Wartofsky scoring system has been proposed [3]. More recently, Akamizu et al. reported diagnostic criteria for thyroid storm based on Japanese nationwide surveys. They utilized five symptoms, which included central nervous system manifestations, fever, tachycardia, congestive heart failure, and gastrointestinal-hepatic manifestations, to define diagnostic criteria for cases of thyroid storm, with "definite" having at least 4 and "suspected" meeting at least three criteria [6]. Overall, the diagnostic criteria for thyroid storm proposed by Akamizu et al. does not appear to offer substantial advantage over the prior Burch and Wartofsky scoring system. It is worth noting that in the Japanese nationwide survey series thyroid storm patients affected by Graves' disease exceeded 95 %, whereas in some non-Asian series a higher incidence of patients with toxic nodular goiter, iodine induced hyperthyroidism, or destructive thyroiditis were seen [6]. Therefore, certain physical and clinical manifestations may be expressed to different degrees in different patient populations [6].

Table 48.3 Diagnostic criteria for thyroid storm

Diagnostic parameters	Point score
Thermoregulatory dysfunction	5
Temperature	10
99–99.9 °F	15
100–100.9 °F	20
101–101.9 °F	25
102–102.9 °F	30
103–103.9 °F	
≥104.0 °F	
Central nervous system effects	0
Absent	10
Mild (agitation)	20
Moderate (delirium, psychosis, extreme lethargy)	30
Severe (seizures, coma)	
Gastrointestinal-hepatic dysfunction	0
Absent	10
Moderate (diarrhea, nausea/vomiting, abdominal pain)	20
Severe (unexplained jaundice)	
Cardiovascular dysfunction	5
Tachycardia (*beats/min*)	10
99–109	15
110–119	20
120–129	25
130–139	
≥140	
Atrial fibrillation	0
Absent	10
Present	
Congestive heart failure	0
Absent	5
Mild (pedal edema)	10
Moderate (bibasilar rales)	15
Severe (pulmonary edema)	
Precipitating event	0
Absent	10
Present	

Adapted from: Burch and Wartofsky [4]
Scoring system: A score of 45 or greater is highly suggestive of thyroid storm; a score of 25–44 is suggestive of impending storm; and a score below 25 makes thyroid storm unlikely

Iodinated Radiocontrast Agents

Sodium ipodate and iopanoic acid, two oral iodine-containing drugs marketed as oral cholecystographic agents, have been used in the treatment of hyperthyroidism and thyroid storm. However, at this time neither iopanoic acid nor ipodate are available in the United States, and it is

unclear if they will ever again be marketed in the United States [27]. These agents are potent inhibitors of 5′-monodeiodinase, thereby impairing the extrathyroidal conversion of T4 to T3. Also, the release of iodine in pharmacologic quantities from these drugs is able to block thyroid hormone release. Doses in most studies have ranged from 500 to 1000 mg as a single daily dose. Both agents do have limitations to their use, as they are not as effective as methimazole or propylthiouracil in controlling the hyperthyroidism, and the relapse rate after therapy is discontinued is higher [27]. There are also additional problems with the use of these drugs. These problems include inducing hyperthyroidism that is resistant to conventional doses of thionamides and providing iodine substrate for de novo hormone synthesis by autonomous thyroid tissue, leading to more severe hyperthyroidism [28]. The agents should only be considered for use in the setting of toxic adenoma or toxic multinodular goiter if thyroid hormone synthesis is first blocked by the administration of a thionamide [27].

Extracorporeal Plasmapheresis

Plasmapheresis is an additional tool for removing circulating T4 and T3 in patients who do not respond quickly to conventional standard therapy [6]. This is possible because a significant proportion of thyroid hormone is bound to serum proteins and plasmapheresis is able to remove protein bound substances including thyroid hormones. Because one of the tenets of conventional treatment of thyroid storm is to subdue the effect of T4 and T3 on peripheral tissue, the removal of circulating T4 and T3 by plasmapheresis represents a possible therapeutic option [14]. There are multiple case reports highlighting the successful use of plasmapheresis in the treatment of patients with thyroid storm. In one report, a woman with Graves' disease and methimazole induced agranulocytosis developed thyroid storm after methimazole was discontinued [29]. Treatment with plasmapheresis resulted in marked improvement in thyrotoxicosis within three days, allowing thyroidectomy for definitive therapy [29].

L-Carnitine

L-Carnitine is a quaternary amine ubiquitous in mammalian tissues. It is a key factor in energy production, and its cellular levels decrease in several diseases, including hyperthyroidism and thyroid storm [30]. L-Carnitine has been shown to inhibit thyroid hormone entry into cell nuclei, indicating that it is a naturally occurring inhibitor of thyroid hormone action [31]. Oral doses usually range between 1 and 4 g per day. L-Carnitine was able to reverse and prevent symptoms of hyperthyroidism in a single randomized, double-blind, and placebo-controlled clinical trial [31]. It has also been used effectively together with low doses of methimazole in successive thyroid storms [30].

References

1. Nylen ES, Alarifi AA. Humoral markers of severity and prognosis of critical illness. Best Pract Res Clin Endocrinol Metab. 2001;15:553–73.
2. Dillmann WH. Thyroid Storm. Curr Ther Endocrinol Metab. 1997;6:81–5.
3. Akamizu T, Satoh T, Iozaki O, Suzuki A, Wakino S, Iburi T, et al. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. Thyroid. 2012;22:661–79.
4. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am. 1993;22:263–77.
5. Sarlis NJ, Gourgiotis L. Thyroid emergencies. Rev Endocr Metab Disord. 2003;4:129.
6. Papi G, Corsello SM, Pontecorvi A. Clinical concepts on thyroid emergencies. Front Endocrinol. 2014;5:102.
7. Chong HW, See KC, Phua J. Thyroid storm with multiorgan failure. Thyroid. 2010;20:333–6.
8. Jiang YZ, Hutchinson KA, Bartelloni P, Manthous CA. Thyroid storm presenting as multiple organ dysfunction syndrome. Chest. 2000;118:877–9.
9. Martinez-Diaz GJ, Formaker C, Hsia R. Atrial fibrillation from thyroid storm. J Emerg Med. 2012;42:e7–9.
10. Kobayashi C. Severe starvation hypoglycemia and congestive heart failure induced by thyroid crisis, with accidentally induced severe liver dysfunction and disseminated intravascular coagulation. Intern Med. 2005;44:234–9.
11. Abbasi B, Sharif Z, Sprabery LR. Hypokalemic thyrotoxic periodic paralysis with thyrotoxic psychosis and hypercapnic respiratory failure. Am J Med Sci. 2010;340:147–53.

12. Hsiao FC, Hung YJ, Hsieh CH, Wu LY, Shih KC, He CT. Abdominal pain and multiorgan dysfunction syndrome in a young woman. Am J Med Sci. 2007;334:399–401.
13. Ngo SY, Chew HC. When the storm passes unnoticed – a case series of thyroid storm. Resuscitation. 2007;73:485.
14. Bajwa SS, Jindal R. Endocrine emergencies in critically ill patients: challenges in diagnosis and management. Indian J Endocr Metab. 2012;16:722–7.
15. Ross DS. Thyroid storm. In: Cooper DS, editor. UpToDate, Waltham: UpToDate. Accessed on 14 Jan 2015.
16. Pimental L, Hansen KN. Thyroid disease in the emergency department: a clinical and laboratory review. J Emerg Med. 2005;28:201–9.
17. Nayak B, Burman K. Thyrotoxicosis and thyroid storm. Endocrinol Metab Clin North Am. 2006;35:663.
18. Hull K, Horenstein R, Naglieri R, Munir K, Ghany M, Celi FS. Two cases of thyroid storm-associated cholestatic jaundice. Endocr Pract. 2007;13:476–80.
19. Brunette DD, Rothong C. Emergency department management of thyrotoxic crisis with esmolol. Am J Emerg Med. 1991;9:232.
20. Cooper DS, Saxe VC, Meskell M, et al. Acute effects of propylthiouracil (PTU) on thyroidal iodide organification and peripheral iodothyronine deiodination: correlation with serum PTU levels measured by radioimmunoassay. J Clin Endocrinol Metab. 1982;54:101.
21. Nabil N, Miner DJ, Amatruda JM. Methimazole: an alternative route of administration. J Clin Endocrinol Metab. 1982;54:180.
22. Walter Jr RM, Bartle WR. Rectal administration of propylthiouracil in the treatment of Graves' disease. Am J Med. 1990;88:69.
23. Kinoshita H, Yasuda M, Furumoto Y, et al. Severe duodenal hemorrhage induced by Lugol's solution administered for thyroid crisis treatment. Intern Med. 2010;49:759.
24. Tsatsoulis A, Johnson EO, Kalogera CH, et al. The effect of thyrotoxicosis on adrenocortical reserve. Eur J Endocrinol. 2000;142:231.
25. Mazzaferri EL, Skillman TG. Thyroid storm. A review of 22 episodes with special emphasis on the use of guanethidine. Arch Intern Med. 1969;124:684.
26. Langley RW, Burch HB. Perioperative management of the thyrotoxic patient. Endocrinol Metab Clin North Am. 2003;32:519.
27. Ross DS. Iodinated radiocontrast agents in the treatment of hyperthyroidism. In: Cooper DS, editor. UpToDate. Waltham: UpToDate. Accessed on 16 Jan 2015.
28. Caldwell G, Errington M, Toft AD. Resistant hyperthyroidism induced by sodium iopodate used as treatment for Graves' disease. Acta Endocrinol (Copenh). 1989;120:215.
29. Vyas AA, Vyas P, Fillipon NL, et al. Successful treatment of thyroid storm with plasmapheresis in a patient with methimazole induced agranulocytosis. Endocr Pract. 2010;16:673.
30. Benvenga S, Lapa D, Cannavo S, Trimarchi F. Successive thyroid storm treated with L-carnitine and low doses of methimazole. Am J Med. 2003;115:417–8.
31. Benvenga S, Ruggeri RM, Russo A, Lapa D, Campenni A, Trimarchi F. Usefulness of L-carnitine, a naturally occurring peripheral antagonist of thyroid hormone action, in iatrogenic hyperthyroidism: a randomized, double-blind, placebo-controlled clinical trial. J Clin Endocrinol Metab. 2001;86:3579–94.

Adrenal Insufficiency

49

Amy M. Ahasic and Anuradha Ramaswamy

Case Presentation

A 54-year-old man with a history of alpha-1 antitrypsin deficiency complicated by cirrhosis, type 2 diabetes mellitus, and hypothyroidism presented after being found unresponsive at home. In the field, he had a heart rate of 44 beats per minute (bpm) in sinus rhythm, and a fingerstick blood glucose of < 30 mg/dL. He was administered 2 amps of 50 % dextrose in water.

On arrival to the Emergency Department, his fingerstick blood glucose was 164 mg/dL but again declined, and a 10 % dextrose drip was initiated. His heart rate ranged as low as 31 bpm with concomitant hypotension; systolic blood pressure was 75 mmHg. Atropine 1 mg was administered intravenously with minimal effect. A central line was placed, and vasopressors were initiated. He was afebrile. Glasgow Coma Score was 12 with ongoing snoring breaths and gurgling of secretions. Respiratory rate was as low as 9 breaths per minute. He was intubated. A head CT revealed no acute intracranial abnormalities. He was admitted to the intensive care unit (ICU).

According to family, he had not been experiencing fever or chills, but he had complained of fatigue, abdominal pain, and feeling cold over the last few months. He had chronic ascites and lower extremity edema controlled with paracenteses and diuretics. His medications at the time of admission included midodrine, rifaximin, lactulose, long-acting insulin, and levothyroxine.

Pertinent laboratory values included a white blood cell count of 8000, a normal ammonia level, a serum sodium of 136 mmol/L, a serum potassium of 3.8 mmol/L, an uncorrected anion gap of 11, and a serum albumin of 2.9 g/dL. Serum creatinine was 1.9 mg/dL, which was improving after a recent episode of acute kidney injury.

Question What is the differential diagnosis?

Answer The differential diagnosis for this patient presenting with altered mental status, hypotension, bradycardia, and hypoglycemia is broad.

Most likely diagnoses include septic shock, hypothyroidism with myxedema coma, drug overdose or ingestion (such as beta-blocker or calcium channel blocker), and adrenal insufficiency.

Given this differential, the patient was started empirically on broad spectrum antibiotics. Ongoing supportive care included dextrose and vasopressor infusion. Cultures of blood, sputum, urine, and ascitic fluid were all negative, and radio-

A.M. Ahasic (✉)
Department of Internal Medicine, Section of Pulmonary, Critical Care and Sleep Medicine, Yale University School of Medicine,
New Haven, CT, USA
e-mail: amy.ahasic@yale.edu

A. Ramaswamy
Section of Pulmonary, Critical Care and Sleep Medicine, Yale University School of Medicine,
New Haven, CT, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_49

graphic imaging did not reveal evidence of a specific infectious focus making septic shock unlikely. Free thyroxine and total T4 were within normal limits, ruling out hypothyroid-related crisis. Serum and urine toxicology screens were negative although these panels do not include beta-blockers or calcium channel blockers. Beta-blocker overdose can present with hypotension, bradycardia, hypoglycemia, and mental status changes. Calcium channel blocker overdose can also present with hypotension and bradycardia, but typically it causes hyperglycemia, although this can be masked in a patient taking long-acting insulin. This patient had not been prescribed and did not have access to either beta-blockers or calcium channel blockers, however, making overdose unlikely.

Adrenal insufficiency with acute crisis was thus considered the most likely diagnosis given symptoms of fatigue and abdominal pain, hypoglycemia and shock. The patient also has other endocrinopathies (i.e. diabetes and hypothyroidism) that increase his risk of coexisting adrenal disease [1]. He was started on intravenous hydrocortisone, which facilitated rapid weaning off of vasopressors. A random cortisol level was drawn and was reported as 7.8 mcg/dL. Sixty minutes after administration of 250 mcg of ACTH, a maximum value of 11 mcg/dL was obtained. His mental status also rapidly improved following the administration of intravenous hydrocortisone, and he was extubated the day after his admission. CT scan of the abdomen and pelvis showed no obvious hemorrhage or other pathology involving the adrenal glands.

Principles of Management

Presentation of Adrenal Insufficiency

The presentation of the patient with adrenal insufficiency will vary based on whether adrenal insufficiency is primary or secondary. Primary adrenal insufficiency, or Addison's disease, is caused by deficiency of all cortical hormones (cortisol, aldosterone, and androgens) due to local adrenocortical disease. It is commonly caused by autoimmune or congenital disease, drugs, infection (e.g. tuberculosis), or adrenal hemorrhage [2]. The remainder of the hypothalamic-pituitary-adrenal (HPA) axis is typically intact. In primary adrenal insufficiency, cortisol levels are low and adrenocorticotropic hormone (ACTH) levels are high.

Secondary or tertiary adrenal insufficiency (commonly grouped together as secondary adrenal insufficiency) occurs due to pituitary or hypothalamic disorders, respectively. In secondary adrenal insufficiency, both cortisol and ACTH levels are low [3]. Broadly speaking, secondary adrenal insufficiency results from dysregulation of the HPA axis and constitutes the most common cause of adrenal insufficiency in the ICU population. Estimates of the incidence of adrenal insufficiency in critically ill patients range from 0 to 30 %, and as high as 40–60 % in septic shock [4–6]. Many drugs can contribute to adrenal insufficiency, including exogenous glucocorticoid therapy, ketoconazole, megestrol, antidepressants (e.g., imipramine), antipsychotics (e.g., chlorpromazine), etomidate, and mifepristone [1–3].

Acute adrenal crisis is a life-threatening medical emergency caused by insufficient levels of cortisol. In some cases, this may be the initial presentation of adrenal insufficiency [3]. Addisonian crisis refers to acute crisis from primary adrenal disease. Clinical features of an acute adrenal crisis can include fever, weakness and fatigue, orthostasis, abdominal pain, vomiting, hypotension refractory to fluid resuscitation and vasopressors, eosinophilia, electrolyte disturbances including hyponatremia, hypoglycemia, and shock. Additionally, in primary adrenal insufficiency (Addison's disease), patients may exhibit salt craving, hyperkalemia with metabolic acidosis, and hyperpigmentation [4, 7].

Absolute Versus Relative Adrenal Insufficiency and Critical-Illness Related Corticosteroid Insufficiency (CIRCI)

"Absolute" adrenal insufficiency refers to decreased baseline production of adrenal cortical hormones, as in primary adrenal insufficiency. In

the absence of acute stress, absolute adrenal insufficiency is diagnosed with a morning cortisol level < 3 mcg/dL that remains lower than 18–20 mcg/dl despite ACTH stimulation testing (see below for discussion of ACTH stimulation testing) [6].

Absolute adrenal insufficiency with acute adrenal crisis is seen less commonly in the ICU than CIRCI, sometimes referred to as "relative" adrenal insufficiency. CIRCI has no standardized diagnostic criteria, but it is defined as inadequate cellular corticosteroid activity for the severity of critical illness [8]. It is commonly seen in the critically ill population and can present much more subtly than acute Addisonian crisis. Patients may have cortisol levels within the normal range or above, but levels are inappropriately low for the acute stress of critical illness.

CIRCI occurs due to various pathophysiologic mechanisms including decrease in corticosteroid-binding globulin (CBG) by up to 50 %, down-regulation of steroid receptors, decreased translocation of receptors into the nucleus, end-organ resistance to cortisol, decreased synthesis of cortisol due to low levels of cholesterol substrates, and excess levels of inflammatory mediators and cytokines which in turn inhibit the HPA axis and adrenal activity [9–11]. CIRCI typically occurs in the setting of an exuberant inflammatory response temporarily blunting cortisol secretion during a severe illness; steroid resistance in tissues and other mechanisms may also contribute to its presentation [5]. While CIRCI is typically seen in ICU patients with diagnoses such as pneumonia, sepsis, acute respiratory distress syndrome (ARDS), trauma, and burns [3, 11], it has also been described after administration of certain medications such as etomidate [3, 5]. Patients with underlying severe liver dysfunction have higher rates of adrenal failure ("hepatoadrenal syndrome"), possibly due to lower lipoprotein levels for steroid synthesis [12].

Physicians should have a high index of suspicion for the occurrence of adrenal insufficiency including CIRCI in any ICU patient who has persistent hypotension requiring vasopressors. CIRCI can develop at any time during critical illness and is not always present at ICU admission. Adrenal insufficiency is known to increase mortality in critically ill patients [7].

Interpretation of Test Results in Critically Ill Patients

The two most common tests used to diagnose adrenal insufficiency in the non-critically ill population are measurement of morning cortisol and the ACTH stimulation test. Both tests are more challenging to interpret in critically ill patients.

Measurement of Serum Cortisol

Free unbound cortisol is the physiologically active form, but the serum cortisol does not distinguish free cortisol; it detects total levels of cortisol circulating in the blood, both protein-bound and unbound. Approximately 90 % of cortisol is protein-bound, either to CBG (70 %) or to albumin (10–20 %) [7]. In critical illness, the concentration of CBG can decrease by up to 50 %, and many ICU patients are also hypoalbuminemic, resulting in a higher percentage of free cortisol in circulation. Serum cortisol levels may thus underrepresent the level of active cortisol in these patients, especially when albumin levels are below 2.5 mg/dL [8, 13].

Measurement of serum free cortisol is possible, but testing is more costly, not widely available, and is difficult to interpret as there is no clearly defined normal range for ICU patients. Turnaround time is also longer, making it impractical when therapeutic decisions need to be made quickly in critically ill patients.

Random (non-morning) cortisol levels are commonly used in the ICU as the diurnal variation in secretion of cortisol is typically lost during critical illness.

ACTH Stimulation Test

The ACTH stimulation test is used to help confirm the presence of adrenal insufficiency, and to characterize the disorder as primary vs. secondary. The test starts by obtaining a baseline serum cortisol level after which 250 mcg of exogenous ACTH is injected intravenously or intramuscularly. Cortisol levels are then measured at 30 and

60 min after ACTH administration. The change in cortisol is calculated by subtracting the baseline level from the highest value measured after ACTH administration. An increase of greater than 9 mcg/dL is considered an adequate adrenal response based on studies in patients with septic shock [6, 8].

The ACTH stimulation test can be performed at any time of day. The major drawback of the test is that it does not measure the intrinsic function of the HPA axis, but merely detects the ability of the stressed adrenal cortex to produce additional cortisol. Thus, partial adrenal insufficiency as can be seen with acute ACTH deficiency, such as after acute hypothalamic or pituitary injury, can be missed [7, 14].

Interpretation of Random Cortisol and ACTH Stimulation Testing

Multiple diagnostic strategies have been studied for detecting CIRCI in ICU patients. Please see Table 49.1 for suggested diagnostic criteria stratified by serum albumin. More simplified criteria of a random cortisol of < 10 mcg/dL, or an increase in cortisol of < 9 mcg/dL after ACTH administration have been proposed in consensus guidelines as diagnostic criteria for CIRCI [8]. The random cortisol and ACTH stimulation tests may be employed to confirm suspected CIRCI; screening ICU patients for CIRCI is not recommended. Of note, there is no clear cutoff value for random cortisol above which ACTH stimulation is not indicated and CIRCI is definitively ruled out. However, some authors have suggested a random cortisol of > 34 mcg/dL as consistent with the absence of CIRCI [15]. See Fig. 49.1 for a diagnostic algorithm for CIRCI.

Table 49.1 Suggested diagnostic criteria for adrenal insufficiency by serum albumin status

	Albumin >2.5 g/dl	Albumin <2.5 g/dl
Total cortisol (μg/dl [nmol/l])		
Baseline	15 (410)	10 (275)
Stimulated	20 (550)	15 (410)
Free cortisol (μg/dl [nmol/l])		
Baseline	1.8 (50)	1.8 (50)
Stimulated	3.0 (85)	3.0 (85)

From Marik [10]. Open Access. Creative Commons Attribution 4.0 International Public License

In patients with septic shock, the routine use of either random serum cortisol or ACTH stimulation testing are not recommended for broad screening for hydrocortisone replacement therapy [5, 16]. (See "Steroid replacement in septic shock" below.)

Steroid Replacement Strategies

Choice of Steroid

Hydrocortisone is considered the steroid of choice for replacement therapy in patients with acute adrenal crisis and with CIRCI including septic shock with persistent hypotension despite fluid resuscitation [16]. There is no evidence to recommend routine mineralocorticoid (fludrocortisone) replacement for patients in the ICU, unless they have known or suspected primary adrenal insufficiency. Even in Addisonian crisis, hydrocortisone along with saline resuscitation is probably sufficient for initial treatment in the acute setting because hydrocortisone does have some mineralocorticoid activity. A study evaluating hydrocortisone alone vs. hydrocortisone plus fludrocortisone in patients with septic shock failed to show any significant differences in outcomes with the addition of the mineralocorticoid [17].

Steroid administration for treatment of presumed adrenal crisis should never be delayed in order to perform random cortisol and ACTH stimulation testing. Dexamethasone may be useful in such patients because, unlike hydrocortisone, it does not interfere with measurements of serum cortisol. Dexamethasone can cause long-term suppression of the HPA axis, however, and thus it is not generally recommended for ongoing steroid replacement [8].

Dose and Duration

In suspected acute adrenal crisis, an initial dose of 100 mg hydrocortisone IV followed by 100–200 mg daily is generally adequate [1, 18]. For CIRCI in the setting of severe sepsis and septic shock, 200 mg of hydrocortisone divided into

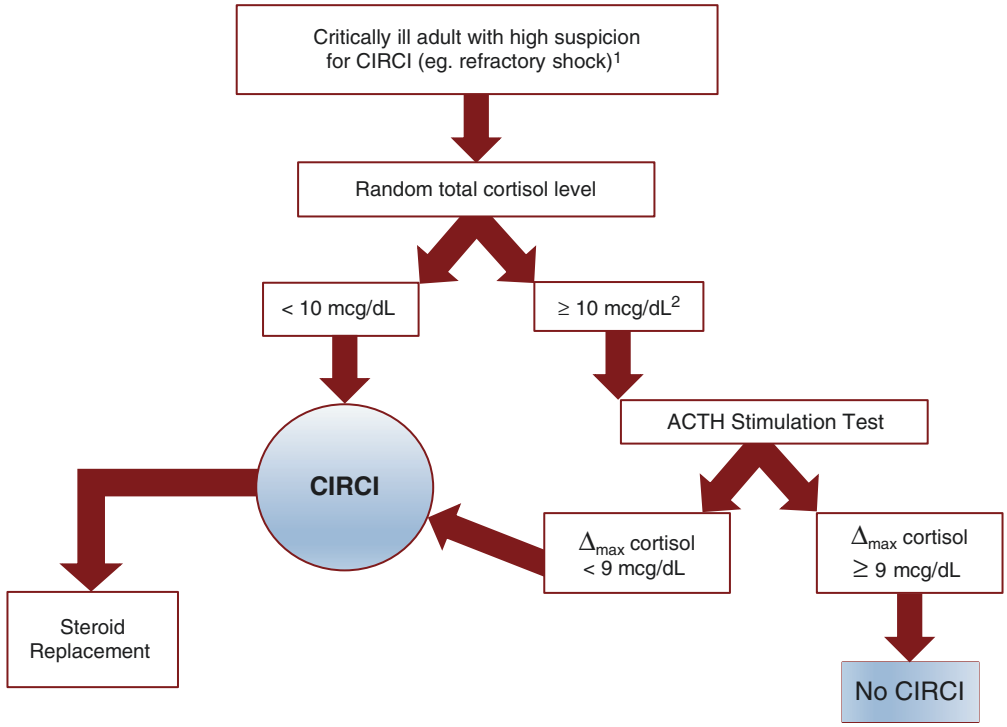


Fig. 49.1 Decision Tree for Investigation of CIRCI in Critically Ill Adults. *CIRCI* critical illness-related corticosteroid insufficiency,;*ACTH* adrenocorticotropic hormone, Δ_{max} maximum change in cortisol level after ACTH stimulation. [1]Routine screening for all patients with septic shock is not recommended. [2]There is no firm cutoff in random cortisol above which CIRCI is ruled out, but some authors have suggested that a random cortisol of >34 mcg/dL rules out significant CIRCI, and thus ACTH stimulation would not be performed (see Cooper and Stewart [15])

3–4 intermittent doses daily has been recommended [16]. Hydrocortisone is typically not tapered until patients are no longer requiring vasopressors. Tapering can occur over several days to prevent rebound hypotension and adverse immunologic effects. Discontinuation of steroids after tapering may be contraindicated in patients with adrenal crisis not consistent with CIRCI as they may require ongoing low-dose corticosteroid replacement.

Concurrent Fluid Management

In primary adrenal insufficiency, patients have urinary salt-wasting with subsequent volume depletion that should be replaced using 0.9% saline. In secondary adrenal insufficiency, patients do not exhibit salt-wasting, but they do have decreased vascular tone resulting in hypotension, and thus isotonic fluid resuscitation is also generally necessary in the acute setting. Dextrose can be administered concurrently in hypoglycemic patients.

Additional Testing

Because CIRCI is dynamic, generally reversible, and can occur at any time during a patient's ICU stay, routine follow-up testing after treatment of acute critical illness is not generally necessary. However, a small number of patients with CIRCI may develop prolonged adrenal dysfunction due to adrenal infarction or hemorrhage as seen with sepsis or coagulopathy, or injury from medication [5, 19]. Such patients warrant close follow-up and additional testing in the outpatient setting.

There are no guidelines to suggest routine adrenal or brain imaging for CIRCI. However, if

infection, bleeding, tumor, or other pathologic disease of the adrenals is specifically suspected, then abdominal CT scanning may be indicated [18]. Additionally, MRI of the pituitary and hypothalamus may be useful in evaluating patients with probable secondary adrenal insufficiency not consistent with CIRCI, and without other obvious causes. Unless there is concern for a more emergent diagnosis, this may be deferred to the outpatient setting if adrenal insufficiency persists.

Evidence Contour

Steroid Replacement in Septic Shock

In 2002, a large prospective study demonstrated that 7 days or hydrocortisone and fludrocortisone reduced the 28-day mortality for patients with septic shock [20]. However, the subsequent Corticosteroid Therapy in Septic Shock (CORTICUS) trial failed to replicate any mortality benefit after treatment with hydrocortisone [21]. Patients receiving hydrocortisone did recover from shock more quickly, regardless of results of ACTH stimulation testing, but had a trend toward increased hospital-acquired infections. Furthermore, an observational study by the Surviving Sepsis Campaign showed an increase in hospital mortality in vasopressor-dependent patients receiving low-dose corticosteroid therapy [22].

Systematic reviews and meta-analyses have attempted to resolve the conflicting evidence. Several such studies have indicated that low dose corticosteroid therapy aids in reversal of shock, and thus patients who are vasopressor-dependent despite adequate fluid resuscitation may benefit from corticosteroid therapy [23–27]. However, ACTH stimulation testing has not been shown to accurately discriminate which patients with septic shock will benefit from steroid replacement [8, 16, 26].

Based on this body of evidence, the Surviving Sepsis Campaign no longer recommends routine use of steroid replacement therapy as part of its sepsis care bundles [28]. However, the most recent Surviving Sepsis Guidelines include a Grade 2C (weak) recommendation to consider steroid therapy in patients with severe, persistent, vasopressor-dependent septic shock [16].

ACTH Stimulation Test: Low Dose Versus High Dose

Administration of 250 mcg of ACTH is commonly used in ACTH stimulation testing. This "high dose" testing uses supraphysiologic dosing of ACTH, and thus a "low dose" test using only 1 mcg of ACTH has been used as an alternative. The low dose test has better sensitivity, is less expensive, and has been shown in at least one study to better delineate groups of patients with relative adrenal insufficiency in septic shock [4]. However, there is the practical concern of how to accurately dilute the 250 mcg dose, as well as concerns that much of the ACTH dose may bind to injection tubing leading to unknown dose delivery [18]. Furthermore, the high dose ACTH test is better validated, having been used in numerous studies in ICU patients [8, 20, 22, 23, 29] and therefore it remains the favored test in critically ill patients.

Role of Salivary Cortisol Testing

Salivary cortisol measurements have been used as a surrogate marker of free cortisol in the diagnosis of adrenal insufficiency [30–32], but salivary cortisol has not been validated as a standalone diagnostic test in adults with suspected CIRCI. A recent study in neurosurgical ICU patients showed a lack of diurnal variation in salivary cortisol production, similar to that seen with serum cortisol, but the authors described challenges in collecting saliva from intubated patients due to decreased salivary flow and dry oral mucosa, medication effects, fluid imbalances, mucosal breakdown, and contamination with blood [33].

Role of Etomidate and Opiates in Development of Adrenal Insufficiency

Etomidate is an anesthetic agent commonly used during rapid sequence intubation in critically ill patients. Etomidate can cause inhibition of adrenal 11-β-hydroxylase, however, and thus has been implicated in adrenal insufficiency. In the CORTICUS trial, patients who received etomidate were less likely to have a significant increase in cortisol after ACTH, and they had decreased survival at 28 days [21]. In the retrospective CORTICUS study, etomidate administration in critically ill patients was associated with a worse prognosis in patients not treated with steroids [29]. Etomidate has other benefits including a very short duration of action, decreased respiratory depression and less hypotension [34]. The balance of risks and benefits using etomidate for induction of anesthesia during intubation remains unclear in the context of adrenal insufficiency.

There is some evidence that opiates may also cause suppression of the HPA axis and could thus contribute to adrenal insufficiency. Opiates implicated have included fentanyl and morphine [35, 36]. Due to widespread opiate use in the intensive care unit it may be relevant to consider opiates as a contributor to adrenal insufficiency in some patients.

References

1. Bornstein SR. Predisposing factors for adrenal insufficiency. N Engl J Med. 2009;360(22):2328–39.
2. Neary N, Nieman L. Adrenal insufficiency: etiology, diagnosis and treatment. Curr Opin Endocrinol Diabetes Obes. 2010;17(3):217–23.
3. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. Lancet. 2014;383(9935):2152–67.
4. Asare K. Diagnosis and treatment of adrenal insufficiency in the critically ill patient. Pharmacotherapy. 2007;27(11):1512–28.
5. Marik PE. Critical illness-related corticosteroid insufficiency. Chest. 2009;135(1):181–93.
6. Annane D, Maxime V, Ibrahim F, Alvarez JC, Abe E, Boudou P. Diagnosis of adrenal insufficiency in severe sepsis and septic shock. Am J Respir Crit Care Med. 2006;174(12):1319–26.
7. Hamrahian A. Adrenal function in critically ill patients: how to test? When to treat? Cleve Clin J Med. 2005;72(5):427–32.
8. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med. 2008;36(6):1937–49.
9. Marik PE, Zaloga GP. Adrenal insufficiency in the critically ill: a new look at an old problem. Chest. 2002;122(5):1784–96.
10. Marik PE. The diagnosis of adrenal insufficiency in the critically ill patient: does it really matter? Crit Care. 2006;10(6):176.
11. Marik PE. Mechanisms and clinical consequences of critical illness associated adrenal insufficiency. Curr Opin Crit Care. 2007;13(4):363–9.
12. Marik PE, Gayowski T, Starzl TE, Group HCRaAPS. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. Crit Care Med. 2005;33(6):1254–9.
13. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. N Engl J Med. 2004;350(16):1629–38.
14. Borst GC, Michenfelder HJ, O'Brian JT. Discordant cortisol response to exogenous ACTH and insulin-induced hypoglycemia in patients with pituitary disease. N Engl J Med. 1982;306(24):1462–4.
15. Cooper MS, Stewart PM. Corticosteroid inusifficiency in acutely ill patients. N Engl J Med. 2003;348(8):727–34.
16. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580–637.
17. Annane D, Cariou A, Maxime V, Azoulay E, D'honneur G, Timsit JF, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. JAMA. 2010;303(4):341–8.
18. Arlt W, Allolio B. Adrenal insufficiency. Lancet. 2003;361(9372):1881–93.
19. O'Beirne J, Holmes M, Agarwal B, Bouloux P, Shaw S, Patch D, et al. Adrenal insufficiency in liver disease – what is the evidence? J Hepatol. 2007;47(3):418–23.
20. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288(7):862–71.
21. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358(2):111–24.
22. Casserly B, Gerlach H, Phillips GS, Lemeshow S, Marshall JC, Osborn TM, et al. Low-dose steroids in

adult septic shock: results of the Surviving Sepsis Campaign. Intensive Care Med. 2012;38(12): 1946–54.
23. Sligl WI, Milner DA, Sundar S, Mphatswe W, Majumdar SR. Safety and efficacy of corticosteroids for the treatment of septic shock: a systematic review and meta-analysis. Clin Infect Dis. 2009;49(1):93–101.
24. Annane D, Bellissant E, Bollaert PE, Briegel J, Confalonieri M, De Gaudio R, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. JAMA. 2009;301(22): 2362–75.
25. Minneci PC, Deans KJ, Natanson C. Corticosteroid therapy for severe sepsis and septic shock. JAMA. 2009;302(15):1643; author reply 4–5.
26. Minneci PC, Deans KJ, Eichacker PQ, Natanson C. The effects of steroids during sepsis depend on dose and severity of illness: an updated meta-analysis. Clin Microbiol Infect. 2009;15(4):308–18.
27. Moran JL, Graham PL, Rockliff S, Bersten AD. Updating the evidence for the role of corticosteroids in severe sepsis and septic shock: a Bayesian meta-analytic perspective. Crit Care. 2010;14(4):R134.
28. Barochia AV, Cui X, Eichacker PQ. The Surviving Sepsis Campaign's Revised Sepsis Bundles. Curr Infect Dis Rep. 2013;15(5):385–93.
29. Lipiner-Friedman D, Sprung CL, Laterre PF, Weiss Y, Goodman SV, Vogeser M, et al. Adrenal function in sepsis: the retrospective Corticus cohort study. Crit Care Med. 2007;35(4):1012–8.
30. Umeda T, Hiramatsu R, Iwaoka T, Shimada T, Miura F, Sato T. Use of saliva for monitoring unbound free cortisol levels in serum. Clin Chim Acta. 1981;110(2–3):245–53.
31. Laudat MH, Cerdas S, Fournier C, Guiban D, Guilhaume B, Luton JP. Salivary cortisol measurement: a practical approach to assess pituitary-adrenal function. J Clin Endocrinol Metab. 1988;66(2):343–8.
32. Gunnala V, Guo R, Minutti C, Durazo-Arvizu R, Laporte C, Mathews H, et al. Measurement of Salivary Cortisol Level for the Diagnosis of Critical Illness-Related Corticosteroid Insufficiency in Children. Pediatr Crit Care Med. 2015;16(4):e101–6.
33. Bartanusz V, Corneille MG, Sordo S, Gildea M, Michalek JE, Nair PV, et al. Diurnal salivary cortisol measurement in the neurosurgical-surgical intensive care unit in critically ill acute trauma patients. J Clin Neurosci. 2014;21(12):2150–4.
34. Walls RM, Murphy MF. Clinical controversies: etomidate as an induction agent for endotracheal intubation in patients with sepsis: continue to use etomidate for intubation of patients with septic shock. Ann Emerg Med. 2008;52(1):13–4.
35. Policola C, Stokes V, Karavitaki N, Grossman A. Adrenal insufficiency in acute oral opiate therapy. Endocrinol Diabetes Metab Case Rep. 2014;2014: 130071.
36. Schimke KE, Greminger P, Brändle M. Secondary adrenal insufficiency due to opiate therapy – another differential diagnosis worth consideration. Exp Clin Endocrinol Diabetes. 2009;117(10):649–51.

Management of Hyperglycemic Hyperosmolar Syndrome

50

Elaine C. Fajardo

Case Presentation

A 68 year old woman with a past medical history of alcohol abuse status post detoxification, chronic kidney disease and type 2 diabetes mellitus was brought into the Emergency Department (ED) by ambulance for slurred speech. She was on the phone with her daughter when she developed the dysarthria. Unable to speak effectively, she got off the phone and went to a neighbor's apartment. The neighbor reported an episode of shaking, lasting approximately 10 s, prior to paramedic arrival. En route to the hospital, the patient became combative, confused and incontinent of stool and urine. She was hypertensive with blood pressure of 226/97 mmHg, tachycardic with heart rate of 109 bpm, and hyperglycemic with capillary blood glucose "critically high". Upon arrival to the ED, a stroke alert was initiated. NIH Stroke Scale was calculated to be 18, with points for level of consciousness, motor drift, language aphasia, and dysarthria. Neurological exam revealed a lethargic patient, not following commands, with reduced withdrawal to noxious stimuli in the right upper and lower extremities. There was an upgoing Babinski sign on the right. Non-contrast CT scan of the head did not show acute intracranial hemorrhage, mass shift or trauma. MRI/MRA of the brain revealed no sign of acute cerebral vascular infarct or cerebroarterial abnormality. Laboratory results were significant for: Sodium = 132 mmol/L, Potassium = 3.6 mmol/L, Bicarbonate = 18.6 mmol/L, Anion gap = 20 mmol/L, Urea 38 = mg/dL, Creatinine = 2.1 mg/dL (baseline 1.3), Glucose = 769, and Serum Osmolality = 331 Osm/kg. The WBC was 3.6 ×1000/ul without neutrophilic predominance. Point of Care lactate was 3.2 mmol/L and Point of Care pH was 7.30. The serum *beta*-hydroxy-butyrate level was not checked. Urine ketones were negative.

Question What is the most appropriate intervention for the patient's neurological symptoms?

Answer Intravenous (IV) Fluid Therapy

This patient presented with focal neurological findings and grand mal seizure without evidence of cerebral vascular accident or other culprit lesion on MRI. She did not have fever, infectious prodrome or elevated WBC that would indicate a CNS infection. With serum glucose >320 mg/dL, serum osmolality >320 mOsm/kg, pH >7.30 and negative urine ketones, she met the diagnostic criteria for Hyperosmolar Hyperglycemic Syndrome (HHS), and her neurological signs are likely due to the hyperosmolar state. The most common admitting diagnosis in patients with HHS is acute stroke [1, 2]. In patients presenting with seizures and stroke-

E.C. Fajardo
Internal Medicine Department,
Section of Pulmonary, Critical Care and Sleep Medicine, Yale University School of Medicine,
New Haven, CT, USA
e-mail: elaine.fajardo@yale.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_50

like symptoms secondary to HHS, their neurological exams return to normal with appropriate management of HHS [3]. Treatment for HHS begins with the immediate restoration of circulatory volume and tissue perfusion with an isotonic saline infusion.

This patient was treated with 2 l of 0.9 % saline rapid infusion, followed by maintenance fluid at a rate of 125 ml/h. Lactic acid level normalized. Within the next 12 h, her serum osmolality declined to 313 mOsm/kg, and continued to normalize over the following 2 days. She was started on a low-dose insulin infusion, and her hourly capillary blood glucose declined over the next 13 h to 208. As the serum glucose corrected, her sodium peaked at 143 and the IV fluids were switched to 0.45 % saline with 5 % dextrose. After 24 h, insulin was transitioned from infusion to subcutaneous dosing. The patient had significant hypokalemia and hypomagnesemia, requiring IV supplementation to maintain potassium >3.5 mmol/L and magnesium >2.0 mmol/L. Broad spectrum antibiotics were started empirically on admission, and discontinued after 2 days once chest X-ray, blood and urine cultures were negative for infection. Upon review of her home medications, hydrochlorothiazide was identified as a potential precipitant of hyperglycemia and was discontinued. The likely trigger for this patient's hyperglycemia was indicated by her daughter, who suspected that the patient may have started drinking again and become non-adherent to her medications. The patient did not have any further episodes of seizure. Her neurological exam slowly improved, and by hospitalization day 5, she had returned to her usual functional status.

Principles of Management

Diagnosis of HHS

Severe serum hyperosmolality, hyperglycemia, and dehydration without significant ketoacidosis define the hyperosmolar hyperglycemic syndrome. Specific laboratory values that support the diagnosis of HHS are plasma glucose >600 mg/dL, arterial pH >7.30, serum bicarbonate >15 mEq/L, small urine ketones, small serum ketones, anion gap <12, and serum osmolality >320 mOsm/kg [1]. Patients often present with alterations in mental status, including lethargy, stupor and coma [1]. Known diagnosis of diabetes mellitus is an insensitive criterion, as up to twenty percent of patients admitted for HHS are unaware of their underlying disease [1]. The clinical syndrome typically begins with progressive polyuria, polydipsia, and weakness over several days. Unlike diabetic ketoacidosis (DKA), patients with HHS have enough endogenous insulin to avoid excessive lipolysis, and do not produce abundant ketoacids (Table 50.1). Instead, osmotic diuresis results in severe dehydration and hypovolemia, triggering the release of counter-regulatory hormones and decreasing glomerular filtration rate. Both mechanisms then exacerbate further hyperglycemia [1]. Electrolyte abnormalities resulting from urinary losses may be severe, and include hypo- and hypernatremia, hypokalemia, hypomagnesemia, hypocalcemia and hypophosphatemia [4]. Often, one can identify precipitating factors which triggered the uncontrolled hyperglycemia. These include: infection, non-adherence to medications or diet, pancreatitis, myocardial infarction, cerebral vascular accident and use of medications known to precipitate hyperglycemia [5].

Common Hyperosmolar Hyperglycemic State Triggers

Alcohol and Drug Abuse
Anesthesia
Burns
GI Hemorrhage
Hypothermia
Infections (UTIs, pneumonia, etc.)
Intracranial Hemorrhage
Myocardial Infarction
Pancreatitis
Pulmonary Embolus
Stroke
Medications, including:

- Antiepileptics
- Antihypertensives
- Antipsychotics
- Beta blockers
- Corticosteroids
- Diuretics

Dehydration is more severe when patients have limited access to water or decreased thirst response, such as in bedridden or elderly patients respectively [6]. Significant free water loss creates the hyperosmolar state which manifests in progressive lethargy and coma.

Fluid Therapy

Rehydration interrupts the cycle of hyperglycemia and hypovolemia by restoring lost intravascular volume, increasing renal perfusion, improving glomerular filtration rate, and reducing glucosuria. Improved systemic perfusion decreases the release of counter-regulatory hormones such as catecholamines, cortisol, glucagon and growth hormone, which exacerbate hyperglycemia. Finally, rehydration decreases the peripheral insulin resistance that is caused by the hyperosmolar state [7]. The American Diabetes Association consensus statement for Hyperglycemic Crisis recommends isotonic saline (0.9 % sodium chloride) at a rate of 15–20 ml/kg body weight (wt) within the first hour [1]. Additional fluid therapy should be adjusted based on hemodynamics, sodium status and urinary output. Fluid deficits should be restored within 24 h. The free water deficit (FWD) may be calculated using the corrected serum sodium, and provide some guidance for free water repletion (Table 50.2). The importance of prompt fluid hydration is supported by the fact that normalization of the hyperosmolar state results in a more robust response to low-dose insulin therapy [7].

Table 50.1 A comparison of characteristics defining DKA and HHS

Characteristic	DKA	HHS
Polyuria, polydipsia, polyphagia, wt loss, vomiting, dehydration, weakness	X	X
Stupor/coma	Severe only	X
Abdominal pain	X	
Insulin deficiency	Absolute	Relative
Principal pathologic metabolic process	Lipolysis and ketogenesis	Dehydration and counter-regulatory hormones
Plasma glucose (mg/dL)	>250	>600
Arterial pH	<7.25	>7.30
Urine ketones	Positive	Small
Serum ketones	Positive	Small
Serum osmolality	Variable	>320
Anion gap	>12	Variable

Data compiled from Refs. [1] and [13]

Insulin Therapy

Current treatment protocols recommend starting either with an insulin IV bolus of 0.1 units/kg body wt followed by 0.1 units/kg/hour(h) infusion or 0.14 units/kg body wt/h continuous infusion [1, 8]. The low dose infusion rates are based on randomized controlled studies for DKA that showed low-dose or physiological insulin performed similarly to high dose insulin in terms of rate of resolution of hyperglycemia as well as reduction in counter-regulatory hormones, and

Table 50.2 Sodium and free water equations

Steps	Equations
Calculate the Corrected Serum Sodium	$\text{Corrected Serum Sodium} = \textit{Measured Sodium} + \left(\frac{1.6\,mEq}{L}\right)\left(\frac{\textit{Measured Glucose}}{100}\right)$
Calculate the free water deficit using the Corrected Serum Sodium	$\text{Free Water Deficit} = 0.6\left(\textit{weight in kg}\right)\left(\frac{\textit{Corrected Sodium}}{140}\right) - 1$
Calculate the rate of free water administration over 24 h	$\frac{\text{free water deficit}}{24\,h}$

Data compiled from Ref. [22]

had lower incidence of hypoglycemia and hypokalemia [9, 10]. A more recent study demonstrated that giving an initial insulin bolus prior to starting a continuous infusion, normalized blood glucose, pH and bicarbonate levels just as quickly as providing a continuous infusion at a slightly higher rate of 0.14 units/kg/h [11]. Therefore, solely providing a continuous infusion rate is equally recommended. If the glucose level does not decline by 10 % in the first hour, it is recommended to bolus 0.14 units/kg body wt and to continue infusion at the previous rate. Once the blood glucose reaches 300 mg/dL, the insulin infusion rate should be lowered to 0.02–0.05 units/kg body wt/h and supplemental dextrose infusion should be given to maintain blood glucose between 200 and 300 mg/dL until the patient's mental status normalizes. This last step is a safeguard against the physiological threat of cerebral edema that may result from the rapid correction of serum hyperosmolality. With insulin treatment, brain osmolality decreases at a rate significantly slower than plasma, and there is a net movement of water into the brain [2]. Oftentimes, patients with HHS will present with a milder form of the metabolic derangements of DKA. These patients should also continue treatment with simultaneous dextrose and insulin infusion until ketogenesis ceases and anion gap acidosis resolves.

Correcting Electrolytes

Sodium

The measured serum sodium concentration in patients with HHS is often deceivingly low. This is because the osmotic pull of hyperglycemia draws water into the extracellular space, thereby diluting the sodium concentration [12]. Serum sodium rises to normal or elevated levels when massive diuresis removes more water than salt from the body. Sodium levels greater than 140 mEq/L are, therefore, indicative of very large fluid deficits [13]. A "corrected" serum sodium is calculated in the setting of hyperglycemia to account for this phenomenon, and considered a more accurate reflection of the patient's true osmotic and dehydrated status [14, 15] (Table 50.2).

Potassium

In HHS, hypokalemia can often require 4–6 mEq/kg body wt of potassium, or 280–420 mEq potassium for the average person. The mechanisms of potassium loss include insulin-driven shifts of potassium into the intracellular compartment, and gastrointestinal and urinary losses. Concomitant hypomagnesaemia may also worsen hypokalemia by activating the renal outer medullary potassium channels to secrete more potassium [4]. Due to the potassium lowering effects of insulin, potassium repletion is recommended once serum levels are less than 5.3 mEq/L in patients with normal kidney function. Patients should have potassium repleted to greater than 3.3 mEq/L when they present with hypokalemia, to decrease risk of cardiac arrhythmia and arrest and respiratory muscle weakness.

Magnesium

The degree of magnesium deficits incurred from diuresis are less than potassium. Repletion is important, particularly when potassium levels are low, for the reasons mentioned above.

Phosphate

The total body deficit of phosphate in HHS is estimated to be 3–7 mmol/kg [1]. Phosphate levels are typically near normal on presentation, and decrease with insulin therapy. While repletion has not been studied in HHS specifically, randomized studies in DKA did not show a benefit. Furthermore, aggressive phosphate therapy is more likely to precipitate severe hypocalcemia [16].

Evidence Contour

Type of IV Fluid

Physiologically, there is justification for use of isotonic fluid for volume resuscitation and hypotonic fluids to correct hypernatremia. Expert opinions diverge regarding the appropriate initial IV fluid for HHS. Isotonic fluids are appropriate for resuscitation, but will not replenish the free water deficit. Hypotonic fluids may address the hypernatremia, but also carry risk for cerebral edema. In a study that compared the effects of

hypotonic, isotonic and hypertonic solutions in DKA patients, there was no difference in fluid retention among the various tonicities [5]. Perhaps for these reasons, it is recommended to initiate IV fluids with isotonic saline and subsequently adjust according to osmolality, sodium level and intravascular volume status [17].

Anticoagulation

Diabetes mellitus alone has been recognized as an inflammatory and hypercoagulable state [18, 19]. As such, there is a significantly increased risk for thrombotic events such as myocardial infarction and deep vein thrombus. Multiple procoagulant factors and reactive oxygen species were found to be elevated in patients with hyperglycemic emergencies [20]. Markers of platelet activation were significantly increased when patients were exposed to short episodes of hyperglycemia [21]. The International Diabetes Federation makes a level 4 recommendation (Expert Opinion) that the use of heparin at prophylactic doses for prevention of deep venous thrombus may be beneficial in the absence of an associated bleeding diathesis [8].

References

1. Kitabchi A, Umpierrez G, Murphy MB, Kreisberg R. Hyperglycemic crisis in adult patients with diabetes. Diabetes Care. 2006;29(12):2739–48.
2. Guisado R, Arieff AL. Neurological manifestations of diabetic comas: correlation with biochemical alterations in the brain. Metabolism. 1975;24(5): 665–79.
3. Arieff AI, Carroll H. Nonketotic hyperosmolar coma with hyperglycemia: clinical features, pathophysiology, renal function, acid-base balance, plasma-cerebrospinal fluid quilibria and the effects of therapy in 37 cases. Medicine. 1972;51(2):73–94.
4. Liamis G, Liberopoulos E, Barkas F, Elisaf M. Diabetes mellitus and electrolyte disorders. World J Clin Cases. 2014;2(10):488–96.
5. Martin HE, Smith K, Wilson ML. The fluid and electrolyte therapy of severe diabetic acidosis and ketosis; a study of twenty-none episodes (twenty-six patients). Am J Med. 1958;24:376–89.
6. Gaglia J, Wycoff J, Abrahamson M. Acute hyperglycemic crisis in the elderly. Med Clin North Am. 2004;88:1063–84.
7. Waldhausl W, Kleinberger G, Korn A, Dudczak R, Bratusch-Marrain P, Nowotny P, et al. Effects of rehydration o endocrine derangements and blood glucose concentration. Diabetes. 1979;28:577–84.
8. Nyenwe E, Kitabchi AE. Evidence-based management of hyperglycemic emergencies in diabetes mellitus. Diabetes Res Clin Pract. 2011;94:340–51.
9. Kitabchi AE, Ayyagari V, Guerra SMO, Medical House Staff. The efficacy of low dose versus conventional therapy of Insulin for treatment of diabetic ketoacidosis. Ann Intern Med. 1976;84:633–8.
10. Kitabchi AE, Umpierrez GE, Fisher JN, Murphy MB, Stentz FB. Thirty years of personal experience in hyperglycemic crisis: diabetic ketoacidosis and hyperglycemic hyperosmolar state. J Clin Endocrinol Metab. 2008;93:1541–52.
11. Kitabchi AE, Murphy MB, Spencer J, Matteri R, Karas J. Is a priming dose of insulin necessary in a low-dose insulin protocol for the treatment of diabetic ketoacidosis? Diabetes Care. 2008;31:2081–5.
12. Daugirdas J, Kronfol N, Tzamaloukas A, Ing T. Hyperosmolar coma: cellular dehydration and the serum sodium concentration. Ann Intern Med. 1989; 110(11):855–8.
13. Kitabchi A, Umpierrez G, Murphy MB, Barrett E. Management of hyperglycemic crisis in patients with diabetes. Diabetes Care. 2001;24(1):131–53.
14. Hillier T, Abbott R, Barrett E. Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med. 1999;106(4):399–403.
15. Katz MA. Hyperglycemia-induced hyponatremia – calculation of expected serum sodium depression. N Engl J Med. 1973;289:843–4.
16. Fisher J, Kitabchi A. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. J Clin Endocrinol Metab. 1983;57:177–80.
17. Kitabchi A, Umpierrez G, Miles J, Fisher J. Hyperglycemic crisis in adult patients with diabetes. Diabetes Care. 2009;32(7):1355–43.
18. Carr ME. Diabetes mellitus: a hypercoagulable state. J Diabetes Complications. 2001;15:44–54.
19. Grant P. Diabetes mellitus as a prothrombotic condiation. J Intern Med. 2007;262:157–72.
20. Stenz FB, Umpierrez GE, Curevo R, Kitabchi AE. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidase in patients with hyperglycemic crisis. Diabetes. 2004;53: 2079–86.
21. Gresele P, Guglielmini G, Angelis M, Ciferri S, Ciofetta M, Falcinelli E, Lalli C, Giabattoni G, Davi G, Bolli G. Acute, short-term hyperglycemia enhances shear stress induced platelet activation in patient with type II diabetes mellitus. J Am Coll Cardiol. 2003; 41(6):1013–20.
22. Fried LF, Palevsky PM. Hyponatremia and hypernatremia. Med Clin North Am. 1997;81(3):585–609.

Management of Myxedema Coma

51

Aydin Uzun Pinar

Case Presentation

A 60 year old woman with no known medical history presented to the hospital with confusion in the setting of longstanding weakness and fatigue. Her family members reported cold intolerance, constipation, weight gain and thickening of skin and hair. She denied any respiratory symptoms and fever. She reported that she had no contact with the health care system for the last 20 years. She took no medications and denied any history of substance use. On physical examination she was noted to have a rectal temperature of 32 ° C and sinus bradycardia with a heart rate of 24 beats per minute. Thyroid stimulating hormone level (TSH) was 42.4 and free thyroxine (T4) level was < 0.03. Serum sodium level was 118 mEq/L. She was transferred to the medical intensive care unit (ICU). Shortly after admission she experienced two episodes of tonic-clonic seizure and was treated with intravenous lorazepam and hypertonic saline. She was intubated and she was mechanically ventilated. She received intravenous thyroxine and phenytoin. Two days later she passed a spontaneous breathing trial and was extubated. She developed severe stridor immediately after extubation requiring reintubation, which was achieved with great difficulty with a pediatric size endotracheal tube. A tracheostomy was performed the same day, and severe laryngeal edema identified (Fig. 51.1). She was eventually transferred to a long term acute care facility where she was liberated from mechanical ventilation over the next three weeks. A repeat laryngoscopy performed 6 weeks later at the time of decannulation revealed resolution of edema (Fig. 51.2).

Questions What approach should guide management of a patient with myxedema coma? How likely are airway complications in patients with myxedema coma?

Answers Intravenous thyroxine combined with supportive care and concomitant management of coexisting problems are the mainstays of treatment of myxedema coma. Upper airway compromise is uncommonly reported among these patients, but high index of suspicion is required as life threatening emergencies can occur.

Myxedema coma, also known simply as myxedema, is a rare but potentially deadly manifestation of severe hypothyroidism. The high mortality rate of 25–50 % makes early diagnosis and treatment imperative [1, 2]. Because most at-risk patients, including those with known hypothyroidism, thyroidectomy or previous radioactive iodine therapy, are routinely followed by readily available TSH assay, myxedema is now a relatively rare presentation of hypothyroidism.

A.U. Pinar
Medical Intensive Care Unit, Department of Medicine, Section of Pulmonary Critical Care and Sleep Medicine, Yale School of Medicine, New Haven, CT, USA
e-mail: aydin.pinar@yale.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_51

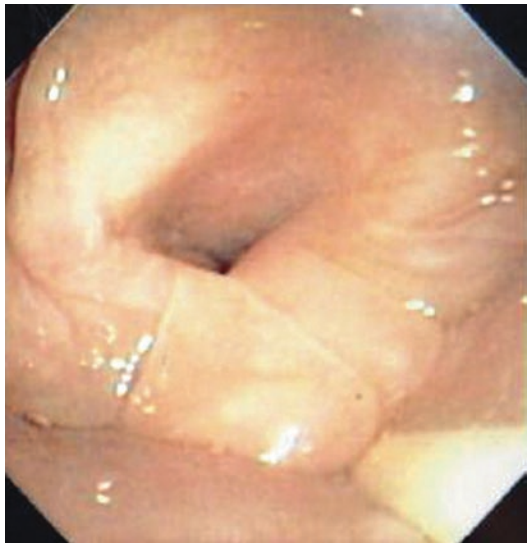


Fig. 51.1 Glottic area in a myxedema patient

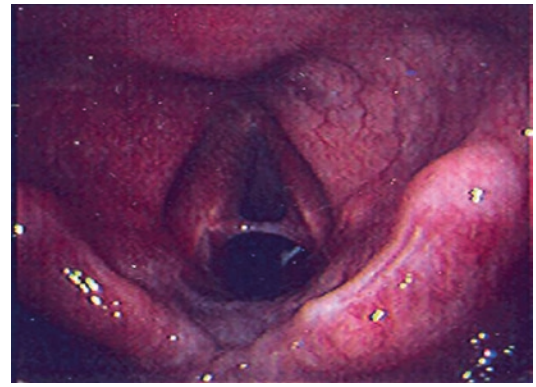


Fig. 51.2 Glottic area, same patient, 6 weeks after treatment initiation

Myxedema coma is more common among older women, reflecting the incidence of thyroid disease in this population. A frequently cited contributory factor is cold weather, with a majority of cases occurring during late fall and winter months [3]. Infections, stroke, congestive heart failure, trauma, surgery and central nervous system depressants are among the other common precipitating factors [4].

Myxedema coma is a medical emergency and treatment with thyroid hormone replacement should be started as soon as the diagnosis is suspected and prior to the report of results from the blood samples for studies are obtained. Prior to initiation of T4, intravenous stress dose steroids are typically administered due to the risk of coexisting adrenal insufficiency. Extreme slowing of the gastrointestinal tract makes enteric absorption unreliable, so initial treatment should be intravenous [5]. Thyroxine is the mainstay of treatment; in some cases addition of triiodothyronine may be considered.

Endotracheal intubation and mechanical ventilation are frequently required in myxedema coma [4]. In some patients altered mental status may lead to concern for inability to protect airway, and in others hypoventilation due to decreased hypoxic and hypercapnic respiratory drive evolves into genuine respiratory failure, especially in the setting of another concomitant critical illness. The development of a difficult airway has been reported in multiple case reports of myxedema coma [6, 7]. Mucopolyscaccharide deposition responsible for the classical changes of myxedema elsewhere in the body also occurs in supraglottic area, and in conjunction with obesity and macroglossia may lead to airway compromise. Clinicians should remain vigilant for the possibility of difficult airway not only during the time of intubation, but at the time of extubation as well.

Principles of Management

Diagnosis

In severely hypothyroid patients, decreased metabolic rate results in progressive fatigue, malaise and weight gain [8]. Other common symptoms include cold intolerance, voice changes, hair loss, constipation, irregular menses, difficulty concentrating, memory problems, and depression (Table 51.1).

The hallmark signs of myxedema coma are depressed mental status and hypothermia. Additional physical findings may include dry and brittle skin and hair, non-pitting edema and delayed reflexes. Patients may have hypotension and shock as a result of depressed cardiac contractility, tamponade, or bradyarrhythmias. Prolongation of the Q-T interval may be seen and

Table 51.1 Common symptoms and signs in severe hypothyroidism and myxedema coma

Symptoms	Signs
Fatigue and malaise	Decreased mental status
Weight gain	Hypothermia
Decreases mental acuity, memory problems	Bradycardia
Cold intolerance	Hypoventilation
Voice cahnges	Periorbital edema
Hair loss	Non-pitting edema
Depression	Delayed tendon reflexes

lead to torsades de pointes [9]. Hypoventilation can cause severe respiratory acidosis [3]. Myxedema-associated coagulopathy may predispose patients to gastrointestinal bleeding [10]. Focal or generalized seizures and status epilepticus have been reported [11].

The test of choice to diagnose hypothyroidism is serum thyrotropin testing, followed by free T4 levels. Ultrasensitive TSH assay is widely available, and results are reliable and reproducible. A normal TSH level is a fairly reliable indicator of normal thyroid function. If TSH levels are found to be normal in a clinical setting suspicious of myxedema, non-thyroidal etiologies must be investigated. In the rare case of central hypothyroidism, TSH levels can be low or normal, accompanied by very low levels of T4 [12].

Thyroxine Replacement

Due to the relative rarity of myxedema coma, large-scale controlled trials comparing different therapeutic regimens do not exist. Most clinical data originate from case series and small trials. The majority of these studies suggest that T4 given in doses of 100–500 μg is safe and effective. Most commonly, T4 monotherapy is started at a loading dose of 200–300 μg IV. Treatment should be started immediately when myxedema coma is suspected, preferably right after diagnostic samples are obtained. The patient is then maintained on 100 μg IV daily and transitioned to enteral treatment when gastric emptying and bowel motility are adequate. Once the patient is stable, an oral replacement dose of 1.6 μg/kg is the typical initial maintenance dose in the first 6 weeks after diagnosis until TSH and free T4 are repeated to guide dose adjustment.

Corticosteroid Replacement

Because 5–10 % of patients with myxedema coma have concomitant adrenal insufficiency, the American Thyroid Association guidelines recommend initial corticosteroid replacement [13, 14]. Prior to initiation of thyroid hormone treatment, 100 mg of IV hydrocortisone should be given every 8 h and continued until adrenal insufficiency is ruled out. A random cortisol level should be drawn before treatment to assess adrenal function. If necessary, a corticotropin stimulation test can be performed later. Hydrocortisone may be discontinued once adrenal insufficiency is ruled out.

Supportive Care

Patients with suspected myxedema coma usually require ICU admission for management of severely depressed mental status or the precipitating conditions, including sepsis, myocardial infarction, and shock. It is generally prudent to initiate a work-up for sepsis in these patients and administer broad-spectrum antibiotics after cultures have been sent. Lumbar puncture should be considered to rule out meningitis as a cause of altered mental status and hypothermia.

Myxedema coma patients commonly present with severe multi-organ impairment. Hemodynamic support with intravenous fluids and vasoactive agents may be necessary. Large pericardial effusions causing cardiac tamponade and requiring pericardiocentesis have been reported [15]. Mild hyponatremia is usually corrected with thyroid replacement therapy alone. Hypothermia is common and in most cases should be managed with passive rewarming alone, as active rewarming can precipitate peripheral vasodilation and circulatory collapse. For severe hypothermia, with core temperature less than 28 ° C, active rewarming is indicated to

reduce the risk for ventricular fibrillation; temperature should be increased by 0.5 ° C per hour to a core temperature of 31 ° C [14].

Evidence Contour

Though thyroid hormone replacement is the mainstay of myxedema coma treatment, there is an ongoing debate over the best thyroid hormone preparation and ideal dosing regimen. There is a wide range of dosing recommendations based on the reported uses in literature. Doses above 500 μg IV thyroxine have been associated with increased mortality and should be avoided [16]. A reasonable approach is to give an initial dose of 200–300 μg of levothyroxine and then monitor the clinical response. If mental status, blood pressure and temperature are not improved, another dose of levothyroxine can be given to bring the total loading dose to 500 μg [14].

Triiodothyronine (T3) is the metabolically active form of thyroid hormone, but despite its biological appeal, its use is controversial. At least one study suggests that at higher doses, use of T3 is associated with higher mortality [17]. Some authors recommend its use in severe cases at the dose of 12.5–25 μg every 6 h; others discuss the use of combination T4 and T3 therapy. Neither of these regimens has demonstrated benefit over levothyroxine therapy alone [18, 19].

References

1. Wartofsky L. Myxedema coma. In: Braverman LE, Utiger RD, editors. Werner and Ingbar's the thyroid: a fundamental and clinical text. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 843–7.
2. Dutta P, Bhansali A, Masoodi SR, Bhadada S, Sharma N, Rajput R. Predictors of outcome in myxoedema coma: a study from a tertiary care centre. Crit Care. 2008;12(1):R1.
3. Dubbs SB, Spangler R. Hypothyroidism: causes, killers, and life-saving treatments. Emerg Med Clin North Am. 2014;32(2):303–17.
4. Klubo-Gwiezdzinska J, Wartofsky L. Thyroid emergencies. Med Clin North Am. 2012;96(2):385–403.
5. Holvey DN, Goodner CJ, Nicoloff JT, Dowling JT. Treatment of myxedema coma with intravenous thyroxine. Arch Intern Med. 1964;113:89–96.
6. Lee CH, Wira CR. Severe angioedema in myxedema coma: a difficult airway in a rare endocrine emergency. Am J Emerg Med. 2009;27(8):1021.
7. Batniji RK, Butehorn 3rd HF, Cevera JJ, Gavin JP, Seymour PE, Parnes SM. Supraglottic myxedema presenting as acute upper airway obstruction. Otolaryngol Head Neck Surg. 2006;134(2):348–50.
8. Devdhar M, Ousman Y, Burman K. Hypothyroidism. Endocrinol Metab Clin North Am. 2007;36:595–615.
9. Schenck JB, Rizvi AA, Lin T. Severe primary hypothyroidism manifesting with torsades de pointes. Am J Med Sci. 2006;331:154–6.
10. Fukunaga K. Refractory gastrointestinal bleeding treated with thyroid hormone replacement. J Clin Gastroenterol. 2001;33:145–7.
11. Jansen HJ, Doebé SR, Louwerse ES, van der Linden JC, Netten PM. Status epilepticus caused by a myxoedema coma. Neth J Med. 2006;64(6):202–5.
12. Dayan CM. Interpretation of thyroid function tests. Lancet. 2001;357:619–24.
13. Farwell AP. Thyroid gland disorders. In: Fink MP, Abraham E, editors. Textbook of critical care. 5th ed. Philadelphia: Elsevier Saunders; 2005. p. 1512–3.
14. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, Cooper DS, Kim BW, Peeters RP, Rosenthal MS, Sawka AM. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid. 2014;24(12):1670–751.
15. Ekka M, Ali I, Aggarwal P, Jamshed N. Cardiac tamponade as initial presenting feature of primary hypothyroidism in the ED. Am J Emerg Med. 2014;32(6):683.
16. Yamamoto T, Fukuyama J, Fujiyoshi A. Factors associated with mortality of myxedema coma: report of eight cases and literature survey. Thyroid. 1999;9:1167–74.
17. Hylander B, Rosenqvist U. Treatment of myxoedema coma – factors associated with fatal outcome. Acta Endocrinol (Copenh). 1985;108(1):65–71.
18. Vaidya B, Pearce S. Management of hypothyroidism in adults. BMJ. 2008;337:a801.
19. Mills L, Lim S. Identifying and treating thyroid storm and myxedema coma in the emergency department. Emerg Med Pract. 2009;11(8):1–26.

Part VII

Infectious Disease

Robert C. Hyzy

Urosepsis

52

Benjamin Keveson and Garth W. Garrison

Case Presentation

A 48-year-old male with history of type II diabetes presented to the Emergency Room with abdominal pain for 4 days associated with dysuria, left sided flank pain, and decreased oral intake. In the Emergency Department his presenting vital signs were HR 175/min, BP 81/51 mmHg, RR 30/min SpO_2 of 98 % on oxygen at 5 L/min. Physical exam was significant for an acutely ill appearing male with left sided costovertebral angle tenderness. Urinalysis was significant for many bacteria and 2+ leukocyte esterase. Labs showed an elevated WBC at 14.2 k with 91 % PMNs, elevated lactic acid of 6.8 and elevated creatinine at 1.5. A CT scan abdomen pelvis revealed an obstructing kidney stone within the left ureter and renal pelvis with resulting hydronephrosis and perirenal fat stranding.

Question What is the appropriate management for this patient with septic shock from a urinary source?

Answer Correct antimicrobial administration and detection/elimination of sequestered infection.

B. Keveson • G.W. Garrison (✉)
Division of Pulmonary and Critical Care Medicine,
University of Vermont Medical Center,
Burlington, VT, USA
e-mail: Garth.garrison@uvmhealth.org

All patients with sepsis from a urinary source should be treated with rapid resuscitation, early appropriate antimicrobial agents and elimination of infection sources that are not accessible to the blood stream. This patient received 4 l of lactated ringers in the Emergency Department without improvement in his vital signs and repeat lactic acid of 2.5 after 3 h. Within the first two hours of presentation that patient received two sets of peripheral blood cultures and was administered 1 g of Ceftriaxone. En route to the intesive care unit the patient was taken to the interventional radiology suite with successful placement of a left nephrostomy tube and decompression of his hydronephrosis. In the intensive care unit, a central line was placed and the patient was initiated on vasopressor support with a goal MAP of 65. On day 2 of hospitalization the patient's blood cultures returned positive in both set with gram negative organisms. He was continued on ceftriaxone and was able to be weaned of vasopressor support on day 3 of his hospitalization and was transferred out of the ICU to the general medical ward the next day.

Principles of Management

Diagnosis

Several risk factors have been identified that predispose patients to developing urosepsis. Any patient who has undergone recent urological intervention is at particularly high risk of developing urosepsis within 24 h following the procedure.

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_52

Additional risk factors include indwelling foreign object (indwelling catheter, ureteric stents, nephrostomy tubes, nephrolithiasis) within the urinary tract and history of previous urinary tract infection [1].

In general the diagnosis for urosepsis can be made in a noncatheterized patient if two of the following are present: fever, urgency, costovertebral or suprapubic tenderness, pyuria, or radiologic evidence of urinary tract infection (pyelonephritis, abscess formation, etc.). In addition if a fluid collection (abscess, phlegmon, hydronephrotic kidney) within the urinary tract is sampled and has a positive gram stain or culture this is indicative of a urinary tract infection. Diagnosis for chronically catheterized patients is similar except requires frank pus express, greater than 10 WBC/uL, or leukocyte esterase/nitrate positivity [1, 2].

Early imaging on presentation is essential to eliminate the possibility of urinary tract obstruction or contained infection. Urinary tract obstruction and contained infection (abscess, phlegmon, hydronephrotic kidney) may require procedural intervention to attain source control. Imaging can include renal ultrasound or CT scan. Of the two, CT with IV contrast has been shown to be more sensative in detecting abnormalities that may require intervention in the patient with urosepsis [3]. CT scans without contrast have decreased sensitivity for detecting abscess and phlegmon development (Fig. 52.1).

Empiric Antimicrobial Administration

Selecting an antimicrobial agent that can effectively treat the infective pathogen is essential to the optimal management of a patient with urosepsis. It is paramount that the antimicrobial selected not only effectively targets the suspected infectious agent but also that it penetrates the urologic system (i.e. is excreted by the kidneys). When selecting an initial antimicrobial prior to the identification of the offending organism is important to consider local susceptibilities, previous patient colonization, recent antimicrobial administratio or recent hospitalization (both lead to increased chance of resistant organisms), foreign body presence, and patient specific circumstances (cystic kidney, acute kidney injury, etc.).

For a patient with no risk factors for development of resistant organisms ceftriaxone or another 3rd generation cephalosporin may be administered. Fluoroquinolones (namely ciprofloxacin and levofloxacin) were previously recommended for first line therapy as often as 3rd generation cephalosporins for treatment of urosepsis however fluroquinolone resistance, particularly in E. coli, have made these agents less appealing [4]. Patients previously treated patients for E coli and K pneumoniae are at risk for extended spectrum beta-lactamase (ESBL) producing organisms. In these patients, empiric treatment with the carbapenem class of antibiotics is preferred. In the patient with previous history of vancomycin resistant enterococcus (VRE) linezolid is the preferred agent. Aminoglycosides, long a mainstay in the treatment of urinary sepsis because of their concentration within the urinary collective system, have fallen out of favor due to the risk of renal toxicity. For the patient with previous fungal colonization of their urinary source and concern for fungal urinary sepsis empiric treatment with fluconazole or amphotericin B deoxycholate are the preferred antifungals because of their urinary tract presentation. Echinocandins and other azoles, as well as amphotericin B lipid formulas do not have good urinary tract penetration and should be avoided [5].

Procedures/Surgery

In order to attain source control of urinary infections caused by obstruction it is necessary to relieve the obstruction. Interventions for relieving obstruction include foley catheter insertion, ureteral stents, nephrostomy tubes, surgical drainage, and nephrectomy. The choice of intervention depends on the location of the obstruction. For post-vesicular obstruction, foley catheter placement may relieve the obstruction. However if the obstruction is ureteral, nephrostomy tube placement or retrograde ureteral stent is necessary.

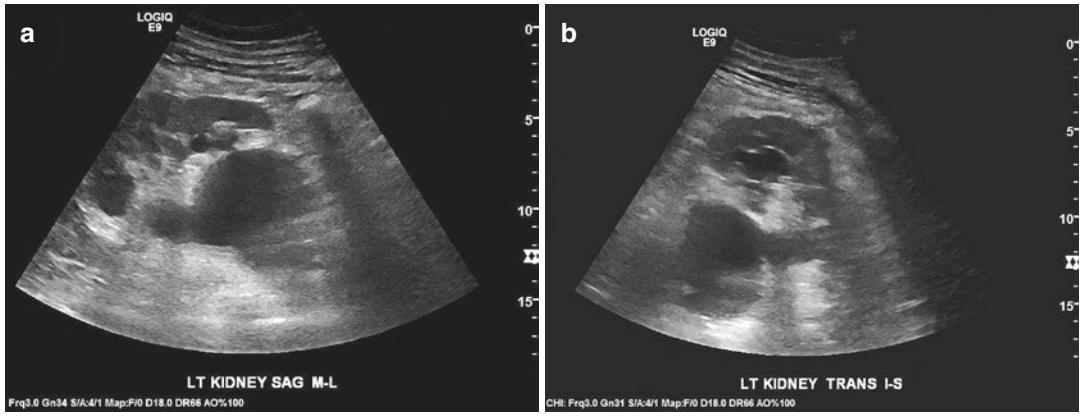


Fig. 52.1 (**a**, **b**) Ultrasound images showing massive dilation of the renal pelvis and collecting system (hydronephrosis) due to ureteral obstruction

Evidence Contour

Several aspects regarding the diagnosis and management of urosepsis remain without consensus.

Empiric Anitbiotic Choice

Given the importance of correctely targeting the correct offending bacteria species within the first couple of hours of sepsis it is essential to select the correct antimicrobial emperically, prior to culture data being available. Some data is available from previous studies regarding the most efficacious empiric antibacterial agent. One study compared empiric intravenous doripenem (a carbapenem) vs. intravenous levofloxacin (a fluoroquinolone) as the treatment of complicated urinary tract infections and found cure rates comparable at approximately 80% each [6]. Another study compared ertapenem (a carbapenem) and ceftriaxone (a third generation cephalosporin) in patients with complicated UTI and found equitable microbiological responses [7]. Thus, it appears as though local susceptibility patterns should be used for antimicrobial selection.

Indications for Imaging

Frequently in patients with a high degree of clinical suspicion for pyelonephritis no imaging is necessary. However, in the septic ICU, patient, imaging should be considered. Computed tomography (CT) has proven to be the most complete evaluation of the genito-urinary tract. However, no direct comparrison studies in the acutely septic patient exist comparing outcomes from initial CT to ultrasound examination, which is also frequently used in this patient population [3]. Ultrasound is almost always more inexpensive test, but has high sensitivity for hydronephrosis from an intervenable obstruction, and spares the patient of radiation exposure. However, this modality often requires a experienced operator or dedicated ultrasound technician to be available (may be difficult in the evening/weekend hours) and is may provide suboptimal images in patients who are obese [3]. Studies evaluating initial use of of CT to ultrasound in the patient with sepsis from a urinary source warrants further investigation (Fig. 52.2).

Intervention Method

Relief of obstruction is critical for source control in patients presenting with urinary sepsis with underlying obstruction (stricture, nephrolithiasis, etc.). A common thought is that while retrograde ureteral stent placement provides more definitive relief of the obstruction it requires general anesthesia which may not be feasible in the acutely unstable septic patient. One study investigating 42 patients with obstructive calculi and sepsis

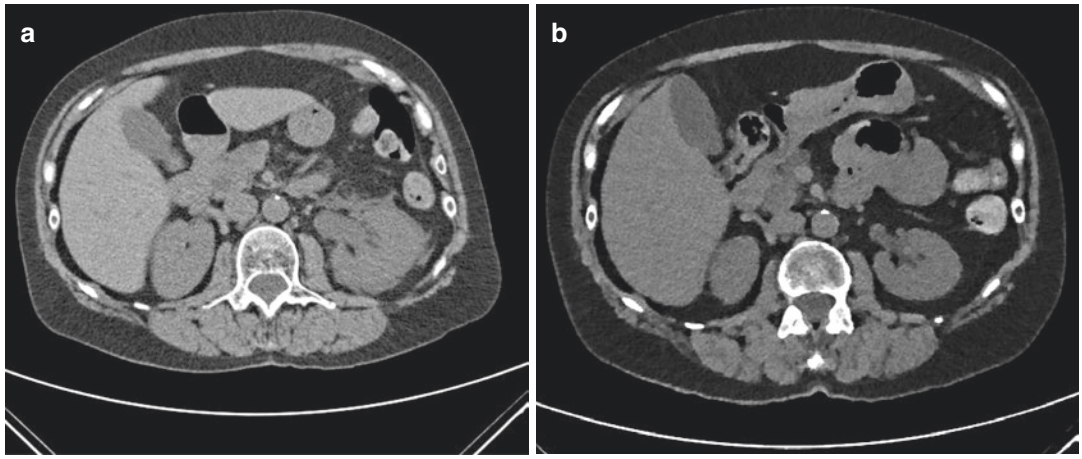


Fig. 52.2 Non-contrast CT of the abdomen showing left sided collecting system dilation with perinephric stranding in the panel on the left (**a**). On the right (**b**), CT shows resolution following relief of obstruction

revealed similar success rates between the two modalities in regards to WBC normalization and fever trend [8]. Success in relief of obstruction following nephrostomy completion is generally greater than 90 % of patients. The rate of major complications secondary to nephrostomy tube placement, namely hemorrhage, varied from 2 to 5 % of cases depending on operator experience [9].

However, there are data suggesting that retrograde ureteral stent placement may offer some benefits. In that same study by Pearle, retrograde stent placement was found to reduce length of hospital stay when compared to patients who received nephrostomy placement (4.5 vs. 3.2 days). This similarity in outcomes with reduction of hospital stay length may argue that when feasible, retrograde ureteral stent placement should be preferred [8, 9].

References

1. Nicolle L. Urinary tract infection. Crit Care Clin. 2013;29:699–715.
2. Calandra T, et al. International Sepsis Forum Definition of Infection in the ICU Consensus Conference. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. Crit Care Med. 2005;33:1538–48.
3. Demertzis J, et al. State of the art: imaging of renal infections. Emerg Radiol. 2007;14:13–22.
4. Grabe M, et al. Guidelines on urological infections. Eur Assoc Urol. 2011.
5. Pappas PG, et al. Clinical practic guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:503–35.
6. Naber KG, et al. Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams with an option to switch to oral therapy, for treatment of complicated lower tract infection and pyelonephritis. Antimicrob Agents Chemother. 2009;53(9):3782–92.
7. Wells WG, et al. Treatment of complicated urinary tract infection in adults: combined analysis of two randomized, double-blind, multicentre trials comparing ertapenem and ceftriaxone followed by appropriate oral therapy. J Antimicrob Chemother. 2004;53 Suppl 2:ii67–74.
8. Pearle M, et al. Optimal method of urgent decompression of the collecting system for obstruction and infection due to ureteral calculi. J Urol. 1998;160:1260–4.
9. Ramsey S. Evidence-based drainage of infected Hydronephrosis secondary to ureteric calculi. J Endourol. 2010;24(2):185–9.

Management of Sepsis and Septic Shock

53

Rommel Sagana and Robert C. Hyzy

Case Presentation

A 70 year old man with a history of hypertension and diabetes presents from his nursing home to the emergency room with fevers, chills, and hypotension. He had complained of a productive cough 2 days prior to presentation to the emergency room. At the time of presentation his temperature was 39 °C, blood pressure was 86/60 mmHg, respiratory rate was 22, pulse was 111. His oxygen saturation (SaO_2) on room air was 86 % and on 2 L NC was 92 %. Laboratory results revealed a WBC count of 18,000 cells per microliter, hemoglobin of 13 g per deciliter, BUN of 55 mg/dl, creatinine of 1.8 mg/dl and initial lactic acid level was 5 mmol/L. Chest x-ray findings are below (Figs. 53.1 and 53.2). The ER began treatment for pneumonia with septic shock.

Question What approach should guide this patient's treatment of septic shock?

Answer Six Hour Sepsis Bundle

The management of patients with severe sepsis and septic shock has evolved into protocols which utilize "bundles." "A bundle is a selected set of elements of care distilled from evidence-based practice guidelines that, when implemented as a group, have an effect on outcomes beyond implementing the individual elements

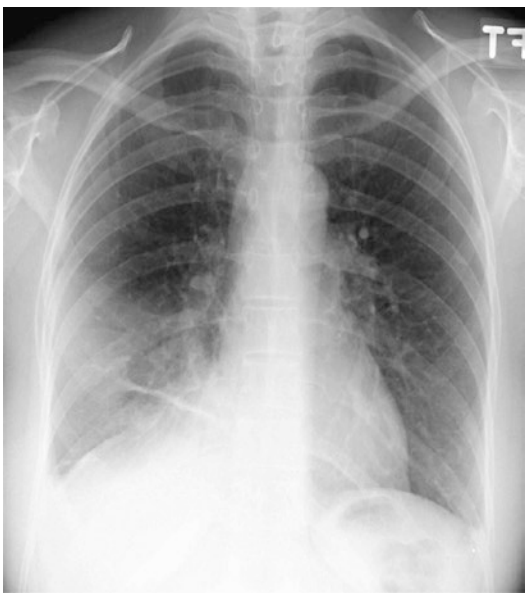


Fig. 53.1 PA CXR

Electronic supplementary material The online version of this chapter (doi:10.1007/978-3-319-43341-7_53) contains supplementary material, which is available to authorized users.

R. Sagana (✉)
Pulmonary & Critical Care, University of Michigan, Ann Arbor, MI, USA
e-mail: rommel@umich.edu

R.C. Hyzy
Critical Care Medicine Unit, Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_53

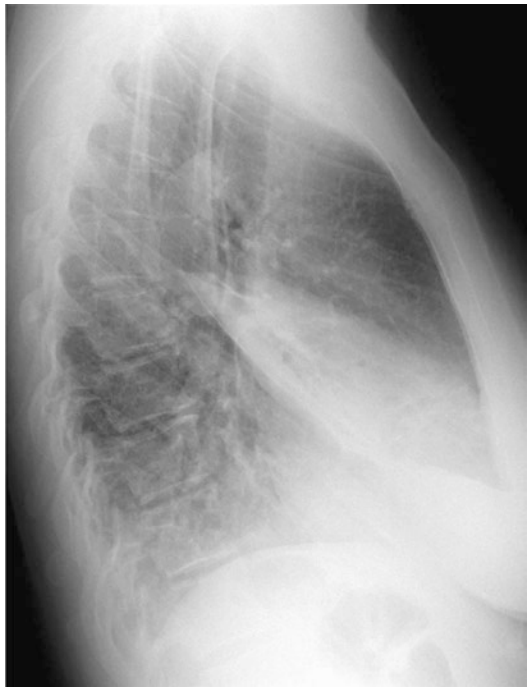


Fig. 53.2 Lateral CXR

alone" [1]. The Surviving Sepsis Campaign provided the first bundled care process for the management of patients with severe sepsis and septic shock [2]. The first bundle involves care for the initial 3 h of sepsis recognition. The second bundle within the first 6 h of therapy, usually in an intensive care unit (ICU).

This patient was initially given a fluid challenge of 30 mL/kg of 0.9% normal saline (NS). Blood, sputum, and urine cultures were sent. He was started on broad spectrum antibiotics; Vancomycin, Piperacillin/Tazobactam, and Azithromycin. Despite additional volume administration, his blood pressure failed to normalize after 5 L of 0.9% NS. A central line was placed and he was started on Norepinephrine. Gram stain from his sputum culture was positive for gram positive cocci in pairs which eventually speciated to *Streptococcus pneumonia*. Lactic acid level decreased to 3 mmol/L after 6 h and normalized by the next day. Norepinephrine was discontinued after 12 h. The patient received at total of 10 L of 0.9 NS. He was transitioned to a general care floor after 36 h in the ICU. After 48 h, the Streptococcus proved to be pan-sensitive and his antibiotic regimen was changed to Ceftriaxone.

Principles of Management

Definition and Recognition

Despite the advances in modern medicine, sepsis continues to be a leading cause of death and a significant inpatient cost. The incidence of severe sepsis in the United States has been reported to be as high as 300 cases per 100,000 population with an annual cost of $14 billion per year. Sepsis is now defined as, "A life-threatening organ dysfunction due to a dysregulated host response to infection." Simply stated, sepsis is a suspected infection in the presence of organ dysfunction, where organ dysfunction is defined as in increase in sepsis organ failure assessment (SOFA) score of at least two points.

New Definitions and Constructs

- Sepsis is defined as life-threatening organ dysfunction due to a dysregulated host response to infection
- Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points
- In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs
- Adult patients with suspected infection who are likely to have a prolonged ICU stay or to die in hospital can be promptly identified using qSOFA, i.e., alteration in mental status, systolic blood pressure ≤100 mmHg or respiratory rate ≥22 breaths/min
- Septic shock is a subset of sepsis where underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
- Adult patients with septic shock can be identified using a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mmHg, AND a blood lactate >2 mmol/l despite adequate volume resuscitation

Septic shock is now defined as, "a subset of septic patients where underlying circulatory and cellular-metabolic abnormalities are profound enough to substantially increase mortality," and is characterized by:

- The requirement vasopressors to maintain mean BP > 65 mmHg
- A lactate > 2 mmol/l
- The absence of other causes, especially hypovolemia

The new definitions no longer utilize the term, "severe sepsis." Additionally the systemic inflammatory response syndrome (SIRS) no longer is part of the definition. The Quick Sepsis Organ Failure Assessment Score (qSOFA) has been found to represent the best screening tool to identify infected patients who are severely ill and at high risk of deterioration:

- Glasgow Coma Score ≤ 13
- Respiratory rate ≥ 22 breaths/min
- Blood pressure ≤ 100 mmHg

This tool works best for patients outside of the intensive care unit. It is meant as a screening tool, instead of SIRS, and is not meant to define sepsis. While the addition of lactate levels failed to improve the qSOFA tool, the addition of other clinical criteria such as lactate can be important in the overall assessment of whether an infected patient requires intervention.

Surviving Sepsis Campaign Sepsis Bundle

Rivers et al. developed a protocol designed to guide the management of severe sepsis and septic shock [5]. The protocol included specific target values for central venous pressure (CVP), mean arterial pressure (MAP), systemic oxygen consumption using mixed venous oxygen saturation (SvO_2), hematocrit, cardiac index, and urine output. In response to accumulated evidence the Surviving Sepsis campaign currently lists only mean arterial pressure 65 mmHg as a hemodynamic goal [6]. The 3 h and 6 h bundles are displayed below. The 3 h bundle emphasizes timely administration of broad spectrum antibiotics and an initial fluid administration of 30 ml/kg of crystalloid in the face of an elevated lactate level. The 6 h bundle provides guidance regarding the potential ongoing need for vasopressor administration and/or additional volume administration in the face of ongoing hypotension.

Surviving Sepsis Campaign Bundle [1]
TO BE COMPLETED WITHIN 3 HOURS OF TIME OF PRESENTATION*:

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 ml/kg crystalloid for hypotension or lactate ≥4 mmol/L
   * "Time of presentation" is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review

TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mmHg
6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mmHg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion
7. Re-measure lactate if initial lactate elevated.

Fluid Management

An important focus of initial treatment in septic shock is sufficient and appropriate early administration of intravenous fluids. Current

guidelines recommend crystalloids as the initial fluid choice, with a minimal initial challenge of 30 mL/kg [6]. Nevertheless, albumin is a colloid frequently used for resuscitation in hypotensive patients. The Saline versus Albumin Fluid Evaluation (SAFE) trial compared resuscitation strategies using 4 % albumin or normal saline in all ICU patients and demonstrated similar outcomes [7]. Two studies have compared saline and albumin administration as resuscitation fluid in septic patients. Both showed no difference in 28 day mortality but one study (CRISTAL) did demonstrate improved survival at 90 days in the albumin group [8]. Normal saline is the most commonly used crystalloid. Administration in the setting of sepsis resuscitation has been associated with hyperchloremic (nonanion gap) metabolic acidosis, which had been considered to pose a risk of acute kidney injury [9, 10]. However the use of a chloride-restrictive fluid strategy using a buffered saline solution did not result in a decreased rate of AKI compared with saline when used for resuscitation in a large randomized trial of intensive care patients [11]. Semisynthetic colloids such as hydroxyethyl starch are not recommended for acute resuscitation. In some studies their use has been associated with renal failure, coagulopathy and increased mortality [9, 12]. Blood transfusions were theorized to improve oxygen carrying capacity and improved oxygen delivery. The Rivers EGDT protocol included a hematocrit goal of 30 % or more if, after the improvement of blood pressure, the SvO_2 remained less than 70 % [5]. This provision was included in the initial Surviving Sepsis guidelines. In the absence of evidence that transfusions were truly beneficial and with increasing evidence for harm secondary to arbitrary transfusion thresholds, the recommendations were modified to have a goal range of 7–9 g/dl unless myocardial ischemia, coronary artery disease, acute hemorrhage, or severe hypoxemia are present [2, 6, 13, 14].

Hemodynamic Response

Presently the Surviving Sepsis Campaign recommends either a repeat focused physical exam (including vital signs, capillary refill, pulse and skin findings) or the measurement of two of the following parameters: central venous pressure; superior vena cava oxygen saturation; bedside cardiovascular ultrasound; or dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge.

Skin mottling has been described in sepsis for over 60 years [15]. Increasing evidence has identified a crucial role of microcirculation impairment in severe infections. One center developed a mottling score (from 0 to 5), based on mottling area extension from the knees to the periphery. There was improved survival in patients whose mottling score decreased during the resuscitation period [16] (Fig. 53.3).

Central venous pressure (CVP) remains a common approach to monitor fluid responsiveness but should be used in conjunction with other dynamic variables. The goal has been 8–12 mmHg for non-ventilated patients and 12–15 mmHg for those requiring mechanical ventilation [17]. Since CVP may not accurately assess volume status especially in mechanically ventilated patients with high airway pressures, measurement of CVP should not be used in isolation.

Mixed venous oxygen saturation measures the net balance between oxygen delivery (influenced by arterial oxygen saturation, hemoglobin, and cardiac output) and oxygen consumption by the tissues. Samples obtained from the subclavian or vena cava typically show higher saturation than samples from the right atrium. The target for adequate venous oxygenation is 70 % or more for superior vena cava and 65 % for the right atria [17]. Pulmonary arterial catheterization and monitoring have not shown to improve outcomes. The procedure may also confer risk to the patient.

Passive leg raise is a simple method of assessing intravascular volume and fluid responsiveness. The patient is moved to a supine position with the legs raised to 45° for several minutes. An increase of venous return causing a ≥ 10 % increase in aortic blood flow measured by esophageal Doppler and arterial pulse pressure signaled a response to fluids [18]. Dynamic variables such as pulse pressure variation or ultrasound evaluation of the inferior vena cava (IVC) can also be used. Pulse pressure variation is calculated via arterial line measurements of maximum

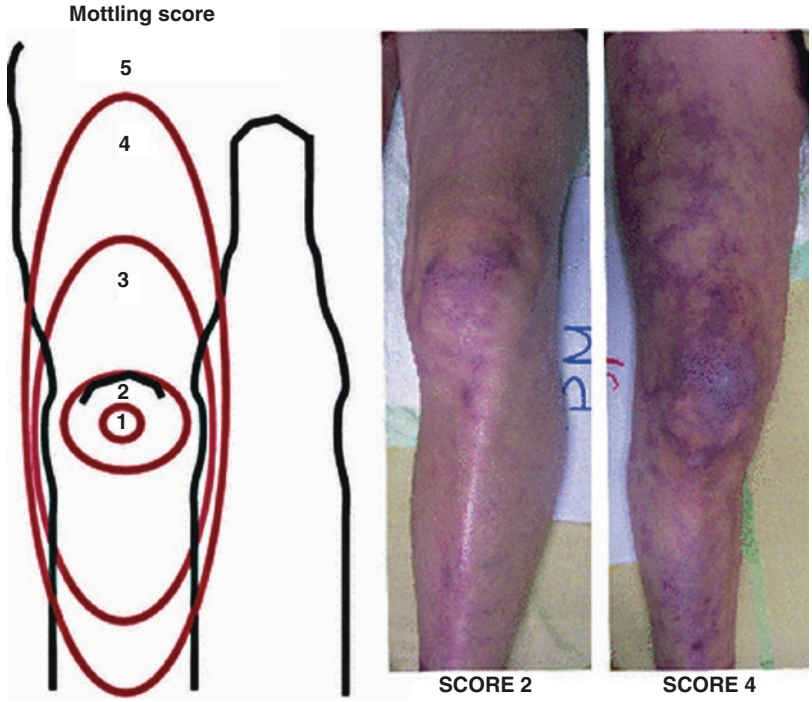


Fig. 53.3 Skin Mottling Score. *Left*: the mottling score is based on a mottling area extension on the legs. Score 0 indicates no mottling; score 1, a modest mottling area (coin size) localized to the center of the knee; score 2, a moderate mottling area that does not exceed the superior edge of the kneecap; score 3, a mild mottling area that does not exceed the middle thigh; score 4, a severe mottling area that does not go beyond the fold of the groin; score 5, an extremely severe mottling area that goes beyond the fold of the groin. *Right*: Examples of the mottling score

and minimum pulse pressure during a single respiratory cycle (Fig. 53.4). Increasing variation predicts fluid responsiveness [19].

Focused ultrasonography is another method to discern central hemodynamics and the etiology of shock. It can reveal right and left cardiac chamber size and contractility, pericardial fluid, and inferior vena cava size and collapsibility suggestive of hypovolemia, among other features. A minimally collapsible IVC is associated with euvolemia or hypervolemia while a highly collapsible IVC is associated with hypovolemia [20] (Video 53.1). Recent guidelines and consensus statements recommend focused ultrasonography as best clinical practice in the initial assessment of hemodynamically unstable patients with septic shock despite no rigorous RCTs of focused cardiac ultrasonography affecting patient-centered outcomes in septic shock [21].

Tissue Perfusion

Elevated lactate level > 2 are part of the diagnostic criteria for septic shock, although the Surviving Sepsis Campaign has previously utilized a level of 4. Lactate clearance is used as a marker of improving tissue perfusion and is a target of early therapy. The goal is normalization of lactate, however early improvement of at least 10–20 % from baseline lactate is associated with a mortality benefit comparable to a SvO_2 of 70 % or more [22]. The rigorous targeting of SvO_2 to over 70 % is not essential for the early management of sepsis. SvO_2 is now considered one of several methods of evaluating successful resuscitation. Strategies to optimize both lactate clearance and SvO_2 may be complimentary and currently, no single measure is clearly superior.

Vasopressors

Norepinephrine is recommended as the first line agent for use in patients with septic shock. Dopamine is associated with a higher rate of dysrhythmias and low-dose dopamine for renal protection is not recommended [23]. Vasopressin at .01 to .03 U per minute was compared to norepinephrine in the VASST study [24]. There was no significant mortality difference at 28 or 90 days in all patients with sepsis. The Surviving

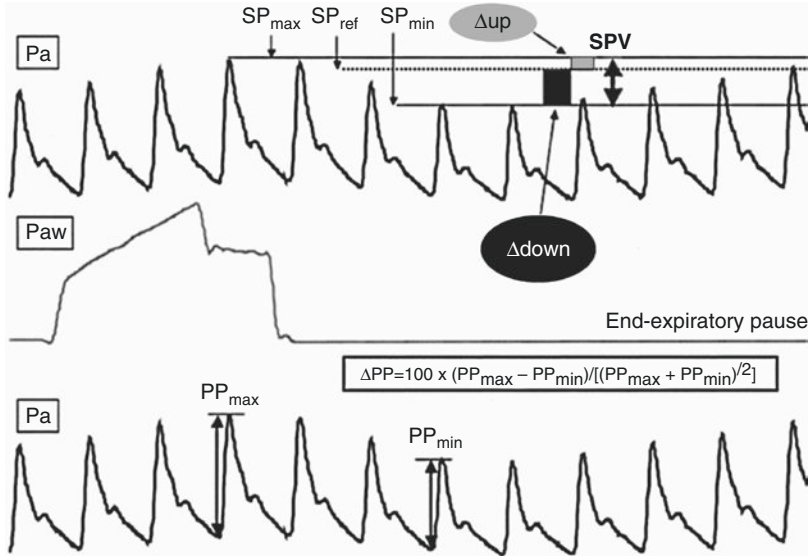


Fig. 53.4 Pulse pressure variation. Analytical description of respiratory changes in arterial pressure during mechanical ventilation. The systolic pressure and the pulse pressure (systolic minus diastolic pressure) are maximum (SPmax and PPmax, respectively) during inspiration and minimum (SPmin and PPmin, respectively) a few heartbeats later, i.e., during the expiratory period. The systolic pressure variation (SPV) is the difference between SPmax and SPmin. The assessment of a reference systolic pressure (SPref) during an end-expiratory pause allows the discrimination between the inspiratory increase (Δup) and the expiratory decrease (Δdown) in systolic pressure. *Pa* arterial pressure, *Paw* airway pressure (From Michard et al. [54]. Reprinted with permission from Wolters Kluwer Health, Inc)

Sepsis Guidelines states that Vasopressin at .03 U/min can be used in an effort to further raise mean arterial pressure (MAP) or to decrease the dose of norepinephrine. It is not recommended as a first line agent. There have been few studies evaluating phenylephrine, an ὰ-1 adrenergic receptor agonist, in sepsis. It is also not recommended as a first line agent.

Treatment of Infection and Antimicrobial Stewardship

Source control is defined as "all physical measures undertaken to eliminate a source of infection, to control ongoing contamination, and to restore premorbid anatomy and function" [25]. The Surviving Sepsis Guidelines define source control as: a) specific diagnosis of infection and intervention within 12 h of diagnosis, b) if infected peripancreatic necrosis is identified, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred, c) effective intervention associated with the least physiologic insult should be used (e.g., percutaneous rather than surgical drainage of an abscess), and d) if intravascular access devices are a possible source of sepsis or septic shock, they should be removed promptly after other vascular access has been established [6].

The initial intravenous antimicrobial therapy should have broad coverage and adequate tissue penetration against all likely pathogens. Therapy should be given within the first hour after the recognition of sepsis or septic shock. Mortality increases for each hour that the patient does not receive adequate antimicrobial therapy while the patient is hypotensive [26]. Two sets of blood cultures along with cultures from other potential sources such as urine or sputum should be obtained before the initiation of antimicrobials if it can be done without significant delay. With the mortality risk associated with a delay in therapy, the initiation of empiric, broad-spectrum antimicrobials has become a recommendation within the six hour window. A side-effect of this practice

may be increased antimicrobial resistance which can potentially result in a prolonged hospital stay with a less clear effect on mortality [4]. Daily assessment is important for potentially de-escalating or modifying therapy [27, 28].

Ventilator Management

In mechanically ventilated patients, lung-protective ventilation is recommended in patients with severe sepsis or septic shock regardless of whether or not the patient has been diagnosed with acute respiratory distress syndrome. A tidal volume of 6 mL/kg of ideal body weight should be combined with a goal plateau pressure <30 cm H_2O along with the application of positive end-expiratory pressure [6, 29, 30].

Glycemic Control and Nutrition

Glucose control in the critically ill patient has evolved significantly over the years. An early study showed improved outcomes and fewer complications with glucose maintained at approximately 80–108 mg/dL. This was especially true in surgical patients [31]. The NICE-SUGAR trial found that tight glycemic control was associated with higher 90 day mortality [32]. The higher mortality in NICE-SUGAR was accounted for by septic patients and therefore a glucose level of 80–110 mg/dL is considered contraindicated in septic patients who are being resuscitated. Current guidelines call for glucose monitoring and management with insulin after 2 consecutive blood glucose values are more than 180 mg/dL. The goal is to maintain a level at 180 mg/dL or less without a lower target other than hypoglycemia [6].

There is little evidence of benefit to starting full enteral or parenteral nutrition early in the course of severe sepsis. Enteral feeding may be initiated after the initial resuscitation, if tolerated. Parenteral feeding should not be provided within the first week and should be avoided if enteral feeding is possible. There is an association with improved outcomes including mortality with hypocaloric feeding when initiated within the first week [6, 33].

Evidence Contour

The EGDT bundle has remained one of the cornerstones in the management of severe sepsis and septic shock. Subsequently, multiple studies have analyzed each component of the bundle which has resulted in an evolution of practice. Those changes are represented in the most recent Surviving Sepsis Campaign guidelines.

Early Goal Directed Therapy (EGDT)

The Protocolized Care for Early Septic Shock (ProCESS) trial prospectively randomized 1341 patients in a 1:1:1 ratio into 1 of 3 groups. One group was a protocol based EGDT group which followed the initial study protocols. The second group was a protocol based therapy that required rapid resuscitation but no requirement for initial central line placement, mixed venous oxygen saturation (SvO_2) monitoring, or blood transfusions for a hematocrit <30. The third group was a "usual care" arm in which care was directed by the bedside clinician. The protocol-based EGDT did not require additional organ support i.e., dialysis or mechanical ventilation or demonstrate any improvement in 2–3 month or 1 year mortality compared to the other 2 arms [34]. Multiple multi-center studies resulted in similar findings. The ARISE trial randomized 1600 patients into an EGDT and a usual care group. The EGDT group did not reduce all-cause mortality at 90 days. There was no significant difference in in-hospital mortality, duration of organ support or length of hospital stay [35]. 1260 patients were enrolled in the ProMISe trial. 630 patients were assigned to the EGDT arm and 630 were assigned to "usual care". There was no difference in all-cause mortality at 90 days [36]. The mortality associated with sepsis from all arms from the first 2 trials ranged from 18.2 to 21 % while the mortality from the ProMISe trial was 29.5 % in the EGDT group and 29.2 % in the usual care group.

In all likelihood that "standard" care for sepsis has improved and evolved since the original publication of EGDT [37]. A retrospective, observational review of >100,000 patients with severe sepsis from Australia and New Zealand from 2000 to 2012 demonstrated improved mortality [38]. The authors attributed part of the improvement on overall changes in ICU practice. The focus on sepsis treatment remains with early fluid resuscitation, timely antibiotic administration, and appropriate use of vasopressors (Table 53.1).

Corticosteroids

The use of corticosteroids in the treatment of sepsis remains controversial. Early studies of short-course high dose methylprednisolone showed no benefit and potentially increased harm with frequent adverse effects. Studies utilizing adrenocorticotropic hormone, stimulation testing, and identifying subgroups with "relative adrenal insufficiency" have yielded conflicting results.

Table 53.1 Guidelines for the treatment of sepsis and septic shock from the Surviving Sepsis Campaign

Element of Care	Grade[a]
Resuscitation	
Begin goal-directed resuscitation during first 6 h after recognition	1C
Begin initial fluid resuscitation with crystalloid and consider the addition of albumin	1B
Consider the addition of albumin when substantial amounts of crystalloid are required to maintain adequate arterial pressure	2C
Avoid hetastarch formulations	1C
Begin initial fluid challenge in patients with tissue hypoperfusion and suspected hypovolemia, to achieve ≥30 ml of crystalloids per kilogram of body weight[b]	1C
Continue fluid-challenge technique as long as there is hemodynamic improvement	UG
Use norepinephrine as the first-choice vasopressor to maintain a mean arterial pressure of ≥65 mmHg	1B
Use epinephrine when an additional agent is needed to maintain adequate blood pressure	2B
Add vasopressin (at a dose of 0.03 units/min) with weaning of norepinephrine, if tolerated	UG
Avoid the use of dopamine except in carefully selected patients (e.g., patients with a low risk of arrhythmias and either known marked left ventricular systolic dysfunction or low heart rate)	2C
Infuse dobutamine or add it to vasopressor therapy in the presence of myocardial dysfunction (e.g., elevated cardiac filling pressures or low cardiac output) or ongoing hypoperfusion despite adequate intravascular volume and mean arterial pressure	1C
Avoid the use of intravenous hydrocortisone if adequate fluid resuscitation and vasopressor therapy restore hemodynamic stability; if hydrocortisone is used, administer at a dose of 200 mg/day	2C
Target a hemoglobin level of 7–9 g/dl in patients without hypoperfusion, critical coronary artery disease or myocardial ischemia, or acute hemorrhage	1B
Infection Control	
Obtain blood cultures before antibiotic therapy is administered	1C
Perform imaging studies promptly to confirm source of infection	UG
Administer broad-spectrum antibiotic therapy within 1 h after diagnosis of either severe sepsis or septic shock	1B/1C
Reassess antibiotic therapy daily for de-escalation when appropriate	1B
Perform source control with attention to risks and benefits of the chosen method within 12 h after diagnosis	1C
Respiratory Support	
Use a low tidal volume and limitation of inspiratory-plateau-pressure strategy for ARDS	1A/1B
Apply a minimal amount of positive end-expiratory pressure in ARDS	1B

(continued)

Table 53.1 (continued)

Element of Care	Grade[a]
Administer higher rather than lower positive end-expiratory pressure for patients with sepsis-induced ARDS	2C
Use recruitment maneuvers in patients with severe refractory hypoxemia due to ARDS	2C
Use prone positioning in patients with sepsis-induced ARDS and a ratio of the partial pressure of arterial oxygen (mm Hg) to the fraction of inspired oxygen of <100, in facilities that have experience with such practice	2C
Elevate the head of the bed in patients undergoing mechanical ventilation, unless contraindicated	1B
Use a conservative fluid strategy for established acute lung injury or ARDS with no evidence of tissue hypoperfusion	1C
Use weaning protocols	1A
Central Nervous System Support	
Use sedation protocols, targeting specific dose-escalation end points	1B
Avoid neuromuscular blockers if possible in patients without ARDS	1C
Administer a short course of a neuromuscular blocker (<48 h) for patients with early, severe ARDS	2C
General Supportive Care	
Use a protocol-specified approach to blood glucose management, with the initiation of insulin after two consecutive blood glucose levels of >180 mg/dl (10 mmol/l), targeting a blood glucose level of <180 mg/dl)	1A
Use the equivalent of continuous venovenous hemofiltration or intermittent hemodialysis as needed for renal failure or fluid overload	2B
Administer prophylaxis for deep-vein thrombosis	1B
Administer stress-ulcer prophylaxis to prevent upper gastrointestinal bleeding	1B
Administer oral or enteral feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 h after a diagnosis of severe sepsis or septic shock	2C
Address goals of care, including treatment plans and end-of-life planning as appropriate	1B

Data are adapted from Dellinger et al. [53]. ARDS denotes acute respiratory distress syndrome and ICU intensive care unit

From Angus and van der Poll [3]. Reprinted with permission from Massachusetts Medical Society

[a]For all grades, the number indicates the strength of the recommendation (1, recommended; 2, suggested), and the letter indicates the level of evidence, from high (A) to low (D), with UG indicating ungraded. Recommendations that are specific to pediatric severe sepsis include therapy with face-mask oxygen, high-flow nasal cannula oxygen, or nasopharyngeal continuous positive end-expiratory pressure in the presence of respiratory distress and hypoxemia (2C); use of physical examination therapeutic end points, such as capillary refill (2C); administration of a bolus of 20 ml of crystalloids (or albumin equivalent) per kilogram of body weight during a period of 5–10 min for hypovolemia (2C); increased use of inotropes and vasodilators in septic shock with low cardiac output associated with elevated system vascular resistance (2C); and use of hydrocortisone only in children with suspected or proven absolute adrenal insufficiency (2C)

[b]The guidelines recommend completing the initial fluid resuscitation within 3 h (UG)

The CORTICUS trial evaluated the effects of IV hydrocortisone vs placebo in patients with septic shock. There was no 28 day mortality benefit and the data suggested steroids caused new episodes of sepsis. A meta-analysis from 2011 challenged the assertion that steroid use in severe sepsis cause new cases of sepsis. It also advocated using adrenocorticotropin hormone (ACTH) test to help guide therapy. Current guidelines recommend against stimulation testing, not using steroids in the absence of shock, advise using intravenous corticosteroids for patients in refractory shock who have remained hemodynamically unstable even after adequate fluid resuscitation and vasopressor use, and tapering steroids when pressors are no longer required [6, 30, 39, 40].

SIRS Criteria in Sepsis

The systemic inflammatory response syndrome (SIRS) was a component of the definition of sepsis for >20 years. The need for patients to meet 2 SIRS criteria has been criticized because of a low specificity for infection especially in patients admitted less than 24 h to the ICU. A recent study demonstrated that requiring 2 SIRS criteria in severe sepsis excluded one in eight otherwise similar patients with infection, organ failure, and substantial mortality [41]. Hence, SIRS lacks both specificity and sensitivity in the identification of septic patients. As a result of these and other considerations, the utilization of SIRS criteria has been removed from the new sepsis definitions.

Blood Pressure Target in Septic Shock

Current guidelines recommend a target MAP of at least 65 mmHg during resuscitation of patients in septic shock. A recent multicenter trial sought to determine if a higher blood pressure target is more effective. 388 patients were targeted with a higher MAP goal (80–85 mmHg) and were compared to 388 patients in a low-target group (65–70 mmHg). The study revealed no difference in 28 or 90 day mortality between the two groups [42].

Fluid Resuscitation in Septic Shock

Despite current mortality rates of approximately 40 %, dosing intravenous fluid during resuscitation of septic shock remains largely empirical. Too little fluid may result in tissue hypoperfusion and worsen organ dysfunction. In several studies, a positive fluid balance was associated with increased time spent on mechanical ventilation and resulted in a trend toward increased mortality [43, 44]. A retrospective study on patients from the VASST trial attempted to quantify the ideal amount of fluids to be given. The study showed that a more positive fluid balance both early in resuscitation and cumulatively over 4 days is associated with an increased risk of mortality in septic shock. Central venous pressure may be used to gauge fluid balance ≤ 12 h into septic shock but becomes an unreliable marker of fluid balance thereafter. Optimal survival in the VASST study occurred with a positive fluid balance of approximately 3 L at 12 h [45]. Presently the optimal approach to fluid management in sepsis patients remains unclear. The Surviving Sepsis Campaign recommendations for a multi-variable assessment reflects an attempt to approximate the approach undertaken in the control group of the ProCESS trial and has been adopted by the Centers for Medicare and Medicaid Services (CMS) as part of a performance measure despite the lack of prospective clinical validation [46].

Bicarbonate Infusion in Lactic Acidosis

Sodium bicarbonate had been used to treat metabolic acidosis in order to correct acidemia, improve myocardial contractility and cardiac output, and to increase the cardiovascular response to circulating catecholamines. Potential adverse effects include hypercapnia and aggravation of intracellular acidosis, hyperosmolality, congestive cardiac failure, and ionized hypocalcemia. One study infused sodium bicarbonate in fourteen patients who had metabolic acidosis and increased arterial lactate. Correction of acidemia using sodium bicarbonate did not improve hemodynamics in critically ill patients who have metabolic acidosis and increased blood lactate or improve the cardiovascular response to infused catecholamines. Sodium bicarbonate decreased plasma ionized calcium and increased $PaCO_2$ [47].

Heart Rate Control in Septic Shock

β-Blocker therapy may control heart rate and attenuate the deleterious effects of β-adrenergic receptor stimulation in septic shock. One study evaluated patients in septic shock vs a control group where the study group received a continuous infusion of esmolol titrated to maintain heart rate between 80/min and 94/min for their ICU

stay. Target heart rate was achieved in the study group. The study group also had lower arterial lactate concentrations, decreased norepinephrine and fluid requirements, and a significantly lower 28 day mortality [48].

Sequella After Surviving Severe Sepsis/Septic Shock

Odds of developing cognitive impairment and physical disability were increased among those who survived an episode of severe sepsis. The new cognitive impairment and functional disability was substantial and persistent among survivors. The magnitude of these new deficits was large, likely resulting in a pivotal downturn in patients' ability to live independently [49]. One year mortality in the elderly (>70 years old) has also been found to be elevated in survivors of severe sepsis. Predictors were severe organ failure, prior functional status, and Mini-Mental State Examination [50].

Various initiatives are underway in an effort to improve functional outcome after surviving sepsis. The ABCDEF bundle is a coordinated effort between multiple disciplines for the management of critically ill patients. Implementation of the bundle has been shown to improve care within the ICU [51]. The bundle involves:

A: Awakening trials for ventilated patients.
B: Spontaneous breathing trials.
C: Coordinated effort between the registered nurse and respiratory therapist to perform the spontaneous breathing trial when the patient is awakened by reducing or stopping the patient's sedation. The combination of sedation and analgesics being used are reviewed, and changes or reductions in the doses are considered.
D: A standardized delirium assessment program, including treatment and prevention options.
E: Early mobilization and ambulation of critical care patients.
F: Family Engagement and Empowerment

The Society of Critical Care (SCCM) Liberation Campaign is designed to decrease the harmful effects of pain, agitation and delirium in the ICU and improve patients' long-term outcomes. The recommendations from the Pain, Agitation, Delirium (PAD) guide [52] include:

- Integrating multi-professional approach to managing pain, agitation/sedation, and delirium to achieve significant, synergistic benefits to improve patient outcomes.
- Utilizing valid and reliable bedside assessment tools for pain, sedation, and delirium, so as to target appropriate treatment strategies.
- Decreasing levels of sedation, while assuring adequate pain control and delirium management, to allow patients active participation in ventilator weaning trials along with early mobility activities.
- Instituting prevention strategies in the ICU to avoid complications and improve clinical outcomes.

References

1. Surviving Sepsis Campaign. Society of Critical Care Medicine. [Revised 4/2015 by the SSC Executive Committee]. Accessed at: http://www.survivingsepsis.org/Bundles/Pages/default.aspx.
2. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Intensive Care Med. 2004;30(4):536–55.
3. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369(9):840–51.
4. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence. 2014;5(1):4–11.
5. Rivers E, Nguyen B, Havstad S, et al. N Engl J Med. 2001;345(19):1368–77.
6. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med. 2013;39(2):165–228.
7. Finfer S, Bellomo R, Boyce N, et al. SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004; 350(22):2247–56.
8. Caironi P, Togoni G, Masson S, et al. ALBIOS Study Investigators. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;370(15):1412–21.
9. Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med. 2013;369(13):1243–51.
10. Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive

intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308: 1566–72.
11. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: The SPLIT Randomized Clinical Trial. JAMA. 2015;314:1701–10.
12. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367(20):1901–11.
13. Holst LB, Haase N, Wetterslev J, et al. Transfusion requirements in septic shock 9TRISS) trial – comparing the effects and safety of liberal versus restrictive red blood cell transfusion in septic shock patients in the ICU: protocol for a randomized controlled trial. Trials. 2013;14:150.
14. Park DW, Chun BC, Kwon SS, et al. Red blood cell transfusions are associated with lower mortality in patients with severe sepsis and septic shock: a propensity-matched analysis. Crit Care Med. 2012; 40(12):3140–5.
15. Ebert RV, Stead EA. Circulatory failure in acute infections. J Clin Invest. 1941;20:671–9.
16. Ait-Oufella H, Lemionne S, Boelle P, et al. Mottling score predicts survival in septic shock. Intensive Care Med. 2011;37(5):801–7.
17. Cawcutt K, Peters S. Severe sepsis and septic shock: clinical overview and update on management. Mayo Clin Proc. 2014;89(11):1572–8.
18. Monnet X, Rienzo M, Osman D, et al. Passive leg raising predicts fluid responsiveness in the critically ill. Crit Care Med. 2006;34:1402–7.
19. Marik P, Cavallazzi R, Vasu T, et al. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med. 2009;37(9):2642–7.
20. Stawicki SP, Ej A, Eiferman ES, et al. Prospective evaluation of intravascular volume status in critically ill patients: does inferior vena cava collapsibility correlate with central venous pressure? J Trauma Acute Care Surg. 2014;76(4):956–64.
21. Seymour C, Rosengart M. Septic shock: advances in diagnosis and treatment. JAMA. 2015;314(7):708–17.
22. Jones AE, Shapiro NI, Trzeciak S, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA. 2010;303(8):739–46.
23. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362(9):779–89.
24. Investigators VASST. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med. 2008;358(9):877–87.
25. Schein M, Marshall J. Source control. A guide to the management of surgical infections. Heidelberg: Springer; 2002.
26. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34(6):1589–96.
27. Gamacho-Montero J, Gutierrez-Pizarraya A, Escoresca-Ortega A, et al. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. Intensive Care Med. 2014;40(1):32–40.
28. Kollef MH. What can be expected from antimicrobial de-escalation in the critically ill? Intensive Care Med. 2014;40(1):92–5.
29. Ginde AA, Moss M. Lung-protective ventilation in emergency department patients with severe sepsis. Acad Emerg Med. 2014;21(1):96–7.
30. Russell JA. Management of sepsis. N Engl J Med. 2006;355(16):1699–713.
31. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;354(19):1359–67.
32. Study Investigators NICE-SUGAR, Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–97.
33. Arabi YM, Tamim HM, Dhar GS, et al. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. Am J Clin Nutr. 2011;93(3):569–77.
34. Investigators PCESS, Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370(18): 1683–93.
35. ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371(16):1496–506.
36. ProMISe Investigators, Mouncey P, Osborn T, Power S, et al. Trial of Early, Goal-Directed Resuscitation for Septic Shock. N Engl J Med. 2015;372:1301–11.
37. Angus DC, Barnato AE, Bell D, et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med. 2015;41(9):1549–60.
38. Kaukonen KM, Bailey M, Suzuki S, et al. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. JAMA. 2014;311(13):1308–16.
39. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288(7):862–71.
40. Moreno R, Sprung C, Annane D, et al. Time course of organ failure in patients with septic shock treated with hydrocortisone: results of the Corticus study. In: Applied physiology in intensive care medicine 1. Heidelberg: Springer; 2012. p. 423–30.
41. Kaukonen KM, Bailey M, Pilcher D, et al. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med. 2015;372:1629–38.
42. Investigators SEPSISPAM. High versus low blood-pressure target in patients with septic shock. N Engl J Med. 2014;370:1583–93.
43. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006;34:344–53.

44. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354: 2564–75.
45. Boyd J, Forbes J, Nakada T, et al. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med. 2011;39:259.
46. Hospital Quality Initiative**,** Outcome Measures. Centers for Medicare and Medicaid Services. [Last Modified: 09/29/2015]. Accessed at: https://www.cms.gov/medicare/quality-initiatives-patient-assessment-instruments/hospitalqualityinits/outcomemeasures.html.
47. Cooper J, Walley K, Wiggs B, et al. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. Ann Intern Med. 1990; 112:492.
48. Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock. JAMA. 2013;310:1683.
49. Iwashyna TJ, Ely EW, Smith DM, et al. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010;304(16):1787–94.
50. Regazzoni CJ, Zamora RJ, Petrucci E, et al. Hospital and 1-year outcomes of septic syndromes in older people: a cohort study. J Gerontol A Biol Sci Med Sci. 2008;63(2):210–2.
51. Balas MC, Vasilevskis EE, Olsen KM, et al. Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. Crit Care Med. 2014;42(5):1024–36.
52. Barr J, Fraser G, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263–306.
53. Dellinger RP, Levy MM, Rhodes A, Annane D, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580–637.
54. Michard F, Warltier DC, Ph D. Changes in arterial pressure during mechanical ventilation. Anesthesiology. 2005;103(2):419–28.

Invasive Aspergillus

54

Elaine Klinge Schwartz

Case Presentation

The patient is a 71 year old male with COPD, Gold Class IV, and bronchiectasis who resides in the Rocky Mountain region of the United States. He required oxygen therapy at 4 L/min continuously and was using tiotropium and inhaled corticosteroids. His lung disease had been stable and without exacerbation for 1 year. In the month of January, the patient developed increased cough and shortness of breath, and required hospitalization for an exacerbation at on outside hospital. Evaluation included routine laboratory studies, sputum gram stain and culture, chest radiograph and chest CT angiogram. Testing was unremarkable except for radiographic imaging consistent with COPD/emphysema. The patient was treated with empiric antibiotics for community acquired organisms and a burst and tapering dose of corticosteroids. Patient was discharged from the hospital after 4 days. Over the next 5 months, the patient was hospitalized twice for recurrent COPD exacerbations. On each hospitalization, the patient was treated similarly. During his last hospitalization, patient was noted to have bilateral lower lobe infiltrates. Following his last hospitalization, the patient was admitted to a rehabilitation facility for severe deconditioning. He was also treated with a 2-week course of levofloxacin and another tapering dose of corticosteroids. The patient returned to his baseline level of function except for an increased oxygen requirement of 6 L/min. One month after returning home, the patient developed worsening dyspnea, cough and fever. He was evaluated by his pulmonologist for his complaints. Evaluation included CBC, IgE, sputum collection, spirometry and Chest CT. Patient was found to have a WBC 16,000, no eosinophilia, a 20 % decline in FEV1 (0.8 L) and sputum culture was unremarkable for bacterial or fungal organisms. CT revealed progressive bilateral infiltrates (Figs. 54.1, 54.2 and 54.3).

Question What are the differential diagnoses, diagnostic approach and treatment of this patient's symptoms and progressive radiographic changes?

Answer The differential diagnosis of this patient's progressive pulmonary infiltrates is broad and includes both infectious and non-infectious etiologies.

Non-infectious etiologies include bronchiolitis obliterans with organizing pneumonia (BOOP), malignancy (although the time course is somewhat rapid), drug-induced lung disease, alveolar hemorrhage, atypical cardiogenic edema and recurrent aspiration bronchiolitis and pneumonitis. Notable, however, is the absence of historical or clinical features suggestive of these

E.K. Schwartz
Department of Medicine, National Jewish Health, Denver, CO, USA
e-mail: schwartze@njhealth.org

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_54

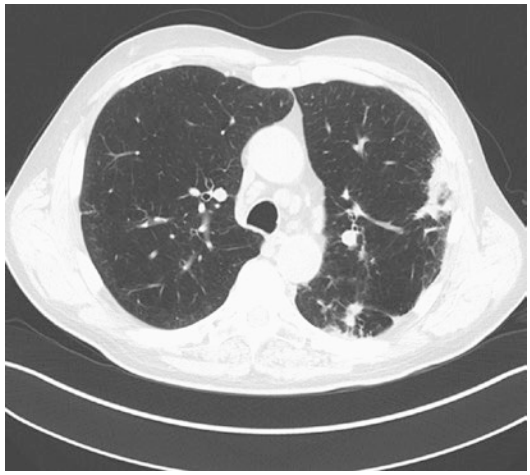


Fig. 54.1 Multiple peribronchovascular opacities with spiculated consolidative peripheral opacity in left upper lobe

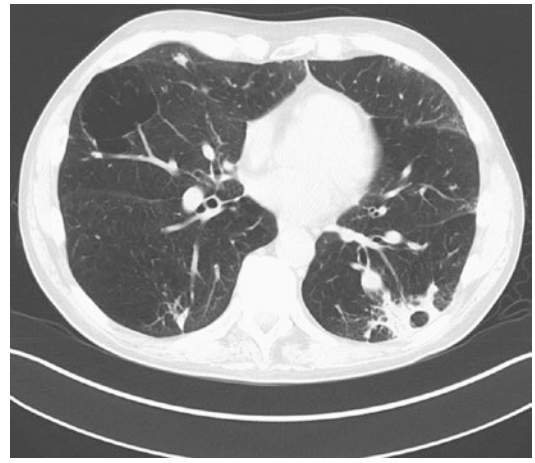


Fig. 54.3 Cavitary foci within the consolidative opacity. Moderate centrilobular and panlobular emphysema with a 5.8 cm bulla in right middle lobe

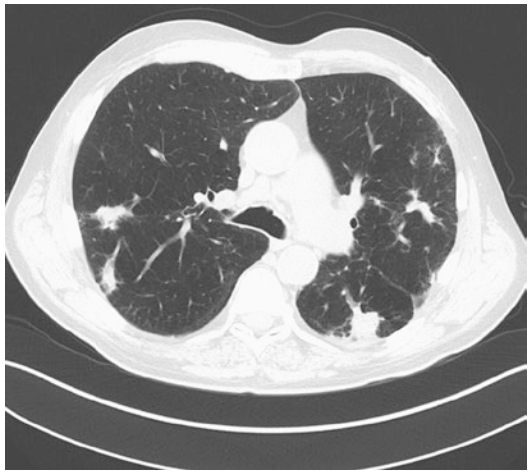


Fig. 54.2 Patchy peribronchovascular opacities present in both lungs

entities. Also noteworthy is his combined duration of moderate to high dose corticosteroid therapy.

Infectious differential diagnoses include recurrent bacterial pneumonia potentially in the setting of noted bronchiectasis. Infectious aspiration bronchiolitis and pneumonitis, and viral infection would be less likely. Fungal pathogens include Pneumocystis jirovecii and other fungal organisms. He had no recent history of travel to endemic areas of fungal infections.

Due to the severity of his underlying lung disease/emphysema, degree of hypoxemia as well as the aforementioned diagnostic considerations, and the potential low yield for bronchoscopy and associated risk for hypoxia with transbronchial biopsy, the patient was referred for video-assisted thoracoscopic biopsy (VATS). The patient underwent a left sided VATS with specimens obtained from the left upper lobe, lingua and lower lobe segments.

The pathology was notable for readily identified fungal organism with acute angle branching, septated hyphae morphologically consistent with Aspergillus, marked acute and chronic intraalveolar hemorrhage, associated bronchiolitis obliterans-organizing pneumonia, necrotizing granulomas centered along bronchovascular structures suggestive of invasive pulmonary aspergillosis (IPA), angioinvasive aspergillosis, and a component of chronic pulmonary necrotizing aspergillosis.

Principles of Management

Diagnostic Approach

Aspergillus is a fungus that is ubiquitous in nature and inhalation of spores are common. In healthy

hosts, spores are eliminated by immune defenses and mucociliary clearance mechanisms of the lung. Germination is the conversion of spores to hypal elements, which branch at a 45-degree angle. There are over 200 species of Aspergillus; however, the most common species that cause illness in descending order are A. fumigatus, A. flavus, A. niger and A. terreus [1, 2]. Aspergillus infection is primarily the result of impaired airway clearance from a compromised immune system or chronic lung disease. Aspergillosis illness can be due to allergy, (Allergic Bronchopulmonary Aspergillosis), airway or lung invasion (Aspergillus Tracheobronchitis or Invasive Pulmonary Aspergillosis (IPA or Chronic Pulmonary Aspergillosis), a cutaneous infection or extra-pulmonary dissemination, including CNS involvement [3].

The diagnosis of IPA can be challenging, as patients may initially be asymptomatic. Criteria for the diagnosis of invasive fungal disease were initially formulated in 2002 and updated in 2008 [4]. Definitions for proven, probable and possible IPA for the susceptible populations have been stated. The population at risk can be broken down into classic risk factors and newer identified risk factors [5–8].

Risk Factors for Invasive Aspergillosis

Classic Risk Factors

- Severe and prolonged neutropenia
- Allogeneic stem cell transplant recipients
- Severe Graft Versus Host Disease
- Systemic corticosteroid use for greater than 3 weeks
- Conditions or drugs that cause chronic impaired cellular immune response such as patients with autoimmune disease, anti-rejection medication

Newer Risk Factors

- Critical illness
- Solid organ transplant recipients
- Chronic Obstructive Pulmonary Disease, including patients on inhaled corticosteroids
- End stage Liver Disease/Alcoholic Hepatitis
- HIV infection
- Diabetes

In a retrospective multicenter study of 1209 patients selected with culture positivity for Aspergillus, 12 % had evidence of disease [1]. Patients with hematologic malignancy or transplants accounted for the majority of cases; malnutrition (27 %), corticosteroid use (20 %), HIV infection (19 %), diabetes mellitus (11 %) and chronic obstructive pulmonary disease (9 %) were associated with evidence of invasive infection. In a single-center retrospective study of 239 patients hospitalized with COPD who had Aspergillus isolated from the lower respiratory tract, 22 % had probable invasive aspergillosis [7]. Inhaled corticosteroids may increase the risk of invasive aspergillosis in patients with COPD [9, 10].

Clinical presentation of IPA can be nonspecific, with patients developing fever, chest pain, dyspnea, cough and/or hemoptysis. A classic triad described in patients with neutropenia is fever, pleuritic chest pain and hemoptysis [11]. Absence of the triad should not exclude patients from the possibility of IPA in patients with risk factors for the disease.

Chest CT radiograph is more sensitive than plain chest radiographic imaging. HRCT is recommended in all cases of suspected IPA [4, 12]. Findings on HRCT indicative of invasive pulmonary disease include macronodules with or without a surrounding "halo" of ground glass changes, air-crescent sign, cavitary lesions, and areas of consolidation. A retrospective study of chest imaging in 235 patients with invasive aspergillosis demonstrated one or more macronodules (94 %), halo sign (61 %), consolidation (30 %), infarct shaped nodules (27 %), cavitary lesions (20 %) and air-crescent signs (10 %) [13].

Diagnosis is based on both isolating the organism or markers of the organism and the probability that it the cause of the disease.

Culture of the organism in combination with evidence of tissue invasion on histopathology or

culture from a normally sterile site provides the most certain evidence of IPA. Tissue biopsy with histopathologic demonstration of tissue invasion by fungal hyphae is considered the "gold standard" [14].

Laboratory testing that can aid in the diagnosis of invasive infection includes enzyme immunoassays that detect galactomannan, a polysaccharide in the Aspergillus cell wall in serum or bronchoalveolar fluid. False-positive galactomannan tests have been reported in patients receiving piperacillin/tazobactam antibiotics.

Testing serum for an additional antigen, 1, 3 Beta-D glucan, is not specific for aspergillus, since the antigen is present in other fungi [6, 12].

Investigative studies looking for DNA evidence by PCR has shown mixed results.

Bronchoscopy is routinely performed in suspected cases of IPA. However, bronchoscopy has several limitations, including sampling error due to patchy involvement in the lung, and the potential risk in this patient population that may be coagulopathic or thrombocytopenic.

Therapy

The Infectious Diseases Society of America (ISDA) released guidelines for the treatment of invasive aspergillus in 2008 and The American Thoracic Society (ATS) published guidelines in 2011 for the treatment of fungal infections [4, 15, 16]. When invasive disease is suspected or documented, early aggressive anti-fungal treatment is essential. Therapy is often prolonged from months to more than a year, with duration of therapy dependent upon the patient's location of infection, underlying disease, and response to therapy, which includes assessment of clinical and radiographic resolution, improvement in immune function and microbiologic clearance.

Antifungal Therapy

Three classes of antifungal agents are used for the treatment of aspergillus: polyenes, azoles and echinocandins. Choice of therapy may be dependent upon the patient's organ function, immune status and prior therapies.

Treatment can be divided into initial therapy or salvage therapy. At present, monotherapy is recommended.

Monotherapy

Triazoles These antifungal agents include voriconazole, posaconazole, itraconazole and fluconazole.

- Voriconazole has emerged as standard therapy for the treatment of invasive aspergillus. An international, multicenter randomized open-label trial involving 277 patients with confirmed or probable invasive aspergillus compared voriconazole with amphotericin B deoxycholate as initial therapy [17]. The majority of patients had hematologic malignancy and many had undergone hematopoietic stem cell transplant. At 12 weeks, 53 % of those patients treated with voriconazole compared to 32 % treated with Amphotericin B had a greater likelihood of complete or partial response, a lower mortality rate (29 % vs. 42 %), a lower rate of adverse reactions and less likelihood of requiring a change in therapy due to intolerance or poor response (36 % vs. 80 %). The efficacy of voriconazole compared with lipid formations of Amphotericin B is unknown since there are no available studies of comparison.

  Voriconazole may also be used in those patients with CNS disease. Despite a mortality rate, which has previously approached 100 %, in one retrospective study, 31 % of patients who were treated with voriconazole survived for a median observation of 390 days. The vast majority of the patients had received other antifungal therapy other than voriconazole for a median of 31 days prior to changing to voriconazole [18].

  The primary treatment dose for voriconazole is IV (6 mg/kg every 12 h for 1 day the 4 mg/kg every 12 h) until improvement. Therapy is then changed to oral voriconazole (200 mg every 12 h) or intraconazole (400–600 mg/day) until resolution or stabilization of disease.

  Monitoring for liver toxicity and potential drug interactions is imperative as the azoles

interact with the human P450 cytochrome system [19]. Potential side effects from voriconazole include visual changes and hallucinations. All of the azoles have the ability to prolong the QTc and should be monitored. Azoles are class C drugs and are contraindicated during pregnancy. In contrast, amphotericin B is rated class B for pregnancy and is preferred during severe infection [20].

- Posaconazole is a broad-spectrum triazole that is highly effective against Aspergillus species *in vitro* [21]. The drug was initially approved by the FDA for prophylaxis of fungal infection in neutropenic patients and treatment for mucocutaneous candidiasis. In 2013 the FDA approved the delayed release tablet for prophylaxis of invasive aspergillus in patients at high risk. The intravenous form was approved in 2014. Posaconazole may be an effective agent but additional studies are needed before recommendations can be given for initial therapy. Side effects of posaconazole include gastrointestinal tract disturbance.
- Itraconazole is considered second line therapy for aspergillus. Oral therapy has been used in patients with mild immunosuppression and non-life threatening aspergillus infection [22].

Polyenes This class of medication is effective against invasive aspergillus, and includes amphotericin B deoxycholate and lipid formulations. The lipid formulations have an advantage over deoxycholate due to their reduction in renal toxicity, and allow for the administration of larger doses of drug with fewer toxicities. A randomized trial of 201 patients with confirmed aspergillus compared the efficacy with high dose (10 mg/kg/day) vs. low dose (3 mg/kg/day) [23]. Patients receiving the high dose had a higher rate of renal toxicity without any additional clinical benefit. A dose of 3–5 mg/kg IV once daily of liposomal amphotericin B is recommended.

Echinocandins The echinocandin class includes caspofungin, micafungin and anidulafungin. This class disrupts the fungal cell walls by inhibiting 1, 3 Beta-D glucan synthase enzymes located in the plasma membrane.

- Caspofungin is used to treat invasive apsergillus in patients who are intolerant to other treatment or as salvage therapy [24]. The dose of caspofungin is 70 mg IV on day 1 followed by 50 mg IV daily. The echinocandins are well tolerated with a modest elevation in liver function enzymes that are generally asymptomatic. The FDA has not approved micafungin or anidulafungin, but these agents also have activity against Aspergillus species and these three agents are felt to have equivalent efficacy.

Combination Therapy

As each individual antifungal medication has its limitations and potential side effects, combination therapy for initial therapy and salvage treatment in experimental models has suggested benefit. A large randomized trial assessed the safety and efficacy of voriconazole with or without anidulafungin for treatment in invasive aspergillosis in patients with hematologic malignancies [25]. Results showed a trend toward improved 6 week survival in the combination therapy. Based on the observed trend, some investigators favor the use of a combination regimen in confirmed invasive aspergillosis. In salvage therapy in patients who do not respond to monotherapy, a combination regimen is also suggested.

Antifungal Resistance

Some species of Aspergillus are known to have variable susceptibilities to antifungal agents. The clinical significance of this relative resistance is poorly defined. Isolates of A. fumigatus have been reported to exhibit relative cross-resistance to multiple azoles and the prevalence of such resistance may be increasing. In patients failing azole monotherapy, possible resistance should be considered [26–28].

Evidence Contour

In addition to antifungal therapy, other modalities need to be considered in treatment of invasive aspergillus. Reversal of immunosuppression when feasible is important. The worst outcomes occur in patients with persistent and severe immune dysfunction and in those with organ

impairment. The importance of immunosuppression on outcome is noted in an international multicenter retrospective series of 525 patients with invasive aspergillosis. Complete or partial responses to treatment occurred in 28 % fewer patients with severe immunosuppression compared to 51 % of patients with less severe immunosuppression. Reduction in and withdrawal of corticosteroids should also be attempted.

Granulocyte colony-stimulating factor (G-CSF) shortens the period of neutropenia after chemotherapy, a leads to fewer documented infections and antibiotic days. However there is no clinical data to support improved antifungal killing capacity in patients with IPA treated with G-CSF. In addition, the increased immune response during therapy may lead to pro-inflammatory tissue injury and potential worsening of disease. Thus, the use of G-CSF in the treatment of invasive aspergillosis needs to be on an individualized basis.

Surgical intervention is also a potential therapy. In the IDSA guidelines for patients at low surgical risk, surgical resection can offer a permanent cure in patients with better lung function and localized pulmonary disease. The decision to proceed with surgery depends on many factors including the location and extent of disease, comorbidities, the ability of the patient to tolerate surgery and the overall goals of therapy (cure vs. palliation) [25]. Surgery may be helpful in the setting of a large amount of necrosis, which can limit antifungal penetration or if there is an imminent threat to vessels [16]. In one series in patients with rhinosinusitis from Aspergillus, surgical debridement was useful when used as an adjunct to antifungal therapy [29]. In another small series, there was mortality benefit with combination therapy of surgery and antifungal treatment in patients with CNS lesions [18]. In general most patients do not require surgical intervention.

References

1. Perfect JR, Cox GM, Lee JY, Kauffman CA, de Repentigny L, Chapman SW, Morrison VA, Pappas P, Hiemenz JW, Stvens DA. The impact of culture isolation of Aspergillus species: a hospital-based survey of aspergillosis. Clin Infect Dis. 2001;33:1824–33.
2. Patterson TF, Kirkpatrick WR, White M, Hiemenz JW, Wingard JR, Dupont B, Rinaldi MG, Stevens DA, Graybill JR. Invasive aspergillosis: disease spectrum, treatment practices, and outcomes. I3 Aspergillus Study Group. Medicine. 2000;79:250–60.
3. Soubani AO, Chandrasekar PH. The clinical spectrum of pulmonary aspergillosis. Chest. 2002;121: 1988–99.
4. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, Pappas PG, Maertens J, Lortholary O, Kauffman CA, Denning DW, Patterson TF, Maschmeyer G, Bille J, Dismukes WE, Herbrecht R, Hope WW, Kibbler CC, Kullberg BJ, Marr KA, Muñoz P, Odds FC, Perfect JR, Restrepo A, Ruhnke M, Segal BH, Sobel JD, Sorrell TC, Viscoli C, Wingard JR, Zaoutis T, Bennett JE. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/ Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46(12):1813–821.
5. Meerseman W, Lagrou K, Maertens J, Van Wijngaerden E. Invasive aspergillosis in the intensive care unit. Clin Infect Dis. 2007;45(2):205–16.
6. Dutkiewicz R, Hage CA. Aspergillus infections in the critically ill. Proc Am Thorac Soc. 2010;7(3):204–9.
7. Guinea J, Torres-Narbona M, Gijon P, et al. Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome. Clin Microbiol Infect. 2010;16(7):870–7.
8. Gustot T, Maillart E, Bocci M, et al. Invasive aspergillosis in patients with severe alcoholic hepatitis. J Hepatol. 2014;60(2):267–74.
9. Bulpa P, Dive A, Sibille Y. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. Eur Respir J. 2007;30(4):782–800.
10. Samarakoon P, Soubani A. Invasive pulmonary aspergillosis in patients with COPD: a report of five cases and systemic review of the literature. Chron Respir Dis. 2008;5(1):19–27.
11. Kosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. Thorax. 2014. pii: thoraxjnl-2014-206291. doi:10.1136/thoraxjnl-2014-206291.
12. Segal BH. Aspergillosis. N Engl J Med. 2009; 360(18):1870–84.
13. Greene RE, Schlamm HT, Oestmann JW, et al. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. Clin Infect Dis. 2007;44(3):373–9.
14. Shelhamer JH, Gill VJ, Quinn TC, Crawford SW, Kovacs JA, Masur H, et al. The laboratory evaluation of opportunistic pulmonary infections. Ann Intern Med. 1996;124(6):585–99.
15. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of Infectious Diseases Society of America. Clin Infect Dis. 2008;46:327.
16. Limper AH, Knox KS, Sarosi GA, et al. An Official American Thoracic Society Statement: treatment of

fungal infections in adult pulmonary and critical care patients. Am J Respir Crit Care Med. 2011;183: 96–128.
17. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, Kern WV, Marr KA, Ribaud P, Lortholary O, et al. Voriconazole versus amphotericin B for primary therapy of invasisve aspergillosis. N Engl J Med. 2002;347:408–15.
18. Schwartz S, Ruhnke M, Ribaud P, et al. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. Blood. 2005;106:2641.
19. McLean KJ, Marshall KR, Richmond A, et al. Azole antifungals are potent inhibitors of cytochrome P450 mono-oxygenases and bacterial growth in mycobacteria and stretpomycetes. Microbiology. 2002;148(Pt 10):2937–49.
20. Limper A. Clinical approach and management fro selected fungal infections in pulmonary and critical care patients. Chest. 2014;146(6):1658–66.
21. Howard SJ, Lestner JM, Sharp A, et al. Pharmacokinetics and pharmacodynamics of posaconazole for invasive aspergillosis: clinical implications for antifungal therapy. J Infect Dis. 2011; 203:1324.
22. Denning DW, Lee JY, Hostetler S, et al. NIAID Mycoses Study Group Multicenter Trial of oral itraconazole therapy for invasive aspergillosis. Am J Med. 1994;97:135.
23. Cornely OA, Maertens J, Bresnik M, Ebrahimi R, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized tiral comparing a high-loading dose regimen with standard dosing (ambiload trial). Clin Infect Dis. 2007;44:1289–97.
24. McCormack PL, Perry CM. Caspofungin: a review of its use in the treatment of fungal infections. Drugs. 2005;65:2049.
25. Marr KA, Schlamm HT, Herbrecht R, et al. Combination antifungal therapy for invasive aspergillosi: a randomized trial. Ann Intern Med. 2015;162:81.
26. Snelders E, van der Lee HA, Kujipers J, et al. Emergence of azole resistance in Aspergillus fumigatus and spread of a single resistance mechanism. PLoS Med. 2008;5, e219.
27. Verweijj PE, Mellado E, Melchers WJ. Multiple-triazole-resistant aspergillosis. N Engl J Med. 2007;356:1481.
28. Bueid A, Howard SJ, Moore CB, et al. Azole antifungal resistance in Aspergillus funigatus: 2008 and 2009. J Antimicrob Chemother. 2010;65:2116.
29. Süslü AE, Oğretmenoğlu O, Süslü N, et al. Acute invasive fungal rhinosinusitis: our experience with 19 patients. Eur Arch Otorhinolaryngol. 2009;266:77.

Management of Strongyloides Hyperinfection Syndrome

55

Shijing Jia, Hedwig S. Murphy, and Melissa A. Miller

Case Presentation

An 85 year old male with a history of asthma, hypothyroidism, steroid-induced diabetes mellitus, and osteopenia presented with worsening shortness of breath shortly after stopping a prednisone taper. Over the year prior to admission, he had experienced seven asthma exacerbations, including one requiring intubation. He had become quite debilitated over this time period, relying on his daughters to care for him. Despite this support, his medication compliance was intermittent. He lived in Michigan with his daughters, had worked 37 years as an auto mechanic, and grew up on a farm in Tennessee. He had previously owned a cat, but gave the animal up because of his repeated asthma exacerbations. At the time of presentation to the hospital, the patient had inspiratory and expiratory wheezing and increased work of breathing, though he was saturating 97 % on room air by pulse oximetry. An arterial blood gas showed respiratory alkalosis: pH 7.49, pCO_2 21 mmHg, pO_2 74 mmHg, with measured bicarbonate of 21 mmol/L. Complete blood count showed 12.7 g/dl hemoglobin and 9.3 K/cmm WBCs, with 48 % neutrophils, 15 % lymphocytes, and 29 % eosinophils on differential. The patient was treated with steroids and bronchodilators, with initial improvement.

However, after 2 days, the patient developed fevers, labored work of breathing, and progressively altered mental status. He was transferred to the ICU for monitoring and intermittent noninvasive positive pressure ventilation. Broad-spectrum antibiotic coverage was initiated with vancomycin and piperacillin/tazobactam; blood and sputum cultures were sent. The patient developed a rash which was suspected to be an allergic drug reaction, so piperacillin/tazobactam was changed to aztreonam and metronidazole. A CT of the chest obtained on ICU day 2 showed scattered areas of mucus plugging, but no focal consolidation. However, the CT did show a dilated esophagus with an air-fluid level and calcifications along the posterior wall (Fig. 55.1).

Blood and sputum cultures from ICU day 3 grew *Enterobacter aerogenes*, sensitive to aztreonam and piperacillin/tazobactam. A gastric emptying study showed significantly slowed motility. The patient did not tolerate enteral

S. Jia (✉) • M.A. Miller
Internal Medicine, Pulmonary and Critical Care, University of Michigan, Ann Arbor, MI, USA
e-mail: sjia@umich.edu

H.S. Murphy
Department of Pathology, University of Michigan and Veterans Affairs Ann Arbor Health System, Ann Arbor, MI, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_55

feedings even with post-pyloric administration, and peripheral parenteral nutrition was started on ICU day 11. A CT of the abdomen and pelvis was obtained, which showed colonic distention and retained barium throughout the large and small intestine from the esophagram 3 days prior. The patient became progressively more somnolent, and developed profound hyponatremia. Follow up chest radiology on ICU day 14 was significant for development of bilateral infiltrates. An IgE level was obtained, which was 3280 IU/mL (Fig. 55.2).

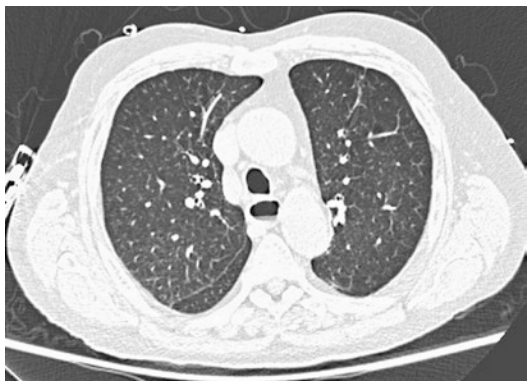


Fig. 55.1 Dilated esophagus with air-fluid level on chest CT

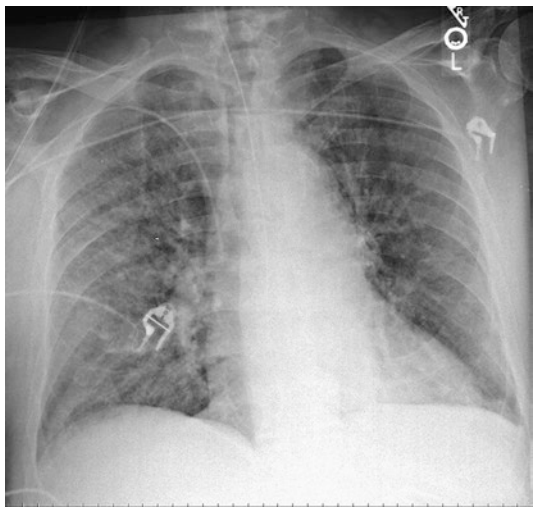


Fig. 55.2 Bilateral infiltrates on chest radiograph

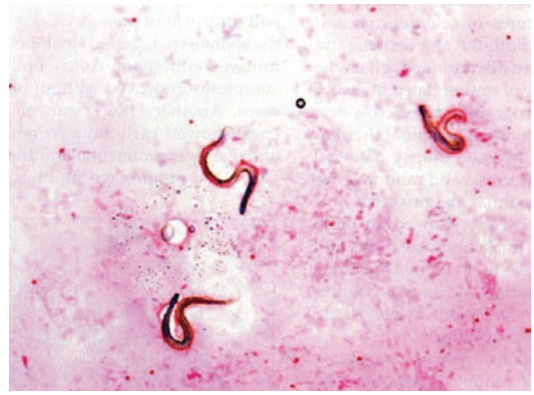


Fig. 55.3 Strongyloides larvae in sputum gram stain

Question What is the diagnosis?

Answer Strongyloides hyperinfection with ileus

Strongyloides serologies, stool ova and parasites, and sputum cytology and smear on LPO agar were sent. Sputum cytology showed the following (Fig. 55.3):

Strongyloides IgG was high at 3.87 IV (>1.0 positive). Larvae were also seen in the fecal exam. The diagnosis of strongyloides hyperinfection was made, and the patient was started on enteral ivermectin therapy. Subsequently, the patient became more obtunded. A decision was made by the family for comfort care, and the patient died shortly thereafter. Autopsy showed diffuse infiltration of larvae in the lungs, wall of the intestines and liver, as well as in the cortex and basal ganglia of the brain (Fig. 55.4). The identification of larvae in the brain on autopsy ultimately defined this case as disseminated strongyloides infection.

Principles of Management

The most important aspect of management includes high index of suspicion in at risk patient populations and recognition of the clinical signs and symptoms of infection, in order to institute early treatment.

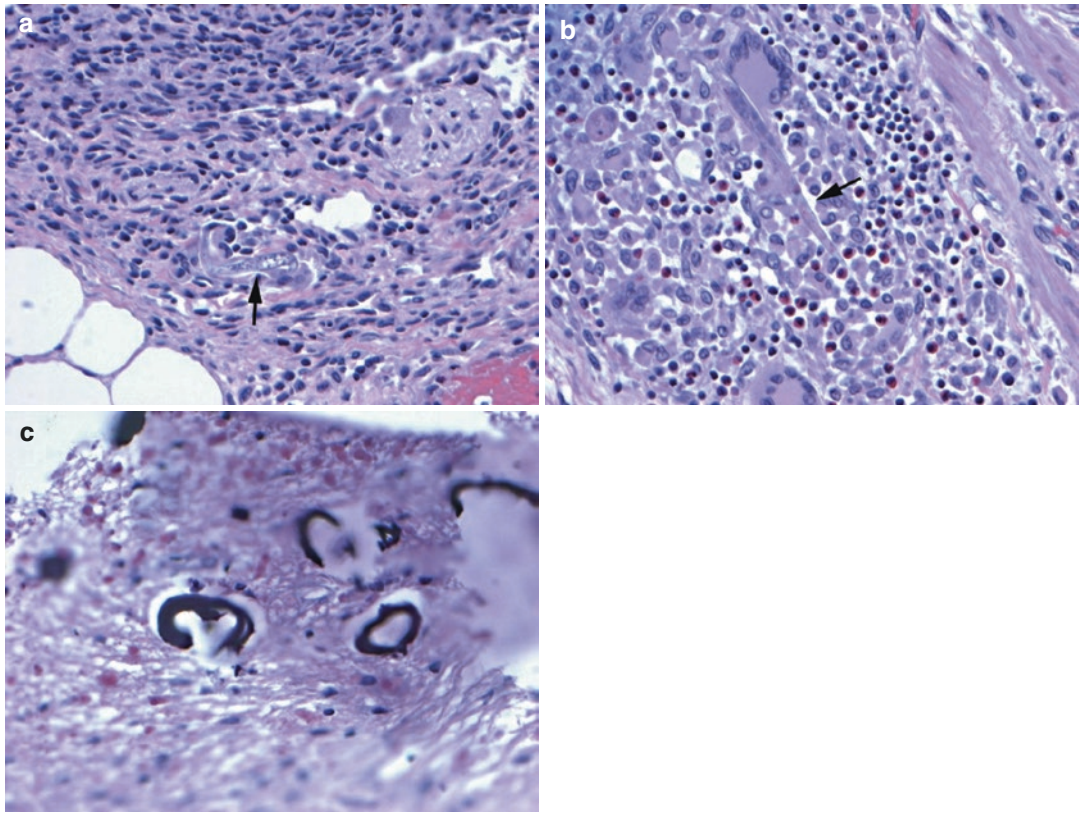


Fig. 55.4 Autopsy findings confirming disseminated strongyloidiasis. (**a**) Adult worm (*arrow*) in the lung with foreign body giant cell reaction and marked inflammation. (**b**) Adult worm form (*arrow*) with a multinucleated giant cell and background of lymphocytes and eosinophils in wall of the large intestine. (**c**) Calcified larvae in the basal ganglia

Epidemiology

Strongyloides stercoralis is a parasitic nematode that is endemic in the tropical and subtropical climates of Southeast Asia, sub-Sahara Africa, and parts of Central and South America [1]. In the United States, the highest incidences of infection are in the Southeastern Appalachian states of Kentucky, Tennessee, and Louisiana; farming and mining confer additional risk [2]. With improved sanitation in these areas and increased globalization, new infections are most frequently seen in immigrants or travelers returning from endemic countries. It is especially important to consider those with impaired immune defense – steroid exposure, immunosuppression, solid organ transplant, hematologic malignancies, and infection with HTLV-1 – as possible hosts for disseminated infection and hyperinfection. Screening is now recommended for patients undergoing transplant evaluation [3].

Life Cycle

The nematode is contracted by skin exposure to soils contaminated with larvae. A complex life cycle starts with hematogenous migration of the infective filariform larvae to the alveolar space of the lungs. The larvae are then coughed up and swallowed into the gut, where they mature into adult worms that penetrate and live within the

small intestinal mucosa. Here, females produce eggs, which hatch a non-infective, rhabditiform larva that is shed in the stool and can molt into infective filariform larvae or adults in humid soils [4]. The typical life cycle takes 3–4 weeks from time of infection to time of appearance of larvae in the stool.

Alternatively, the non-infective rhabditiform larvae can mature to the infective filariform larvae within the gut in an autoinfective life cycle. These filarial larvae then burrow through the colonic or perianal mucosa, and restart the typical life cycle as above. Autoinfection can occur at low levels with minimal symptoms in some hosts. This autoinfection cycle allows Strongyloides to be uniquely capable of persisting within an infected host for decades without subsequent environmental exposures, especially in cases of asymptomatic chronic infections [4, 5].

Disseminated Infection and Hyperinfection

Decreased cell mediated immunity such as steroid use and HTLV-1 infection increase the propensity for autoinfection [6]. Accelerated autoinfection leads to severe strongyloidiasis, with hyperinfection and disseminated infection. Both entities can carry mortality rates of up to 60–70 % despite appropriate treatment [6]. In hyperinfection syndromes, increased worm burden along the typical life-cycle leads to nausea, vomiting, diarrhea, pulmonary infiltrates and dyspnea, and can eventually lead to ileus, bowel obstruction, and GI bleeding, as well as pulmonary infection and respiratory failure [6]. Pulmonary symptoms are more common in those with prior lung disease, and may even progress to inflammatory pneumonitis, bronchitis, pneumonia, or pulmonary hemorrhage [7]. Disseminated infection is defined as larval presence in organs not part of the typical parasitic life cycle (skin, GI tract, lungs) [6]. Hyperinfection and disseminated infection are often accompanied by bacterial infections involving enteric pathogens. This occurs as the migrating worms transport these bacteria from the gut flora, or through seeding of the blood stream via mucosal ulceration [4].

Diagnosis

Infected patients with intact immune response can have asymptomatic peripheral eosinophilia or mild symptoms at the typical sites of parasite habitat within the host. Acutely infected patients can initially have localized rash or pruritus at site of filariform larvae entry, followed by pulmonary symptoms of cough, wheezing, or dyspnea days later when larvae spread to the lungs [7]. Diarrhea and abdominal pain follow weeks after, when nematodes infect the intestinal mucosa. In chronic infection, pulmonary symptoms corresponding to larval migration through the lungs can mimic asthma unresponsive to steroids [5].

Diagnosis can be made by identifying rhabditiform larvae on microscopy of stool or sputum. The autoinfective cycle of a chronically infected person may involve only a very few reproducing larvae, therefore yield may be low. Repeated samples increase the diagnostic sensitivity. Various exams including the filter paper culture or agar plating method can increase diagnostic yield slightly, but are time consuming and rarely standard laboratory protocol [8]. EGD or colonoscopy can reveal skip lesions of inflammation, ulcerations, or simply mucosal thickening, with biopsy samples occasionally containing larvae [9]. Chest radiography can be normal in mild infection, or may show nonspecific findings such as reticulonodular infiltrates or patchy alveolar opacities [7]. Emerging techniques – including serum ELISA and luciferase immunoprecipitation of IgG antibodies, as well as PCR for strongyloides DNA – can achieve diagnostic yields up to 90 % [10].

Anti-parasitics

Standard therapy for uncomplicated strongyloidiasis is oral ivermectin 200 ug/kg for two consecutive days or given 2 weeks apart, with eradication rates reaching 100 % [5]. A comparative randomized controlled trial of ivermectin versus thiabendazole showed a better side effect profile [11], and better efficacy compared to thiabendazole [12]. Second line treatment is

albendazole 400 mg twice daily for 10–14 days, as cure rates are inferior [4].

Supportive Care and Follow Up

Immunosuppressed patients with strongyloidiasis should have immunosuppressive therapy held if possible, as these medications increase the propensity for disseminated disease and hyperinfection. Not uncommonly, patients with strongyloides infections develop bacteremia and sepsis due to translocation of gut and lung flora with invasion of larvae. Therefore, treatment in severe cases of strongyloidiasis should include antibacterials with activity against enteric gram negative organisms [4]. Hyperinfection and disseminated infection often lead to critical illness including DIC, sepsis, hemodynamic instability, and respiratory failure. Aggressive hemodynamic and respiratory support is crucial to patient recovery. As ileus and bowel obstruction can be common with severe infection, nutritional support can be challenging, and parenteral nutrition may be required [6]. Follow up confirmation for eradication of disease should include stool exams for up to 1 year, or serology testing for 1–2 years with decreasing IgG levels and resolving peripheral eosinophilia [9].

Evidence Contour

The treatment of disseminated infection and hyperinfection is challenging, especially in the setting of bowel obstruction or ileus, when oral preparations of anti-helminths are difficult to deliver and absorb.

Severe Infections

There are no randomized trials for treatment regimens of either hyperinfection or disseminated strongyloidiasis. Recommended therapy is based on expert opinion and case reports of successful trials. In the case of severe infections, any immunosuppression should be stopped as mortality is high despite treatment. Oral ivermectin at the standard dose of 200 ug/kg should be administered daily until stool and sputum exam is persistently negative for 2 weeks [4, 13].

Hyperinfection Associated with Paralytic Ileus

Patients with severe strongyloidiasis often present with vomiting, diarrhea, or paralytic ileus due to larval induced gastrointestinal inflammation. These scenarios present a uniquely difficult treatment challenge for reliable delivery of oral anti-helminths. Enteral ivermectin 200 ug/kg/day can be administered by orogastric or nasogastric tube in the setting of nausea or vomiting, or by rectal enema in the cases of progressive ileus [4, 13, 14]. However, several case reports showed that absorption of enteral ivermectin can be impaired in severe infection [15]. A parenteral veterinarian formulation of ivermectin can be given subcutaneously. Based on available case reports, Mejia and Nutman recommend 200 ug/kg/day in divided doses in each arm [13]. Though there are no clinical trials, case reports show improved serum drug concentrations and successful treatment of severe infections [13, 15, 16].

References

1. Schar F, Trostdorf U, Giardina F, Khieu V, Muth S, Marti H, et al. Strongyloides stercoralis: global distribution and risk factors. PLoS Negl Trop Dis. 2013; 7(7), e2288.
2. Starr MC, Montgomery SP. Soil-transmitted Helminthiasis in the United States: a systematic review – 1940–2010. Am J Trop Med Hyg. 2011;85(4):680–4.
3. Roxby AC, Gottlieb GS, Limaye AP. Strongyloidiasis in transplant patients. Clin Infect Dis Off Publ Infect Dis Soc Am. 2009;49(9):1411–23.
4. Maguire JH. Intestinal nematodes (roundworms). In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Elsevier/ Saunders; 2015. p. 3199–207.
5. Greaves D, Coggle S, Pollard C, Aliyu SH, Moore EM. Strongyloides stercoralis infection. BMJ (Clin Res Ed). 2013;347:f4610.
6. Buonfrate D, Requena-Mendez A, Angheben A, Munoz J, Gobbi F, Van Den Ende J, et al. Severe

strongyloidiasis: a systematic review of case reports. BMC Infect Dis. 2013;13:78.
7. Woodring JH, Halfhill 2nd H, Reed JC. Pulmonary strongyloidiasis: clinical and imaging features. AJR Am J Roentgenol. 1994;162(3):537–42.
8. Siddiqui AA, Berk SL. Diagnosis of Strongyloides stercoralis infection. Clin Infect Dis Off Publ Infect Dis Soc Am. 2001;33(7):1040–7.
9. Requena-Mendez A, Chiodini P, Bisoffi Z, Buonfrate D, Gotuzzo E, Munoz J. The laboratory diagnosis and follow up of strongyloidiasis: a systematic review. PLoS Negl Trop Dis. 2013;7(1), e2002.
10. Levenhagen MA, Costa-Cruz JM. Update on immunologic and molecular diagnosis of human strongyloidiasis. Acta Trop. 2014;135:33–43.
11. Bisoffi Z, Buonfrate D, Angheben A, Boscolo M, Anselmi M, Marocco S, et al. Randomized clinical trial on ivermectin versus thiabendazole for the treatment of strongyloidiasis. PLoS Negl Trop Dis. 2011;5(7), e1254.
12. Suputtamongkol Y, Premasathian N, Bhumimuang K, Waywa D, Nilganuwong S, Karuphong E, et al. Efficacy and safety of single and double doses of ivermectin versus 7-day high dose albendazole for chronic strongyloidiasis. PLoS Negl Trop Dis. 2011;5(5), e1044.
13. Mejia R, Nutman TB. Screening, prevention, and treatment for hyperinfection syndrome and disseminated infections caused by Strongyloides stercoralis. Curr Opin Infect Dis. 2012;25(4):458–63.
14. Tarr PE, Miele PS, Peregoy KS, Smith MA, Neva FA, Lucey DR. Case report: rectal adminstration of ivermectin to a patient with Strongyloides hyperinfection syndrome. Am J Trop Med Hyg. 2003;68(4):453–5.
15. Grein JD, Mathisen GE, Donovan S, Fleckenstein L. Serum ivermectin levels after enteral and subcutaneous administration for Strongyloides hyperinfection: a case report. Scand J Infect Dis. 2010;42(3):234–6.
16. Turner SA, Maclean JD, Fleckenstein L, Greenaway C. Parenteral administration of ivermectin in a patient with disseminated strongyloidiasis. Am J Trop Med Hyg. 2005;73(5):911–4.

Treatment of Viral Hemorrhagic Fever in a Well-Resourced Environment

56

Amit Uppal and Laura Evans

Case Presentation

A 38 year old physician with no medical history presents to the Emergency Department with fever, abdominal pain, and diarrhea 10 days after returning from West Africa where she had been working in an Ebola Treatment Center (ETC). She directly cared for multiple patients with suspected or confirmed Ebola Virus Disease (EVD). She reports extensive training in the use of personal protective equipment (PPE) prior to patient contact, and had no known breaches in protocol while caring for patients. She received all appropriate vaccinations prior to travelling to West Africa. While there, she suffered multiple insect bites, but was compliant with malaria prophylaxis. She drank only bottled water. Aside from the fatigue that she attributed to her work and the long journey, she felt well upon leaving West Africa and during travel home. The fatigue persisted and worsened over the several days after returning to the United States, when she developed fever, abdominal pain, and diarrhea approximately 8 h prior to presentation. She reported her symptoms to the local department of health and was transported to the hospital under appropriate precautions. She is currently in a single-bed, respiratory isolation room in the Emergency Department.

Question What approach should be taken to the evaluation, workup, and management of this patient?

Answer Diagnostic workup, supportive therapy, and targeted treatments performed under appropriate isolation precautions.

The patient described in this scenario has a moderate to high probability of having EVD. However, she is also at risk for entities such as malaria, typhoid, cholera, trypanosomiasis, Lassa fever, dengue fever, and more typical viral and bacterial infections.

Each of these diseases requires urgent diagnostic evaluation and, if confirmed, supportive and/or targeted therapies. However, when there is a possibility of a highly infectious disease such as EVD, the need for urgent evaluation and management must be balanced with the need for strict infection control measures and consideration of the safety of involved healthcare workers [1].

Principles of Management

Isolation and Infection Control

Measures will be based on the possible routes of transmission for the disease(s) being considered.

A. Uppal (✉) • L. Evans
Division of Pulmonary, Critical Care, and Sleep Medicine, New York University School of Medicine, New York, NY, USA
e-mail: Amit.Uppal@nyumc.org

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_56

In the case of EVD, the disease is transmitted via direct contact with body fluids or contaminated objects. The infectious dose is low and thus strict contact precautions must be enforced. The CDC and WHO have provided recommendations on isolation and infection control in this circumstance [2, 3].

Active Screening

The first, and perhaps most important, step in preventing disease transmission is to identify patients who may be carrying the disease. In the case of the 2014 EVD outbreak, many institutions began screening all patients for recent travel to any of the affected West African nations and for symptoms potentially compatible with EVD. Patients who screen positive may be placed in isolation pending further evaluation. If concern for EVD persists after this initial evaluation, the patient may be thereafter monitored and managed in a dedicated isolation unit.

Isolation Unit

Ideally, a dedicated isolation room or unit would be available in order to keep the patient, the staff caring for them, and the potentially contaminated equipment separate from other patients and staff [2]. In the case of EVD, the unit would need to be designed for strict contact precautions – including components such as an ante-room that transitions into the patient room and a dedicated area for donning and doffing PPE. The patient room should be outfitted with capabilities to provide intensive monitoring and support. This includes power outlets supported by emergency generators, plumbing capable of supporting hemodialysis, central oxygen, central vacuum for suctioning, and monitors capable of continues telemetry, pulse oximetry, arterial pressure, venous pressure, and End-tidal CO2 monitoring. Strict logs of all personnel on the unit should be kept so that, in the event of a breech in protocol, all exposed individuals can be monitored. A satellite laboratory located within the isolation unit should be utilized. This removes the risk of transmission associated with transporting patient samples outside of the isolation unit to be analyzed on central laboratory equipment.

Protective Equipment

The CDC and WHO have published recommendations on the appropriate PPE for use in patients with suspected or confirmed EVD [2, 3]. While several variations of this equipment are commercially available, it should be noted that familiarity with the equipment is perhaps more important than the equipment itself. The moment of highest risk for transmission is during the removal of contaminated PPE, when a provider's skin could come in direct contact with the infectious materials. Thus, the donning and doffing process should be stepwise and methodical. A trained observer should provide instructions and monitor every step in the process. Every potential provider should demonstrate familiarity with this process on a regular basis. If available, this process should be practiced in an open or simulated isolation unit that is identical to the unit a patient would be admitted to (Fig. 56.1).

Protocols and Policies

The precautions instituted when caring for a patient with suspected or confirmed EVD add complexity to nearly every aspect of patient care. In many ways, the precautions necessitate a deviation from regular work flow, creating a risk for errors. Therefore, when time allows, protocols should be drafted and distributed ahead of time. Some issues that are particularly amenable to prospective planning include:

Specimen Collection and Handling

Most of the blood samples from the patient will be obtained within the contaminated isolation room, and will be packaged and transported the satellite laboratory. Depending on the design of the isolation unit, the samples may be carried through clean areas en route to the laboratory.

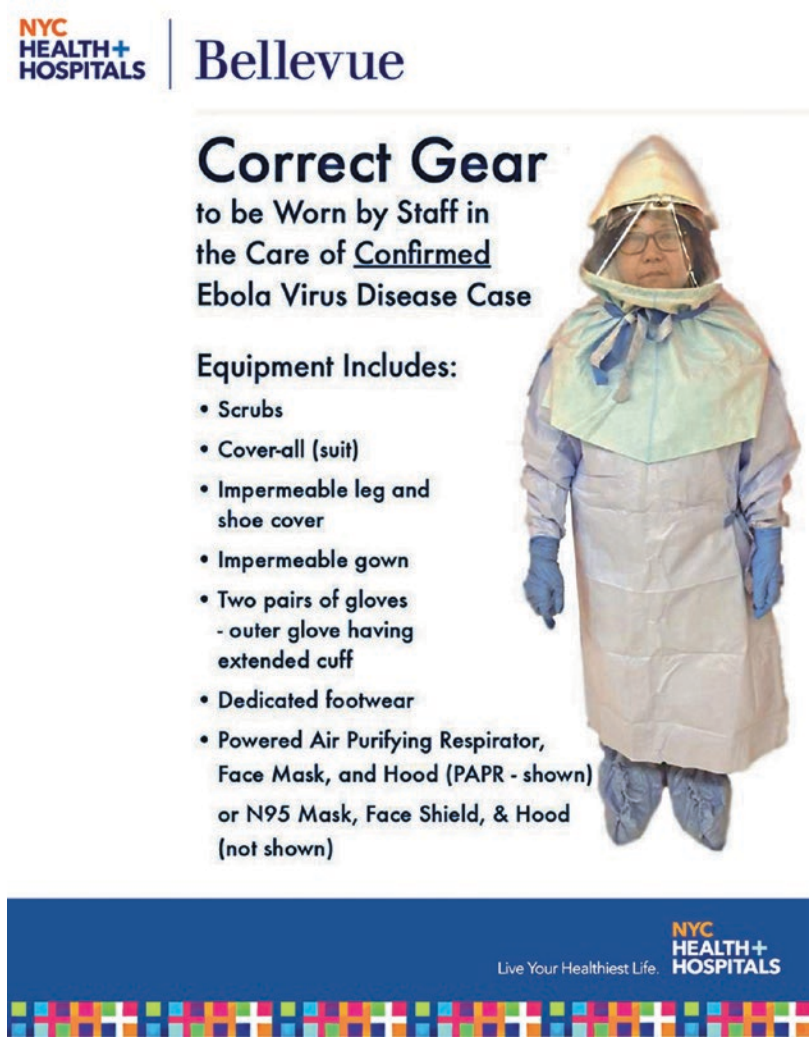


Fig. 56.1 Correct Gear EVD flyer. Courtesy of NYC Health + Hospitals, Bellevue

Some samples (such as those for EVD PCR) will need to be packaged and transported out of the hospital to specialized laboratories capable of running the test. The way in which the samples are collected, packaged, and transported should be practiced ahead of time.

Decontamination

Equipment used in the room of a patient with confirmed EVD cannot be immediately removed from that room without special precautions. Protocols for disinfecting or destroying such equipment should be developed. Staff should be aware of this issue before bringing equipment into the room that is vitally important to other patients in the hospital.

Waste Management

The PPE of providers combined with contaminated patient materials (especially those with severe nausea, vomiting, or hemorrhagic complications) can create a tremendous amount of waste. This waste is considered highly infectious, and potentially represents a public health risk if mismanaged during transport within or outside the hospital [1]. Some have raised concern about the use of EVD as an agent of bioterrorism, making this waste a potential national

security threat. Thus, the process by which this waste is collected, transported, and destroyed is of paramount importance. The protocols that outline waste management should include waste in trash cans and sharps containers, waste in the patient toilets, dialysis effluent, supplies used to clean the room, and anything else potentially contaminated with infectious materials.

Provisions of Clinical Care

The precautions described above will significantly alter the way in which critical care services are delivered to patients with suspected or confirmed EVD. This alteration in workflow creates a potential for errors that may put the patient or staff at risk. If time allows, all aspects of clinical care should be considered ahead of time. Some example of topics to be considered are:

Team Structure

Typically, a critically ill patient has a complex interdisciplinary team addressing their needs. This team may include physicians, nurses, respiratory therapists, physical therapists, clinical pharmacists, social workers, nutritionists, chaplaincy personnel, and others [1]. In patient with suspected or confirmed EVD, all efforts should be made to limit the number of people who come into direct contact with the patient. Below are considerations for many of these disciplines:

- **Physicians**: Clearly, the patient will have a team of primary physicians. While a larger team of physicians may distribute the work more evenly, this will also impact other clinical services substantially if these physicians are not allowed to care for other patients while caring for a patient with suspected or confirmed EVD. Thus, a smaller physician team may be more sustainable. Consideration should be given to the necessary skill set to serve as one of these primary providers. Ideally, one would be comfortable with airway management, central line placement, and the use of bedside ultrasound to make assessments of the cardiac and respiratory symptoms (rationale discussed in detail below.) When specialty consultation is required, careful consideration should be given to whether the consultant needs to perform a bedside assessment. If possible, "cognitive consultation" can be performed via chart review, discussion with primary physician, and possibly patient interview via video conferencing. If a small team of physicians cares for a patient for a prolonged period, attention should be paid to the psychological impact of caring for such a disease under social isolation.
- **Nurses**: Patients with suspected or confirmed EVD are extremely nurse-intensive. These patients may require frequent assessments and interventions. However, as mentioned above, the moment of highest risk for disease transmission is during the doffing of PPE. Therefore, efforts should be made to minimize the number of times the bedside nurse enters and exits the room. One solution is for the nurse to stay in the room in full PPE for longer periods, thus minimizing the number of doffing procedures. The amount of time one can spend in full PPE will vary to some degree based on the equipment being used. However, the equipment is heavy and occlusive, leading to significant discomfort when worn for prolonged periods. Based on the need to relieve this nurse, to have another nurse available to obtain supplies, and to allow necessary breaks during a shift, at least 6 nurses per day are required to care for a patient under these precautions. It should be noted that the nurses are in the closest contact with the patient for the longest periods of time and are more likely to be exposed to infectious materials. The psychological stress put on nurses performing this role cannot be overstated. This should be accounted for during and after the care of a patient with suspected or confirmed EVD.
- **Respiratory Therapists**: Consideration should be given to respiratory therapists providing cognitive consultation as well. This would require that they train either the physicians or nurses on how to perform the standard

tasks they typically perform at the bedside. Specific examples include setup and initiation of mechanical ventilators, daily ventilator checks, alarm modulation, and ventilator troubleshooting. Even if this method is employed, however, a group of therapists should be trained in EVD precautions and PPE in the event that an unanticipated circumstance arises and they are required to enter the patient room. The therapists staffing structure should be designed such that at least one therapist trained in EVD precautions and the use of PPE is on duty at any given time.

- **Others**: the remainder of the critical care team (pharmacists, nutritionists, social workers, chaplains, and others) can likely provider their services by chart review and patient interview without the need to enter the room.

Monitoring

Much of the monitoring that is typically done in a critical care patient can be done under these precautions. Telemetry, non-invasive blood pressure measurements, and pulse oximetry are not affected. The risks/benefits of invasive blood pressure monitoring should be considered carefully given the desire to minimize contact with blood specimens and the possibility that these patients may develop hemorrhagic complications. If available, End-tidal CO2 monitoring may make it possible to avoid arterial blood sampling.

Bedside Assessments

In patients under EVD precautions, the process of going to the bedside is complicated. Careful consideration should be made about which assessments truly require a provider to go to the bedside and which can be done via video conferencing or other means. Efforts should be made to "bundle" necessary bedside tasks to avoid the need for multiple donning and doffing procedures. With all of this being said, consideration should also be given to the mental health of the patient. If they remain awake and alert, they are likely to suffer from social isolation and may benefit greatly from seeing their providers on a regular basis.

Diagnostic Testing

Blood Analysis

The array of testing available for a patient with suspected or confirmed EVD is likely to be limited, particularly if the analysis is being done in a satellite laboratory. If time allows, providers should work with laboratory staff to discuss the testing that will be available and ensure that it will be adequate to monitor a patient at risk for severe volume losses, electrolyte abnormalities, multi-organ failure, and bleeding complications [4]. Point of care testing, to the extent it is available, may be an option that simplifies many of these issues. As noted above, the process of drawing and analyzing a blood sample under these precautions is complex and also requires laboratory staff to don and doff PPE. Therefore, whenever possible, all necessary testing should be done at one time to avoid having to repeat this process throughout the day.

Imaging

While it may be possible to perform standard imaging studies (such as xrays and CT scans) under EVD precautions, it is quite complex. Efforts should be made to avoid such testing unless absolutely critical. In well-trained hands, bedside ultrasound may provide an alternative to many of the imaging studies typically done in critically ill patients, and also eliminates the need for an additional person (such as an ultrasound technician) to enter the room. It should be noted, however, that the ultrasound machine used will likely be unavailable for immediate use on other patients once used on a patient with confirmed or suspected EVD.

Invasive Procedures

The use of PPE significantly alters the process of performing invasive procedures by restricting range of motion, altering tactile sensation, and limiting the field of view [1]. These changes create a risk for errors that represent a danger to both the patient and the providers. If time allows, careful planning and simulation of procedures while wearing PPE should be performed. Some specific areas of consideration are given below.

Central Venous Catheter(CVC) Placement

Threshold for Placement

Consideration should be given to establish a low threshold to place a CVC in a patient with confirmed EVD. First, the procedure may be easier and safer earlier in the course of disease, before significant volume loss or other complications (such as DIC) have developed. Second, the presence of a central line allows access for venous blood sampling without the need for repeated peripheral needle sticks.

Location of Placement

For the most part, site selection for CVC is the same as for other critically ill patients. Given that altered tactile sensation may make landmark palpation more difficult, and that these patients have potential for bleeding complications, one might consider ultrasound-guided internal jugular the preferred approach.

Sterile Precautions

Efforts should be made to maintain sterility during CVC placement, especially considering that the patient may have a prolonged course and that the CVC may remain in place for much of that course. However, the standard precautions taken during CV C placement are difficult to fully adhere to while wearing PPE. Decisions should be made ahead of time as to how the non-sterile exam gloves will be covered or replaced by sterile procedure gloves. PPE will be covering the provider's hair, mouth, and nose, removing the need for a cap and mask. However, an extra-large sterile gown may be required to fit over the layers of PPE. Providers should be aware of how these several layers of equipment will feel and be provided with an opportunity to practice CVC placement under these conditions.

Endotracheal Intubation

Threshold for Intubation

All efforts should be made to avoid the need for an urgent or emergent intubation in patients with confirmed or suspected EVD, as this creates risk to both patient and staff. Therefore, the threshold to perform intubation in these patients may be lower, particularly if the patient's condition is clearly worsening.

Modality

PPE significantly limits the field of vision and thus providers may have more difficulty obtaining an adequate view during attempted direct laryngoscopy. Therefore, strong consideration should be given to video laryngoscopy. This has the additional advantage of potentially lowering the risk of disease transmission by keeping the provider's face away from the patient in case there is coughing or vomiting. Again, it should be recognized that the device used under these precautions will not be immediately available to be used on other patients. The use of short acting neuromuscular blockade may also be considered for these patients in order to improve visualization, increase the likelihood of success on first attempt, and reduce the likelihood of active vomiting during the procedure.

Emergency Response Teams

Careful consideration should be given to the role of emergency response teams (medical response team, rapid response team, airway team, code team, etc.) in patients with suspected or confirmed EVD. If such a team is activated and attempts to enter the room hurriedly, it will be extremely difficult to control the number of people in the unit, track the people who need to be monitored, and ensure 100 % compliance with appropriate precautions.

Diagnostic Evaluation

As discussed above, patients being evaluated for EVD are also likely at risk for other infectious diseases. The process of evaluating a patient for this disease involves multiple steps.

Establishing the Likelihood of EVD

Ideally, patients will be placed into isolation when any suspicion of EVD is raised by their history or symptoms. Once in isolation, a more detailed history is obtained to clarify the likelihood of active EVD as the explanation for the patient's symptoms. This should include a timeline of their travels and contacts, as well as a detailed description of their symptom onset. A physical exam to identify alternative explanations for symptoms or for findings common in EVD (such as pharyngitis, rash, etc.) should be performed. An assessment of volume status and any evidence of end-organ hypoperfusion (mental status, blood pressure, skin mottling, capillary refill, etc.) should be made. In some cases, the history alone may be sufficient to rule out EVD. Consider, for example, a patient who was placed in isolation after presenting with fever and reporting history of travel to a country affected by an outbreak of EVD. If a more detailed history reveals that travel to that country were several months prior to the onset of symptoms, a diagnosis of EVD needs not be further pursued. If, however, concern for EVD persists after this initial evaluation, then a more formal assessment for EVD will need to be made. Such decisions should be made in collaboration with infectious disease and public health experts.

Identifying Alternative or Concomitant Diagnoses

At the same time that testing is being done for EVD (as described below) a host of other infectious diseases should be evaluated. This should be done in consultation with infectious disease specialists and tailored to the countries visited, known ongoing outbreaks, the time of year, etc. In general, the list will include malaria, typhoid fever, trypanosomiasis, Lassa fever, and cholera [2, 4]. If specific testing for a suspected condition is available, the testing should be sent as early as possible.

Specific Testing for EVD

Confirmation of EVD requires detection of viral RNA or viral antigens in the blood or body fluid of the patient. The sensitivity of this testing is dependent on the viral load in the sample and thus false negatives are possible early in the course of disease. A patient with suspected EVD who tests negative early after the onset of symptoms may require ongoing isolation and repeat testing in 48–72 h [4]. The testing, and its interpretation, should be done in collaboration with infectious disease and public health experts.

Supportive Therapy

While targeted therapies against EVD are under investigation and are likely to be employed in patients with the disease, the critical care approach to these patients is not significantly different than other critically ill patients. Much of the focus is to provide supportive therapies in order to sustain life while the underlying disease is being treated and/or the patient's immune system is mounting a response to it.

Fluid and Electrolytes

Patients with EVD are at high risk for volume depletion and electrolyte disturbances given anorexia, vomiting, diarrhea, and insensible losses related to high fever. Thus, fluid resuscitation and electrolyte repletion are a key component to the supportive management of these patients [1, 4, 5]. If diarrhea is a dominant symptom, the patient may be at risk for metabolic

acidosis, and consideration should be given to using balanced fluids. As described above, frequent lab assessments should be avoided unless absolutely necessary. Therefore, preemptive electrolyte repletion (with particular attention to potassium and magnesium) should be considered in patients with active volume losses, unless contraindicated for other reasons. Aggressive symptomatic treatment for diarrhea and nausea may limit volume losses while also providing comfort to the patient [1, 4].

Mechanical Ventilation

There are multiple potential reasons a patient with EVD may require ventilatory support: altered mental status due to end-organ hypoperfusion, bleeding complications threatening airway patency, EVD related Acute Respiratory Distress Syndrome, Transfusion-Associated Lung Injury, and others. EVD precautions alter this means of support by affecting the way in which the intubation is performed, the personnel involved in setting up and troubleshooting the ventilator, and the means by which the intubated patient is monitored. Each of these is discussed in detail above. Aside from these adjustments, the management of mechanical ventilation is similar to other critically ill patients. Means to minimize sedation when possible, identify delirium, and assess the patient for liberation from the ventilator should be employed. However, there may be an increased risk of disease transmission should the patient display agitated behavior. Further, reintubating the patient under urgent circumstances may represent a risk to patient and staff. Therefore, the goal level of sedation, the risk of interruption of sedation, and the threshold for extubation should be considered carefully.

Renal Replacement Therapy

Renal injury is common among patients with advanced EVD. Standard approaches to prevent or limit this injury (restoring intravascular volume, maintaining blood pressure, avoiding nephrotoxins) remain relevant. The indications for the initiation of renal replacement therapy (RRT) are the same in patients with suspected or confirmed EVD as in other critically ill patients. However, EVD precautions present unique challenges in delivering RRT. There is potential for disease transmission during placement of the dialysis catheter as well as during initiation, maintenance, and discontinuation of RRT. The conventional RRT machine is large and may be difficult to safely move in and out of the isolation unit. Conventional RRT is usually performed by a dedicated nurse. Patients with EVD and volume depletion may not be able to tolerate the volume shifts associated with conventional HD. For all of these reasons, strong consideration should be given to using continuous RRT when treating patients under EVD precautions. This minimizes the number of times the catheter must be manipulated, utilizes a smaller machine that may be able to stay in the isolation room for the duration of the patients course, and can potentially be monitored and adjusted by the same bedside critical care nurse(s) that is already caring for the patient.

Nutrition

The principles that guide nutrition in critically ill patients also apply to patients with EVD. Nutrition should be delivered enterally whenever possible. Parenteral nutrition should be reserved for situations in which enteral is not possible for a prolonged period. If employed, parenteral nutrition should be converted back to enteral nutrition as soon as possible.

Evidence Contour

To date, there is limited evidence on Ebola Virus Disease. Previous outbreaks involved too few cases and were of too short a duration to provide an opportunity for rigorous study. While the 2014 outbreak has provided an opportunity for observation and research, much of this has focused on how the outbreak spread and the efficacy of different methods to contain it. There is very limited data on management strategies for affected patients, and only a fraction of this evidence applies to care of an EVD patient in a well-resourced environment. Some of the interventions described above are currently under active investigation, but no conclusive data is yet available.

Targeted Therapy

No previous outbreak has had an adequate size or duration to allow adequate study of targeted therapy for EVD. However, several interventions exist that have either shown in vitro efficacy or have a strong mechanistic rationale. The 2014 outbreak has provided the opportunity to study some of these interventions. Currently, the interventions below remain experimental and their use in patients with EVD should be guided by discussions with experts in the field [1, 4, 6]:

Brincidofovir: An oral nucleotide analog that has shown in vitro activity against the Ebola virus. It has been authorized for emergency use in patients with EVD.

ZMapp: A combination of monoclonal antibodies against the Ebola virus that has demonstrated efficacy in laboratory animals. However, the product is not currently being produced and the existing supply has been exhausted.

TKM-Ebola: An antiviral agent that has also been authorized for emergency use in patients with EVD.

Convalescent Plasma: Plasma from EVD survivors, presumably containing anti-EVD antibodies. Supply is currently limited by the number of willing and eligible donors.

Ethical Considerations

Staffing Model

Trainee Involvement: Consideration should be given to the involvement of physicians-in-training in the care of patients with suspected or confirmed EVD. The need to impart professionalism and sense of duty to those in training must be balanced with the need to limit the number of providers exposed to the patient, and to utilize the most experienced providers in the care of the patient. In academic centers, removing trainees from the care of a patient may represent a major change in usual workflow. Thus, careful planning is needed to prevent errors that threaten the safety of the patient and staff [7].

Mandatory vs. Voluntary Staffing: In general, providers do not "choose" which patients they will care for. However, it could be argued that management of a disease such as EVD could not possibly have been anticipated when providers such as physicians and nurses made their commitment to the institution. While a mandatory staffing model is inherently more fair, it is also likely to be met with resistance from some providers and may negatively impact staff morale. If a large enough voluntary pool is available, this may be preferable [8, 9].

Provisions of Care

Patients under Investigation: As detailed above, EVD precautions significantly impact the way in which critical care is delivered and, in some ways, represent a risk to the patient. In the case of confirmed EVD, the need to protect staff and the public likely justifies this risk. However, the situation may not be as clear when evaluating a patient with a relatively low likelihood of EVD. The precautions, in this situation, may be more likely to harm the patient and less likely to protect the staff [4].

Patients with Confirmed EVD: Consideration should be given to limitations on resuscitative care in patients with EVD. Consider a patient who has developed advanced disease, complicated by multi-organ failure that culminates in cardiac arrest. In this situation, attempts at cardiopulmonary resuscitation are extremely unlikely to benefit the patient, but represent a significant risk to the staff. Alternatively, one could consider a patient with early EVD and no organ failures, who develops a lethal arrhythmia related to electrolyte abnormalities. The risk/benefit ratio in this circumstance is clearly different [1, 8].

References

1. West TE, von Saint Andre-von Arnim A. Clinical presentation and management of severe Ebola virus disease. Ann Am Thorac Soc. 2014;11(9):1341–50.
2. Centers for Disease Control. [Internet]. Ebola virus disease: US healthcare workers and settings (accessed 10 June 2015]. Available for: http://www.cdc.gov/vhf/ebola/healthcare-us/index.html.

3. World Health Organization [Internet]. Interim infection prevention and control guidance for care of patients with suspected or confirmed filovirus haemorrhagic fever in health-care settings, with focus on Ebola [accessed 10 June 2015]. Available from: http://www.who.int/csr/disease/ebola/evd-guidance-summary/en/.
4. Beeching NJ, et al. Ebola virus disease. BMJ. 2014;349:g7348.
5. Lyon GM, et al. Clinical care of two patients with Ebola virus disease in the United States. N Engl J Med. 2014;371:2402–9.
6. Hampton T. Vaccines against Ebola and Marburg viruses show promise in primate studies. JAMA. 2005;294(2):163–4.
7. Rosenbaum L. License to serve – U.S. trainees and the Ebola epidemic. N Engl J Med. 2015;372:504–6.
8. Gonsalves G, Staley P. Panic, paranoia, and public health – the AIDS epidemic's lessons for Ebola. N Engl J Med. 2014;371:2348–9.
9. Hampton T. Largest-ever outbreak of Ebola virus disease thrusts experimental therapies, vaccines into spotlight. JAMA. 2014;312:987–9.

Management of Severe Malaria

57

Jorge Hidalgo, Pedro Arriaga,
and Gloria M. Rodriguez-Vega

Case Presentation

A 25-year-old male presented to the emergency department with a history of abdominal pain in the right hypochondrium, jaundice, fever, and a decrease in consciousness. He was businessman who had recently returned from Nigeria, where he had spent 3 weeks. Laboratory tests at presentation showed WBC: 20,650 Neu:88 Lymph:12 Platelets: 38,000 SGOT: 88 SGPT: 120 Billirubins: T: 4.3 mg/dl I: 29 mg/dl, severe metabolic acidosis, thrombocytopenia, a creatinine of 5.6 mg/dl, and dark urine (macroscopic hemoglobinuria see Fig. 57.1). His APACHE II score was 37, with an estimated risk of death of 88%. The patient was admitted to the intensive care unit with septic shock. A thick blood smear revealed *P. falciparum* malaria. The patient was initiated with anti-malaria IV drugs: quinidine gluconate plus doxycycline. Despite antimalarial drug administration and supportive care the patient developed acute respiratory distress syndrome, acute renal failure requiring renal replacement therapy, and an Important Thrombocytopenia (Fig. 57.2).

J. Hidalgo
Adult Intensive Care, Critical Care Division, Karl Heusner Memorial Hospital, Belize City, Belize

P. Arriaga
Internal Medicine, Karl Heusner Memorial Hospital, Belize City, Belize

G.M. Rodriguez-Vega (✉)
Department of Critical Care Medicine, Hospital Hima – San Pablo – Caguas, Rio Piedras, PR, USA
e-mail: glorie68@gmail.com

Question What are the challenges in the diagnosis and management of the returning traveller with severe malaria?

Answer People now move across the world with great facility, whether on vacation or business. Endemic diseases, such as malaria, can affect the travelers upon return to home. Malaria.com maps the regions of the world where *Plasmodium falciparum*, the type intensivists might encounter, may be transmitted [1].

In a returning traveler, fever can be a benign and self-limiting infection, but initially must be considered seriously. Table 57.1 displays the top illnesses encountered in returning travelers. In order to make a diagnosis a comprehensive history with details regarding places visited, duration, purpose, activities undertaken, any chemoprophylaxis taken before or while traveling is critical for the initial work-Up. Knowledge of incubation period and disease risk by geographic are helps in making a differential diagnosis. Table 57.2 displays various diseases potentially encountered by the returning traveler by the duration of incubation period.

Principles of Management in Severe Falciparum Malaria

Patients with severe malaria usually present with a high level of parasitemia and/or major signs of organ dysfunction. Populations at

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_57

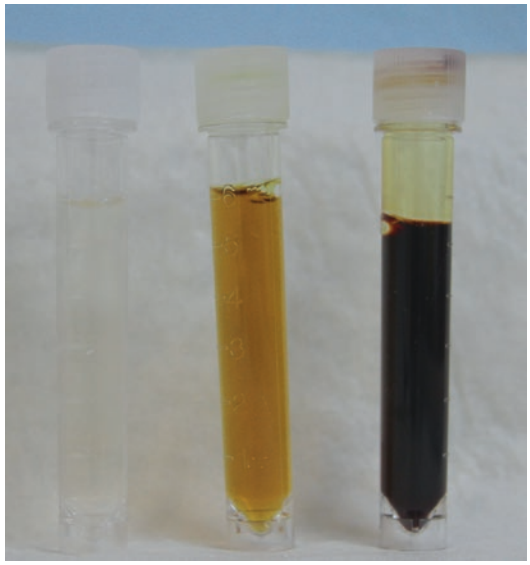


Fig. 57.1 "Blackwater Fever" – Urine sample showing dark urine due to hemoglobinuria (right tube)

greatest risk for severe falciparum malaria are young children, pregnant women and travelers to endemic areas. In endemic areas, elder children and adults develop partial immunity after repeated infections and are at relatively low risk for severe disease. Travelers to areas where malaria is endemic generally have no previous exposure to malaria parasites and are at high risk for severe disease. Pregnant women are more likely to develop severe P. falciparum malaria than other adults, particularly in the second and third trimesters. Complications such as hypoglycemia and pulmonary edema are more common than in non-pregnant individuals. Maternal mortality can approach 50 %, and fetal death and premature labor are common [2].

Patients with severe malaria represent a clinical challenge for the clinician given the complex pathophysiology of the infection involving multiple organ systems. Seizures and severe anemia are relatively more common in children, whereas hyperparasitemia, acute renal failure, and jaundice are more common in adults. Cerebral malaria (with coma), shock, acidosis, and respiratory arrest may occur at any age [2–4].

Definition of Severe Malaria

Severe malaria is generally defined as acute malaria with high levels of parasitemia (>5 %) and/or major signs of organ dysfunction

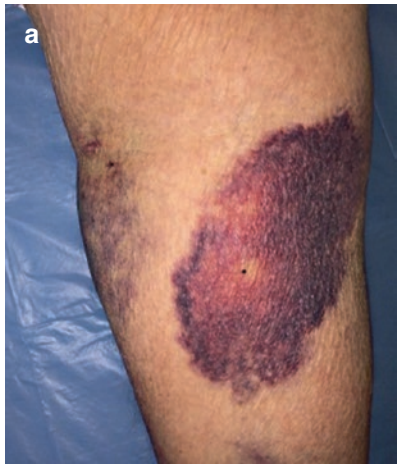
1. Altered consciousness with or without convulsions
2. Use of accessory muscles, nasal alar flaring, Tachypnea.
3. Metabolic acidosis (plasma bicarbonate M 15 mmol/L or whole blood lactate >5 mmol/L)
4. Circulatory collapse
5. Pulmonary edema or acute respiratory distress syndrome (ARDS)
6. Renal failure, hemoglobinuria ("Blackwater Fever")
7. Jaundice
8. Disseminated Intravascular coagulation
9. Severe Anemia
10. Hypoglycemia

Diagnosis

The clinician must have a high index of suspicion for malaria in travelers presenting with fever and a history of travel to malaria endemic regions within the previous year and especially in the prior 3 months. In uncomplicated malaria apart from fever, patients usually present with nonspecific clinical features. If the diagnosis of falciparum malaria has been delayed, a seemingly well-appearing patient may rapidly deteriorate and present with jaundice, confusion, or seizures and have a high fatality rate. Hence, it is critical to make a rapid and accurate diagnosis when malaria is suspected clinically [3, 4].

Microscopy is the gold standard and preferred option for the diagnosis of malaria. In most cases the examination of thin and thick blood films will reveal Malaria parasites (Figs. 57.3 and 57.4).

Thick films are more sensitive to detect low levels of parasitemia. In general the greater the parasite density in the peripheral blood, the higher likelihood that severe disease is present or will develop, especially in immunocompromised



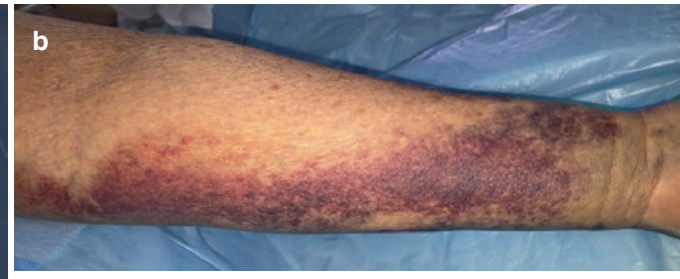


Fig. 57.2 (**a**, **b**) Ecchymosis from thrombocytopenia

Table 57.1 Top illnesses in returning travelers

Diagnosis	%
1. Systemic Illnesses	35
Malaria	21
Malaria due to P Falciparum	14
Malaria due to P Vivax	6
Malaria due to other species	2
Dengue	6
Salmonella enterica serovar Typhi or paratyphi	2
Rickettsia	2
2. Acute diarrhea	15
3. Respiratory illness	14
4. Genitourinary diseases	4
5. Gastro intestinal illness	4

From: Wattal and Goel [22]. Reprinted with permission from Elsevier Limited

Table 57.2 Incubation period of various diseases potentially encountered in returning travelers

Incubation period	Diseases
<7 days	Common: Malaria, Traveler's diarrhea, dengue, enteric fever, respiratory tract infection Others: rickettsiosis, leptospirosis, meningitis, yellow fever, arbovirus, meningococcal
7–21 days	Common: Malaria, enteric fever Others: rickettesioses, viral hepatitis, leptospirosis, HIV, Q Fever, brucellosis, African Trypanosomiasis
>21 days	Common: Malaria, Enteric Fever Others: tuberculosis, hepatitis B virus, bacterial endocarditis. HIV, Q fever, brucellosis, amebic liver diseases, melioidosis.

From: Wattal and Goel [22]. Reprinted with permission from Elsevier Limited

patients. Thick smears are more sensitive diagnostically but the thin smear subsequently helps in determining the malaria species and the level of parasitemia (the percentage of a patient's red blood cells that are infected with malaria parasites).

Clinical Management

General Principles

Most of the time uncomplicated malaria have a good prognosis with a fatality case less 0.1 %. Uncomplicated malaria caused by *P. ovale*, *P. vivax*, *and P. malariae* can usually be managed with oral drugs on an outpatient basis, unless a patient has other comorbidities or is unable to take drugs orally [4, 5].

Due to little immunity against these infections, *P. falciparum* infections in travelers can rapidly progress to severe illness or death in as little as 1–2 days, so prompt assessment and initiation of antimalarial therapy is essential. Patients should be evaluated with attention to findings consistent with malaria as well as additional and/or alternative causes of presenting symptoms. Of primary importance in the

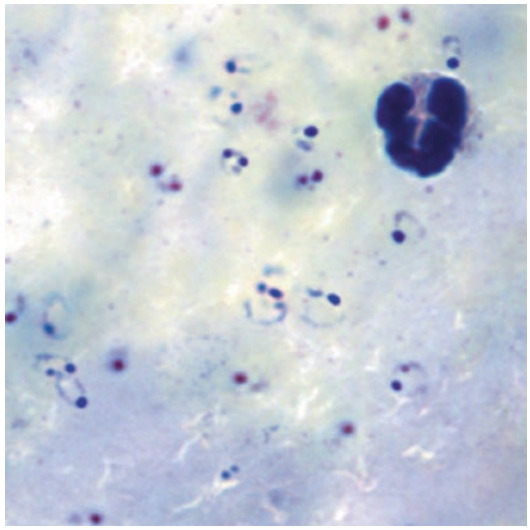


Fig. 57.3 P falciparum on thick smear (From: Centers for Disease Control and Prevention (CDC) [23])

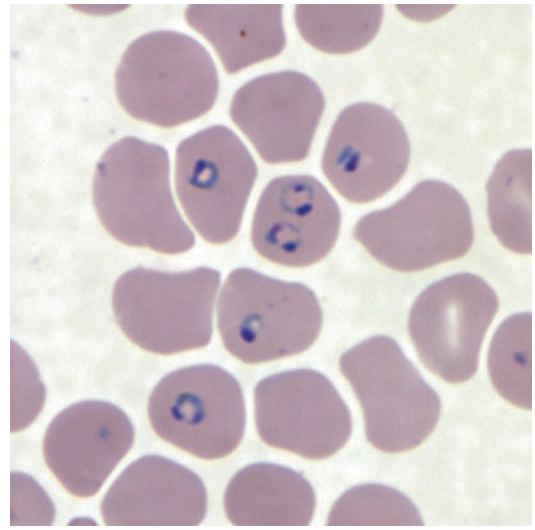


Fig. 57.4 P. falciparum on thin smear (From: Centers for Disease Control and Prevention (CDC) [23])

treatment of malaria is the provision of prompt, effective therapy and concurrent supportive care to manage life-threatening complications of the disease. Supportive measures, such as fluid management, oxygen, ventilatory support, cardiac monitoring, and pulse oximetry, should be instituted as needed. During this time, intravenous access should be obtained immediately. Point-of-care testing can be used for rapid determination of hematocrit [packed cell volume (PCV) or hemoglobin (HemoCue)], glucose, and lactate. Parasitemia can also be determined quickly but requires a microscope. Additional tests can be done if/when indicated: electrolytes, full blood count, type and cross, blood culture, and clotting studies. Unconscious patients should have a lumbar puncture to rule out concomitant bacterial meningitis in the absence of contraindications (i.e., papilledema). These tasks should overlap with institution of antimalarial treatment as well as other ancillary therapies as needed (including anticonvulsants, intravenous glucose and fluids, antipyretics, antibiotics, and blood transfusion) [6, 7].

Repeat clinical assessments should be performed every 2–4 h for prompt detection and management of complications in an intensive care setting, if possible. If the Glasgow Coma Score (or in children the Blantyre coma score [see Table 57.3]) decreases after initiation of treatment, investigation should focus on the possibility of seizures, hypoglycemia, or worsening anemia. Repeat laboratory assessments of parasitemia, hemoglobin/hematocrit, glucose, and lactate should be performed in 6-h intervals. A flow chart summarizing the vital information may be used to guide management decisions [6–8].

Important independent predictors for fatality among African children with severe malaria include acidosis, impaired consciousness (coma and/or convulsions), elevated blood urea nitrogen, and signs of chronic disease (lymphadenopathy, malnutrition, candidiasis, severe visible wasting, and desquamation). Clinical features previously identified as being poor prognostic features that did not correlate with mortality in this study included age, glucose level, axillary temperature, parasite density, and Blackwater Fever [9–11].

Careful observation and thoughtful responses to changes in clinical status are the most important elements in looking after patients with severe malaria. Patients can make remarkable recoveries, and the time and effort to address the components of clinical care described in the following

Table 57.3 Blantyre coma score

Type of response	Response	Score
Best Motor	Localize painful stimulus	2
	Withdraws limbs from pain	1
	Nonspecific or absent response	0
Verbal	Appropriate cry	2
	Moan or innapropiate cry	1
	None	0
Eye movements	Eg: directed (follows mother's face)	1
	Not directed	0
Total		**0–5**

The Blantyre coma scale is a modification of the Pediatric Glasgow Coma Scale, designed to assess malarial coma in children
It was designed by Drs. Terrie Taylor and Malcolm Molyneux in 1987, and named for the Malawian city of Blantyre, site of the Blantyre Malaria Project

sections can reap tangible rewards in a relatively short period of time.

Clinical evaluation includes full physical exam, a complete neurologic examination, calculation of Glasgow or Blantyre coma score (Table 57.3), and funduscopic evaluation. Malarial retinopathy is pathognomonic for cerebral malaria in patients who satisfy the standard clinical case definition (Fig. 57.5).

Patients with altered sensorium should undergo lumbar puncture (in the absence of contraindications) to exclude concomitant bacterial meningitis. If clinical instability or papilledema on ocular fundus examination preclude lumbar puncture, presumptive antibiotic therapy for bacterial meningitis should be initiated. Usual findings are: mean opening pressure about 16 cm of CSF, slightly elevated total protein level and cell count.

Antimalarial Therapy (See Treatment Table 57.4)

Monitoring Parasite Density

Parasitemia should be monitored during treatment to confirm adequate response to therapy. The CDC recommends daily repeat blood smear

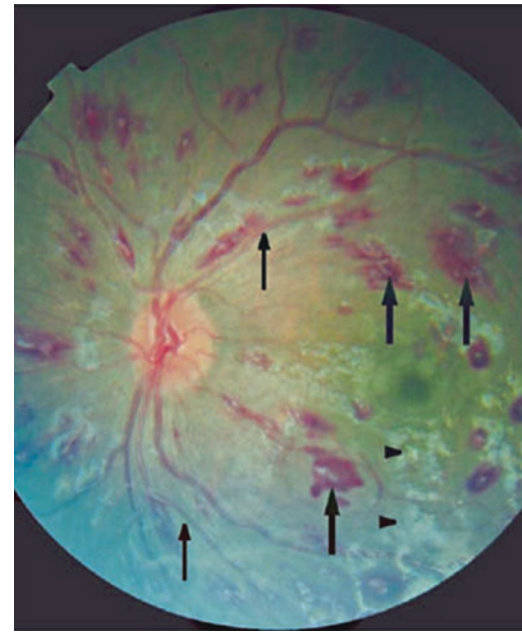


Fig. 57.5 Photograph of the retina in patient with malaria, which shows exudates (*arrowheads*), hemorrhages (*thick arrows*) and changes in the color of the blood vessels (*thin arrows*) (From Mishra and Newton [24]. Reprinted with permission from Nature Publishing Group)

to document declining parasite density until negative or until treatment day 7 (if discharged prior to complete parasitemia clearance). During treatment of severe malaria, parasite density should be monitored every 12 h during the first 2–3 days or until negative; some recommendations suggest switching from parenteral to oral therapy as tolerated after parasitemia falls below 1 % [10, 11].

Respiratory System

Hypoxemia and rales are not common in the setting of severe malaria; the presence of either should raise suspicion for a concomitant lower respiratory tract infection. Pulmonary edema may develop, particularly in the settings of renal impairment or severe malarial anemia. Acute respiratory distress syndrome (ARDS) can also complicate severe malaria.

Deep breathing (Kussmaul respirations) is a clinical indicator of metabolic acidosis and is

Table 57.4 Treatment of malaria

Clinical diagnosis/*Plasmodium* species	Region infection acquired	Recommended drug and Adult dose[a]	Recommended drug and pediatric Dose[a] *Pediatric dose should NEVER exceed adult dose*
Uncomplicated malaria/*P. falciparum* or species not identified If "species not identified" is subsequently diagnosed as *P. vivax* or *P ovale*: see *P. vivax* and *P ovale* (below) re. treatment with primaquine	**Chloroquine-resistant or unknown resistance**[b] (All malarious regions except those specified as chloroquine-sensitive listed in the box below.)	**A. Atovaquone-proguanil (Malarone™)[c]** **Adult tab = 250 mg atovaquone/100 mg proguanil** 4 adult tabs po qd × 3 days	**A. Atovaquone-proguanil (Malarone™)[c]** **Adult tab = 250 mg atovaquone/100 mg proguanil** **Peds tab = 62.5 mg atovaquone/25 mg proguanil** 5–8 kg: 2 peds tabs po qd × 3 days 9–10 kg: 3 peds tabs po qd × 3 days 11–20 kg: 1adult tab po qd × 3 d 21–30 kg: 2 adult tabs po qd × 3days 31–40 kg: 3 adult tabs po qd × 3days >40 kg: 4 adult tabs po qd × 3days
		B. Artemether-lumefantrine (Coartem™)[c] **1 tablet = 20 mg artemether and 120 mg lumefantrine** A 3-day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 h later, then 1 dose po bid for the following 2 days. 5 – <15 kg: 1 tablet per dose 15 – <25 kg: 2 tablets per dose 25 – <35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose	
		C. Quinine sulfate plus one of the following: Doxycycline, Tetracycline, or Clindamycin **Quinine sulfate**: 542 mg base (=650 mg salt)[d] po tid × 3 or 7 days[e] **Doxycycline**: 100 mg po bid × 7 days **Tetracycline**: 250 mg po qid × 7 days **Clindamycin**: 20 mg base/kg/day po divided tid × 7 days	**C. Quinine sulfate[d] plus one of the following:** **Doxycycline[f], Tetracycline[f] or Clindamycin Quinine sulfate**: 8.3 mg base/kg (=10 mg salt/kg) po tid × 3 or 7 days[e] **Doxycycline**: 2.2 mg/kg po every 12 h × 7 days **Tetracycline**: 25 mg/kg/day po divided qid × 7 days **Clindamycin**: 20 mg base/kg/day po divided tid × 7 days
		D. Mefloquine (Lariam™ and generics)[g] 684 mg base (=750 mg salt) po as initial dose, followed by 456 mg base (=500 mg salt) po given 6–12 h after initial dose Total dose = 1,250 mg salt	**D. Mefloquine (Lariam™ and generics)[g]** 13.7 mg base/kg (=15 mg salt/kg) po as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) po given 6–12 h after initial dose. Total dose = 25 mg salt/kg

Table 57.4 (continued)

Uncomplicated malaria/*P. falciparum* or ***Species not identified***	**Chloroquine-sensitive** (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East)	**Chloroquine phosphate** (**Aralen™ and generics**)[h] 600 mg base (=1,000 mg salt) po immediately, followed by 300 mg base (=500 mg salt) po at 6, 24, and 48 h Total dose: 1,500 mg base (=2,500 mg salt) **OR Hydroxychloroquine** (**Plaquenil™ and generics**) 620 mg base (=800 mg salt) po immediately, followed by 310 mg base (=400 mg salt) po at 6, 24, and 48 h Total dose: 1,550 mg base (=2,000 mg salt)	**Chloroquine phosphate** (**Aralen™ and generics**) [h] 10 mg base/kg po immediately, followed by 5 mg base/kg po at 6, 24, and 48 h Total dose: 25 mg base/kg **OR Hydroxychloroquine** (**Plaquenil™ and generics**) 10 mg base/kg po immediately, followed by 5 mg base/kg po at 6, 24, and 48 h Total dose: 25 mg base/kg
Uncomplicated malaria/*P. malariae or P. knowlesi*	**All regions**	**Chloroquine phosphate**: [h]Treatment as above **OR Hydroxychloroquine**: Treatment as above	**Chloroquine phosphate**: [h] Treatment as above **OR Hydroxychloroquine**: Treatment as above
Uncomplicated malaria/*P. vivax* or ***P. ovale***	**All regions** Note: for suspected chloroquine-resistant *P. vivax*, see row below	**Chloroquine phosphate[h] plus Primaquine phosphate[i]** **Chloroquine phosphate**: Treatment as above **Primaquine phosphate**: 30 mg base po qd×14 days **OR Hydroxychloroquine plus Primaquine phosphate[i]** **Hydroxychloroquine**: Treatment as above **Primaquine phosphate**: 30 mg base po qd×14 days	**Chloroquine phosphate[h] plus Primaquine phosphate[i]** **Chloroquine phosphate**: Treatment as above **Primaquine**: 0.5 mg base/kg po qd×14 days **OR Hydroxychloroquine plus Primaquine phosphate[i]** **Hydroxychloroquine**: Treatment as above **Primaquine phosphate**: 0.5 mg base/kg po qd×14 days
Uncomplicated malaria/*P. vivax*	**Chloroquine-resistant[j]** (Papua New Guinea and Indonesia)	**A. Quinine sulfate plus either Doxycycline or Tetracycline plus Primaquine phosphate[i]** **Quinine sulfate**: Treatment as above **Doxycycline or Tetracycline**: Treatment as above **Primaquine phosphate**: Treatment as above	**A. Quinine sulfate plus either Doxycycline[f] or Tetracycline[6] plus Primaquine phosphate[i]** **Quinine sulfate**: Treatment as above **Doxycycline or Tetracycline**: Treatment as above **Primaquine phosphate**: Treatment as above
		B. Atovaquone-proguanil plus Primaquine phosphate[i] **Atovaquone-proguanil**: Treatment as above **Primaquine phosphate**: Treatment as above	**B. Atovaquone-proguanil plus Primaquine phosphate[i]** **Atovaquone-proguanil**: Treatment as above **Primaquine phosphate**: Treatment as above
		C. Mefloquine plus Primaquine phosphate[i] **Mefloquine**: Treatment as above **Primaquine phosphate**: Treatment as above	**C. Mefloquine plus Primaquine phosphate[i]** **Mefloquine**: Treatment as above **Primaquine phosphate**: Treatment as above

(continued)

Uncomplicated malaria: alternatives for pregnant [women][k,l, m]	**Chloroquine-sensitive** (see uncomplicated malaria sections above for chloroquine-sensitive species by region)	**Chloroquine phosphate**: Treatment as above **OR** **Hydroxychloroquine**: Treatment as above	Not applicable
	Chloroquine-resistant (see sections above for regions with chloroquine resistant ***P. falciparum*** *and* ***P. vivax***)	**Quinine sulfate plus Clindamycin** **Quinine sulfate**: Treatment as above **OR** **Clindamycin**: Treatment as above **Mefloquine**: Treatment as above	Not applicable
Severe malaria[n,o, p]	**All regions**	**Quinidine gluconate**[n] **plus one of the following**: **Doxycycline**, **Tetracycline**, **or Clindamycin** **Quinidine gluconate**: 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1–2 h, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 h. An alternative regimen is 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 h, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 h every 8 h, starting 8 h after the loading dose (see package insert). Once parasite density <1 % and patient can take oral medication, complete treatment with oral quinine, dose as above. Quinidine/quinine course = 7 days in Southeast Asia; = 3 days in Africa or South America. **Doxycycline**: Treatment as above. If patient not able to take oral medication, give 100 mg IV every 12 h and then switch to oral doxycycline (as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. **Tetracycline**: Treatment as above **Clindamycin**: Treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 h. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. ***Investigational new drug*** **(*contact CDC for information*)**: **Artesunate followed by one of the following**: **Atovaquone-proguanil (Malarone™), Doxycycline (Clindamycin in pregnant women), or Mefloquine**	**Quinidine gluconate**[n] **plus one of the following**: **Doxycycline**[d], **Tetracycline**[d], **or Clindamycin** **Quinidine gluconate**: Same mg/kg dosing and recommendations as for adults. **Doxycycline**: Treatment as above. If patient not able to take oral medication, may give IV. For children <45 kg, give 2.2 mg/kg IV every 12 h and then switch to oral doxycycline (dose as above) as soon as patient can take oral medication. For children ≥45 kg, use same dosing as for adults. For IV use, avoid rapid administration. Treatment course = 7 days. **Tetracycline**: Treatment as above **Clindamycin**: Treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 h. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. ***Investigational new drug*** **(*contact CDC for information*)**: **Artesunate followed by one of the following**: **Atovaquone-proguanil (Malarone™), Clindamyciny or Mefloquine**

Source: Malaria Treatment Guidelines from CDC Public Library. July 2013

[a]If a person develops malaria despite taking chemoprophylaxis, that particular medicine should not be used as a part of their treatment regimen. Use one of the other options instead

[b]NOTE: There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. falciparum*. Options A, B, and C are equally recommended. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, we do not recommend option D (mefloquine) unless the other options cannot be used. For option C, because there is more data on the efficacy of quinine in combination with doxycycline or tetracycline, these treatment combinations are generally preferred to quinine in combination with clindamycin

[c]Take with with food or whole milk. If patient vomits within 30 min of taking a dose, then they should repeat the dose

[d]US manufactured quinine sulfate capsule is in a 324 mg dosage; therefore 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult due to unavailability of non-capsule forms of quinine

[e]For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days

[f]Doxycycline and tetracycline are not indicated for use in children less than 8 years old. For children less than 8 years old with chloroquine-resistant *P. falciparum*, atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children less than 8 years old with chloroquine-resistant *P. vivax*, mefloquine is the recommended treatment. If it is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead

[g]Treatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia due to drug resistance

[h]When treating chloroquine-sensitive infections, chloroquine and hydroxychloroquine are recommended options. However, regimens used to treat chloroquine-resistant infections may also be used if available, more convenient, or preferred

[i]Primaquine is used to eradicate any hypnozoites that may remain dormant in the liver, and thus prevent relapses, in *P. vivax* and *P. ovale* infections. Because primaquine can cause hemolytic anemia in G6PD-deficient persons, G6PD screening must occur prior to starting treatment with primaquine. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg orally one time per week for 8 weeks; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine must not be used during pregnancy

[j]NOTE: There are three options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. vivax*. High treatment failure rates due to chloroquine-resistant *P. vivax* have been well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant *P. vivax* have also been documented in Burma (Myanmar), India, and Central and South America. Persons acquiring *P. vivax* infections outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant *P. vivax* regimen and CDC should be notified (Malaria Hotline number listed above). For treatment of chloroquine-resistant *P. vivax* infections, options A, B, and C are equally recommended

[k]For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* or chloroquine-resistant *P. vivax* infection, treatment with doxycycline or tetracycline is generally not indicated. However, doxycycline or tetracycline may be used in combination with quinine (as recommended for non-pregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks

[l]Atovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women, particularly in the first trimester due to lack of sufficient safety data. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil or artemether-lumefantrine may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks

[m]For *P. vivax* and *P. ovale* infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with *P. vivax* and *P. ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (=500 mg salt) orally once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine

[n]Persons with a positive blood smear OR history of recent possible exposure and no other recognized pathology who have one or more of the following clinical criteria (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of >5 %) are considered to have manifestations of more severe disease. Severe malaria is most often caused by *P. falciparum*

[o]Patients diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy. Treatment with IV quinidine should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria should be given an intravenous loading dose of quinidine unless they have received more than 40 mg/kg of quinine in the preceding 48 h or if they have received mefloquine within the preceding 12 h. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine. During administration of quinidine, blood pressure monitoring (for hypotension) and cardiac monitoring (for widening of the QRS complex and/or lengthening of the QTc interval) should be monitored continuously and blood glucose (for hypoglycemia) should be monitored periodically. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion

[p]Pregnant women diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy

associated with a worse outcome in patients with falciparum malaria [10, 11].

Neurologic Involvement

The standard clinical case definition of cerebral malaria includes the following criteria:

1. Blantyre coma score ≤2
2. *P. falciparum* parasitemia (any density)
3. No other identifiable cause of coma (e.g., hypoglycemia, meningitis, or a post-ictal state)

The histologic hallmark of cerebral malaria is cerebral sequestration of parasitized erythrocytes.

Establishing whether retinopathy is present is an important marker for cerebral malaria. In the absence of this finding, alternative causes for coma (such as bacterial infection) should be pursued and treated, even in the presence of established malaria infection [11, 12].

Seizure Management

Seizures occur in up to 70 % of children with severe malaria; subclinical seizures occur in 15–20 % of cases. Seizures may be generalized or focal, and the clinical signs may be subtle (nystagmus, irregular respirations, hypoventilation, or a drop in the Blantyre coma score). It is also important to evaluate for causes of seizure besides cerebral malaria (e.g., hypoglycemia, fever) and to treat accordingly as outlined in the following sections.

Benzodiazepines are useful first-line agents for seizure treatment. Diazepam (0.4 mg/kg) can be administered intravenously or per rectum; lorazepam (0.1 mg/kg) can be administered intravenously or intraosseously. These doses can be repeated once if seizures do not cease within five minutes of the initial dose. Benzodiazepines should not be combined due to risk of respiratory depression. If seizures are not controllable with benzodiazepines, other options include phenobarbitone (phenobarbital 15–20 mg/kg, slow IV push) or phenytoin (18 mg/kg diluted in 100 mL normal saline, infused over 20 min).

If seizures recur, repeat single doses of benzodiazepine may be administered. Alternatively, maintenance doses of phenobarbital (5–15 mg/kg/day, administered orally, via NG tube, or via slow IV push in divided doses every 12 h) or phenytoin (10 mg/kg/day IV in divided doses every 12 h) may be initiated.

Paraldehyde was used as an intramuscular injection to treat seizures in the setting of severe malaria (0.2–0.4 mL/kg); its chief advantage is that it does not cause respiratory suppression. The cost of this agent has increased dramatically, and it is therefore out of reach for many formularies in malaria-endemic areas.

Patients with severe malaria should not receive routine seizure prophylaxis in the absence of clinical seizure activity [12–14].

Anemia and Coagulopathy

Severe hemolysis, which is mainly extravascular, occurs in hyperparasitemic falciparum malaria. Removal of both infected and uninfected erythrocytes from the circulation, mainly by the spleen, is associated with rapid development of anemia. Patients with severe anemia may present with or without altered consciousness; in addition, severe anemia has been associated with long-term neurocognitive impairment. In endemic areas hemoglobin concentration may decrease gradually over the course of repeated malaria infections. As a result, patients can be fully alert with hemoglobin concentrations of 2–3 g/dL (hematocrit <10 %). Evaluation for pallor of the conjunctivae, nail beds, and palms can provide a rough estimate of the degree of anemia, since blood vessels in these areas are close to the surface.

Hemoglobin concentration and hematocrit are routinely measured components of complete blood counts, but this may not be available in resource-limited settings or the results may not be available in a timely manner. In such circumstances the hematocrit can be measured on a fingerprick sample of blood collected into a heparinized capillary tube and centrifuged using a mechanical device. Alternatively, the hemoglobin concentration can be determined from fingerprick samples of blood collected into cuvettes.

This method is more expensive than manually spinning a hematocrit, but can be performed readily near the bedside.

Clinically evident disseminated intravascular coagulation in the setting of severe malaria is rare (<5 %), but profound thrombocytopenia is common, and the microcirculation in many organs is occluded by fibrin thrombi [15, 16].

Blood Products

Blood products should be administered in patients with dire prognoses, i.e., patients with altered consciousness, high output heart failure, respiratory distress, a cool periphery, hyperlactatemia, and/or high density parasitemia. Laboratory parameters of concern include low hemoglobin concentration (≤4–5 g/dL) or low hematocrit (≤10–15 %). The degree of anemia and the level of parasitemia may be useful parameters for predicting the need for a blood transfusion and for determining the volume of blood to transfuse. In general, 10 mL/kg of packed red blood cells or 20 mL/kg of whole blood transfused over 2–4 h is appropriate. Blood should be typed and crossmatched prior to infusion.

Blood transfusions are generally well-tolerated in the setting of severe malaria, since patients are relatively hypovolemic; diuretics are rarely needed. Monitoring of hemoglobin concentration or hematocrit should continue until the parasitemia clears, since repeat transfusion may be required [16].

Hypoglycemia

Defined as blood glucose <40 mg/dL or <2.2 mmol/L), hypoglycemia is a common complication of malaria and a marker of severe disease. It should be suspected in any patient who is comatose or who deteriorates suddenly.

The pathogenesis of hypoglycemia is not fully understood; it may be related to parasite glucose consumption and/or impaired host gluconeogenesis. Malnutrition, adrenal insufficiency, and hyperinsulinemia are not likely causes of hypoglycemia. In addition to primary hypoglycemia, administration of quinine or quinidine (insulin secretagogues) can cause iatrogenic hypoglycemia. Hypoglycemia with artesunate therapy is less common than with quinine or quinidine.

Patients presenting with normoglycemia can develop hypoglycemia during the course of treatment. When determining maintenance intravenous fluids, the clinician should consider the possibility of hypoglycemia and use glucose containing solutions. In addition, those managed promptly for hypoglycemia at presentation can have subsequent recurrent hypoglycemia. Therefore, blood glucose should be monitored closely during the course of illness with prompt management as outlined above. Patients with recurrent hypoglycemia should receive 10 % dextrose. Ten percent dextrose can be prepared quickly by withdrawing 100 mL from a one liter bag of a 5 % dextrose solution and replacing it with 100 mL of a 50 % dextrose solution [15–17].

Volume Management

Adults with malaria appear to be more vulnerable to fluid overload than children. There is a fine line between under hydration, and thus worsening renal impairment, and over hydration, risking pulmonary and cerebral edema. Hence, fluid requirements should be assessed on an individual basis, using commonly employed tools such as delayed capillary refill, low central venous pressure, and low urine output. Deep breathing, reflecting lactic acidosis, may also be a reasonable indicator of hypovolemia [16, 17].

Nutrition

Nutritional supplementation should be provided by nasogastric tube (NG) for patients with prolonged coma who are unable to eat and drink within 24–48 h.

Fever

High fevers (>38.5 °C) are common in the setting of malaria infection and may reflect the host response to endogenous pyrogens released at the time of schizont rupture. The optimal approach to treatment of fever is uncertain, although use of antipyretics in patients with high fever is

appropriate given the association between high fever and convulsions. Aggressive temperature control may help reduce long-term neurologic outcomes in pediatric patients with retinopathy-positive cerebral malaria.

Paracetamol (acetaminophen); 15 mg/kg every 6 h; maximum dose 1000 mg) is a reasonable antipyretic agent; oral therapy can be used for patients able to swallow. Otherwise, suppository formulations are acceptable. If fever persists, ibuprofen (10 mg/kg every 6 hours; maximum dose 1,200 mg per day) can be administered (orally, via nasogastric tube, or intravenously) alone or on an alternating schedule with paracetamol every 3 h [17–19].

Bacterial Infection

Concomitant bacterial infection is an important contributor to morbidity and mortality in the setting of severe malaria, and severe anemia has been implicated as a primary risk factor for nontyphoidal *Salmonella* septicemia. Bacterial infection should be suspected in patients with severe anemia together with signs or symptoms of sepsis (hypotension, cool extremities, delayed capillary refill, hyperlactatemia). In such cases, blood cultures should be obtained and broad spectrum antibiotic therapy with activity against gram-negative bacilli should be initiated [18, 19].

Evidence Contour

Other Diagnostic Modalities

A major drawback of light microscopy is that the efficiency of the test depends on the type and quality of the smear, skill of the technician, parasite density, and time spent on examining the smear. In addition, mixed infections with *P. malariae* or *P. ovale* are often missed, because their densities are often low in comparison to that of P falciparum. These problems may occur more frequently in non-endemic areas where malaria microscopy is performed infrequently.

Quantitative Buffy Coat

Quantitative buffy coat (QBC) is fluorescent microscopy based on the principle of concentrating the red blood cell-containing parasites within a narrow zone by centrifugation of blood in capillary tubes and staining of malarial parasite nucleic acid with acridine dyes. The sensitivity of QBC almost equals that of Giemsa-stained films. The advantage of QBC is ease of interpretation and rapidity. Species identification and quantification are difficult, however, with this technique and, therefore, thick and thin blood film examination is still required. This technique requires the use of expensive fluorescent microscopy equipment for the interpretation of results. This is an important limitation especially in the poor resource countries [19].

Antigen Rapid Detection Test (RDT)

Antigen detection RDTs detect malaria antigen in blood by immunochromatographic test with monoclonal antibodies directed against the target parasite antigen, which is impregnated on a test strip. The result is usually obtained in 5–20 min. Currently, different combinations of immunochromatographic tests are commercially available, targeting different genus specific or species-specific antigen for malaria diagnosis. Some of the commonly used antigens in RDTs are HRP-2 (*P. falciparum* specific), aldolase (pan-specific), plasmodium lactate dehydrogenase (pLDH) (*P. falciparum* specific), pLDH (*P. vivax*- specific), and pLDH (panspecific) [19, 20].

Serology

Serology detection of antibodies against malaria parasites, using either indirect immunofluorescence assay or ELISA, does not indicate current infection but rather measures past exposure. Therefore, it has no role in diagnosis of acute infections. Serology may be used to screen donors to prevent transfusion-related malaria, however, and to confirm the diagnosis of malaria in recently treated cases in which the diagnosis could not be confirmed previously [19–21].

Molecular Methods

Molecular technologies have been developed to improve the diagnosis of malaria by detecting specific parasite nucleic acid. The advantage of molecular methods is their exquisite sensitivity down to the level of 5 parasites/mL or 0.0001 % parasitemia [20, 21].

Exchange Transfusion

Exchange transfusion has been proposed as a means of removing infected red blood cells from the circulation, thereby lowering the parasite burden and replacing with unparasitized cells. There is no evidence supporting efficacy of exchange transfusion as adjunctive therapy in severe malaria, and there is no consensus on the indications, approach, benefits, or risks of this procedure.

The CDC no longer recommends exchange transfusion for treatment of severe malaria, based on a review that demonstrated no differences in outcome among patients who underwent exchange transfusion; previously, the CDC recommended exchange transfusion for patients with parasite density of >10 % with end organ complications. The WHO guidelines indicate that it is not possible to make any recommendations regarding the use of exchange transfusion based on the available evidence. The American Society for Apheresis (ASFA) supports exchange transfusion as an adjunctive therapy for patients with >10 % parasitemia, although its consideration of adverse events associated with exchange transfusion for malaria is limited [19–21].

References

1. Malaria.com – Uniting Against Malaria. High risk areas for malaria [Internet]. Cited 4 Apr 2016. Available from: http://www.malaria.com/questions/high-risk-areas-malaria-map.
2. White NJ, Pukrittayakamee S, Hien TT, et al. Malaria. Lancet. 2014;383:723.
3. WHO guidelines for the treatment of malaria. Geneva: World Health Organization; 2010. http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf. Accessed on 30 Dec 2010.
4. Intervention in infectious disease emergencies. Med Clin North Am. 2012;96(6):1225–55.
5. White NJ. The treatment of malaria. N Engl J Med. 1996;335:800.
6. Crawley J, Chu C, Mtove G, Nosten F. Malaria in children. Lancet. 2010;375:1468.
7. Bejon P, Warimwe G, Mackintosh CL, et al. Analysis of immunity to febrile malaria in children that distinguishes immunity from lack of exposure. Infect Immun. 2009;77:1917.
8. Mali S, Steele S, Slutsker L, et al. Malaria surveillance – United States, 2006. MMWR Surveill Summ. 2008;57:24.
9. Phillips A, Bassett P, Zeki S, et al. Risk factors for severe disease in adults with falciparum malaria. Clin Infect Dis. 2009;48:871.
10. Dondorp AM, Lee SJ, Faiz MA, et al. The relationship between age and the manifestations of and mortality associated with severe malaria. Clin Infect Dis. 2008;47:151.
11. Taylor T, Olola C, Valim C, et al. Standardized data collection for multi-center clinical studies of severe malaria in African children: establishing the SMAC network. Trans R Soc Trop Med Hyg. 2006;100:615.
12. von Seidlein L, Olaosebikan R, Hendriksen IC, et al. Predicting the clinical outcome of severe falciparum malaria in african children: findings from a large randomized trial. Clin Infect Dis. 2012;54:1080.
13. Dondorp AM, Fanello CI, Hendriksen IC, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet. 2010;376:1647.
14. Sinclair D, Donegan S, Isba R, Lalloo DG. Artesunate versus quinine for treating severe malaria. Cochrane Database Syst Rev. 2012;(6):CD005967.
15. Esu E, Effa EE, Opie ON, et al. Artemether for severe malaria. Cochrane Database Syst Rev. 2014;(9):CD010678.
16. Rosenthal PJ. Artesunate for the treatment of severe falciparum malaria. N Engl J Med. 2008;358:1829.
17. New medication for severe malaria available under an investigational new drug protocol. MMWR Surveill Summ. 2007;56:769. http://www.cdc.gov/mmWR/preview/mmwrhtml/mm5630a5.htm. Accessed on February.
18. Sweetman SC, editor. The complete drug reference 36th edition [online]. London: Pharmaceutical Press. Available at: http://www.medicinescomplete.com/. Accessed 05 Mar 2009.
19. World Health Organization. Management of severe malaria: a practical handbook. 3rd ed. WHO; 2012. http://apps.who.int/iris/bitstream/10665/79317/1/9789241548526_eng.pdf. Accessed on 18 Sept 2013.
20. Centers for Disease Control and Prevention. Treatment of malaria: guidelines for clinicians (United States). Part 3: alternatives for pregnant women and treatment of severe malaria. http://www.

cdc.gov/malaria/diagnosis_treatment/clinicians3.html. Accessed on 18 Sept 2013.
21. Centers for Disease Control and Prevention. Treatment of malaria: exchange transfusion for treatment of severe malaria no longer recommended. http://www.cdc.gov/malaria/new_info/2013/exchange_transfusion.html. Accessed on 31 Jan 2014.
22. Wattal C, Goel N. Infectious Disease Emergencies in Returning Travelers: Special Reference to Malaria, Dengue Fever, and Chikungunya. Med Clin North Am. 2012;96:1226.
23. Centers for Disease Control and Prevention (CDC). DPDx – laboratory identification of parasitic diseases of public health concern. http://www.cdc.gov/dpdx/malaria/gallery.html#pfalringformtrophs.
24. Mishra SK, Newton CRJC. Diagnosis and management of the neurological complications of falciparum malaria. Nat Rev Neurol. 2009;5(4):189–98.

Dengue

58

Pedro Arriaga, Jorge Hidalgo,
and Gloria M. Rodriguez-Vega

Case Presentation

A 25 year old male patient was admitted to the Emergency Department with a history of 5 days of acute onset fever, generalized body ache, myalgias, arthralgias, retro-orbital eye pain, intense headache, and rash involving both extremities. The day before his admission, the patient started having nausea and vomiting. He also had noticed bleeding from the gums. The patient had no previous medical history. Ten days before presentation he had returned from a trip to South America. Physical examination revealed a temperature of 39°C, blood pressure of 80/50 Torr, heart rate of 120 beats/min. The patient looked lethargic but was mentally alert. Conjunctival injection was present. Oral mucosae was dry and pale but had mild bleeding in the gums. There was no evidence of respiratory distress. In the abdomen the patient had generalized abdominal pain with more intensity in the epigastrium and a petechial rash on his limbs (Fig. 58.1). White blood cell was reported to be 3000 cells/mm^3, with a differential showing a predominance of lymphocytes. Platelet count was reported of 30,000.

Question What approach should guide this patient diagnosis?

Answer The abrupt onset of fever with myalgias and arthralgias and rash is suggestive of a viral process.

In this case the epidemiological background, clinical symptoms, leucopenia and thrombocytopenia suggests a possible Arbovirus infection called Chikungunya, Hemorrhagic Fever Viral infections, Leptospirosis, Rickettsiosis, Yellow fever, or possibly Malaria.

The patient was initially managed with IV crystalloid administration, and having only a modest improvement in blood pressured was transferred to an isolation area in the intensive care unit. Cultures and serological test were drawn. ELISA IgM test for Chikungunya infection was reported as negative, ELISA test for Yellow fever was sent and pending, while an ELISA IgM test for Dengue was reported as positive. A Chest x ray demonstrated mild bilateral pleural effusions, and an abdominal ultrasound

P. Arriaga
Internal Medicine, Karl Heusner Memorial Hospital, Belize City, Belize

J. Hidalgo
Adult Intensive Care, Critical Care Division, Karl Heusner Memorial Hospital, Belize City, Belize

G.M. Rodriguez-Vega (✉)
Department of Critical Care Medicine, Hospital Hima – San Pablo – Caguas, Rio Piedras, PR, USA
e-mail: glorie68@gmail.com

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_58

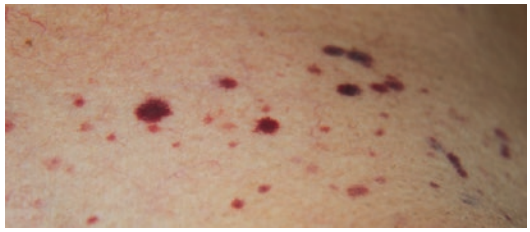


Fig. 58.1 Petechial rash (Courtesy of Dr. Jorge Hidalgo, from Karl Heusner Memorial Hospital Belize)

showed the presence of a small amount of intraabdominal fluid. Observation in the ICU continued with the monitoring of vital signs and levels of platelets along with the administration of intravenous fluid for the next 4 days. The patient improved symptomatically, the petechial rash vanished and the gum bleeding stopped. Bedside ultrasound confirmed disappearance of pleural and intra-abdominal fluid. Results for Yellow fever test were reported as negative and the patient was transferred out of ICU to the general medical ward the following day.

Principles of Management

Dengue is one of the most rapidly spreading mosquito borne viral diseases in the world. An estimated 50-million dengue infections occur annually in the world. Dengue is endemic in at least 100 Countries in Asia, the Pacific, the Americas, Africa and the Caribbean. This tropical disease is caused by the dengue virus, a single stranded, positive sense RNA virus, which has four different serotypes (DEN-1–4) that belong to genus Flavivirus, family Flaviviridae. Infection with one serotype does not protect against the others, and reinfection with a different serotype puts the patient at risk of severe disease. The disease is transmitted by the bite of infected mosquitoes of the genus Aedes, mostly A aegypti and A albopictus. Symptoms usually begin 4–7 days after the mosquito bite and last between 3 and 10 days [1–4].

According to WHO Dengue is classified as follows: Dengue Fever (DF), Dengue hemorrhagic fever (DHF) and Dengue Shock Syndrome (DSS).

Classification of Dengue (WHO)

Dengue Fever: Acute illness that manifests itself with fever and two or more of the following: retroorbital or ocular pain, headache, rash, myalgia, arthralgia, leucopenia or hemorrhagic manifestations (gum bleeding, epistaxis, blood in urine, vomitus or stool or vaginal bleeding).

Dengue Hemorrhagic Fever (*DHF*): Fever lasting 2–7 days with hemorrhagic manifestations, thrombocytopenia, evidence of plasma leakage, abnormal hematocrit (increased in >20 % above average for age), pleural effusion, ascites.

Dengue Shock Syndrome (*DSS*): Symptoms as in DHF plus a hypotension with fast and weak pulse, narrow pulse pressure, and cold clammy skin [1, 2].

Phases of Illness and Diagnosis

After the incubation period the disease has an abrupt onset and three phases have been described: febrile, critical and recovery.

Febrile phase lasts typically 2–7 days with the classical symptoms described above and mild hemorrhagic manifestations; a Rumpel Leede test/Tourniquet test can be positive (Fig. 58.2).

Critical Phase Usually on days 3–7 of illness, the temperature drops to 38 °C, there is increase in capillary leakage, lasting 24–48 h. Shock occurs when a critical volume of plasma is lost and usually is preceded by warning signs such as vomiting and abdominal pain, with or without respiratory distress, in some patients organ hypoperfusion produces progressive organ impairment with metabolic acidosis and disseminated intravascular coagulation.

If the patient survives the critical phase, a gradual reabsorption of fluid from the extravascular compartment takes place. The general condition of the patient improves with

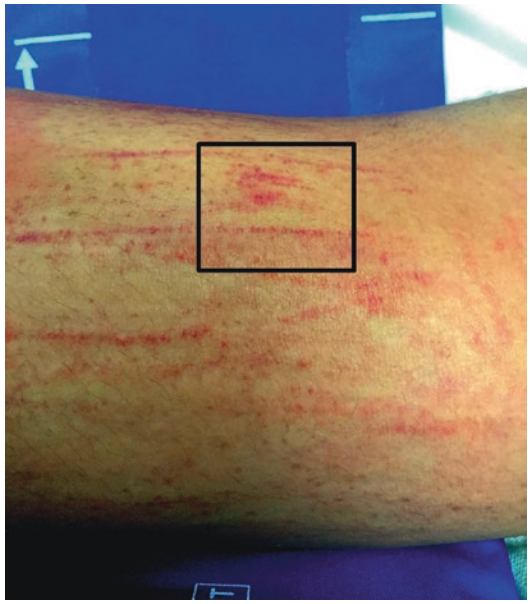


Fig. 58.2 How to do a tourniquet test. (1) Take the patient's blood pressure and record it, for example, 100/70. (2) Inflate the cuff to a point midway between SBP and DBP and maintain for 5 min (100 + 70) ÷ 2 = 85 mmHg. (3) Reduce and wait 2 min. (4) Count petechiae below antecubital fossa. A positive test is ten or more petechiae per 1 square inch (Courtesy of Dr. Jorge Hidalgo, from Karl Heusner Memorial Hospital Belize)

stabilization of the hemodynamic status marking the recovery phase of the disease. During the febrile phase, detection of viral nucleic acid in serum using RT-PCR, or detection of the virus expressed soluble nonstructural protein 1 (NS1) or an ELISA IgM test positive are sufficient for a confirmatory test or if there is IgM seroconversion in paired sera [1, 2, 5].

Supportive Treatment

There is no specific treatment for Dengue. The management of patients with Dengue consists of providing support treatment to maintain the hemodynamic status through hydration and antipyretics. Because of the possible hemorrhagic manifestations the use of nonsteroidal anti-inflammatory medications is usually contraindicated [1–5].

Evidence Contour

Volume Replacement

Isotonic crystalloid should be used, reassessing the patient's vital signs and monitoring levels of hematocrit every 6–8 h. If the hematocrit increases or is high the additional administration of intravenous should be considered (10–20 cc/kg for 1 h). If the hematocrit decreases compared to the previous value (less than 40 % in children and female adults or less than 45 % in male adults) it is likely a significant blood loss has occurred and transfusion with fresh whole blood should be initiated. Urine output should be checked every hour. Bleeding usually occurs after a period of prolonged shock that is preceded by plasma leakage, during which the hematocrit increases to relative high values before the onset of severe bleeding. When this occurs, the hematocrit will decrease from this high level. This can explain why the hematocrit levels may not be as low as in the absence of plasma leakage [1, 2, 4, 5].

Other Aspects of Care

Thrombocytopenia can be severe in some cases reaching sometimes levels of less than 1000 but there is no evidence to support transfusion of platelets and of fresh frozen plasma for severe hemorrhagic manifestations.

Close monitoring of glucose levels is recommended as patients can become hypoglycemic. There is no evidence for the use of steroids in the treatment of patients with Dengue [1–5].

References

1. WHO 2012. Handbook for clinical management of dengue, WHO ISBN 978 92 4 150471 3.
2. WHO 2009. Dengue guidelines for diagnosis, treatment, prevention and control- New edition 2009, ISBN 978 92 4 154787 1.
3. Chen LH, et al. The role of the traveler in emerging infections and magnitude of travel. Med Clin North Am. 2008;92:1409–32.
4. Wattal C. Infectious disease emergencies in returning travelers special reference to malaria, dengue fever, and Chikungunya. Med Clin North Am. 2012;96:1225–55.
5. Simmons C, et al. Dengue. N Engl J Med. 2012;366:1423–32.

Chikungunya

59

Pedro Arriaga and Jorge Hidalgo

Case Presentation

A 54 years old female patient was admitted to the emergency department with 5 days of high fever and chills which were associated with severe arthralgia, myalgia, anorexia and malaise. The patient complained of severe pain affecting both hands, elbows, and knee joints with slight swelling on her hands. The joint pain was incapacitating and she was not able to walk without assistance. Two days after the onset of fever she had noticed a maculopapular rash in her torso and both extremities (Fig. 59.1). She also reported the onset of vomiting and weakness at that time. The patient had a history of travelling to the Caribbean Islands 1 week before presentation. At the time of admission to the hospital, the patient looked dehydrated and had a temperature of 39.5 C, a heart rate of 115 beats per minute, and a blood pressure of 90/50 mmHg. On laboratory, her CBC showed a platelet count of 95,000/mm^3 and a white blood cell count of 3500/mm^3 with predominance of lymphocytes. Blood chemistries demonstrate an elevated SGOT (75 U/L) and SGPT (125 U/L).

Question What diagnostic approach should be undertaken?

Answer The presence of fever and arthralgias is a common clinical presentation in viral infections. In patients from tropical areas or with an appropriate travel history diseases sharing these symptoms include: Malaria, Rickettsiosis, Leptospirosis, Dengue, Chikungunya, and Group A Streptococcal infections. Early diagnosis of these conditions is based on a high index of clinical suspicion due to epidemiologic considerations (travel history, exposure, etc.) and the clinical presentation.

In this case, the history of recent traveling to the Caribbean and the abrupt onset fever with arthralgias and maculopapular rash serves to suggest certain diagnostic possibilities: Malaria, Chikungunya, Dengue and/or Leptospirosis. Thrombocytopenia and leucopenia are also suggestive of a viral process. The main laboratory finding in Chikungunya infection is lymphopenia, and is associated with viremia when the lymphocyte count is less than 1000 per cubic millimeter. Elevation of liver function tests are also reported, with SGOT and SGPT values elevated up to 1.5 times de normal level in up to 50 % of cases [1–8].

P. Arriaga (✉)
Internal Medicine, Karl Heusner Memorial Hospital, Belize City, Belize
e-mail: prarr62@yahoo.com

J. Hidalgo
Adult Intensive Care, Critical Care Division, Karl Heusner Memorial Hospital, Belize City, Belize

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_59

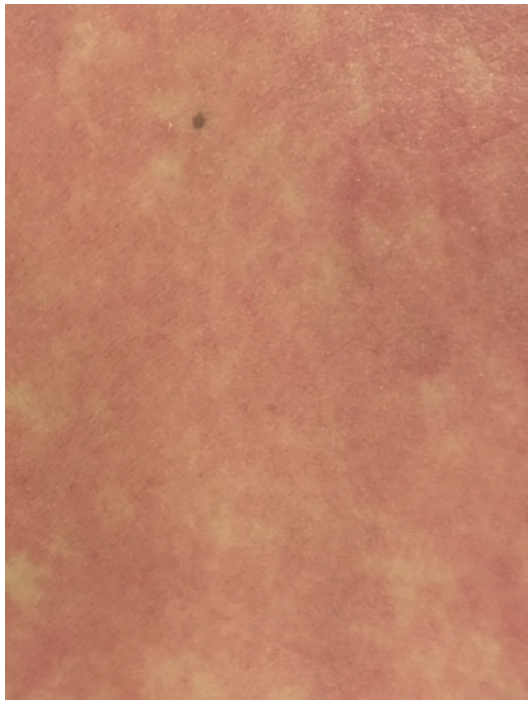


Fig. 59.1 Maculopapular rash (Courtesy of Dr. Jorge Hidalgo, from Karl Heusner Memorial Hospital Belize)

From the clinical point of view the presence of symmetrical arthritis, fever and a maculopapular rash in this patient are strongly suggestive of Chikungunya infection. An array of optic symptoms can develop, most commonly anterior uveitis, but conjunctivitis, even with injection similar to Leptospirois, may develop (Fig. 59.2) [9]. In patients with Dengue Fever the presence of arthritis is not as common, whereas hemorrhagic manifestations and shock are more frequent when compared to patients with Chikungunya. Table 59.1 compares the presentation of Chikungunya to that of Dengue.

The patient was initially managed with IV crystalloid administration in the emergency department. After a bolus of 20 cc/Kg her blood pressure returned to normal. Acetaminophen was used to control her temperature and arthralgias. Tests for serology were drawn. ELISA IgM for Chikungunya infection was reported as positive, ELISA IgM for Dengue and Leptospirosis were reported as negative. Tests for malaria were also reported negative. The patient, already stable, was admitted to the hospital and 4 days later was discharged home [1–3, 6].

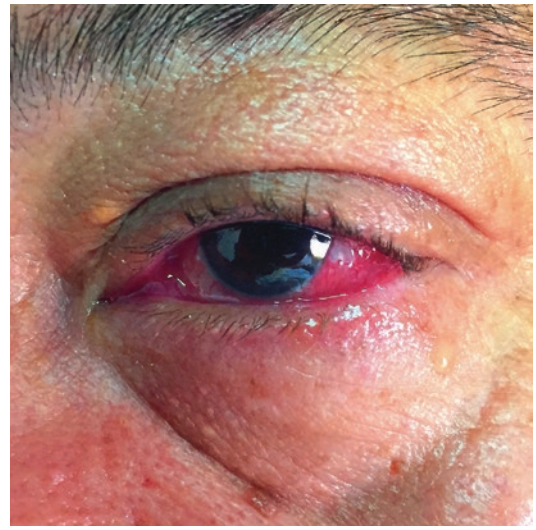


Fig. 59.2 Conjunctivitis (Courtesy of Dr. Jorge Hidalgo, from Karl Heusner Memorial Hospital Belize)

Table 59.1 Clinical and laboratory features of Chikungunya virus infections compared with Dengue virus infections

	Chikungunya	Dengue
Fever (>39°)	+++	++
Arthralgia	+++	+/–
Arthritis	+	–
Headache	++	++
Rash	++	+
Myalgia	+	++
Hemorrhage	+/–	++
Shock	–	+
Lymphopenia	+++	++
Neutropenia	+	+++
Thrombocytopenia	+	+++
Hemoconcentration	–	++

(http://www.cdc.gov/chikungunya/pdfs/CHIKV_DengueEndemic.pdf)

Principles of Management

Diagnosis

Chikungunya infection is caused by a RNA virus that belongs to the Alphavirus genus in the family

Togaviridae, that encodes four nonstructural proteins and three main structural proteins: the capsid and two envelope glycoproteins, E1 and E2 which forms spikes in the virion surface, E2 initiates cell entry through endocytosis and E1 initiates the release of nucleocapsids into the host cell system [2].

The name Chikungunya is derived from the Makonde language used in the Southeast area of Tanzania, which means: "That which bends up" this is due to the severity of the joint pain and the posture that patients acquired during the disease. The virus is transmitted in humans following the bite by the mosquito species *Aedes aegypti*, and *Aedes albopictus*. Fever is present in 70–90 % of cases. Arthralgias have been reported in more than 60 % of cases and can last up to 36 months after the acute infection. A maculopapular rash is present in up to 50 % of patients and usually affects trunk and extremities (Fig. 59.1) [1, 6]. Atypical presentations of the disease have been described, with neurological signs, pancreatitis, and/or hepatitis which usually affect neonates, elderly people and patients with co-morbidities such as diabetes or renal failure [1, 2, 4].

The gold standard test for diagnosing Chikungunya infection, a viral culture, is often is not done due its difficulty, availability and its time consuming nature. Alternatively and ELISA for IgM antibodies can be obtained. Antibodies levels are present after the fourth day and reach the highest level 3–5 weeks after the clinical onset and can persist elevated for about 2 months [1–3].

Volume Management

Adequate venous access must be guaranteed for volume resuscitation, when hypovolemia and sepsis is suspected. Two large bore (16 gauge) intravenous lines should be placed if possible to allow for administration of fluids. An infusion of 300–500 cc of fluid is administered during a period of 20–30 min [7, 8]. Fluids to control hypotension must be infused rapidly to induce a fast response, and as with other shock patients, the use of bedside ultrasound can be of additional help to quantify the degree of deficit and for further replacement guidance using measurements of the diameter of the inferior vena cava before and after the bolus or using the passive leg raising method [10, 11].

Evidence Contour

Epidemiology

Weaver and Lecuit published a map showing origin, spread, and distribution of Chikungunya virus [2]. Most Caribbean islands have reported local transmission of the virus (Fig. 59.3).

Presently, Chikungunya has been reported in travelers returning to the United States in all states except Alaska, Wyoming and North Dakota. It has been recently reported autochthonously in the Florida Keys. It is likely that the virus will increase its' reach in North America in the coming years.

Treatment

There is no specific antiviral medication for Chikungunya infection. During the acute period of the disease the management should be to provide supportive treatment to maintain the hemodynamic status through hydration and antipyretics. The use of nonsteroidal anti-inflammatory medications must be considered only after the diagnosis of an infection with Dengue has been ruled out. There have been reports of patients suffering from the two diseases at the same time in endemic areas [1, 6, 12].

After a period of more or less 10 days most patients will see an improvement, but some of them will have a post viral reactive arthritis that can relapse with symptoms; this defines the beginning of the chronic phase of the disease that can persist for more than 3 months [13–15].

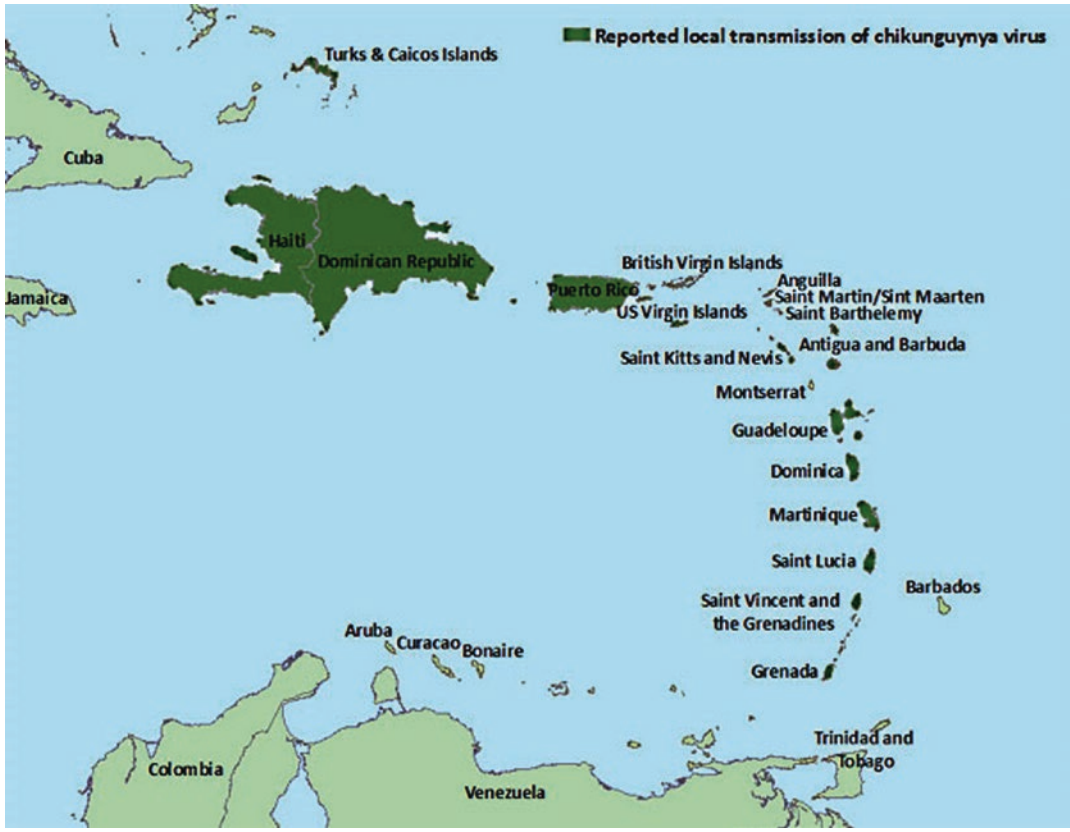


Fig. 59.3 2004 map showing islands where Chikungunya has been transmitted to inhabitants. From: http://www.caribbean360.com/news/this-is-a-sobering-statistic-on-the-spread-of-chikugunya-across-the-caribbean (*Credit*: *cdc.gov*)

References

1. Centers for Disease Control / Pan American Health Organization. Preparedness and response for Chikungunya virus: introduction in the Americas. PAHO 2011. p. 150.
2. Weaver SC, et al. Chikungunya virus and the global spread of a mosquito borne disease. N Engl J Med. 2015;372(13):1231–9.
3. Powers AM. Chikungunya. Clin Lab Med. 2010;30:209–19.
4. Hamer DH, et al. Chikungunya: establishing a new home in the Western hemisphere. Ann Intern Med. 2014;161:827–8.
5. Charrel RN, et al. Chikungunya outbreaks – the globalization of vectorborne diseases. NEJM. 2007;356(8):769–71.
6. Chen LH, et al. The role of the traveler in emerging infections and magnitude of travel. Med Clin North Am. 2008;92:1409–32.
7. Staples JE, et al. Chikungunya fever: an epidemiological review of a re-emerging infectious disease. Clin Infect Dis. 2009;49:942–8.
8. Wattal C. Infectious disease emergencies in returning travelers special reference to Malaria, dengue fever, and Chikungunya. Med Clin North Am. 2012;96:1225–55.
9. Mahendradas P, Avadhani K, Shetty R. Chikungunya and the eye: a review. J Opthal Inflam Infection. 2013;3:35.
10. Chew LP, et al. Outbreak of Chikungunya in Johor Bahru, Malaysia: clinical and laboratory features of hospitalized patients. Med J Malaysia. 2009;64(3):220–2.
11. Tape D, et al. Chikungunya and dengue virus antibodies in a traveler with severe arthralgia returning from India. J Clin Virol. 2010;49:148–50.
12. Vincen JL, et al. Circulatory shock. N Engl J Med. 2013;369:1726–34.
13. Dellinger R, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock. Crit Care Med. 2012;41(2):580–637.
14. Lamia B, et al. Echocardiographic prediction of volume responsiveness in critically ill patients and spontaneous breathing activity. Intensive Care Med. 2007;33:1125–32.
15. Maizel J, et al. Diagnosis of central hypovolemia by using passive leg raising. Intensive Care Med. 2007;33:1133–8.

Leptospirosis

60

Jorge Hidalgo, Gloria M. Rodriguez-Vega, and Pedro Arriaga

Case Presentation

A 32 years old male patient, who recently went into a camping trip and who had a history of swallowing water while swimming in a pool, was admitted to the hospital with the complaints of weakness, cough, bloody sputum, generalized jaundice (Fig. 60.1), ecchymosis and dark urine (Fig. 60.2). At presentation to the hospital the patient was found to have conjunctival suffusion (Fig. 60.3) acute renal failure, and bilateral lung infiltrates. On laboratory examination his WBC was 16,000 with 78 % neutrophils, and 22 % lymphocites. His Platelet count was 45,000. Liver chemistries showed an SGOT: 102; SGPT: 110, Total bilirubin 2.3 with an indirect of 8; alkaline Phosphatase: 120, albumin: 3.2. PT: 18 PTT: 32. Creatinine was 7.3 with a BUN: 90. After collection of blood, urine and sputum cultures and serum samples for serological tests, intravenous ceftriaxone and ciprofloxacin were administered and the patient was placed on renal replacement therapy. None of the cultures yielded pathogenic microorganisms.

Question What is the diagnosis?

Answer Leptospirosis (Weil's Disease)

Microscopic agglutination test (MAT) was applied to two serum samples which were collected with a 10 days interval. The first serum sample revealed antibody positivity at 1/200 titer against *Leptospira interrogans*. After the diagnosis was confirmed he was keep only on Ceftriaxone. By the administration of antibiotic therapy and early supportive care the patient improved clinically and was discharged from the ICU to a step-down unit.

Leptospirosis is a zoonosis that affects the humans and is caused by pathogenic spirochetes of the genus *Leptospira*. It is a frequent type of zoonosis, especially in tropical regions. Data is insufficient regarding its frequency in non-tropical regions. Half of the cases reported in the United States emanate from Hawaii. Leptospirosis presents with a self-limited to mildly icteric form in nearly 90 % of cases. However in approximately 5–10 % of cases it leads to Weil's disease, which is characterized by fever, hepatic failure, renal failure and respiratory failure. Weil's disease is also known as Weil-Vasilyev disease, Swineherd's disease, rice-field fever, waterborne fever, Nanukayami Fever, cane-cutter fever, swamp fever, mud fever, Stuttgart disease, and Canicola fever.

J. Hidalgo
Adult Intensive Care, Critical Care Division, Karl Heusner Memorial Hospital, Belize City, Belize

G.M. Rodriguez-Vega (✉)
Department of Critical Care Medicine, Hospital Hima – San Pablo – Caguas, Rio Piedras, PR, USA
e-mail: glorie68@gmail.com

P. Arriaga
Internal Medicine, Karl Heusner Memorial Hospital, Belize City, Belize

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_60

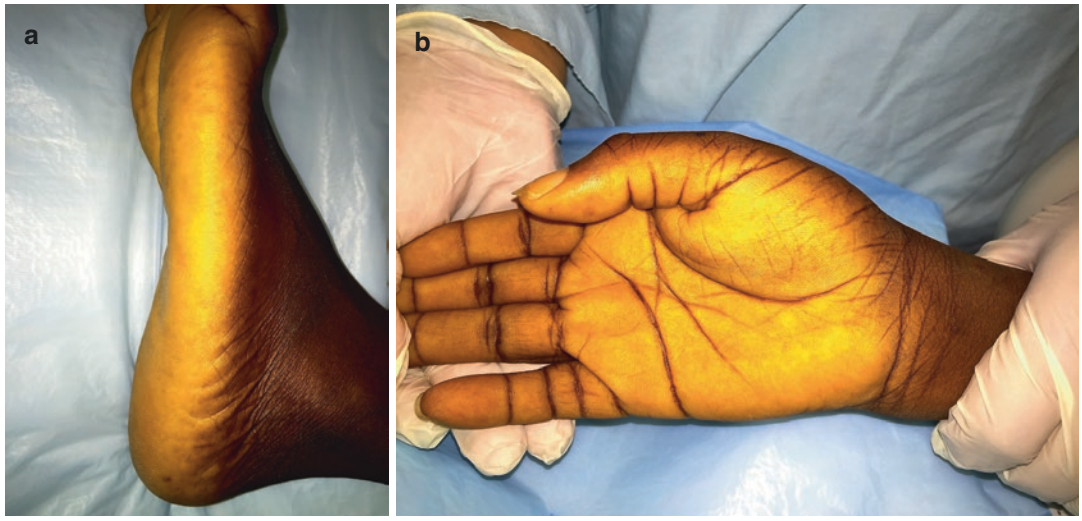


Fig 60.1 (**a, b**) Generalized jaundice

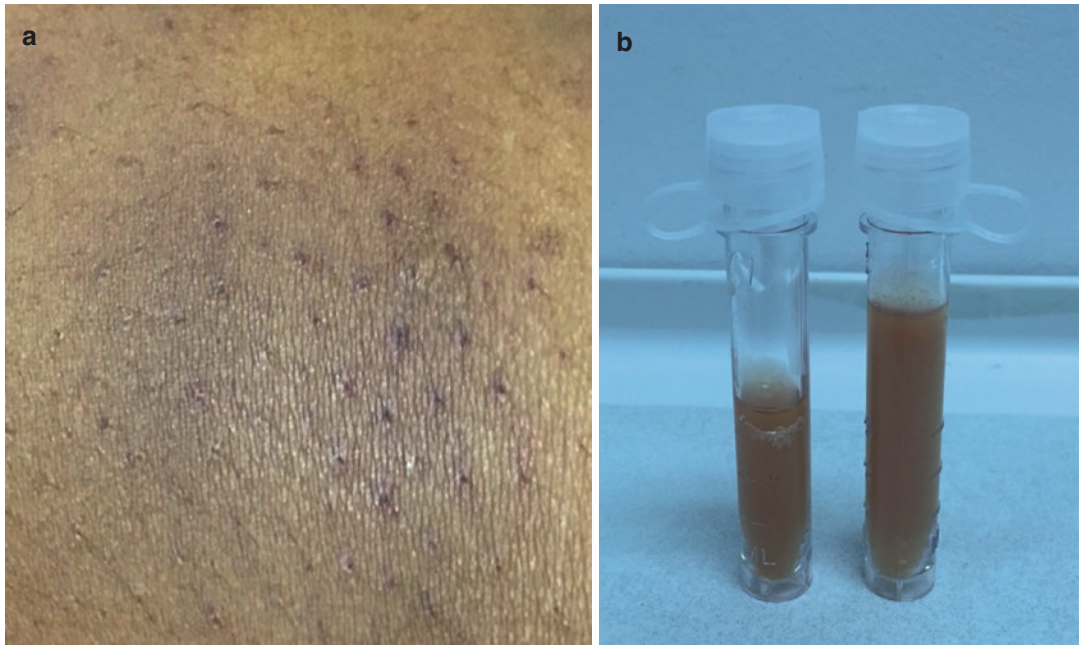


Fig. 60.2 (**a, b**) Ecchymosis (*left*) and dark urine demonstrating hemoglobinuria

Principles of Management

Epidemiology

Leptospirosis is usually a result of environmental exposures to infected animal urine or contaminated water or soil. Rarely, it may be contracted after the ingestion of food contaminated with urine or via aerosols [1].

In the United States, the incidence of leptospirosis is relatively low; most cases are reported from the southern and Pacific coastal states. Hawaii consistently reports the most cases of any state, though this may partly be because

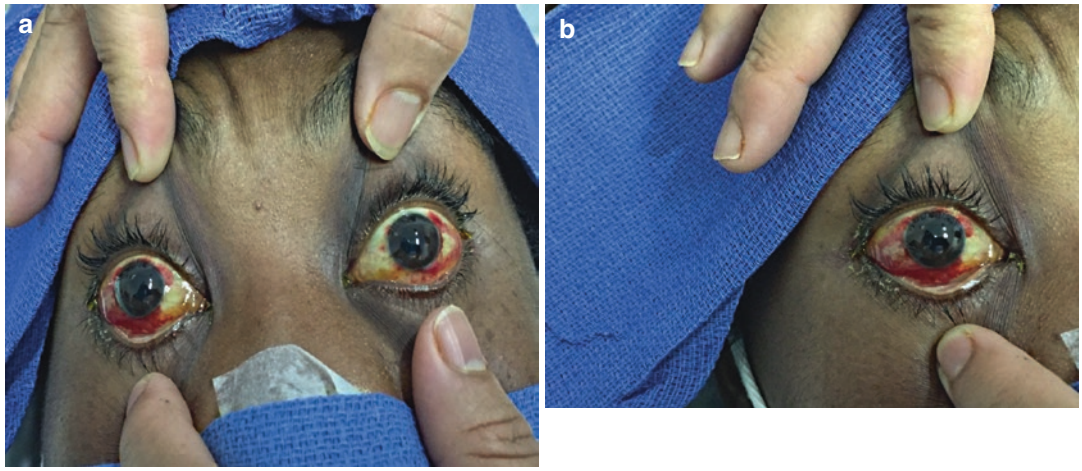


Fig. 60.3 (**a, b**) Conjunctival suffusion

leptospirosis ceased to be a reportable disease nationally in 1995 but remains reportable in Hawaii. A leptospirosis outbreak was also reported among adventure race participants in Florida [2].

In the tropics, endemic leptospirosis is mainly a disease of poverty (including low education, poor housing, absence of sanitation, and poor income). It is acquired through occupational exposure such as subsistence farming and living in rodent-infested, flood-prone urban slums. Large outbreaks affecting thousands of people and leading to hundreds of deaths are common occurrences. These are often associated with increased rainfall or flooding, such as was the case in epidemics in Guyana and Queensland, Australia [3]. Disease in humans is often sporadic, although outbreaks may occur from common source exposures. See Table 60.1 for risk factors for infection.

Physicians caring for travelers following return from vacations involving recreational activities associated with potential environmental *Leptospira* exposure in high-risk regions such as Southeast Asia should consider the possibility of leptospirosis [4–6].

Table 60.1 Risk factors for leptospirosis infection

Occupational exposure:	Farmers, ranchers, abattoir workers, trappers, veterinarians, loggers, sewer workers, rice farmers, pet traders, military personnel, laboratory workers
Recreational activities:	Freshwater swimming, canoeing, kayaking, trail biking
Household exposure:	Pet dogs, domesticated livestock, rainwater catchment systems, infestation by infected rodents
Other:	Walking barefoot through surface water, skin lesions, contact with wild rodents, accidental laboratory exposure

Microbiology

The genus *Leptospira* contains 20 species; nine are regarded as pathogenic (*Leptospira interrogans*, *L. kirschneri*, *L. noguchii*, *L. alexanderi*, *L. weilii*, *L. alstonii*, *L. borgpetersenii*, *L. santarosai, and L. kmety*. Five are of intermediate or unclear pathogenicity and the remaining six are nonpathogenic free-living saprophytic species that do not infect animal hosts.

Leptospira are spiral-shaped, highly motile aerobic spirochetes and are best visualized by dark field microscopy, silver stain, or fluorescent microscopy. They can be distinguished morphologically from other spirochetes by their unique "question mark" hook at the end of the bacterium [6–8].

Pathogenic *Leptospira* spp can be grown in vitro from clinical specimens including blood, urine, and cerebrospinal fluid (CSF). Special media are required for isolation such as Fletcher's, Ellinghausen-McCullough-Johnson-Harris

(EMJH) or polysorbate 80 media. Therefore, the laboratory needs to be notified if an attempt to isolate leptospires is desired. Growth is usually observed in 1–2 weeks but may take up to 3 months. A method of growing leptospires on solid agar has been developed to facilitate more rapid growth, isolation of single colonies, and simple antimicrobial sensitivity testing [6–8].

Clinical Presentation

Most cases of Leptospirosis are mild and self-limited or subclinical, while some are severe and potentially fatal. The majority of patients describe an abrupt onset of fever, rigors, myalgias, and headache in 75–100 % of patients, following an incubation period of 2–26 days (average 10 days). Nonproductive cough occurs in 25–35 % of cases; nausea, vomiting, and diarrhea occur in approximately 50 % of cases [8, 9].

Less common symptoms include arthralgias, bone pain, sore throat, and abdominal pain. Acalculous cholecystitis and pancreatitis have been described in children. Leptospirosis has been described as a biphasic illness (with an acute bacteremic phase followed by an "immune" phase) but, clinically, the two phases usually merge, particularly in severe disease [8–10].

Conjunctival suffusion is an important but frequently overlooked sign; in one case series, it occurred in 55 % of patients. This is not a common finding in other infectious diseases, and its presence in a patient with a nonspecific febrile illness should raise the possibility of leptospirosis. Muscle tenderness, splenomegaly, lymphadenopathy, pharyngitis, hepatomegaly, muscle rigidity, abnormal respiratory auscultation, or skin rash occur in 7–40 % of patients [9, 10]. Aseptic meningitis is observed in 50–85 % of patients if cerebrospinal fluid (CSF) is examined after 7 days of illness [1].

Severe, potentially fatal illness, "Weil's disease," is characterized by jaundice and renal failure and occurs only in a minority of patients. Pulmonary hemorrhage is a potential complication. Mortality rates in hospitalized patients with leptospirosis range from 4 to 52 % [8–10].

Leptospirosis may be complicated by renal failure, uveitis, pulmonary hemorrhage, acute respiratory distress syndrome (ARDS), myocarditis, and rhabdomyolysis. Renal failure is often nonoliguric and associated with hypokalemia. Supportive renal replacement therapy may be required during the acute phase; renal recovery is generally complete. Liver failure generally is reversible and not a cause of death. Vasculitis with necrosis of extremities may be seen in severe cases [7–9].

Laboratory Presentation

A high index of suspicion is required to make the diagnosis based on epidemiologic exposure and clinical manifestations, since clinical and laboratory findings are nonspecific. The diagnosis is made most frequently by serologic testing. Molecular techniques are promising for rapid diagnosis but are not widely available. The organism can be cultured, but this can take several weeks. A constellation of laboratory findings occurring in the right clinical setting is highly suggestive of a diagnosis of leptospirosis [9, 10].

White blood cell (WBC) counts are generally less than 10,000/microL but may range from 3000 to 26,000/microL; a left shift occurs in about two-thirds of patients. Thrombocytopenia can occur; in one series of 79 patients with leptospirosis in Thailand, it was present in 38 % of cases. Pancytopenia has been reported as the presenting manifestation in case reports [8, 10, 11].

Hyponatremia is common in severe leptospirosis and results from sodium wasting. Urinalysis frequently shows proteinuria, pyuria, granular casts, and occasionally microscopic hematuria. Renal failure may be observed in severe leptospirosis. Elevated creatine kinase is observed in approximately 50 % of patients and may be a useful clue to diagnosis.

Approximately 40 % of patients have minimal to moderate elevations of hepatic transaminases (usually <200 IU/L). Jaundice may be observed in severe leptospirosis. In some cases, the serum bilirubin concentration reaches 60–80 mg/dL (1026–1368 mmol/L).

The CSF may show a lymphocytic or neutrophilic pleocytosis with minimal to moderately elevated protein concentrations and normal glucose concentration; a low glucose concentration is seen rarely.

Chest radiography may demonstrate small nodular densities, which can progress to confluent consolidation or a ground glass appearance. Pathologically, these infiltrates may represent alveolar hemorrhage, ARDS, or pulmonary edema.

Findings associated with adverse outcomes include oliguria, WBC count above 12,900/mm^3, repolarization abnormalities on electrocardiogram, and alveolar infiltrates on chest radiography.

Differential Diagnosis

Conjunctival suffusion, when it occurs, is one of the most reliable distinguishing features since it rarely occurs with any infectious illness other than leptospirosis. Differential diagnosis includes:

1. Malaria and dengue share some common clinical features and similar endemic patterns with leptospirosis.
2. Scrub typhus is a common disease in some tropical regions where leptospirosis also occurs.
3. Other rickettsial disease, infections with Rickettsia typhi (murine typhus), or spotted fever group rickettsiae may mimic leptospirosis.
4. Leptospirosis may mimic infection with Salmonella typhi in areas of the tropics where typhoid fever is common, particularly in patients with prominent gastrointestinal complaints.
5. Ehrlichiosis may present with similar clinical manifestations, including fever and nonspecific complaints.
6. Acute viral illnesses including influenza may mimic leptospirosis, particularly in patients with prominent respiratory tract symptoms.
7. Hantavirus can cause a renal syndrome and/or pulmonary syndrome similar to the renal and/or pulmonary complications observed in leptospirosis.

Antibiotic Administration

In the setting of moderate or high clinical suspicion for leptospirosis in the absence of a definitive laboratory diagnosis, administration of empiric treatment is appropriate.

Outpatients with Mild Disease

Doxycycline (adults: 100 mg orally twice daily; children ≥8 years of age: 2 mg/kg per day in two equally divided doses, not to exceed 200 mg daily).

Azithromycin (adults: 500 mg orally once daily for 3 days; children: 10 mg/kg orally on day one [maximum dose 500 mg/day] followed by 5 mg/kg/day orally once daily on subsequent days [maximum dose 250 mg/day]).

Pregnant women, we favor treatment with either azithromycin or Amoxicillin (25–50 mg/kg in three equally divided doses, maximum 500 mg/dose).

Hospitalized Adults with Severe Disease

Penicillin (1.5 million units intravenously [IV] every 6 h)

Doxycycline (100 mg IV twice daily)

Ceftriaxone (1–2 g IV once daily), or Cefotaxime (1 g IV every 6 h).

The duration of treatment in severe disease is usually 7 days. Studies from Thailand have noted comparable efficacy for penicillin, ceftriaxone, cefotaxime, and doxycycline for treatment of leptospirosis. Pregnant women with severe leptospirosis may be treated with penicillin, ceftriaxone, cefotaxime, or azithromycin; but doxycycline should not be used.

Penicillin and cephalosporins lack activity against rickettsiae and so should be avoided in circumstances in which leptospirosis cannot be definitively distinguished from rickettsial infection. Intravenous doxycycline is an appropriate therapy for treatment of severely ill patients in areas endemic for both leptospirosis and rickettsial infection. A Jarisch-Herxheimer reaction may occur following antimicrobial therapy for leptospirosis; this represents an acute inflammatory response to clearance of spirochetes from the circulation and is characterized clinically by fever, rigors, and hypotension [11–13].

Evidence Contour

Diagnostic Tools

Reference Standard

The only inconvenience is that is no available in all centers. There is the lack of a sensitve reference standard for the diagnosis of leptospirosis. The microscopic agglutination test (MAT) and culture are both imperfect, either alone or in combination. This limitation has important implications for the assessment of new assays, as they may perform poorly compared with the reference standards used, even if they are superior to it. MAT is positive when is >1/100.

Serology

Serology is less sensitive than the MAT. Serological tests are used most frequently for diagnosis of leptospirosis. Assays include the microscopic agglutination test, macroscopic agglutination test, indirect hemagglutination, and enzyme-linked immunosorbent assay (ELISA). A number of rapid IgM ELISA and lateral flow tests have been developed, though many have been inadequately validated and their diagnostic performance in an endemic setting is variable.

Molecular Tests

Molecular tests are more sensitive than the cultures. Molecular techniques such as real time PCR and loop-mediated isothermal amplification (LAMP) have been developed for diagnosis of leptospirosis. These are not widely available but are promising for rapid, accurate diagnosis. Next-generation sequencing is a technology for determining DNA sequence by analyzing multiple DNA fragments in parallel; it allows sequencing of an exponentially greater number of genes than conventional DNA sequencing.

Culture

We use Fletcher medium. Organism growth can be very slow, to 4 months. Leptospirosis can be confirmed by culture of the organism from clinical specimens in appropriate media if antibiotic therapy has not been administered before samples are taken. Blood and CSF specimens are generally positive during the first 10 days of the illness. Blood culture is insensitive; isolation of the organism is successful in 5–50 % of cases, and may take several weeks. Urine cultures become positive during the second week of the illness and remain positive for up to 30 days after the resolution of symptoms.

Drug Resistance

Activity against leptospires has been observed in vitro and in animal models for penicillins, cephalosporins, tetracyclines, chloramphenicol, fluoroquinolones, macrolides, and telithromycin, and in vitro studies have demonstrated that carbapenems and aztreonam also have excellent activity against leptospires. Antibiotic susceptibility testing is not done routinely as it is difficult to do and, thus far, resistance does not appear to be a problem based on susceptibility studies that have been done as well as favorable clinical response to the antibiotics generally used for treatment. The development of a new solid media (LVW) for leptospirosis may facilitate more routine testing, which may enable quicker identification of drug resistance should it arise in the setting of inadequate clinical response.

Role of Corticosteroids

The use of corticosteroids has been proposed as potentially beneficial given the vasculitic nature of severe leptospirosis, particularly in the setting

of pulmonary involvement. Some reports have suggested a possible benefit to use of steroids as an adjunct to antibiotic therapy in severe disease. There is insufficient evidence to support the routine use of corticosteroids.

Prevention

No Human vaccine is available. Control measures for preventing human leptospirosis include avoiding potential sources of infection such as stagnant water and animal farm water runoff, rodent control, and protection of food from animal contamination. The CDC recommends doxycycline 200 mg orally per week, begun 1–2 days before and continuing through the period of exposure for people at high risk of leptospirosis.

References

1. Hartskeerl RA, Collares-Pereira M, Ellis WA. Emergence, control and re-emerging leptospirosis: dynamics of infection in the changing world. Clin Microbiol Infect. 2011;17:494.
2. Stern EJ, Galloway R, Shadomy SV, et al. Outbreak of leptospirosis among adventure race participants in Florida, 2005. Clin Infect Dis. 2010;50:843.
3. Smith JK, Young MM, Wilson KL, Craig SB. Leptospirosis following a major flood in Central Queensland, Australia. Epidemiol Infect. 2013; 141:585.
4. Jesus MS, Silva LA, Lima KM, Fernandes OC. Cases distribution of leptospirosis in City of Manaus, State of Amazonas, Brazil, 2000–2010. Rev Soc Bras Med Trop. 2012;45:713.
5. Reis RB, Ribeiro GS, Felzemburgh RD, et al. Impact of environment and social gradient on Leptospira infection in urban slums. PLoS Negl Trop Dis. 2008;2:e228.
6. Kawaguchi L, Sengkeopraseuth B, Tsuyuoka R, et al. Seroprevalence of leptospirosis and risk factor analysis in flood-prone rural areas in Lao PDR. Am J Trop Med Hyg. 2008;78:957.
7. Miyazato KE, Fonseca A, Caputto LZ, et al. Incidence of Leptospirosis infection in the East Zone of Sao Paulo City. Brazil Int Arch Med. 2013;6:23.
8. Dechet AM, Parsons M, Rambaran M, et al. Leptospirosis outbreak following severe flooding: a rapid assessment and mass prophylaxis campaign; Guyana, January-February 2005. PLoS One. 2012;7:e39672.
9. Thaipadungpanit J, Wuthiekanun V, Chierakul W, et al. A dominant clone of Leptospira interrogans associated with an outbreak of human leptospirosis in Thailand. PLoS Negl Trop Dis. 2007;1:e56.
10. Nardone A, Capek I, Baranton G, et al. Risk factors for leptospirosis in metropolitan France: results of a national case–control study, 1999–2000. Clin Infect Dis. 2004;39:751.
11. Wilson MR, Naccache SN, Samayoa E, et al. Actionable diagnosis of neuroleptospirosis by next-generation sequencing. N Engl J Med. 2014;370:2408.
12. André-Fontaine G, Branger C, Gray AW, Klaasen HL. Comparison of the efficacy of three commercial bacterins in preventing canine leptospirosis. Vet Rec. 2003;153:165.
13. Hancock GA, Wilks CR, Kotiw M, Allen JD. The long term efficacy of a hardjo-pomona vaccine in preventing leptospiruria in cattle exposed to natural challenge with Leptospira interrogans serovar hardjo. Aust Vet J. 1984;61:54.

Part VIII

Gastrointestinal Disease

Robert C. Hyzy

Management of Acute Upper Gastrointestinal Hemorrhage

61

David Schrift and Carol H. Choe

Case Presentation

A 45 year-old male with a past medical history notable for hypertension and atrial fibrillation on warfarin presented to the emergency department with syncope. On taking his history he noted 2 days of black stools. He denied vomiting, abdominal pain or bright red blood per rectum. The patient's blood pressure was 95/60 and his heart rate was 120. He was ill appearing with conjunctival pallor and melena on rectal exam. Labs were notable for a hemoglobin (Hgb) of 7.6 g/dL, blood urea nitrogen (BUN) 60, serum creatinine (sCr) 1.3, INR 5.6, 325,000 platelet count and 18,000 white cell count. Peripheral intravenous access was obtained and volume resuscitation was begun. At this point, the emergency department consulted the intensivist to assist in the management of this patient.

Question How can this patient's coagulopathy be most quickly reversed?

Answer Four-factor prothrombin complex concentrate (PCC).

This patient was given 25-units/kg of four-factor PCC and an hour later his INR was 1.2. Simultaneously, he received fluid resuscitation and one unit of blood when his hemoglobin dropped below 7 g/dL. His hemodynamics stabilized and overt evidence of bleeding stopped. An upper endoscopy was then performed that revealed a gastric ulcer with a non-bleeding visible vessel. Intensive proton pump inhibitor therapy was initiated for 72 h. During this time he remained hemodynamically stable without evidence for recurrent bleeding. He was discharged home 4 days after admission.

Principles of Management

Diagnosis

Ascertaining the site of a gastrointestinal bleed (GIB) is crucial to the diagnostic approach, therapeutic management and risk stratification. Sixty-three percent of all patients presenting with an acute GIB will be determined to have an upper gastrointestinal source [1]. The presence of melena on exam or a BUN/sCr ratio >30 are

Electronic supplementary material The online version of this chapter (doi:10.1007/978-3-319-43341-7_61) contains supplementary material, which is available to authorized users.

D. Schrift (✉)
Pulmonary and Critical Care Medicine,
University of South Carolina School of Medicine,
Columbia, SC, USA
e-mail: davidschriftmd@gmail.com

C.H. Choe
Critical Care Medicine, Lexington Medical Center,
West Columbia, SC, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_61

powerful predictors of an UGIB (Table 61.1). However, the BUN/sCr should be used with caution in those with renal or liver disease because it is less reliable in these patients. The clinical factors that substantially decrease the probability of an UGIB are clots in the stool, and a prior history of a LGIB (Table 61.2). A negative NG lavage does not significantly decrease the probability of an UGIB. Hematochezia can be a concerning complaint because it can occur in a severe, brisk UGIB and be misdiagnosed as a LGIB. This emphasizes the need to properly assess the location of bleeding to ensure a severe UGIB is not overlooked.

Table 61.1 Clinical factors that increase the probability of an UGIB

Clinical factor	Pretest probability of an UGIB	Likelihood ratio	Posttest probability of an UGIB
Melena on exam	63 %	25	98 %
BUN/sCr >30	63 %	7.5	93 %
Prior history of UGIB	63 %	6.2	91 %
Subjective melena	63 %	5.5	90 %
Positive NG lavage	63 %	4.7	89 %

Data from Tai et al. [2]

Table 61.2 Clinical factors that decrease the probability of an UGIB

Clinical factor	Pretest probability of an UGIB	Likelihood ratio	Posttest probability of an UGIB
Clots in Stool	63 %	0.05	8 %
Prior history of LGIB	63 %	0.17	22 %
Lack of subjective melena	63 %	0.22	27 %
Negative NG lavage	63 %	0.6	51 %

Data from Tai et al. [2]

Risk Stratification

Risk assessment is uniformly recommended for all UGIB patients to determine the timing of endoscopy and the level of care the patient will need. Factors such as a history of malignancy or cirrhosis, syncope, tachycardia, shock, hemoglobin <8 g/dL, BUN >90 mg/dL and white blood cell count >12,000 all increase the probability of a severe gastrointestinal bleed that will have active bleeding on endoscopy [1]. The Glasgow-Blatchford Score (GBS) is a well-validated clinical score that was developed using many of these clinical factors (Table 61.3) to predict mortality and the need for a clinical intervention (blood transfusion, endoscopic therapy, or surgery). A score ≤2 safely predicts patients that can be managed as an outpatient with a sensitivity ≥98 %. A higher score represents higher risk patients that should receive an endoscopy within 24 h. The Rockall score was developed with the same purpose, but has two main drawbacks. It requires endoscopic information, which is not available

Table 61.3 Glasgow-blatchford score

Admission risk marker	Score value
Blood urea nitrogen (mmol/L)	
6.5–7.9	2
8.0–9.9	3
10.0–24.9	4
≥25.0	6
Hgb (g/dl) for men	
12–12.9	1
10–11.9	3
<10	6
Hgb (g/dl) for women	
10–11.9	1
<10	6
Systolic blood pressure (mm Hg)	
100–109	1
90–99	2
<90	3
Pulse ≥100 (per min)	1
Presentation with melena	1
Presentation with syncope	2
Hepatic disease	2
Cardiac failure	2

on the initial evaluation, and it does not perform as well as the GBS score [1]. For these reasons many professional guidelines recommend using the GBS score [3].

Blood Transfusion

Blood transfusions should generally be withheld until the hemoglobin is ≤7 g/dL [4, 5]. In 2013, a large randomized control trial (RCT) found that patients treated with a restrictive strategy (Hgb <7 g/dL) had better outcomes, including a 40 % relative reduction in mortality, less bleeding, less surgery, fewer transfusion reactions, and fewer cardiac complications. Exsanguinating patients were not enrolled and the protocol allowed blood transfusions in symptomatic patients. Consequently it is important to carefully weigh the clinical situation in the decision to transfuse [6].

Post-endoscopic Intensive Proton Pump Inhibitor Therapy

Patients with a bleeding peptic ulcer and high-risk lesions on endoscopy have improved outcomes when treated with 3 days of intensive proton pump inhibitor (PPI) therapy consisting of an intravenous bolus followed by a continuous infusion for 72 h. A 2006 Cochrane Review found patients with a high-risk peptic ulcer lesion who received PPI therapy had lower rates of rebleeding and surgery. Patients with very high-risk lesions had an even greater benefit from PPI therapy, including a mortality benefit [7]. Lesions are graded using the Forrest classification, and each lesion has a specific rebleeding, surgery and mortality risk (Fig. 61.1). Intensive PPI therapy will have the greatest impact on high-risk lesions because they have the worst outcomes. Low-risk lesions have excellent outcomes so intensive PPI therapy is unlikely to be beneficial. The benefits of intensive PPI therapy are so clear that professional guidelines unanimously recommend them in patients with high-risk peptic ulcer lesions [3–5] (Video 61.1).

Evidence Contour

Nasogastric Lavage

Significant controversy exists regarding nasogastric (NG) lavage in a patient with a GIB. The NG lavage is theorized to help differentiate an UGIB from a LGIB and aid in the timing of endoscopy. However, a systematic review found the NG lavage was a poor predictor of an UGIB. The sensitivity ranged from 42 to 84 % and the specificity ranged from 54 to 91 %. Most importantly, a negative NG lavage was

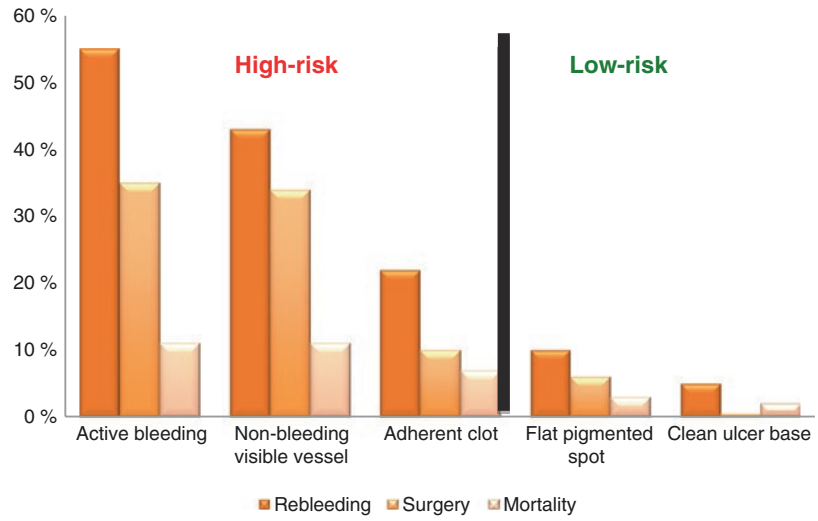


Fig. 61.1 Forrest classification. The risk of rebleeding, surgery and mortality based on the Forrest classification of the ulcer seen on endoscopy. Only high-risk lesions benefit from intensive PPI therapy (Data from Barkun et al. [4])

unable to exclude an UGIB, and this is the main purpose of the procedure [8]. These disappointing results are not that surprising if one considers the limitations of the procedure. False-negative results are known to occur from bleeding duodenal ulcers because the blood may not be able to reflux across the pyloric sphincter. Physicians are also not accurate in detecting bile in the aspirate, which is critical for determining a truly negative lavage. False-positives can come from the trauma of insertion or the subjective interpretation of the aspirate. Is it positive if just a few bloody flecks are seen? Is it positive if it clears with 50 cc of saline? Simply put, the NG lavage cannot rule out an UGIB, and other clinical factors are superior to the NG lavage to confirm or exclude an UGIB.

The second theorized benefit of the NG lavage is to determine who may benefit from early endoscopy. Endoscopy is currently recommended within 24 h for patients with an UGIB. However, very little is known about which patients, if any, would benefit from an urgent endoscopy (within 12 h). Conceptually, patients with bloody NG lavages may have high-risk lesions that could benefit from urgent endoscopy. However, many studies have not found any benefit using the NG lavage to select patients for an urgent endoscopy [2, 9].

Additionally, the NG lavage has been described as the most painful emergency department procedure and is more painful than a lumbar puncture or fracture reduction [10]. NG tubes also have rare complications that include pulmonary malposition, pneumothorax, respiratory failure, perforation, vocal cord injury, pneumonia, epistaxis and death.

In summary, the use of the NG lavage has little diagnostic and prognostic value, does not alter clinical management, and does not improve patient outcomes. Given its lack of value and known risks, the routine use of the NG lavage is not recommended [5].

Optimal Dosing of Post-endoscopic Proton Pump Inhibitor Therapy

As previously mentioned, patients with a high-risk peptic ulcer lesion have a clear benefit from intensive PPI therapy, although the lowest effective PPI dose to achieve these benefits is uncertain. Current guidelines recommend using a high-dose, continuous PPI infusion, but several RCTs and systematic reviews have consistently found a lower-dose PPI regimen (intermittent dosing) is equivalent to a high-dose, continuous infusion. However these RCTs generally lacked the quality and power to definitively conclude that high or low dose PPI regimens are equivalent. It is unlikely that a large-scale RCT will ever be conducted to clarify this topic, although future guidelines may alter this recommendation. [11, 12].

Pre-endoscopic Proton Pump Inhibitor Therapy

The routine use of pre-endoscopic proton pump inhibitors (PPI) has been disproven to offer any benefit to patients with an acute UGIB. A Cochrane Review analyzed six RCTs with over 2000 patients and found no difference in mortality, rebleeding, surgery or blood transfusions [13]. Hence, some professional guidelines have strong recommendations to avoid pre-endoscopic PPIs [14]. PPI therapy is not without potential harm. PPI therapy has been linked to hospital acquired pneumonia, ventilator associated pneumonia, *Clostridium difficile* colitis and spontaneous bacterial peritonitis.

Salvage Therapy

It is generally accepted that patients that develop rebleeding following initial endoscopic therapy should undergo a second endoscopy. If bleeding cannot be controlled or recurs then clinicians should proceed to salvage therapy. Options include trans-arterial embolization (TAE) or emergency surgery. A 2014 meta-analysis found there was no difference in mortality, about 23 % in both groups. Rates of rebleeding were significantly less with surgery (15 %) compared to TAE (25 %). Determining if surgery is better than TAE is still problematic because the quality of published data is poor [15]. A RCT is currently being conducted which may help to resolve this issue (ClinicalTrials.gov NCT00766961). Presently, it

is reasonable to consider TAE prior to surgery because it is less invasive and still has a 75 % success rate. Most major guidelines also recommend considering TAE as an alternative to emergency surgery, but recognize the lack of high quality data to guide decision-making [3–5]. When a patient requires salvage therapy we recommend simultaneously consulting surgery and interventional radiology to determine the best course of action.

Reversal of Coagulopathy and Thrombocytopenia

It may seem axiomatic that coagulopathic patients with an acute UGIB will experience more bleeding complications. However, few studies exist on this topic and what has been published does not show an increase in bleeding complications [16, 17]. In contrast, the reversal of a coagulopathic patient places them at risk for thromboembolic events. Pending additional data, guidelines based on expert opinion still recommend reversing coagulopathic patients having an acute UGIB [4]. Despite this recommendation, there is no consensus for the INR or platelet level that should be targeted [4]. One guideline, based on expert opinion, recommends targeting a platelet count ≥50,000 and an INR ≤1.5 [18].

Reversal of Warfarin

Vitamin K supplementation can reverse and bypass the effects of warfarin. Multiple RCTs have found IV vitamin K can substantially reduce the INR level in 8–12 h, but it is unlikely to normalize the INR by 24 h [19]. Despite a 0.03 % risk of anaphylaxis, IV vitamin K should be given to reverse warfarin-related coagulopathies in any patient with serious bleeding [20]. Due to its delayed and incomplete effects, vitamin K should be used to supplement more immediate forms of reversal. The optimal dose is suggested to be 5–10 mg [21].

Fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC) are the two main options to rapidly normalize an elevated INR due to warfarin. Reversal with FFP often requires large volumes, requires ABO compatibility testing and can take several hours to infuse. FFP can also cause transfusion reactions and volume overload. PCC contains factors II, IX and X and the absence or presence of factor VII classifies the PCC as a three or four-factor PCC. PCC is much more concentrated, requires much less volume, does not require ABO compatibility testing and does not need to be thawed. In clinical trials, PCC has resulted in much faster normalization of the INR, less volume administered and improved outcomes compared to FFP [22].

Four-factor PCC is preferable to three-factor PCC because it is more reliable across INR ranges. The dosing of three and four-factor PCC ranges between 25 and 50 units/kg and depends on the baseline INR. A 25-unit/kg dose will likely be effective for modest elevations of the INR, but a 50-unit/kg dose will be needed for extreme elevations in the INR. Alternatively, a 25-unit/kg dose of PCC can be given and repeated if the INR does not normalize with the first dose [21].

Reversal of Newer Oral Anticoagulants

Dabigatran has a short half-life. Patients with renal failure may have high drug levels and/or a prolonged clearance time [23]. The activated partial thromboplastin time (aPTT) can be useful as a normal aPTT excludes significant levels of dabigatran [24]. In patient with normal renal function and in patients with renal failure who only exhibit mild to moderate bleeding, bleeding may be managed by withholding dabigatran and allowing it to fully clear rather than attempting reversal. In renal failure patients with severe, persistent bleeding, an attempt at reversal can be made although reversal strategies are largely unproven. aPCC seems to be the best choice for the reversal of dabigatran. If aPCC is not available, then four-factor PCC can be used [25]. Both agents may be administered at a dose of 25-unit/kg [26]. If significant bleeding persists and coagulation markers have not substantially improved a second dose can be administered. The FDA is fast-tracking an antidote for dabigatran

Table 61.4 Pharmacokinetics of select new oral anticoagulants

Property	Dabigatran	Rivaroxaban
Maximal absorption	2–4 h	2 h
Half-life	14 h	8–9 h
Renal clearance	80 %	36 %
Dialyzable	Yes	No
Half-life in CKD IV patients	28 h	9–10 h

which currently is being studied in a phase III trial (Clinicaltrials.gov NCT02104947).

Rivaroxaban is a direct factor Xa inhibitor, has a shorter half-life than dabigatran, and is not significantly affected by renal failure (Table 61.4). Twelve hours after taking rivaroxaban factor Xa inhibition will fall below 20 %, which is near the bottom of its therapeutic window [27]. For these reasons, the vast majority of UGIB patients on rivaroxaban may be managed by withholding the medication rather than attempting reversal. Rivaroxaban is not dialyzable leaving aPCC, four-factor PCC and rfVIIa as the only agents studied for attempted reversal. An initial 25-units/kg dose of aPCC or PCC can sufficiently reverse rivaroxaban without posing a significant risk of over-correction. If significant bleeding persists and coagulation markers have not substantially improved a second dose of 25 units/kg can be administered.

References

1. Srygley D, Gerardo C, Tran T, Fisher D. Does this patient have a severe upper gastrointestinal bleed? JAMA. 2012;307(10):1072–9.
2. Tai C, Huang S, Wang H, Lee T, Chang C, Tu C, et al. High-risk ED patients with nonvariceal upper gastrointestinal hemorrhage undergoing emergency or urgent endoscopy: a retrospective analysis. Am J Emerg Med. 2007;25:273–8.
3. Sung J, Chan F, Chen M, Ching J, Ho K, Kachintorn U, et al. Asia-Pacific Working Group consensus on non-variceal upper gastrointestinal bleeding. Gut. 2011;60:1170–7.
4. Barkun A, Bardou M, Kuplers E, Sung J, Hunt R, Martel M, Sinclair P, International Consensus Upper Gastrointestinal Bleeding Conference Group. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med. 2010;152:101–13.
5. Laine L, Jensen D. Management of patients with ulcer bleeding. Am J Gastroenterol. 2012;107:345–60.
6. Villanueva C, Colomo A, Bosch A, Concepcion M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:11–21.
7. Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. Cochrane Database Syst Rev. 2006;(1):CD002094.
8. Palamidessi N, Sinert R, Falzon L, Zehtabchi S. Nasogastric aspiration and lavage in emergency department patients with hematochezia or melena without hematemesis. Acad Emerg Med. 2010;17:126–32.
9. Huang E, Karsan S, Kanwal F, Singh I, Makhani M, Spiegel B. Impact of nasogastric lavage on outcomes in acute GI bleeding. Gastrointest Endosc. 2011;74(5):971–80.
10. Singer A, Richman P, Kowalska A, Thode H. Comparison of patient and practitioner assessments of pain from commonly performed emergency department procedures. Ann Emerg Med. 1999;33(6):652–8.
11. Neumann I, Letelier LM, Rada G, Claro JC, Martin J, Howden CW, Yuan Y, Leontiadis GI. Comparison of different regimens of proton pump inhibitors for acute peptic ulcer bleeding. Cochrane Database Syst Rev. 2013;(6):CD007999.
12. Sachar H, Vaidya K, Laine L. Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis. JAMA Intern Med. 2014;174(11):1755–62.
13. Sreedharan A, Martin J, Leontiadis GI, Dorward S, Howden CW, Forman D, et al. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. Cochrane Database Syst Rev. 2010;(7):CD005415.
14. Scottish Intercollegiate Guidelines Network. Management of acute upper and lower gastrointestinal bleeding: a national clinical guideline. 2008;(4.3):13–4.
15. Beggs A, Dilworth M, Powell S, Atherton H, Griffiths E. A systematic review of transarterial embolization versus emergency surgery in treatment of major non-variceal upper gastrointestinal bleeding. Clin Exp Gastroenterol. 2014;7:93–104.
16. Barkun A, Bardou M, Gralnek I, Shingina A, Razzaghi A. T1941 impact of elevated INR and of Low platelet count on outcomes in acute upper GI bleeding [abstract]. Gastroenterol. 2009;136(5):A605.
17. Shingina A, Barkun A, Razzaghi A, Martel M, Bardou M, Gralnek I. RUGBE Investigators Systematic review: the presenting international normalized ratio as a predictor of outcome in patients with upper non-variceal gastrointestinal bleeding. Aliment Pharmacol Ther. 2011;33:1010–8.
18. Stainsby D, MacLennan S, Thomas D, Isaac J, Hamilton P, et al. Guidelines on the management of massive blood loss. Br J Hematol. 2006;135:634–41.

19. Lubetsky A, Yonath H, Olchovsky D, Loebstein R, Halkin H, Ezra D. Comparison of oral vs intravenous phytonadione in patients with excessive anticoagulation. Arch Intern Med. 2003;163(10):2469–73.
20. Riegert-Johnson D, Volcheck G. The incidence of anaphylaxis following intravenous phytonadione: a 5-year retrospective review. Ann Allergy Asthma Immunol. 2002;89:400–6.
21. Holbrook A, Witt D, Fish J, Veenstra D. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl):e152S–84.
22. Karaca M, Erbil B, Ozmen M. Use and effectiveness of prothrombin complex concentrates vs fresh frozen plasma in gastrointestinal hemorrhage due to warfarin usage in the ED. Am J Emerg Med. 2014;32:660–4.
23. Stangier J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet. 2010;49(4):259–68.
24. Lindahl T, Baghael F, Blixter I, Gustafsson K, Stigendal L, Sten-Linder M, et al. Effects of the oral, direct thrombin inhibitor dabigatran on five common coagulation assays. Thromb Haemost. 2011;105:371–8.
25. Lee F, Chan A, Lau K, Chan H. Reversal of New, factor-specific oral anticoagulants by rFVIIa, Prothrombin complex concentrate and activated Prothrombin complex concentrate: a review of animal and human studies. Thromb Res. 2014;133:705–13.
26. Nutescu E, Dager W, Kalus J, Lewin J, Cipolle M. Management of bleeding and reversal strategies for oral anticoagulants: Clinical practice considerations. Am J Health Syst Pharm. 2013;70:e82–97.
27. Kubitza D, Becks M, Wensing G, Voith B, Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939—an oral, direct Factor Xa inhibitor—after multiple dosing in healthy male subjects. Eur J Clin Pharmacol. 2005;61:873–80.

Variceal Hemorrhage

62

Elizabeth A. Belloli and Steven E. Gay

Case Presentation

A 33 year old man with history of alcoholic cirrhosis complicated by esophageal varices, recent alcoholic hepatitis, and gastroesophageal reflux disease presented to the Emergency Department with lightheadedness and melena. Initial vital signs showed a temperature of 36.6, BP 128/65, HR 113, RR 24, and SpO2 100 %. During evaluation in the Emergency Department, he developed large-volume hematemesis and hypotension. Labs initially demonstrated a hemoglobin of 7.0, platelets 255, INR 1.5, and total bilirubin 36. A nasogastric tube was inserted with return of more than 1 L of blood.

Question How Should This Patient be Managed?

Answer Patients with presumed variceal bleeding and increasing instability will require two primary steps in management: (1) Aggressive hemodynamic resuscitation with both volume and blood products, and (2) Hemostasis of the bleeding site which may include vasoconstrictor therapy and endoscopic intervention.

In this patient, two large bore intravenous lines were placed and intravenous fluids and packed red blood cells were transfused. Pantoprazole and octreotide continuous infusions were initiated. The patient was emergently intubated and sedated prior to endoscopy. A massive resuscitation protocol was initiated. The patient's condition worsened with hypovolemic shock leading to a 2-min episode of pulseless electrical activity which resolved with one dose of atropine, epinephrine and brief chest compressions. A Sengstaken-Blakemore tube was placed with inflation of the esophageal and gastric balloons. Erythromycin was administered as a bolus prior to endoscopy. Esophagogastroduodenoscopy (EGD) revealed massive edema and copious bright red blood in the oropharynx with large amounts of clotted blood in the entire esophagus. The scope could not be advanced past the distal esophagus due to abundant clot. No clear bleeding source was visualized, but variceal bleeding was assumed to be the etiology. The Sengstaken-Blakemore tube was replaced. Ceftriaxone was started for infection prophylaxis. Throughout this time, the patient

Electronic supplementary material The online version of this chapter (doi:10.1007/978-3-319-43341-7_62) contains supplementary material, which is available to authorized users.

E.A. Belloli (✉)
Internal Medicine, Division of Pulmonary & Critical Care Medicine, University of Michigan Health System, Ann Arbor, MI, USA
e-mail: bellolie@med.umich.edu

S.E. Gay
Division of Pulmonary & Critical Care Medicine, University of Michigan Health System, Ann Arbor, MI, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_62

received nine units of packed red blood cells, five units of fresh frozen plasma, and 1 5-pack of platelets through a rapid infuser.

The patient underwent emergent transjugular intrahepatic portosystemic shunt (TIPS) placement. His condition stabilized in the following day. Diuresis was performed in the subsequent days, and he was extubated 5 days after initial presentation. Unfortunately although he survived his initial episode of massive variceal bleed, the patient experienced multiple episodes of recurrent bleeding in the following weeks requiring repeat endoscopies and variceal ligation. He also underwent a TIPS revision. Despite interventions, the patient continued to have frequent episodes of variceal hemorrhage and was not a liver transplant candidate. He eventually changed his goals of care to comfort and was allowed to die.

Principles of Management

Initial Resuscitation

The initial resuscitation of a patient with suspected variceal bleeding *must* occur expediently. Multiple large bore intravenous catheters should be inserted as soon as possible with subsequent administration of fluids to maintain perfusion. The need for packed red blood cell transfusion should be assessed. Discussion of transfusion thresholds and indications for crystalloid versus colloid therapies will occur in the Evidence Contour.

In patients with massive blood loss, variably defined as loss of the entire blood volume in a 24-h period, loss of 50 % of the blood volume in a 3-h period, or transfusion of ≥ ten units of packed red blood cells in 24 h, a number of other possible complications may occur in the setting of massive transfusion [1, 2]. Hypothermia and metabolic acidosis are frequent, and in the setting of massive transfusion are known risk factors for worsening coagulopathy. While this relationship has mostly been defined in trauma patients without underlying liver disease [3], the data can potentially be extrapolated to the cirrhotic population. Patients with variceal bleeding that receive massive transfusion should have temperature monitoring performed, and hypothermia should be expected and prevented. While some causes of metabolic acidosis may be inevitable, the critical care provider should aim to avoid iatrogenic causes of metabolic acidosis such as hyperchloremic acidosis secondary to aggressive normal saline administration. Worsening of coagulopathy may also occur, and this issue will be addressed in a future section.

Vasoactive Medications

Routine management of suspected gastroesophageal variceal bleeding includes immediate administration of a splanchnic vasoconstrictor, prior to endoscopy if possible [4]. The most commonly used medications are terlipressin, somatostatin and octreotide. Use of vasopressin is limited by side effects of peripheral, cardiac and bowel ischemia [4]. A meta-analysis published in 2012 suggested that vasoactive agents significantly decrease 7-day mortality, improve likelihood of hemostasis, decrease transfusion requirements and decrease hospital length of stay [5]. Hemostasis was better with octreotide compared to vasopressin. A large randomized study found terlipressin, somatostatin, and octreotide to be equivalent in efficacy with no significant differences between groups in rates of re-bleeding or mortality [6]. Currently, octreotide and vasopressin are the only medications available in the United States for this indication. Octreotide is most commonly used. Typically, these agents are continued for 5 days as re-bleeding risk is highest during this time period (Table 62.1) [4, 7].

Hemostasis Interventions

Emergent endoscopy should be performed within 12 h of presentation in patients suspected of having active gastroesophageal variceal bleeding (Fig. 62.1) [8, 9]. Multiple studies have demonstrated endoscopic variceal ligation is superior to endoscopic sclerotherapy [8]. A meta-analysis of seven studies revealed that ligation therapy

Table 62.1 Vasoconstrictor agents used for variceal hemorrhage

Agent	Dose	Mechanism of action	Length of therapy	Notes
Octreotide	50 μg bolus IV; then 50 μg/h continuous infusion	Somatostatin analogue	3–5 days	May result in tachyphylaxis Most commonly used in U.S.
Somatostatin	250 μg bolus IV; then 250 μg/h continuous infusion	Inhibits release of vasodilatory hormones	3–5 days	Hormones inhibited include glucagon, insulin, serotonin, acetylcholine
Terlipressin	2 mg IV every 4 h; may decrease to 1 mg every 4 h when hemorrhage controlled	Synthetic vasopressin analogue	3–5 days	Longer half-life allows intermittent therapy Not available in U.S.
Vasopressin	0.4 unit bolus IV; then 0.4–1.0 units/min	Vasoconstricts mesenteric arterioles	3–5 days	Higher risk of extrasplanchnic ischemic side effects May administer with IV Nitroglycerin to decrease side effect risks Rarely used in U.S.

Data from Refs. [4, 6, 7]

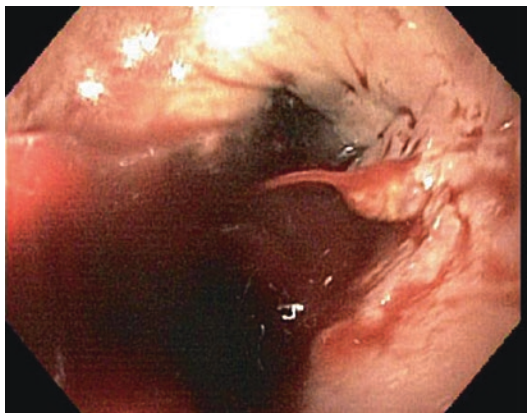


Fig. 62.1 Esophageal varix with active bleeding as seen during EGD

compared to sclerotherapy results in a similar rate of hemostasis, but significantly less re-bleeding and lower mortality [10]. Sclerotherapy is more commonly used when variceal ligation is technically difficult or as a rescue procedure.

Transjugular Intrahepatic Portosystemic Shunt

Approximately 10–20 % of patients will fail standard medical therapy for acute variceal bleeding [11]. Risk factors for treatment failure in the first 5 days following initial hemostasis include low systolic blood pressure at presentation, active bleeding at endoscopy, bleeding from gastric varices, and higher Child-Pugh grades [6]. Placement of a transjugular intrahepatic portosystemic shunt (TIPS), a stent connecting the portal and hepatic veins, results in a decreased portal pressure gradient and is commonly used as rescue therapy in patients in whom initial hemostasis is not achieved and in patients with recurrent variceal bleeding following initial hemostasis (Fig. 62.2) [12]. One potential complication of TIPS placement is thrombus formation in the stent. The use of coated stents recently has seemed to decrease the rate of this event [11]. The interventional radiologist may also place coils or apply sclerosant to varices directly at the time of TIPS placement (Fig. 62.3 and Video 62.1).

Antibiotic Prophylaxis

Prevention of complications such as worsening hepatic function, renal dysfunction and bacterial infections may improve survival following an acute bleeding episode [13]. The most common

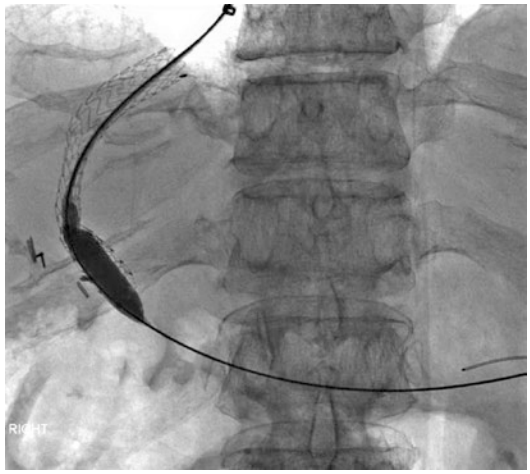


Fig. 62.2 A TIPS stent has been inserted to connect the right hepatic and right portal veins. The stent is post-dilated to ensure adequate flow (Images courtesy of Dr. Bill Majdalany of the University of Michigan)

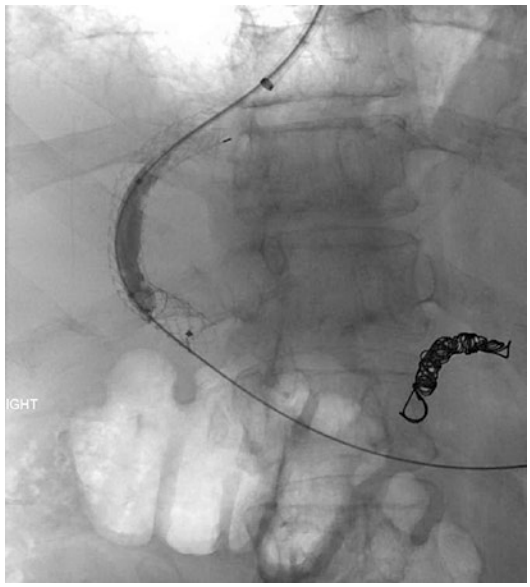


Fig. 62.3 Coil embolization of the gastric coronary varix seen in Fig. 62.3 has now been performed (Images courtesy of Dr. Bill Majdalany of the University of Michigan)

infections include bacteremia, urinary tract infections and spontaneous bacterial peritonitis [14]. Antibiotic prophylaxis in the peri-bleed period has been shown to decrease all-cause mortality by 20% and also decreases overall re-bleeding episodes [15]. Cephalosporins and quinolones are the most effective therapies. Antibiotics should routinely be administered to patients with acute variceal hemorrhage [9].

Evidence Contour

While certain therapies are proven in variceal bleeding, others are performed according to expert recommendations or guidelines and are more controversial. A discussion of these management strategies will follow.

Red Blood Cell Transfusion

The threshold for transfusion in actively bleeding patients has been debated throughout the years. In 2013, a landmark trial demonstrated the utility of a restrictive transfusion protocol in patients with suspected upper gastrointestinal bleeding. A restrictive protocol (transfusion for hemoglobin <7.0) as compared to a liberal protocol (transfusion for hemoglobin <9.0) resulted in a lower 45-day mortality rate (5% versus 9%, p=0.02), lower risk of further bleeding, lower likelihood of requiring rescue therapies, and a lower rate of complications including pulmonary edema and transfusion reactions. The authors postulated that the increase in mean hepatic venous pressure gradient in the liberal group likely contributed to these findings [16]. Of note, only around a quarter of the patients in this study had variceal bleeding. Furthermore, patients with poorly defined "massive exsanguinating bleeding" were excluded from this study. In general, a goal hemoglobin level of 7.0 is reasonable in patients with variceal bleeding for these reasons, although in the setting of massive exsanguination, red blood cell transfusion should not be directed at a hemoglobin level but should be based on the clinical situation.

There have been no randomized, controlled trials evaluating the administration of crystalloid compared to colloid fluids in patients with acute variceal bleeding. However, in other patient populations with hemorrhagic shock, colloid fluids such as albumin or hetastarch have no advantage

compared to crystalloids [17]. In the cirrhotic patient population with variceal bleeding, it is reasonable to transfuse red blood cells if the hemoglobin is less than 7.0 and crystalloid fluids when the hemoglobin is 7.0 or greater and the patient has signs of hypoperfusion.

Correction of Coagulopathy

Cirrhosis often results in decreased levels of all clotting factors, dysfibrinogenemia, and thrombocytopenia, all of which can contribute to ongoing bleeding. In addition, multiple transfusions can result in a dilutional coagulopathy. Frequent monitoring of prothrombin time, platelet count and fibrinogen levels is warranted.

Unfortunately, prothrombin time has *not* been shown to correlate well with clinical bleeding in cirrhotic patients [18, 19]. No randomized trials of Vitamin K supplementation in patient with variceal bleeding have been performed, and routine use is neither recommended nor discouraged [20]. Providers should aim to avoid over-transfusion solely to correct numerical lab values as this will likely result in higher portal venous pressures and possibly more bleeding. Recommendations for a threshold at which to transfuse fresh frozen plasma, cryoprecipitate and platelets vary and become even more complicated in the setting of cirrhosis. While trauma literature supports the use of a "massive transfusion protocol," which entails transfusing packed red blood cells, fresh frozen plasma and platelets in a 1:1:1 ratio [2], this strategy has not been tested in a randomized trial of cirrhotic patients with variceal bleeding. It is unknown if this is the correct resuscitation approach in our patient population, and it should not be universally applied.

Recombinant factor VIIa, a product first available for patients with hemophilia-related bleeding, has been considered as an agent that could halt gastrointestinal bleeding in cirrhotic patients by activating the extrinsic pathway and increasing thrombin production. While recombinant activated factor VIIa has been shown to normalize prothrombin time in patients with cirrhosis and variceal bleeding [21], a Cochrane review that included approximately 500 patients with various stages of cirrhosis and active upper gastrointestinal bleeding from two trials did *not* find a mortality benefit when this factor was administered in addition to usual care. Furthermore, there was no significant difference in packed red blood cell transfusion requirement [22]. An exploratory analysis from one of the two trials suggested that the subgroup of patients with variceal bleeding, Child-Pugh scores B or C, and more severe coagulopathy may benefit from recombinant factor VIIa [23]. Therapy with recombinant factor VIIa remains controversial in this setting.

Case reports have described success in achieving hemostasis in cirrhotic patients with the administration of Prothrombin Complex Concentrate (PCC), a mixture of coagulation factors II, VII, IX and X. This agent cannot be recommended on the basis of current evidence [24].

Endotracheal Intubation

Elective intubation has not been proven to improve outcomes or prevent aspiration events or pneumonia in patients undergoing endoscopy in the intensive care unit. A retrospective cohort study compared patients with suspected variceal hemorrhage who underwent elective pre-endoscopy intubation and those who did not. All patients had active bleeding or stigmata suggestive of high risk of bleeding on endoscopy. Patients who underwent elective intubation had higher mortality and higher rates of aspiration pneumonia. However, patients with a known aspiration event prior to presentation, respiratory distress, intoxication, or hepatic encephalopathy greater than stage 1 were excluded. Patients who were alert at the time of endoscopy protected their own airways better [25].

In another retrospective study, pre-endoscopy intubation did not change the likelihood of witnessed aspiration during EGD, new radiographic infiltrates post-EGD, hospital length of stay, or mortality [26], although it may have prevented massive aspiration events. To this date, no prospective randomized trial has been performed to truly demonstrate the utility or lack thereof of

pre-endoscopy elective intubation. Intubation prior to endoscopic therapy should not routinely be employed and should be carefully considered for each individual patient with hemodynamics, mental status and respiratory status in mind.

Acid Suppression

Proton pump inhibitor administration following esophageal variceal ligation has been demonstrated to speed the resolution of post-ligation ulcer healing [27], but their use has been challenged [28]. In a retrospective cohort study, prolonged infusion of proton pump inhibitors in addition to octreotide infusion was compared to short term infusion. No difference in transfusion requirements or mortality rate was observed [29]. However longer proton pump inhibitor infusions may have been selectively administered to patients who were more critically ill, biasing the results.

A randomized trial examined whether patients who had successful control of variceal bleeding with ligation have improved hemostasis with continued octreotide infusion versus proton pump inhibitor infusion alone. In this study, there was no significant difference in treatment failure, transfusion requirements or mortality in the two groups. These authors suggest that proton pump inhibitor therapy following successful variceal ligation may be substituted for vasoconstrictor therapy [30]. This observation awaits confirmation.

Balloon Tamponade

In treatment of massive variceal bleeding that fails to respond to medical therapy and endoscopic interventions, the armamentarium of the critical care provider includes mechanical tamponade with the Sengstaken-Blakemore tube (Fig. 62.4). Major complications such as esophageal perforation have limited the use of this device to dire situations [31], and randomized trials of this tube and similar devices are lacking. Experts recommend this therapy be utilized only as a bridge prior to definitive therapies such as TIPS, balloon-occluded retrograde transvenous obliteration (BRTO), or surgery [9].

Transjugular Intrahepatic Portosystemic Shunt

The efficacy of early TIPS placement following endoscopy for acute esophageal variceal bleeding was studied in a select group of cirrhotic patients in a multicenter randomized, controlled trial. Patients were included if they had Child-Pugh class B disease with active bleeding at endoscopy or had Child-Pugh class C disease. The intervention group received TIPS within 72 h of the initial hemorrhage, even if they attained initial hemostasis with medical therapy and endoscopic intervention. Patients who did *not* receive early TIPS were more likely to have failure to control acute bleeding and were more likely to experience clinically significant variceal re-bleeding in the year following enrollment. Early TIPS improved 6-week and 1-year survival [32]. Hence, TIPS placement in all patients at high risk of re-bleeding may be of benefit.

Balloon-Occluded Retrograde Transvenous Obliteration

Management of gastric varices generally entails the same management as esophageal varices [33], but these varices can be refractory to the usual approach. A relatively new technique to target gastric varices is balloon-occluded retrograde transvenous obliteration (BRTO), which makes use of a spontaneously formed portosystemic shunt, the gastrorenal shunt, to perform an intervention. This technique involves accessing either the femoral or internal jugular vein and threading a catheter through the left renal vein to a gastrorenal shunt, and then to the gastric varix where an endovascular sclerosant is injected (Fig. 62.5). There are many versions of this technique depending on patient anatomy [33]. Although not clearly defined, suggested indications for BRTO include actively bleeding gastric varices in patients who

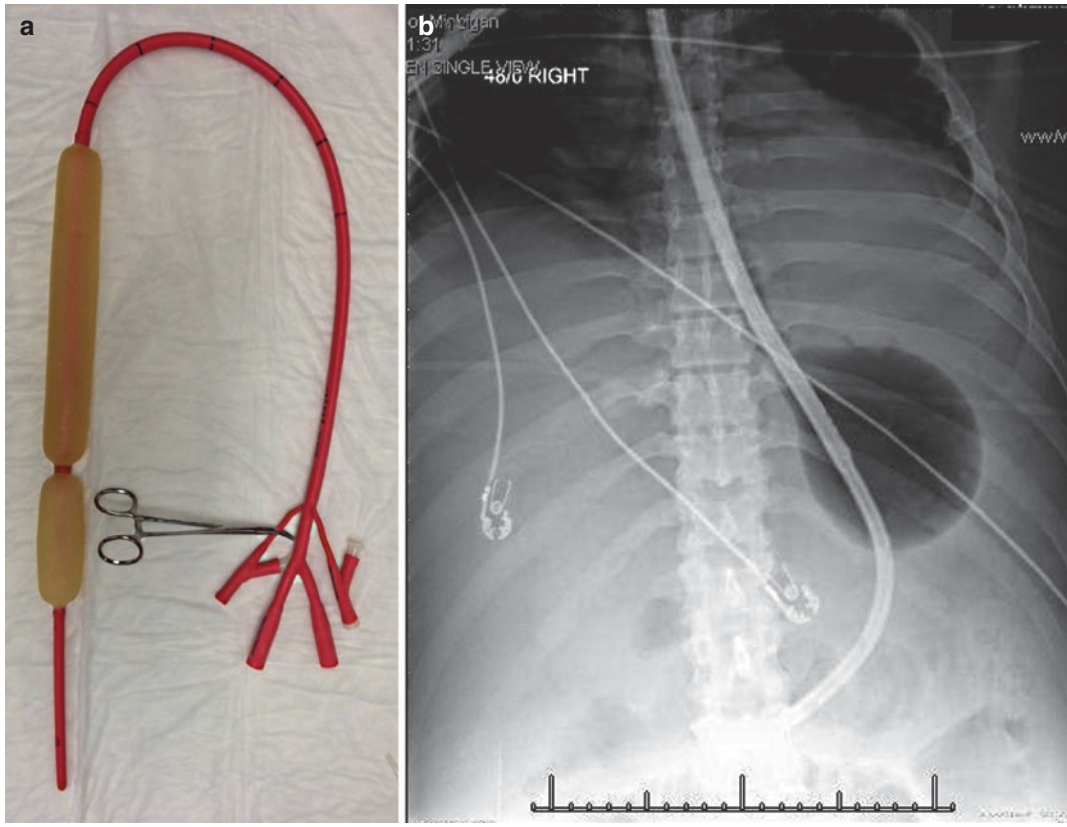


Fig. 62.4 (**a**) A Sengstaken-Blakemore tube is shown. Prior to placement, balloon patency should be confirmed. The tube should be lubricated and then inserted approximately 50 cm into the esophagus and stomach. Insufflation of the gastric suction port should be performed with auscultation over the stomach to ensure proper placement. Then, 50 ccs of air is injected into the gastric balloon. (**b**) An abdominal x-ray is ordered to confirm the gastric balloon is positioned in the stomach. Further steps include traction application to assist with control of bleeding

are poor candidates for TIPS (e.g., Model for End-Stage Liver Disease score >19, encephalopathy, portal vein thrombosis) [33]. An early retrospective study indicates that short-term success rates of TIPS and BRTO are similarly high, with 1-year re-bleeding rates of gastric varices nearly favoring BRTO (0 % vs. 15 %, p = 0.12) [34].

Surgery

When endoscopic therapy fails to control variceal bleeding, the clinician must consider rescue therapies which include TIPS or emergency surgical therapy. The widespread use of TIPS and now BRTO procedures has decreased the use of emergency surgery [9, 11]. Two recent randomized controlled trials, together enrolling more than 350 patients, suggest the role of emergent surgery should not be overlooked. One study compared emergency shunt surgery to emergency sclerotherapy, while the other compared emergency shunt surgery to TIPS. Emergency surgery had significantly higher successful control of bleeding than either TIPS or sclerotherapy. While there was a trend toward higher 14-day mortality in the surgery group, there was significantly better long-term survival in this group. Significantly fewer patients in the surgery group developed recurrent hepatic encephalopathy, and surgery was less costly overall. In patients with life-threatening variceal hemorrhage, a surgeon should be consulted early in the course of care.

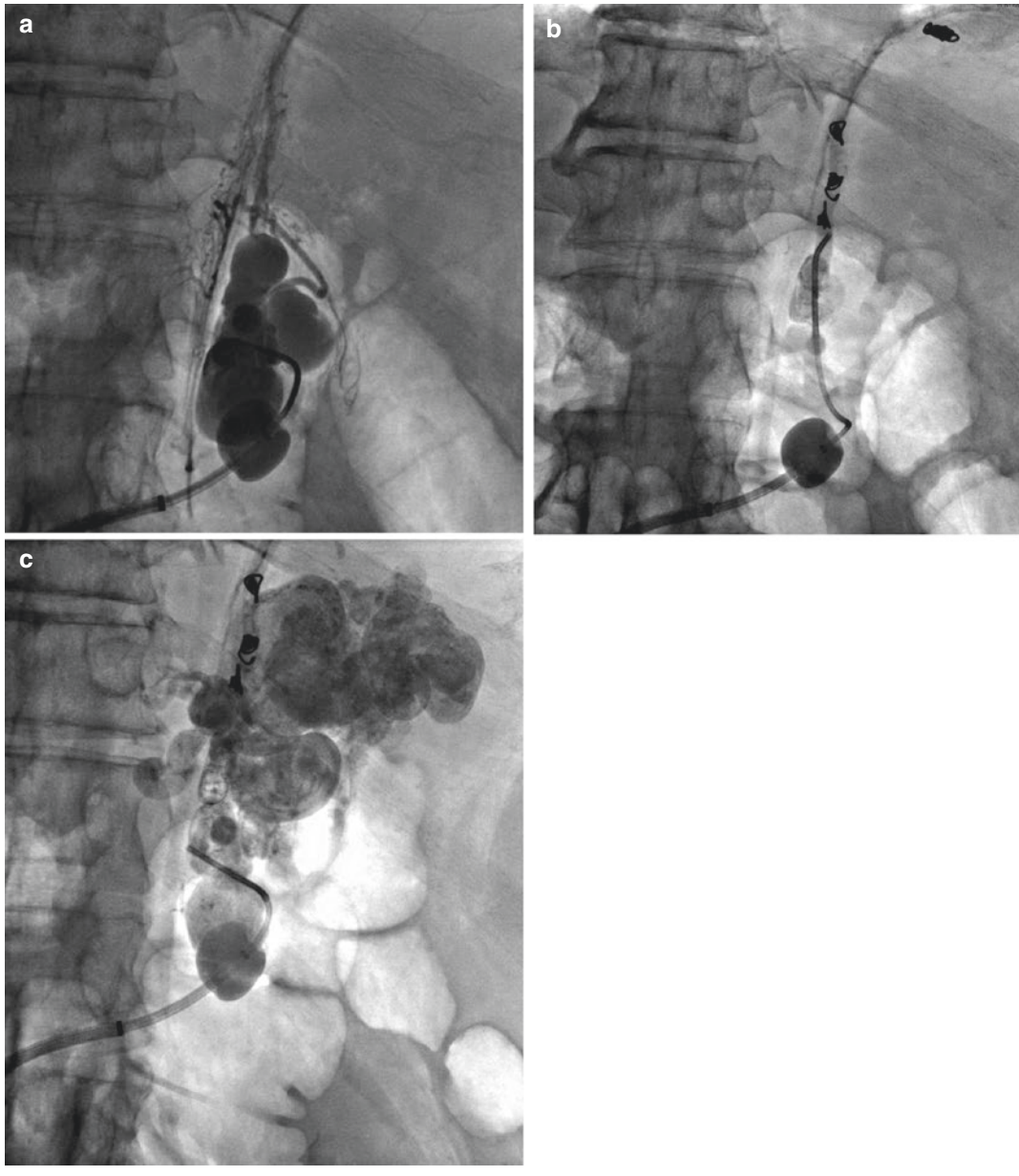


Fig. 62.5 A 66 year old man with cryptogenic cirrhosis with known esophageal and gastric varices presented with hematemesis. A CT angiography demonstrated prominent true gastric varices, and he was referred for a BRTO procedure. (**a**) Angiographic view of a large gastric varix. (**b**) Coils were placed in the phrenic venous circulation to exclude outflow. (**c**) Sclerosant has been injected into the gastric varix. The balloon occlusion catheter is inflated to prevent mobilization of the sclerosant into the venous circulation (*Images courtesy of Dr. Bill Majdalany from the University of Michigan)

References

1. British Committee for Standards in Haematology, Stainsby D, MacLennan S, Thomas D, Isaac J, Hamilton PJ. Guidelines on the management of massive blood loss. Br J Haematol. 2006;135(5):634–41.
2. Waters JH. Role of the massive transfusion protocol in the management of haemorrhagic shock. Br J Anaesth. 2014;113 Suppl 2:ii3–8.
3. Cosgriff N, Moore EE, Sauaia A, Kenny-Moynihan M, Burch JM, Galloway B. Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidoses revisited. J Trauma. 1997;42(5):857–61; discussion 61–2.
4. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W, Practice Guidelines Committee of the American Association for the Study of Liver Disease, Practice Parameters Committee of the American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007;46(3):922–38.
5. Wells M, Chande N, Adams P, Beaton M, Levstik M, Boyce E, et al. Meta-analysis: vasoactive medications for the management of acute variceal bleeds. Aliment Pharmacol Ther. 2012;35(11):1267–78.
6. Seo YS, Park SY, Kim MY, Kim JH, Park JY, Yim HJ, et al. Lack of difference among terlipressin, somatostatin, and octreotide in the control of acute gastroesophageal variceal hemorrhage. Hepatology. 2014; 60(3):954–63.
7. Banares R, Albillos A, Rincon D, Alonso S, Gonzalez M, Ruiz-del-Arbol L, et al. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. Hepatology. 2002;35(3):609–15.
8. Committee ASoP, Hwang JH, Shergill AK, Acosta RD, Chandrasekhara V, Chathadi KV, et al. The role of endoscopy in the management of variceal hemorrhage. Gastrointest Endosc. 2014;80(2):221–7.
9. de Franchis R, Baveno VF. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol. 2010;53(4):762–8.
10. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. Ann Intern Med. 1995; 123(4):280–7.
11. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med. 2010;362(9):823–32.
12. Boyer TD, Haskal ZJ, American Association for the Study of Liver Disease. The role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension. Hepatology. 2005;41(2):386–400.
13. Augustin S, Muntaner L, Altamirano JT, Gonzalez A, Saperas E, Dot J, et al. Predicting early mortality after acute variceal hemorrhage based on classification and regression tree analysis. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2009;7(12):1347–54.
14. Hou MC, Lin HC, Liu TT, Kuo BI, Lee FY, Chang FY, et al. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial. Hepatology. 2004;39(3):746–53.
15. Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila F, Soares-Weiser K, Mendez-Sanchez N, Gluud C, et al. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding – an updated Cochrane review. Aliment Pharmacol Ther. 2011;34(5):509–18.
16. Villanueva C, Colomo A, Bosch A, Concepcion M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368(1):11–21.
17. Lira A, Pinsky MR. Choices in fluid type and volume during resuscitation: impact on patient outcomes. Ann Intensive Care. 2014;4:38.
18. Caldwell SH, Hoffman M, Lisman T, Macik BG, Northup PG, Reddy KR, et al. Coagulation disorders and hemostasis in liver disease: pathophysiology and critical assessment of current management. Hepatology. 2006;44(4):1039–46.
19. Youssef WI, Salazar F, Dasarathy S, Beddow T, Mullen KD. Role of fresh frozen plasma infusion in correction of coagulopathy of chronic liver disease: a dual phase study. Am J Gastroenterol. 2003;98(6):1391–4.
20. Marti-Carvajal AJ, Sola I. Vitamin K for upper gastrointestinal bleeding in patients with acute or chronic liver diseases. Cochrane Database Syst Rev. 2012;(9): CD004792.
21. Ejlersen E, Melsen T, Ingerslev J, Andreasen RB, Vilstrup H. Recombinant activated factor VII (rFVIIa) acutely normalizes prothrombin time in patients with cirrhosis during bleeding from oesophageal varices. Scand J Gastroenterol. 2001;36(10):1081–5.
22. Marti-Carvajal AJ, Karakitsiou DE, Salanti G. Human recombinant activated factor VII for upper gastrointestinal bleeding in patients with liver diseases. Cochrane Database Syst Rev. 2012;(3):CD004887.
23. Bosch J, Thabut D, Bendtsen F, D'Amico G, Albillos A, Gonzalez Abraldes J, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. Gastroenterology. 2004;127(4):1123–30.
24. Patanwala AE, Acquisto NM, Erstad BL. Prothrombin complex concentrate for critical bleeding. Ann Pharmacother. 2011;45(7–8):990–9.
25. Koch DG, Arguedas MR, Fallon MB. Risk of aspiration pneumonia in suspected variceal hemorrhage: the value of prophylactic endotracheal intubation prior to endoscopy. Dig Dis Sci. 2007;52(9):2225–8.
26. Rudolph SJ, Landsverk BK, Freeman ML. Endotracheal intubation for airway protection during endoscopy for severe upper GI hemorrhage. Gastrointest Endosc. 2003;57(1):58–61.
27. Shaheen NJ, Stuart E, Schmitz SM, Mitchell KL, Fried MW, Zacks S, et al. Pantoprazole reduces the size of postbanding ulcers after variceal band ligation: a randomized, controlled trial. Hepatology. 2005; 41(3):588–94.

28. Lo EA, Wilby KJ, Ensom MH. Use of proton pump inhibitors in the management of gastroesophageal varices: a systematic review. Ann Pharmacother. 2015;49(2):207–19.
29. Alaniz C, Mohammad RA, Welage LS. Continuous infusion of pantoprazole with octreotide does not improve management of variceal hemorrhage. Pharmacotherapy. 2009;29(3):248–54.
30. Lo GH, Perng DS, Chang CY, Tai CM, Wang HM, Lin HC. Controlled trial of ligation plus vasoconstrictor versus proton pump inhibitor in the control of acute esophageal variceal bleeding. J Gastroenterol Hepatol. 2013;28(4):684–9.
31. Chojkier M, Conn HO. Esophageal tamponade in the treatment of bleeding varices. A decadel progress report. Dig Dis Sci. 1980;25(4):267–72.
32. Garcia-Pagan JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med. 2010;362(25):2370–9.
33. Saad WE, Simon Jr PO, Rose SC. Balloon-occluded retrograde transvenous obliteration of gastric varices. Cardiovasc Intervent Radiol. 2014;37(2): 299–315.
34. Sabri SS, Abi-Jaoudeh N, Swee W, Saad WE, Turba UC, Caldwell SH, et al. Short-term rebleeding rates for isolated gastric varices managed by transjugular intrahepatic portosystemic shunt versus balloon-occluded retrograde transvenous obliteration. J Vasc Interv Radiol JVIR. 2014;25(3): 355–61.

Acute Pancreatitis

63

Margaret F. Ragland and Curtis H. Weiss

Case Presentation

Mr. Johnson is a 52-year-old man with a history of diabetes mellitus type II and hyperlipidemia who presents to the emergency department with 6 h of severe epigastric pain, nausea, and vomiting. His pain radiates to the back, is worsened with eating, and he had emesis initially of undigested food, now of clear liquid. There is no additional past medical or surgical history. He is intermittently adherent to his prescribed medications, including atorvastatin, metformin, and glipizide. He has no significant family history. He works as a certified public accountant, has an 18 pack-year smoking history, drinks four alcoholic drinks most nights of the week, and uses no recreational drugs.

His temperature is 99.7 °F, blood pressure 152/91, pulse 124 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation 98 % on ambient air. He appears uncomfortable, diaphoretic, has dry mucus membranes, and his abdomen is diffusely tender to palpation, though most notably in the epigastrium and left upper quadrant. Initial laboratory examination is significant for the following: white blood cell count 10.9 cells per microliter (cells/μL), hemoglobin 16.4 g per deciliter, platelets 345 cells/μL, sodium 131 milliequivalents per liter (mEq/L), potassium 3.3 mEq/L, chloride 101 mEq/L, bicarbonate 25 mEq/L, blood urea nitrogen (BUN) 22 mg/dl (mg/dL), creatinine 1.7 mg/dL (his baseline creatinine of 0.9 mg/dL was last measured 2 months ago). Liver function tests are within normal limits, serum amylase is 347 units per liter (U/L), and serum lipase is 634 U/L.

Question What is the diagnosis?

Answer Current guidelines from the American College of Gastroenterology (ACG) suggest at least two of the following criteria be present to make a diagnosis of acute pancreatitis: (1) abdominal pain consistent with acute pancreatitis, (2) serum amylase and/or lipase at least three times the upper limit of normal, and/or (3) characteristic imaging findings (Fig. 63.1) [1, 2].

These recommendations acknowledge that initial serum amylase is less sensitive for acute pancreatitis than serum lipase (especially in alcoholic and gallstone pancreatitis) and remains elevated for a shorter period of time than serum lipase, and is therefore not necessary to make the diagnosis [3, 4]. Sensitivity of lipase alone in diagnosing acute pancreatitis within the first day of onset has been estimated at 100 %, with specificity during this same time period around 84 %

M.F. Ragland (✉)
Department of Medicine, Northwestern Feinberg School of Medicine, Chicago, IL, USA
e-mail: margaret.ragland@northwestern.edu

C.H. Weiss
Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_63

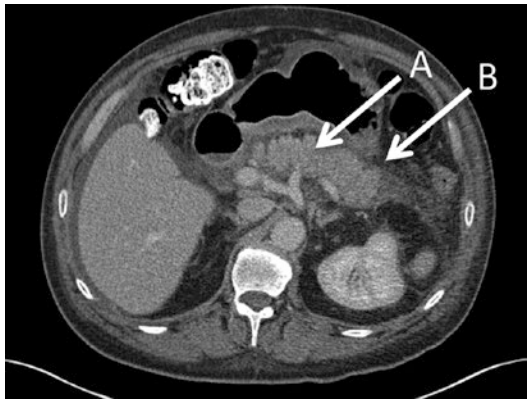


Fig. 63.1 Axial contrast-enhanced CT showing a mildly enlarged pancreas (*A*), with normal contrast enhancement and peripancreatic fat stranding and fluid (*B*), consistent with acute interstitial edematous pancreatitis

(lipase above the upper limit of normal) [4]. Lipase can be elevated in non-pancreatic pathology including kidney disease, appendicitis, cholecystitis, and other diseases of the gastrointestinal system, so diagnosis cannot be based on this laboratory value alone. Radiographic imaging is not necessary but can be helpful if the history and/or laboratory parameters do not confirm the diagnosis but suspicion for acute pancreatitis remains.

Principles of Management

Disease Burden, Diagnosis, and Assessment of Severity

Acute pancreatitis is the most common gastrointestinal diagnosis necessitating hospital admission, with US estimations in 2012 totaling 274,119 discharges, almost 1.5 million hospital days, and a total annual cost of $2.6 billion [5]. While estimations of risk of mortality due to acute pancreatitis are generally low (around 1 %) [5], significant morbidity can result from local complications including pancreatic pseudocyst and necrosis as well as systemic complications including sepsis, renal failure, and the acute respiratory distress syndrome. There are a number of different scoring systems to assess pancreatitis severity, and two commonly used systems are the Atlanta Criteria and more recently, the BISAP criteria [6]. The Atlanta Criteria have long been used to assess severity in acute pancreatitis, and most recently were updated in 2012 (Table 63.1) [2, 7]. While they are easy to use and can assist in triage and decisions regarding specialist consultation and/or referral, they do not predict outcomes. The BISAP criteria were more recently presented, and have the advantage of being simple to calculate, with only one subjective measure and are able to predict mortality (Table 63.2) [6].

Table 63.1 Pancreatitis severity, revised atlanta criteria

Mild acute pancreatitis	Moderately severe acute pancreatitis	Severe acute pancreatitis
No organ failure **and** no local complications	Local complications **and/or** transient organ failure (less than 48 h)	Persistent organ failure (greater than 48 h), may involve one or more organs

Data from Banks et al. [7]

Table 63.2 BISAP criteria

BISAP score	In-hospital mortality (percent)
0	0.1
1	0.2
2	1.6
3	3.6
4	7.4
5	9.5

Data from Wu et al. [6]
BISAP score = add together one point for each of the following: BUN > 25 mg/dL; 2 or more systemic inflammatory response syndrome criteria (SIRS); age > 60 years; pleural effusion. Predicted mortality (right) is listed according to the to BISAP score (left).

Intravenous Fluids

There are no approved pharmacologic treatments for acute pancreatitis, and the only intervention that has strong data to suggest reduced morbidity and mortality is aggressive fluid resuscitation [8]. The optimal timing, dose, and monitoring strategy are still not agreed upon, and there is little prospective data to inform recommendations [9].

One of the few prospective studies to investigate volume resuscitation in acute pancreatitis was a four arm trial of forty patients that compared goal-directed fluid therapy with normal saline, goal-directed fluid therapy with Lactated Ringer's (targeting BUN decrease or normalization), standard fluid therapy with normal saline, and standard fluid therapy with Lactated Ringer's. Mean volume administered in both goal-directed and standard therapy groups was similar, and there was a significant decrease in the systemic inflammatory response syndrome and C-reactive protein at 24 h in the Lactated Ringer's groups compared to the normal saline groups, but no difference in length of stay, infection, organ failure, or death [10]. Reviews and professional societies recommend variations in dosing, however a common practice is to provide 250–500 ml/h isotonic crystalloid solution for the first 12–24 h in the absence of limiting cardiac and renal comorbidities [1].

Antibiotics

Routine antibiotics in acute pancreatitis are not recommended [1]. A recent meta-analysis of six clinical trials of patients with necrotizing pancreatitis found that prophylactic antibiotic use was not associated with reduced risk of infected necrosis or mortality, but did find a statistically significant reduction in hospital stay [11]. ACG recommends empiric antibiotics only in extrapancreatic infection (including cholangitis and bacteremia), no antibiotics for sterile necrosis, and consideration of antibiotics in patients with necrosis who fail to improve after 7–10 days of supportive management, with consideration of CT-guided fine-needle aspiration to guide therapy, using antibiotics only if there is a positive Gram stain or culture [1].

Pain Control

Analgesia in acute pancreatitis is typically achieved with intravenous opioids. Data surrounding optimal drug, route, dose, and monitoring has not been established. A recent Cochrane review on the topic concluded the existing evidence does not support any one practice for pain control over another and additional evidence should be pursued [12].

Etiology

The most common etiologies of acute pancreatitis are alcoholic and gallstone, while hypertriglyceridemia, post-endoscopic retrograde cholangiopancreatography, acute human immunodeficiency virus infection, and medications (commonly furosemide, vinca alkaloids, azothiaprine, and didanosine) are also frequent causes [13]. In the United States, recent estimations suggest that the etiology of acute pancreatitis is most commonly idiopathic (36 %), followed by gallstones (28 %), and alcoholic (19 %) [14]. In addition to taking a thorough history focusing on previous episodes of acute pancreatitis, alcohol use, history of gallstone disease, and medications, ACG recommends performing a transabdominal ultrasound in all patients with acute pancreatitis to assess for gallstone disease [1]. The Dutch Pancreatitis Study Group notes that abdominal ultrasound is widely available, noninvasive, and inexpensive, although it is not sensitive for common bile duct stones [15, 16]. In patients without another clear explanation for their pancreatitis and in whom abdominal ultrasound was negative for cholelithiasis, contrast enhanced computed tomography and/or magnetic resonance cholangiopancreatography should be considered, with the latter demonstrating higher sensitivity for smaller stones than the former (40 % vs. 80 %, respectively) [16]. Imaging should only be pursued if there is no clear etiology of the acute pancreatitis or the patient fails to improve clinically within 48–72 h of presentation [11]. In the absence of suggestive alcohol use or obstructing gallstone on imaging, serum triglycerides should be checked with >1000 mg/dL consistent with triglyceride-induced pancreatitis [1]. Risks and benefits of ERCP should be discussed in light of clinical suspicion of a radiographically occult obstructive stone or other foreign body in the biliary tree [1] Fig. 63.2, Table 63.3.

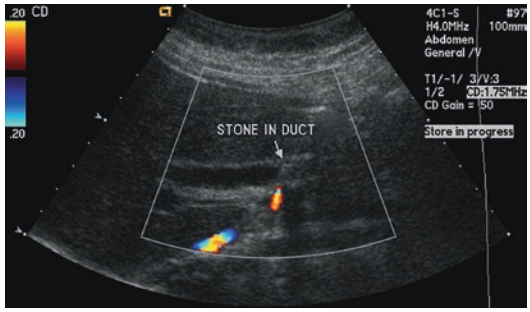


Fig. 63.2 Transabdominal ultrasound showing an echogenic structure in the common bile duct with acoustic shadowing and no internal flow causing dilatation of the common bile duct, consistent with choledocholithiasis

Table 63.3 ACG recommendations for ERCP in acute pancreatitis

1. Patients with acute pancreatitis and concurrent acute cholangitis should undergo ERCP within 24 h of admission (strong recommendation, moderate quality of evidence)
2. ERCP is not needed early in most patients with gallstone pancreatitis who lack laboratory or clinical evidence of ongoing biliary obstruction (strong recommendation, moderate quality of evidence)
3. In the absence of cholangitis and/or jaundice, MRCP or endoscopic ultrasound rather than diagnostic ERCP should be used to screen for choledocholithiasis if highly suspected (conditional recommendation, moderate quality of evidence)
4. Pancreatic duct stents and/or postprocedure rectal non-steroidal anti-inflammatory drug suppositories should be utilized to lower the risk of severe post-ERCP pancreatitis in high-risk patients (conditional recommendation, moderate quality of evidence)

From Tenner et al. [1]. Reprinted with permission from Nature Publishing Group

Evidence Contour

Early Nutritional Support

While the management of acute pancreatitis has remained mostly unchanged for many years, currently the most hotly debated aspect of treatment is the timing and method of nutritional support. Traditionally, it was thought that enteral feeding stimulates the pancreas to secrete proteolytic enzymes, which in turn stimulate further local inflammation. Current understanding, however, supports the thought that withholding enteral feeding causes hypomotility in the gastrointestinal tract, changing intraintestinal microflora and resulting in bacterial overgrowth and translocation, leading to both local and systemic complications such as abscess, necrosis, and sepsis [17]. Furthermore, data suggests that a substantial number of patients experience a decline in their nutritional status during their hospital stay and that these patients experience a significant increase in number of complications during their stay [18]. Based on this information, ACG suggests oral feedings be started immediately once nausea, vomiting, and abdominal pain have resolved [1]. Recent studies have focused on determining the appropriate method and timing of feeding in acute pancreatitis when symptoms have *not* yet resolved. A number of randomized controlled trials have looked at the safety and appropriateness of enteral versus parental nutrition in acute pancreatitis. A meta-analysis of six studies found a significantly lower risk of infectious complications when enteral nutrition was used over parental nutrition [19]. There was also a trend towards significance in favor of enteral nutrition when looking at complications aside from infection (including the acute respiratory distress syndrome, multi-organ failure, acute pseudocyst, and pancreatic fistula), need for surgical intervention, and mortality [19]. Regarding timing of feeding, a recent meta-analysis combined data of 11 studies (prospective and retrospective) of nasojejunal and nasogastric feeding and demonstrated that early enteral nutrition (within 48 h of admission) compared to late feeding (enteral or parenteral) demonstrated a significantly decreased risk of infectious complications, decreased length of hospital stay, and risk of mortality [20]. Regarding nasogastric compared to nasojejunal feedings, some providers are concerned about stimulating gastric acid secretion and worsening local pancreatic inflammation with gastric feeding while others are concerned about delaying feedings due to the higher complexity of placing a nasojejunal tube compared to a nasogastric tube [17]. While additional studies need to be completed to further clarify which method is preferred, current evidence based on a

meta-analysis of three studies totaling just over 150 patients suggests that there is a trend towards reduced mortality with nasogastric feeding compared to nasojejunal feeding with minimal difference in risk of exacerbation of pain between the two methods [21].

References

1. Tenner S, Baillie J, DeWitt J, Vege SS, American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108(9):1400–15; 16.
2. Bollen TL, van Santvoort HC, Besselink MG, van Leeuwen MS, Horvath KD, Freeny PC, et al. The Atlanta classification of acute pancreatitis revisited. Br J Surg. 2008;95(1):6–21.
3. Winslet M, Hall C, London NJ, Neoptolemos JP. Relation of diagnostic serum amylase levels to aetiology and severity of acute pancreatitis. Gut. 1992;33(7):982–6.
4. Keim V, Teich N, Fiedler F, Hartig W, Thiele G, Mossner J. A comparison of lipase and amylase in the diagnosis of acute pancreatitis in patients with abdominal pain. Pancreas. 1998;16(1):45–9.
5. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology. 2012;143(5):1179–87.e1–3.
6. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut. 2008;57(12):1698–703.
7. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis – 2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102–11.
8. Wall I, Badalov N, Baradarian R, Iswara K, Li JJ, Tenner S. Decreased mortality in acute pancreatitis related to early aggressive hydration. Pancreas. 2011;40(4):547–50.
9. Trikudanathan G, Navaneethan U, Vege SS. Current controversies in fluid resuscitation in acute pancreatitis: a systematic review. Pancreas. 2012;41(6):827–34.
10. Wu BU, Hwang JQ, Gardner TH, Repas K, Delee R, Yu S, et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterological Assoc. 2011;9(8):710–7. e1.
11. Mazaki T, Ishii Y, Takayama T. Meta-analysis of prophylactic antibiotic use in acute necrotizing pancreatitis. Br J Surg. 2006;93(6):674–84.
12. Basurto Ona X, Rigau Comas D, Urrutia G. Opioids for acute pancreatitis pain. Cochrane Database Syst Rev. 2013;(7):CD009179.
13. Sekimoto M, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. JPN guidelines for the management of acute pancreatitis: epidemiology, etiology, natural history, and outcome predictors in acute pancreatitis. J Hepatobiliary Pancreat Surg. 2006;13(1):10–24.
14. Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. Am J Gastroenterol. 2012;107(7):1096–103.
15. Schepers NJ, Besselink MG, van Santvoort HC, Bakker OJ, Bruno MJ, Dutch Pancreatitis Study Group. Early management of acute pancreatitis. Best Pract Res Clin Gastroenterol. 2013;27(5):727–43.
16. Moon JH, Cho YD, Cha SW, Cheon YK, Ahn HC, Kim YS, et al. The detection of bile duct stones in suspected biliary pancreatitis: comparison of MRCP, ERCP, and intraductal US. Am J Gastroenterol. 2005;100(5):1051–7.
17. Olah A, Romics Jr L. Enteral nutrition in acute pancreatitis: a review of the current evidence. World J Gastroenterol WJG. 2014;20(43):16123–31.
18. Braunschweig C, Gomez S, Sheean PM. Impact of declines in nutritional status on outcomes in adult patients hospitalized for more than 7 days. J Am Diet Assoc. 2000;100(11):1316–22; quiz 23–4.
19. Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. BMJ. 2004;328(7453):1407.
20. Li JY, Yu T, Chen GC, Yuan YH, Zhong W, Zhao LN, et al. Enteral nutrition within 48 hours of admission improves clinical outcomes of acute pancreatitis by reducing complications: a meta-analysis. PLoS One. 2013;8(6):e64926.
21. Chang YS, Fu HQ, Xiao YM, Liu JC. Nasogastric or nasojejunal feeding in predicted severe acute pancreatitis: a meta-analysis. Crit Care. 2013;17(3):R118.

Management of Acute Liver Failure

64

Jessica L. Mellinger and Robert J. Fontana

Case Presentation

A 27 year old Caucasian woman with a history of intravenous drug use, narcotic abuse, and depression presented to the emergency department after being found down by her family. The patient had been unable to obtain her psychiatric medications of mirtazapine, escitalopram, and lorazepam and was reporting increasing symptoms of depression and anxiety in the past few weeks. There was a history of Percocet abuse in the past 6 months, and she had recently been diagnosed as a carrier of Huntington's disease.

At presentation, she was hypothermic (33.7 °C) and hypotensive (70/40), which improved to 90/56 with fluid resuscitation. Initial ABG revealed pH 7.0, pCO_2 of 17 and pO_2 of 153 on 4 l of supplemental oxygen with a lactate level of 19 mmol/l (nl <2.0). She was unresponsive and moaning with dilated but reactive pupils and normal reflexes throughout. Initial serum AST was 9349 IU/l, ALT 6550 IU/l, total bilirubin 3.0 mg/dl, INR 5.9 and serum creatinine 1.63 mg/dl. The initial white blood cell count was 36.9 k/ml, hemoglobin 15.9 mg/dl, and platelets were 204,000/ml. Her initial serum acetaminophen (APAP) level was 35 ug/mL and urine drug screen was positive for opioids, benzodiazepines, and oxycodone. She was intubated for airway protection and transferred to the ICU for further management.

The patient was started on IV NAC (Acetadote©, Cumberland Pharmaceuticals, Nashville, TN) for presumed narcotic-APAP overdose in the setting of poorly controlled depression with high serum aminotransferase levels and lactic acidosis at presentation. Initial head CT (Fig. 64.1) and chest x-ray were unremarkable and propofol sedation was used while maintaining the head of the bed >30°. Sedation was periodically weaned for neurologic exams, and she was able to follow simple commands, open her eyes, and localize pain. After several liters of volume expansion, she was transiently placed on norepinephrine for hypotension, which was subsequently weaned off over the following 24 h.

Broad-spectrum antibiotics consisting of vancomycin and cefepime were started given her leukocytosis and concern for possible aspiration pneumonia. Sputum culture grew pan-sensitive *Streptococcus pneumonia* and her antibiotic regimen was narrowed to cefepime at ICU day #2. Her initial Factor V level was undetectable (i.e. <5 %), but lactate level improved to 5.1 mmol/l. After initial improvement with

Grant Support: Support for Dr. Fontana provided in part by the National Institutes of Diabetes, Digestive, and Kidney Diseases (DK U-01-58369) as a member of the Acute Liver Failure Study Group. Support for Dr. Mellinger provided by the AASLD Advanced Transplant Hepatology Fellowship

J.L. Mellinger • R.J. Fontana (✉)
Division of Gastroenterology, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA
e-mail: rfontana@med.umich.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_64

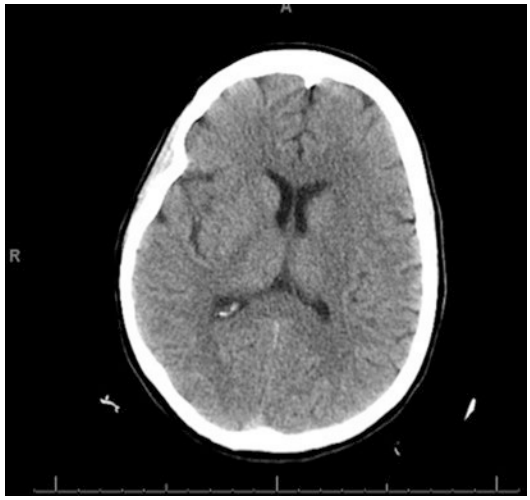


Fig. 64.1 Non-contrast head CT at initial presentation. There was no evidence of cerebral edema despite markedly impaired mental status

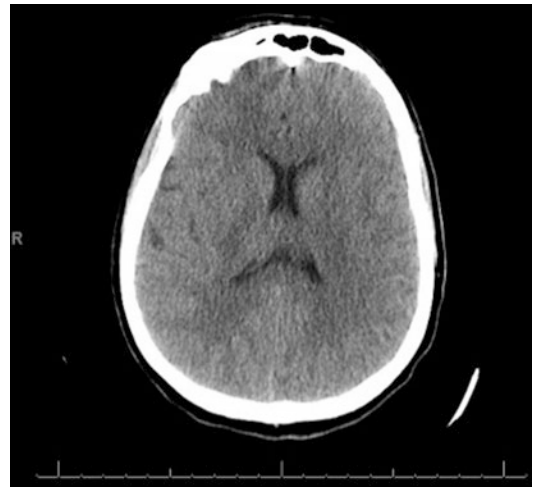


Fig. 64.2 Non-contrast head CT at hospital day 2. The scan demonstrates evidence of diffuse cerebral edema with loss of the grey-white juncture and reduced sulcal folds throughout

aggressive fluid resuscitation, her creatinine rose to 1.86 mg/dl by 48 h. IV vitamin K was given with initial improvement in her INR to 1.2, but this began to rise again to 2.5 by ICU day #2. Approximately 48 h into her hospitalization, her neurologic exam worsened, and she was unable to follow commands. A repeat non-contrast head CT showed evidence of cerebral edema (Fig. 64.2).

Question What intervention is now recommended?

Answer Intracranial pressure monitoring for cerebral edema.

After infusion of 3 units of FFP and 5000 Units of recombinant FVIIa, a codman ICP monitor (DePuy Synthes, Raynham, MA) was placed by neurosurgery, which showed an initial ICP of 35 mmHg. Resumption of the propofol infusion improved the ICP to 6–15 (goal <20). In addition, target levels of serum sodium (>150 mg/dl), osmolality (>120 mOsm/l), and a pCO_2 (25–30 mmHg) were met without additional treatment. Due to the history of recurrent illicit drug abuse and severe psychiatric disease, she was not felt to be a liver transplant candidate.

On hospital day 3, her ICP monitor registered an acute increase from <20 to 45 mmHg. Intravenous mannitol 60 g and hypertonic saline were initiated, despite serum sodium level of 151 and osmolarity of 336, respectively. Sedation was also increased with propofol. She then developed seizure-like activity with rhythmic twitching of her jaw and a pentobarbitol bolus with subsequent continuous infusion was given. Approximately 5 h later, her ICP dropped precipitously to 4 mmHg with a neurologic exam showing fixed, dilated pupils bilaterally. A repeat head CT showed worsening cerebral edema with blurring of the grey- white interface and early left uncal herniation. An EEG showed no seizure activity.

Due to the concern of possible brain herniation, her sedation was held. After 6 h of completely absent corneal, gag/cough reflex and with persistently fixed and dilated pupils, neurology assessed the patient as having a grim prognosis with high risk of brain death. A Technetium sulfur-colloid scan was proposed to confirm the absence of intracranial blood flow but due to her persistently poor hepatic function with an ALT of 2978 IU/l, INR 4.4 and concomitant multi-organ failure, her family elected to withdraw care and she passed away after extubation.

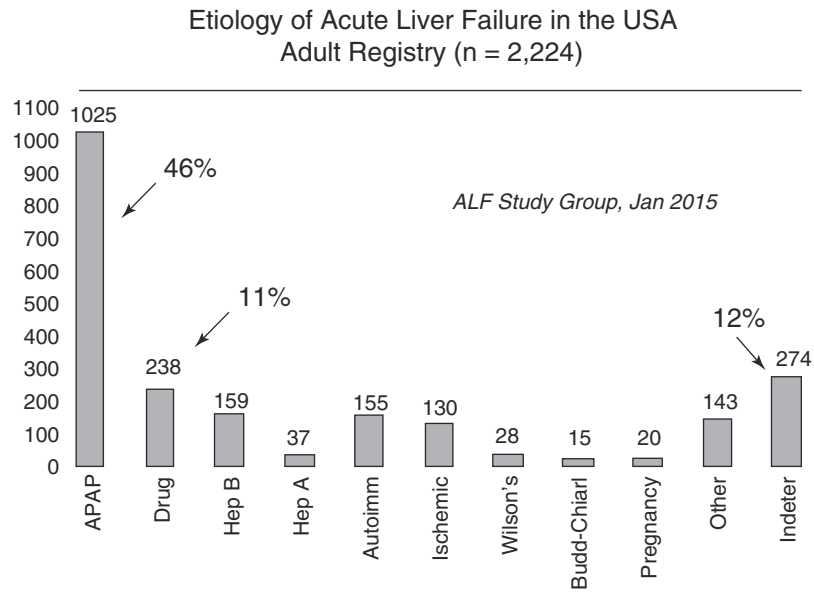


Fig. 64.3 Etiology of ALF in adults enrolled in the ALFSG from 1998 to 2014 (Figure courtesy of William M. Lee, MD and the Acute Liver Failure Study Group)

Acute liver failure (ALF) is defined as the sudden onset of severe liver injury resulting in coagulopathy (i.e. INR >1.5) and encephalopathy, in a patient with no prior history of liver disease. Most studies define ALF as injury onset in the past 26 weeks, but the majority of patients present with non-specific symptoms of malaise, lethargy, and nausea/vomiting for <8 weeks [1, 2]. APAP overdose is the most common cause of ALF in western countries accounting for nearly 50% of consecutive adult cases (Fig. 64.3). Although the majority of the 60,000 annual APAP overdoses in the US are intentional and recover with supportive care, non-intentional APAP overdoses account for nearly 50% of the >500 patients who progress to ALF each year [3]. Most non-intentional APAP overdose cases result from the ingestion of excessive quantities of over-the-counter products that contain APAP and/or prescription narcotic-APAP analgesic congeners taken over several days for various ailments. The frequency of alcohol abuse and psychiatric co-morbidity is similar in the intentional versus non-intentional APAP patients [3]. Although non-intentional overdose patients have more advanced encephalopathy at presentation, they have a similar rate of 3-week spontaneous survival as the intentional overdose patients (70%).

Principles of Management

Etiology of ALF

Due to the inability to reliably obtain a medication and medical history, all adults with ALF should have a serum APAP level checked. In addition, *any* suspicion of APAP-induced liver injury should lead to immediate treatment with n-acetylcysteine (NAC) (Table 64.1 Treatment of APAP-induced ALF) [4]. The Rumack-Matthew nomogram is helpful in determining the likelihood of APAP hepatotoxicity developing in patients with a single time point APAP overdose and should also be repeated 4 h after initial presentation. However, the nomogram should not be used to guide NAC treatment decisions in patients who inadvertently ingest excessive quantities of APAP over several days and have low or undetectable serum APAP levels at presentation. Patients with APAP overdose may initially have normal serum aminotransferase levels or only evidence of an isolated INR elevation or metabolic acidosis. However, the majority of patients with hepatotoxicity develop a serum ALT >1000 within 24 h of hospitalization and most of them have normal or only minimally elevated total bilirubin levels. The possibility of acute viral hepatitis (hepatitis A, B, C, and cytomegalovirus

Table 64.1 Recommended treatment of acetaminophen overdose

Oral treatments
Within 4 h of APAP ingestion Ipecac syrup, 15 ml once; repeat in 20 min if needed to induce emesis Nasogastric lavage of pill fragments Activated charcoal, 1 g/kg body weight (max dose 50 g) Should be given before oral NAC
Within 24 h of APAP ingestion and ability to tolerate oral intake Oral NAC to replete glutathione stores Oral NAC dosing: 140 mg/kg load followed by 70 mg/kg every 4 h for 17 doses or until INR <1.5[a] Give ondansetron/prochlorperazine or mix with carbonated beverage to improve GI tolerability
Intravenous N-acetylcysteine infusion
Indications: Subjects with severe nausea/vomiting unable to tolerate oral NAC, short-gut, known ileus, and pregnant women Dose 1. Loading Dose: 150 mg/kg NAC in 200 ml D_5W over 1 h Dose 2. 50 mg/kg NAC in 500 ml D_5W over 4 h Dose 3. 125 mg/kg NAC in 1000 ml D_5W over 19 h Dose 4. 150 mg/kg NAC in 1000 ml D_5W over 24 h Dose 5. 150 mg/kg NAC in 1000 ml D_5W over 24 h
Cautions 1. Contraindications: *sulfa allergy* 2. If Acetadote (Cumberland Pharmaceuticals, Nashville, TN) is unavailable, standard oral NAC can be mixed for IV administration using a leukopore filter. (Consultation with local ICU pharmacy) 3. Telemetry monitoring recommended for arrhythmias and adverse effects 4. Potentially *severe anaphylactoid and hypersensitivity reactions* reported in up to 3 % of treated patients Bronchospasm, nausea, rash, and pruritis have been reported If reaction occurs, hold infusion, administer IV fluids, IV diphenydramine, and corticosteroids as needed Consider restarting infusion at 50 % rate if reaction abates and not severe

Adapted from Bari and Fontana [3]
[a]Consider antiemetics or switch to IV NAC for refractory nausea and vomiting

(CMV), Epstein-Barr virus (EBV), and herpes simplex virus (HSV)) should be excluded early on as well as potential hepatic ischemia due to underlying cardiopulmonary disease or volume depletion. A thorough diagnostic workup is recommended to identify treatable causes of ALF such as autoimmune hepatitis, Wilson's disease, or acute HBV infection (Table 64.2).

The etiology of ALF is closely linked with the likelihood of hepatic recovery and spontaneous survival. For example, subjects with APAP overdose, hepatitis A, hepatic ischemia, and pregnancy related ALF generally have a favorable prognosis for spontaneous recovery (50–70 %) while subjects with idiosyncratic drug-induced liver injury (DILI), autoimmune hepatitis, and indeterminate ALF only have a 20–50 % likelihood of spontaneous recovery [1,5]. The modified King's College Criteria (Table 64.3) are frequently used to help guide treatment and management decisions in both APAP and non-APAP related ALF patients [7].

Correction of Coagulopathy

ALF is frequently associated with thrombocytopenia as well as marked derangements in various clotting factor levels leading to an elevated INR, low Factor V levels (<50 %), and evidence of disseminated intravascular coagulation. Serial measurement of INR and Factor V levels can provide important prognostic information at the bedside regarding the recovery of hepatic function. However, clinically significant spontaneous bleeding is observed in <10 % of patients presumably due to reduced synthesis of clotting inhibitors as well [8]. Therefore, blood products, such as fresh frozen plasma (FFP), platelets, and cryoprecipitate should not routinely be given, unless invasive procedures are planned or there is active bleeding. However, parenteral vitamin K (10 mg SQ or IV for 3 days) is recommended for all ALF patients.

Hemodynamic Support

ALF patients frequently require fluid challenges as well as vasopressor support during their ICU course to support adequate tissue perfusion. Resuscitation with normal saline is an appropriate first-line response to hypotension in ALF patients, but the potential for exacerbation of

Table 64.2 Recommended diagnostic evaluation for adults with ALF

Etiology	Diagnostic testing	Treatment
Acetaminophen	Acetaminophen level Urine tox screen	N-acetylcysteine
Acute viral hepatitis	anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HCV, HCV RNA, HSV-DNA (PCR)[a], CMV-DNA (PCR)[a], EBV-DNA (PCR) or serologies[b]	Entecavir for HBV Acyclovir for HSV
Wilson's disease	Ceruloplasmin, 24-h urine copper, slit-lamp exam[c]	Chelation therapy
Autoimmune hepatitis	Anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA), Immunoglobulin levels, liver biopsy	Corticosteroids
Ischemia	Transthoracic echocardiogram[a]	Fluids/pressors
Budd-Chiari	Liver ultrasound with Doppler	Anticoagulation
Pregnancy-related Toxemia HELLP Acute fatty liver of pregnancy	Serum pregnancy testing	Urgent delivery
Idiosyncratic DILI	Medical history and drug exposure	Drug cessation Consider N-acetylcysteine

[a]If clinically indicated based on clinical suspicion
[b]EBV viral capsid antigen (*VCA*) IgG and IgM, EBV early antigen (*EA*) IgG, EBV nuclear antigen (*NA*) IgG
[c]If high-level of clinical suspicion (age <40, other etiologic workup negative) (Adapted from Lee et al. [5])

Table 64.3 King's college criteria for adverse outcomes in ALF

Acetaminophen overdose	Non-acetaminophen ALF
Arterial lactate >3.5 mmol/l 4 h after resuscitation OR pH <7.30 or arterial lactate >3.0 mmol/l 12 h after resuscitation OR INR >6.5 (PT >100 s) Serum creatinine >3.4 mg/dL Stage 3 or 4 encephalopathy	INR >6.5 (PT >100 s) OR any three of the following INR >3.5 (PT > 50 s) Age <10 or >40 years Serum bilirubin >17.5 mg/dL Duration of jaundice >7 days Etiology: drug reaction

[a]Prognostic models should not be the sole criteria to determine appropriateness for liver transplant [6]

cerebral and pulmonary edema particularly in patients with AKI must be considered. While IV albumin is useful in the management of cirrhotics with spontaneous bacterial peritonitis, large-volume paracentesis, and hepatorenal syndrome, there is little evidence to guide its use in ALF patients. In volume-refractory hypotension, norepinephrine or dopamine should be used to maintain an adequate MAP (i.e.≥60 mmHg), though there is little data to recommend a specific agent [5]. Norepinephrine can provide blood pressure support while minimizing tachycardia and preserving hepatic blood flow [5]. Vasopressin can also be used, though caution is needed in patients with an elevated ICP [9]. In patients with hypotension that is refractory to fluids and vasopressor support, hydrocortisone treatment for adrenal insufficiency may be of value. Studies have shown that patients with ALF can have adrenal insufficiency, with both low baseline cortisol levels as well as failure to respond appropriately to cosyntropin stimulation testing [10]. Patients who fail to respond to stimulation testing have a greater likelihood of hemodynamic instability requiring vasopressor support [10]. However, corticosteroids are not routinely recommended

for ALF patients due to the lack of improved outcomes and potential for increased infections [5,11].

Renal Insufficiency

Approximately 70 % of ALF patients (and APAP patients in particular) develop AKI and 30 % require renal replacement therapy during their hospital course which is associated with a lower rate of spontaneous survival [12]. Most ALF patients with AKI have either a pre-renal or acute tubular necrosis (ATN) component, but some may develop hepatorenal physiology as well. Preservation of renal perfusion, early recognition and treatment of infection, and avoidance of nephrotoxic agents (e.g. iodinated contrast media, NSAID's, aminoglycosides) is recommended to preserve renal function. Oliguric patients with progressive azotemia or fluid overload should have central venous pressure monitoring and be initiated on renal replacement therapy. Continuous venovenous hemofiltration (CVVH) is preferred over hemodialysis due to the less frequent hemodynamic instability and improved outcomes in ALF patients [5,13].

Infection

ALF patients are functionally immunocompromised and at high risk for both bacterial (>80 %) and fungal infections (>20 %) during their hospital course, most often from catheters and intravenous lines. Since severe infections may preclude liver transplantation, daily urine, sputum, and blood cultures as well as chest x-rays and paracentesis of ascitic fluid are recommended. Broad-spectrum antibiotics covering Gram positive cocci and Gram negative rods should be started for any suspected infection, unexplained leukocytosis or worsening of mental status, and/or fever. However, prophylactic antibiotics and enteral decontamination in the absence of a clinical suspicion for infection have not been shown to improve outcomes [5]. Fungal infections are notoriously difficult to identify and may present with unexplained hypotension, worsening encephalopathy or multi-organ failure at 3–5 days after initial presentation in 10–20 % of ALF patients and are associated with a poorer prognosis [2,14].

Neurologic Complications

Neurologic manifestations in ALF are complex and require the intensivist to pay careful attention to metabolic derangements, infections, and medications as well as the potential for cerebral edema to develop. The development of encephalopathy in ALF patients can be subtle early on with rapid progression to full coma. Management differs depending upon the stage of encephalopathy (Table 64.4 Stages of Encephalopathy), but timely recognition of worsening mental status should prompt consideration of cerebral edema versus medication effects, infection, or other metabolic causes. The pathogenesis of cerebral edema in ALF is poorly understood but is hypothesized to be the result of rapid increases in the circulating levels of ammonia and proinflammatory cytokines which can lead to increased conversion of glutamate to glutamine by astrocytes that results in cellular swelling. In addition, loss

Table 64.4 Stages of hepatic encephalopathy and likelihood of recovery

Stage[a]	Spontaneous survival (%)	Mental status evaluation
I	70	Mild changes in mood; personality, slurred speech; sleep disorder; shortened attention span
II	60	Inappropriate behavior; agitation or lethargy, minimal disorientation to place and time
III	40	Somnolent but arousable to verbal command; marked confusion, incoherent speech; gross disorientation
IV	20	Unarousable to painful stimuli (comatose); decorticate or decerebrate posturing

[a]Adapted from Lee et al. [5]

of the autoregulation of intracranial bloodflow is frequently observed in more advanced encephalopathy leading to increased cerebral bloodflow. Cerebral edema is perhaps the most serious complication of ALF and remains a leading cause of death through uncal herniation.

Grade 1 encephalopathy in ALF patients can be managed expectantly with avoidance of neuroactive drugs, maintaining a quiet environment, and addressing any metabolic abnormalities including an elevated temperature and hypoglycemia. Although lactulose is routinely used in hospitalized cirrhotic patients with encephalopathy, lactulose has not been shown to improve outcomes and can lead to bowel ischemia in some ALF patients. Patients are often intubated and sedated prior to completion of a full neurologic exam so attempts to hold sedation and perform serial exams are warranted. As patients evolve into Grade 2/3 encephalopathy, a non-contrast head CT can help exclude other causes of neurologic decline such as intracranial bleeding which is seen in <5 % of ALF patients. However, a head CT is insensitive for detecting intracranial hypertension in ALF patients as are physical exam findings such as papilledema, clonus, and loss of pupillary reflexes. Nonetheless, serial neurological exams are vital for tracking a patient's clinical course over time.

Direct intracranial pressure (ICP) monitoring should be considered when encephalopathy progresses to grade III/IV to help guide management of systemic hemodynamics, fluid status, and optimize cerebral bloodflow [5]. Prior studies have shown that monitored patients receive more interventions (including renal replacement therapy, vasopressors, and blood product administration) and are more likely to be transplanted, but do not have improved mortality overall [15]. The goal of ICP monitoring is to detect and effectively manage potentially life-threatening intracranial hypertension. The precise ICP and cerebral perfusion pressure (CPP = MAP − ICP) targets are not known in ALF but extrapolating from the traumatic brain injury literature, an ICP goal of 20–25 mmHg and a CPP goal of 50–60 mmHg may be reasonable. To reduce the risk of bleeding complications with ICP monitor placement, FFP and platelet infusions are frequently administered in combination with recombinant FVIIa (Table 64.5). Currently, intraparenchymal ICP monitors are most commonly used while external ventricular drains are rarely placed due to bleeding concerns although they do allow direct drainage of CSF to improve ICP.

Simple measures to reduce the incidence of intracranial hypertension in ALF patients include keeping the head of the bed >30° from horizontal and minimizing suctioning, coughing, and straining, as well as controlling pain. In addition, hyperventilation of a patient to a PCO_2 of

Table 64.5 Recombinant factor VIIa infusion protocol

Indication[a]
Reduction in risk of peri-operative bleeding in ALF patients with persistent hypoprothrombinemia despite FFP infusion
Urgent ICP monitor placement or other invasive surgery/procedure
Mechanism of action
Tissue factor release leads to localized clot formation
rFVIIA enhances clot formation at sites of tissue factor release for 2–8 h with a half-life of 2–4 h
Contraindications
Budd-Chiari
Known or suspected malignancy
History of DVT/PE or current pregnancy
Hypersensitivity to vitamin K or mouse/bovine/hamster proteins
Administration
Pre-op FFP (2 to 4 units) with persistent INR >1.5
Pre-op cryoprecipitate if fibrinogen <100 mg/dL
Pre-op platelets to achieve >50 k/ml
Dose[b]: 80 μg/kg IV bolus over 2–5 min immediately prior to ICP placement (provides up to 4 h window to place ICP monitor)
Do not wait to confirm INR correction due to short half-life
Lab studies
Pre-infusion: CBC, INR, aPTT, Factor V, fibrinogen, D-dimer
1 h (60 min) post-infusion: CBC, INR, aPTT, Factor V
4 h (240 min) post-infusion: CBC, INR, aPTT, Factor V
8 h (480 min) post-infusion: CBC, INR, aPTT, Factor V

[a]Not approved by FDA
[b]Vial sizes are 1200, 2400, and 4800 ug (round up or down to nearest vial size due to cost)

28–30 mmHg can enhance intracranial vascular tone which is frequently reduced in ALF patients.

First-line therapy for an episode of ICP elevation that persists for more than 5–10 min despite hyperventilation is typically IV mannitol. Mannitol may be administered as an initial bolus of 0.5–1.0 g/kg over 5 min, followed by additional doses every 2–6 h as need to maintain ICP within goal parameters (20–25 mmHg). Serum osmolarity is typically monitored every 2–6 h and mannitol held if serum osmolarity >320 mOsm/l, to minimize the risk of dehydration and acute renal failure. However, caution should be used when giving mannitol in the setting of AKI due to potential worsening of pulmonary edema and volume overload.

Second-line therapy for cerebral edema in ALF patients is infusion of hypertonic saline (3 %), with a target serum sodium level of 145–155 meq/l. Advantages of hypertonic saline include less frequent hypovolemia compared to mannitol with potentially less rebound cerebral edema. A meta-analysis in traumatic brain injury suggests greater efficacy with hypertonic saline compared to mannitol. Hypertonic saline can be administered as bolus dosing, typically with 23.4 % NaCl, in the setting of an acute decline or a maintenance infusion of varying concentrations to achieve a serum sodium concentration of 145 to 155 meq/l. Potential concerns with hypertonic saline include hyperchloremic non-anion gap metabolic acidosis especially with renal failure and circulatory volume overload. The use of hypertonic saline has been demonstrated as an effective prophylactic measure in patients at high risk of cerebral edema (ammonia >150 mM, AKI, grade III/IV encephalopathy, and vasopressor requirement) [5]. Both prophylactic and therapeutic hypertonic saline are increasingly used in patients with a traumatic brain injury who frequently have cerebral edema [16].

If hyperventilation and osmotic agents fail to improve an elevated ICP, pentobarbitol can be administered as a 100–150 mg bolus over 15 min followed by a continuous infusion of 1–3 mg/kg/h. However, barbiturate infusions are typically associated with significant side effects including hypotension, ileus, and pneumonia. Vasopressors may be needed to maintain an adequate CPP. In addition, the serum half-life of barbituates is long and the clinical neurological exam, including that for brain death, is typically obscured for several days. Monitoring serum pentobarbital levels every 12–24 h to maintain a therapeutic (but non-toxic) level of 20–35 mg/l is recommended in ALF patients due to their reduced clearance of this hepatically metabolized drug.

Any identified seizure activity in ALF patients should be swiftly treated as seizures can lead to worsening cerebral edema. Subclinical seizures can be confirmed with continuous EEG monitoring. If seizure activity is present, a loading dose of phenytoin (20 mg/kg with dose adjusted in the setting of renal failure) should be administered followed by maintenance dosing based on blood levels. In ALF patients with refractory seizures, infusions of midazolam, propofol or pentobarbital may be necessary for seizure control. Because ALF patients are prone to hypoglycemia, blood sugar levels should be monitored every 2 h with administration of D_{10} and D_{50} drips as needed.

Evidence Contour

Recombinant Factor VIIa to Correct Coagulopathy

Recombinant Factor VIIa (rFVIIa) was approved in the United States in 1999 as an antihemophilic agent and has been used in ALF patients, largely for correction of coagulopathy prior to invasive procedures. Several small case series have shown improved coagulation parameters with decreased PT/INR and improved ability to place ICP monitors, all while decreasing the requirement for FFP in the immediate peri-procedural setting [17–19]. A dose of 80 ug/kg given as an IV bolus over 3–5 min provides up to 4 h of coagulation correction for placement of the ICP monitor, when given with cryoprecipitate, fresh frozen plasma, and platelets as needed. Frequent lab monitoring peri-procedure is indicated, but waiting for a repeat INR after infusion of rFVIIa is not recommended. Both bleeding and thrombotic complications are rare in published case series [18,19].

Serial NH_3 Levels in ALF Patients

Ammonia plays a key role in the development of encephalopathy in ALF patients, with rapid rises in arterial ammonia concentrations implicated in cerebral edema. Although an ammonia threshold level has not been identified, higher ammonia levels in general have been associated with more severe encephalopathy, increased intracranial hypertension and cerebral herniation, as well as increased mortality [20–22]. Though the use of lactulose is not recommended due to a concern for intestinal distension and ischemia, research is ongoing into the use of other ammonia-lowering agents to improve outcomes. At present, serial monitoring of arterial ammonia concentrations can provide additional prognostic information, particularly as a patient's mental status worsens.

Targeted Temperature Management

Moderate hypothermia (core temperature of 33–34 °C) in ALF is thought to improve cerebral edema by reducing cerebral bloodflow and oxygen utilization as well as decreasing conversion of glutamate to glutamine. Therapeutic hypothermia using cooling blankets has been used in ALF patients but has not been shown to improve survival [23,24]. Experience with arctic suits and intravascular cooling devices is limited in ALF patients, and most experts recommend use of a cooling blanket in these vasodilated patients. Known risks of hypothermia include bradyarrhythmias, coagulopathy, and infections which may be particularly problematic in patients requiring emergency liver transplantation. Furthermore, the optimal means to warm cooled ALF patients are not established.

Bioartificial Hepatic Support Systems

Extracorporeal hepatic support systems have been studied in both ALF and acute-on-chronic liver failure. Several types of bioartificial support have been introduced including albumin dialysis, plasma separation and adsorption, and therapeutic plasma exchange. The Molecular Adsorbent Recirculating System (MARS) (Gambro, Lund, Sweden) is an albumin dialysis circuit that facilitates the clearance of albumin-bound toxins including ammonia. A recent prospective randomized controlled trial of MARS therapy failed to show a 6-month survival benefit in ALF patients, but the study was hampered by a higher rate of early transplantation in patients receiving MARS therapy [25]. As such, bioartificial support systems are not recommended but may be considered under extenuating circumstances.

Criteria for Liver Transplantation

Determining if and when a liver transplant is needed remains one of the most important decisions in the care of an ALF patient. Decisions regarding transplantation should be made by an experienced multidisciplinary transplant team on a case by case basis. Therefore, the transplant team should be consulted early in the patient's hospital course as evaluation for liver transplant requires an extensive biopsychosocial evaluation which must be undertaken rapidly. After determining the etiology of ALF (see Table 64.2), use of standard prognostication tools (see Table 64.3) can aid in determining which patients are likely to recover without a transplant and which are not. Factors that favor transplantation include persistent liver failure with ongoing poor prognostic factors (according to criteria in Table 64.3), the absence of comorbid conditions such as cardiopulmonary disease, malignancy, and a favorable psychosocial profile with anticipated compliance to post-op immunosuppression [26]. Patients who are poor candidates for transplant include patients who have clear evidence of cerebral herniation or brainstem dysfunction (such as fixed, dilated pupils in the absence of any sedation), those with invasive fungal infections, and subjects with evidence of progressive multiorgan failure and refractory hypotension [26]. Of note, the decision to transplant or not is a dynamic decision which can rapidly change based upon the clinical condition of the patient. Therefore, early referral and transfer to a liver transplant center should be undertaken in ALF patients admitted at a non-transplant center.

Acknowledgements The authors would like to thank Dr. William M. Lee of the University of Texas Southwestern, Dallas, for data used in Fig. 64.3. The authors would also like to thank Dr. Krishna Rajajee of the Neuro Critical Care Division at the University of Michigan for his careful review of the manuscript.

References

1. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013;369(26):2525–34.
2. Lee WM. Recent developments in acute liver failure. Best Pract Res Clin Gastroenterol. 2012;26(1):3–16.
3. Bari K, Fontana RJ. Acetaminophen overdose: what practitioners need to know. Clin Liver Dis. 2014;4(1):17–21.
4. Craig DGN, Bates CM, Davidson JS, Martin KG, Hayes PC, Simpson KJ. Staggered overdose pattern and delay to hospital presentation are associated with adverse outcomes following paracetamol-induced hepatotoxicity. Br J Clin Pharmacol. 2012;73(2):285–94.
5. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology. 2012;55(3):965–7.
6. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology. 1989;97(2):439–45.
7. Bernal W, Donaldson N, Wyncoll D, Wendon J. Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. Lancet. 2002;359(9306):558–63.
8. Stravitz RT, Lisman T, Luketic VA, Sterling RK, Puri P, Fuchs M, et al. Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. J Hepatol. 2012;56(1):129–36.
9. Shawcross DL, Davies NA, Mookerjee RP, Hayes PC, Williams R, Lee A, et al. Worsening of cerebral hyperemia by the administration of terlipressin in acute liver failure with severe encephalopathy. Hepatology. 2004;39(2):471–5.
10. Harry R, Auzinger G, Wendon J. The clinical importance of adrenal insufficiency in acute hepatic dysfunction. Hepatology. 2002;36(2):395–402.
11. Rakela J, Mosley JW, Edwards VM, Govindarajan S, Alpert E. A double-blinded, randomized trial of hydrocortisone in acute hepatic failure. The Acute Hepatic Failure Study Group. Dig Dis Sci. 1991;36(9):1223–8.
12. Tujios SR, Hynan LS, Vazquez MA, Larson AM, Seremba E, Sanders CM, et al. Risk factors and outcomes of acute kidney injury in patients with acute liver failure. Clin Gastroenterol Hepatol. 2014;13(2):352–9.
13. Davenport A, Will EJ, Davidson AM. Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure. Crit Care Med. 1993;21(3):328–38.
14. Rolando N, Gimson A, Wade J, Philpott-Howard J, Casewell M, Williams R. Prospective controlled trial of selective parenteral and enteral antimicrobial regimen in fulminant liver failure. Hepatology. 1993;17(2):196–201.
15. Karvellas CJ, Fix OK, Battenhouse H, Durkalski V, Sanders C, Lee WM, et al. Outcomes and complications of intracranial pressure monitoring in acute liver failure: a retrospective cohort study. Crit Care Med. 2014;42(5):1157–67.
16. Kheirbek T, Pascual JL. Hypertonic saline for the treatment of intracranial hypertension. Curr Neurol Neurosci Rep. 2014;14(9):482.
17. Shami VM, Caldwell SH, Hespenheide EE, Arseneau KO, Bickston SJ, Macik BG. Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. Liver Transpl. 2003;9(2):138–43.
18. Pavese P, Bonadona A, Beaubien J, Labrecque P, Pernod G, Letoublon C, et al. FVIIa corrects the coagulopathy of fulminant hepatic failure but may be associated with thrombosis: a report of four cases. Can J Anaesth. 2005;52(1):26–9.
19. Le TV, Rumbak MJ, Liu SS, Alsina AE, van Loveren H, Agazzi S. Insertion of intracranial pressure monitors in fulminant hepatic failure patients: early experience using recombinant factor VII. Neurosurgery. 2010;66(3):455–8. –discussion458.
20. Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, Ott P. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology. 1999;29(3):648–53.
21. Bhatia V, Singh R, Acharya SK. Predictive value of arterial ammonia for complications and outcome in acute liver failure. Gut. 2006;55(1):98–104.
22. Bernal W, Hall C, Karvellas CJ, Auzinger G, Sizer E, Wendon J. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. Hepatology. 2007;46(6):1844–52.
23. Karvellas CJ, Todd Stravitz R, Battenhouse H, Lee WM, Schilsky ML, US Acute Liver Failure Study Group. Therapeutic hypothermia in acute liver failure: a multicenter retrospective cohort analysis. Liver Transpl. 2015;21(1):4–12.
24. Jalan R, Olde Damink SWM, Deutz NEP, Hayes PC, Lee A. Moderate hypothermia in patients with acute liver failure and uncontrolled intracranial hypertension. Gastroenterology. 2004;127(5):1338–46.
25. Saliba F, Camus C, Durand F, Mathurin P, Letierce A, Delafosse B, et al. Albumin dialysis with a noncell artificial liver support device in patients with acute liver failure: a randomized, controlled trial. Ann Intern Med. 2013;159(8):522–31.
26. Willars C. Update in intensive care medicine: acute liver failure. Initial management, supportive treatment and who to transplant. Curr Opin Crit Care. 2014;20(2):202–9.

Acute Lower Gastrointestinal Bleeding

65

Ali Abedi and Anoop M. Nambiar

Case Presentation

A 76 year old man with history of hypertension, chronic kidney disease, osteoarthritis, and alcohol abuse presented to the emergency department with a 1 day history of bleeding per rectum. In the early morning prior to admission, he reported intermittent painless bright red rectal bleeding. By the afternoon, he had experienced several large bowel movements consisting primarily of bright red blood and a few clots. He subsequently began feeling weak and lightheaded with ambulation. He denied any abdominal pain, nausea, or emesis. On initial assessment, he was afebrile, tachycardic with heart rate of 109 beats/min, and borderline hypotensive with blood pressure of 93/59 mmHg. Focused examination revealed a benign abdomen and fresh bright blood on digital rectal examination. Repeat vital signs while standing was notable for heart rate of 121 beats per minute and blood pressure 81/57 mmHg. Laboratory assessment was notable for hemoglobin 8.1 g/dL, stable mild renal dysfunction, and no coagulopathy.

Question While aggressive resuscitation is initiated, what should be the first diagnostic consideration?

Answer Accurate discrimination between upper and lower gastrointestinal source of hemorrhage.

Patients presenting with acute lower gastrointestinal bleeding (i.e., hemodynamically significant hematochezia) should undergo immediate focused history and physical, urgent laboratory evaluation, and initiation of aggressive volume resuscitation with fluids and blood product transfusions (if needed) without delay. The clinician needs to accurately discriminate between upper and lower gastrointestinal source of bleeding, as prognostic, diagnostic, and urgent management considerations may differ greatly. After placement of two large-bore peripheral intravenous catheters, he was aggressively resuscitated with crystalloid fluids in the emergency department. Due to evidence of ongoing bleeding and downtrending hemoglobin levels, the patient was transfused two units of packed red blood cells (PRBCs). A nasogastric tube (NGT) was placed and gastric lavage revealed bilious return without evidence of blood. Urgent gastroenterology consultation was requested and purge bowel

A. Abedi
Department of Medicine, Division of Pulmonary Diseases and Critical Care Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

A.M. Nambiar (✉)
Department of Medicine, Division of Pulmonary Diseases and Critical Care Medicine, University of Texas Health Science Center at San Antonio and the Audie L. Murphy VA Hospital, South Texas Veterans Health Care System, San Antonio, TX, USA
e-mail: nambiar@uthscsa.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_65

preparation was initiated via NGT. He was then transferred to the intensive care unit (ICU). Once hemodynamically stabilized and bowel preparation was deemed acceptable, urgent colonoscopy was performed but a bleeding source could not be identified due to overt hemorrhage that significantly limited endoscopic visualization. Emergency interventional radiology consultation was requested. In light of his increased risk for further decompensation, members of the ICU team accompanied him to the radiology suite. He successfully underwent mesenteric angiography by interventional radiology that successfully identified an active bleeding source in the proximal portion of the descending colon. Superselective coil embolization of the arterial supply to the bleeding lesion achieved hemostasis (see Fig. 65.1). The patient subsequently stabilized with normalization of his vital signs and absence of any further blood loss. He was monitored in the ICU overnight, remained stable, and subsequently downgraded to the general medicine service the next morning.

Principles of Management

Definitions

Acute lower gastrointestinal bleeding (LGIB) historically refers to gastrointestinal bleeding of recent onset (less than 3 days) from a location distal to the ligament of Treitz, located at the third portion of the duodenum, resulting in hemodynamic instability, anemia, and/or the need for blood transfusions [1]. This clinical presentation of hemodynamically unstable hematochezia (i.e., passage of fresh blood mixed with stool) differs from the majority of lower gastrointestinal bleeding episodes that tend to be self-limited bleeding and usually follows an uncomplicated clinical course [1–3]. A patient with acute LGIB may have similar clinical features to a patient with a brisk upper gastrointestinal bleed (UGIB); therefore, such a patient must be urgently evaluated for this possibility. Given that nearly all of LGIB are related to diverticular disease, ischemic colitis, vascular angiodysplasias, hemorrhoids, and colorectal cancer, it is not surprising that most patients are older (mean age at presentation ranges from 63 to 77 years) and have multiple other comorbidities, such as underlying cardiovascular, liver, and/or renal disease (Table 65.1).

Initial Evaluation

A focused history and physical examination is essential in the initial evaluation of a patient with acute LGIB. Key elements of the history include characteristics and duration of current bleeding (e.g., stool color, frequency), any associated symptoms (e.g., abdominal pain, recent change in bowel habits, fever, urgency/tenesmus, weight loss), history of similar prior bleeding episodes, relevant past medical history (e.g., recent

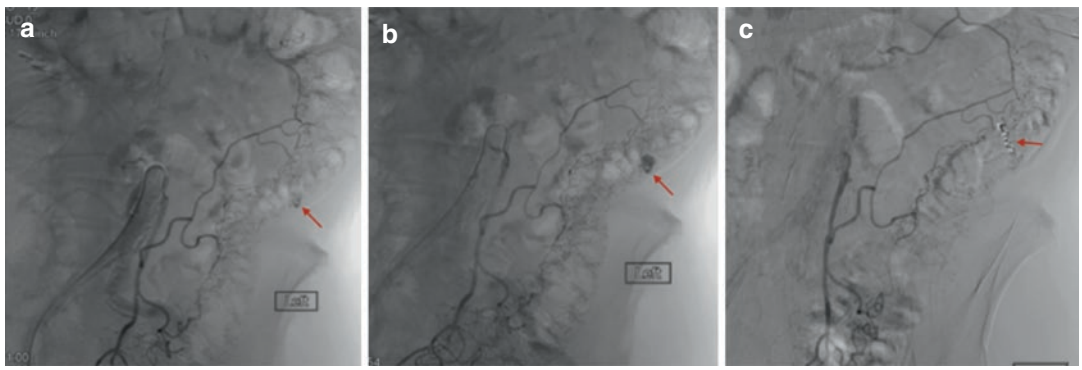


Fig. 65.1 Mesenteric angiography with coil embolization. Angiography of the colic branches with positive blush sign (Panel *A* and *B*) and following coil embolization (Panel *C*)

Table 65.1 Differential diagnosis for lower gastrointestinal bleeding

Etiology	Frequency (%)	Comments
Diverticulosis	20–65	Presents with painless hematochezia; usually resolves spontaneously in 75–80 % of patients
Angioectasia (also known as angiodysplasias or vascular ectasias)	3–15	More than two-thirds seen in patients aged >70 years; risk factors include advanced age, comorbidities, presence of multiple angioectasias, and use of anticoagulants or antiplatelet drugs
Ischemic colitis	1–19	Presents with sudden onset of abdominal cramping, followed by hematochezia; "watershed" areas of colon: splenic flexure and rectosigmoid junction typically affected
Hemorrhoids	2–64	May be incidental finding in up to 75 % of LGIB; typically present with painless, intermittent, scant hematochezia
Colorectal cancer	17	Typically present with bowel habit changes and unintentional weight loss; right-sided colonic tumors more commonly cause occult bleeding and left-sided tumors often cause hematochezia
Post-polypectomy bleeding	2–8	Complication of colonoscopy
Inflammatory bowel disease	N/A	Uncommonly present with LGIB requiring hospitalization

Adapted from ASGE Guidelines 2014 [2] with permission from Elsevier Limited
NSAID nonsteroidal anti-inflammatory drug, *N/A* not available

endoscopy with polypectomy, trauma, previous abdominal surgeries, history of peptic ulcer disease or inflammatory bowel disease, etc.), and current medications (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, anticoagulants, etc.) [1, 3, 4]. Initial and serial measurements of the patient's vital signs are essential. Resting supine tachycardia, tachypnea, and hypotension are nonspecific, but sensitive, signs of a critically ill patient. Postural changes in blood pressure (decrease by >10 mmHg) and/or heart rate (increase by 10 beats/min) from supine to standing position (i.e., orthostasic hypotension) correlates with an acute blood loss of more than 800 mL (or about 15 % of total circulatory blood volume). Marked tachycardia, tachypnea, hypotension, and depressed mental status correlates with an acute blood loss of more than 1500 mL (or about 30 % of total circulatory blood volume) [5]. In addition to focused neurologic, cardiac, pulmonary, and abdominal examinations, a digital rectal examination should be performed. Initial laboratory assessment should include a complete blood cell count, serum electrolytes, renal indices, liver function tests, coagulation profile, type and crossmatch. Additional studies such as a chest x-ray and/or electrocardiogram should be individualized to those patients also presenting with cardiopulmonary symptoms or risk factors for development of complications.

Initial Resuscitation and Management

Hemodynamic monitoring of vital signs, rapid establishment of intravenous access, and initiation of volume resuscitation should take place without delay in the emergency department. Hemodynamic monitoring should include continuous assessment of heart rate, blood pressure,

respiratory rate, and oxygen saturation by pulse oximetry. At least two large-bore diameter (18 gauge or greater) peripheral intravenous (PIV) catheters (18G or greater) should be promptly placed. Advantages of PIVs over central venous catheters (CVC) are multiple in this setting: (1) quickly establish intravenous access, (2) ease of placement by nursing staff, (3) less invasive than CVCs with reduced chance for potentially significant complications, especially in those who are hemodynamically unstable and/or coagulopathic, and (4) allowance for more rapid volume resuscitation compared to CVCs due to the shorter length and larger diameter. These advantages of PIVs must be weighed against their disadvantages that include less secure intravenous access, susceptibility to dislodgement, and inability to administer multiple medications safely, such as vasopressors. Crystalloid formulations, such as 0.9 % saline or lactated Ringer's solution, are the fluids of choice for initial resuscitation. Decisions regarding transfusion of red blood cells and other blood products, such as fresh frozen plasma and/or platelets, should be individualized, carefully weighing potential benefits in the setting of active symptomatic bleeding with the potential risks of volume overload or transfusion reactions.

Appropriate Patient Disposition

Following initial resuscitative measures in the emergency department, reassessment of the patient with acute LGIB must be performed to determine clinical stability for specific diagnostic and/or therapeutic interventions. If there remains persistent hemodynamic instability, further resuscitation is necessary with crystalloids and/or blood products (as needed) and central venous access should be established for invasive monitoring and possible use of vasopressors. At this time, the patient should be transferred to the ICU for close hemodynamic and cardiopulmonary monitoring. Although there have been multiple risk prediction scores and models reported for acute LGIB, none have been adopted in everyday clinical practice yet (see below). In general, patients with clinical evidence of ongoing or severe bleeding, those with a transfusion requirement of greater than two units of PRBCs, and those with significant comorbidities may require admission and monitoring in an ICU [6, 7].

Nasogastric Tube Lavage

Expert guidelines generally favor an algorithmic approach for determining the etiology of acute LGIB (Fig. 65.2) [1, 2]. This most commonly occurs as the result a colonic bleeding source; however, hematochezia in the setting of hemodynamic compromise should raise the clinical suspicion for a brisk UGIB [4, 8]. Therefore, patients presenting with acute LGIB should be evaluated with a NGT lavage. If gastric lavage aspirate is positive for blood, or is clear without either blood or bile, an upper GI source of bleeding has not yet been ruled out [9] and urgent gastroenterology consultation should be requested for esophagogastroduodenoscopy (EGD). Aspiration of bilious fluid in the absence of blood on NGT lavage makes UGIB unlikely. A lower gastrointestinal source of bleeding should be suspected and appropriate diagnostic testing for LGIB should now ensue.

Urgent Colonoscopy

Patients with acute LGIB who have been successfully resuscitated and are clinically stable without evidence of ongoing hemorrhage are candidates for urgent colonoscopy. This single procedure may be both diagnostic and therapeutic. According to the most recent American Society of Gastrointestinal Endoscopy (ASGE) guidelines published in 2014, urgent colonoscopy is recommended within 24 h of admission after a rapid bowel preparation in the evaluation of patients with severe hematochezia (per ASGE guidelines, this recommendation is supported by moderate quality of evidence) [2]. The overall diagnostic yield of colonoscopy in the evaluation of acute LGIB ranges from 45 to 100 %, according to multiple studies [10–12]. The most common site of bleeding in the largest series by

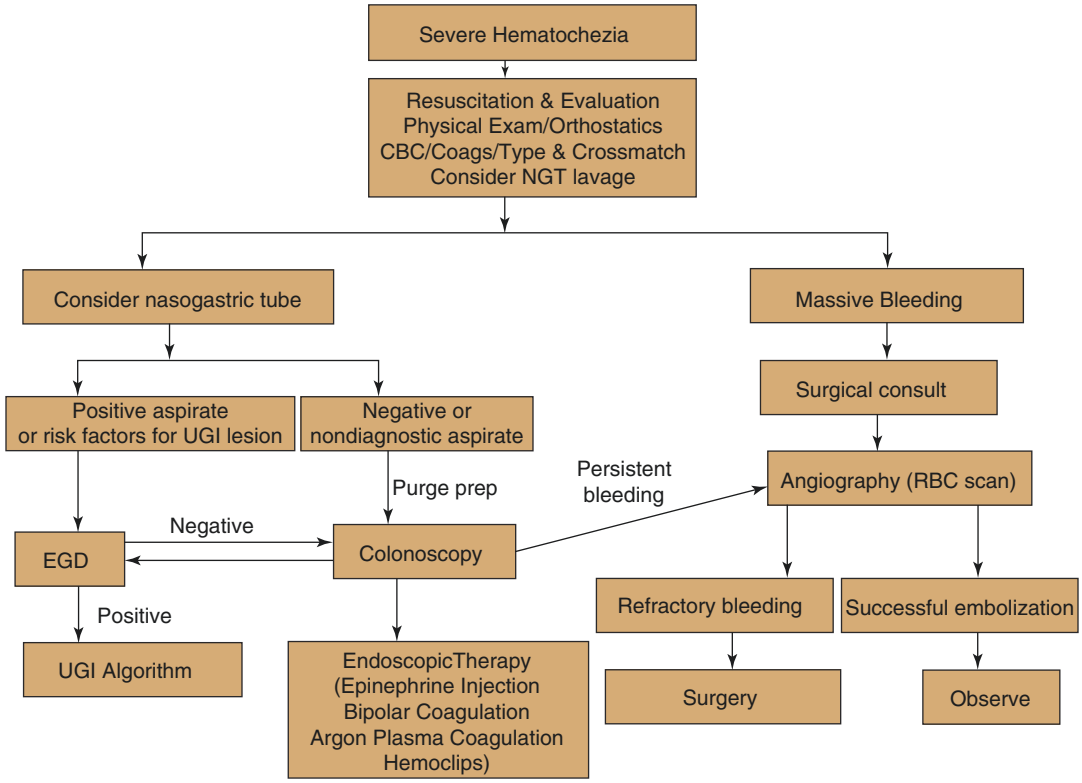


Fig. 65.2 Algorithm for management of LGIB (From ASGE Guidelines [2] with permission from Elsevier Limited)

Rossini et al. was the left colon caused most often by ulcerated carcinomas and diverticular disease [10, 13]. Colon preparation with polyethylene glycol-based solutions administered enterally (either by mouth or via NGT) is important before colonoscopy to improve visualization, increase the diagnostic yield, and reduce the risk of perforation [14]. Importantly, there is no evidence of a deleterious effect on the rate of hemorrhage with bowel preparation. Several modalities are available for endoscopic treatment of LGIB. Endoscopic treatment with epinephrine solution injection combined with thermal coagulation or endoscopic clip placement as the preferred management in patients presenting with diverticular bleeding (high quality of evidence according to ASGE guidelines) [2]. Endoscopic treatment with argon plasma coagulation as preferred management in patients with bleeding angioectasis (high quality of evidence according to ASGE guidelines) [2].

Mesenteric Angiography

For patients with severe acute LGIB with massive ongoing bleeding, hemodynamically unstable for colonoscopy, unable to be prepped, and/or for those who have failed endoscopic management, emergency consultation with interventional radiology for mesenteric angiography is essential. Mesenteric angiography can detect bleeding rate at 0.5 mL/min [15]. Superselective embolization with microcoils, polyvinyl alcohol particles, or water-insoluble gelatin (gel foam) has improved the success rate of this technique and decreased occurrence of adverse event of bowel infarction. A meta-analysis of angiography and embolization as first-line therapy for acute LGIB found embolization to be an effective treatment for diverticular bleeding, with successful hemostasis in 85 % of patients as compared to 50 % of those with bleeding from other sources at 30-day follow-up [16]. In contrast, rebleeding

after embolization for non-diverticular bleeding, such as angioectasias, may occur in greater than 40 % of patients [6].

Surgery

Surgical bowel resection is now rarely required and should only be reserved for a minority of patients who have persistent or refractory diverticular bleeding. In addition, those patients that are deemed surgical candidates with ongoing hemodynamic instability despite aggressive resuscitation, transfusion requirement of greater than six units of PRBCs, and lack of a diagnosis despite a pan-intestinal evaluation should also be considered for surgery [17]. High mortality rates have been reported with emergent surgical intervention [18].

Evidence Contour

Predicting Severity and Outcomes of LGIB

A number of different risk factors, clinical prediction scores and rules, and models have been developed and some have been validated [6, 7, 19–24]. These tools may be helpful in guiding decision-making for patients with acute LGIB regarding inpatient management, appropriate level of care, and necessity of urgent interventions. However, their usefulness and validity in everyday clinical practice has not been firmly established and, as a result, they have not yet been widely adopted.

Blood Transfusion Goals

A recently published randomized controlled trial in patients with severe acute UGIB assessed the safety and efficacy of two blood transfusion strategies: a restrictive one (transfusion when the hemoglobin level fell below 7 g/dL) versus a liberal one (transfusion when the hemoglobin level fell below <9 g/dL). They found improved survival and less bleeding in the restrictive-strategy group [25]. In the absence of available published data comparing a restrictive versus liberal blood transfusion strategy specifically for acute LGIB, decisions regarding transfusion of red blood cells and other blood products, such as fresh frozen plasma and/or platelets, should be individualized, carefully weighing potential benefits in the setting of active symptomatic bleeding with the potential risks of volume overload or transfusion reactions. It is important to recognize that patients with acute LGIB are older and have more comorbidities, such as cardiovascular disease and at increased risk for myocardial infarction [26].

Massive Transfusions

Uncontrolled hemorrhage, as may be seen in acute LGIB but more commonly in traumas, may necessitate massive blood transfusions, typically defined as ten units of red cells over 24 h or rapid infusion or five units red cells over 3 h [27]. Rapid transfusion of these large volumes can present additional management issues, such as hemostatic and metabolic abnormalities. Coagulopathy with thrombocytopenia or platelet dysfunction can result from a combination of factors related to massive transfusion. These include ongoing consumption due to active hemorrhage, as well as hypothermia and dilution of plasma components resulting from large volumes of infused crystalloids and packed red cells. Current data largely compiled from experience in the trauma setting suggests basing decisions on replacement of plasma coagulation components and platelets on measurement of hemostatic parameters rather than predetermined formulas, such as a 1:1:1 ratio of packed RBC, fresh frozen plasma and platelets [28, 29]. For this purpose, coagulation parameters (PT, aPTT), fibrinogen level, and platelet counts should be monitored after every five to ten units of red cells transfused. PT and aPTT values greater than 1.5 times the upper limit of normal should prompt transfusion of two to four units of FFP. Cryoprecipitate transfusion should be considered to maintain fibrinogen level greater than 100 mg/dL, and transfusion

of platelets is generally recommended for values below 50,000/microL [29]. Common metabolic abnormalities related to massive transfusion include hyperkalemia due to presence of extracellular potassium in packed red blood cell supernatant, hypocalcemia due to binding of free ionized calcium by citric acid resent in red cell collection bag anticoagulants, and metabolic alkalosis resulting from the metabolism of citrate to bicarbonate. Therefore, monitoring of acid–base status, ionized calcium levels, and serum potassium should be conducted frequently in patients receiving massive volume of red cell transfusions. Finally, for transfusions of more than three to five units of red blood cells, a commercial blood warmer should be used to prevent or minimize the incidence of clinically significant hypothermia [27, 28].

Diagnostic Imaging Modalities

There exists uncertainty regarding the use of diagnostic imaging modalities for patients with acute LGIB. Nuclear red blood cell scanning is the most sensitive diagnostic test for active bleeding with the ability to detect bleeding rates as low as 0.1 to 0.5 mL/min [30–32]. The use of nuclear red blood cell scanning is indicated when a bleeding source cannot be identified by colonoscopy and providing guidance for more directed application of arteriography or surgical exploration for massive LGIB. Disadvantages included lack of specificity to localize a source beyond a general area of the stomach and the relatively timely process of pre-imaging preparation [31, 32]. Recent advances in multidetector computed tomography (CT) techniques have significantly increased the sensitivity of CT angiography for the detection of active hemorrhage with sensitivity and specificity of 85 % and 92 %, respectively [33]. CT angiography is highly available, provides rapid detection and localization of a bleeding site, and is minimally invasive. Further research is needed to determine exactly where nuclear red blood cell scanning and CT angiography will be positioned in the diagnostic algorithm of acute LGIB.

Provocation Testing

Provocative challenges using anticoagulants or thrombolytics have been shown to improve rates of detection and subsequent angiographic management of previously unidentified bleeding sources [34]. However, given the life-threatening nature of acute LGIB, the risk versus benefit of provocative challenges with mesenteric angiography should be carefully assessed on a case-by-case basis. Further study is needed for fully evaluate the efficacy and safety of this approach.

References

1. Zuccaro Jr G. Management of the adult patient with acute lower gastrointestinal bleeding. American College of Gastroenterology Practice Parameters Committee. Am J Gastroenterol. 1998;93:1202.
2. ASGE Standards of Practice Committee, Pasha SF, Shergill A, Acosta RD, et al. The role of endoscopy in the patient with lower GI bleed. Gastrointest Endosc. 2014;79(6):875–85.
3. Cappell MS, Friedel D. Initial management of acute upper gastrointestinal bleeding: from initial evaluation up to gastrointestinal endoscopy. Med Clin North Am. 2008;92:491.
4. Farrell JJ, Friedman LS. Review article: the management of lower gastrointestinal bleeding. Aliment Pharmacol Ther. 2005;21:1281.
5. Ebert RV, Stead EA, Gibson JG. Response of normal subjects to acute blood loss. Arch Intern Med. 1941;68:578.
6. Bounds BC, Kelsey PB. Lower gastrointestinal bleeding. Gastrointest Endosc Clin N Am. 2007;17:273.
7. Barnert J, Messmann H. Diagnosis and management of lower gastrointestinal bleeding. Nat Rev Gastroenterol Hepatol. 2009;6:637.
8. Srygley FD, Gerardo CJ, Tran T, Fisher DA. Does this patient have a severe upper gastrointestinal bleed? JAMA. 2012;307:1072.
9. Cuellar RE, Gavaler JS, Alexander JA, Brouillete DE, et al. Gastrointestinal tract hemorrhage. The value of nasogastric aspirate. Arch Intern Med. 1990;150:1380.
10. Jensen DM, Machicado GA. Diagnosis and treatment of severe hematochezia. The role of urgent colonoscopy after purge. Gastroenterology. 1988;95:1569.
11. Green BT, Rockey DC, Portwood G, et al. Urgent colonoscopy for evaluation and management of acute lower gastrointestinal hemorrhage: a randomized controlled trial. Am J Gastroenterol. 2005;100:2395.
12. Strate LL, Syngal S. Predictors of utilization of early colonoscopy vs radiography for severe lower intestinal bleeding. Gastrointest Endosc. 2005;61:46.

13. Rossini FP, Ferrari A, Spandre M, et al. Emergency colonoscopy. World J Surg. 1989;13:190.
14. Elta GH. Urgent colonoscopy for acute lower GI bleeding. Gastrointest Endosc. 2004;59:402.
15. Wong Kee Song LM, Baron TH. Endoscopic management of acute lower gastrointestinal bleeding. Am J Gastroenterol. 2008;103:1881.
16. Khanna A, Ognibene SJ, Koniaris LG. Embolization as first-line therapy for diverticulosis-related massive lower gastrointestinal bleeding: evidence from a meta-analysis. J Gastrointest Surg. 2008;9:343.
17. Bokhari M, Vernava AM, Ure T, Longo WE. Diverticular hemorrhage in the elderly—is it well tolerated? Dis Colon Rectum. 1996;39:191.
18. Ansari MZ, Collopy BT, Hart WG, et al. In-hospital mortality and associated complicatons after bowel surgery in Victorian public hospitals. Aust N Z J Surg. 2000;70:6.
19. Velayos FS, Williamson A, Sousa KH, et al. Early predictors of severe lower gastrointestinal bleeding and adverse outcomes: a prospective study. Clin Gastroenterol Hepatol. 2004;2:485.
20. Kollef MH, Canfield DA, Zuckerman GA. Triage considerations for patients with acute gastrointestinal hemorrhage admitted to a medical intensive care unit. Crit Care Med. 1995;23:1048.
21. Kollef MH. Crit Care Med. 1997;25:1125; Strate LL, Orav EJ, Syngal S. Early predictors of severity in acute lower intestinal tract bleeding. Arch Int Med. 2003;163:838.
22. Strate LL, Orav EJ, Syngal S. Early predictors of severity in acute lower intestinal tract bleeding. Arch Intern Med. 2003;163:838.
23. Strate LL, Saltzman JR, Ookubo R, et al. Validation of a clinical prediction rule for severe acute lower intestinal bleeding. Am J Gastroenterol. 2005;100:1821.
24. Das A, Ben-Menachem T, Cooper GS, et al. Prediction of outcome in acute lower-gastrointestinal haemorrhage based on an artificial neural network: internal and external validation of a predictive model. Lancet. 2003;362:1261.
25. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:11.
26. Wu WC, Wu WC, Rathore SS, Wang Y, et al. Blood transfusion in elderly patients with acute myocardial infarction. N Engl J Med. 2001;345:1230.
27. American College of Surgeons Committee on Trauma. Advanced trauma life support (ATLS) student course manual. 9th ed. Chicago: American College of Surgeons; 2012.
28. Kautza BC, Cohen MJ, Cuschieri J, et al. Changes in massive transfusion over time: an early shift in the right direction? J Trauma Acute Care Surg. 2012;72:106.
29. Hardy JF, De Moerloose P, Samama M, et al. Massive transfusion and coagulopathy: pathophysiology and implications for clinical management. Can J Anaesth. 2004;51:293.
30. Dusold R, Burke K, Carpentier W, Dyck WP. The accuracy of technetium-99m-labeled red cell scintigraphy in localizing gastrointestinal bleeding. Am J Gastroenterol. 1994;89:345.
31. Olds GD, Cooper GS, Chak A, et al. The yield of bleeding scans in acute lower gastrointestinal hemorrhage. J Clin Gastroenterol. 2005;39:273.
32. Feingold DL, Caliendo FJ, Chinn BT, et al. Does hemodynamic instability predict positive technetium-labeled red blood cell scintigraphy in patients with acute lower gastrointestinal bleeding? A review of 50 patients. Dis Colon Rectum. 2005;48:1001.
33. García-Blázquez V, Vicente-Bártulos A, Olavarria-Delgado A, et al. Accuracy of CT angiography in the diagnosis of acute gastrointestinal bleeding: systematic review and meta-analysis. Eur Radiol. 2013;23:1181.
34. Kim CY, Suhocki PV, Miller Jr MJ, et al. Provocative mesenteric angiography for lower gastrointestinal hemorrhage: results from a single-institution study. J Vasc Interv Radiol. 2010;21:477.

Diagnosis and Management of Clostridium Difficile Infection (CDI)

66

Paul C. Johnson, Christopher F. Carpenter, and Paul D. Bozyk

Case Presentation

A 75 year old Caucasian male presented to the hospital with 1 week history of watery diarrhea, five to six episodes daily, accompanied by progressive weakness. Three weeks prior to onset of symptoms, he was admitted for acute exacerbation of chronic obstructive pulmonary disease and was treated with a 5-day course of moxifloxacin and systemic steroids. On presentation he had no leukocytosis (7.0) but had acute kidney injury with a creatinine of 3.6 compared to his baseline of 1.0.

Question What is the patient's most likely diagnosis?

Answer *Clostridium difficile* diarrhea.

PCR testing for toxigenic *Clostridium difficile* returned positive, and he was started on vancomycin 125 mg PO q6h. He had borderline hypotension initially, with some improvement with fluid resuscitation. Over the first several days of admission he had persistent watery stools, about six episodes daily associated with abdominal distension. Infectious Diseases was consulted given lack of improvement and development of leukocytosis (13.5), and vancomycin was increased to 500 mg PO q6h with addition of metronidazole 500 mg IV q8h. Despite this escalation of antibiotic therapy, he developed worsening abdominal distension and hypotension requiring vasopressor support. CT abdomen/pelvis was performed, demonstrating diffuse colonic dilatation with multiple air-fluid levels, consistent with toxic megacolon (Figs. 66.1, 66.2, and 66.3). He underwent total colectomy with end ileostomy and subsequently stabilized.

Principles of Management

Symptoms of C. Difficile Infection

Patients may present with a wide range of clinical manifestations, varying from asymptomatic carriage to shock and colon perforation. Asymptomatic carriage is more frequent than previously thought, ranging geographically from 4.4 to 23.2 % of patients admitted from the community [1]. Watery diarrhea, with or without the presence of mucus, is the classic presenting symptom, but patients may eventually progress to colitis, megacolon, and shock. Significant neutrophilic leukocytosis and acute kidney injury are commonly found with severe disease.

P.C. Johnson (✉)
Section of Infectious Diseases and International Medicine, Beaumont Hospital, Royal Oak, MI, USA
e-mail: paul.johnson@beaumont.edu

C.F. Carpenter
Section of Pulmonary, Critical Care, and Sleep Medicine, Beaumont Hospital, Royal Oak, MI, USA

P.D. Bozyk
Medical Intensive Care Unit, Department of Medicine, Beaumont Hospital, Royal Oak, MI, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_66

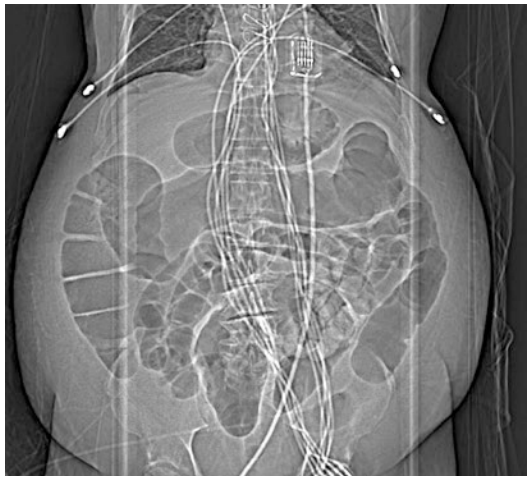


Fig. 66.1 Plain abdominal film

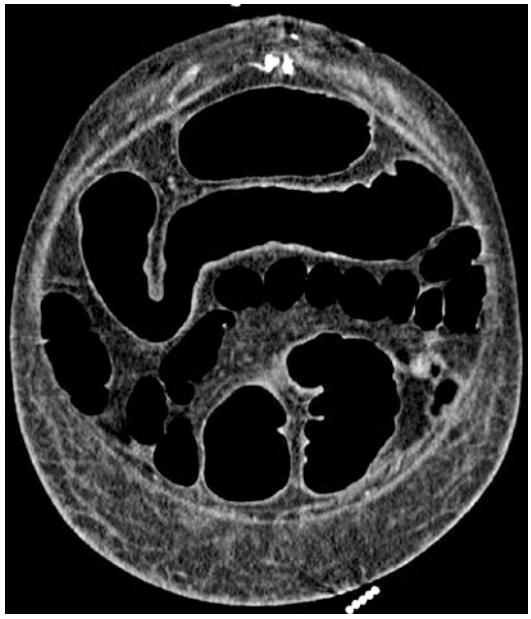


Fig. 66.2 Coronal view CT abdomen

Extracolonic manifestations, including bacteremia and ileitis, are rare, but when present are associated with a 25 % mortality rate [2].

Diagnosis

Diagnosis can be made by several methods, including toxin enzyme immunoassays, toxin gene nucleic acid amplification tests, direct culture, and detection of glutamate dehydrogenase. Toxigenic assay method is preferred, as some patients may be asymptomatic carriers [3]. Direct visualization of pseudomembranes can be performed, however the specificity is low for *C. difficile* and operator-dependent, and the procedure carries an increased risk of perforation [4].

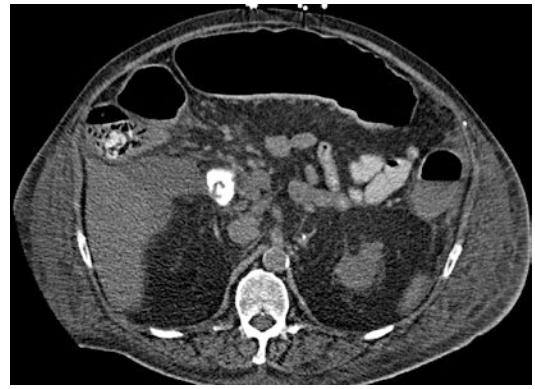


Fig. 66.3 Axial view CT abdomen

Risk Factors

The predominant risk factor for acquisition of *C. difficile* infection is antibiotic use, particularly clindamycin, cephalosporins, and fluoroquinolones. Other risk factors include inflammatory bowel disease, immunodeficiency, malnutrition, solid organ transplantation, and hematopoietic stem cell transplantation. Use of proton pump inhibitors has conflicting evidence as a risk factor for *C. difficile* infection [5].

Severity of Disease

The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) have described criteria for defining severity of disease, based on presence of leukocytosis, AKI, and shock (Table 66.1) in 2010. Medical therapies are aimed at treating *C. difficile* colitis based upon the severity of disease [6].

Table 66.1 IDSA/SHEA 2010 *C. difficile* treatment recommendations

Clinical definition	Supportive clinical data	Recommended treatment	Strength of recommendation
Initial episode, mild or moderate	WBC ≤15,000 and serum creatinine <1.5× baseline	Metronidazole 500 mg PO TID for 10–14 days	A-I
Initial episode, severe[a]	WBC ≥15,000 or serum creatinine ≥1.5× baseline	Vancomycin 125 mg PO QID for 10–14 days	B-I
Initial episode, severe, complicated	Hypotension or shock, ileus, megacolon	Vancomycin 500 mg PO QID plus metronidazole 500 mg IV q8h. Consider PR vancomycin if ileus present	C-III
First recurrence		Same as for initial episode	A-II
Second recurrence		Vancomycin in a tapered and/or pulsed regimen	B-III

[a]The criteria proposed for defining severe or complicated CDI are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI
From Cohen et al. [6]. © Cambridge University Press

Medical Therapies

Clostridium difficile infection can induce hypovolemia, shock, and multiple electrolyte abnormalities; hence, a cornerstone of appropriate treatment is supportive critical care. Several antimicrobials are currently available to treat *C. difficile* infection. Metronidazole, a commonly used initial therapy for non-severe *Clostridium difficile* infection despite lack of FDA approval, is a nitroimidazole antibiotic which functions by interrupting the helical form of DNA. Vancomycin inhibits cell wall synthesis of *C. difficile*. It must be administered via an enteral route and it is the drug of choice for severe disease, and prolonged treatment regimens have been devised to successfully treat repeatedly recurrent disease. A staggered taper and withdrawal method of vancomycin administration with a probiotic has been described to be as effective as fecal microbiota transplant [7].

Fidaxomicin is a macrocyclic antibiotic that inhibits RNA polymerase in Gram-positive bacteria. It was approved by the FDA in April 2011 for treatment of *C. difficile* infection after being found to be non-inferior to treatment with vancomycin. As of now, a major limiting factor to fidaxomicin's use is cost of therapy, though there is data that suggests it may reduce recurrence rates in select populations, which may offset the increased cost. Rifaximin is a less commonly used treatment adjunct that inhibits RNA polymerase, thereby interfering with transcription of DNA. Administration had previously been used anecdotally after a course of standard antibiotic therapy as a "chaser" with seemingly good results. A recent randomized, double-blinded study demonstrated that administration of rifaximin 400 mg PO TID for 20 days after completing standard *C. difficile* therapy resulted in fewer recurrences of infection [8].

Guidelines published in the American Journal of Gastroenterology provide similar recommendations regarding medical therapies guided by severity of disease [9].

Surgical Intervention

When medical therapies fail and patients develop worsening sepsis and shock, surgical intervention is warranted. There are multiple approaches to this including partial or total colectomy. Recently, more surgeons have been using the approach of creation of a diverting ileostomy with vancomycin colonic lavage. Studies have demonstrated reduced mortality and morbidity compared to historical controls when this method is pursued [10].

Epidemiology and Infection Control

Infections due to *C. difficile* are on the rise and are more prevalent than previously assumed. In

2011, it is estimated that there were nearly half a million infections, associated with approximately 29,000 deaths [11]. Every intensive care unit should have protocols in place for infection prevention and control measures when patients are admitted with *C. difficile* infection. Many ICU-related outbreaks have been described, resulting in a significant impact on morbidity, mortality, and healthcare costs for these high-risk patients. Typical prevention and control measures include appropriate hand hygiene with soap and water, gowning and gloving, private rooms, chlorine-based disinfection, and aggressive antimicrobial stewardship [12]. Studies have revealed healthcare workers' colonization rates to range between 0 and 13 %, suggesting this may have less impact than indirect transmission between hospitalized patients via the environment and healthcare workers hands [13]. Hypervirulent strains of *C. difficile* have emerged, particularly NAP1/BI/027, which are associated with lower clinical cure rates than other *C. difficile* strains [14].

Evidence Contour

Fecal Microbiota Transplant

Fecal transplantation, or the introduction of fresh donor feces into the recipient's GI tract, has been successful in treatment of refractory recurrent *C. difficile* infection. Transplantation may be performed via nasogastric tube or direct inoculation during colonoscopy, with studies demonstrating approximately 90 % sustained cure rate in patients with disease refractory to antibiotic therapy [15]. Duodenal infusion through a nasoduodenal tube has also been shown to be effective in treatment of *C.* difficile infection [16]. However, no large studies have been performed to provide more than anecdotal evidence for this intervention in this setting.

Capsulized Frozen Fecal Microbiota

Recent studies using frozen fecal microbiota transplantation through a frozen encapsulated form have demonstrated similar efficacy to traditional allogenic fecal transplantation [17].

Probiotics

Studies on probiotics for C. difficile infection do not support their use as a treatment adjunct; however there is evidence suggesting benefit in the prevention of *C. difficile* infection for patients who are on antibiotic therapy and are at risk for disease.

Monoclonal Antibodies and Vaccines

Monoclonal antibodies against toxin A and toxin B have been developed, with promising phase II study results. These are currently in phase III of development. Clostridium difficile vaccines are also in development.

Nontoxogenic C. Difficile Spores

Studies are in process regarding purposeful colonization with non-toxogenic strains of *C. difficile* as a competitive inhibitor of toxigenic C. difficile. No significant adverse events have been reported with their use and this intervention may provide clinical benefit [18].

Investigational Antibiotics

Several new antimicrobials are currently in the pipeline, also with promising data. These include cadazolid (an oxazolidinone), LFF571 (a semisynthetic thiopeptide), and SMT 19969. A bile salt analogue in development, referred to as CamSA, has been found to prevent germination of *C. difficile* spores [19].

References

1. Hung YP, Lee JC, Lin HJ, Liu HC, Wu YH, Tsai PJ, et al. Clinical impact of Clostridium difficile colonization. J Microbiol Immunol Infect. 2014;48(3):241–8.
2. Gupta A, Patel R, Baddour LM, Pardi DS, Khanna S. Extraintestinal Clostridium difficile infections: a single-center experience. Mayo Clin Proc. 2014;89(11):1525–36.

3. Planche TD, Davies KA, Coen PG, Finney JM, Monahan IM, Morris KA, et al. Differences in outcome according to Clostridium difficile testing method: a prospective multicentre diagnostic validation study of C difficile infection. Lancet Infect Dis. 2013;13(11):936–45.
4. Wei SC, Wong JM, Hsueh PR, Shieh MJ, Wang TH, Luh KT, et al. Diagnostic role of endoscopy, stool culture, and toxin A in Clostridium difficile-associated disease. J Formos Med Assoc. 1997;96(11):879–83.
5. Lo Vecchio A, Zacur GM. Clostridium difficile infection: an update on epidemiology, risk factors, and therapeutic options. Curr Opin Gastroenterol. 2012; 28(1):1–9.
6. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431–55.
7. Bakken JS. Staggered and tapered antibiotic withdrawal with administration of kefir for recurrent Clostridium difficile infection. Clin Infect Dis. 2014; 59(6):858–61.
8. Garey KW, Ghantoji SS, Shah DN, Habib M, Arora V, Jiang ZD, et al. A randomized, double-blind, placebo-controlled pilot study to assess the ability of rifaximin to prevent recurrent diarrhoea in patients with Clostridium difficile infection. J Antimicrob Chemother. 2011;66(12):2850–5.
9. Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol. 2013;108(4):478–98.
10. Neal MD, Alverdy JC, Hall DE, Simmons RL, Zuckerbraun BS. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated Clostridium difficile associated disease. Ann Surg. 2011;254(3):423–7; discussion 7–9.
11. Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of Clostridium difficile infection in the United States. N Engl J Med. 2015;372(9):825–34.
12. Loo VG. Environmental interventions to control Clostridium difficile. Infect Dis Clin North Am. 2015;29(1):83–91.
13. Friedman ND, Pollard J, Stupart D, Knight DR, Khajehnoori M, Davey EK, et al. Prevalence of Clostridium difficile colonization among healthcare workers. BMC Infect Dis. 2013;13:459.
14. Petrella LA, Sambol SP, Cheknis A, Nagaro K, Kean Y, Sears PS, et al. Decreased cure and increased recurrence rates for Clostridium difficile infection caused by the epidemic C. difficile BI strain. Clin Infect Dis. 2012;55(3):351–7.
15. Mattila E, Uusitalo-Seppala R, Wuorela M, Lehtola L, Nurmi H, Ristikankare M, et al. Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection. Gastroenterology. 2012;142(3):490–6.
16. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med. 2013;368(5):407–15.
17. Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing Clostridium difficile infection. JAMA. 2014;312(17):1772–8.
18. Villano SA, Seiberling M, Tatarowicz W, Monnot-Chase E, Gerding DN. Evaluation of an oral suspension of VP20621, spores of nontoxigenic Clostridium difficile strain M3, in healthy subjects. Antimicrob Agents Chemother. 2012;56(10):5224–9.
19. Tran MC, Claros MC, Goldstein EJ. Therapy of Clostridium difficile infection: perspectives on a changing paradigm. Expert Opin Pharmacother. 2013;14(17):2375–86.

Principles of Nutrition in the Critically Ill Patient

67

Jacqueline L. Gierer, Jill Gualdoni, and Paul D. Bozyk

Case Presentation

A 53 year old female presented to the Emergency Center complaining of increased sputum production and dyspnea. She was recently discharged from the hospital. She had a body mass index (BMI) of 27, with serum albumin of 2.0 mg/dL. Her blood pressure was 168/105 mmHg and heart rate was 144 beats per minute. Temperature was 38.6 °C. EKG showed sinus tachycardia. Respiratory rate was 28 breaths per minute with SpO_2 89% on 100% FiO_2. Arterial blood gas (ABG) revealed a mixed metabolic and respiratory acidosis, and she had a leukocytosis with left shift. Chest radiograph showed patchy bilateral infiltrates with a dense consolidation in the right upper lobe. She was intubated and started on IV fluids and empiric antibiotics for hospital-acquired pneumonia. She was admitted to the ICU.

Question What is the best approach to nutrition in this intubated patient?

Answer Start enteric feeding as soon as possible. No indication for parenteral nutrition.

J.L. Gierer • J. Gualdoni
Internal Medicine, Beaumont Health, Royal Oak, MI, USA

P.D. Bozyk (✉)
Medical Intensive Care Unit, Department of Medicine, Beaumont Health, Royal Oak, MI, USA
e-mail: Paul.Bozyk@beaumont.edu

Patients can benefit from early enteric feeding that can protect the digestive tract, have systemic anti-inflammatory effects and improve mortality. This patient experienced hypotension after initiation of mechanical ventilation despite adequate fluid resuscitation. A central line was placed and vasopressor support was initiated with improvement in hemodynamics. She was stabilized and approximately 4 h later an orogastric tube was placed. Enteral nutrition was initiated with a lipid and protein rich formula, to a goal of 50 mL/h. Increased residuals and hypoactive bowel sounds were noted, and subsequently managed with metoclopramide. Despite increased gastric residuals, the patient was advanced to full feeds. The patient clinically improved over the next 3 days and was subsequently extubated. She passed a swallow evaluation and an oral diet was initiated.

Principles of Nutrition

If the Gut Works, Use It

Enteral Nutrition (EN) is considered by all medical societies to be the preferred route of providing nutrition to critically ill patients, including those who are intubated, and should be ideally be initiated within 48 h of hospitalization [1–7]. Enteric feeding has been associated with significant reduction in 28-day mortality, while being more accessible and less expensive than parenteral nutrition [3, 8, 9]. Early enteric feeding with

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_67

a lipid and protein-rich formula has an anabolic effect essential to the healing process in critical illness and in preservation of the gut mucosa, maintaining gut associated lymphoid tissue, and promoting protection via the gut's natural flora [10–12]. Parenteral nutrition (PN) has been associated with a higher degree of infection, especially nosocomial infection, and mortality than EN, particularly among patients with higher severity of critical illness as assessed by Acute Physiologic Assessment and Chronic Health Evaluation (APACHE II) score. The Impact of Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients trial (EPaNIC,) a 2011 RCT involving 4640 ICU patients evaluated early vs. late initiation of PN [11]. It demonstrated reduced rates of early alive discharge from the ICU and hospital with supplemented PN than with EN alone. Additionally, the earlier PN is initiated, the worse the outcome [3, 6]. With PN the patient does not benefit from stimulating the gut and endures complications associated with infusing a high glucose concentration and fat globules directly into the venous system [13]. A meta-analysis of PN compared with no nutrition found an almost doubled risk of dying in the PN group [14]. In the circumstance that early EN is impossible, nutrition should be withheld for up to 7 days, unless the patient has evidence of protein-calorie malnutrition [6]. This has become a Critical Care recommendation of the Choosing Wisely campaign. If the decision is made to provide PN, consider discontinuation once EN becomes feasible or when markers of nutritional status improve.

Full Feedings are Preferred; Trophic Feedings May Be Acceptable

The Surviving Sepsis Campaign [15] advises that, if a septic patient cannot tolerate full caloric needs through EN, trophic feeds are acceptable for up to 6 days, and PN should not be initiated. This assumes the patient is not malnourished prior to ICU admission. Trophic feeds of at least 25 % of daily nutritional needs may have a protective effect on the bowel [2, 10, 16–18]. The EDEN trial, a multi-center RCT evaluating 1000 patients with acute lung injury, found no significant difference in mortality between trophic and full feedings, though it is important to note that all patients in the study were well-nourished, with a mean BMI of 30 [18]. Moderate obesity is shown to be protective during critical illness; however, increased protein supplementation does not appear to limit muscle wasting or loss of lean body mass [19–21].

Immunologic Benefits of Enteric Feedings

Small enteral feeds are enough to cause enzyme secretion from the brush border and preserve gut epithelium and structure, thus preventing increased permeability [3]. Feeding also preserves commensal bacteria which further contribute to gut integrity by stimulating mucous production, while allowing competitive inhibition of pathogens and interfering with expression of virulence factors on pathogenic bacteria [3]. Enteric feeds have an anti-inflammatory effect on the gut via the gut-brain axis, and as such, should be considered a therapeutic modality amongst conditions of gastrointestinal (GI) inflammation such as pancreatitis or colitis [12].

Do Not Use Increased Gastric Residuals or Decreased Bowel Sounds as Markers upon Which to Hold Feedings

Despite all of the benefits of early enteric feedings, this goal is not always accomplished. One major barrier to appropriate early nutrition is the practice of holding feedings for gastric residuals or decreased bowel sounds [6]. Patients in the ICU are often too ill to have swallowed enough air to allow for bowel sounds. Multiple studies have shown that gastric emptying and reflux has no correlation with incidence of ventilator-associated pneumonia (VAP) [22–24]. Aspiration pneumonia is likely more resultant of oropharyngeal/subglottic secretions with pathogenic microbes

than reflux of gastric contents [23, 24]. If gastric residuals are checked, there appears to be no worsening of outcome with gastric residuals up to 500 mL [24]. Absence of gastric residual monitoring may not be inferior to monitoring residuals in terms of the likelihood of nosocomial pneumonia [23]. Therefore, in the absence of a known GI dysmotility, orogastric or nasogastric feeding should be initiated. If EN is poorly tolerated based on residuals or coughing, prokinetic agents such as metoclopramide, or erythromycin, can be started [25]. If these practices are still unsuccessful, post-pyloric feeds could be considered, with the understanding that the patient-important outcomes, such as VAP, emesis, aspiration, diarrhea, and mortality may not change [25].

Evidence Contour

The CALORIES Trial Did Not Reliably Support PN due to Study Design

In the CALORIES Trial [26], 2400 patients in 33 ICUs in England were randomized to either EN or PN for up to 5 days. The authors hypothesized that more patients in the PN arm would be able to achieve nutritional goals earlier, leading to a relative risk reduction in mortality. Although there was no difference in 30 day mortality between groups (33 % vs. 34 %) the patients in the PN group did not get more calories than those in the EN group in this pragmatic trial. In addition, although there was no increase in rate of infection in the PN group, this is likely because infection rate in PN is dose-dependent [1–3, 5]. Pragmatic trials are important in demonstrating the challenges of protocol implementation but are not explanatory in nature and the superiority of one method over another cannot be concluded from this trial.

Actual Caloric Goals Remain an Area of Ongoing Research

The actual caloric goals in critical illness have not yet been defined. Most are estimated through calculations based on characteristics of the patient prior to illness onset and illness-severity scores [27]. A table of commonly used predictive equations can be found here [28]. Indirect calorimetry is suggested to be the gold standard in measuring resting energy expenditure [29], though its standard and frequent use is often impractical [30]. There can be significant differences between measured and predicted energy expenditures [28], though the effect on patient outcomes is not well defined.

Actual Micronutrient Goals Are Not Clear

Adequate intake of micronutrients and electrolytes, especially phosphate, are essential to adenosine tri-phosphate (ATP) formation and the catabolic process of critical illness. Deficiency is implicated in refeeding syndrome, in which intake after starvation results in insulin-mediated phosphate uptake, with resultant cardiac and/or respiratory failure. The administration of high dose selenium, copper, manganese, zinc, iron, and Vitamins E, C, and beta carotene have been proposed to reduce oxidative cellular damage and organ failure [1, 10]. A meta-analysis evaluating micronutrient supplementation during acute critical illness to prevent refeeding syndrome suggested supplementation with high dose trace elements and vitamins may improve outcomes of critically ill patients [31]. However, a subsequent well-designed RCT showed no benefit of micronutrient supplementation, and supplementation with glutamine was associated with increased mortality [32].

No Recommendations Can Be Made for or Against Specific Lipid Choices in Tube Feeds

Ω-3 fatty acids that are present in fish oil have been shown to have anti-inflammatory effects, whereas other types of lipids have neutral or pro-inflammatory immune effects. Hence, it was hypothesized the use of Ω-3 fatty acids would have a beneficial effect in treatment of acute lung

injury and sepsis. In a study published in 2008, a modified enteric feed with increased ratio of Ω-3 fatty acids to other lipids was administered and was shown to reduce rates of death and new organ failure [33]. However, the OMEGA trial, a multicenter RCT testing the effects of omega supplementation on the rate of sudden cardiac death in survivors of acute myocardial infarction, was stopped early for futility when it showed no benefit with the administration of Ω-3 fatty acids plus antioxidants. No recommendations can be made at this time for or against specific lipid choice in tube feeds [18].

Obese Patients Should Be Treated Like Normal or Underweight Patients

Obesity has been suggested to be protective in critical illness [17, 27], which may often lead to delayed initiation of nutrition. However, an observational cohort study found many obese critically ill patients were malnourished, and had worse outcomes than obese patients with adequate nutritional status [14, 20]. This suggests that obese patients with malnutrition may not have the same protective effect, and should be treated the same as normal-weight or underweight malnourished patients.

References

1. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med. 2014;370(13):1227–36.
2. Cook D, Arabi Y. The route of early nutrition in critical illness. N Engl J Med. 2014;371(18):1748–9.
3. Desai SV, McClave SA, Rice TW. Nutrition in the ICU: an evidence-based approach. Chest. 2014;145(5):1148–57.
4. Doig GS, Simpson F, Sweetman EA, Finfer SR, Cooper DJ, Heighes PT, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA. 2013;309(20):2130–8.
5. McClave SA, Martindale RG, Rice TW, Heyland DK. Feeding the critically ill patient. Crit Care Med. 2014;42(12):2600–10.
6. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2009;33(3):277–316.
7. Peter JV, Moran JL, Phillips-Hughes J. A metaanalysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients. Crit Care Med. 2005;33(1):213–20; discussion 260–1.
8. Halpern SD, Becker D, Curtis JR, Fowler R, Hyzy R, Kaplan LJ, et al. An official American Thoracic Society/American Association of Critical-Care Nurses/American College of Chest Physicians/Society of Critical Care Medicine policy statement: the Choosing Wisely(R) Top 5 list in Critical Care Medicine. Am J Respir Crit Care Med. 2014;190(7):818–26.
9. Kutsogiannis J, Alberda C, Gramlich L, Cahill NE, Wang M, Day AG, et al. Early use of supplemental parenteral nutrition in critically ill patients: results of an international multicenter observational study. Crit Care Med. 2011;39(12):2691–9.
10. van Zanten AR, Sztark F, Kaisers UX, Zielmann S, Felbinger TW, Sablotzki AR, et al. High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomized clinical trial. JAMA. 2014;312(5):514–24.
11. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506–17.
12. Lewis SJ, Andersen HK, Thomas S. Early enteral nutrition within 24 h of intestinal surgery versus later commencement of feeding: a systematic review and meta-analysis. J Gastrointest Surg. 2009;13(3):569–75.
13. Marik PE, Pinsky M. Death by parenteral nutrition. Intensive Care Med. 2003;29(6):867–9.
14. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P, Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr. 2003;27(5):355–73.
15. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med. 2013;39(2):165–228.
16. Arabi YM, Tamim HM, Dhar GS, Al-Dawood A, Al-Sultan M, Sakkijha MH, et al. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. Am J Clin Nutr. 2011;93(3):569–77.
17. Griffiths RD. Nutrition for critically ill patients: how much is enough? JAMA. 2012;307(8):845–6.
18. Rice TW, Mogan S, Hays MA, Bernard GR, Jensen GL, Wheeler AP. Randomized trial of initial trophic

versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. Crit Care Med. 2011;39(5):967–74.
19. Pickkers P, de Keizer N, Dusseljee J, Weerheijm D, van der Hoeven JG, Peek N. Body mass index is associated with hospital mortality in critically ill patients: an observational cohort study. Crit Care Med. 2013;41(8):1878–83.
20. Robinson MK, Mogensen KM, Casey JD, McKane CK, Moromizato T, Rawn JD, et al. The relationship among obesity, nutritional status, and mortality in the critically ill. Crit Care Med. 2015;43(1):87–100.
21. Villet S, Chiolero RL, Bollmann MD, Revelly JP, Cayeux RNMC, Delarue J, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr. 2005;24(4):502–9.
22. Montejo JC, Minambres E, Bordeje L, Mesejo A, Acosta J, Heras A, et al. Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. Intensive Care Med. 2010;36(8):1386–93.
23. Reignier J, Mercier E, Le Gouge A, Boulain T, Desachy A, Bellec F, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA. 2013;309(3):249–56.
24. Torres A, Serra-Batlles J, Ros E, Piera C, Puig de la Bellacasa J, Cobos A, et al. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. Ann Intern Med. 1992;116(7):540–3.
25. Davies AR, Morrison SS, Bailey MJ, Bellomo R, Cooper DJ, Doig GS, et al. A multicenter, randomized controlled trial comparing early nasojejunal with nasogastric nutrition in critical illness. Crit Care Med. 2012;40(8):2342–8.
26. Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med. 2014;371(18):1673–84.
27. Frankenfield DC, Ashcraft CM. Estimating energy needs in nutrition support patients. JPEN J Parenter Enteral Nutr. 2011;35(5):563–70.
28. Kross EK, Sena M, Schmidt K, Stapleton RD. A comparison of predictive equations of energy expenditure and measured energy expenditure in critically ill patients. J Crit Care. 2012;27(3):321.e5-321.12.
29. Frankenfield D, Hise M, Malone A, Russell M, Gradwell E, Compher C, et al. Prediction of resting metabolic rate in critically ill adult patients: results of a systematic review of the evidence. J Am Diet Assoc. 2007;107(9):1552–61.
30. Wooley JA. Indirect calorimetry: applications in practice. Respir Care Clin N Am. 2006;12(4):619–33.
31. Manzanares W, Dhaliwal R, Jiang X, Murch L, Heyland DK. Antioxidant micronutrients in the critically ill: a systematic review and meta-analysis. Crit Care. 2012;16(2):R66.
32. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013;368(16):1489–97.
33. Pontes-Arruda A, Demichele S, Seth A, Singer P. The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis of outcome data. JPEN J Parenter Enteral Nutr. 2008;32(6):596–605.

Spontaneous Bacterial Peritonitis

68

Abdul W. Raif Jawid and Indhu M. Subramanian

Case Presentation

A 60-year-old male with history of alcohol dependence and cirrhosis presented from a skilled nursing facility with a 1 day history of altered level of consciousness. His cirrhosis had been complicated by portal hypertension resulting in hepatic encephalopathy, recurrent ascites and esophageal varices requiring multiple recent hospitalizations. The family reported that the patient had non-colicky abdominal pain, subjective fever, and nausea for 2 days. He had been receiving therapeutic large-volume paracentesis every month for the previous year and his last paracentesis had been 3 weeks prior to presentation. His past medical history also included chronic obstructive pulmonary disease and depression. His medications included furosemide, spironolactone, fluticasone/salmeterol, tiotropium bromide and citalopram.

Vital signs on admission showed a heart rate of 112 beats/min, blood pressure of 80/50 mmHg, temperature of 39.4 °C, and respiratory rate of 28 breaths/min. Exam was notable for abdominal distention, diffuse abdominal tenderness, shifting dullness and altered level of consciousness with a Glasgow Coma Scale (GCS) of 6. He was initiated on intravenous fluids but due to persistent hypotension, vasopressor therapy with norepinephrine was required for hemodynamic stabilization. He was intubated for airway protection and admitted to the intensive care unit (ICU).

His labs revealed a white blood cell count of 13,800/mm^3, hemoglobin of 9.0 g/dL, creatinine of 2.6 mg/dL (baseline 1.0 mg/dL), lactic acid of 5 mmol/L, albumin: 1.9 g/dL, billirubin:1.8 mg/dL, and an international normalized ratio (INR) of 2.0. His Child-Pugh-Turcotte (CTP) and model of end stage liver disease (MELD) scores were 11 and 25, respectively. Chest X-ray and urine analysis were within normal limits. Abdominal CT revealed moderate ascites, splenomegaly and a nodular liver (Fig. 68.1). A paracentesis was performed and ascitic fluid analysis showed a white blood cell count of 450 cells/mcL, with a polymorphonuclear cell (PMN) count of 255 cells/mcL and a total protein of 1.0 g/dl.

Question What is the most likely diagnosis?

Answer Spontaneous bacterial peritonitis leading to septic shock.

A.W.R. Jawid (✉)
Department of Internal Medicine, Highland Hospital, Alameda Health System, Oakland, CA, USA
e-mail: ajawid@alamedahealthsystem.org

I.M. Subramanian
Pulmonary and Critical Care Faculty, Department of Internal Medicine, Highland Hospital, Alameda Health System, Oakland, CA, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_68

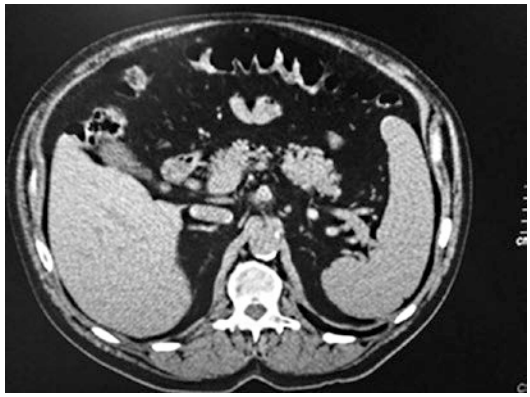


Fig. 68.1 CT scan image of liver cirrhosis (Courtesy of Dr. Eric Yasumoto)

All patients with the presence of cirrhosis and ascites, who are symptomatic with abdominal pain, nausea, vomiting or fever, should be suspected as having spontaneous bacterial peritonitis (SBP) and should undergo a paracentesis and be treated with antibiotics, regardless of their ascitic fluid polymorphonuclear (PMN) count until ascitic fluid culture results are available [1, 2]. It is important to rule out a secondary etiology for peritonitis such as a surgical cause. In this case, the patient had a CT of the abdomen which did not indicate a surgical etiology. Differentiating between SBP and secondary bacterial peritonitis is further covered under the diagnosis section of this chapter.

This patient was admitted to the intensive care unit (ICU) for septic shock secondary to presumed SBP. He was started on piperacillin-tazobactam and was continued on norepinephrine. He was also given albumin 1.5 g/kg on the first day of admission. He continued to have fevers, but his hemodynamics progressively improved.

On the third day of ICU admission, his blood pressure normalized and vasopressor support was discontinued. His ascitic fluid cultures grew *Escherichia coli* sensitive to Cefotaxime, and his antibiotic coverage was subsequently narrowed. He was also given his second dose of albumin (1 g/kg). The patient was extubated later that day and was transferred out of the ICU in stable condition to continue an antibiotic course of 5 days followed by prophylaxis with a daily fluoroquinolone.

Principles of Management

Since the initial description of SBP in the 1960s, studies have reflected better management and earlier recognition resulting in a marked reduction in mortality from 90 % quoted in some older studies to now a predominantly treatable complication of decompensated cirrhosis. Although cases of SBP have been reported in patients with nephrotic syndrome and congestive heart failure, it is most prevalent in patients who have advanced cirrhosis and portal hypertension. Different variants of SBP and ascitic fluid infections have been characterized and are important to recognize [1, 3–5].

Diagnosis

All patients with cirrhosis and ascites have a high risk of developing SBP; therefore a paracentesis should be performed to rule out SBP for all hospitalized patients with cirrhosis and ascites (Fig. 68.2). This has been proven to reduce mortality [1, 6, 7]. There are several additional criteria which suggest an increased risk of developing SBP

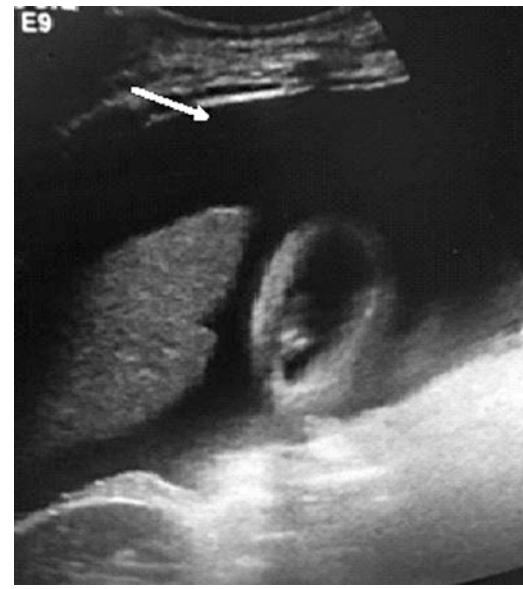


Fig. 68.2 Ultrasound images of ascitic fluid (*arrow*) (Courtesy of Dr. Eric Yasumoto)

and in these patients, the suspicion for SBP should be even higher: ascitic fluid total protein level of <1.0 g/dl, prior history of SBP, a serum total bilirubin >2.5 mg/dl, concomitant variceal bleeding, and recent use of a proton pump inhibitor [1, 3, 8].

The ascitic fluid should be sent for aerobic and anaerobic cultures, cell count and differential, and fluid chemistries (albumin, protein, glucose, lactate dehydrogenase, amylase, and in some cases bilirubin). It is important that diagnostic paracentesis be performed prior to the administration of antibiotics. The yield of the ascitic fluid cultures is greatly reduced even with the administration of a single dose of broad-spectrum antibiotics within 6 h prior to the paracentesis [1, 2, 7]. Appropriate handling of the ascitic fluid is crucial to minimize the risk of skin flora contaminating the cultures, and to avoid obtaining a false-positive culture. When culturing ascitic fluid, immediate bedside inoculation of the ascitic fluid into routine blood culture bottles with at least 10–20 ml of fluid has been shown to increase the sensitivity of cultures and to avoid false negative results [1, 9].

A total absolute neutrophils count of >250 cells/mm^3, a positive ascitic fluid bacterial culture and absence of secondary causes of peritonitis (i.e. bowel perforation) usually confirm the diagnosis of SBP [1]. However, different variants of spontaneous ascitic infections exist which may not present with the classic neutrophil count. These are depicted in Table 68.1.

It is imperative to rule out secondary bacterial peritonitis, such as due to bowel perforation or intra-abdominal abscess, prior to diagnosing SBP. Failure to correctly diagnose secondary bacterial peritonitis from a surgical etiology can be catastrophic. Several findings can help differentiate SBP from a secondary bacterial peritonitis caused by perforation. SBP is often associated with less abdominal pain, lower ascitic fluid total protein levels, a lower ascitic fluid neutrophil count (<1000 cells/mm), lower ascitic fluid bilirubin levels (<6.0 mg/dl), normal or low ascitic fluid amylase levels (higher levels correlate with a perforation), and the presence of a monomicrobial culture result [10]. The presence of two of the three following "Runyon criteria" is very sensitive for the diagnosis of secondary bacterial peritonitis: ascitic fluid total protein >1.0 g/dl; glucose of <50 mg/dl; and an elevated serum LDH in the presence or absence of a polymicrobial blood culture [1, 10]. In the event that a patient that was initially diagnosed as having SBP is not clinically improving, a repeat paracentesis may be helpful as a rising ascitic fluid neutrophil count is highly concerning for secondary bacterial peritonitis. The presence of less common pathogenic bacteria (see below) or fungal growth in the ascitic cultures should also prompt a search for an intraabdominal abscess leading to secondary peritonitis.

Marked peripheral leukocytosis (or neutrophilia) does not seem to have an effect on the leukocyte (or neutrophil) count in ascitic fluid [11]. However, a traumatic paracentesis leading to hemorrhagic ascites fluid may alter the neutrophil count. The commonly used correction factor is to subtract 1 neutrophil for each 250 red blood cells/mm^3 in the ascitic fluid [12].

Microbiologic Etiology

Several explanations exist for how bacteria enter the ascitic fluid and lead to infection. The most widely accepted mechanism is that of

Table 68.1 Characterization of ascitic fluid infections

Type of infection	PMN cell count (/mm^3)	Bacterial culture result
Spontaneous bacterial peritonitis	≥250	Positive (usually 1 organism)
1. Culture-negative neutrocytic ascites	≥250	Negative
2. Monomicrobial nonneutrocytic bacterascites	<250	Positive (1 organism)
3. Polymicrobial bacterascites	<250	Positive (polymicrobial)
Secondary bacterial peritonitis	≥250 (usually in the thousands)	Positive (polymicrobial)

Data from Refs. [4, 5, 10]

translocation of gut bacteria across the leaky intestinal wall of cirrhotic patients into the mesenteric lymph nodes with subsequent seeding of the ascites [3, 13]. Intestinal bacterial overgrowth, either due to decreased intestinal motility or through the use of proton pump inhibitors has also been proposed but remains controversial [1, 3, 8, 14]. The bacteria that usually result in SBP are those that require a functionally intact immune system with adequate complement levels for opsonization and removal. Advanced cirrhosis certainly reduces the function of the complement system and phagocyte activity [3, 15].

Most cases of SBP are due to gut bacteria such as *Escherichia coli and Klebsiella*; however *Streptococcus pneumonia*, Enterobacteriaceae, Staphylococcus and Pseudomonas infections can also occur. Additional bacterial pathogens have geographic prevalence such as *Aeromonas hydrophila*, which is seen in Korea [16]. The presence of more than one type of bacteria in the ascitic fluid should prompt a consideration for a secondary peritonitis. Additionally, unusual organisms such as fungi found on culture analysis of the ascitic fluid can also suggest a secondary bacterial peritonitis from an abscess. There have also been case reports of spontaneous fungal peritonitis [17] and SBP due to *Listeria monocytogenes* [18], in immune-suppressed and elderly patients, respectively.

Treatment

All patients with SBP should be started on broad spectrum antibiotics as soon as the diagnosis is suspected. Appropriate and timely treatment has been shown to significantly decrease morbidity and mortality [1, 7, 14]. Figure 68.3 is a useful table to help guide therapy in patients with suspected or confirmed SBP.

Antibiotics

In patients with cirrhosis and ascites who have elevated temperature greater than 37.8 °C or 100 °F, abdominal pain, altered mental status,

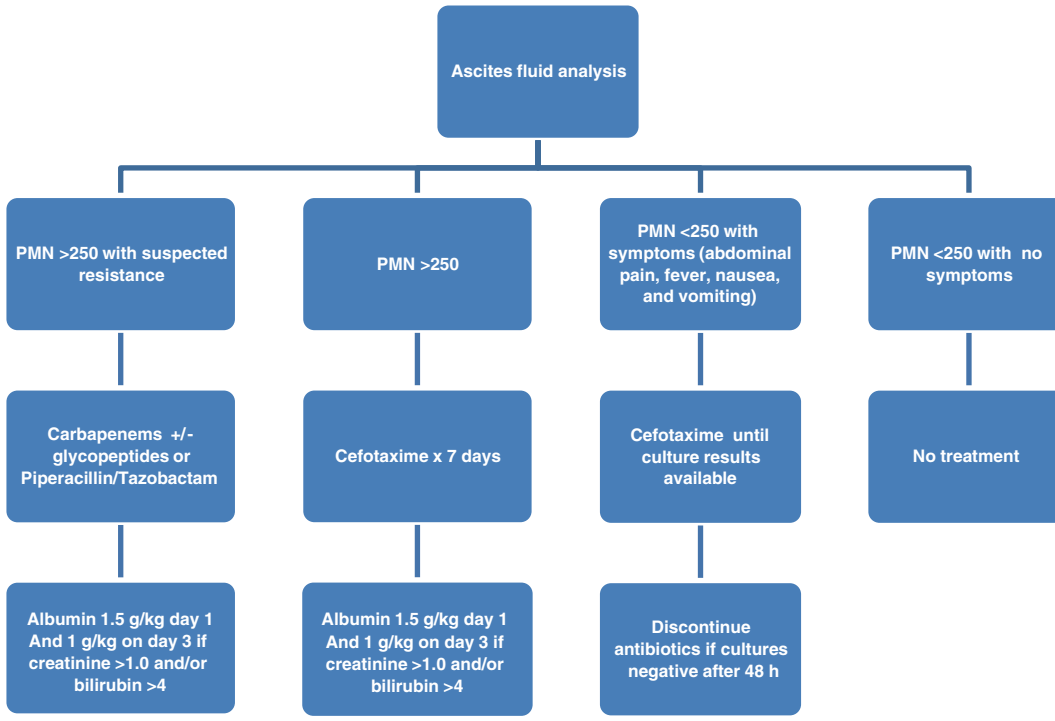


Fig. 68.3 Algorithm for initial management of suspected spontaneous bacterial peritonitis

or evidence of sepsis, treatment for SBP should be initiated as soon as ascitic fluid, blood, and urine have been obtained for culture and analysis [1, 14, 19]. In patients without these findings, it is reasonable to wait until the results of the PMN count are available, with subsequent initiation of treatment if the ascitic fluid PMN count is ≥250 cells/mm^3. Collection and processing of the ascitic fluid should be done rapidly from the time of patient presentation and suspicion of SBP. The ascitic fluid PMN count is more readily available than the culture results and can reliably identify patients who need empiric antibiotic coverage [6].

Cefotaxime 2 g intravenously every 8 h has been shown to have excellent penetration into ascitic fluid and is generally the first line antibiotic used [1, 19]. Ceftriaxone has been shown to prevent SBP in the setting of gastrointestinal hemorrhage in patients with cirrhosis [1, 20]. Levofloxacin can be used for patients with penicillin allergy, although it does not have the same penetration into ascitic fluid compared to cefotaxime. Broad-spectrum antimicrobial agents, such as carbapenems with or without glycopeptides or piperacillin-tazobactam, should be considered for the initial treatment of nosocomial infections and healthcare-associated infections when the risk factors for multi-resistant bacteria are apparent [16]. For spontaneous fungal peritonitis, systemic anti-fungal therapy is recommended [17] but as mentioned previously, a search for an intraabdominal abscess leading to secondary peritonitis should ensue. For *Listeria monocytogenes* infections, ampicillin, with or without additional aminoglycosides, are effective [18].

Albumin

Renal failure as a result of hepatorenal syndrome develops in a significant percent of patients with SBP and is a major cause of morbidity and mortality. Hepatorenal syndrome is a clinical diagnosis, without any specific pathognomonic feature.

Albumin infusions have been shown to decrease mortality in patients with cirrhosis and SBP [21]. Albumin infusions should be given if the serum creatinine is >1 mg/dL, the blood urea nitrogen is >30 mg/dL or the total bilirubin is >4 mg/dL. It is recommended to give 1.5 g/kg on the first day of admission and 1 g/kg on the third day of admission [1, 22, 23]. This albumin administration is recommended in addition to the regular large volume paracentesis albumin requirements.

Clinical Diagnosis of Hepatorenal Syndrome

Presence of cirrhosis with ascites

Development of Acute Kidney Injury (AKI) (increase in serum creatinine of 0.3 mg/dL (26.5 micromol/L) or more within 48 h, or an increase from baseline of 50 % or more within 7 days)

Absence of other causes of AKI including nephrotoxic drugs, shock, hypovolemia

Absence of parenchymal kidney disease (i.e. microhematuria, proteinuria)

Discontinue Nonselective Beta Blockers (NSBB)

Among patients with SBP, NSBB use is associated with significantly worse outcomes compared to those not receiving NSBB. Increased overall mortality and incidence of hepatorenal syndrome have been observed [24]. Most experts recommend discontinuing NSBB permanently in patients with SBP.

Prophylaxis

Antibiotic Prophylaxis

The benefits of antibiotic prophylaxis must be weighed against the risk of developing antibiotic resistance. However, in patients with ascites who are at high risk for developing SBP (i.e. previous history of SBP and low ascitic fluid total protein), antibiotic prophylaxis improves patient outcomes. The opsonic activity of ascitic fluid is reflected by the ascitic fluid total protein level. Thus, patients with low total protein level concentrations are at higher risk for developing SBP. Conversely, patients with malignant ascites or congestive heart failure associated with

high fluid total protein content are relatively resistant to SBP [15, 25]. Of note, diuretic therapy is also integral to the prevention of SBP by concentrating the ascites and improving host defense [25]. Cirrhotic patients with ascitic fluid total protein levels below 1 g/dL are at the highest risk for SBP and should be given antibiotic prophylaxis [20, 26]. Patients should also be given prophylaxis if the ascitic fluid protein is <1.5 g/dl in the setting of any of the following settings: serum creatinine >1.2 mg/dl; serum sodium <130 mEq/L, or serum bilirubin >3 mg/dl [1].

Prophylactic regimens include daily fluoroquinolone or trimethoprim-sulfamethoxazole therapy (one double-strength tablet per day). Inpatient fluoroquinolone or trimethoprim-sulfamethoxazole therapy should be given for patients with cirrhosis and ascites hospitalized for other reasons and have an ascitic protein concentration of less than 1 g/dl [26–29].

Intravenous ceftriaxone (1 g daily) or oral fluoroquinolone daily should be given prophylactically for those with cirrhosis and active gastrointestinal bleeding regardless of the presence of ascites [20].

Evidence Contour

Duration of Therapy

The duration of treatment is somewhat controversial and consensus does not exist. One randomized controlled trial demonstrated that 5 days of treatment is as efficacious as 10 days in the treatment of carefully characterized patients with SBP [30]. However, consideration for a longer treatment period can be made in patients who grow unusual organisms (e.g., pseudomonas, enterobacteriaceae), an organism resistant to standard antibiotic therapy, or an organism routinely associated with endocarditis (e.g. staphylococcus aureus or viridans group streptococci) [16]. Patients with concurrent variceal bleeding and ascites should definitively be given 7 days of ceftriaxone for SBP prophylaxis [1, 25].

Choice of Antibiotics

The first choice of antibiotics for treatment of SBP remains cefotaxime, but several recent studies have identified the growth of multi-resistant organisms and recommend antibiotics with broader coverage such as carbapenems with or without glycopeptides or piperacillin-tazobactam as an initial treatment, especially in patients at risk of developing nosocomial or healthcare-associated infections [16].

Patient with Non-neutrocytic Bacterascites

It is unclear if patients with bacterascites (bacteria are present in the ascitic fluid, but the PMN count is less than 250 cells/mm^3) have infection or colonization and so clinical correlation is important. Patients who have non-neutrocytic bacterascites but demonstrate signs and symptoms of SBP, should be diagnosed as having presumed SBP and should be started on antibiotics. This condition can be seen early in the development of SBP. If the patient is asymptomatic, bacterascites could suggest colonization and a repeat paracentesis should be obtained 48 h after the initial paracentesis or if the patient develops symptoms. A follow up PMN count of more than 250 cells/mm^3 would require therapy [4, 5].

References

1. Runyon BA. Management of adult patient with ascites due to cirrhosis: update 2012. The American Association for the Study of Liver Diseases. AASLD Practice Guideline. 2013 Feb. 27; 1–87.
2. Sundaram V, Manne V, Al-Osaimi AM. Ascites and SBP: recommendations from two United States centers. Saudi J Gastroenterol. 2014;2D(5):279–87. doi:10.4103/1319-3767.141686.
3. Such J, Runyon BA. Spontaneous bacterial peritonitis. Clin Infect Dis. 1998;27(4):669–74.
4. Runyon BA. Monomicrobial nonneutrocytic bacterascites: a variant of spontaneous bacterial peritonitis. Hepatology. 1990;12(4 pt 1):710–5.
5. Pelletier G, Lesur G, Ink O, Hagege H, Attali P, Buffet C, et al. Asymptomatic bacterascites: is it spontaneous bacterial peritonitis? Hepatology. 1991;14(1):112–5.

6. Orman ES, Hayashi PH, Bataller R, Barritt AS. Paracentesis is associated with reduced mortality in patients hospitalized with cirrhosis and ascites. Clin Gastroenterol Hepatol. 2014;12(3):496–503.
7. Kim JJ, Tsukamoto MM, Mathur AK, Ghomri YM, Hou LA, Sheibani S, et al. Delayed paracentesis is associated with increased in-hospital mortality in patients with SBP. Am J Gastroenterol. 2014;1D9(9): 1436–42.
8. Deshpande A, Pasupuleti V, Thota P, Pant C, Mapara S, Hassan S, et al. Acid-suppressive therapy is associated with spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. J Gastroenterol Hepatol. 2013;28(2):235–42.
9. Runyon BA, Canawati HN, Akriviadis EA. Optimization of ascetic fluid culture technique. Gastroenterology. 1988;95(5):1351–5.
10. Akriviadis EA, Runyon BA. Utility of an algorithm in differentiating spontaneous from secondary bacterial peritonitis. Gastroenterology. 1990;98(1):127–33.
11. Antillon MR, Runyon BA. Effect of marked peripheral leukocytosis on the leukocyte count in ascites. Arch Intern Med. 1991;151(3):509–10.
12. Hoefs JC. Increase in ascites white blood cell and protein concentrations during diuresis in patients with chronic liver disease. Hepatology. 1981;1(3):249.
13. Moore CM, Van Thiel DH. Cirrhotic ascites review: pathophysiology, diagnosis and management. World J Hepatol. 2013;5(5):251–63.
14. Runyon BA, AASLD. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology. 2013;57(4):1651–3. doi:10.1002/hep.26359.
15. Runyon BA, Morrissey RL, Hoefs JC, Wyle FA. Opsonic activity of human ascitic fluid: a potentially improtant protective mechanism against SBP. Hepatology. 1985;5(4):634–7.
16. De Mattos AA, Costabeber AM, Lionco LC, Tovo CV. Multi-resistant bacteria in spontaneous bacterial peritonitis: a new step in management? World J Gastroenterol. 2014;20(39):14D79–86. doi:10.3748/wjg.v20.i39.14D79.
17. Bal CK, Bhatia V, Khillan V, Rathor N, Saini D, Daman R, et al. Spontaneous cryptococcal peritonitis with fungemia in patients with decompensated cirrhosis: report of two cases. Indian J Crit Care Med. 2014;18(8):536–9. doi:10.4103/D972-5229.138161.
18. Diaz-Fontenla F, Perez- Valderas M, Ibanez-Samaniego L, Gracia-Fernandez CP, Flores-Fernandez V. Spontaneous Listeria monocytogenes bacterial peritonitis. Rev Clin Esp. 2014;214(5):285–6. doi:10.1016/j.rce.2014.02.007. Epud 2014 Mar 29.
19. Runyon BA, Akriviadis EA, Sattler FR, Cohen J. Ascitic fluid and serum cefotaxime and desacetyl cefotaxime levels in patients treated for bacterial peritonitis. Dig Dis Sci. 1991;36(12):1782–6.
20. Fernandez J, Ruiz del Arbol L, Gomez C, Durandez R, Serradilla R, Guarner C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. Gastroenterology. 2006;131(4):1049–56; quiz 1285.
21. Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. Clin Gastroenterol Hepatol. 2013;11(2):123.
22. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-arbol L, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med. 1990;34(6):403–9.
23. Siqal SH, Stanca CM, Fernandez J, Arroyo V, Navasa M. Restricted use of albumin for spontaneous bacterial peritonitis. Gut. 2007;56(4):597–9.
24. Mandorfer M, Bota S, Schwabl P, Bucsics T, Pfisterer N, Kruzik M, et al. Nonselective B-blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. Gastroenterology. 2014;146(7):1680.
25. Runyon BA, Anillon MR, Montano AA. Effect of diuresis versus therapeutic paracentesis on ascitic fluid opsonic activity and serum complement. Gastroenterology. 1989;97(1):158–62.
26. Fernández J, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology. 2007;133(3):818.
27. Terg R, Fassio E, Guevara M, Cartier M, Longo C, Lucero R, et al. Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: a randomized, placebo-controlled study. J Hepatol. 2008;48(5):774.
28. Grangé JD, Roulot D, Pelletier G, Pariente EA, Denis J, Ink O, et al. Norfloxacin primary prophylaxis of bacterial infections in cirrhotic patients with ascites: a double-blind randomized trial. J Hepatol. 1998;29(3):430.
29. Soares-Weiser K, Brezis M, Tur-Kaspa R, Paul M, Yahav J, Leibovici L. Antibiotic prophylaxis of bacterial infections in cirrhotic inpatients: a meta-analysis of randomized controlled trials. Scand J Gastroenterol. 2003;38(2):193.
30. Runyon BA, McHutchison JG, Antillon MR, Akriviadis EA, Montano AA. Short-course versus long-course antibiotic treatment of spontaneous bacterial peritonitis. A randomized controlled study of 100 patients. Gastroenterology. 1991;100(6):1737.

ICU Management of the Patient with Alcoholic Liver Disease

69

Jessica L. Mellinger and Robert J. Fontana

Case Presentation

A 34 year old woman presented to the clinic for evaluation. She had a history of morbid obesity with a body mass index (BMI) of 35 kg/m^2 and had undergone uncomplicated Roux-en-Y gastric bypass surgery 9 months prior. She had a history of heavy alcohol use, but stated that her last drink occurred 3 years ago. Within the past 1–2 months, she noticed increasing jaundice, fatigue, and abdominal distension but denied any recent travel, new medications or sick contacts. She had not vomited blood, but noted that her stools were consistently dark and tar-like. Her behavior in clinic included emotional lability and rambling speech. Lab testing revealed a positive blood alcohol level of 269 mg/dL (reference <10 mg/dL) and a urine drug screen was positive for benzodiazepines and opioids, though these medications did not appear on her medication list. Labs also revealed a WBC 13 K/uL with neutrophilic predominance, hemoglobin 10 g/dL, MCV = 112, platelets 100 K/uL, AST 202 IU/mL, ALT 38 IU/mL, alkaline phosphatase of 196 IU/mL, and total bilirubin 25.3 mg/dL. Her serum creatinine was 0.84 mg/dl, INR was 5.2, and a liver ultrasound revealed increased parenchymal echotexture consistent with diffuse hepatocellular disease, splenomegaly and ascites.

She was admitted to the general care floor with plans for an upper endoscopy the following day. She was initially alert and oriented x 3 with a BP = 114/56 mmHg and pulse of 120 beats per minute. She received IV vitamin K for her elevated INR and was started on ceftriaxone 1 g IV daily for infection prophylaxis in the setting of melena while awaiting endoscopy. Due to her recent drinking and mild tremulousness, 1–2 mg of lorazepam by mouth every 1–2 h was given based upon agitation, and she was reassessed on an hourly basis per protocol. Overnight, she began to experience worsening sinus tachycardia with heart rates in the 130s, blood pressures in the 190s/100s which were nonresponsive to lorazepam, and a fever to 101° Fahrenheit. She also developed refractory tremor in her upper extremities and became increasingly agitated and confused. She reported seeing bugs crawling on the walls and door frame, which increased her agitation.

Question How would you classify her liver disease status?

Answer Acute alcoholic hepatitis with alcohol withdrawal syndrome

Grant Support: Support for Dr. Fontana provided in part by the National Institutes of Diabetes, Digestive and Kidney Diseases as a member of the U.S. Acute Liver Failure Study Group (DK U-01-58369). Support for Dr. Mellinger provided by the AASLD Advanced Transplant Hepatology Fellowship

J.L. Mellinger • R.J. Fontana (✉)
Division of Gastroenterology,
Department of Internal Medicine,
University of Michigan Medical Center,
Ann Arbor, MI, USA
e-mail: rfontana@med.umich.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_69

The patient was transferred to the ICU for further monitoring given severe alcohol withdrawal/delirium tremens. An infectious workup was initiated including blood cultures and a chest x-ray and antibiotics were broadened to zosyn and vancomycin. Potassium, magnesium, and thiamine replacement were initiated. Approximately 12 h after her admission to the hospital, she had 2–3 episodes of large volume bloody emesis. She was hypotensive to 50/30s and tachycardic to the 140s. Because of her hematemesis and altered mental status, she was emergently intubated for airway protection. Her hemoglobin level decreased to 5 g/dL and arterial blood lactate level was 16.3. A central line was placed and she was given 3 units blood and 3 units of fresh frozen plasma, in addition to normal saline. Her blood pressure responded to resuscitation and improved to 89/53.

The patient underwent emergency upper endoscopy and was found to have grade III esophageal varices with red wale marks and active hemorrhage. Several bands were placed with successful control of bleeding but with incomplete eradication of her varices. Approximately 8 h after the upper endoscopy, she was noted have hypotension with copious amounts of bright red blood suctioned from her orogastric tube. Given concern for recurrent variceal bleeding, a TIPS was placed following a hepatic ultrasound which showed hepatic steatosis but no masses or portal vein thrombosis. Her initial porto-systemic pressure gradient of 34 mmHg decreased to 14 mmHg following successful TIPS placement. The patient was ultimately able to be extubated and transferred to the floor with improving mental status and functional status at hospital day 5. At day 7 of her hospitalization, she developed anuric AKI which was felt to be related to ATN from repeated periods of hypotension and was started on hemodialysis. She passed away approximately 4 weeks after her discharge from multi-organ failure with a bilirubin of 30.4 mg/dl and INR of 3.1.

Principles of Management

Classification of Alcoholic Liver Disease

The key principles of management of the patient with ALD in an ICU setting are twofold: medical management of the ALD and its associated complications and concomitant management of alcohol withdrawal syndromes.

Alcoholic liver disease occurs along a spectrum ranging from asymptomatic hepatic steatosis to steatohepatitis with variable amounts of hepatic fibrosis (Table 69.1). Alcoholic hepatitis, by contrast, can occur at any time point along this spectrum and is characterized by a clinical syndrome of new onset-jaundice within the past 3 weeks, coagulopathy, leukocytosis, and fever occurring in the presence of a history of recent heavy alcohol use with no other identified cause of liver injury [1]. The evaluation of the patient with suspected alcoholic liver disease, including alcoholic hepatitis, includes a thorough workup for alternative causes of liver injury including testing for hepatitis B and C which may be present in 5–10 % of patients with established ALD; concomitant acetaminophen toxicity; obstructive jaundice due to choledocholithiasis; and autoimmune hepatitis. Lab testing can help diagnose alcoholic hepatitis with patients often having an AST:ALT ratio of > 2:1, leukocytosis with neutrophilic predominance and elevated bilirubin and INR levels. The liver biopsy in patients with AH typically demonstrates evidence of neutrophilic infiltration of the liver with Mallory's hyaline, cholestasis, and varying severity of steatohepatitis (Figs. 69.1 and 69.2). Although liver biopsies are frequently required for clinical trials, most practitioners do not obtain a biopsy unless there is substantial clinical uncertainty.

Patients with ALD often, if not always, have, concomitant alcohol use disorders (AUD) which are classified by clinical symptoms (Table 69.2). Alcohol use disorders (AUD) are a major source of morbidity and mortality in the general population with an estimated prevalence of 6–8 % in North America [2]. Approximately 10–33 % of all medical ICU patients have an AUD which places them at risk of developing alcohol withdrawal syndrome [3]. A thorough history for heavy and chronic alcohol use should be taken, as alcoholic hepatitis can occur even weeks after the patient has stopped drinking. Though the pattern of alcohol use resulting in alcoholic liver disease (chronic vs binge drinking [i.e., consuming five or more drinks in less than 2 h]) is still unclear, chronic daily use of >30 g (approximately two

standard drinks) alcohol increases the risk for cirrhosis. Alcoholic hepatitis patients report a mean use of 100 g or greater daily (~7 standard drinks or more per day), frequently in the days or weeks prior to presentation [1]. A standard drink is defined as 12 oz of beer, 5 oz of wine, or 1.5 oz hard liquor.

Lab testing for alcohol use can be helpful in the proper setting as patients may be reluctant to disclose the true nature of their alcohol and/or co-occurring illicit drug use. Ethanol testing in the blood or urine can be used, though the short half-life results in a narrow time window for positive results (blood ~10-12 h, urine ~18-24 h) [4]. Ethyl glucuronide, a metabolite of ethanol formed in the liver by the conjugation of ethanol with glucuronic acid via UDP-glucuronosyltransferase, can be detected in the urine approximately 72–90 h after the last ingestion of alcohol and can be helpful in verifying reports of abstinence [4]. Since there can be substantial inter-individual variation in the production of urinary ethyl glucuronide, results should always be interpreted in the appropriate clinical context.

Prognosis in Alcoholic Hepatitis

Once a clinical diagnosis of AH is established, prognosis can be determined based on the Maddrey's discriminant function or Model for

Table 69.1 Spectrum of alcoholic liver disease

Disease phenotype	Clinical features	Objective laboratory and prognostic markers
Asymptomatic hepatic steatosis	**Incidence**: 2–5 % of US population **Symptoms**: occasional hepatomegaly/RUQ pain, good muscle tone, appear medically well **Risk factors:** daily alcohol consumption > 2 to 3 drinks/day, female gender **Prognosis:** generally favorable and reversible with abstinence **Treatment:** alcohol detox to sobriety, multivitamin, counseling, psychiatric meds to prevent relapse	**Labs**: Serum AST and ALT may be mildly elevated or > 2:1 ratio Normal or minimally elevated MCV without anemia Urine ethylglucuronide to verify alcohol use in past 5 days Normal albumin, bilirubin and INR **Imaging**: increased hepatic steatosis on CT/MRI. **Biopsy**: variable steatosis with mild inflammation and pericellular fibrosis **Prognosis**: may improve/resolve with abstinence or lead to progressive liver damage/fibrosis with continued alcohol use
Alcoholic hepatitis	**Incidence**: 5–10 per 100,000 **Symptoms**: acute jaundice, nausea, abdominal pain, fever, encephalopathy. **Risk Factors**: binge intake > 4 weeks in chronic user, younger age, genetic polymorphisms **Prognosis:** 10–30 % 1 month mortality; 50 % 1-year mortality with abstinence; 90 % mortality without abstinence **Treatment:** Manage acute alcohol withdrawal Thiamine, folate, enteral nutrition Steroids x 6 weeks in highly selected patients Alcohol abstinence Management of encephalopathy, bleeding, ascites Not candidates for liver transplant in most centers	**Labs**: Serum AST: ALT > 2:1 frequently seen but both < 1000 IU/mL Urinary ethylglucuronide detectable if alcohol use in past 5–7 days CBC: moderate to severe macrocytosis with anemia, frequent thrombocytopenia, leukocytosis with left shift if severe Moderate to severely ↑ bilirubin and INR, low albumin. **Imaging**: hepatic steatosis in CT/MRI +/− hepatosplenomegaly, +/− ascites and venous collaterals **Biopsy**: steatosis with neutrophilic inflammation, cirrhosis in 40–60 % **Prognosis**: discriminant function ≥ 32 has 30–50 % mortality at 1 month

(continued)

Table 69.1 (continued)

Disease phenotype	Clinical features	Objective laboratory and prognostic markers
Decompensated alcoholic cirrhosis	**Incidence**: unknown but 10–15 % of patients with heavy alcohol will go on to develop cirrhosis **Symptoms**: anorexia, weight loss, ascites, muscle wasting/weakness, palmar erythema, telangiectasias **Risk Factors**: lifetime alcohol consumption exceeding 3–4 drinks/day over 10 years or more **Prognosis**: determined by severity of portal HTN complications (variceal bleeding, ascites, encephalopathy). If MELD > 20, then ~70 % 1 year survival even with abstinence **Treatment**: Thiamine, folate, and multivitamins Medical management of ascites with diuretics Lactulose/rifaximin for encephalopathy Endoscopy for varices Transplant in selected patients with favorable prognosis for long-term abstinence and compliance	**Labs**: Serum AST and ALT frequently normal or minimally elevated CBC: Moderate to severe macrocytosis with anemia, low WBC and platelets due to portal HTN. Bilirubin and INR variably elevated, low albumin **Imaging**: small shrunken, nodular liver with ascites, collaterals and splenomegaly **Biopsy**: cirrhosis with minimal steatosis/inflammation **Prognosis**: MELD score predicts mortality at 3 months: <9 = ~2 % mortality 10=19 = 6 % mortality 20=29 = 20 % mortality 30=39 = 53 % mortality >40 = 71 % mortality

Abbreviations: *US* United States, *AST* aspartate transaminase, *ALT* alanine transaminase, *INR* international normalized ratio, *CT* computed tomography, *MRI* magnetic resonance imaging, *IU* international units, *mL* milliliter, *HTN* hypertension, *CBC* complete blood count, *WBC* white blood cell count, *MELD* Model for End-Stage Liver Disease

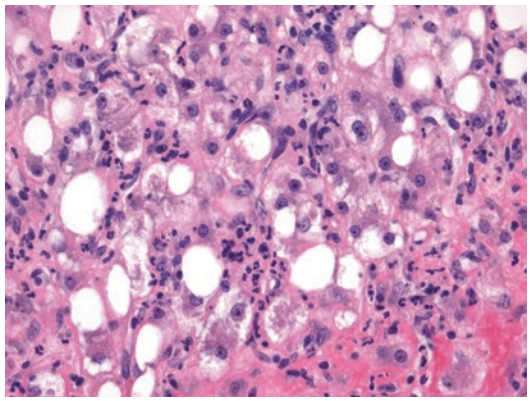


Fig. 69.1 Alcoholic hepatitis. An example of acute alcoholic hepatitis with Mallory-Denk bodies, steatosis, and neutrophilic inflammation (400× magnification)

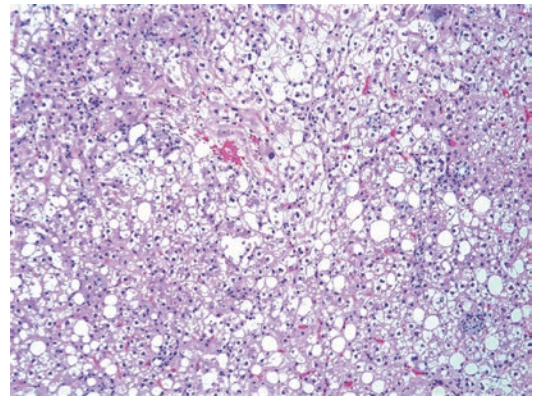


Fig. 69.2 Hepatic steatosis. Low-grade steatohepatitis showing predominantly steatosis (100× magnification)

endstage liver disease (MELD) scores which both predict 1 month mortality of approximately 20–35 % [5].[1]Other prognostic scoring models have been used, such as the Chronic Liver Failure- Sequential Organ Failure Scoring System (CLIF-SOFA) and have been validated in cohorts which included ALD and AH, showing as good or better prognostic performance when compared to the MELD score [6].

[1]The MELD score is calculated according to the following formula: $(0.957 \times \log_e(\text{creatinine mg/dL}) + (0.378 \times \log_e(\text{bilirubin mg/dL}) + (1.120 \times \log_e(\text{INR})) + 0.643$. Score should be multiplied by 10 and rounded to the nearest whole number. Lab values <1.0 are set to 1.0 for MELD calculation.

Table 69.2 Diagnostic criteria for alcohol use disorder and alcohol withdrawal syndrome

Alcohol use disorders	
Diagnostic Criteria Mild: 2–3 symptoms Moderate: 4–5 symptoms Severe: 6+ symptoms	At least two of the following: 1. Alcohol taken in larger amounts or over longer period than intended 2. Persistent desire or failed efforts to cut down/control use 3. Great deal of time spent obtaining, using, or recovering from effects of alcohol 4. Craving, or strong desire/urge to use alcohol 5. Recurrent alcohol use resulting in failure to fulfill major role obligations at work, home, school 6. Continues alcohol use despite persistent/recurrent social or interpersonal problems related to alcohol use 7. Important social, occupational, or recreational activities given up/reduced due to alcohol use 8. Recurrent alcohol use when physically hazardous 9. Continued alcohol use despite knowledge of persistent/recurrent physical or psychological problem related to alcohol use 10. Tolerance: (a) Either a need for markedly increased amounts of alcohol to achieve the desired effect/intoxication (b) OR markedly diminished effect of continues use of same amount of alcohol 11. Withdrawal: (a) Symptoms consistent with alcohol withdrawal syndrome (see below) (b) Alcohol (or closely related substance such as benzodiazepine) taken to relieve/avoid withdrawal symptoms
Remission definitions	**In early remission**: After full criteria for AUD diagnosis met, NO criteria for AUD have been for 3 months, but less than 12 months (Craving criteria can still be met but considered to be in early remission) **In sustained remission:** After full criteria for AUD diagnosis met, NO criteria for AUD met for 12 or more months (Craving criteria can still be met but considered to be in sustained remission)
Alcohol withdrawal Syndrome	
Diagnostic criteria	1. Cessation/reduction of heavy/prolonged alcohol use 2. Two or more of the following, developing within several hours to a few days following cessation/reduction in alcohol use: (a) Autonomic hyperactivity (sweating, pulse >100 beats per minute) (b) Increased hand tremor (c) Insomnia (d) Nausea or vomiting (e) Transient visual, tactile, or auditory hallucinations (f) Psychomotor agitation (g) Anxiety (h) Generalized tonic-clonic seizures 3. Signs/symptoms of above criteria cause clinically significant distress/impairment in social, occupational, or other important areas of functioning 4. Above signs/symptoms not attributable to another medical condition and not better explained by another mental disorder, including withdrawal or intoxication with another substance

The standard medical management of AUD includes vitamin and mineral supplementation as well as management of AWS (Table 69.3). Patients with AUD have a higher risk of requiring mechanical ventilation and are more prone to develop sepsis and pulmonary infections which contributes substantially to morbidity and mortality [8]. In addition, complications of alcoholic cirrhosis, such as GI bleeding or spontaneous bacterial peritonitis, may also prompt ICU admission.

Table 69.3 Clinical institute withdrawal assessment of alcohol scale, revised (CIWA-Ar)

Record heart rate and blood pressure for 1 min	
NAUSEA AND VOMITING—Ask "Do you feel sick to your stomach? Have you vomited?" Observation 0 No nausea or vomiting 1 Mild nausea with no vomiting 2 3 4 Intermittent nausea with dry heaves 5 6 7 Constant nausea, frequent dry heaves and vomiting	**TACTILE DISTURBANCES—Ask "Do you have any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?"** 0 None 1 Very mild itching, pins/needles, burning or numbness 2 Mild itching, pins/needles, burning or numbness 3 Moderate itching, pins/needles, burning or numbness 4 Moderately severe hallucinations 5 Severe hallucinations 6 Extremely severe hallucinations 7 Continuous hallucinations
TREMOR- Arms extended and fingers spread apart. Observation. 0 No tremor 1 Not visible, but can be felt fingertip to fingertip 2 3 4 Moderate, with patient's arms extended 5 6 7 Severe, even with arms not extended	**AUDITORY DISTURBANCES- Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?"** 0 Not present 1 Very mild harshness or ability to frighten 2 Mild harshness or ability to frighten 3 Moderate harshness or ability to frighten 4 Moderately severe hallucinations 5 Severe hallucinations 6 Extremely severe hallucinations 7 Continuous hallucinations
PAROXYSMAL SWEATS- Observation. 0 No sweat visible 1 Barely perceptible sweating, palms moist 2 3 4 Beads of sweat obvious on forehead 5 6 7 Drenching sweats	**VISUAL DISTURBANCES- Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things that you know are not there?" Observation.** 0 Not present 1 Very mild sensitivity 2 Mild sensivity 3 Moderate sensivitiy 4 Moderately severe hallucinations 5 Severe hallucinations 6 Extremely severe hallucinations 7 Continuous hallucinations
ANXIETY- Ask "Do you feel nervous?" 0 No anxiety 1 Mildly anxious 2 3 4 Moderately anxious 5 6 7 Equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions	**HEADACHE, FULLNESS IN HEAD—Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.** 0 Not present 1 Very mild 2 Mild 3 Moderate 4 Moderately severe 5 Severe 6 Very severe 7 Extremely severe
AGITATION- Observation 0 Normal activity 1 Somewhat more than normal activity 2 3 4 Moderately fidgety and restless 5 6 7 Paces back and forth during most of the interview, or constantly thrashes about	**ORIENTATION AND CLOUDING OF SENSORIUM- Ask "What day is this? Where are you? Who am I?"** 0 Oriented and can do serial additions 1 Cannot do serial additions or is uncertain about date 2 Disoriented for date by no more than 2 calendar days 3 Disoriented for date by more than 2 calendar days 4 Disoriented for place/or person
Total score:_____ (maximum: 67)	

Scores are used in individual hospital withdrawal protocols to guide medication administration [7]

ICU Management of Alcohol Use Disorders, Including Alcohol Withdrawal Syndrome (AWS) and Delirium Tremens (DTs)

The ICU management of alcohol withdrawal must occur in parallel with the medical management of their liver disease. Alcohol withdrawal syndrome (AWS) is defined as a complex of symptoms developing within hours to days of reduction or cessation of alcohol use that has been heavy and prolonged, in the absence of another medical cause for the symptoms (DSM-V) [9]. Symptoms are protean and may fluctuate including autonomic hyperactivity, hand tremor, insomnia, nausea and vomiting, visual, tactile, or auditory hallucinations, psychomotor agitation, anxiety, and generalized seizures. Delirium tremens (DT) or withdrawal delirium (as it is termed in the DSM-V), is a more severe form of AWS, characterized by alcohol withdrawal symptoms coupled with delirium, including decreased attention and awareness with disturbance in, memory, orientation, perception or visuospatial abilities (DSM-V) (Table 69.4). Patients with DT have as high as a 10–20% inpatient mortality rate particularly within the first 48 h of presentation. Delirium symptoms should also prompt a thorough evaluation for other medical problems that could produce delirium such as infection, GI bleeding, hypoglycemia, electrolyte disturbances, occult head injury, or ingestion of other toxins/psychoactive drugs. Alcohol withdrawal symptoms can appear several hours after cessation of all alcohol use and reach full severity approximately 50–60 h after stopping alcohol [10].

There are no formal practice guidelines for the treatment of AWS, but numerous studies have evaluated the effectiveness of various medication strategies (see Table 69.2). Standardized, symptom-driven protocols for administration of benzodiazepines as first-line therapy have been shown to be more effective, safer, and less expensive than continuous, non-symptom driven infusions, resulting in lower overall use of benzodiazepines, faster time to symptom control, shorter ICU and overall hospital stay, and reduced need for mechanical ventilation [10–12]. Such protocols are commonly nurse-administrated and involve frequent, serial assessments of CNS excitation, autonomic symptoms, and delirium. Several scores have been developed to assess for AWS, but perhaps the most commonly used score is the revised Clinical Institute Withdrawal Assessment for Alcohol Use score (CIWA-Ar), though this has not been validated in critically ill patients nor intubated patients [7, 10, 13] (see Table 69.3). Benzodiazepines are given in standard dose increments based on the total score obtained and all patients should have frequent assessment of their vitals and respiratory status.

A meta-analysis of sixty-four studies that included over 4000 participants, demonstrated a trend towards better outcomes for benzodiazepines versus other medications in AWS but when comparing different benzodiazepines amongst each other, no evidence supported using one over another [12]. However, lorazepam or midazolam are frequently preferred over diazepam due to their shorter half-life.

In patients with severe AWS or DTs (i.e. CIWA-Ar $\geq$20), ICU admission for clinical and hemodynamic monitoring is strongly advised due to their high short-term mortality via aspiration, seizures, or cardiac arrest. A recent meta-analysis revealed that patients with a prior history of alcohol withdrawal seizures or DTs, thrombocytopenia, and hypokalemia were at greater risk of developing seizures or DTs on subsequent hospitalizations [14]. Other predictors of DTs include higher CIWA-Ar scores $\geq$15, hypertension, tachycardia, older age, and comorbid medical problems, such as respiratory, cardiac, or GI disease [15]. Specific management recommendations for DTs is limited by a lack of well-controlled trials but benzodiazepines remain the first-line agent for initial treatment. Although diazepam and lorazepam are frequently used and available in IV formulations, lorazepam has a shorter half-life. Shorter-acting benzodiazepines may be preferred in patients with ALD due to prolonged sedative effects in patients with hepatic dysfunction. In patients who require adjunctive therapy, propofol (0.3–1.25 mg/kg/h, max dose 4 mg/kg/h) or dexmedetomidine (up to 0.7 mcg/kg/h) can be considered [15]. Patients must be in a ICU setting for administration of these agents (as discussed below in the Evidence Contour).

Table 69.4 Michigan alcohol withdrawal severity (MAWS) scoring system

Symptom classes	Scoring
Type A (CNS excitation) Anxiety or nervousness Restless Bothered by bright light Bothered by sounds	Assign one point for each Maximum 4 points
Type B (Adrenergic hyperactivity) Nausea or vomiting Visible tremor Sweat visible (palms/forehead) SBP more than 30 mmH over baseline or >170 mmHg OR DBP more than 20 mmHg over baseline or >100 mmHg Heart rate >110	Assign one point for each Maximum 5 points
Type C (Delirium) Inappropriate behavior, not redirectable Disinhibited, not redirectable Disoriented Hallucinations (auditory, visual, tactile) AND not redirectable	Maximum 1 point

Severity-based treatment protocol		
Severity	Clinical Guidance	Cautions/Side Effects
Mild/Moderate MAWS score 0–5	Baseline EKG Assess every 1–2 h (or more frequently if clinical instability present) MAWS 1–5 **Lorazepam** 1–2 mg PO/IV every 1 h as needed until patient calm or MAWS score 0 If 2 or more **Type B** symptoms non-responsive to lorazepam, consider **clonidine** 0.1 mg PO every 2 h (maximum 3 doses) after ruling out other contributing factors (ex. hypoglycemia, electrolyte disturbance, dehydration, cardiac problems, etc) If **Type C** symptoms present and nonresponsive to lorazepam, consider **haloperidol** 0.5–2.0 mg PO/IM every 2 h until Type C symptoms resolve OR patient is calm/cooperative OR redirectable	**Clonidine** STOP if SBP decreases 30 mmHg or more OR DBP decreases by 20 mmH or more with any **one** dose **Haloperidol** Requires at least hourly monitoring by nursing Do not use in patients with Parkinson's disease Monitor for fever, new hypertension or dystonic reaction and discontinue use immediately if these occur
Severe MAWS Score 6+	Transfer to monitored telemetry bed Consider ICU Transfer if MAWS >6 after 6 h treatment OR clinical instability (SBP <85 or >185 mmHg; HR >125; RR >30 or inability to protect airway) **Lorazepam 2–4** mg PO/IV every 1 h as needed until patient calm or MAWS score 0 If 2 or more **Type B** symptoms non-responsive to lorazepam, consider **clonidine 0.1–0.2** mg PO every 2 h (maximum 3 doses) after ruling out other contributing factors (ex. hypoglycemia, electrolyte disturbance, dehydration, cardiac problems, etc) If **Type C** symptoms present and nonresponsive to lorazepam, consider **haloperidol** 0.5–2.0 mg PO/IM every 2 h until Type C symptoms resolve OR patient is calm/cooperative OR redirectable For intubated patients with ongoing signs and symptoms of severe withdrawal not responsive to above measures, consideration can be given to propofol or dexmedetomidine infusions.	Same as above

The MAWS protocol is an institution-specific example of AWS management. Consult your local institutional protocols, if available, for management. Other examples of suggested protocols are included in Shukit, NEJM 2014 (371)

Nutritional and Micronutrient Supplementation

Vitamin deficiencies are common in hospitalized patients with AUD and ALD. The most common electrolyte disturbance is hypomagnesemia, which is thought to occur due to increased urinary excretion as well as GI losses through diarrhea [16]. Repletion of magnesium and potassium is standard of care for patients with alcohol use disorders, though supplementation has not been shown to improve outcomes or decrease risk of developing severe AWS or DTs. Thiamine (vitamin B1) deficiency is also common in alcoholic patients and arises due to poor dietary intake, reduced intestinal absorption, and impaired cellular utilization. Thiamine deficiency can result in Wernicke-Korsakoff syndrome, a neurologic syndrome with both acute and chronic manifestations including ataxia, oculomotor disturbances (Wernicke's encephalopathy), and confusion in the acute setting which can progress to more chronic and intractable amnestic symptoms, characteristic of the Korsakoff syndrome [17]. Early recognition and repletion of thiamine can reverse the acute manifestations, but chronic changes are often permanent. Alcoholic dementia and alcohol-related cerebellar degeneration have also been linked to thiamine deficiency [17]. Thiamine repletion in the ICU should be via the parenteral route as intestinal absorption of oral thiamine is poor [10]. Magnesium repletion should also be addressed since magnesium acts as a cofactor for the conversion of thiamine. Care should be taken to replace thiamine prior to initiation of glucose-containing intravenous infusions to avoid precipitating Wernicke's encephalopathy. Folate deficiency is also common in AUD patients and results in a macrocytic anemia.

Many other vitamins and minerals may be deficient in alcoholics due to combination of poor nutritional status, decreased absorption and increased losses through the urinary or GI tract. This includes vitamin B6 (pyridoxine), vitamin B2 (riboflavin), vitamin C, iron, phosphorus and calcium. A daily multivitamin often meets requirements for supplementation of water-soluble vitamins and minerals. Fat-soluble vitamins, including vitamins A, D, E, and K, are often deficient in patients with ALD and chronic alcohol use. Recommended daily intake of various vitamins and minerals for patients with ALD are listed in Table 69.4. Additional supplementation may be necessary for patients in whom some levels are low. Nutritional consultation for the ICU patient with ALD may be helpful. Enteral nutrition via tube feeds is recommended over parenteral where possible [18]. Placement of enteral feeding tube via oral or nasal route is safe, even in the presence of varices and should be favored over parenteral nutrition, which increases infection risk [18]. Furthermore, percutaneously-placed gastrostomy tubes are contraindicated in the setting of ascites, coagulopathy [19].

Upper GI Bleeding in Patients with Alcoholic Liver Disease

Varices are responsible for nearly 70% of UGI bleeding in ALD patients, but other causes of hemodynamically significant bleeding in cirrhotic patients can include peptic ulcer disease, or Mallory-Weiss tear with an exposed vessel (particularly in patients with recent nausea and vomiting). Practice guidelines are available (see Table 69.3) to aid in management.

All patients with chronic liver disease and UGI bleeding should be transferred to the ICU for management (Table 69.5). Large-bore IV access is essential, and central vein access with a Cordis™ or other large caliber device is preferred to allow for rapid infusion of blood products and crystalloid. Blood transfusion should be initiated if hemoglobin is <8 g/dl, but over-resuscitation with blood products or crystalloid should be avoided in order to prevent a rise in portal pressures which could precipitate worsened bleeding. A recent study confirmed the benefit of a restrictive transfusion strategy. In a randomized controlled trial of over 800 patients with upper GI bleeding, those who received transfusions to maintain a target hgb of ~ 8 g/dl (restrictive strategy) versus ~ 10 g/dL (liberal strategy) had improved 6 week survival (HR 0.55, p = 0.02) [20]. The subgroup of patients with cirrhosis, particularly Childs A/B cirrhotics, had even better survival (HR 0.30, p = 0.02). Of note, patients with massive exsanguinating bleeding, acute coronary syndromes, stroke or TIA, symptomatic

Table 69.5 Management of alcoholic liver disease and alcohol withdrawal

Alcohol Withdrawal	Suspect in patients who report a history of recent drinking or who answer any CAGE questions positively or who have signs/symptoms of alcohol withdrawal Utilize a protocol-based assessment approach, (see Tables 69.3 and 69.4 for examples) or institution-specific protocol, to regularly assess patients for signs/symptoms of withdrawal: CNS excitation (anxiety, restlessness, bothered by light/sound) Adrenergic Activation (Nausea/vomiting, visible tremor, diaphoresis, hypertension, tachycardia) Delirium (inappropriate or disinhibited behavior that is not re-directable, disorientation, hallucinations) See Table 69.4 for management and pharmacotherapy options
Indication for ICU Monitoring	Severe alcohol withdrawal syndrome/DTs Inability to protect airway/need for intubation Upper GI bleeding concerning for variceal bleeding Hemodynamic instability (HR >125, RR >30, SBP <85, or >185) Refractory symptoms unresponsive to benzodiazepine treatment

peripheral vascular disease, or lower GI bleeding were excluded. Therefore, a target hemoglobin ~8 g/dL is appropriate in patients with suspected variceal bleeding [21].

As soon as variceal bleeding is suspected, octreotide should be initiated in a continuous intravenous infusion. A bolus dose of 50 mcg followed by 50 mcg/h infusion rate is recommended with infusion continued for 3–5 days after confirmation of variceal bleeding on endoscopy. The mechanism of action of octreotide is due to splanchnic vasoconstriction which decreases portal pressures; however, somatostatin and its analogues (including octreotide) alone offer only marginal benefit and should always be accompanied by early endoscopic therapy. Patients are often placed on proton-pump inhibitor infusions prior to diagnostic and therapeutic endoscopy, given concern for peptic ulcer bleeding. If varices are found to be the cause of upper GI bleeding, PPI infusions can be replaced with once or twice daily oral PPI, depending upon other endoscopic findings and risk for stress ulcers in the ICU setting. Finally, antibiotic prophylaxis should be initiated in *all* cirrhotic patients, with or without ascites, presenting with GI hemorrhage. In multiple studies, a mortality benefit has been shown for cirrhotic patients with GI bleeds receiving prophylactic antibiotics initiated as soon as possible after presentation to the hospital. The presence or absence of ascites in ALD patients with GI bleeding *is not required* to initiate antibiotic prophylaxis. Third-generation cephalosporins, such as ceftriaxone are preferred over fluoroquinolones due to studies showing greater efficacy with cephalosporin and can be continued for up to 7 days [21]. Non-selective beta-blockers for prevention of variceal bleeding should be avoided in the acute setting.

Early endoscopy within a maximum of 12 h should occur [21]. In order to optimize visualization of the UGI tract, gastric lavage via placement of an NG tube is recommended to help clear the stomach of old blood. Contrary to popular belief, placement of an NG tube is not associated with a greater risk of inducing bleeding from esophageal varices. Lavage with 500 ml or more of normal saline is recommended until clear. In addition, some endoscopists recommend administration of a rapid acting prokinetic agent such as IV metoclopramide (10 mg) or erythromycin (125 mg) to facilitate removal of retained clots.

Endoscopic treatment options for esophageal varices include band ligation and sclerotherapy. Band ligation is usually the first-line endoscopic treatment, with sclerotherapy, using either ethanolamine or sodium morrhuate as sclerosants, often reserved for use if banding fails. Endoscopic therapy is successful in controlling variceal bleeding in 80–90 % of cases. In cases where endoscopic therapy is unsuccessful, salvage therapy with a transjugular intrahepatic portosystemic shunt (TIPS) is the next step in management. TIPS is *contraindicated* in patients with uncontrolled systemic infections or sepsis, congestive heart failure, severe pulmonary hypertension or severe tricuspid regurgitation. Obstruction of hepatic veins, presence of portal vein thrombus, hepatocellular carcinoma, severe coagulopathies and thrombocy-

topenia (<20,000 cells/mm^3), and severe hepatic encephalopathy are also relative contraindications to placing a TIPS. Therefore, a hepatic ultrasound with dopplers and bedside echocardiogram (if there is clinical suspicion of heart failure or pulmonary hypertension) should be performed prior to TIPS, though this should not delay TIPS if the patient is hemodynamically unstable with ongoing bleeding. If bleeding continues after endoscopic therapy, balloon tamponade can be used for up to 24 h to temporize until the patient can be taken to the Interventional Radiology suite for TIPS. The most common tamponade device available is the Sengstaten-Blakemore tube (Fig. 69.3). This tube, composed of both an esophageal and gastric balloon, should only be inserted in intubated and sedated patients. The balloon can be inserted blindly following endoscopy with inflation of the gastric balloon often sufficient to provide tamponade of bleeding. A portable abdominal x-ray should be performed prior to full balloon inflation to confirm position in the stomach prior to securing the balloon. Balloon tamponade devices should only be placed and monitored by individuals skilled and familiar with their use and should not be left in place longer than 24 h. If TIPS is unavailable, consideration should be given to transferring to a center which offers the procedure.

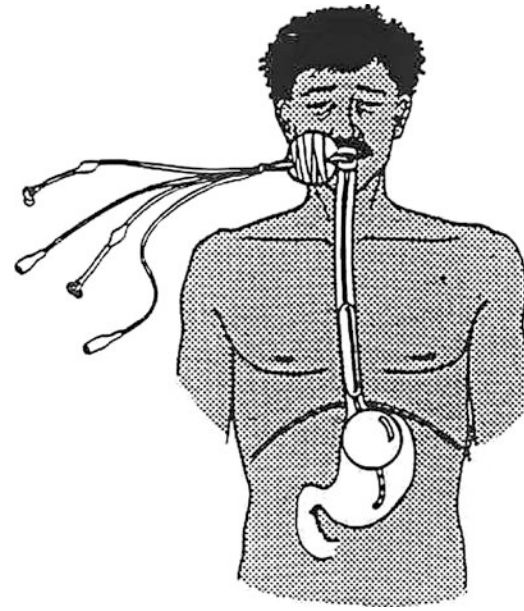


Fig. 69.3 Sengstaten- Blakemore Tube. Prior to insertion, patients should be electively intubated and sedated. After the esophageal and gastric balloons are inflated to exclude a leak, the lubricated tip of the tube is passed through a nares or the mouth into the hypopharynx and esophagus. Following confirmation of a secussion splash in the stomach, the gastric balloon is inflated with 30 ml of air and a STAT confirmatory x-ray obtained to insure proper tube placement. The gastric balloon is inflated to 200–250 ml followed by active traction on the tube at the oropharynx to create a tamponade effect at the gastroesophageal junction. All tubes require external fixation to prevent tube retraction. The maximum recommended duration of balloon inflation is 12 and 24 h for the esophageal and gastric balloons, respectively, to prevent mucosal necrosis

Medical Management of Acute Alcoholic Hepatitis

The medical management of acute alcoholic hepatitis includes supportive care, nutritional support, vitamin and mineral supplementation, and surveillance for and treatment of infection (See Table 69.5). Glucocorticoids or pentoxifylline were suggested as part of management in selected patients until the recently completed STOPAH trial called into question the effectiveness of these therapies [22, 23]. In a multicenter, double-blind, randomized trial, 1103 patients with a clinical diagnosis of acute alcoholic hepatitis and Maddrey's Discriminant Function score ≥32 were randomized to either placebo, pentoxifylline plus placebo, prednisolone plus placebo, or pentoxifylline plus prednisolone. There was no difference in 28 day mortality, though there was a trend towards improved 90 day and 1-year mortality with corticosteroids that did not reach statistical significance. Based on this data, as well as prior meta-analyses, pentoxifylline appears to be ineffective in improving outcomes for patients with acute alcoholic hepatitis and should not be used [24, 25]. Though some meta-analyses had previously shown some moderate short-term benefit with prednisolone, the STOPAH trial calls its use into question. Higher rates of infection have also been reported in patients receiving prednisolone [26].

Only patients with a clinical diagnosis of acute AH and Maddrey's DF score ≥32 who have no evidence of active infection should be considered for corticosteroids after considering the risks versus benefits. Because treatment for 1 month

would be required, patients in whom long-term follow-up is uncertain or questionable should not be placed on prednisolone. The dose of prednisolone given is 40 mg PO daily. The Lille score, a composite of age, creatinine, albumin, prothrombin time, and bilirubin, can be calculated at day 7 of glucocorticoid treatment to determine if patients are responding to prednisolone therapy [27]. If the score is ≥0.45, this suggests that the patient is not responding and consideration should be given to stopping steroids.

Additional medical management options for acute AH include nutritional therapy. Enteral therapy, preferred over parenteral nutrition due to increased risk of infection, should be considered given the frequent finding of protein-calorie malnutrition in patients with chronic AUDs and acute AH. One multi-center randomized open-label trial of corticosteroids versus enteral nutrition showed similar 28 day survival, suggesting that enteral nutrition is non-inferior to corticosteroids [28]. Vitamin and mineral supplementation, as noted above, is recommended.

Management of Hepatorenal Syndrome

Acute kidney injury (AKI) develops in up to 20% of hospitalized cirrhotic patients [29]. Most instances of acute kidney injury in patients with chronic liver disease are pre-renal and acute tubular necrosis (ATN). General principles of AKI management in cirrhotic patients apply: surveillance for and treatment of infection; stopping any medications that precipitate dehydration or renal injury (such as diuretics, ACE-inhibitors, NSAIDs, or aminoglycoside antibiotics). However, hepatorenal syndrome (HRS), due to splanchnic vasodilation and renal vasoconstriction in the setting of advanced liver disease, occurs in approximately 20% of patients with ALD or acute AH. Hepatorenal syndrome is diagnosed in a cirrhotic with ascites who has a serum creatinine >1.5 mg/dL which does not improve with administration of a fluid challenge (given as 1 g/kg albumin daily to a maximum of 100 g/day for at least 2 days) with no evidence for shock, treatment with nephrotoxic drugs, or parenchymal kidney disease. There are two type of HRS: type 1 HRS, which is characterized by a rapid rise in creatinine to >2.5 mg/dL or a 50% reduction in creatinine clearance to <20 ml/min in 2 weeks or less, and type II HRS which is slower, more progressive renal failure occurring over several weeks to months [30]. Both carry a very high mortality, but type 1 HRS is more commonly encountered in the ICU setting.

HRS can frequently occur in the setting of infection, particularly in patients with spontaneous bacterial peritonitis (SBP). Therefore, in addition to antibiotics, albumin should be given on day 1 (1.5 g/kg) and day 3 (1.0 g/kg) to prevent development of HRS and improve mortality in patients with SBP [30]. In patients who have a confirmed diagnosis of HRS, treatment with a combination of daily albumin infusion, octreotide (200 mcg subcutaneously three times daily) and midodrine (5–12.5 mg orally three times daily titrated to achieve an increase in mean arterial pressure of 15 mmHg) has been shown in a small randomized trial and in a larger retrospective trial to be effective [31, 32]. Octreotide and midodrine work by increasing splanchnic vasoconstriction. Other medications that have been investigated include terlipressin, a vasopressin analogue that increases splanchnic vasoconstriction. In the first direct comparison between terlipressin/albumin versus midodrine/octreotide/albumin, terlipressin-based therapy was found to be superior to octreotide and midodrine [33]. Since terlipressin is not available in the United States, it is not recommended for use at this time. Terlipressin also carries with it an increased risk of vasoconstrictive complications, including myocardial infarction, stroke, and intestinal ischemia. A meta-analysis of trials comparing terlipressin and norepinephrine showed equivalent efficacy, with fewer adverse events in the norepinephrine-treated patients [34]. This study was limited, however, by the high risk of bias in the included studies, which were all single-center, non-blinded studies with small sample sizes.

Evidence Contour

Optimal Medications for Alcohol Withdrawal Syndrome

Although benzodiazepines are the first line agents for AWS, other medications that are not well studied but have been used in an ICU setting include

propofol, phenobarbital, alpha-2 agonists, such as clonidine and dexmedetomidine; and antipsychotics such as haloperidol. Haloperidol has been described as adjunctive therapy to treat severe agitation and hallucinations, but its use is complicated by an increased likelihood of seizures and QT prolongation. Newer atypical antipsychotics such as risperidone, quetiapine, or olanzapine, have not been studied in patients with AWS or DTs. Alpha-2 agonists, such as dexmedetomidine, work to decrease CNS sympathetic outflow, thus decreasing the autonomic symptoms associated with AWS. Dexmedetomidine in particular has emerged as a potentially attractive adjunctive agent given its much shorter half-life and greater ease of titration but should not be used in patients with heart block. In addition, the lack of GABA or opioid activation produces less respiratory depression, possibly preventing intubation. In the only prospective, randomized trial to date in 24 patients receiving primary symptom-driven benzodiazepine therapy for AWS, adjunctive dexmedetomidine reduced 24 h lorazepam requirements compared to placebo but did not show benefit in any other secondary outcomes [3].

Intubation for EGD

Decisions regarding intubation and choice of sedation are complex and require individualization. Sedation in ICU patients with underlying AUD and ALD, including those who are not undergoing withdrawal, is complex. Patients with AUDs may require higher doses of sedatives, including higher opioid and anxiolytic doses to achieve similar sedation outcomes as patients without AUDs. However, in patients with ALD, commonly used sedation agents, including propofol, midazolam, and fentanyl, undergo hepatic metabolism and can result in more prolonged sedation at lower doses. Because of the complexity of sedation in patients with both active AUD and ALD, the choice of sedative should be individualized to the patient. Available evidence to date supports the use of propofol as effective and safe in cirrhotic patients with no evidence of precipitation of hepatic encephalopathy [35, 36]. A recent meta-analysis of propofol use in cirrhotic patients (most of whom were Childs Class A or B) undergoing upper GI endoscopy showed that propofol was safe and effective with no increased risk of adverse events, though the trials did not indicate if patients had AWS [37]. In cases where endoscopy is required, the choice of sedative agent should be made in conjunction with the consulting gastroenterologist and the ICU team.

The decision to intubate before endoscopy should also be individualized based on patient characteristics and severity of clinical bleeding. Patients with large-volume upper GI bleeding and those with altered mental status who may not be able to protect their airway should be considered for intubation prior to endoscopy. However, routine intubation for all patients with liver disease and upper GI bleeding is not recommended [38, 39].

References

1. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. N Engl J Med. 2009;360:2758–69.
2. Gowing LR, Ali RL, Allsop S, Marsden J, Turf EE. Global statistics on addictive behaviours: 2014 status report. Addiction. 2015;110:904–19.
3. Mueller SW, Preslaski CR, Kiser TH, Fish DN, Lavelle JC, Malkoski SP, et al. A Randomized, double-blind, placebo-controlled dose range study of dexmedetomidine as adjunctive therapy for alcohol withdrawal*. Crit Care Med. 2014;42:1131–9.
4. Walsham NE, Sherwood RA. Ethyl glucuronide. Ann Clin Biochem. 2012;49:110–7.
5. Dunn W, Jamil LH, Brown LS, Wiesner RH, Kim WR, Menon KVN, et al. MELD accurately predicts mortality in patients with alcoholic hepatitis. Hepatology. Wiley Subscription Services, Inc., A Wiley Company; 2005;41:353–8.
6. McPhail MJW, Shawcross DL, Abeles RD, Chang A, Patel V, Lee G, et al. Increased survival for patients with cirrhosis and organ failure in liver intensive care and validation of the chronic liver failure-sequential organ failure scoring system. Clin Gastroenterol Hepatol. 2014;13:1353–60.
7. Sullivan JT, Sykora K, Schneiderman J, et al. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict. 1989;84:1353–7.
8. de Wit M, Jones DG, Sessler CN, Zilberberg MD, Weaver MF. Alcohol-use disorders in the critically ill patient. Chest J Am Coll Chest Physicians. 2010;138:994–1003.
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington: American Psychiatric Association; 2013.
10. Awissi D, Lebrun G, Fagnan M, Skrobik Y. Alcohol, nicotine, and iatrogenic withdrawals in the ICU. Crit Care Med. 2013;41:S57–68.

11. DeCarolis DD, Rice KL, Ho L, Willenbring ML, Cassaro S. Symptom-driven lorazepam protocol for treatment of severe alcohol withdrawal delirium in the intensive care unit. Pharmacother J Hum Pharmacol Drug Ther. 2007;27:510–8.
12. Amato L, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. Cochrane Database Syst Rev.2010; (3):CD005063.
13. Awissi D, Lebrun G, Coursin DB, Riker RR, Skrobik Y. Alcohol withdrawal and delirium tremens in the critically ill: a systematic review and commentary. Intensive Care Med. 2012;39:16–30.
14. Goodson CM, Clark BJ, Douglas IS. Predictors of severe alcohol withdrawal syndrome: a systematic review and meta-analysis. Alcohol Clin Exp Res. 2014;38:2664–77.
15. Schuckit MA. Recognition and management of withdrawal delirium (delirium tremens). N Engl J Med. 2014;371:2109–13.
16. Elisaf M, Merkouropoulos M, Tsianos EV, Siamopoulos KC. Acid–base and electrolyte abnormalities in alcoholic patients. Miner Electrolyte Metab. 1994;20:274–81.
17. Martin PR, Singleton CK, Hiller-Sturmhöfel S. The role of thiamine deficiency in alcoholic brain disease. Alcohol Res Health. 2004;27:134–42.
18. Singal AK, Charlton MR. Nutrition in alcoholic liver disease. Clin Liver Dis. 2012;16:805–26.
19. Baltz JG, Argo CK, Al A. Mortality after percutaneous endoscopic gastrostomy in patients with cirrhosis: a case series. Gastrointest Endosc. 2010;72(5):1072–5.
20. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:11–21.
21. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey WD. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Am J Gastroenterol. Nature Publishing Group; 2007;102:2086–102.
22. O'Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. Am J Gastroenterol. 2010;105:14–32.
23. Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med. 2015;372:1619–28.
24. Whitfield K, Rambaldi A, Wetterslev J et al. Pentoxifylline for alcoholic hepatitis. Cochrane Database of Sys Rev. 2009;(4):CD007339.
25. Parker R, Armstrong MJ, Corbett C, Rowe IA, Houlihan DD. Systematic review: pentoxifylline for the treatment of severe alcoholic hepatitis. Aliment Pharmacol Ther. 2013;37:845–54.
26. Mathurin P, O'Grady J, Carithers RL, Phillips M, Louvet A, Mendenhall CL, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. Gut. 2011;60:255–60.
27. Louvet A, Naveau S, Abdelnour M, Ramond M, Diaz E, Fartoux L, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology. 2007;45:1348–54.
28. Alvarez MA, Cabré E, Lorenzo-Zúñiga V, Montoliu S, Planas R, Gassull MA. Combining steroids with enteral nutrition: a better therapeutic strategy for severe alcoholic hepatitis? Results of a pilot study. Eur J Gastroenterol Hepatol. 2004;16:1375–80.
29. Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology. 2008;48:2064–77.
30. Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. Hepatology. 2009;49(6):2087–107.
31. Angeli P, Volpin R, Gerunda G, Craighero R, Roner P, Merenda R, et al. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. Hepatology. W.B. Saunders; 1999;29:1690–97.
32. Esrailian E, Pantangco ER, Kyulo NL, Hu K, Runyon BA. Octreotide/midodrine therapy significantly improves renal function and 30-day survival in patients with type 1 hepatorenal syndrome digestive diseases and sciences. Kluwer Academic Publishers-Plenum Publishers; 2007;52:742–8.
33. Cavallin M, Kamath PS, Merli M, Fasolato S, Toniutto P, Salerno F, et al. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: a randomized trial. Hepatology. 2015;62:567–74.
34. Junior A, Farias AQ, d'Albequerque L, et al. Terlipressin versus norepinephrine in the treatment of hepatorenal syndrome: a systematic review and meta-analysis. PlosOne. 2014;9(9):e107466.
35. Sharma P, Singh S, Sharma BC, Kumar M, Garg H, Kumar A, et al. Propofol sedation during endoscopy in patients with cirrhosis, and utility of psychometric tests and critical flicker frequency in assessment of recovery from sedation. Endoscopy. 2011;43:400–5.
36. Fagà E, De Cento M, Giordanino C, Barletti C, Bruno M, Carucci P, et al. Safety of propofol in cirrhotic patients undergoing colonoscopy and endoscopic retrograde cholangiography: results of a prospective controlled study. Eur J Gastroenterol Hepatol. 2011;24:70–6.
37. Tsai H, Lin Y, Ko C, Lou H, Chen T, Tam k, et al. Propofol versus midazolam for upper gastrointestinal endoscopy in cirrhotic patients: a meta-analysis of randomized controlled trials. PLoS ONE Public Libr Sci. 2015;10:1–13.
38. Rudolph SJ, Landsverk BK, Freeman ML. Endotracheal intubation for airway protection during endoscopy for severe upper GI hemorrhage. Gastrointest Endosc. 2003;57:58–61.
39. Herrera JL. Management of acute variceal bleeding. Clin Liver Dis. 2014;18(2):347–57.

Part IX

Hematologic Disease

Robert C. Hyzy

70 Diagnosis and Management of Thrombotic Thrombocytopenic Purpura

Bravein Amalakuhan and Anoop M. Nambiar

Case Presentation

A 45 year-old African-American female with morbid obesity presented to the emergency department with a 2-day history of abdominal pain, nausea, vomiting, and skin lesions. She was found to have a low-grade fever, but all other vitals were within normal limits. Her physical examination was unremarkable, except for diffuse abdominal tenderness on palpation and diffuse purpuric lesions (Fig. 70.1). Her white blood cell count and differential count were normal, hemoglobin was 8 g per deciliter (g/dL), and platelet count was 12,000 per cubic millimeter (mm^3). Her peripheral blood smear shows multiple fragmented red blood cells per microscopic high-powered field (Fig. 70.2) as well as reticulocytosis. Her serum creatinine level was 1.1 mg per decilitier (mg/dL), total bilirubin 3.3 mg/dL, direct bilirubin 2.1 mg/dL, lactate dehydrogenase 800 U/L, normal coagulation profile, negative direct Coombs' test and a negative pregnancy test.

Question What empiric treatment should be instituted urgently for this medical emergency prior to confirmation of the diagnosis?

Answer Therapeutic plasma exchange

All patients presenting with microangiopathic hemolytic anemia (MAHA) and thrombocytopenia in the absence of an alternative explanation should be recognized rapidly as possible thrombotic thrombocytopenic purpura (TTP). Prompt

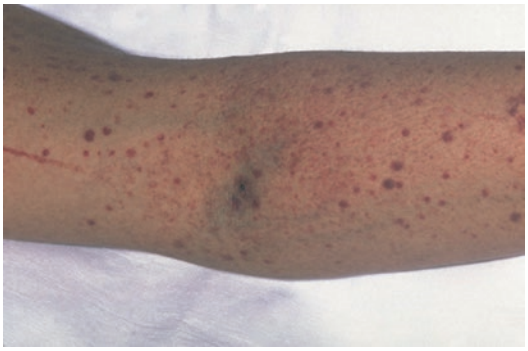


Fig. 70.1 Purpura (bruises) and petechiae (*red and purple dots*) on the skin. Bleeding under the skin causes the purple, brown, and red color of the purpura and petechiae (Source: NIH National Heart, Lung and Blood Institute. What Is Thrombotic Thrombocytopenic Purpura? http://www.nhlbi.nih.gov/health/health-topics/topics/ttp)

B. Amalakuhan
Division of Pulmonary Diseases and Critical Care Medicine, Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

A.M. Nambiar (✉)
Division of Pulmonary Diseases and Critical Care Medicine, Department of Medicine, University of Texas Health Science Center at San Antonio and the Audie L. Murphy VA Hospital, South Texas Veterans Health Care System, San Antonio, TX, USA
e-mail: nambiar@uthscsa.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_70

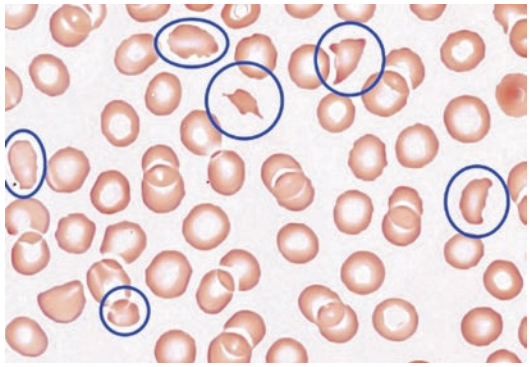


Fig. 70.2 Peripheral blood smear demonstrates schistocytes (*circled in blue*) (By Central Hematology Laboratory Hemostasis Research Laboratory Bern University Hospital & University of Bern – Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=36741808)

initiation of therapeutic plasma exchange (TPE) may be life-saving. This patient was admitted to the intensive care unit and a central venous catheter was placed under direct ultrasound guidance without complication following urgent platelet transfusion due to her severe thrombocytopenia. A complete laboratory evaluation was sent including ADAMTS13 level, ADAMTS autoantibody screen, hepatitis panel and HIV testing. Multiple units of fresh frozen plasma (FFP) were administered until TPE could be initiated. TPE was started at 1.5 plasma volumes for the first 3 days. High-dose pulsed intravenous methylprednisolone (1000 mg per day) was administered for the next 3 days. Two units of packed red blood cells and folic acid were also given. Her hemodynamic and cardiopulmonary status was closely monitored. Once her platelet count was greater than in the 50,000/mm^3, thromboprophylaxis was started with low molecular weight heparin and aspirin. By day three, her platelet count increased to 150,000/mm^3. TPE was then continued at one plasma volume exchanged for two more days and then discontinued. During this time, her ADAMTS13 activity level from admission returned low at 4%. Hepatitis panel and HIV testing were negative. ADAMTS13 autoantibody was still pending. Her platelet count and LDH continued to improve, and she was downgraded from the intensive care unit by day 10 in stable condition.

Principles of Management

Diagnosis of Thrombotic Thrombocytopenic Purpura

The diagnosis of thrombotic thrombocytopenic purpura (TTP) is primarily a clinical one that is based on the presenting clinical features of MAHA, thrombocytopenia, and organ failure, in the absence of a plausible alternative explanation. A timely diagnosis is essential, because if left unrecognized and untreated, TTP has a mortality rate of 90% [1, 2]. Clinical presentation of TTP is significantly heterogeneous (Fig. 70.3). The classic pentad of TTP (MAHA, thrombocytopenia, fever, neurologic abnormalities, and acute kidney injury), previously described as occurring commonly, is now quite rare. In one case series of 65 patients with severe ADAMTS13 deficiency, only 5% were affected by all five of the clinical abnormalities [3]. Prior to advent of early and empiric TPE, patients with TTP would often experience more severe and advanced disease, thus increasing the likelihood of exhibiting the classic pentad prior to death. This likely highlights the greatly improved early recognition of TTP and subsequent initiation of effective therapy which have greatly reduced the risk of developing severe disease with associated multisystem organ failure and mortality. In the same series mentioned earlier, only 37% had severe neurologic abnormalities and 34% had no evidence of neurologic dysfunction at all [3]. Acute kidney injury is rare in TTP (seen in only 8% in that series), as opposed to hemolytic uremic syndrome where it is much more common [3]. Fever was seen in 23% of the patients with severe ADAMTS13 deficiency and is usually low-grade [3]. A high fever and chills should raise the suspicion for an alternative diagnosis such as sepsis. Since the presence of the classic pentad is now rare and usually present in severe and advanced TTP, clinicians should maintain a high level of suspicion for TTP when only MAHA and thrombocytopenia are found. In these cases, urgent TPE should be undertaken in parallel with an aggressive evaluation for alternative diagnoses. Diseases that may mimic TTP and should be

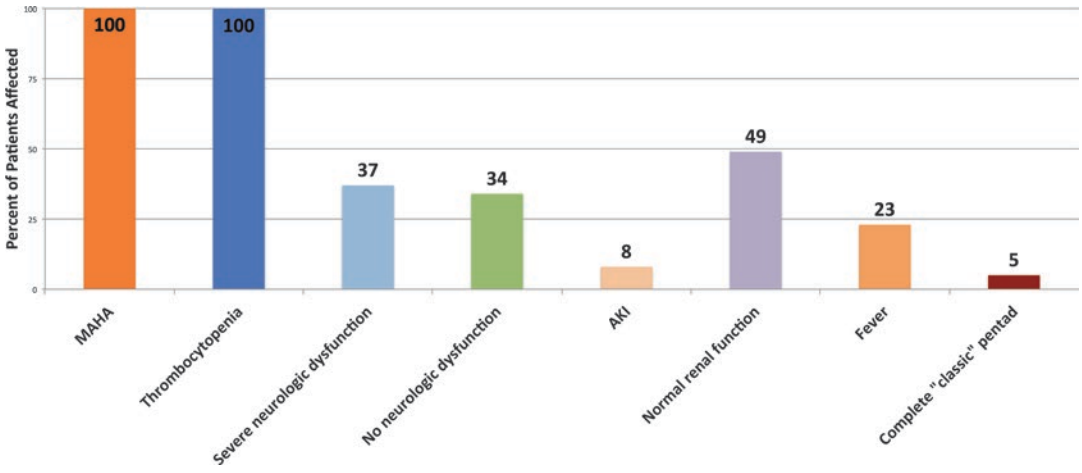


Fig. 70.3 Presenting clinical features in patients with severely reduced ADAMTS13 levels. Data are from day of diagnosis, defined as day of the first plasma exchange treatment. Severe ADAMTS13 activity defined as less than 10% of normal. Neurologic dysfunction ranged from minor (confusion, headache, etc.) to severe (coma, stroke, seizure, focal signs). Acute kidney injury (AKI) is defined as increased serum creatinine of more than 0.5 mg/dL/day for 2 consecutive days or dialysis together with a serum creatinine of greater than 4.0 mg/dL. Normal renal function is defined as all creatinine values less than 1.5 mg/dL. Complete "classic" pentad of TTP is defined as MAHA, thrombocytopenia, fever, neurologic abnormalities, and renal dysfunction Abbreviations: *MAHA* microangiopathic hemolytic anemia, *CNS* central nervous system, *AKI* acute kidney injury. (Data from: George JN. Diagnosis of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome in adults. UpToDate, 2015; and from George [3])

excluded are sepsis, disseminated intravascular coagulation (DIC), autoimmune diseases such as systemic lupus erythematosus (SLE) and scleroderma, vasculitis, malignant hypertension, and malignancy (Table 70.1).

ADAMTS13 Activity Level and Autoantibody Testing

In 1982, patients with hereditary TTP were observed to have unusually large multimers of von Willebrand factor (ULvWF). This led to the discovery and subsequent characterization of a von Willebrand factor-cleaving protease called ADAMTS13 (or **A** **D**isintegrin **A**nd **M**etalloproteinase with a **T**hrombo**S**pondin type 1 motif, member **13**) [3, 4]. In the absence of ADAMTS13, ULvWF multimers released from the vascular endothelium are not cleaved properly resulting in spontaneous platelet-rich microvascular thrombosis in conditions of high shear, such as in the brain, heart, and kidneys with resultant ischemic-induced organ dysfunction. ADAMTS13 deficiency is now well-described to be the causal factor for both hereditary TTP (in association with a confirmed ADAMTS13 mutation) and acquired TTP (in association with an ADAMTS13 autoantibody). Hereditary TTP, also known as Upshaw-Schulman syndrome, is caused by homozygous or compound heterozygous ADAMTS13 mutations, and may be apparent at birth or present later into adulthood when precipitated by a stressor such as pregnancy, infection, or surgery [5]. In acquired TTP, severely reduced ADAMTS13 activity levels of less than 5% and presence of ADAMTS13 autoantibodies confirm the diagnosis [6, 7] and can help distinguish TTP from HUS with a specificity of 90% [8, 9]. However, reduced ADAMTS13 activity (greater than 5%, up to 40%) may be seen in non-TTP disorders such as uremia, inflammatory states, post-operatively, and during pregnancy [10–12]. In addition to aiding in diagnosis, ADAMTS13 activity levels may help identify patients at increased risk for relapse after treatment. Importantly, definitive therapy with TPE should not be delayed while determining these levels.

Table 70.1 Differential diagnosis of thrombocytopenia and microangiopathic hemolytic anemia and their clinical features, ADAMTS13 activity, treatment, and clinical course

Clinical course	80% of patients recover; in patients with severe ADAMTS13 deficiency, the relapse rate is 50%.	Death/ ESRD in 12% of children; 45% mortality rate in adults; relapse may not occur	Mortality rate is only 7%; recurrent episodes of bleeding, pancyto penia, infections	Chronic course with a high mortality rate	Favorable with frequent relapses	Relapse may occur, but most subsequent pregnancies are unnaffected	If treated early minimal end-organ damage; recurrence low long term anti-hyperten sives	Good outcomes if source control obtained & infection treated early	Depends on staging and type of cancer	Variable, with recurrent thrombosis despite anticoa gulation	Mortality is high because of multiple complications	Favorable	High risk of ESRD and death without anticomplement therapy.
Treatment	TPE, steroids	Supportive care	Steroids or IVIG	Immunosup-pression and TPE	Immunosuppres-sion	Immunosup-pression and TPE	Anti-hyperten sives	Antimi-crobials	Surgery, chemo, radiation	Anticoa gulation	Immunosuppres-sion	Removal of drug, supportive care	Steroids, TPE, anticomplement therapy
ADAMTS13 Level	<10%	<10% or >25%	Variable	Variable	Variable	<10% or >25%	>10%	>10%	>10%	>10%	>10%	>25%	Variable
Clinical features	Evidence of ischemic organ injury either in childhood or adulthood	Diarrhea, more common in young children, typically with acute renal failure	Features of TTP with pancyto penia and infectious complica tions	Severe manifestations of the primary autoimmune disorder, usually including renal failure	Dependent on vessels involved and type of vasculitis	Preeclampsia ore eclampsia, features of HELLP	High blood-pressure, ischemic/ neurological symptoms	Features of the primary infection and the organ affected	Features of the primary malignancy	Recurrent miscarriages, with end-organ damnage from arterial/ venous clots	Thrombotic microangiopathy usually limited to the kidney	Gradual onset of renal failure over weeks to months	Iniitally presents with acute renal failure in children or adults
Etiology	TTP: Hereditary or Acquired	HUS	Autoimmune Hemolysis / Evans Syndrome	Autoimmune Disease (lupus nephritis, acute scleroderma)	Vasculitis	Pregnancy-Associated (e.g. HELLP syndrome or eclampsia)	Malignant Hyperten sion	Infections, either Viral severe bacterial (menor or fungal	Malignancy	Catastrophic Antiphos polipid Syndrome	Hematopoietic Stem Cell Transplant	Medication/ drug indueced	Complement-mediated thrombotic microangiopathy

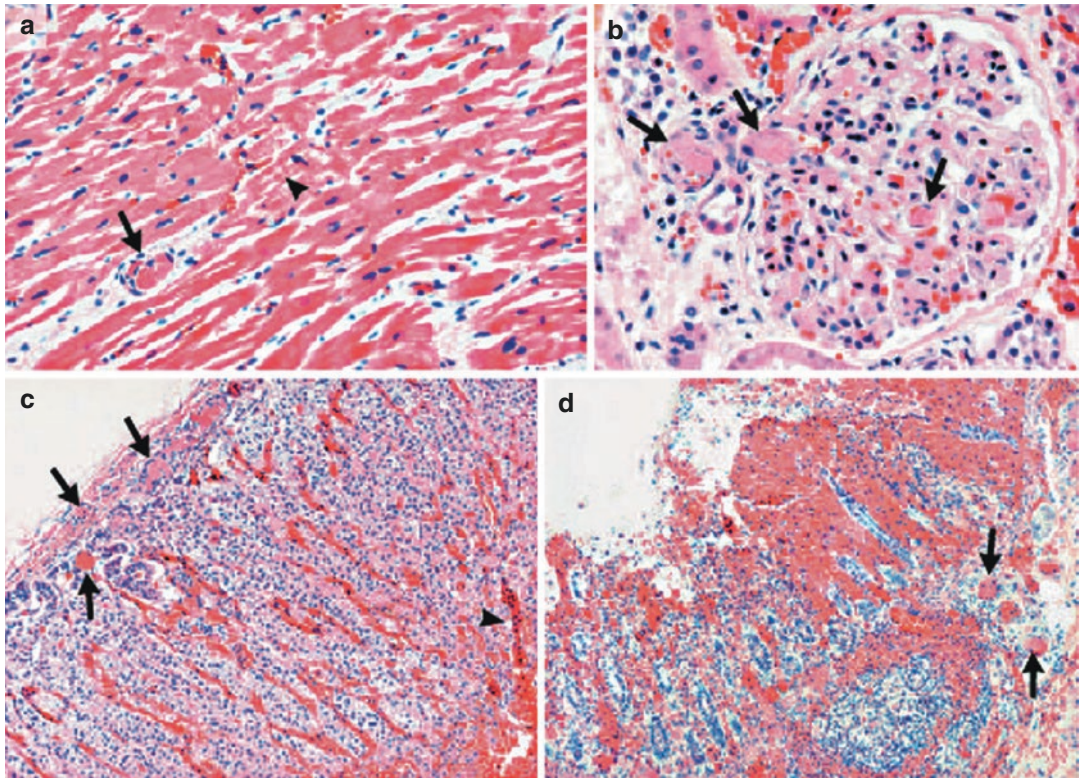


Fig. 70.4 Therapeutic plasma exchange versus plasma infusion in TTP. Response rates and death between plasma infusion and plasma exchange were reported as statistically significant following the first treatment cycle (p=0.025 and p=0.035, respectively) and after 6 months (p=0.002 and p=0.036, respectively) (Data from Buskard et al. [14])

Therapeutic Plasma Exchange

Since the advent of therapeutic plasma exchange (TPE) for treatment of TTP, mortality has significantly fallen from 90 % to nearly 10 % [13]. In addition to replenishment of ADAMTS13 levels, TPE also facilitates removal of ADAMTS13 autoantibodies. TPE, when compared to plasma infusion alone, can significantly improve treatment response rates and survival for patients with TTP. This was highlighted in a 1991 study by the Canadian Apheresis Study Group [14] where 123 TTP patients were randomly treated with either TPE or plasma infusion. Response rate, as defined by an increase in the platelet count, was significantly greater with TPE than plasma infusion at the end of the first treatment cycle (47 % vs. 25 %, p=0.025) and at 6 months (78 % vs. 49 %, p=0.002) (Fig. 70.4). In addition, significantly fewer patients treated with TPE died compared to plasma infusion, at both the end of the first treatment cycle (4 % vs. 16 %, p=0.035) and at 6 months (22 % vs. 37 %, p=0.036). Daily TPE at 1.5 plasma volumes should be exchanged for the first 3 days and then one plasma volume exchanged daily thereafter (Fig. 70.5). British guidelines recommend continuing TPE for an additional 2 days after the normalization of platelets (greater than 150,000 per cubic milliliter) to prevent relapse [2]. TPE is associated with a 2 % mortality rate and 26 % incidence of major complications (mostly central venous catheter-related), but considering the poor prognosis of untreated TTP, the benefits outweigh the risks [15, 16].

Fresh Frozen Plasma (FFP)

ADAMTS13 is a component in FFP and therefore FFP infusion can help replenish ADAMTS13 levels. As mentioned earlier, TPE improved outcomes better than FFP infusions alone; however, it still may be used in the treatment for TTP if there is any

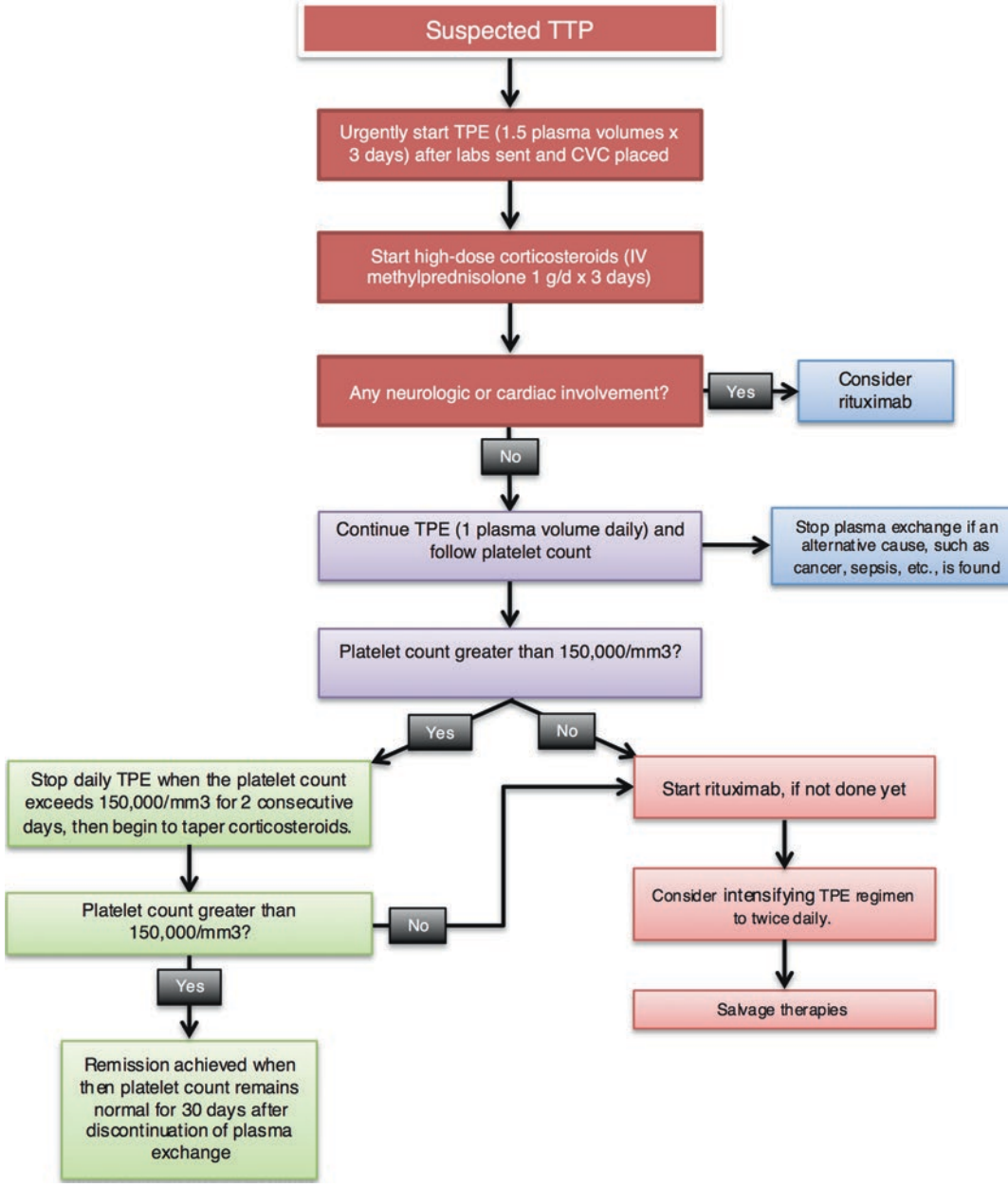


Fig. 70.5 Treatment algorithm for thrombotic thrombocytopenic purpura. Abbreviations: *TTP* thrombotic thrombocytopenic purpura, *TPE* therapeutic plasma exchange (Data from George JN, *NEJM* 2006 and British Guidelines, *British Journal of Haematology* 2012)

delay in starting TPE [2, 14]. If the patient is at an institution where TPE is not available, rapid and timely transfer to an institution with experience performing TPE is essential. There should be an ongoing infusion of FFP before and during transfer.

Immunosuppressive Agents

Expert consensus and various international hematologic society guidelines recommend high-dose corticosteroid therapy, such as pulsed

Table 70.2 Most common causes for drug-induced thrombotic microangiopathy (DITMA)

Drug class/uses	Drug name
Antimalarial, leg cramps, beverages	Quinine
Immunosuppressives	Cyclosporine
	Tacrolimus
	Sirolimus
	Interferon alpha
	Interferon beta
Cancer therapy	Gemcitabine
	Bevacizumab
	Mitomycin
	Pentostatin
	Sunitinib
Antibiotic	Trimethoprim-sulfamethoxazole
Drugs of abuse	Cocaine
	Ecstasy (MDMA, street name: Molly)
	Oxymorphone extended release (Opana ER)

Drugs known to cause DITMA are listed in order of most common to less common in each drug class/use
Of note, despite multiple published reports, antiplatelet agents such as clopidogrel and ticlodipine, have not been definitively proven to cause DITMA (Data from Reference [19])

methylprednisolone (1 g/day) for 3 days then prednisone taper, for all patients with TTP at presentation to ensure a durable remission. Rituximab has been shown to be safe and effective in TTP, especially for refractory disease (failure of platelets to improve despite TPE and corticosteroids), relapsing disease or if there is neurological or cardiac complications on presentation [2, 17, 18].

Drug-Induced Thrombotic Microangiopathy

Achieving and maintaining remission in TTP also depends on the discontinuation of any identified underlying drugs, if found. For example, the most common drugs implicated in drug-induced thrombotic microangiopathy (DITMA) are quinine, cyclosporine, and tacrolimus as a result of either immune-mediated or toxicity-mediated mechanisms [19]. Despite multiple published reports, there is an absence of high quality conclusive evidence implicating thienopyridine antiplatelet agents, such as clopidogrel and ticlodipine, in DITMA. Drugs most commonly associated with DITMA are listed in Table 70.2, and should be immediately discontinued in patients with suspect TTP. The precise incidence of each of these drugs in DITMA is unknown [20].

Venous Thromboembolism Prophylaxis

Once the platelet count is greater than 50,000 per cubic milliliter, British guidelines recommend low-molecular weight heparin to help reduce the risk of developing venous thromboembolism [21]. Platelet transfusions are contraindicated unless necessary for invasive procedures to reduce bleeding risk or if there is active life-threatening hemorrhage [2].

Evidence Contour

Several aspects of the management of patients with TTP have weak evidence and require further research and validation.

Prevention of Relapses with Other Immunosuppressive Agents

Based on limited low-quality evidence, cyclosporine or tacrolimus may be considered a second-line therapy for relapsing TTP. Other immunosuppressives, such as vincristine and cyclophosphamide, with significant potential toxicity and unproven benefit, are not recommended. Splenectomy for acute refractory and relapsed disease is associated with favorable long-term relapse-free survival at the expense of high mortality [22, 23].

Anti-platelet Agents

Efficacy of aspirin and dipyramidole along with standard of care treatment (TPE and

corticosteroids) for TTP was evaluated in a single small randomized controlled trial by the Italian Co-operative Group. They randomized 72 TTP patients to TPE and corticosteroids with or without aspirin and dipyramidole. Although response rates were no different between the two groups, there was a non-significant improvement in survival in the first 15 days in the anti-platelet group (14 % vs. 3 %) without increased bleeding rates [24]. The clinical effectiveness of anti-platelet agents remains unproven, but they are relatively safe and are reasonable additions to management once platelet counts are greater than 50 x 10^9/l [2].

Duration and Intensity of TPE

Although TPE is continued until the platelet count normalizes and then 2 days thereafter, the duration of treatment to prevent relapses is unknown [25]. Twice-daily TPE could be considered for resistant cases or those with progressive neurologic or cardiac dysfunction despite daily TPE [2], but has shown inconsistent results in studies [26].

Amount of FFP

The exact amount and frequency of FFP to be administered is unknown. It is generally accepted that if a delay in the initiation of TPE is anticipated, the equivalent of 1.5 plasma volumes of FFP should be infused daily (approximately 30–60 ml/kg/IV) until TPE is initiated [14].

References

1. Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura: report of 16 cases and review of the literature. Med (Baltimore). 1966;45:139–59.
2. Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, Peyvandi F, Cheung B, Machin SJ. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012;158(3):323–35.
3. George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. Blood. 2010;116:4060.
4. Levy GG, Nichols WC, Lian EC, Foroud T, McClintick JN, McGee BM, Yang AY, Siemieniak DR, Stark KR, Gruppo R, Sarode R, Shurin SB, Chandrasekaran V, Stabler SP, Sabio H, Bouhassira EE, Upshaw Jr JD, Ginsburg D, Tsai HM. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. Nature. 2001;413:488–94.
5. Schneppenheim R, Budde U, Oyen F, Angerhaus D, Aumann V, Drewke E, Hassenpflug W, Haberle J, Kentouche K, Kohne E, Kurnik K, Mueller-Wiefel D, Obser T, Santer R, Sykora KW. von Willebrand factor cleaving protease and ADAMTS13 mutations in childhood TTP. Blood. 2003;101:1845–50.
6. Ferrari S, Scheiflinger F, Rieger M, Muddle G, Wolf M, Coppo P, Girma JP, Azoulay E, Brun-Buisson C, Fakhouri F, Mira JP, Oksenhendler E, Poullin P, Rondeau E, Schleinitz N, Schlemmer B, Teboul JL, Vanhille P, Verant JP, Meyer D, Veyradier A. Prognostic value of anti-ADAMTS 13 antibody features (Ig isotype, titer and inhibitory effect) in a cohort of 35 adult French patients undergoing a first episode of thrombotic microangiopathy with undectable ADAMTS 13 activity. Blood. 2007;109:2815–22.
7. George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med. 2014;371:654–66.
8. Bianchi V, Robles R, Alberio L, Furlan M, Lammle B. Von Willebrand factor-cleaving protease (ADAMTS13) in thrombocytopenic disorders: a severely deficient activity is specific for thrombotic thrombocytopenic purpura. Blood. 2002;100:710–3.
9. Zheng XL, Kaufman RM, Goodnough LT, Sadler JE. Effect of plasma exchange on plasma ADAMTS13 metalloprotease activity, inhibitor level, and clinical outcome in patients with idiopathic and nonidiopathic thrombotic thrombocytopenic purpura. Blood. 2004;103:4043–9.
10. Loof AH, van Vliet HH, Kappers-Klunne MC. Low activity of von Willebrand factor-cleaving protease is not restricted to patients suffering from thrombotic thrombocytopenic purpura. Br J Haematol. 2001;112:1087–8.
11. Mannucci PM, Canciani MT, Forza I, Lussana F, Lattuada A, Rossi E. Changes in health and disease of the metalloprotease that cleaves von Willebrand factor. Blood. 2001;98:2730–5.
12. Moore JC, Hayward CP, Warkentin TE, Kelton JG. Decreased von Willebrand factor protease activity associated with thrombocytopenic disorders. Blood. 2001;98:1842–6.
13. Pereira A, Mazzara R, Monteagudo J, Sanz C, Puig L, Martinez A, Ordinas A, Castillo R. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome: a multivariate analysis of factors predicting the response to plasma exchange. Ann Hematol. 1995;70:319–23.
14. Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, Spasoff RA. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura.

Canadian Apheresis Study Group. N Eng J Med. 1991;325:393–7.
15. George JN. Thrombotic thrombocytopenic purpura. N Engl J Med. 2006;354(18):1927–35.
16. Howard MA, Williams LA, Terrell DR, Duvall D, Vesely SK, George JN. Complications of plasma exchange in patients treated for clinically suspected thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Transfusion. 2006;46:154–6.
17. Fakhouri F, Vernant JP, Veyradier A, Wolf M, Kaplanski G, Binaut R, Rieger M, Scheiflinger F, Poullin P, Deroure B, Delarue R, Lesavre P, Vanhille P, Hermine O, Remuzzi G, Grunfeld JP. Efficiency of curative and prophylactic treatment with rituximab in ADAMTS13-deficient thrombotic thrombocytopenic purpura: a study of 11 cases. Blood. 2005;106:1932–7.
18. Scully M, Cohen H, Cavenagh J, Benjamin S, Starke R, Killick S, Mackie I, Machin SJ. Remission in acute refractory and relapsing thrombotic thrombocytopenic purpura following rituximab is associated with a reduction in IgG antibodies to ADAMTS-13. Br J Haematol. 2007;136:451–61.
19. Al-Nouri ZL, Reese JA, Terrell DR, Vesely SK, George JN. Drug-induced thrombotic microangiopathy: a systematic review of published reports. Blood. 2015;125:616–8.
20. Medina PJ, Sipols JM, George JN. Drug-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Curr Opin Hematol. 2001;8:286–93.
21. Yarranton H, Cohen H, Pavord SR, Benjamin S, Hagger D, Machin SJ. Venous thromboembolism associated with the management of acute thrombotic thrombocytopenic purpura. Br J Haematol. 2003;121:778–85.
22. Bohm M, Betz C, Miesbach W, Krause M, von Auer C, Geiger H, Scharrer I. The course of ADAMTS-13 activity and inhibitor titre in the treatment of thrombotic thrombocytopenic purpura with plasma exchange and vincristine. Br J Haematol. 2005;129:644–52.
23. Kappers-Klunne MC, Wijermans P, Fijnheer R, Croockewit AJ, van der Holt B, de Wolf JT, Lowenberg B, Brand A. Splenectomy for the treatment of thrombotic thrombocytopenic purpura. Br J Haematol. 2005;130:768–76.
24. Bobbio-Pallavicini E, Gugliotta L, Centurioni R, Porta C, Vianelli N, Billio A, Tacconi F, Ascari E. Antiplatelet agents in thrombotic thrombocytopenic purpura (TTP). Results of a randomized multicenter trial by the Italian Cooperative Group for TTP. Haematologica. 1997;82:429–35.
25. Coppo P, Wolf M, Veyradier A, Bussel A, Malot S, Millot GA, Daubin C, Bordessoule D, Pene F, Mira JP, Heshmati F, Maury E, Guidet B, Boulanger E, Galicier L, Parquet N, Vernant JP, Rondeau E, Azoulay E, Schlemmer B. Prognostic value of inhibitory anti-ADAMTS13 antibodies in adult-acquired thrombotic thrombocytopenic purpura. Br J Haematol. 2006;132:66–74.
26. Nguyen L, Li X, Duvall D, Terrell DR, Vesely SK, George JN. Twice-daily plasma exchange for patients with refractory thrombotic thrombocytopenic purpura: the experience of the Oklahoma Registry, 1989 through 2006. Transfusion. 2008;48:349–57.

Acute Leukemia Presentation with DIC

71

Laurie A. Manka and Kenneth Lyn-Kew

Case Presentation

A 36 year old female presented to the hospital with tongue swelling and bleeding after she bit her tongue. Due to worsening swelling of her tongue, she was emergently intubated in the emergency department and transferred to the ICU for further management of her airway. Her recent history was significant for fatigue, menorrhagia, multiple "colds" and sore throats, and recurrent infections of her umbilical piercing. On exam she was noted to have shotty cervical lymphadenopathy and a swollen tongue without evidence of lip swelling. There was evidence of cellulitis around her umbilical piercing, which was subsequently removed. CT neck demonstrated no abscess of the posterior oropharynx but was limited in ability to evaluate the tongue due to the presence of the endotracheal tube. Initial laboratory work showed a pancytopenia with a white blood cell count of $4.0 \times 10^3/\mu L$, hemoglobin 7.5 g/dl, and platelets $116 \times 10^3/\mu L$. Her peripheral smear showed evidence of "rare" blasts. Her coagulation derangements consisted of a prolonged prothrombin time (PT) of 16.1 s, INR of 1.32, partial thromboplastin time (PTT) of 36.5 s. Her D-dimer was greater than the upper level of detection at 500 μg/dL. Fibrin split products were >20 μg/dL, and her Fibrinogen was 344 mg/dL. Because of the patient's pancytopenia, a bone marrow biopsy was obtained and showed a hypercellular marrow with markedly increased blasts, accounting for 95% of the total cells. Chromosomal analysis demonstrated t(15;17) rearrangement.

Question What is the diagnosis?

Answer DIC in the setting of Acute Promyelocytic Leukemia (APML or AML M3)

Acute Promyelocytic leukemia (APML) is a form of acute myelocytic leukemia (AML), comprising approximately 10% of AMLs diagnosed. APML is specifically characterized by a reciprocal translocation between the retinoic acid receptor-alpha (RAR-α) gene on chromosome 17 and the PML gene on chromosome 15. This rearrangement is known as t(15;17). APML often acutely presents clinically with extensive bleeding diathesis requiring ICU admission at the time of diagnosis [1]. Up to 15% of APMLs will present with DIC. This can be due to the disease itself or the effect of undergoing induction chemotherapy [2, 3].

In the setting of acute APML, the extensive bleeding characteristics are due to hyper

L.A. Manka (✉) • K. Lyn-Kew
Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, National Jewish Health, Denver, CO, USA
e-mail: mankal@njhealth.org; Lyn-KewK@NJHealth.org

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_71

fibrinolysis driven primarily by fibrinolytics such as u-PA, t-PA, as well as protease elastase and chemotrypsin [4, 5] which are found in high levels in leukemic blast cells [4, 5]. The over production of these fibrinolytics in the setting of profound thrombocytopenia due to bone marrow dysfunction yield the profound bleeding disorder [1].

DIC is also closely associated with the induction therapy in APML. Treatment of APML consists primarily of use of All-*trans*-retinoic acid (ATRA). ATRA promotes differentiation of leukemic blasts. This process can transiently worsen DIC by consumption of pro-coagulation factors, namely Tissue Factor (TF) and Cancer Procoagulant (CP) [6, 7]. However, within approximately 48 h, as the leukemic blast burden improves so do the markers of DIC.

Principles of Management

Confirm the Diagnosis of AML

AML is a group of hematopoietic neoplasms arising from the precursors of the myeloid cell lines. AML is the most common cause of acute leukemia in adults, with approximately 20,000 cases annually and 10,000 deaths [8]. AML is classified based on specific genetic abnormalities (as in this case), or if it does not fit a specific genetic abnormality, by cell morphology.

Clinical features of AML are primary related to pancytopenia and high cellular turnover in proliferating leukemia cells. These include fatigue, weakness and pallor due to anemia, fever due to immune dysregulation and subsequent infection, infiltrative skin lesions (leukemia cutis), acute neutrophilic dematosis (Sweet syndrome) and petechiae and fundal hemorrhages due to thrombocytopenia or, as in the above case, DIC. Additionally patients may present with tumor lysis syndrome, characterized by hypocalcemia, hyperuricemia, hypokalemia and/or hyperphosphatemia. Circulating leukemic blast cells are frequently found on peripheral smear.

Confirmation of the diagnosis of AML is made by bone marrow aspiration or bone marrow biopsy, particularly when aspiration fails to yield the diagnosis. The diagnosis requires documentation of bone marrow infiltration and the myeloid origin of the cells, with the exception of genetic abnormalities specific to AML such as the t(15;17) in this case.

Make the Correct Diagnosis of DIC

Differential Diagnosis of DIC

The first step to treatment of DIC in the ICU is correct diagnosis. The differential diagnosis of DIC often revolves around discovery of new thrombocytopenia. The differential diagnosis of acute thrombocytopenia in the ICU is extensive and includes a multitude of commonly seen disorders in the ICU.

Common Causes of Thrombocytopenia in the ICU

Sepsis Induced Destruction
Sepsis Induced Sequestration
Sepsis Induced Bone Marrow Suppression via Bacterial Toxins
Pseudothrombocytopenia
Hemodilution
Acute and Chronic Liver Diseases
Drug Induced Thrombocytopenias
Disseminated Intravascular coagulation
Heparin Induced Thrombocytopenia
Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndroem
HELLP syndrome (hemolysis, elevated liver test, and low platelets)
Acute Hemorrhage
Surgical Losses

Laboratory Profile of DIC

The diagnosis of DIC is a clinical one made based on the coagulation parameters in the appropriate patient with the appropriate clinical situation. In a critically ill patient with thrombocytopenia, the classic coagulation profile of DIC consists of:

1. a prolonged prothrombin time (PT),
2. a prolonged partial thromboplastin time (PTT),

3. a decreased fibrinogen levels, and
4. an elevated D-dimer or fibrin degradation products.

DIC can present in a fulminant manner with dramatic derangements of the above parameters. It's also noted in the ICU in a much more subtle sub-acute smoldering manner which is why clinical suspicion is an important aspect in the recognition of DIC in the ICU.

Treat the Underlying Disease

The first and most important step in the clinical treatment of DIC is the treatment of the underlying cause. Correction of the underlying pathology will in turn correct the clotting derangements.

Common Causes of DIC in the ICU*
Infection
Malignancy
Fulminant Liver Disease
Trauma and Burns*
Obstetric Complications
Vasculitides
Catastrophic Antiphospholipid Antibody Syndrome
Fat Embolism
Drugs
Viper Envenomation*
Extra-corporal Circulation
Hemolytic transfusion reactions
**Some experts consider some of these causes to be separate coagulopathies*

The treatment of AML varies based on a variety of factors including cytogenetics, age, occurrence in the course of therapy with cytotoxic agents for other conditions, and relapse or resistant AML. The most common regimens are the "7 + 3" regimens which consist of 7 days of a continuous infusion of standard dose cytarabine with dosing of a anthracycline, such as daunorubicin on days 1–3.

Depending on other factors, other drugs may be added to the above regimen or alternative regiment may be used. For example, ATRA can be combined with cytarabine and daunorubicin or with arsenic trioxide for therapy of APML.

Supportive care during chemotherapy is aimed at treating side effects of the specific regimens, electrolyte management, and hydration for tumor lysis syndrome (with additional treatment as needed), infection prophylaxis, and treatment of infections as a result of the immunosuppression induced by chemotherapy.

Supportive Care/Blood Product Transfusion for DIC

Once the underlying disease has been identified and treatment is directed toward the inciting event, the patient can then be supported with blood products as dictated by the laboratory abnormalities and clinic situations. No data exists determining appropriate transfusion thresholds, but common guidelines are usually followed. Fresh frozen plasma (FFP) and platelet transfusions should be reserved for those patients with active clinical bleeding or undergoing invasive procedures [9, 10]. Cryoprecipitate should be used to replace fibrinogen when the fibrinogen level has dropped below 100 g/dL. Transfusion of prothrombin complexes are not recommended as they can contain small amounts of activated complexes that can, in turn, worsen the clinical coagulopathy [9].

Evidence Contour

Several adjunctive therapies have been explored in the treatment of DIC, but their use remain controversial. These include heparin, anti-thrombin III, and recombinant factor VIIa.

Heparin

Empiric therapeutic doses of heparin is not recommended in DIC despite the fact that DIC is thought to be characterized by activation of the coagulation system. Therapeutic doses of heparin should only be considered in cases of DIC where thrombosis is diagnosed. However, some data do

suggest that continuing low dose heparin in the setting of DIC is beneficial. In the severe sepsis population, several small studies do, in fact, show improved outcomes in patients on low dose heparin despite the presence of abnormal coagulation parameters [11].

Anti-thrombin III

A large randomized control trial was published in JAMA investigating the role of Anti-thrombin III in the setting of severe sepsis with thrombocytopenia between 30 $\times 10^3/\mu L$ and 100 $\times 10^3/\mu L$. Approximately 2000 patients were enrolled. There was no difference in 28-day mortality between the two groups, which was the primary outcome [12].

Recombinant Factor VIIa

Widespread use of recombinant factor VIIa is not recommended in the setting of DIC, however 1 case report and a small case series have been published describing its use in the setting of active clinical bleeding refractory to conservative supportive measures. One case report notes the use of recombinant factor VIIa in a patient with APML with development of DIC in the setting of differentiation syndrome with treatment of ATRA. The patient had evidence of hemorrhagic shock after an iatrogenic puncture of the femoral artery. The patient received two doses of rFVIIa with improvement in clinical bleeding and hemodynamic parameters [13]. A second small case series reported as a letter to the editor noted improvement in the respiratory status in seven patients with APML with differentiation syndrome and diffuse alveolar hemorrhage [14].

References

1. Warrell RP, De The H, Zhen-Yi W, Degos L. Acute Promyelocytic Leukemia. N Engl J Med. 2002;329:177–89.
2. Sarris AN, Kempin S, Berman E, et al. High incidence of disseminated intravascular coagulation during remission induction of adult patients with acute lymphoblastic leukemia. Blood. 1992;79:1305–10.
3. Colman RW, Rubin RN. Disseminated intravascular coagulation due to malignancy. Semin Oncol. 1990;17:172–86.
4. Francis Jr RB, Seyfert U. Tissue plasminogen activator antigen and activity in disseminated intravascular coagulation: clinicopathologic correlations. J Lab Clin Med. 1987;110:541–7.
5. Bennett B, Booth NA, Croll A, et al. The bleeding disorder in acute promyelocytic leukemia: fibrinolysis due to u-TPA rather than defibrination. Br J Haematol. 1989;71:511–7.
6. Falanga A, Consonni R, Marchetti M, et al. Cancer procoagulant in the human promyelocytic cell line NB4 and its modulation by all-*trans*-retinoic-acid. Leukemia. 1988;8:156–9.
7. DeStefano V, Teofili L, Sica S, et al. Effect of all-*trans* retinoic acid on procoagulant and fibrinolytic activities of cultured blast cells from patients with acute promyelocytic leukemia. Blood. 1995;86:3535–41.
8. Dores GM, et al. Acute leukemia incidence and patient survival among children and adults in the United States, 2001–2007. Blood. 2012;119:34–43.
9. Levi M. Disseminated intravascular coagulation; what's new. Crit Care Clin. 2005;21:449.
10. O'Shaughnessy DF, Atterbury C, Boton Maggs P, et al. Guidelines for the use of fresh frozen plasma, cryoprecipate and cryosupernatant. Br J Haematol. 2004;126:11.
11. Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. J Intensive Care. 2014;2:15.
12. Warren BL, Eid A, Singer P, et al. High-dose antithrombin III in severe sepsis. JAMA. 2001;286:1869–78.
13. Zver S, Andoljsek D, Cernelc P. Effective treatment of life-threatening bleeding with recombinant activated factor VII in a patient with acute promyelocytic leukaemia. Eur J Haematol. 2004;72:455–6.
14. Alimoghaddam K, Ghavamzadeh A, Jahani M. Use of NovoSeven for arsenic trioxide-induced bleeding in PML. Am J Hematol. 2006;81:720.

Disseminated Intravascular Coagulation

72

Mario V. Fusaro and Giora Netzer

Case Presentation

A 64-year old woman with a history of non-small cell lung cancer, Type 2 diabetes, and hypertension presented to the emergency department with altered mental status and flank pain. In the emergency department, her initial blood pressure was 83/44 mmHg, with a pulse of 110 beats per minute. On physical examination, she was somnolent but arousable. She had a fine petechial rash on both lower extremities and bleeding from her peripheral IV sites. Laboratory testing results included: white blood cell count of 3,100/μl, creatinine of 2.5 mg/dl (her baseline being 1.0), International Normalized Ratio (INR) of 3.1, Partial Thromboplastin Time of 50 s, and platelet count of 33,000 cells/μl. The urine microscopy revealed 20–50 WBC/high-powered field; the urine culture is growing 100,000 colony-forming units of a gram negative bacillus. A computerized tomography (CT) scan of the abdomen and pelvis revealed left hydronephrosis, hydroureter, and perinephric stranding. A slide of the patient's peripheral blood smear is shown in the Fig. 72.1.

Question What is the diagnosis?

Answer Disseminated Intravascular Coagulation (DIC)

Disseminated Intravascular Coagulation (DIC) is a microangiopathic hemolytic anemia (MAHA) characterized by endothelial dysfunction, hemolysis, platelet aggregation, fibrin clot formation, and degradation. After clotting factors and platelets become depleted, bleeding may occur [1]. Because of this simultaneous thrombosis and bleeding, DIC is sometimes referred to as a "consumptive coagulopathy." The underlying pathophysiology is generally initiated by endothelial or other cell injury, releasing thromboplastic factors which propagate the extrinsic coagulation pathway. This leads to overproduction of thrombin and systemic fibrin, and platelet activation, leading to systemic thrombosis. The simultaneous release of tissue plasminogen activator results in fibrin degradation, contributing to the bleeding diathesis [2]. Depending on the underlying etiology, the onset can be variable ranging from chronic to fulminant. Clinical manifestations of MAHAs include thrombocytopenia, altered mental status, bleeding, myocardial infarction, hemorrhagic/ischemic stroke, renal failure, bowel and limb ischemia, skin necrosis and purpura fulminans (discussed below). The differential diagnosis

M.V. Fusaro
Division of Pulmonary and Critical Care, New York Medical College, Westchester Medical Center, Valhalla, NY, USA

G. Netzer (✉)
Division of Pulmonary and Critical Care Medicine, Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD, USA
e-mail: gnetzer@medicine.umaryland.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_72

includes other MAHAs (hemolytic uremic syndrome and thrombotic thrombocytopenic purpura), as well as idiopathic thrombocytopenic purpura, end-stage liver disease, and heparin-induced thrombocytopenia (HIT). The most common underlying etiologies for DIC are sepsis, trauma, both hematologic and solid malignancies, ABO blood mismatch, obstetrical emergencies, and medications (particularly chemotherapeutic agents). Identification of a precipitating event is critical for diagnosis and treatment.

Causes of DIC
Sepsis
Trauma
Hematologic and Solid malignancies
ABO blood mismatch
Obstetrical emergencies
Medications (particularly chemotherapeutic agents)
Envenomation

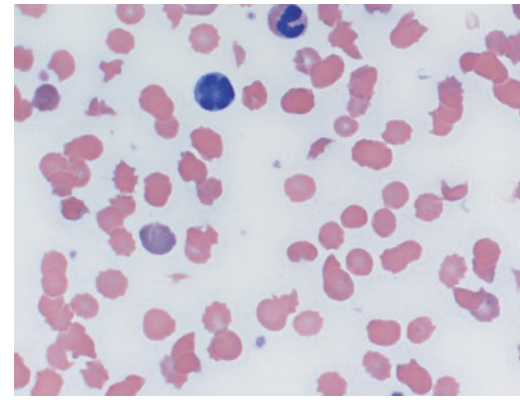


Fig. 72.1 Peripheral Smear of DIC

Principles of Management

Diagnosis

The evaluation of DIC generally includes laboratory investigation of the INR, PTT, platelet count, fibrinogen level, D-dimer and peripheral blood smear. The distinguishing characteristics of DIC are the elevation in both the PT and PTT, with simultaneous reduction of fibrinogen and platelet counts [3]. Although no single laboratory parameter is specific for DIC, this constellation in the proper setting is highly suggestive. Severe derangements in only one or two of these values may suggest an alternative diagnosis. ITP and HIT do not have associated elevation in INR or PTT, while TTP and HUS may sometimes cause elevations. DIC and TTP can have overlapping laboratory features such as elevated LDH, schistocytes and low ADAMTS-13 levels. ADAMTS-13 is a metalloproteinase which cleaves von Willebrand factor and promotes clotting. In DIC, levels can be <30 % of normal while in TTP these are generally <5 % of normal [4]. Liver dysfunction may also confound the diagnosis of DIC, given the constellation of deranged PT/PTT, fibrinogen, and thrombocytopenia. Factor VIII levels may be low in DIC but normal in isolated liver dysfunction. These laboratory values are summarized in Table 72.1. Ultimately, DIC is a clinical diagnosis incorporating history of a causative etiology and characteristic laboratory derangements.

Treatment of the Underlying Disorder

The mainstay of therapy for DIC remains treatment of the underlying disorder. Patients with sepsis should be treated with early antibiotics and fluid resuscitation [5]. When malignancy is the underlying cause, chemotherapy, surgical resection, and/or radiation should be pursued to treat the underlying tumor to remove the driving process. In these cases, DIC may worsen as tumor cells are destroyed and leak cytoplasmic contents into the circulation. Care should be given to obstetrical patients to avoid placental damage.

Management of Acute Coagulopathy in Hemorrhaging Patients

Current guidelines caution against blood product administration in DIC patients who are not bleeding. In these non-bleeding patients, AABB guidelines recommend a red cell transfusion

Table 72.1 Patterns of coagulopathy by disorder

	INR	PTT	Platelets	Factor VIII	Factor V	ADAMTS-13
DIC	Elevated	Elevated	Low	Low	Low	Low
HUS/TTP	Normal/elevated	Normal/elevated	Low	Normal/elevated	Normal/elevated	Very low
Liver	Elevated	Elevated	Low	Low	Normal	Low/Very low
HIT	Normal	Normal/Elevated	Low	–	–	Low/Very low
Warfarin	Elevated	Normal	Normal	Normal	Normal	–
ITP	Normal	Normal	Low	Normal	Normal	Normal
Heparin	Normal	Elevated	Normal	Normal	Normal	Normal

DIC Disseminated Intravascular Coagulation, *HUS* Hemolytic Uremic Syndrome, *TTP* Thrombotic Thrombocytopenic Purpura, *Liver* Dysfunction, *HIT* Heparin Induced Thrombocytopenia, *ITP* Idiopathic Thrombocytopenic Purpura

threshold of <7 g/dL [6], platelet counts of $<10\times10^9$ cells/L [7], and against fresh frozen plasma (FFP) administration unless the patient is going for surgery or otherwise being massively transfused [8]. In hemorrhaging patients, platelets should be transfused if the count is below 50,000/dL. If the PTT or INR is elevated beyond 1.5, and bleeding is present, FFP may be given [8], though FFP administration may be of little benefit if the INR <1.85 [9]. If the fibrinogen level is <100 g/dL [10] in the setting of hemorrhage, cryoprecipitate should be given.

Thrombotic Predominant DIC and Purpura Fulminans

Perhaps the most devastating manifestation of DIC is widespread micro- and macro-thrombosis leading to a diffuse livedo rash known as purpura fulminans (Fig. 72.2). Additional manifestations include bowel ischemia, limb necrosis, stroke and myocardial infarction. Predominantly seen in children and infants, this phenomenon can also occur in adults, often secondary to *Neisseria meningitidis*, *Staphylococcal* or *Streptococcal* infections. Its pathophysiology likely multifactorial, potentially involving acquired deficiencies in protein C antithrombin III (ATIII), and endothelial cell infection [11]. Treatment for these patients remains poorly studied. The use of heparin to treat and prevent propagation of thrombosis is the mainstay of treatment; however, this is based on low quality data [12].

Evidence Contour

DIC's complex pathophysiology, with both bleeding and thrombosis, has made the establishment of a single, effective therapy elusive.

Heparin Therapy

Routine heparin therapy for all sepsis-related DIC has been proposed. A randomized controlled trial in healthy volunteers of unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) versus placebo, found less

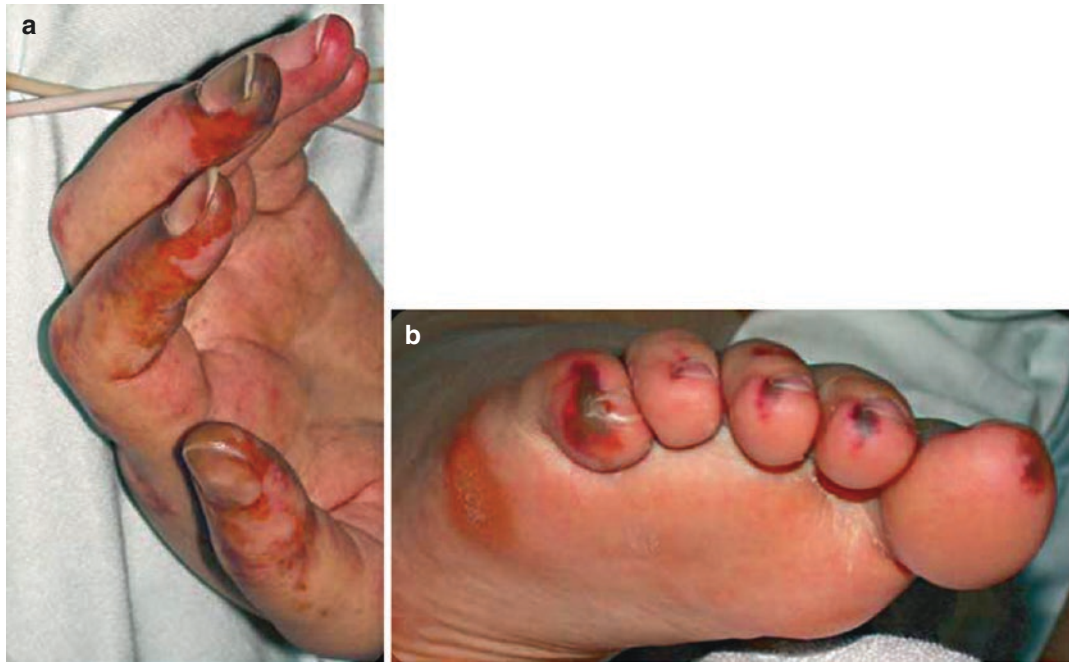


Fig. 72.2 Example of skin lesions of purpura fulminans. (**a**) peripheral microembolization with inflammatory reaction; (**b**) peripheral microembolization with inflammatory reaction (From [21]. Reprinted with permission)

activation of the coagulation cascade after endotoxin administration measured by levels of prothrombin fragments and polymerized soluble fibrin [13]. A recent, small, randomized controlled trial (n=37) in patients with sepsis and early DIC suggested that low dose UFH administration may leads to a shorter ICU stay, less risk of DIC and organ dysfunction with an non-significant reduction in mortality at 28 days compared to placebo [14]. A recent meta-analysis of nine studies evaluating patients with severe sepsis and DIC found a non-significant trend towards reduced mortality in patients receiving UFH, LWMH or dalteparin compared with placebo [15]. Given these small trials, the routine use of therapeutic anticoagulation with heparin for all patients with DIC is not considered the standard of care. As discussed above, patients with thrombotic-predominant DIC should receive anticoagulation. The use of prophylactic heparin is recommended for all DIC patients in the absence of contraindications [10].

Thrombomodulin-α

Thrombomodulin-α is an endothelial protein that binds to thrombin and then activates protein C which, in turn, inactivates factors VIIIa and Va. This therapy is designed to halt the coagulation cascade by upstream activation of protein C. Uncontrolled prospective single arm trials have been promising in the setting of hematologic malignancy and sepsis [16, 17]. A large multicenter phase 2b randomized controlled trial of thrombomodulin-α versus placebo resulted in a non-significant trend reduction in case fatality in the treatment group, in patients with sepsis related DIC [18]. This drug is presently unavailable in the US and further study is needed before recommending for or against its use.

Antithrombin III (ATIII)

ATIII functions in the coagulation cascade by inactivating thrombin. This halts propagation of the coagulation cascade and blocks consumptive coagulopathy, though increasing the potential risk of bleeding. ATIII supplementation has been studied for use in sepsis with variable success. A meta-analysis of patients with DIC and sepsis noted a significant combined reduction in mortality with use of ATIII versus placebo [19]. A small, multicenter randomized controlled trial found that use of ATIII in patients with DIC from sepsis achieved lower DIC scores and higher platelet levels after 3 days but without change in 28-day mortality [20], though this study was not powered to detect a significant mortality difference. The Surviving Sepsis Guidelines recommend against use of ATIII in sepsis, and insufficient data exist to recommend this therapy for DIC at present.

References

1. Schmaier AH. Disseminated intravascular coagulation. N Engl J Med. 1999;341(25):1937–8.
2. Kitchens CS. Thrombocytopenia and thrombosis in disseminated intravascular coagulation (DIC). Hematology Am Soc Hematol Educ Program. 2009:240–246.
3. Toh CH, Hoots WK. SSC on disseminated intravascular coagulation of the ISTH. The scoring system of the Scientific and Standardisation Committee on disseminated intravascular coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview. J Thromb Haemost. 2007;5(3):604–6.
4. Peigne V, Azoulay E, Coquet I, Mariotte E, Darmon M, Legendre P, et al. The prognostic value of ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13) deficiency in septic shock patients involves interleukin-6 and is not dependent on disseminated intravascular coagulation. Crit Care. 2013;17(6):R273.
5. Gu WJ, Wang F, Bakker J, Tang L, Liu JC. The effect of goal-directed therapy on mortality in patients with sepsis - earlier is better: a meta-analysis of randomized controlled trials. Crit Care. 2014;18(5):570.
6. Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK, et al. Red blood cell transfusion: a clinical practice guideline from the AABB*. Ann Intern Med. 2012;157(1):49–58.
7. Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, et al. Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2015;162(3):205–13.
8. Roback JD, Caldwell S, Carson J, Davenport R, Drew MJ, Eder A, et al. Evidence-based practice guidelines

for plasma transfusion. Transfusion. 2010;50(6): 1227–39.
9. Abdel-Wahab OI, Healy B, Dzik WH. Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. Transfusion. 2006;46(8):1279–85.
10. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol. 2009; 145(1):24–33.
11. Lerolle N, Carlotti A, Melican K, Aubey F, Pierrot M, Diehl JL, et al. Assessment of the interplay between blood and skin vascular abnormalities in adult purpura fulminans. Am J Respir Crit Care Med. 2013; 188(6):684–92.
12. Wada H, Thachil J, Di Nisio M, Mathew P, Kurosawa S, Gando S, et al. Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines. J Thromb Haemost. 2013;11(4):761–67.
13. Pernerstorfer T, Hollenstein U, Hansen J, Knechtelsdorfer M, Stohlawetz P, Graninger W, et al. Heparin blunts endotoxin-induced coagulation activation. Circulation. 1999;100(25):2485–90.
14. Liu XL, Wang XZ, Liu XX, Hao D, Jaladat Y, Lu F, et al. Low-dose heparin as treatment for early disseminated intravascular coagulation during sepsis: a prospective clinical study. Exp Ther Med. 2014; 7(3):604–8.
15. Zarychanski R, Abou-Setta AM, Kanji S, Turgeon AF, Kumar A, Houston DS, et al. The efficacy and safety of heparin in patients with sepsis: a systematic review and metaanalysis*. Crit Care Med. 2015;43(3):511–8.
16. Tamura K, Saito H, Asakura H, Okamoto K, Tagawa J, Hayakawa T, et al. Recombinant human soluble thrombomodulin (thrombomodulin alfa) to treat disseminated intravascular coagulation in solid tumors: results of a one-arm prospective trial. Int J Clin Oncol. 2015;20(4):821–8.
17. Ogawa Y, Yamakawa K, Ogura H, Kiguchi T, Mohri T, Nakamori Y, et al. Recombinant human soluble thrombomodulin improves mortality and respiratory dysfunction in patients with severe sepsis. J Trauma Acute Care Surg. 2012;72(5):1150–7.
18. Vincent JL, Ramesh MK, Ernest D, LaRosa SP, Pachl J, Aikawa N, et al. A randomized, double-blind, placebo-controlled, Phase 2b study to evaluate the safety and efficacy of recombinant human soluble thrombomodulin, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation. Crit Care Med. 2013;41(9):2069–79.
19. Wiedermann CJ, Kaneider NC. A systematic review of antithrombin concentrate use in patients with disseminated intravascular coagulation of severe sepsis. Blood Coagul Fibrinolysis. 2006;17(7):521–6.
20. Gando S, Saitoh D, Ishikura H, Ueyama M, Otomo Y, Oda S, et al. A randomized, controlled, multicenter trial of the effects of antithrombin on disseminated intravascular coagulation in patients with sepsis. Crit Care. 2013;17(6):R297.
21. Schellongowski P, et al. Treatment of adults with sepsis-induced coagulopathy and purpura fulminans with a plasma-derived protein C concentrate (ceprotin). In: 34th Hemophilia symposium hamburg 2003. Heidelberg: Springer Medizin Verlag ; 2005. p. 79–88.

Hemophagocytic Lymphohistiocytosis

73

Benjamin H. Singer and Hillary A. Loomis-King

Case Presentation

A 57 year old man with history of idiopathic panniculitis on long-term steroid treatment presented tothe hospital with a 1 month history of dyspnea, malaise, nausea and vomiting. He was hypotensive and tachycardic with an acute kidney injury. Prior to this presentation, he had been hospitalized for 2 weeks at a nearby hospital with similar symptoms and had been found to have multifocal ground glass opacities on CT of the chest. His condition after admission improved with fluid resuscitation, stress-dose steroids, and treatment for presumed sepsis. Infectious and rheumatologic workups were negative. He was noted to have bilateral pulmonary infiltrates (Fig. 73.1a, b). One week after discharge, however, he presented again with systemic inflammatory response syndrome (SIRS). A bronchoscopy was performed which revealed only acute and chronic organizing pneumonia, with no evidence of infection. A bone marrow biopsy was performed, which demonstrated a hypercellular marrow. Pulse dose steroids were initiated for organizing pneumonia and he improved significantly over the next week with continuation of empiric antimicrobials and tapering of steroids. After one week of this regimen, however, he again decompensated with hypoxia and hypotension. Worsening infiltrates were noted on his chest radiograph (Fig. 73.1c). Ferritin was elevated at 7652 ng/mL, and sIL-2R was elevated at 3432 U/mL. Trigylcerides were normal and fibrinogen was elevated. Given his unremarkable bone marrow biopsy 7 days before and elevated fibrinogen, the possibility of hemophagocytic lymphohistiocytosis (HLH) was dismissed as his hyperferritinemia and elevated sIL-2R were attributed to history of blood transfusion and occult infection. He continued to improve with empiric antimicrobials and steroids, and was discharged from the hospital 5 days after admission to the ICU to complete a course of levofloxacin on 40 mg of prednisone daily (Fig. 73.1d).

He presented to the hospital for the third time 2 days after discharge with hypotension and hypoxia requiring endotracheal intubation and vasopressors, and antibiotics and steroids were restarted. He was admitted to the ICU and his pulmonary status rapidly improved. After 3 days, however, he again decompensated with hypotension and an elevated lactate. He received intravenous fluids and intravenous steroids. Given the unclear association between changes in his antimicrobial regimen, steroid dosing, and clinical condition, his steroid dose was decreased from 40 mg prednisone daily by 10 mg each day. A repeat bone marrow biopsy was performed, which showed rare hemophagocytic macrophages but no evidence of malignancy. The next day, in

B.H. Singer (✉) • H.A. Loomis-King
Internal Medicine, Division of Pulmonary and Critical Care Medicine, University of Michigan Medical School, Ann Arbor, MI, USA
e-mail: singerb@med.umich.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_73

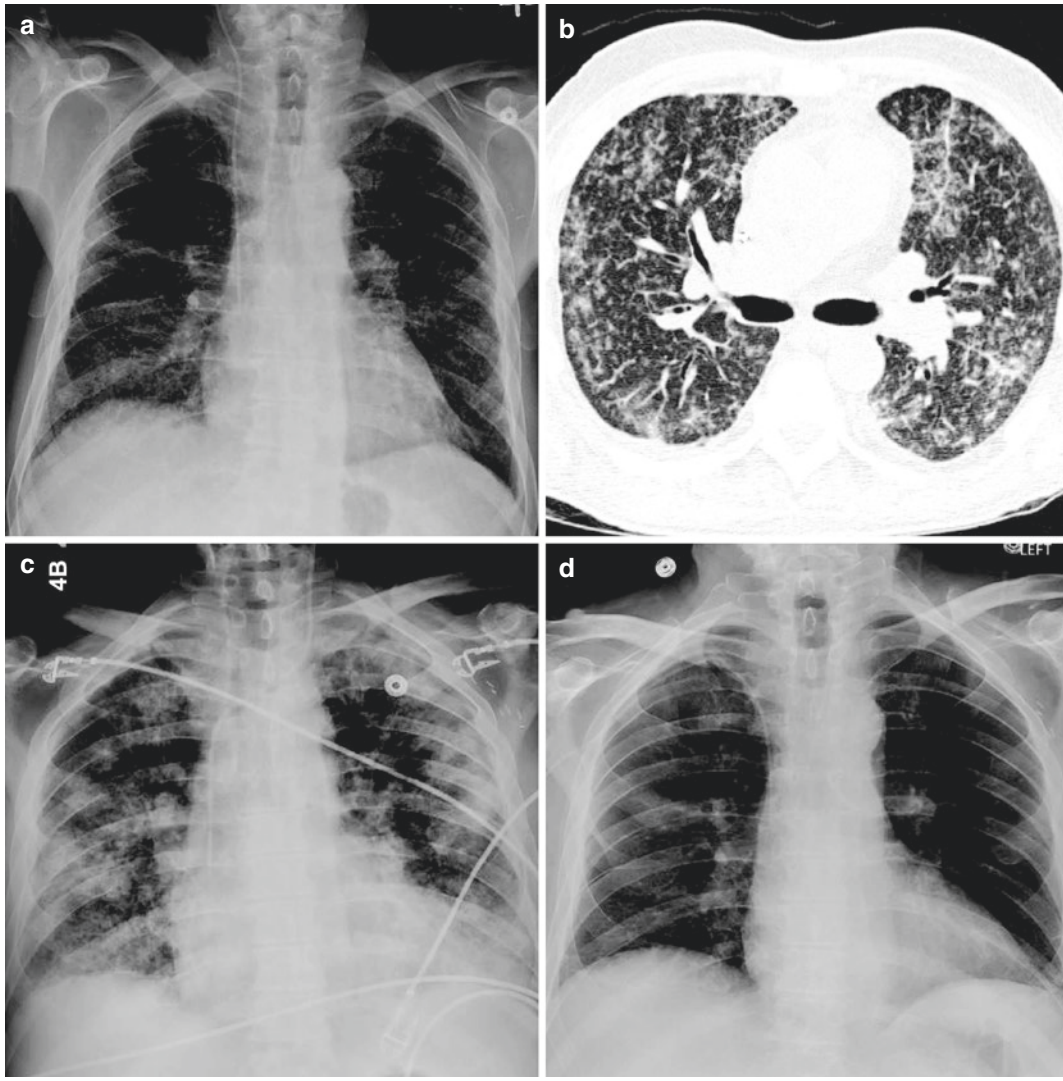


Fig. 73.1 Chest radiograph on admission (**a**) demonstrated bilateral infiltrates, which corresponded to bilateral ground glass opacities and interstitial thickening on a CT performed the same day (**b**). After 1 month, pulmonary infiltrates were consistently more severe, despite multiple courses of antibiotics and diuresis (**c**). After treatment with etoposide and dexamethasone, infiltrates resolved by the time of discharge (**d**)

the setting of reducing his steroid dose, he again had an episode of hypoxia and hypotension. Ferritin was measured at that time and was 9148 ng/mL, increased from 4074 ng/mL the day before (Fig. 73.2). sIL2-R was measured and was elevated at 3494 U/mL. A diagnosis of HLH was made, and he was started on chemotherapy with etoposide and high dose dexamethasone. Eight weeks had elapsed since his initial presentation.

Question How is hemophagocytic lymphohistiocytosis treated?

Answer The patient was initiated on etoposide and dexamethasone without cyclosporine per the HLH-94 protocol. He rapidly improved and was moved to the hematology/oncology ward. His course was complicated by recurrent fevers and rising ferritin with the addition of filgrastim to his regimen after 3 weeks of therapy. This was discontinued and he

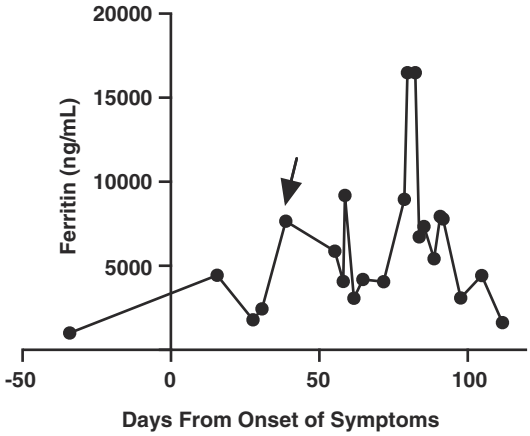


Fig. 73.2 Degree of hyperferritinemia varied significantly over the patient's hospital course, with marked elevations at the time of diagnosis (*arrow*) and relapse of HLH

improved uniformly from then on. After 1 month he was transferred to the physical medicine service for rehabilitation, and was subsequently discharged to home. He continued to do well 2 months after his diagnosis, and was preparing for allogeneic bone marrow transplant at that time.

HLH is a group of disorders characterized by aberrant immune activation leading to uncontrolled inflammation and, in many cases, critical illness. The underlying causes of HLH have been divided into primary causes, which encompass genetic defects in immune system regulation and often present in the neonatal period or early childhood, and secondary causes, which may be related to autoimmune disease, viral infection, or malignancy [1, 2]. However, there is growing appreciation that many adolescent and adult patients develop HLH due to the interaction of an underlying genetic defect with an environmental trigger, such as viral infection with Epstein-Barr virus or cytomegalovirus [3].

Presentation

In adults, HLH often presents with dramatic, but nonspecific, features of including fever, organomegaly, cytopenias, kidney injury, disseminated intravascular coagulation and altered mental status [4, 5]. As illustrated in the case above, in our experience rapid fluctuating hemodynamic instability and hypoxic respiratory failure are also common features resulting from the abnormal inflammatory response. These presenting symptoms and laboratory findings overlap significantly with severe sepsis. It is not uncommon for adult patients with HLH to have recently been hospitalized for presumed sepsis, and HLH is entertained as a diagnosis after one or more unexplained relapses. The most important step in recognizing HLH in the critically ill patient, therefore, is to consider it in the differential diagnosis alongside more common causes of shock and respiratory failure.

Diagnosis

While primary HLH is a genetic disorder and may be diagnosed by molecular testing with a suggestive family history and clinical presentation, secondary HLH is a clinical syndrome with diverse causes. Diagnostic criteria for HLH are currently based on the selection criteria for the HLH-2004 trial, which enrolled pediatric patients (Table 73.1, [6]).

The presence of fever, organomegaly, cytopenia, and hypertriglyceridemia or hypofibrinogenemia, while nonspecific, is widely accepted as helpful criteria in defining the syndrome. The presence of hemophagocytosis, despite lending HLH its name, is also nonspecific [7]. The search for appropriate biomarkers, then, remains an area of active and important investigation, as detailed below. In practice, the most critical information leading to the diagnosis of HLH is often derived from following the patient over several days, observing the response, or lack thereof, to treatment for sepsis or other common conditions, and the relationship of biomarkers to the patient's evolving clinical condition.

Treatment

The largest trial of HLH treatment are the HLH-94 and HLH-2004 trials, which investigated the treatment of HLH with etoposide, dexamethasone, and

Table 73.1 Diagnostic criteria for HLH derived from the HLH-2004 study

The diagnosis of HLH may be established by
A. Molecular diagnosis consistent with HLH
Or
B. Five of the 8 criteria listed below:
1. Fever>38.5 C
2. Splenomegaly
3. Cytopenias affecting 2 of 3 lineages in peripheral blood (RBC, platelets, or neutrophils)
4. Hypertriglyceridemia or hypofibrinogenemia
5. Hemophagocytosis in biopsy of the bone marrow, spleen, or liver
6. Low or absent NK cell activity
7. Hyperferritinemia
8. Elevated sCD25 (soluble IL-2 receptor)

Data from Jordan et al. [2]

cyclosporine in children and adolescents [6, 8]. Etoposide and dexamethasone have become the mainstay of treatment in adult patients with HLH. Early consultation with a hematologist and center experienced in the treatment of HLH is critical, both because immunomodulatory therapy for HLH is an area of active investigation, and because bone marrow transplantation is considered the curative therapy for patient with a known or suspected genetic cause of HLH.

Early therapies for HLH may be limited by end-organ damage present at the time of diagnosis, especially liver and kidney injury. As highlighted in the case presented here, treatment with high dose steroids may provide adequate temporizing therapy, allowing the patient to stabilize and ultimately receive definitive therapy.

Evidence Contour

Prognosis

As the case above highlights, adult patients in the ICU are often diagnosed with HLH after several episodes of apparent improvement followed by worsening, with periods of critical illness.

There are no randomized controlled trials of HLH treatment. The most comprehensively, longitudinally studied cohort of patients with HLH was enrolled in the HLH-1994 study, which exclusively studied children under age 16 [9]. In this cohort, cumulative 5 year mortality was 46%, with 25% mortality within 8 weeks of diagnosis. Survival was 66% among those patients who underwent HSCT. HLH in adults is far more likely to be secondary than HLH in the pediatric population, though late presentations of primary HLH are possible [3]. While survival to discharge in many adult cohorts mirrors the pediatric population, long-term mortality in secondary HLH may be more reflective of underlying malignancy [10, 11].

Short-term mortality from HLH depends strongly on local treatment resources and supportive care, and varies widely among single-center studies from 50 to nearly 80% prior to discharge [4, 12]. Across centers, however, HLH related to malignancy is found to have the highest mortality, followed by autoimmune and then infectious causes. These differences may be particularly striking when advanced supportive care is available. In a North American tertiary care center, patients with HLH secondary to causes other than malignancy had a median survival of 48 months, compared to less than 2 months in cases associated with malignancy [13]. Severity of illness at the time of diagnosis of HLH also appears to bear on outcome despite treatment, with thrombocytopenia, marked hyperferritinemia, and shock at ICU admission associated with mortality [13, 14].

Biomarker Testing

As highlighted in the case presentation, diagnosis of HLH is often difficult and delayed. Multiple conditions share at least several of the diagnostic criteria of HLH. Therefore, specific biomarkers for HLH would likely shorten time to diagnosis and therapy. Bone marrow hemophagocytosis, while lending its name to HLH, is neither sensitive nor specific for the disorder [7]. NK cell activity and sIL-2R levels are part of the HLH diagnostic criteria, but these laboratory studies are available in only a few reference laboratories. Ideally, biomarker testing would rely

on commonly and rapidly available assays, such as those for determining ferritin levels.

In the pediatric population, hyperferritinemia (>10,000 μg/L) has a greater than 90 % specificity for HLH [15]. Furthermore, ferritin levels also reflect disease course and activity, and in children a marked decrease in ferritin (>96 %) portends decreased short term mortality during HLH treatment [16]. In critically ill adults, however, the increased prevalence of conditions which elevate ferritin, such as infection, malignancy, autoimmune disease, liver injury and chronic blood transfusion make hyperferritinemia a nonspecific finding for HLH [17, 18]. In addition, particular causes of secondary HLH may be associated with variable biomarker patterns. For example, HLH due to lymphoma may present with a high ratio of sIL-2R to ferritin compared to other causes [19]. Given that HLH is a disorder of immune dysregulation, efforts have been made to differentiate HLH from infection based on cytokine patterns in the pediatric population [20]. Whether this approach will be fruitful in adults requires further study.

References

1. Janka GE, Lehmberg K. Hemophagocytic syndromes–an update. Blood Rev. [Internet]. 2014 [Cited 27 May 2014]; Available from: http://www.sciencedirect.com/science/article/pii/S0268960X14000289.
2. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. Blood [Internet]. 2011 [Cited 27 May 2014];118:4041–52. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3204727&tool=pmcentrez&rendertype=abstract.
3. Wang Y, Wang Z, Zhang J, Wei Q, Tang R, Qi J, et al. Genetic features of late onset primary hemophagocytic lymphohistiocytosis in adolescence or adulthood. PLoS One [Internet]. 2014 [Cited 16 Jan 2015];9:e107386. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4169386&tool=pmcentrez&rendertype=abstract.
4. Li J, Wang Q, Zheng W, Ma J, Zhang W, Wang W, et al. Hemophagocytic lymphohistiocytosis: clinical analysis of 103 adult patients. Medicine (Baltimore). [Internet]. 2014 [Cited 13 Jun 2014];93:100–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24646466.
5. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet [Internet]. 2014 [Cited 28 May 2014];383:1503–16. Available from: http://www.sciencedirect.com/science/article/pii/S014067361361048X.
6. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer [Internet]. 2007 [Cited 31 May 2014];48:124–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16937360.
7. Goel S, Polski JM, Imran H. Sensitivity and specificity of bone marrow hemophagocytosis in hemophagocytic lymphohistiocytosis. Ann Clin Lab Sci. [Internet]. 2012 [Cited 13 Jun 2014];42:21–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22371906.
8. Henter JI, Samuelsson-Horne A, Aricò M, Egeler RM, Elinder G, Filipovich AH, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood [Internet]. 2002 [Cited 16 Jun 2014];100:2367–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12239144.
9. Trottestam H, Horne A, Aricò M, Egeler RM, Filipovich AH, Gadner H, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood [Internet]. 2011 [Cited 27 May 2014];118:4577–84. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3208276&tool=pmcentrez&rendertype=abstract.
10. Han A-R, Lee HR, Park BB, Hwang IG, Park S, Lee SC, et al. Lymphoma-associated hemophagocytic syndrome: clinical features and treatment outcome. Ann Hematol. [Internet]. 2007 [Cited 16 Jun 2014];86:493–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17347847.
11. Yu JT, Wang CY, Yang Y, Wang RC, Chang KH, Hwang WL, et al. Lymphoma-associated hemophagocytic lymphohistiocytosis: experience in adults from a single institution. Ann Hematol. [Internet]. 2013 [Cited 13 Jun 2014];92:1529–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23700280.
12. Rivière S, Galicier L, Coppo P, Marzac C, Aumont C, Lambotte O, et al. Reactive hemophagocytic syndrome in adults: a multicenter retrospective analysis of 162 patients. Am J Med. [Internet]. 2014 [Cited 23 May 2014]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/24835040.
13. Otrock ZK, Eby CS. Clinical characteristics, prognostic factors and outcomes of adult patients with hemophagocytic lymphohistiocytosis. Am J Hematol. [Internet]. 2014 [Cited 16 Jan 2015];00:1–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25469675.
14. Buyse S, Teixeira L, Galicier L, Mariotte E, Lemiale V, Seguin A, et al. Critical care management of patients with hemophagocytic lymphohistiocytosis. Intensive Care Med. [Internet]. 2010 [Cited 7 Jun 2014];36:1695–702. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20532477.

15. Allen CE, Yu X, Kozinetz CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer [Internet]. 2008 [Cited 16 Jun 2014];50:1227–35. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18085676.
16. Lin TF, Ferlic-Stark LL, Allen CE, Kozinetz CA, McClain KL. Rate of decline of ferritin in patients with hemophagocytic lymphohistiocytosis as a prognostic variable for mortality. Pediatr Blood Cancer [Internet]. 2011 [Cited 14 Jun 2014];56:154–5. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3444147&tool=pmcentrez&rendertype=abstract.
17. Tothova Z, Berliner N. Hemophagocytic syndrome and critical illness: new insights into diagnosis and management. J Intensive Care Med. [Internet]. 2014 [Cited 13 Jun 2014]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/24407034.
18. Schram AM, Campigotto F, Mullally A, Fogerty A, Massarotti E, Neuberg D, et al. Marked hyperferritinemia does not predict for HLH in the adult population. Blood [Internet]. 2015 [Cited 16 Jan 2015];1–19. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25573993.
19. Tsuji T, Hirano T, Yamasaki H, Tsuji M, Tsuda H. A high sIL-2R/ferritin ratio is a useful marker for the diagnosis of lymphoma-associated hemophagocytic syndrome. Ann Hematol. [Internet]. 2014 [Cited 13 Jun 2014];93:821–6. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3976506&tool=pmcentrez&rendertype=abstract.
20. Xu XJ, Tang YM, Song H, Yang SL, Xu WQ, Zhao N, et al. Diagnostic accuracy of a specific cytokine pattern in hemophagocytic lymphohistiocytosis in children. J. Pediatr. [Internet]. 2012 [Cited 27 May 2014];160:984–90.e1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22226576.

ICU Complications of Hematopoietic Stem Cell Transplantation Including Graft Versus Host Disease

74

Peter C. Stubenrauch, Kenneth Lyn-Kew, and James Finigan

Case Presentation

A 43 year old woman was admitted to the ICU with altered mental status (AMS) and respiratory failure. Her medical history was notable for chronic lymphocytic leukemia and was status post non-myeloablative allogeneic hematopoietic stem cell transplant (HCT) with graft versus host disease (GVHD) of the skin treated with topical corticosteroids and ocular involvement treated with cyclosporine. Several months after her HCT she developed progressive shortness of breath and dry cough. Since her transplant, her FVC and FEV1 had fallen from 104 % and 106 % predicted to 42 % and 25 % respectively. High-resolution chest CT scan demonstrated mosaic attenuation and she was diagnosed with bronchiolitis obliterans syndrome (BOS). Despite treatment with prednisone 60 mg daily and tacrolimus 2 mg twice daily the patient experienced progressive symptoms over the following 2 months. She was admitted to the ICU for altered mental status and respiratory failure. CT scanning of the chest and brain demonstrated a cavitary right lung mass (Fig. 74.1) and a cavitary left brain mass (Fig. 74.2). Cultures from bronchoalveolar lavage and brain biopsy grew mucormycoses. Despite antifungal therapy and supportive care the she further deteriorated and care was withdrawn.

Question How does time from transplant affect consideration of which complications may be present?

Answer Complications following HCT pertain to the patient's immune statuse and may be roughly divided into three "phases:" pre-engraftment during approximately the first month; engraftment during months 2-3; and post-engraftment after approximately the first 100 days following HCT.

Due to the transplant and the therapies an HCT patient receives for maintenance, the innate and acquired immune systems of this patient

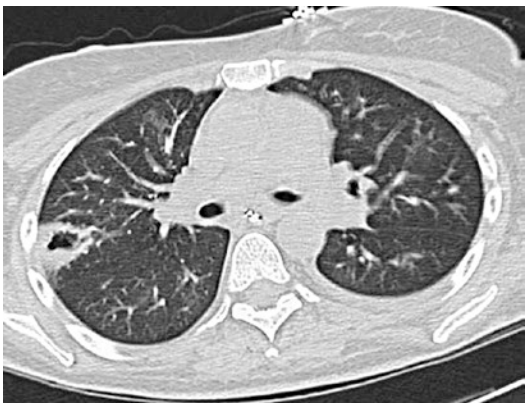


Fig. 74.1 Chest CT. A CT of the chest show a right sided cavitary lesion concerning for fungal pneumonia

P.C. Stubenrauch • K. Lyn-Kew (✉) • J. Finigan
Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, CO, USA
e-mail: Lyn-KewK@NJHealth.org

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_74

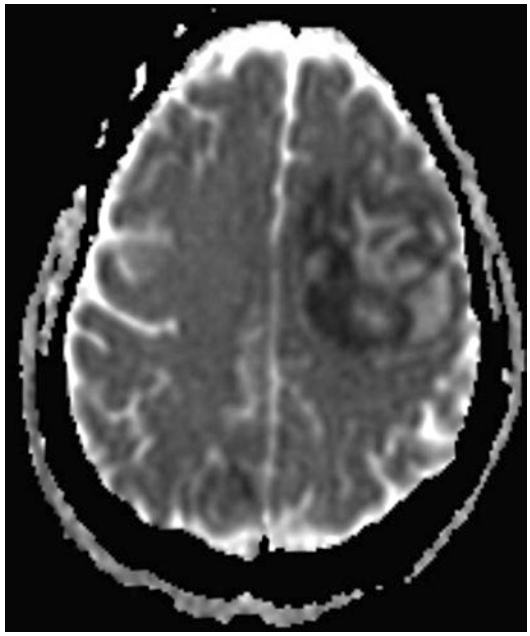


Fig. 74.2 Head CT. A CT of the head reveals a mass lesion concerning for spread of her fungal infection

population do not function normally. This places these patients at increased risk for a host of infectious and non-infectious diseases.

Common ICU Admission Etiologies in HCT Patient

Respiratory Failure

See Etiologies of Respiratory Failure on HCT Patient below

Shock

Septic shock
Hypovolemic shock
Cardiogenic shock
Obstructive shock (thrombosis)

Renal failure resulting in metabolic derangements

Hyperkalemia
Acidosis

Gastrointestinal System

GI bleeding
Enterocolitis
Liver failure

Central Nervous system

Intracranial hemorrhage
Seizure
Altered Mental Status

Currently there are greater than 50,000 HCTs performed yearly [1] thus, there are many patients at all stages in the post-transplant periods that could potentially develop a process requiring admission the ICU. This patient experienced several devastating complications related to her HCT including graft-versus-host disease, respiratory failure, and opportunistic infection. This chapter will focus on these issues that are commonplace in HCT patients that are admitted to the ICU, in particular, the impact of GVHD and the pulmonary complications of HCT.

Principles of Management

Hematopoietic stem cell transplantation has become a relatively common procedure worldwide with a diverse array of indications. The indications range from leukemias and lymphomas to inborn errors of metabolism to autoimmune diseases. Other considerations include patient age, functional status, and suitable graft availability. There are four sources for a hematopoietic stem cell transplant: autologous transplantation refers to a patient receiving his own stem cells, in syngeneic transplantation a patient receives stem cells from an identical twin sibling, in allogeneic transplantation a patient receives stem cells from a non-identical sibling or an unrelated donor and in umbilical cord blood

transplantation stem cells harvested from the umbilical cord and placental soon after a baby is born. In allogeneic transplantation, recipient and donor human leukocyte-associated antigens (HLA) are matched as best as possible. Graft-versus-host disease is common in allogeneic transplants and uncommon in autologous transplants. GVHD is generally more severe in the patients receiving transplants from mismatched donors [2].

In preparation for the transplant, conditioning regimens are used to treat the patient prior to the transplant and the severity of graft-versus-host disease appears be influenced by the conditioning regimen chosen [3]. The regimens are meant to suppress the recipient's immune system enough that the graft is not rejected as well as eliminate the disease for which the patient is receiving the transplant. The myeloablative regimens are meant to completely destroy the recipient's stem cell population and regimens often are made up of both chemotherapy and total body irradiation (TBI). Non-myeloablative regimens generally use lower doses of chemotherapy and TBI and are not designed to completely eradicate the recipient's stem cell (or diseased cell) population. Eradication of the malignancy relies on the graft-versus tumor effect provided by the donor stem cells. Choice of regimen is influenced by the patient's co-morbities, the condition that is being treated, the status of the disease being treated, and the likelihood of graft rejection [2].

Impact of Graft-Versus-Host Disease on the Critically Ill HCT Patient

Importantly, recipients of allogeneic HCT commonly develop GVHD and the graft versus tumor effect is generally associated with reduced relapse of malignancy however GVHD (both acute and chronic) is associated with significant morbidity and mortality [4]. GVHD is a common multisystem "side-effect" of HCT seen in patients with allogeneic HCT. It occurs when donor hematopoietic cells recognize the recipient's organ tissues as foreign resulting in end-organ injury [5]. Acute GVHD typically occurs within 100 days of transplantation and is characterized by skin, GI tract and liver involvement. However, all organ systems can be involved [6]. Chronic GVHD commonly occurs outside the first 100 days after HCT though the clinical manifestations noted in the patient as opposed to the timing are perhaps more important in making the diagnosis of acute or chronic GVHD. While skin, GI tract and liver are also commonly involved in chronic GVHD, the findings of chronic GVHD are much different than what is seen in acute GVHD and tend to have an appearance similar to that of a patient with advanced autoimmune disease. Sclerotic skin lesions, which are strikingly similar to the cutaneous findings of scleroderma, are commonplace in chronic GVHD [7]. Both acute and chronic GVHD are associated with significant non-relapse morbidity and mortality in the HCT patient [8].

Mortality after HCT is higher in patients who have GVHD as opposed to those who do not and as the severity of GVHD increases, so does mortality. It has also been demonstrated that patients who receive allogeneic transplants from unrelated donors also have higher rates of GVHD and non-relapse mortality [9]. Al-Khadhimi et al. retrospectively evaluated 414 patients with related and unrelated HCT and demonstrated the incidence of severe acute GVHD was much higher in the recipient from unrelated donors (22.3 % vs 36.5 %). It was also shown that non-relapse mortality was significantly higher (33.3 % vs 46.5 %) at 60 months. In this cohort, only 15 % of patients with the severest (grade III and IV) level of acute GVHD were alive at 5 years [10]. While the clinical manifestations of acute and chronic GVHD share some similarities, having a history of acute GVHD is, in and of itself, a risk factor for chronic GVHD [11].

The patient described developed multiple manifestations of chronic GVHD disease includ-

ing skin, ocular, and pulmonary. Bronchiolitis obliterans syndrome (BOS) is a common pulmonary manifestation of chronic GVHD and is thought to occur in between 1.7 and 26% of patient receiving allogeneic HCT [12]. In a study by Au et al., the survival analysis hazard ratio was 1.6 for HCT patients with BOS when compared with those with HCT without BOS. Its incidence is closely associated with chronic GVHD, prior history of acute GVHD, older donor and recipient age, poor lung function prior to transplantation, early post-transplant respiratory viral infections, and the type of conditioning regimen prior to transplant [12]. Treatment generally includes systemic corticosteroids with and without other immune suppressing medications. The immune suppressing regimen often includes a prolonged course of high dose prednisone and in the event there is minimal response to prednisone, calcineurin inhibitors are added [13, 14]. Unfortunately, BOS often progresses despite attempts at therapy. These treatments for BOS often result in medication side effects and increased risk of opportunistic infections due to their significant immune suppressing properties [14].

Etiologies of Respiratory Failure in HCT Patient

Infectious

Bacteria:
- GPC, GNR, polymicrobial with aspiration

Viruses:
- CMV, Herpesviruses, Respiratory viruses

Fungus:
- Aspergillus, Candida, Mucormycoses

Mycobacteria:
- Tuberculosis, non-tuberculous mycobacteria

Non-Infectious

Diffuse Alveolar Hemorrhage
Idiopathic Pneumonia syndrome
Cryptogenic Organizing Pneumonia
Pulmonary Edema
Bronchiolitis Obliterans Syndrome
Pulmonary veno-occlusive disease
Radiation Pneumonitis

Pulmonary Complications in the GVHD Patient

Respiratory failure, as occurred in this patient, exemplifies a common, yet heterogeneous problem in any ICU population. However, the HCT population is a unique group in which certain infectious and non-infectious pulmonary complications can be expected at various periods post-HCT. A retrospective review of 250 consecutive HCT patients, of who 33 were admitted to the ICU and the most common reason for ICU admit were pulmonary complications [16]. Indeed, respiratory failure carries a particularly poor prognosis in this population and can be a result of both infectious and non-infectious etiologies.

Due to the immunologic derangements and subsequent immune system recovery that occurs after an HCT, the patient will be at higher risk for numerous pulmonary complications depending on the post-transplant phase.

Recovery "Phases" Post-HCT

Recovery from HCT can divided into three phases which is helpful in allowing the physician rapidly assess and treat a broad differential. Phase 1 is the period immediately post-transplant to the point of cellular engraftment (defined as an absolute neutrophil count $>0.5 \times 10^9$ cells/L), which occurs about 3–4 weeks post-transplant. Many of the infectious pulmonary

complications in this period are related to the neutropenia that make risk of opportunistic infection from bacteria, fungi, and viruses commonplace. Phase 2 encompasses the period from engraftment to the point at which full immunity from the allograft is conferred, which can take up to 100 days post-transplant. During this period, humoral and cell-mediated immunity remain impaired. The final recovery stage, phase 3, commonly is characterized by ongoing defects in cell-mediated and humoral immunity, as well as diminished function of the reticuloendothelial system.

Common Infectious Complications of Phase 1

Bacterial infections, including gram negative, gram positive and anaerobic organisms, are commonplace during phase 1 due to the resultant neutropenia from the regimens used to perform the HCT itself. Patients who experience mucositis during phase 1 are at increased risk of bacterial translocation into the bloodstream and also aspiration from the dysphagia they often experience which can result in bacterial pneumonias. As such, during phase 1, when patients present with fever they require empiric broad spectrum antibiotic prophylaxis to treat both gram positive and gram negative organisms even if the source of the fever is elusive [17].

During the prolonged periods of neutropenia of phase 1, opportunistic infections from invasive Aspergillus are commonly seen, even with antifungal prophylaxis [18]. Notable risk factors include allogeneic HCT, acute GVHD, and older age. Clinical features often include dyspnea, fever, pleuritic chest pain and occasionally hemoptysis. Imaging will often show nodular opacities on chest radiograph and the "halo" sign on CT scanning. Treatment is generally with voriconazole or amphotericin, though the echinocandins are also used [19].

Herpesviruses are common viral infections seen in phase 1 [20, 21]. Disease activity results from reactivation of latent infection. In patients who do not receive prophylaxis with acyclovir, HSV will be shed in up to 80 % of seropositive patients. HSV pneumonitis requires evidence of tissue invasion for diagnosis and generally patients with pneumonitis will also have evidence of mucocutaneous involvement. Imaging can demonstrate diffuse or patchy opacities [21]. Treatment is generally with acyclovir.

Common Non-Infectious Phase 1 Pulmonary Complications of HCT

Diffuse alveolar hemorrhage (DAH), a phenomena occurring more commonly in autologous HCT than allogeneic HCTs, is characterized by fever, hypoxemia, coughing, and central bilateral pulmonary opacities. The diagnosis of DAH is made on bronchoalveolar lavage (BAL) when non-clearing hemorrhagic return is seen on successive lavage aliquots [22]. Due to the patchy nature of DAH, performing BALs in multiple areas of the lung may be required to establish a diagnosis. As with other non-infectious complications of HCT, there must be no evidence of infection present to establish a diagnosis of DAH. Corticosteroids are often used for treatment, though the in-hospital mortality of DAH approaches 80 % [23].

During phase 1, patients regularly develop pulmonary edema which can be either cardiogenic or non-cardiogenic in nature [24]. It is characterized by dyspnea, hypoxemia, bilateral rales, bilateral pulmonary interstitial opacities, and occasionally associated with pleural effusion. The etiology of the pulmonary edema is diverse though patients often have cardiac or renal dysfunction as a result of previous chemotherapeutics used (platinum based, anthracyclines, or cyclophosphamide being the most common), and hypoalbuminemia can also play a role. Increased vascular permeability as a result of sepsis, viral infection, aspiration, or hyper acute GVHD can result in non-cardiogenic pulmonary edema [25]. Typically, pulmonary edema will improve with

diuresis and often has a good prognosis though patients with hepatic veno-occlusive disease can develop pulmonary edema that has significantly worse outcomes [26].

Engraftment syndrome occurs in about 7–10 % of patients with autologous HCT and is less common in patients with allogeneic HCT. Common features include fever, dyspnea, hypoxia, maculopapular rash (not attributable to medication), and bilateral pulmonary opacities. This syndrome occurs at the same time as the patient's neutrophils recover. Infectious and cardiogenic etiologies must be ruled out to make the diagnosis. Patients tend to have a better prognosis than many of the other etiologies of respiratory failure and one case series reported excellent resolution of hypoxia and fever when treated with corticosteroids [27].

Common Infectious and Non-Infectious Pulmonary Complications in Phase 2

In the immunocompetent host, Cytomegalovirus (CMV) remains latent in the host's leukocytes though will reactivate in the seropositive patient who becomes immunosuppressed. Most HCT patient receive prophylaxis for CMV and as such, CMV pneumonitis is no longer as common as previously in the transplant population [28]. It is seen in about 5 % of HCT patients and tends to occur between 6 and 12 weeks post-transplant. As is commonly seen with many forms of pneumonitis, it is characterized by fevers, dyspnea, hypoxia, and diffuse opacities on radiograph. Primary risk factors for CMV include previous CMV viremia, GVHD and use of high-dose glucocorticoids. The treatment typically includes intra-venous (IV) ganciclovir or valganciclovir. The mortality in the HCT patient with CMV pneumonia is quite high at 80–90 % [29].

There are a number of other viruses known to cause pulmonary complications in the HCT patient including RSV, influenza, parainfluenza, and human metapneumonvirus. While some may not carry the high mortality associated with CMV pneumonitis, most carry significant morbidity and mortality when they result in pneumonia [30].

The idiopathic pneumonia syndrome (IPS) is a common non-infectious complication of phase 2. This usually occurs 4 months post-HCT and is characterized by two phases: an early inflammatory phase followed by a fibrotic phase likely resulting from an impaired ability to recover in a normal fashion from an insult leading to injury [31]. The diagnosis of IPS is predicated on the fulfillment of two criteria: diffuse alveolar injury with symptoms suggestive of pneumonia without evidence of congestive heart failure or volume overload and no evidence of lower respiratory tract infection. Risk factors for IPS include the diagnosis of acute leukemia, the type of conditioning regimen – myleoablative, total body irradiation, severe acute GVHD, and age greater than 40 [31, 32]. A compelling study published in Blood in 2015 re-evaluated BAL samples of 69 patients previously diagnosed with IPS between 1992 and 2006 using PCR screening for 3 bacteria and 25 viruses. Pathogens were discovered in 39 patients, a significant proportion of whom had worse 100 day survival than those without pathogens. While the significance of these findings are uncertain, they suggest that aggressive search for infectious pathogens must be undertaken prior to making the diagnosis of IPS [33]. The HCT patient diagnosed with IPS is typically treated with high-dose corticosteroids though, unfortunately, prognosis is quite poor and ranges from 50 to 75 % [34]. More recently, a study looking at the etanercept in addition to corticosteroids did not confer an improved response. Interestingly, this study demonstrated better 28-day survival rates than historically documented perhaps owing to the fact that conditioning regimens, supportive care and frequency of BAL (thus allowing for identification of pathogens) has changed [35]. Unfortunately the 1-year survival rates post-IPS are high [34].

Phase 3 Pulmonary Complications Post HCT

Bronchiolitis Obliterans (BO) is a phase 3 complication which is characterized by progressive airflow obstruction (reduced FEV1 and FEV1/FVC ratio) seen in about 9 % of patients with allogeneic HCT [36]. GVHD is an important risk factor associated with BO. On high-resolution CT scanning will mosaic attenuation will commonly be seen, indicative of air-trapping. Many experts are initiating "FAM therapy" (inhaled fluticasone, azithromycin three times weekly, and montelukast) with any evidence of airflow obstruction HCT [37]. While there is no gold-standard therapy, immune suppression is most often increased, typically with prednisone and subsequent steroid sparing agents (cyclosporine or azathioprine are often chosen). Improvement in the obstructive physiology is unusual and the more rapid the fall in the patient's FEV1, the worse the outcome. Mechanistically, is likely related to a progressive bronchial epithelial injury from the donor immune cells [38]. Unfortunately, as was seen in the patient presented, chronic immune suppressing therapy used to treat BO increases risk of opportunistic infection.

Organizing pneumonia (OP) is characterized by patchy bilateral pulmonary opacities on imaging and restrictive physiology. The etiology may be related to previously treated infection, chronic GVHD, radiation, or cryptogenic. Infection must be ruled out as patients will often present with dry cough, fevers and dyspnea. About 2/3 of patients with COP will respond well to treatment with corticosteroids. The risk factors associated with the development of COP include GVHD and allogeneic HCT [39].

Fungal infections and CMV infections are also seen during phase 3 depending upon whether the patient is receiving prophylactic medications against these organisms. Risk of opportunistic infection is also increased in patients receiving treatment for GVHD with prednisone and other immune suppressing agents.

Evaluation of Respiratory Failure

In an HCT patient admitted to the ICU with acute respiratory failure, knowing the time from transplant is helpful to the clinician in predicting what infectious and non-infectious processes are highest on the differential. Information regarding the severity of GVHD status and whether immune suppressing medications for control GVHD are being used can further whether the patient is at increased risk for opportunistic infections. In addition, knowledge of whether the patient has any active pulmonary disease either as a result of their HCT, such as radiation induced lung injury, BOS or other chronic lung diseases, such as emphysema, further adds to the understanding of how much pulmonary reserve the patient will have.

As with any critically ill patient in the ICU, diagnostic imaging is often the initial test of choice.

Having a low threshold to obtain cross sectional imaging is important in the HCT population given the broad differential for respiratory failure in this group. Unfortunately, many of the pulmonary processes affecting the post-HCT patient result in similar findings on CT scanning and fiber optic bronchoscopy with BAL is often the procedure of choice in separating between infectious and non-infectious pulmonary complications associated with HCT. Bronchoscopy is a useful adjunct to making a diagnosis in patients with respiratory failure, or abnormalities on CT scanning and has been shown to be useful in making diagnoses about 50 % of the time [1, 40]. Non-invasive diagnostics such as echocardiogram, blood cultures, fungal serologic testing, and induced sputum have been shown to be useful depending on the reason for respiratory failure [40].

In regards to the patient presented, multiple studies have demonstrated patients HCT patients diagnosed with invasive mold were receiving high dose corticosteroids daily are at greater risk for developing invasive fungal disease [41, 42]. This patient had a large cavity seen on CT scanning and in her and subsequent bronchoscopy

was diagnostic for mucormycoses. Besides corticosteroid use, other common risks for invasive mold infection in the HCT include a matched unrelated donor, and GVHD [42] - both notable findings in this patient. This patient was treated with amphotericin and generally the choice of antifungal therapy depends on the type of infection suspected or proven and the mainstays of therapies include amphotericin, the azoles, and the echinocandins [43]. Most, if not all, critically ill HCT patients with suspected infection require the input of an infectious disease specialist.

Evidence Contour

When to Withhold or Withdraw Life Support

Much has been written about withholding care in the critically ill when deemed to be futile. To be sure, the prognosis for the HCT patient critically ill with respiratory failure or multi-system organ failure is poor though there is some data to suggest improving outcomes in patients admitted to the ICU [44–46]. Unfortunately, there is not yet a scale such as the APACHE III or SAPS II that can reliably predict an HCT patient's mortality during their stay in the ICU. This is problematic as the ability to prognosticate to the patients, their family members or decision makers is useful for them to clarify their goals of care. In the past, there has been discussion in the medical literature about refusing ICU care for certain subpopulations of HCT patients particularly those with respiratory failure [47]. However, there is not yet a way of identifying a group with such poor prognosis that withholding care is appropriate. Post-Intensive Care Syndrome (PICS) is a growing area of study looking at the long term outcomes of patients who have been critically ill for longer than 1 week. The 1- and 5-year outcomes in mortality and quality of life patients with PICS are poor [48] though this growing body of work have provided us with direction of area to focus on to improve long-term outcomes. It would be beneficial to study the long term survival of HCT recipients who have survived critical illness in order to better allow the intensivist to prognosticate to families in the short- and long-term.

References

1. Afessa B, Azoulay E. Critical care of the hematopoietic stem cell transplant recipient. Crit Care Clin. 2010;26(1):133–50.
2. Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med. 2006;354:1813–26.
3. Pérez-Simón JA, Díez-Campelo M, Martino R, Brunet S, Urbano A, Caballero MD, et al. Influence of the intensity of the conditioning regimen on the characteristics of acute and chronic graft-versus-host disease after allogeneic transplantation. Br J Haematol. 2005;130(3):394–403.
4. Lee SJ, Klein JP, Barret AJ, Ringden O, Antin JH, Cahn JY, et al. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. Blood. 2002;100(2):406–14.
5. Ferrara JL, Reddy P. Pathophysiology of graft-versus host disease. Semin Hematol. 2006;43(1):3–10.
6. Vigorito AC, Campregher PV, Storer BE, Carpenter PA, Moravec CK, Kiem HP, et al. Evaluation of NIH consensus criteria for classification of late acute and chronic GVHD. Blood. 2009;114:702.
7. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11(12):945–56.
8. Filipovich AH. Diagnosis and manifestations of chronic graft-versus-host disease. Best Pract Res Clin Haematol. 2008;21(2):251–7.
9. Jagasia M, Arora M, Flowers ME, Chao NJ, McCarthy PL, Cutler CS. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. Blood. 2012;119(1):296–307.
10. Al-Kadhimi Z, Gul Z, Chen W, Smith D, Abidi M, Deol A, et al. High incidence of severe acute graft-versus-host disease with tacrolimus and mycophenolate mofetil in a large cohort of related and unrelated allogeneic transplantation patients. Biol Blood Marrow Transplant. 2014;20(7):979–85.
11. Flowers ME, Inamoto Y, Carpenter PA, Lee SJ, Kiem HP, Petersdorf EW, et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. Blood. 2011;117(11):3214–9.
12. Au BK, Au MA, Chien JW. Bronchiolitis obliterans syndrome epidemiology after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2011;17:1072–8.

13. Afessa B, Litzow MR, Tefferi A. Bronchiolitis obliterans and other late onset non-infectious pulmonary complications in hematopoietic stem cell transplantation. Bone Marrow Transplant. 2001;28(5):425–34.
14. Chien JW, Duncan S, Williams KM, Pavletic SZ. Bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation - an increasingly recognized manifestation of chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2010;16(1 Suppl):S106–14.
15. Wingard JR, Hsu J, Hiemenz JW. Hematopoietic stem cell transplantation: an overview of infection risks and epidemiology. Infect Dis Clin North Am. 2010;24:257–72.
16. Benz R, Schanz U, Maggiorini M, Seebach JD, Stussi G. Risk factors for ICU admission and ICU survival after allogeneic hematopoietic SCT. Bone Marrow Transplant. 2014;49(1):62–5.
17. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52(4):427–31.
18. Soubani AO, Miller KB, Hassoun PM. Pulmonary complications of bone marrow transplantation. Chest. 1996;109(4):1066–77.
19. Wingard JR. New approaches to invasive fungal infections in acute leukemia and hematopoietic stem cell transplant patients. Best Pract Res Clin Haematol. 2007;20(1):99–107.
20. Taplitz RA, Jordan MC. Pneumonia caused by herpesviruses in recipients of hematopoietic cell transplants. Semin Respir Infect. 2002;17:121–9.
21. Krowka MJ, Rosenow EC, Hoagland HC. Pulmonary complications of bone marrow transplantation. Chest. 1985;87(2):237–46.
22. Afessa B, Tefferi A, Litzow MR, Krowka MJ, Wylam ME, Peters SG. Diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. Am J Respir Crit Care Med. 2002;166(5):641–5.
23. Metcalf JP, Rennard SI, Reed EC, Haire WD, Sisson JH, Walter T, et al. Corticosteroids as adjunctive therapy for diffuse alveolar hemorrhage associated with bone marrow transplantation. Am J Med. 1994;96(4):327–34.
24. Afessa B, Abdulai RM, Kremers WK, Hogan WJ, Litzow MR, Peters SG. Risk factors and outcome of pulmonary complications after autologous hematopoietic stem cell transplant. Chest. 2012;141(2):442–50.
25. Cost C, Brock E, Adams-Huet B, Siegel JD, Ardura MI. 2009 pandemic influenza A (H1N1) virus infection in pediatric oncology and hematopoietic stem cell transplantation patients. Pediatr Blood Cancer. 2011;56(1):127.
26. McDonald GB, Hinds MS, Fisher LD, Schoch HG, Wolford JL, Banaji M, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. Ann Intern Med. 1993;118(4):255.
27. Lee CK, Gingrich RD, Hohl RJ, Ajram KA. Engraftment syndrome in autologous bone marrow and peripheral stem cell transplantation. Bone Marrow Transplant. 1995;16(1):175–82.
28. Center for International Blood and Marrow Transplant Research (CIBMTR); National Marrow Donor Program (NMDP); European Blood and Marrow Transplant Group (EBMT); American Society of Blood and Marrow Transplantation (ASBMT); Canadian Blood and Marrow Transplant Group (CBMTG), et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. Bone Marrow Transplant. 2009;44(8):453–558.
29. Sable CA, Donowitz GR. Infections in bone marrow transplant recipients. Clin Infect Dis. 1994;18(3):273–81.
30. Young JA, Logan BR, Wu J, Wingard JR, Weisdorf DJ, Mudrick C, et al. Infections after transplantation of bone marrow or peripheral blood stem cells from unrelated donors. Biol Blood Marrow Transplant. 2016;22(2):359–70.
31. Shankar G, Cohen DA. Idiopathic pneumonia syndrome after bone marrow transplantation: the role of pre-transplant radiation conditioning and local conditioning and local cytokine dysregulation in promoting lung inflammation and fibrosis. Int J Exp Pathol. 2001;82(2):101–13.
32. Fukuda T, Hackman RC, Guthrie KA, Sandmaier BM, Boeckh M, Maris MB, et al. Risks and outcomes of idiopathic pneumonia syndrome after nonmyeloablative and conventional conditioning regimens for allogeneic hematopoietic stem cell transplantation. Blood. 2003;102(8):2777–85.
33. Seo S, Renaud C, Kuypers JM, Chiu CY, Huang ML, Samayoa E, et al. Idiopathic pneumonia syndrome after hematopoietic stem cell transplantation: evidence of occult infectious etiologies. Blood. 2015;125(24):3789–97.
34. Panoskaltsis-Mortari A, Griese M, Madtes DK, Belperio JA, Haddad IY, Folz RJ, et al. An official American Thoracic Society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. Am J Respir Crit Care Med. 2011;183(9):1262–79.
35. Yanik GA, Horowitz MM, Weisdorf DJ, Logan BR, Ho VT, Soiffer RJ, et al. Randomized, double-blind, placebo-controlled trial of soluble tumor necrosis factor receptor: Enbrel (etanercept) for the treatment of idiopathic pneumonia syndrome after allogeneic stem cell transplantation: blood and marrow transplant clinical trials network protocol. Biol Blood Marrow Transplant. 2014;20(6):858–64.
36. Marras TK, Chan CK. Obliterative bronchiolitis complicating bone marrow transplantation. Semin Respir Crit Care Med. 2003;24(5):531–42.
37. Norman BC, Jacobsohn DA, Williams KM, Au BK, Au MA, Lee SJ, et al. Fluticasone, azithromycin and montelukast therapy in reducing corticosteroid exposure in bronchiolitis obliterans

syndrome after allogeneic hematopoietic SCT: a case series of eight patients. Bone Marrow Transplant. 2011;46(10):1369–73.
38. Clark JG, et al. Obstructive lung disease after allogeneic marrow transplantation. Clinical presentation and course. Ann Intern Med. 1989;111(5):368–76.
39. Metcalf JP, Rennard SI, Reed EC, Haire WD, Sisson JH, Walter T, et al. Corticosteroids as adjunctive therapy for diffuse alveolar hemorrhage associated with bone marrow transplantation. Am J Med. 1994;96(4):327–34.
40. Azoulay E, Mokart D, Rabbat A, Pene F, Kouatchet A, Bruneel F. Diagnostic bronchoscopy in hematology and oncology patients with acute respiratory failure: prospective multicenter data. Crit Care Med. 2008;36(1):100–7.
41. Baddley JW, Stroud TP, Salzman D, Papps PG. Invasive mold infections in allogeneic bone marrow transplant recipients. Clin Infect Dis. 2001;32(9): 1319–24.
42. Hung CY, Kao KC, Wang PN, Hu HC, Hsieh MJ, Fu JY, et al. Invasive fungal infection among hematopoietic stem cell transplantation patients with mechanical ventilation in the intensive care unit. BMC Infect Dis. 2012;12:44.
43. Vazquez JA, Miceli MH, Alangaden G. Invasive fungal infections in transplant recipients. Ther Adv Infect Dis. 2013;1(3):85–105.
44. Kostakou E, Rovina N, Kyriakopoulou M, Koulouris NG, Koutsoukou A. Critically ill cancer patient in intensive care unit: issues that arise. J Crit Care. 2014; 29(5):817–22.
45. Daher M. Ethical issues in the geriatric patient with advanced cancer 'living to the end'. Ann Oncol. 2013; 24 Suppl 7:vii55–8.
46. van Vliet M, van der Burgt MP, van der Velden WJ, van der Hoeven JG, de Haan AF, Donnelly JP, et al. Trends in the outcomes of Dutch haematological patients receiving intensive care support. Neth J Med. 2014;72(2):107–12.
47. Pène F, Aubron C, Azoulay E, Blot F, Thiéry G, Raynard B, et al. Outcome of critically ill allogeneic hematopoietic stem-cell transplantation recipients: a reappraisal of indications for organ failure supports. J Clin Oncol. 2006;24(4):643–9.
48. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364(14):1293–304.

Tumor Lysis Syndrome

75

Himaja Koneru and Paul D. Bozyk

Case Presentation

A 72 year old woman with no significant past medical history presented with abnormal labs from an urgent care facility. Her initial labs showed marked absolute lymphocyte leukocytosis of 1789.4 × 10^6 cells/mm^3 with morphology suggesting Chronic Lymphocytic Leukemia. There was no evidence of acute tumor lysis syndrome at initial presentation as suggested by a potassium of 4.4 mEq/dL, uric acid of 4.7 mg/dL, calcium of 9.1 mg/dL and phosphorus level of 3.9 mg/dL. She was started on hydroxyurea, intravenous hydration, and allopurinol for prevention of tumor lysis syndrome. Flow cytometry revealed positivity for ATM and MYB gene deletions as well as del(13q) chromosome. Following initiation of therapy, the patient developed hyperkalemia resistant to medical treatment including sodium polystyrene sulfonate, calcium gluconate and insulin with dextrose, and was started on hemodialysis. Due to her confirmed diagnosis of chronic lymphocytic leukemia (CLL), she was started on induction chemotherapy with Rituximab and Bendamustine. A day later, her labs demonstrated elevated potassium to 6.7 mEq/dL, phosphorus to 16.6 mg/dL, and uric acid to 9.0 mg/dL. She also exhibited hypocalcemia, at 6.9 mg/dL.

Question What is the cornerstone of management of acute tumor lysis syndrome?

Answer Intensive supportive care for renal insufficiency and electrolyte abnormalities.

The optimal management of acute tumor lysis syndrome is preservation of renal function and prevention of life threatening cardiac arrhythmias and neuromuscular irritability by providing the best supportive care. The patient was transferred to the medical ICU for management of acute tumor lysis syndrome. She was given aggressive fluid hydration. Continuous renal replacement therapy was considered, though deferred given normal hemodynamics. Her potassium, phosphate, calcium and uric acid levels were monitored every 6 h and were managed appropriately. No significant dysrhythmias occurred during her course. Her electrolyte abnormalities subsequently resolved. She was transferred back to the general medical floor. Her renal function completely recovered eliminating the need for further renal replacement and she was subsequently discharged home and therapy. She was continued on allopurinol as an outpatient and has not had a recurrent episode of tumor lysis syndrome.

H. Koneru
Internal Medicine, Beaumont Health, Royal Oak, MI, USA

P.D. Bozyk (✉)
Medical Intensive Care Unit, Department of Medicine, Beaumont Health, Royal Oak, MI, USA
e-mail: Paul.Bozyk@beaumont.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_75

Principles of Management

There Are Laboratory and Clinical Classifications of Tumor Lysis Syndrome (TLS)

There are several different definitions of TLS which contain laboratory and clinical classifications, as can be found here [1]. According to Cairo and Bishop [2] laboratory TLS is diagnosed when two or more of the following metabolic abnormalities occur within 3 days before or up to 7 days after the initiation of therapy: hyperuricemia, hypocalcemia, hyperkalemia and hyperphosphatemia. They define clinical TLS as laboratory TLS accompanied by presence of acute kidney injury, seizures, cardiac dysrhythmia, or death. Acute kidney injury may result from urate nephropathy, endothelial dysfunction, local ischemia, or pro-inflammatory and pro-oxidative state secondary to elevated uric acid [3, 4]. Electrolyte abnormalities may lead to neuromuscular irritability including seizures and cardiac dysrhythmia that can be fatal. Laboratory TLS confers high risk of developing clinical TLS [5].

Risk Stratification for Development of Clinical TLS Is Complex, but Useful

Several models have been developed for adults with acute myeloid leukemia [6, 7] and children with acute lymphoblastic leukemia [8] to predict the risk of the tumor lysis syndrome. These models lack a standard definition of the tumor lysis syndrome, use different primary end points (i.e., either clinical tumor lysis syndrome or any type of the tumor lysis syndrome), do not have standardized supportive care guidelines, and scoring systems are complex. However, Howard et al. [5] proposed an algorithm for risk stratification depicted here, which suggests escalation of management including intravenous fluids, hypouricemic agents, progressively more frequent laboratory monitoring, and cardiac monitoring, depending on risk to develop clinical TLS.

Treatment Prephase with Low Intensity Chemotherapy May Prevent TLS in High-Risk Patients

Patients at high risk for developing tumor lysis syndrome may receive low-intensity initial therapy. The hypothesis is that slower lysis of tumor cells allows renal homeostasis to clear metabolites before their accumulation and subsequent organ damage. In patients with advanced B-cell Non-Hodgkin's lymphoma and Burkitt's lymphoma, this approach has involved treatment with low-dose cyclophosphamide, vincristine and prednisone for a week prior to the initiation of intensive chemotherapy. Several groups also subscribe to a week of prednisone monotherapy for childhood acute lymphoblastic leukemia [5].

Hydration Is Essential to Prevention and Treatment of TLS

All patients at risk for, or with, clinical TLS should receive intravenous hydration to optimize glomerular filtration and renal perfusion while maximizing urinary excretion of uric acid and phosphate [9]. Patients at intermediate or high risk for TLS should receive "hyperhydration", with goal of 4–6 L per day up to 48 h prior to chemotherapy through 72 h following therapy [10]. Some have advocated for up to 3000 ml/m^2/day for those at the highest risk [11]. The choice of hydration fluid varies depending upon the clinical circumstances. One expert panel suggests the initial use of 5 % dextrose in one-quarter normal (isotonic) saline [9]. In patients with hyponatremia or volume depletion, isotonic saline should be the initial hydration fluid. As there is a risk of hyperkalemia and hyperphosphatemia with calcium phosphate precipitation once tumor breakdown begins, potassium and calcium should be withheld from the initial hydration fluids. Use of sodium bicarbonate to cause urinary alkalization, while increasing urate excretion, reduces the solubility of calcium phosphate, and is no longer recommended for TLS management, particularly

when hypouricemic agents are available [9]. Urinary alkalization has been associated with renal failure in pediatric patients treated with rasburicase [12]. Diuretics may be used to maintain increased urinary flow, though this is controversial (see section "Evidence Contour").

Hypouricemic Agents Are Essential to the Prevention and Treatment of TLS

Reduction of uric acid with allopurinol and rasburicase can preserve or improve renal function [13]. Rasburicase additionally reduces serum phosphate as a secondary benefit. Allopurinol is a xanthine oxidase inhibitor that reduces the formation of uric acid though has no demonstrable effects on the excretion of already formed uric acid. This delay in therapeutic effect can allow urate nephropathy to develop. Furthermore, despite treatment with allopurinol, xanthine can accumulate and this can result in xanthine nephropathy [14, 15]. In a multicenter randomized study of the use of allopurinol versus rasburicase in pediatric patients at risk for TLS, the mean uric acid was significantly decreased in the rasburicase arm in intention to treat analysis. There was also a significant decrease in serum phosphorus, and favorable trends in serum creatinine in patients managed with rasburicase [16]. The serum creatinine level improved by 31 % in the rasburicase group but worsened by 12 % in the allopurinol group. In the study done by Pui et al. [13], there was no increase in phosphorus levels and decrease in creatinine levels among 131 patients who were at high risk for the tumor lysis syndrome and were treated with rasburicase. While either allopurinol or rasburicase may be considered for patients at intermediate risk for development of TLS, rasburicase is advised for a laboratory or clinical diagnosis of TLS [5]. However, Glucose 6 Phosphate Dehydrogenase deficiency is an absolute contraindication to rasburicase, related to risk of hemolysis, and at risk populations should be screened prior to rasburicase initiation if feasible.

Close Monitoring Is Essential in TLS

It is very important to strictly monitor urine output, laboratory values, and cardiac conduction in patients at risk for, and diagnosed with, TLS. As above, the degree of monitoring is related to the severity of risk, or diagnosis [5]. This monitoring should be done during the entire period for which the patient is at risk for development of TLS as this varies according to the therapeutic regimen.

Prevention of Cardiac Arrhythmias

Hyperkalemia and hypocalcemia are the most common electrolyte abnormalities in tumor lysis syndrome that can cause life-threatening dysrhythmias. Appropriate management of these abnormalities is outlined below:

Hyperkalemia Limitation of oral intake of potassium and phosphate during the period at risk for acute tumor lysis syndrome is an important aspect of management [17]. Frequent measurement of potassium levels, with frequencies dependent on degree of risk or presence for TLS, should be performed. Oral sodium polystyrene sulfonate can be administered if hyperkalemia is detected. Hemodialysis and hemofiltration are effective in removal of potassium. Glucose in combination with insulin or beta agonists may be used as temporary measures. Calcium gluconate can be used in addition for cardiac membrane stabilization while awaiting the initiation of renal replacement therapy.

Hypocalcemia Hypocalcemia can cause neuromuscular instability in addition to dysrhythmias. Management of elevated serum phosphorus level can be helpful in preventing hypocalcemia. Asymptomatic hypocalcemia does not need treatment. The treatment of symptomatic hypocalcemia should target the lowest dose of ionized calcium that is required to relieve the symptoms. Caution is required as excess calcium increases the calcium phosphate product formation and thereby increases the rate of crystallization (when the concentration exceeds 60 mg^2). Phosphate binders are

typically given to patients with acute tumor lysis syndrome although there is no definite evidence for benefit (See section "Evidence Contour").

Acute Renal Failure Requiring Renal Replacement Therapy May Develop Despite Best Practice

Despite optimal attempts at prevention, acute renal failure develops in approximately 3–5% of the patients with TLS. The introduction of rasburicase has brought down the need for dialysis during the induction phase of chemotherapy of high-risk hematologic malignancies. Despite the optimal use of rasburicase, approximately 5% of adults and 1.5% of children need dialysis during induction phase of chemotherapy [18]. Indications for renal replacement therapy in acute tumor lysis syndrome are similar to other causes, but the threshold for initiation can be lower as there is a potential for rapid potassium release from cell lysis and subsequent hyperkalemia particularly when urine output is low. Indications for renal replacement therapy include oliguria or anuria, persistent hyperkalemia, symptomatic hypocalcemia secondary to hyperphosphatemia, or calcium-phosphate product >70 mg^2. The prognosis of complete renal recovery is excellent if dialysis is initiated early during the course, which thereby reduces serum uric acid and phosphate concentrations. Oliguria secondary to urate nephropathy responds well to hemodialysis with diuresis occurring with serum uric acid concentration below 10 mg/dL.

Evidence Contour

Although acute tumor lysis syndrome is extensively studied, there are several aspects of management, which remain controversial.

Use of IV Diuretics in Addition to IV Hydration Has Conflicting Clinical Outcomes

Administration of diuretics to patients with TLS to increase urinary outflow is believed by some to be renal protective. Based on the animal study of urate nephropathy involving elevated levels of serum uric acid that are induced by continuous infusion of uric acid, high urine output due to either high-dose furosemide or genetically induced diabetes insipidus protected the kidneys equally, while acetazolamide causing mild diuresis and bicarbonate provided only moderate renal protection [19]. However in human studies involving the prevention of AKI, the use of diuretics can lead to worse outcome [20, 21]. Randomized controlled trials are needed in order to establish the definite benefits of use of IV diuretics in conjunction with hydration in tumor lysis syndrome.

There Is Unclear Utility of Phosphate Binders in TLS with AKI

Phosphate binders may be used in the management of acute TLS. There is lack of definite evidence of efficacy of phosphate binders in patients with other etiologies of acute renal failure [22, 23]. However, this treatment is typically provided, with case support for its use [5, 22].

Choice of Renal Replacement Therapy Has Variable Outcomes

There is no clear consensus regarding which modality of renal replacement to choose in patients with acute tumor lysis syndrome. Hemodialysis is effective in removing uric acid with clearance of about 70–100 ml/min with reduction of serum uric acid levels by about 50% with 6 h treatment [24]. Peritoneal dialysis is much less efficient. With regards to phosphate clearance, the rate usually ranges from 60 to 100 mL/min with hemodialysis depending on the dialyzer and blood flow. The usual phosphate burden in the patients with tumor lysis syndrome is about 2–7 g per day. This would warrant hemodialysis at 12–24 h. Continuous renal replacement modalities such as arteriovenous hemodialysis (CAVHD) with high dialysate rate, continuous veno-venous hemodialysis (CVVHD) and continuous veno-venous hemofiltration (CVVH) may be tolerated better. These modalities are also often

effective in cases of renal failure from tumor lysis syndrome. The clearance of phosphorus with CAVHD can reach 40 mL/min at a dialysate flow rate of 4 l per hour. This can aid in the removal of up to 10 g of phosphorus per day. Furthermore, continuous renal replacement therapy does not cause rebound hyperphosphatemia which often occurs with intermittent hemodialysis. At present the modality chosen should reflect practitioner experience guided by the need for a high dialysate rate dictated by the perceived need for rapid correction of serum abnormalities.

References

1. McBride A, Westervelt P. Recognizing and managing the expanded risk of tumor lysis syndrome in hematologic and solid malignancies. J Hematol Oncol. 2012;5:75-8722-5-75.
2. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004;127(1):3–11.
3. Chaudhary K, Malhotra K, Sowers J, Aroor A. Uric Acid – key ingredient in the recipe for cardiorenal metabolic syndrome. Cardiorenal Med. 2013;3(3):208–20.
4. Han HJ, Lim MJ, Lee YJ, Lee JH, Yang IS, Taub M. Uric acid inhibits renal proximal tubule cell proliferation via at least two signaling pathways involving PKC, MAPK, cPLA2, and NF-kappaB. Am J Physiol Renal Physiol. 2007;292(1):F373–81.
5. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844–54.
6. Mato AR, Riccio BE, Qin L, Heitjan DF, Carroll M, Loren A, et al. A predictive model for the detection of tumor lysis syndrome during AML induction therapy. Leuk Lymphoma. 2006;47(5):877–83.
7. Montesinos P, Lorenzo I, Martin G, Sanz J, Perez-Sirvent ML, Martinez D, et al. Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model. Haematologica. 2008;93(1):67–74.
8. Truong TH, Beyene J, Hitzler J, Abla O, Maloney AM, Weitzman S, et al. Features at presentation predict children with acute lymphoblastic leukemia at low risk for tumor lysis syndrome. Cancer. 2007;110(8):1832–9.
9. Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26(16):2767–78.
10. Lorigan PC, Woodings PL, Morgenstern GR, Scarffe JH. Tumour lysis syndrome, case report and review of the literature. Ann Oncol. 1996;7(6):631–6.
11. Wilson FP, Berns JS. Tumor lysis syndrome: new challenges and recent advances. Adv Chronic Kidney Dis. 2014;21(1):18–26.
12. van den Berg H, Reintsema AM. Renal tubular damage in rasburicase: risks of alkalinisation. Ann Oncol. 2004;15(1):175–6.
13. Pui CH, Mahmoud HH, Wiley JM, Woods GM, Leverger G, Camitta B, et al. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma. J Clin Oncol. 2001;19(3):697–704.
14. LaRosa C, McMullen L, Bakdash S, Ellis D, Krishnamurti L, Wu HY, et al. Acute renal failure from xanthine nephropathy during management of acute leukemia. Pediatr Nephrol. 2007;22(1):132–5.
15. Pais VM Jr, Lowe G, Lallas CD, Preminger GM, Assimos DG. Xanthine urolithiasis. Urology 2006;67(5):1084.e9-1084.11.
16. Goldman SC, Holcenberg JS, Finklestein JZ, Hutchinson R, Kreissman S, Johnson FL, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood. 2001;97(10):2998–3003.
17. Bellinghieri G, Santoro D, Savica V. Emerging drugs for hyperphosphatemia. Expert Opin Emerg Drugs. 2007;12(3):355–65.
18. Jeha S, Kantarjian H, Irwin D, Shen V, Shenoy S, Blaney S, et al. Efficacy and safety of rasburicase, a recombinant urate oxidase (Elitek), in the management of malignancy-associated hyperuricemia in pediatric and adult patients: final results of a multicenter compassionate use trial. Leukemia. 2005;19(1):34–8.
19. Conger JD, Falk SA. Intrarenal dynamics in the pathogenesis and prevention of acute urate nephropathy. J Clin Invest. 1977;59(5):786–93.
20. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med. 1994;331(21):1416–20.
21. Majumdar SR, Kjellstrand CM, Tymchak WJ, Hervas-Malo M, Taylor DA, Teo KK. Forced euvolemic diuresis with mannitol and furosemide for prevention of contrast-induced nephropathy in patients with CKD undergoing coronary angiography: a randomized controlled trial. Am J Kidney Dis. 2009;54(4):602–9.
22. Tonelli M, Pannu N, Manns B. Oral phosphate binders in patients with kidney failure. N Engl J Med. 2010;362(14):1312–24.
23. Prie D, Friedlander G. Genetic disorders of renal phosphate transport. N Engl J Med. 2010;362(25):2399–409.
24. Kjellstrand CM, Cambell DC, von Hartitzsch B, Buselmeier TJ. Hyperuricemic acute renal failure. Arch Intern Med. 1974;133(3):349–59.

Management of Hyperviscosity Syndromes

76

Brian P. O'Connor and Indhu M. Subramanian

Case Presentation

A 74 year old man with a history of hypertension, hyperlipidemia, and diabetes mellitus presented with worsening fatigue, blurry vision, headache and shortness of breath over the previous 3 months. In addition, he noted gum bleeding when he brushed his teeth, despite proper oral care. Vitals were remarkable for tachypnea and an oxygen saturation of 82% which improved to 87% on 15 L O_2 via nonrebreather. Physical exam was notable for 4/5 weakness in his right arm and leg, an enlarged spleen, and Roth spots, cotton wool spots, and tortuous veins (as seen in Fig. 76.1) on fundoscopic exam. His initial set of labs revealed a WBC of 145 thou/mcL, hemoglobin of 7.4 g/dL (decreased from a baseline of 13 g/dL 2 years prior), a creatinine of 1.3 mg/dL, a total protein of 8.4 g/dL and an albumin of 4.3 g/dL. CXR showed bilateral infiltrates in the lower lung bases (Fig. 76.2). CT of the chest showed no pulmonary emboli, but did confirm the presence of bilateral lower lobe infiltrates. Noncontrast CT of the brain was notable for age appropriate atrophy without signs of ischemia or hemorrhage. Peripheral blood smear was remarkable for marked blasts and a normocytic anemia.

Question What is the most likely diagnosis?

Answer Hyperviscosity Syndrome due to Hyperleukocytosis

This patient exhibited the classic triad of mucosal bleeding, visual changes, and focal neurologic deficits seen in hyperviscosity syndromes. The elevated WBC with blasts on the differential suggested the possibility of an underlying hematologic malignancy as the etiology of the patient's symptoms. In this case, emergent intubation was necessary given the patient's impending hypoxic respiratory failure. Flow cytometry was performed and the patient was preliminarily diagnosed with acute myelogenous leukemia (AML). Oncology was consulted, who recommended emergent leukapheresis. After the leukapheresis, the patient markedly improved and was subsequently extubated. He later received two more sessions of leukapheresis resulting in complete resolution of his symptoms and a reduction in his WBC count to 33 thou/mcL. As seen in Fig. 76.3, the patient's CXR also cleared completely after treatment. Bone marrow biopsy

B.P. O'Connor (✉)
Department of Internal Medicine, Highland Hospital, Alameda Health System, Oakland, CA, USA
e-mail: boconnor@alamedahealthsystem.org

I.M. Subramanian
Pulmonary and Critical Care Faculty, Department of Internal Medicine, Highland Hospital, Alameda Health System, Oakland, CA, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_76

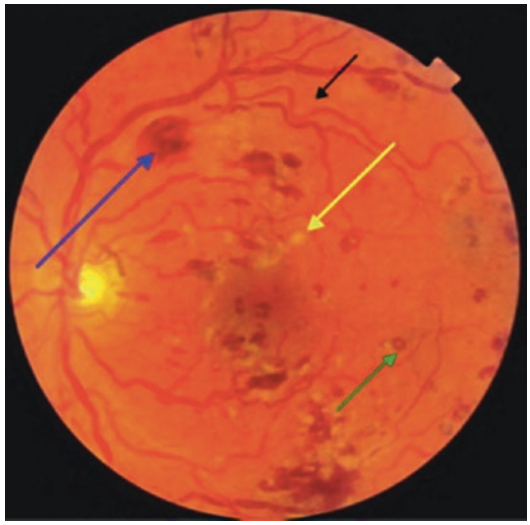


Fig. 76.1 Fundoscopic photograph showing intraretinal hemorrhage (*blue arrow*), tortuous blood vessel (*black arrow*), cotton wool spots (*yellow arrow*), and Roth spots (*green arrow*) (From Shirley and McNicholl [1]. Reprinted with permission from BMJ Publishing Group Ltd.)

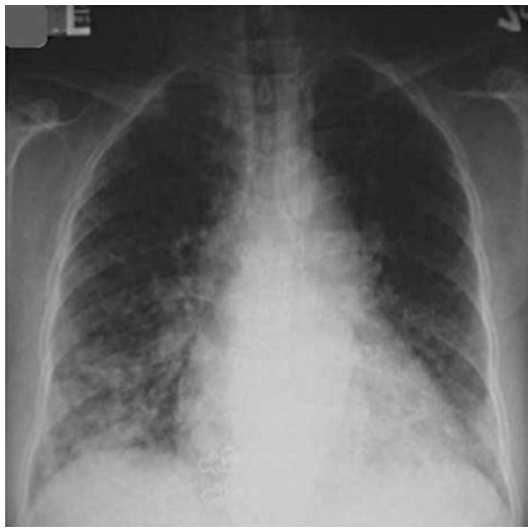


Fig. 76.2 Initial chest x-ray showing bilateral infiltrates in the lower lung zones (From Wu et al. [2]. Reprinted with permission from Elsevier Limited)

and flow cytometry confirmed the diagnosis of AML. The patient was started on chemotherapy and tolerated his medical treatment well and was later discharged with outpatient follow up of his AML.

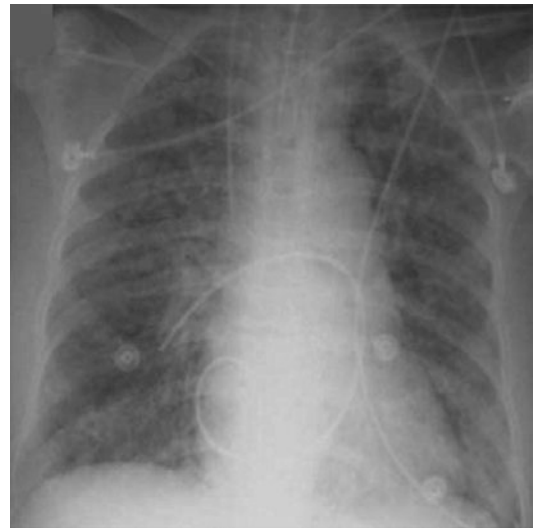


Fig. 76.3 Post chemotherapy CXR showing resolution of the patient's lower lobe infiltrates (From Wu et al. [2]. Reprinted with permission from Elsevier Limited)

Principles of Management

Pathophysiology

Hyperviscosity syndrome (HVS) refers to the clinical constellation of symptoms exhibited due to an increase in serum viscosity. This increase in serum viscosity is the result of two major pathologic processes: most commonly paraproteinemias and less commonly excess cellular components (such as leukocytes and platelets). The resultant sluggish blood flow leads to a relative hypoperfusion and circulating proteins interfere with platelet aggregation causing prolonged bleeding time [3]. Classically, the patient will present with (among other symptoms) the triad of visual changes, mucosal bleeding, and focal neurological deficits [4]. Table 76.1 shows many of the end organ manifestations that can result from hyperviscosity syndromes.

In plasma, the main determinant of blood viscosity is protein concentration [5, 6]. Spherical proteins have a smaller effect on blood viscosity whereas larger proteins with high ratios of length to width (such as the pentameric IgM) can have an inordinate effect on viscosity [7]. This underlying mechanism explains the high incidence of

Table 76.1 Clinical symptoms which can be seen in various hyperviscosity syndromes

Organ system	Hyperviscosity signs and symptoms	Diagnostic modalities
Neurologic	Focal neurological deficits Headache Dizziness Altered Level of Consciousness Seizures Coma	CT Noncontrast Brain MRI Brain MRA Brain
Pulmonary	Shortness of Breath Dyspnea Hypoxemia Wheezing	CXR CT Chest
CVS	Chest Pain Palpitations Chest Tightness Acute MI	Cardiac Enzymes Echocardiogram
Hematologic	Increased Bleeding Time Mucosal Bleeding Anemia Fatigue	CBC with diff PT/INR, PTT, fibrinogen, haptoglobin
Ophthalmologic	Blurry Vision Retinal Vein Engorgement Progressive loss of sight Papilledema	Fundoscopic Exam

HVS in lymphoplasmacytic lymphoma (formerly known as Waldenstroms Macrogloulinemia), a B cell lymphoma in which there are high levels of circulating IgM pentamers. The distribution of the gamma globulins also plays an important clinical role. IgM, predominantly an intravascular protein, exerts a greater effect on plasma viscosity compared to IgG and IgA (which are distributed more extravascularly) [5].

Leukostasis is the occlusion of blood vessels caused by hyperviscous blood due to an excessive number of circulating white blood cells. Hyperleukocytosis can be seen in both acute and chronic leukemias when the WBC is greater than 100,000 cells/mm^3 and is more common when in their blast form [8]. Typically, it occurs in acute lymphoblastic leukemia (especially T cell variants), acute myeloid leukemia, and chronic myeloid leukemia during a blast crisis [8]. These immature blast cells (either myeloblasts or lymphoblasts) are larger and have a more rigid cellular membrane, making them more likely to cause leukostasis. Occlusion happens in small capillaries, and the excess WBCs release toxins that can damage the vascular endothelium resulting in local rupture and hemorrhage [8]. Leukostasis is a medical emergency when life-threatening symptoms develop and requires emergent cytoreduction. In our case, the patient exhibited hyperleukocytosis, as evidenced by his WBC of 145 thou/mcL and symptoms of leukostasis.

Diagnosis

The diagnosis of HVS requires a high degree of clinical suspicion supported by laboratory evidence showing an elevated protein level or hyperleukocytosis. Table 76.2 shows common cutoffs for which symptoms may be seen in both paraproteinemias as well as various blood disorders. It is important to emphasize that HVS remains primarily a clinical diagnosis that is additionally supported by laboratory data.

When one clinically suspects HVS due to paraproteinemia, the total protein level must be checked to see if it is elevated. If so, the next step is to perform a serum protein electrophoresis. HVS due to paraproteinemia is most commonly seen in Waldenstrom macroglobulinemia with an IgM level >3 g/dL [5]. In multiple myeloma with monoclonal IgG paraproteins, HVS does not

appear until levels are >15 g/dL [5]. In IgA myeloma, the symptoms usually occur with plasma IgA levels >10 g/dL [5]. The intravascular distribution of IgM explains why symptoms of HVS occur at a much lower IgM protein level compared to both IgG and IgA paraproteinemias. In our case, the normal albumin-protein gap suggests that a paraproteinemia was not the underlying etiology of the patient's symptoms and pointed more to hyperleukocytosis.

It is also important to differentiate hyperleukocytosis from a leukemoid reaction when there is a nonmalignant etiology for the leukocytosis. Leukemoid reactions are seen in certain infections, including *S. Aureus*, Pneumococcus, tuberculosis, pertussis, and various inflammatory conditions. Differentiation is made by performing a thorough history, physical examination, and a peripheral smear. The peripheral smear in a leukemoid reaction will show mature lymphocytes and granulocytes. The total leukocyte count in a leukemoid reaction is typically greater than 50,000/mm^3 but rarely exceeds 100,000/mm^3 [9].

Hyperleukocytosis resulting in end-organ dysfunction is far more common in acute myeloid leukemia (AML) compared to acute lymphoblastic leukemia (ALL). This is in spite of the fact that ALL typically has a higher WBC count [8]. Certain subsets of AML are associated with hyperleukocytosis, namely myelomonocytic AML (FAB M4) and Monocytic AML (FAB M5) [10]. Hyperleukocytosis is often seen in ALL, though clinical leukostasis is uncommon [10]. Hyperleukocytosis can be seen in two different phases of CML: when CML progresses to a blast crisis, or when it has been untreated in the chronic phase. Similar to ALL, chronic lymphocytic leukemia (CLL) commonly presents with hyperleukocytosis, though leukostasis is not seen until the WBC is much higher. Table 76.2 lists the common cell count cutoffs for which leukostasis may present i in various leukemias. While these values provide a good guideline, it is important to realize that symptoms may be present at much lower levels.

Essential thrombocytosis, a chronic myeloproliferative disorder can present as a hyperviscosity syndrome when platelet counts are >1000 thou/dL [11]. In this case, the extreme thrombocytosis can cause symptoms similar to leukostasis and platelet pheresis must be considered to decrease the platelet levels.

Management

In the critical care setting, it is important to manage the complications of HVS as they arise. Large bore central venous access (preferentially with a dialysis catheter) should be established while awaiting the pheresis team. Pheresis involves the removal of a specific component of the patient's blood. The type of pheresis required depends on the specific component removed (e.g. leukapheresis, plasmapheresis, platelet pheresis, etc.) [12]. Given the high tumor burden in hyperleukocytosis, it is important to monitor for signs of tumor lysis syndrome (TLS) and uric acid, potassium, phosphate, and renal function should be checked

Table 76.2 A general guide for common cutoffs where the symptoms of hyperviscosity may present

Common cutoffs for hyperviscosity syndromes		
Paraproteinemia	IgM	>3 g/dL
	IgA	>10 g/dL
	IgG	>15 g/dL
Excessive cellular components	AML	>300 thou/dL
	ALL	>600 thou/dL
	CML, Blast Phase	>100 thou/dL
	CML, Accelerated Phase	>100 thou/dL
	CML, Chronic Phase (when pregnant)	>100 thou/dL
	Essential Thrombocytosis	>1000 thou/dL

It is important to note that it is possible for symptoms to appear at lab values lower than those listed

immediately upon identification of hyperleukocytosis [13, 14]. Initial management includes aggressive hydration, allopurinol to prevent TLS, and correction of any electrolyte abnormalities. IV fluids should be free of both potassium and calcium and should be started at 2–5 times normal maintenance fluids [8]. Fluids can be increased in symptomatic patients and in those with persistent TLS. Fluid rates should be decreased in anemic patients with a hemoglobin of <6 as this hemodilution may precipitate congestive heart failure [9]. Platelets should be transfused if <20,000/mm^3 to decrease the possibility of a CNS bleed. Platelet transfusions do not significantly increase blood viscosity. In cases of severe anemia, transfusions must be used very judiciously before pheresis is initiated as RBCs may increase serum viscosity exacerbating the patient's clinical symptoms [4]. Monitoring of vitals Q3-4 hours should be performed and any development of hemodynamic instability could indicate a hemorrhage or congestive heart failure. Pulmonary leukostasis can result in respiratory distress and hypoxic respiratory failure (as in our case) potentially requiring mechanical ventilator support [15]. Arterial pO_2 can be falsely decreased because of the metabolic activity of malignant cells, a phenomenon termed 'leukocyte larceny' [16]. The reduced pO_2 in the ABG sample is attributed to O_2 consumption by the activated leukocytes after the blood has been drawn. Pulse oximetry provides a more accurate assessment of O_2 saturation [16]. Pheresis should continue until the patient's symptoms resolve and the components being pheresed are near normal.

Leukapheresis results in a reduction of a patient's white blood cell count by 20–60 % per session [12]. Most patients only require a single session to see improvement in symptoms. It is important to remember that leukapheresis is only a temporizing measure while the definitive diagnosis is being determined. Definitive systemic therapy directed at the underlying condition should be instituted as early as possible. As a general rule of thumb, leukapheresis should be considered in most cases of symptomatic leukostasis that are the result of hyperleukocytosis. The exception to this is the chronic phase of CML, which is managed differently when hyperleukocytosis is present. In this phase, it is recommended to start systemic therapy with both hydroxyurea and a tyrosine kinase inhibitor (TKI) [17]. Hydroxyurea, given at a dose of 50–100 mg/kg PO has been shown to decrease WBC by 50–80 % in 24–48 h [18]. In chronic phase CML, leukapheresis is typically reserved for those that are pregnant, given that hydroxyurea and TKIs are not recommended during pregnancy [18]. Leukapheresis should however be considered when CML has progressed to either acute blast phase or accelerated phase and has resulted in hyperleukocytosis.

The management of hyperviscosity syndrome due to a paraproteinemia involves supportive management and treatment of the underlying etiology. Plasmapheresis was first performed in the 1950s and has been demonstrated to reverse many of the clinical manifestations of HVS [19]. Plasmapheresis involves the removal of whole plasma (which includes both the pathogenic substance as well as essential substances) and replaces it with a substitution fluid that is appropriately similar to the plasma removed. Typically, the choice of replacement fluid is either fresh frozen plasma or 4–6 % albumin and the choice of replacement fluid depends on both the coagulation state of the patient as well as their immune status [20]. Plasmapheresis is generally well tolerated and adverse reactions are similar to those of transfusing the replacement fluid alone (i.e. in administering FFP there is concern for allergic reaction, hypocalcemia, and a risk for viral infection) [20]. Plasmapheresis can be performed daily until the resolution of symptoms and then intermittently for symptom control [3]. If plasmapheresis cannot be instituted immediately, phlebotomy in conjunction with hydration can temporize symptoms until plasmapheresis can begin.

Evidence Contour

There are many potentially controversial aspects in the management hyperviscosity syndromes: how to measure blood viscosity, the lack of procedural standardization, and whether leukapheresis has a positive effect on overall survival.

How to Measure Viscosity

The measurement of plasma viscosity has not changed significantly since the 1940s. Viscosity is assessed via a 'capillary tube' called an Ostwald tube and is measured by observing the time required for serum or plasma to flow through this thin 'U' shaped glass tube under the influence of gravity [9]. The more viscous the sample, the slower it flows through the Ostwald tube. Viscosity of normal serum is 1.4–1.8 centipose and it is rare that symptoms of hyperviscosity appear until the serum viscosity is >3.0 centipose [12]. There are two major limitations in using this method to diagnose hyperviscosity. First, this method only measures plasma viscosity and while this is useful for paraproteinemias, it cannot be used to assess hyperviscosity from hyperleukocytosis. Second, the test itself is difficult to perform given that the Ostwald tubes are fragile and are easily broken. Some clinical laboratories do not offer this test, so diagnosis must be made primarily by clinical symptoms and corroborative lab findings.

Lack of Procedural Standardization

Though there have been many studies illustrating an improvement in symptoms after leukapheresis in HVS, there ultimately lacks standardization in regards to the procedure. No studies identify when it is best to begin and end leukapheresis, nor is it known which clinical and laboratory values should be followed in order to assess adequate response to therapy [12]. There have been no randomized trials for the use of leukapheresis for hyperleukocytosis, but given that the procedure is generally well tolerated, many oncologists choose to have the procedure performed while awaiting a definitive diagnosis [10].

Efficacy of Leukapheresis in AML

Multiple studies have looked at the efficacy of leukapheresis in the treatment of AML and have demonstrated variable outcomes. Leukapheresis was associated with a decrease in the 2-week mortality rate, but the procedure showed no improvement in overall survival [21]. This lack of survival outcome date is believed to be a result of the grim prognosis of the underlying disease [21]. It appears that the features most predictive of early death in AML is not related to leukapheresis, but rather other patient factors such as performance status, age, and disease complications [10]. Despite this, there is a general improvement in morbidity with both leukapheresis, mostly relating to a decrease in end organ hypoperfusion. For this reason, leukapheresis is still recommended initially in HVS due to AML.

References

1. Shirley K, McNicholl FP. Blurred vision and epistaxis. BMJ. 2014;348:g91.
2. Wu YK, Huang YC, Huang SF, Huang CC, Tsai YH. Acute respiratory distress syndrome caused by leukemic infiltration of the lung. J Formos Med Assoc. 2008;107(5):419–23.
3. Khan UA, Shanholtz CB, McCurdy MT. Oncologic mechanical emergencies. Emerg Med Clin North Am. 2014;32(3):495–508.
4. Adams BD, Baker R, Lopez JA, Spencer S. Myeloproliferative disorders and the hyperviscosity syndrome. Emerg Med Clin North Am. 2009;27(3):459–76.
5. Kwaan HC. Role of plasma proteins in whole blood viscosity: a brief clinical review. Clin Hemorheol Microcirc. 2010;44(3):167–76.
6. Késmárky G, Kenyeres P, Rábai M, Tóth K. Plasma viscosity: a forgotten variable. Clin Hemorheol Microcirc. 2008;39(1-4):243–6.
7. Gertz MA, Kyle RA. Hyperviscosity syndrome. J Intensive Care Med. 1995;10(3):128–41.
8. Lawrence J. Critical care issues in the patient with hematologic malignancy. Semin Oncol Nurs. 1994;10(3):198–207.
9. Jain R, Bansal D, Marwaha RK. Hyperleukocytosis: emergency management. Indian J Pediatr. 2013;80(2):144–8.
10. Blum W, Porcu P. Therapeutic apheresis in hyperleukocytosis and hyperviscosity syndrome. Semin Thromb Hemost. 2007;33(4):350–4.
11. Gugliotta L, et al. Epidemiological, diagnostic, therapeutic, and prognostic aspects of essential thrombocythemia in a retrospective study of the GIMMC group in two thousand patients. Blood. 1997;90:348a.

12. Nakanishi T, Suzuki N, Kuragano T, Nagasawa Y, Hasuike Y. Current topics in therapeutic plasmapheresis. Clin Exp Nephrol. 2014;18(1):41–9.
13. Shelat Suresh G. Practical considerations for planning a therapeutic apheresis procedure. Am J Med. 2010;123(9):777–84.
14. Porcu P, Cripe LD, Ng EW, Bhatia S, Danielson CM, Orazi A, McCathy LJ. Hyperleukocytic leukemias and leukostasis: a review of pathophysiology, clinical presentation and management. Leuk Lymphoma. 2000;39(1-2):1.
15. Azoulay E, Fieux F, Moreau D. Acute monocytic leukemia presenting as acute respiratory failure. Am J Respir Crit Care Med. 2003;167:1329.
16. Sacchetti A, Grynn J, Pope A, Vasso S. Leukocyte larceny: spurious hypoxemia confirmed with pulse oximetry. J Emerg Med. 1990;8(5):567–9.
17. Cortes J, Kantarjian H. How I treat newly diagnosed chronic phase CML. Blood. 2012;120(7):1390–7.
18. Grund FM, Armitage JO, Burns P. Hydroxyurea in the prevention of the effects of leukostasis in acute leukemias. Arch Internal Med. 1977;137(9):1246–7.
19. Stone MJ, Bogen SA. Evidence-based focused review of management of hyperviscosity syndrome. Blood. 2012;119(10):2205–8.
20. Kwaan HC. Hyperviscosity in plasma cell dyscrasias. Clin Hemorheol Microcirc. 2013;55(1):75–83.
21. Porcu P, Danielson CF, Orazi A, Heerema NA, Gabig TG, McCarthy LJ. Therapeutic leukapheresis in hyperleucocytic leukaemias: lack of correlation between degree of cytoreduction and early mortality rate. Br J Haematol. 1997;98(2):433–6.

Part X

Surgical

Lena M. Napolitano

Thoracic Trauma

77

Katherine M. Klein and Krishnan Raghavendran

Case Presentation

A 47 year old man with a history of hypertension and coronary artery disease was involved in a multiple car motor vehicle accident. He was the restrained driver in a head-on collision going approximately 55 mph. He was noted to have a GCS of 12 (eyes 3, verbal 4, motor 5) at the scene and was transported to the emergency department for further evaluation. Upon examination in the emergency department his first set of vitals were T 37C, HR 110, BP 110/85, RR 22, SpO_2 90%, GCS 11 (eyes 3, verbal 3, motor 5). He was noted to have paradoxical chest rise, diminished breath sounds on the left, tracheal deviation to the right, multiple ecchymosis to his anterior chest wall bilaterally, and subcutaneous emphysema to his left anterior chest wall. The remainder of his exam was unremarkable (Fig. 77.1).

Question What is the diagnosis and what should be the next step of management?

Answer Tension pneumothorax and needle decompression with subsequent tube thoracostomy insertion.

Evacuation of pleural air is the most important first step in a tension pneumothorax and can be done via needle decompression or catheter drainage [1]. After a tube thoracostomy was placed, 100 mL of blood was evacuated from the chest. The chest tube was placed to suction through a pleur-evac system. A post procedure chest x-ray was obtained which showed the chest tube in proper posterior-apical position with the last drainage hole within the chest cavity. The patient was stabilized and a chest CT was performed which revealed multiple rib fractures, consistent with a flail chest segment, multiple areas of lung contusion, and bilateral basilar pleural effusions.

The patient's inspiratory effort became poor and he had multiple episodes of desaturation. An arterial blood gas showed a pH 7.27, CO_2 55, O_2 65, HCO_3 25. The patient was subsequently intubated and placed on volume control mechanical ventilation, tidal volume 400 mL, respiratory rate 18, pressure support 10, PEEP 8, FIO_2 100%. Fluid balance was carefully monitored during his intubated status and protective lung ventilation was maintained.

The patient required IV pain control with placement of an epidural catheter for pain associated with his multiple rib fractures and flail segment. Over the next few days the pain was well controlled, hypoxia associated with lung contusions improved, daily spontaneous breathing and

Electronic supplementary material The online version of this chapter (doi:10.1007/978-3-319-43341-7_77) contains supplementary material, which is available to authorized users.

K.M. Klein
Surgical Critical Care, General Surgery, Department of Surgery, University of Toledo, Toledo, OH, USA

K. Raghavendran (✉)
Department of Surgery, University of Michigan, Ann Arbor, MI, USA
e-mail: kraghave@med.umich.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_77

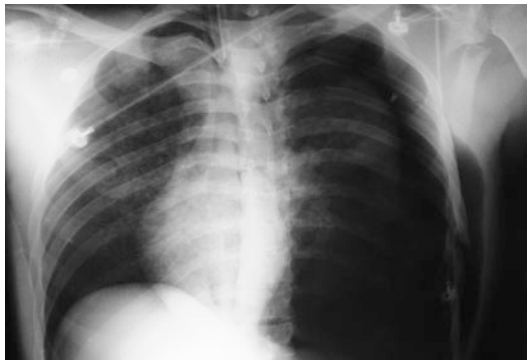


Fig. 77.1 Chest x-ray of a 45 year old male a victim of blunt trauma demonstrating left sided tension pneumothorax with rib fractures

awakening trials were performed and the patient was successfully extubated. Chest tubes were removed after complete resolution of his pneumothorax and hemothorax and the patient was subsequently discharged to a rehabilitation center.

Principles of Management

Pneumothorax

Pneumothoraces associated with trauma can be diagnosed by clinical exam and radiological studies. Patients often present with shortness of breath, chest pain, cough, and tachypnea [2]. Clinical presentations of tension pneumothorax also include chest pain, dyspnea, tachypnea, and hypoxia, but additionally present with jugular venous distention, contralateral tracheal deviation, subcutaneous emphysema, and hyper-resonance to percussion [3]. High clinical suspicion for tension pneumothorax should lead to immediate needle decompression and then tube thoracostomy insertion. Diagnosis of pneumothorax can be done with chest x-ray, ultrasound (Videos 77.1 and 77.2) or chest CT[2]. Small spontaneous pneumothoraces, not associated with trauma, can be observed clinically and a chest tube can be deferred unless the patient becomes symptomatic or the pneumothorax expands [4]. Traumatic pneumothorax should be treated with closed tube thoracostomy (chest tube) placement.

Hemothorax

Once there is suspicion for a hemothorax, on either radiological findings or clinical concern, a tube thoracostomy should be performed. Diagnosis can be confirmed with plain chest films, looking for a meniscus sign of fluid blunting the costo-phrenic angle or diaphragmatic surface (Fig. 77.2). Approximately 400–500 mL of fluid is required to cause blunting of the costophrenic angle in a traditional upright chest x-ray. Additionally, ultrasound can be useful to detect fluid; however, the precise quantitative measurement of the amount of blood in the pleural cavity is often user dependent. Finally, computed tomography with the administration of intravenous contrast of the chest allows for a global picture of thoracic anatomy and can be useful in patients who may also have to be ruled out for aortic injury and operative planning for repair.

If the initial placement of a chest tube drains more than 1500 mL within a 24-h period or demonstrates a continuing bloody output for more than 150–200 ml per hour for 4 h, massive hemothorax is diagnosed and a surgical intervention in the form of a postero-lateral thoracotomy should be considered for hemorrhage control [5]. Persistent retained hemothorax, as defined as a hemothorax that persists after chest tube insertion and attempted drainage procedures, should be treated with early video-assisted thoracoscopic surgery (VATS) rather than repeated attempted drainage with additional chest tubes to avoid long-term lung scarring, pleural thickening, and infection/empyema formation [5] (Fig. 77.2).

Rib Fractures

Rib fractures are the most common injury in blunt chest trauma and can occur in 50 % of cases [6]. Injury to the first 3 ribs usually requires high-energy trauma, fractures of fourth to eighth ribs are most common, and fractures of the ninth to twelfth ribs usually indicate the possibility of co-existing intra-abdominal injury. Clinical suspicion for rib fractures includes,

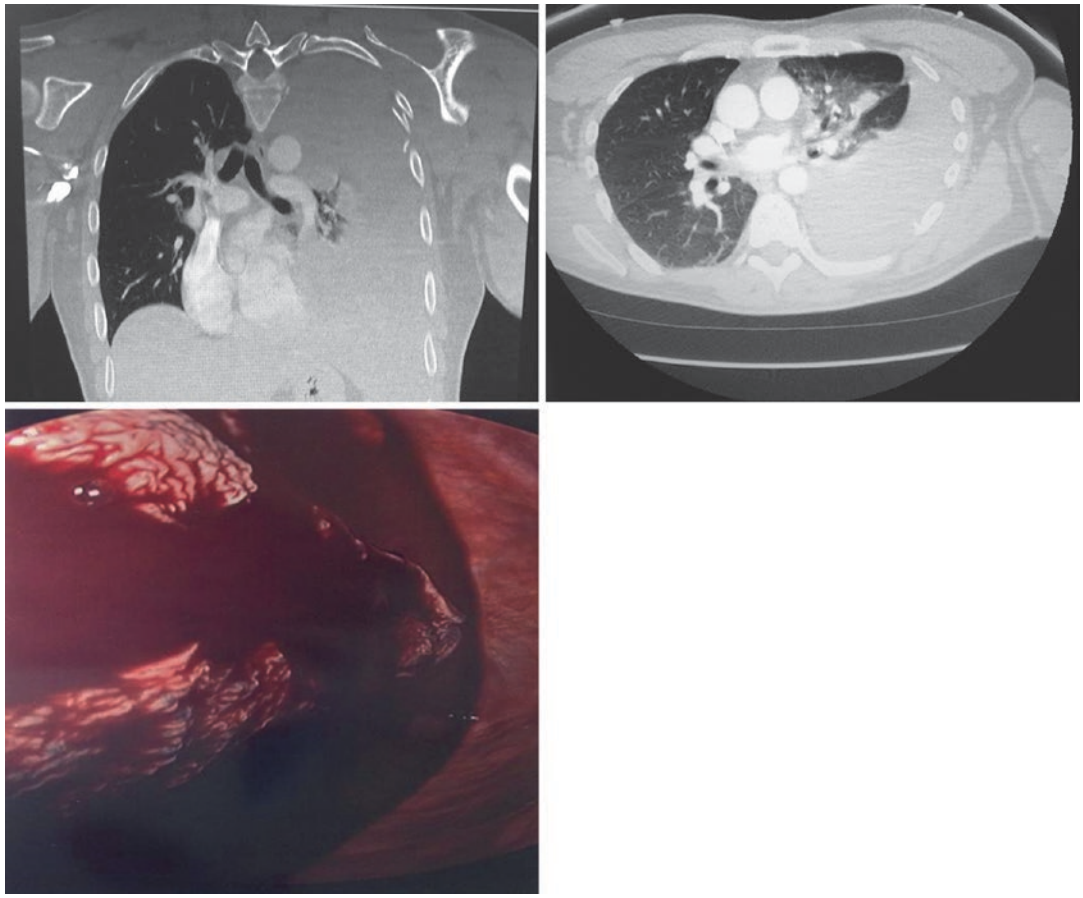


Fig. 77.2 Patient with a retained left Hemothorax- Was taken to the operating room 4 days following initial trauma. A video-assisted thoracoscopy was performed. Intra-operative pictures confirm the presence of a large hemothorax

splinting, localized pain, overlying skin changes including ecchymosis or subcutaneous emphysema, and/or respiratory distress. A paradoxical chest rise with inspiration and expiration is typically consistent with rib fractures involving multiple sites and ribs. Diagnosis can be made with plain films of the chest, but this method has sensitivity as low as 15 % [7]. Therefore, use of CT imaging of the thorax allows for confirmation of the diagnosis of rib fractures and 3-D reconstruction of the thoracic wall for potential operative planning [7]. The treatment of rib fractures includes adequate pain control and aggressive pulmonary toilet [8]. Typically the physiological derangement associated with rib fractures is predominantly due to the underlying lung contusion [9, 10].

Lung Contusion

Blunt chest trauma is involved in nearly one-third of acute trauma admissions to the hospital, and lung contusion (LC) (Fig. 77.3) is an independent risk factor for the development of acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and ventilator-associated pneumonia (VAP) [9, 11]. The lung is also the second commonest organ involved in blast trauma-induced LC, which often has a peri-hilar distribution and carries a high risk of mortality [12]. When LC injury leads to hypoxemia severe enough to meet the definition of ARDS, the prognostic and economic impacts are significant. In a 2004 study of trauma patients, the incremental hospital cost per patient with ARDS ($36,713

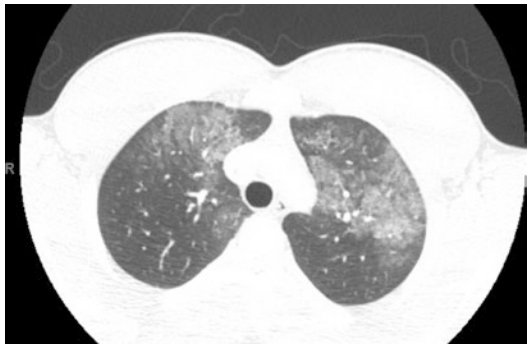


Fig. 77.3 Chest CT scan showing bilateral lung contusion-presence of involvement of the non-dependent lobes with evidence of trauma are indicative of lung contusion. Other pertinent differential diagnosis should include gastric-aspiration induced lung injury

or $59,633, respectively) was much higher than for patients without ARDS ($24,715) [13].

The pathophysiology of pulmonary contusion and blunt chest trauma includes inflammation, increased alveolo-capillary permeability and pulmonary edema, ventilation/perfusion mismatching, increased intrapulmonary shunting, and a loss of compliance [14]. Treatment modalities outside of the standard treatment of other forms of lung injury such as a conservative fluid strategy, mechanical ventilation with lung protective strategy and analgesic management of associated rib fractures are currently under investigation.

Evidence Contour

Pneumothorax

Several areas of management of pneumthoraces still remain controversial. Traditionally, all sizes of post-traumatic pneumothoraces required chest tube drainage. However, a small pneumothorax in a clinically stable patient can be observed with repeat chest x-ray and a tube can be avoided unless the patient develops respiratory distress or the pneumothorax expands on chest plain film [5].

The use of smaller 14-Fr pigtail catheters has also been a new addition to the treatment algorithm in the management of pneumothorax. This procedure has been shown to reduce pain associated with chest tube placement as well as tube placement duration, and is equally effective at draining pleural air as larger, more traditional chest tubes [15].

The use of continuous negative pressure once the chest tube is placed, as well as the optimal timing for water seal prior to removal has also had some controversy. In patients without a continued air-leak, the chest tube can be placed to water seal and does not require negative pressure [16].

The routine use of chest x-rays after insertion as well as removal of chest tubes has also been investigated. Many institutions have created protocols that require a chest x-ray (CXR) after insertion of a chest tube. Newer studies are now finding that this routine study rarely changes the clinical course for the patient and clinical evaluation of the patient and tube drainage can alert the practitioner to problems that may exist [17]. Traditional protocols have centered on obtaining CXRs after chest tube removal. If a patient is not mechanically ventilated and has appropriate mental status to communicate symptoms of respiratory distress, a post-chest tube removal CXR is not required [18, 19].

Hemothorax

Much of the controversy surrounding hemothorax management is related to utilization and timing of thoracotomy versus video-assisted thoracoscopic surgery (VATS). Traditional criteria for an urgent thoracotomy included more than 1500 mL of blood evacuated from the chest with initial chest tube insertion, persistent bleeding from the chest with 150 mL/h to 200 mL/h for 2–4 h, or persistent blood transfusion required to maintain hemodynamic stability [5]. The use of VATS versus open thoracotomy has also been evaluated given that open thoracotomies are associated with severe incisional pain, increased hospital length of stay, and high infection rates [20]. In multiple meta-analyses, VATS has been shown to be as effective as open thoracotomy and can reduce the amount of chest tube drainage, duration of tube drainage, duration of hospitalization,

operation time, and amount of bleeding and need for transfusion when compared to non-operative management and open thoracotomy [20, 21].

For retained hemothorax, the timing of VATS has been investigated. Early VATS, before day three, for retained hemothorax has been shown to decrease operative difficulty, contamination of the clot, and hospital length of stay when compared to procedures that were performed later than 6 days [5, 21]. In an effort to reduce the number of operative procedures performed for retained hemothorax, the use of fibrinolytics has also been proposed. Based on clinical evidence, the routine use of fibrinolytics for retained hemothorax cannot be routinely recommended and is reserved for patients who are otherwise high risk for surgical intervention [5].

Rib Fractures

Traditionally, rib fractures have been managed non-operatively with a major emphasis on appropriate pain control. Patients with multiple rib fractures are at increased risk for atelectasis, hospital-acquired pneumonia, and subsequent deterioration into respiratory failure requiring mechanical ventilation [22]. The particular use of thoracic epidural analgesia has been shown to improve clinical status, reduced rates of pneumonia, a reduced length of ICU stay, and improved pain ratings by patients [22]. However, further research still needs to be completed in this area regarding trauma patients that are mechanically ventilated, have coagulopathy disorders, or have rib fractures involving the first four ribs.

Operative management of rib fractures has also been extensively studied and is still routinely under-utilized. Appropriate timing for surgical rib fixation (Fig. 77.4) is still unknown and early data has suggested that earlier fixation of flail segments can lead to shorter ICU and hospital lengths of stay [23]. Two systematic reviews suggest that surgical fixation of rib fractures and flail chest may have benefits, however the analyses are based on the pooling of primarily small retrospective and few prospective studies [24, 25]. However, a review of current literature does suggest that the overall morbidity of rib fractures may be a result of underlying lung contusion. Routine availability of plating material, as well as knowledge and training in surgical implantation is still growing and may become the standard of care for these patients in the future.

Lung Contusion

The areas of controversy with respect to lung contusion is the relationship to ARDS. While there are some studies that show that the percentage of area involved (typically more than 40%) is associated with an increased risk for ARDS, this relationship is not linear. Additionally from multiple studies done using animal models, it is well understood that the generation of acute inflammatory response following lung contusion is responsible for deterioration to ARDS. Finally, other factors that have been studied to be responsible for the deterioration of contusion to ARDS involves associated second hit injuries to the lung such as VAP and aspiration-induced lung injury.

As described above, lung contusion is an independent risk factor for ARDS and VAP. The treatment of lung contusion, independent of ARDS and VAP, has few specific elements independent of conservative fluid therapy, lung protective strategy, and pain control for associated rib fractures. Specific therapeutic strategies to improve oxygenation and alter the inflammatory response in trauma patients with LC continues to be a challenge. A few studies have suggested improvements with intravenous corticosteroids or antioxidants in animal models [26], but precise randomized studies in trauma patients have not yet been carried out. Similarly, improvements in lung function with exogenous surfactants in LC have been noted in animal models [27, 28], but this has not been translated to clinical studies in patients with LC. Finally, specific modalities of mechanical ventilation, such as APRV, have been investigated in non-randomized trials with improved benefit.

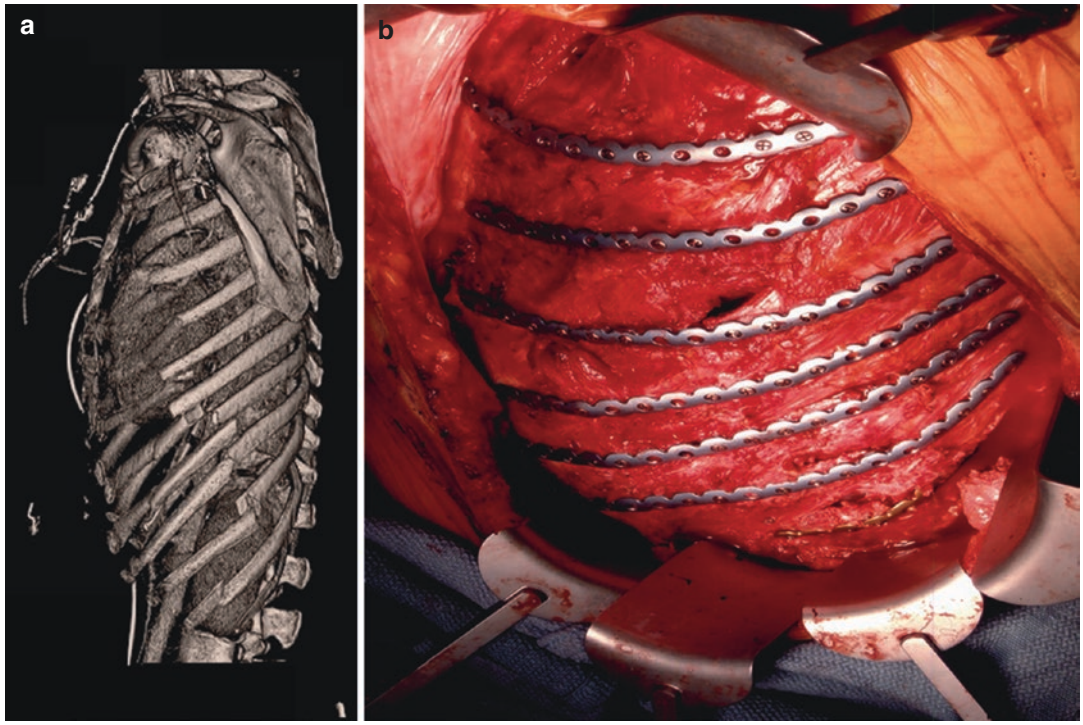


Fig. 77.4 (**a**) Chest CT scans reconstructions shows multiple rib fractures. This type of imaging is typically done prior to plate fixation seen in image (**b**) This procedure requires an extensive extra-pleural approach

References

1. Huang Y, Huang H, Li Q, Browning RF, Parrish S, Turner Jr JF, Zarogoulidis K, Kougioumtzi I, Dryllis G, Kioumis I, Pitsiou G, Machairiotis N, Katsikogiannis N, Courcoutsakis N, Madesis A, Diplaris K, Karaiskos T, Zarogoulidis P. Approach of the treatment for pneumothorax. J Thorac Dis. 2014;6 Suppl 4:S416.
2. Ince A, Ozucelik DN, Avci A, Nizam O, Dogan H, Topal MA. Management of pneumothorax in emergency medicine departments: multicenter trial. Iranian Red Crescent Med J. 2013;15(12).
3. Roberts DJ, Leigh-Smith S, Faris PD, Blackmore C, James MT, Kirkpatrick AW, Stelfox HT. Clinical presentation of patients with tension pneumothorax: a systematic review. Ann Surg. 2015;261(6): 1068–78.
4. Mahmood I, Tawfeek Z, El-Menyar A, Zarour A, Afifi I, Kumar S, Al-Thani H. Outcome of concurrent occult hemothorax and pneumothorax in trauma patients who required assisted ventilation. Emer Med Int. 2015(2015):6.
5. Mowery NT, Gunter OL, Collier BR, Jose'J Jr D, Haut E, Hildreth A, Streib E. Practice management guidelines for management of hemothorax and occult pneumothorax. J Trauma Acute Care Surg. 2011;70(2): 510–8.
6. Oikonomou A, Prassopoulos P. CT imaging of blunt chest trauma. Insights Imaging. 2011;2(3):281–95.
7. Cho SH, Sung YM, Kim MS. Missed rib fractures on evaluation of initial chest CT for trauma patients: pattern analysis and diagnostic value of coronal multiplanar reconstruction images with multidetector row CT. Br J Radiol. 2012;85(1018):e845–50.
8. Fowler TT, Taylor BC, Bellino MJ, Althausen PL. Surgical treatment of flail chest and rib fractures. J Am Acad Orthop Surg. 2014;22(12):751–60.
9. Cohn SM. Pulmonary contusion: review of the clinical entity. J Trauma. 1997;42(5):973–9.
10. Raghavendran K, Notter RH, Davidson BA, Helinski JD, Kunkel SL, Knight PR. Lung contusion: inflammatory mechanisms and interaction with other injuries. Shock. 2009;32(2):122–30.
11. Miller PR, Croce MA, Bee TK, Qaisi WG, Smith CP, Collins GL, Fabian TC. ARDS after pulmonary contusion: accurate measurement of contusion volume identifies high-risk patients. J Trauma. 2001;51(2):223–8; discussion 229–30.
12. DePalma RG, Burris DG, Champion HR, Hodgson MJ. Blast injuries. N Engl J Med. 2005;352(13):1335–42.
13. Treggiari MM, Hudson LD, Martin DP, Weiss NS, Caldwell E, Rubenfeld G. Effect of acute lung injury and acute respiratory distress syndrome on outcome in critically ill trauma patients. Crit Care Med. 2004; 32(2):327–31.

14. Oppenheimer L, Craven KD, Forkert L, Wood LD. Pathophysiology of pulmonary contusion in dogs. J Appl Physiol. 1979;47(4):718–28.
15. Kulvatunyou N, Erickson L, Vijayasekaran A, Gries L, Joseph B, Friese RF, Rhee P. Randomized clinical trial of pigtail catheter versus chest tube in injured patients with uncomplicated traumatic pneumothorax. Br J Surg. 2014;101(2):17–22.
16. Morales CH, Mejía C, Roldan LA, Saldarriaga MF, Duque AF. Negative pleural suction in thoracic trauma patients: a randomized controlled trial. J Trauma Acute Care Surg. 2014;77(2):251–5.
17. Kong VY, Oosthuizen GV, Clarke DL. What is the yield of routine chest radiography following tube thoracostomy for trauma? Injury. 2015;46(1):45–8.
18. Goodman MD, Huber NL, Johannigman JA, Pritts TA. Omission of routine chest x-ray after chest tube removal is safe in selected trauma patients. Am J Surg. 2010;199(2):199–203.
19. Palesty JA, McKelvey AA, Dudrick SJ. The efficacy of X-rays after chest tube removal. Am J Surg. 2000;179(1):13–5.
20. Wu N, Wu L, Qiu C, Yu Z, Xiang Y, Wang M, Li Y. A comparison of video-assisted thoracoscopic surgery with open thoracotomy for the management of chest trauma: a systematic review and meta-analysis. World J Surg. 2014;39(4):950–52.
21. Lin HL, Huang WY, Yang C, Chou SM, Chiang HI, Kuo LC, Chou YP. How early should VATS be performed for retained haemothorax in blunt chest trauma? Injury. 2014;45(9):1359–64.
22. Hashemzadeh S, Hashemzadeh K, Hosseinzadeh H, Maleki RA, Golzari S. Comparison thoracic epidural and intercostal block to improve ventilation parameters and reduce pain in patients with multiple rib fractures. J Cardiovasc Thorac Res. 2011;3(3):87.
23. Nirula R, Diaz Jr JJ, Trunkey DD, Mayberry JC. Rib fracture repair: indications, technical issues, and future directions. World J Surg. 2009;33(1):14–22.
24. Slobogean GP, MacPherson CA, Sun T, Pelletier ME, Hameed SM. Surgical fixation vs nonoperative management of flail chest: a meta-analysis. J Am Coll Surg. 2013;216(2):302–11.e1.
25. Leinicke JA, Elmore L, Freeman BD, Colditz GA. Operative management of rib fractures in the setting of flail chest: a systematic review and meta-analysis. Ann Surg. 2013;258(6):914–21.
26. Turut H, Ciralik H, Kilinc M, Ozbag D, Imrek SS. Effects of early administration of dexamethasone, N-acetylcysteine and aprotinin on inflammatory and oxidant-antioxidant status after lung contusion in rats. Injury. 2008.
27. Strohmaier W, Trupka A, Pfeiler C, Thurnher M, Khakpour Z, Gippner-Steppert C, Jochum M, Redl H. Bilateral lavage with diluted surfactant improves lung function after unilateral lung contusion in pigs. Crit Care Med. 2005;33(10):2286–93.
28. Raghavendran K, Davidson BA, Knight PR, Wang Z, Helinski J, Chess PR, Notter RH. Surfactant dysfunction in lung contusion with and without superimposed gastric aspiration in a rat model. Shock. 2008;30(5):508–17.

Blunt Abdominal Trauma

78

Elizabeth C. Gwinn and Pauline K. Park

Case Presentation

A 38 year old male with no significant past medical history presents as a Class 1 trauma after a motorcycle collision at 60 miles per hour. The patient was wearing a helmet and had loss of consciousness. En route to the hospital, the patient had a blood pressure of 86/40 and a heart rate of 120. EMS placed a cervical collar, inserted 2 large-bore peripheral IVs and administered 2 L of isotonic crystalloid. On arrival to emergency room, the patient has a blood pressure of 110/60 and a heart rate of 80. His Glasgow Coma Scale is 15. He complains of left-sided shoulder pain. He has bilateral equal but decreased breath sounds. His abdomen is soft and mildly tender in the left upper quadrant. He has no evidence of other injuries.

Question How should this patient be managed?

Answer Advanced Trauma Life Support (ATLS) guidelines [1]

This is a multiply injured blunt trauma patient with hypotension responsive to fluid administration. Management should proceed along ATLS guidelines. This starts with the ABCs of trauma: evaluation of the Airway with cervical spine stabilization, Breathing and Circulation with external hemorrhage control. The patient is able to talk and currently does not need an airway. Cervical spine protection is maintained. He is breathing easily. The patient has already received 2 L of crystalloid. If the patient demonstrates continued signs of bleeding, his resuscitation should continue with blood products.

The next task is to figure out if the initial hypotension reflects intra-cavitary hemorrhage. A chest x-ray, pelvis film and a focused assessment of sonography in trauma (FAST) exam should be performed [1–4].

If there is fluid on FAST exam and the patient becomes hemodynamically unstable, he should be taken to the operative room. However, as this patient is hemodynamically stable, further imaging can be performed.

Minimal fluid was seen on FAST exam in the left upper quadrant. CT imaging confirmed multiple left-sided rib fractures with underlying pulmonary contusions, left scapula fracture and grade III splenic laceration with active contrast extravasation (Fig. 78.1). Splenic angioembolization was indicated for treatment as the patient was hemodynamically stable (Fig. 78.2). Post-procedure ICU admission was indicated for serial abdominal examinations and monitoring for bleeding. His hemoglobin remained stable and his scapula fracture was managed with closed reduction and a sling. Thoracic epidural analgesia was used for pain management associated with his rib fractures. He was discharged in stable condition on hospital day 5 (Fig. 78.3).

E.C. Gwinn • P.K. Park (✉)
Acute Care Surgery, University of Michigan,
Ann Arbor, MI, USA
e-mail: parkpk@umich.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_78

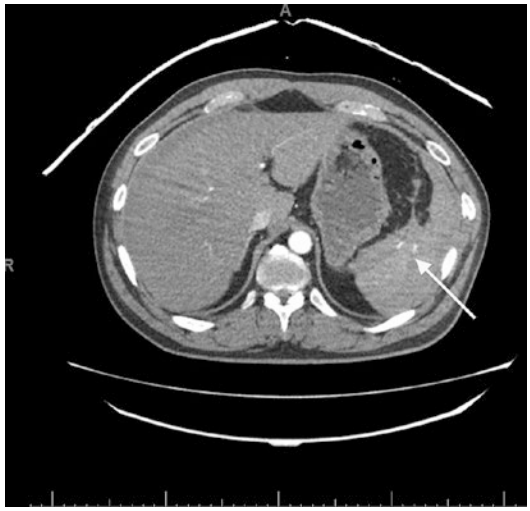


Fig. 78.1 Arrows mark site of active extravasation following splenic trauma

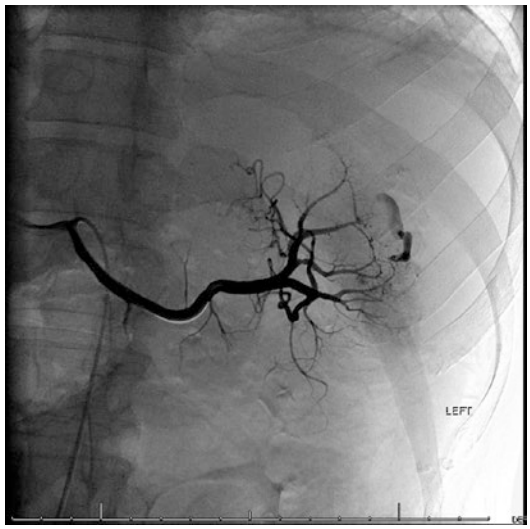


Fig. 78.2 Splenic bleeding site confirmed by angiography

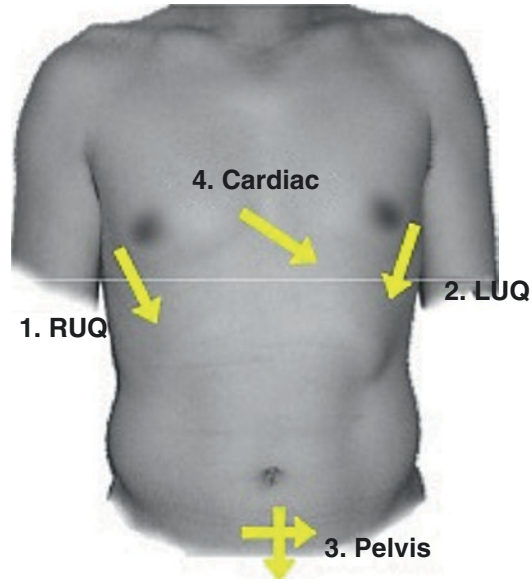


Fig. 78.3 FAST – Location of probe placement for the trauma examination (u.surgery. (2009). Focused Abdominal Sonography for Trauma [PowerPoint slides]. Retrieved from http://www.slideshare.net/u.surgery/focused-abdominal-sonography-for-trauma)

Principles of Management

Unstable Versus Stable Blunt Abdominal Trauma

The initial management of blunt intra-abdominal injuries depends crucially on whether the patient is hemodynamically stable or unstable. Trauma patients who are unstable are bleeding until proven otherwise, and prompt evaluation is indicated to determine the source of bleeding. There are 5 areas into which a trauma patient can bleed to death – the chest, the abdomen, the pelvis and retroperitoneum, the thigh and externally [1].

The location of bleeding can be determined quickly with minimal testing in the trauma bay. A chest x-ray and pelvis film will determine if a patient has a massive hemothorax or an open pelvic fracture, respectively. The FAST exam rapidly evaluates 4 areas: the pericardium, the area between liver and right kidney, the area between spleen and left kidney, and the suprapubic area, with any free fluid presumed to represent hemorrhage [1]. Alternatively, a diagnostic peritoneal aspiration (DPA) or lavage (DPL) can be used to determine if there is fluid or blood within the peritoneal cavity.

Patients with blunt injury who are hemodynamically unstable with evidence of intraperitoneal hemorrhage on FAST or DPL should be taken to the operating room for an immediate laparotomy [5–9]. Patients who are hemodynamically stable can proceed with further 3D imaging and nonoperative management. The current

Table 78.1 Spleen injury scale

Grade	Injury type	Description of injury	AIS-90
I	Hematoma	Subcapsular, <10 % surface area	2
	Laceration	Capsular tear, <1 cm parenchymal depth	2
II	Hematoma	Subcapsular, 10–50 % surface area intraparenchymal, <5 cm in diameter	2
	Laceration	Capsular tear, 1–3 cm parenchymal depth that does not involve a trabecular vessel	3
III	Hematoma	Subcapsular, >50 % surface area of expanding; ruptured subcapsular or parenchymal hematoma; intraparenchymal hematoma >5 cm or expanding	3
	Laceration	>3 cm parenchymal depth or involving trabecular vessels	3
IV	Laceration	Laceration involving segmental or hilar vessels producing major devascularization (>25 % of spleen)	4
V	Laceration	Completely shattered spleen	5
	Vascular	Hilar vascular injury which devascularizes spleen	5

management of blunt hepatic and splenic injury is selective nonoperative management (NOM) with operative management in those patients who present with hemodynamic instability or have ongoing evidence of bleeding [9–12].

Balanced Resuscitation

A tenet of trauma resuscitation is ensuring that patients have appropriate intravenous access [1]. Most patients can be managed with two large-bore (14–16 g) peripheral intravenous catheters. The type and amount of IVF that is optimal for trauma patients is constantly debated. Crystalloids are associated with improved survival in trauma patients compared to colloids [13]. Lactated Ringer's is preferred to Normal Saline because it is associated with less metabolic acidosis in the setting of massive hemorrhagic shock in animal models [14].

The Inflammation and Host Response to Injury Project defined a systolic blood pressure less than 90 mmHg and/or a heart rate greater than 130 beats per minute as indicative of shock in a traumatically injured patient [15]. ATLS guidelines also recommend the initial administration of 1–2 l of isotonic crystalloid in the resuscitation of a trauma patient [1]. For a patient that requires further resuscitation, the administration of blood products is recommended, as excessive crystalloid resuscitation has been associated with increased morbidity and length of stay in blunt trauma patients [16]. Two recent trials investigating the timing and ratio of blood product administration have shown improved mortality with the early administration of plasma [17] and better hemostasis with fewer deaths from exsanguination without adverse effects with the administration of blood, plasma and platelets in a 1:1:1 ratio [18].

Prompt hemorrhage control should be the main goal of hemorrhagic shock management, and can be accomplished through the use of external hemorrhage control, Interventional Radiology for angioembolization or a surgical procedure.

Imaging and Diagnosis

Solid organ injury after blunt abdominal trauma in stable patients is best visualized by CT scan abdomen and pelvis with IV contrast [5–8]. The severity of liver and spleen injuries can be classified according to the American Association for the Surgery of Trauma organ grading scales (Tables 78.1 and 78.2) [19]. Blunt hollow viscus injury is uncommon but should be suspected in patients with extraluminal air on 3-D imaging, frank succus or particulate material on peritoneal lavage or evolving peritonitis on serial examination.

Nonoperative Management (NOM) of Blunt Solid Organ Injury

Patients who are hemodynamically stable without peritonitis and are found to have a blunt

Table 78.2 Liver injury scale

Grade	Injury type	Description of injury	AIS-90
I	Hematoma	Subcapsular, <10 % surface area	2
	Laceration	Capsular tear, <1 cm parenchymal depth	2
II	Hematoma	Subcapsular, 10–50 % surface area intraparenchymal <10 cm in diameter	2
	Laceration	Capsular tear 1–3 parenchymal depth, <10 cm in length	2
III	Hematoma	Subcapsular, >50 % surface area of ruptured subcapsular or parenchymal hematoma; intraparenchymal hematoma >10 cm or expanding	3
	Laceration	>3 cm parenchymal depth	3
IV	Laceration	Parenchymal disruption involving 25–75 % of hepatic lobe or 1–3 Couinaud's segments	4
V	Laceration	Parenchymal disruption involving >75 % of hepatic lobe or >3 Couinaud's segments within a single lobe	5
	Vascular	Juxtahepatic venous injuries; ie, retrohepatic vena cava/central major hepatic veins	5
VI	Vascular	Hepatic avulsion	6

spleen or liver injury can undergo NOM [5–8, 10, 20]. NOM involves a period of in-hospital observation, serial abdominal examinations, serial hematocrit measurements and possibly a period of bedrest [5, 6]. NOM should be undertaken in an environment and institution where patients can be appropriately monitored, undergo serial abdominal exams and the capability to provide operative intervention is readily available. Blunt kidney injuries are, in general, also treated successfully with NOM.

Angioembolization for Blunt Solid Organ Injury

Angioembolization should be considered as an adjunct to nonoperative management of blunt splenic injury in patients with a grade 3 or higher injury, a contrast blush on CT scan, moderate hemoperitoneum on CT scan and evidence of ongoing bleeding [5, 6]. Having an institutional protocol for angioembolization has led to decreased LOS and decreased use of hospital resources [21]. The implementation of protocols for angioembolization in patients who are high risk for failure of NOM (contrast blush and grades 3–5) are associated with increased success of NOM [22, 23]. For blunt hepatic injuries, angioembolization should be considered for stable patients with contrast extravasation on CT. Early embolization in blunt hepatic injury is associated with decreased transfusion requirements and decreased need for hepatic operative intervention [24, 25]. Angioembolization can also be used as an adjunct to operative management [26–28].

Post-splenectomy Vaccinations

An initial report by King and Schumacker in 1951 documented severe infection after splenectomy in infants [29]. Since then, overwhelming post-splenectomy infection (OPSI) and mortality from it has been documented and recognized in asplenic patients from a variety of different mechanisms, including patients who have undergone a splenectomy due to trauma [30]. The CDC recommends ensuring a complete vaccination panel after splenectomy: 13-valent and 1, 2 or 3 doses of 23-valent pneumococcal vaccine depending on previous vaccination, two doses of quadrivalent meningococcal vaccination followed by a dose every 5 years, *Haemophilus Influenza* type B vaccination and evaluation for influenza, Td/Tdap [tetanus, diphtheria, pertussis), varicella, human papillomavirus, zoster and measles, mumps, rubella vaccines [31]. Shatz and colleagues found that administration of vaccinations at 2 weeks post-splenectomy were associated with the best antibody response compared to vaccination at 1, 7, or 28 days [32].

Evidence Contour

Who Should Be Managed Nonoperatively?

Previously, age greater than 55, neurologic status, high grade of injury and associated injuries were considered contraindications to NOM of blunt splenic injury. Subsequent studies have shown that NOM is feasible and safe in these populations, although patients greater than 55 years old have a higher mortality rate with blunt splenic injury despite the choice of management strategy [33, 34]. These patients had a higher mortality with failure of NOM than the younger cohort [35]. Head injury or altered mental status is also not a contraindication to NOM of either hepatic or splenic injuries [36]. A review from 2013 cautioned clinicians to be aware of factors in the literature which are associated with increased failure of NOM: age greater than 40 years old, ISS of 25 or greater, and a AAST splenic injury grade 3 or higher [37]. Most studies agree that increasing grade of injury and an increased ISS are associated with an increased rate of failed NOM, but we are still able to achieve high levels of NOM success in these patients [11, 38, 39]. Patients with multiple injuries, including multiple solid organ injuries, can be managed nonoperatively, although they do have a higher failure rate [40]. For blunt hepatic injuries, intraperitoneal contrast and hemoperitoneum in multiple quadrants are predictive of the need for operative intervention, even in hemodynamically stable patients [41].

How Should Nonoperative Management Be Accomplished?

There are no guidelines published to outline the timing and frequency of hematocrit measurements, serial abdominal examinations, length of monitoring and duration of bed rest, if at all. A retrospective cohort study of blunt solid organ injury and the timing of mobilization did not demonstrate an increase in delayed hemorrhage based on early mobilization, and led the authors to conclude that bed rest should not be a part of NOM protocols for blunt solid organ injury [42]. Centers with established protocols for NOM have decreased LOS and a low rate of NOM failure. A protocol with clear inclusion and exclusion criteria for NOM along with an outline for the frequency and duration of serial abdominal examinations, hematocrit draws and length of bed rest has led to a decrease in hospital and ICU LOS and an increase of NOM success without an increase in mortality [43–45].

Is Follow-Up Imaging Necessary?

For blunt splenic injury managed initially without angioembolization, the need for or timing of follow up imaging is not clearly documented in the literature. A Delphi consensus statement regarding blunt splenic injury found a fifty-fifty split between experts regarding the need for repeat imaging during the initial hospital admission [9]. Shapiro and colleagues found that, among their trauma population, in the absence of clinical signs and symptoms of bleeding, a repeat CT scan did not change management [46]. However, subsequent studies have suggested that repeat imaging allows for the identification and subsequent angioembolization of splenic artery pseudoaneurysm (SPA) or arterial extravasation (AE) and reduces failure of NOM. Weinberg and colleagues described a protocol of repeat CT imaging at 24–48 h in all patients except those greater than 55 with a grade I injury and demonstrated a 97 % splenic salvage rate [47]. Leeper and colleagues developed a protocol of repeat CT imaging at 48 h after a sentinel event, which was associated with a decrease in the failure of NOM from 12 % to less than 1 % [48]. They recommend early repeat imaging to improve detection of SPA and AE, which can then be managed with SAE.

Routine follow up imaging for blunt hepatic injuries should be determined by patient's signs and symptoms and does not need to be routinely done prior to discharge [49, 50]. When repeat imaging demonstrates complications, there is generally a variety of interventional or operative management strategies. Bile duct disruptions

generally present in a delayed fashion after high-grade hepatic injuries [51]. HIDA scan is almost 100 % sensitive and specific for diagnosing biliary leaks, and high output leaks can be managed with endoscopic stenting of the biliary tree [52]. Hepatic abscesses after blunt trauma are managed with antibiotics and percutaneous catheter drainage at minimum and operative intervention at maximum [53]. Hemorrhage in patients initially treated nonoperatively usually occurs early, while biliary and infectious complications occur later [54].

When Should We Initiate Venous Thromboembolism (VTE) Prophylaxis in Solid Organ Injury Patients?

Trauma patients have the highest rate of VTE among all subgroups of hospitalized patients with rates up to 40 % for deep venous thrombosis and 20 % for pulmonary embolism [55, 56]. *The Inflammation and the Host Response to Injury project* guidelines and the CHEST guidelines for VTE in the trauma patient recommends the initiation of low-molecular weight heparin (LMWH) in conjunction with mechanical prophylaxis in the absence of contraindications [55, 56]. A retrospective study by Eberle and colleagues demonstrated no increase in failure rates of NOM or blood transfusion requirements when LMWH was initiated early (within 3 days of injury) versus late in patients with blunt solid organ injury [57]. Joseph and colleagues also demonstrated that there was no difference between the early (under 48 h), intermediate (48–72 h), and late (greater then 72 h) groups in terms of operative intervention or post prophylaxis blood transfusion in patients with blunt solid organ injury [58]. The EAST Practice Management Guidelines for both blunt hepatic and splenic injury states that there is no evidence that chemical VTE prophylaxis increases bleeding complications or the failure of NOM, however there are no prospective studies defining a "safe" initiation time for LMWH following blunt solid organ injury [5, 6].

References

1. Advanced Trauma Life Support for doctors ATLS: manuals for coordinators and faculty. 9th ed. Chicago: American College of Surgeons; 2012.
2. Dolich MO, McKenney MG, Varela JE, Compton RP, McKenney KL, Cohn SM. 2,576 ultrasounds for blunt abdominal trauma. J Trauma. 2001;50(1):108–12.
3. Ollerton JE, Sugrue M, Balogh Z, D'Amours SK, Giles A, Wyllie P. Prospective study to evaluate the influence of FAST on trauma patient management. J Trauma. 2006;60(4):785–91.
4. Robert Reardon MD. Ultrasound in trauma – The FAST Exam. Focused assessment with sonography in trauma [Internet]. Ultrasound Guide for Emergency Physicians © 2008. Available from: http://www.sonoguide.com/FAST.html.
5. Stassen NA, Bhullar I, Cheng JD, Crandall ML, Friese RS, Guillamondegui OD, et al. Selective nonoperative management of blunt splenic injury: an Eastern Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg. 2012;73(5 Suppl 4):S294–300.
6. Stassen NA, Bhullar I, Cheng JD, Crandall M, Friese R, Guillamondegui O, et al. Nonoperative management of blunt hepatic injury: an Eastern Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg. 2012;73(5 Suppl 4):S288–93.
7. Moore FA, Davis JW, Moore Jr EE, Cocanour CS, West MA, McIntyre Jr RC. Western Trauma Association (WTA) critical decisions in trauma: management of adult blunt splenic trauma. J Trauma. 2008;65(5):1007–11.
8. Kozar RA, Feliciano DV, Moore EE, Moore FA, Cocanour CS, West MA, et al. Western Trauma Association/critical decisions in trauma: operative management of adult blunt hepatic trauma. J Trauma. 2011;71(1):1–5.
9. Olthof DC, van der Vlies CH, Joosse P, van Delden OM, Jurkovich GJ, Goslings JC, et al. Consensus strategies for the nonoperative management of patients with blunt splenic injury: a Delphi study. J Trauma Acute Care Surg. 2013;74(6):1567–74.
10. Cogbill TH, Moore EE, Jurkovich GJ, Morris JA, Mucha Jr P, Shackford SR, et al. Nonoperative management of blunt splenic trauma: a multicenter experience. J Trauma. 1989;29(10):1312–7.
11. Haan JM, Bochicchio GV, Kramer N, Scalea TM. Nonoperative management of blunt splenic injury: a 5-year experience. J Trauma Injury Infect Crit Care. 2005;58(3):492–8.
12. Hurtuk M, Reed 2nd RL, Esposito TJ, Davis KA, Luchette FA. Trauma surgeons practice what they preach: the NTDB story on solid organ injury management. J Trauma. 2006;61(2):243–54; discussion 54–5.
13. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, et al. A comparison of albumin and saline

for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350(22):2247–56.
14. Todd SR, Malinoski D, Muller PJ, Schreiber MA. Lactated Ringer's is superior to normal saline in the resuscitation of uncontrolled hemorrhagic shock. J Trauma. 2007;62(3):636–9.
15. Moore FA, McKinley BA, Moore EE, Nathens AB, West M, Shapiro MB, et al. Inflammation and the Host Response to Injury, a large-scale collaborative project: patient-oriented research core--standard operating procedures for clinical care. III. Guidelines for shock resuscitation. J Trauma. 2006;61(1):82–9.
16. Kasotakis G, Sideris A, Yang Y, de Moya M, Alam H, King DR, et al. Aggressive early crystalloid resuscitation adversely affects outcomes in adult blunt trauma patients: an analysis of the Glue Grant database. J Trauma Acute Care Surg. 2013;74(5):1215–21; discussion 21–2.
17. Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, Alarcon LH, Bai Y, Brasel KJ, Bulger EM, Cotton BA, Matijevic N, Muskat P, Myers JG, Phelan HA, White CE, Zhang J, Rahbar MH, PROMMTT Study Group. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg. 2013;148(2):127–36.
18. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015;313(5):471–82.
19. Tinkoff G, Esposito TJ, Reed J, Kilgo P, Fildes J, Pasquale M, et al. American Association for the Surgery of Trauma Organ Injury Scale I: spleen, liver, and kidney, validation based on the National Trauma Data Bank. J Am Coll Surg. 2008;207(5):646–55.
20. Croce MA, Fabian TC, Menke PG, Waddle-Smith L, Minard G, Kudsk KA, et al. Nonoperative management of blunt hepatic trauma is the treatment of choice for hemodynamically stable patients. Results of a prospective trial. Ann Surg. 1995;221(6):744–53; discussion 53–5.
21. Haan J, Ilahi ON, Kramer M, Scalea TM, Myers J. Protocol-driven nonoperative management in patients with blunt splenic trauma and minimal associated injury decreases length of stay. J Trauma. 2003;55(2):317–21; discussion 21–2.
22. Bhullar IS, Frykberg ER, Tepas 3rd JJ, Siragusa D, Loper T, Kerwin AJ. At first blush: absence of computed tomography contrast extravasation in Grade IV or V adult blunt splenic trauma should not preclude angioembolization. J Trauma Acute Care Surg. 2013;74(1):105–11; discussion 11–2.
23. Miller PR, Chang MC, Hoth JJ, Mowery NT, Hildreth AN, Martin RS, et al. Prospective trial of angiography and embolization for all grade III to V blunt splenic injuries: nonoperative management success rate is significantly improved. J Am Coll Surg. 2014;218(4):644–8.
24. Wahl WL, Ahrns KS, Brandt MM, Franklin GA, Taheri PA. The need for early angiographic embolization in blunt liver injuries. J Trauma. 2002;52(6):1097–101.
25. Mohr AM, Lavery RF, Barone A, Bahramipour P, Magnotti LJ, Osband AJ, et al. Angiographic embolization for liver injuries: low mortality, high morbidity. J Trauma. 2003;55(6):1077–81; discussion 81–2.
26. Asensio JA, Roldan G, Petrone P, Rojo E, Tillou A, Kuncir E, et al. Operative management and outcomes in 103 AAST-OIS grades IV and V complex hepatic injuries: trauma surgeons still need to operate, but angioembolization helps. J Trauma. 2003;54(4):647–53; discussion 53–4.
27. Letoublon C, Morra I, Chen Y, Monnin V, Voirin D, Arvieux C. Hepatic arterial embolization in the management of blunt hepatic trauma: indications and complications. J Trauma. 2011;70(5):1032–6; discussion 6–7.
28. Misselbeck TS, Teicher EJ, Cipolle MD, Pasquale MD, Shah KT, Dangleben DA, et al. Hepatic angioembolization in trauma patients: indications and complications. J Trauma. 2009;67(4):769–73.
29. King H, Shumacker Jr HB. Splenic studies. I.Susceptibility to infection after splenectomy performed in infancy. Ann Surg. 1952;136(2):239–42.
30. Krivit W. Overwhelming postsplenectomy infection. Am J Hematol. 1977;2(2):193–201.
31. Services USDoHaH. Recommended Adult Immunization Schedule – United States – 2016. http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-schedule.pdf.
32. Shatz DV, Romero-Steiner S, Elie CM, Holder PF, Carlone GM. Antibody responses in postsplenectomy trauma patients receiving the 23-valent pneumococcal polysaccharide vaccine at 14 versus 28 days postoperatively. J Trauma. 2002;53(6):1037–42.
33. Nix JA, Costanza M, Daley BJ, Powell MA, Enderson BL. Outcome of the current management of splenic injuries. J Trauma. 2001;50(5):835–42.
34. Cocanour CS, Moore FA, Ware DN, Marvin RG, Duke JH. Age should not be a consideration for nonoperative management of blunt splenic injury. J Trauma. 2000;48(4):606–10; discussion 10–2.
35. Harbrecht BG, Peitzman AB, Rivera L, Heil B, Croce M, Morris Jr JA, et al. Contribution of age and gender to outcome of blunt splenic injury in adults: multicenter study of the eastern association for the surgery of trauma. J Trauma. 2001;51(5):887–95.
36. Archer LP, Rogers FB, Shackford SR. Selective nonoperative management of liver and spleen injuries in neurologically impaired adult patients. Arch Surg. 1996;131(3):309–15.
37. Olthof DC, Joosse P, van der Vlies CH, de Haan RJ, Goslings JC. Prognostic factors for failure of nonoperative management in adults with blunt splenic injury: a systematic review. J Trauma Acute Care Surg. 2013;74(2):546–57.
38. McIntyre LK, Schiff M, Jurkovich GJ. Failure of nonoperative management of splenic injuries: causes and

consequences. Arch Surg. 2005;140(6):563–8; discussion 8–9.
39. Jeremitsky E, Smith RS, Ong AW. Starting the clock: defining nonoperative management of blunt splenic injury by time. Am J Surg. 2013;205(3):298–301.
40. Malhotra AK, Latifi R, Fabian TC, Ivatury RR, Dhage S, Bee TK, et al. Multiplicity of solid organ injury: influence on management and outcomes after blunt abdominal trauma. J Trauma. 2003;54(5):925–9.
41. Fang JF, Wong YC, Lin BC, Hsu YP, Chen MF. The CT risk factors for the need of operative treatment in initially hemodynamically stable patients after blunt hepatic trauma. J Trauma. 2006;61(3):547–53; discussion 53–4.
42. London JA, Parry L, Galante J, Battistella F. Safety of early mobilization of patients with blunt solid organ injuries. Arch Surg. 2008;143(10):972–6; discussion 7.
43. Brasel KJ, Weigelt JA, Christians KK, Somberg LB. The value of process measures in evaluating an evidence-based guideline. Surgery. 2003;134(4):605–10.
44. McCray VW, Davis JW, Lemaster D, Parks SN. Observation for nonoperative management of the spleen: how long is long enough? J Trauma. 2008; 65(6):1354–8.
45. Izu BS, Ryan M, Markert RJ, Ekeh AP, McCarthy MC. Impact of splenic injury guidelines on hospital stay and charges in patients with isolated splenic injury. Surgery. 2009;146(4):787–91; discussion 91–3.
46. Shapiro MJ, Krausz C, Durham RM, Mazuski JE. Overuse of splenic scoring and computed tomographic scans. J Trauma. 1999;47(4):651–8.
47. Weinberg JA, Magnotti LJ, Croce MA, Edwards NM, Fabian TC. The utility of serial computed tomography imaging of blunt splenic injury: still worth a second look? J Trauma. 2007;62(5):1143–7; discussion 7–8.
48. Leeper WR, Leeper TJ, Ouellette D, Moffat B, Sivakumaran T, Charyk-Stewart T, et al. Delayed hemorrhagic complications in the nonoperative management of blunt splenic trauma: early screening leads to a decrease in failure rate. J Trauma Acute Care Surg. 2014;76(6):1349–53.
49. Cuff RF, Cogbill TH, Lambert PJ. Nonoperative management of blunt liver trauma: the value of follow-up abdominal computed tomography scans. Am Surg. 2000;66(4):332–6.
50. Cox JC, Fabian TC, Maish GO, Bee TK, Pritchard FE, Russ SE, et al. Routine follow-up imaging is unnecessary in the management of blunt hepatic injury. J Trauma Injury Infect Crit Care. 2005;1175–80.
51. Christmas AB, Wilson AK, Manning B, Franklin GA, Miller FB, Richardson JD, et al. Selective management of blunt hepatic injuries including nonoperative management is a safe and effective strategy. Surgery. 2005;138(4):606–10; discussion 10–1.
52. Wahl WL, Brandt MM, Hemmila MR, Arbabi S. Diagnosis and management of bile leaks after blunt liver injury. Surgery. 2005;138(4):742–7; discussion 7–8.
53. Claridge JA, Young JS. A successful multimodality strategy for management of liver injuries. Am Surg. 2000;66(10):920–5; discussion 5–6.
54. Kozar RA, Moore FA, Cothren CC, Moore EE, Sena M, Bulger EM, et al. Risk factors for hepatic morbidity following nonoperative management: multicenter study. Arch Surg. 2006;141(5):451–8; discussion 8–9.
55. Cuschieri J, Freeman B, O'Keefe G, Harbrecht BG, Bankey P, Johnson JL, et al. Inflammation and the host response to injury a large-scale collaborative project: patient-oriented research core standard operating procedure for clinical care X. Guidelines for venous thromboembolism prophylaxis in the trauma patient. J Trauma. 2008;65(4):944–50.
56. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl): e227S–77.
57. Eberle BM, Schnuriger B, Inaba K, Cestero R, Kobayashi L, Barmparas G, et al. Thromboembolic prophylaxis with low-molecular-weight heparin in patients with blunt solid abdominal organ injuries undergoing nonoperative management: current practice and outcomes. J Trauma. 2011;70(1):141–6; discussion 7.
58. Joseph B, Pandit V, Harrison C, Lubin D, Kulvatunyou N, Zangbar B, et al. Early thromboembolic prophylaxis in patients with blunt solid abdominal organ injuries undergoing nonoperative management: is it safe? Am J Surg. 2015;209(1):194–8.

Abdominal Sepsis and Complicated Intraabdominal Infections

79

Sara A. Buckman and John E. Mazuski

Case Presentation

A 52 year-old male with a history of hypertension, obesity, and depression presented to the emergency room with increasing abdominal pain. In the emergency room he was found to be hypotensive, with a blood pressure of 80/40, tachycardic to 120, and febrile with a temperature of 38.9 F. He had evidence of peritonitis on physical exam. His abdomen was rigid and distended, with diffuse tenderness to palpation and involuntary guarding in his lower abdomen. Abnormal laboratory exam values included a white blood cell count of 18,000 cells/mm^3, and a serum creatinine concentration of 1.4 mg/dL. Cross-sectional imaging of his abdomen and pelvis is shown below (Fig. 79.1).

Question How should this patient's intraabdominal condition be managed?

Answer This patient has an intraabdominal infection from a perforated transverse colon, as demonstrated by his physical exam findings, laboratory values and cross-sectional imaging. The patient should receive early goal-directed resuscitation based on the Surviving Sepsis Guidelines in the emergency room or the ICU [1]. Broad spectrum antibiotics to cover gram negative *Enterobacteriaceae* and enteric anaerobes should be initiated. He should be taken to the operating room expeditiously for exploratory laparotomy while undergoing ongoing resuscitation.

Principles of Management

Diagnosis

Intraabdominal infections should be suspected in patients with evidence of gastrointestinal symptoms such as nausea, anorexia, vomiting, diarrhea and abdominal pain. They may or may not have signs of inflammation including fever, tachycardia or tachypnea [2]. A history including recent abdominal operations may help identify the source of the intraabdominal infection. Physical exam is important but may be nonspecific in patients that are obtunded, intubated, sedated, elderly or on immunosuppressive therapy [2, 3]. Patients presenting with signs of peritonitis including abdominal rigidity, guarding and rebound tenderness should be considered for urgent laparotomy [4].

S.A. Buckman • J.E. Mazuski (✉)
Department of Surgery, Washington University in Saint Louis School of Medicine, Saint Louis, MO, USA
e-mail: mazuskij@wudosis.wustl.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_79

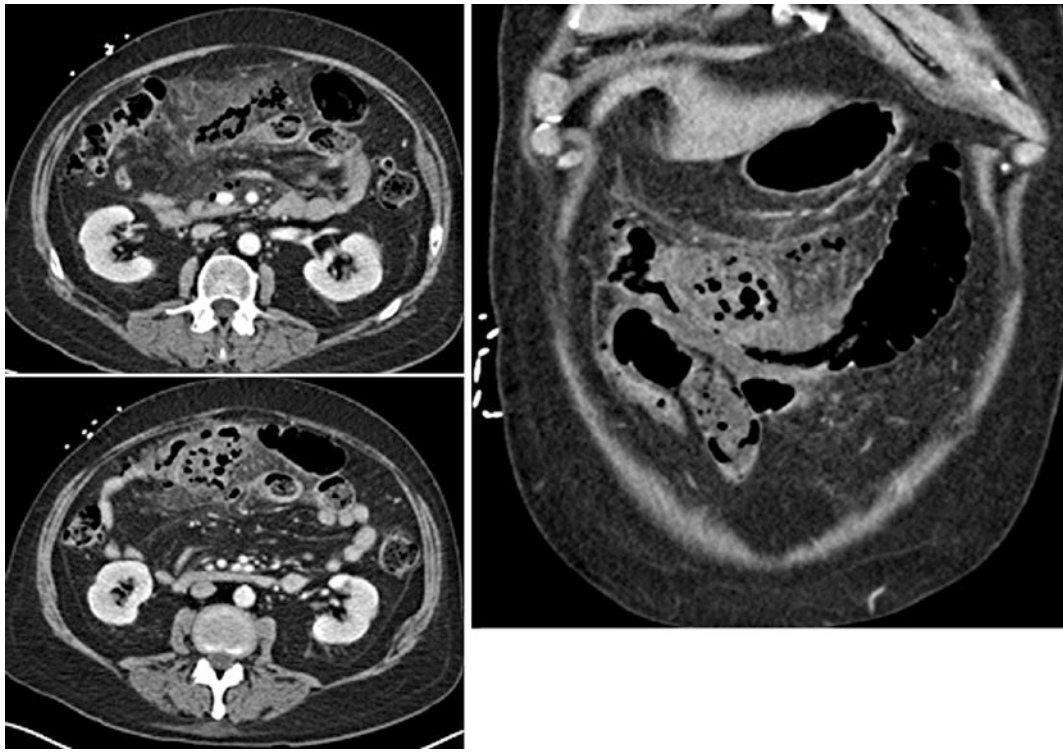


Fig. 79.1 Perforated diverticulitis in the transverse colon

Basic laboratory tests including complete blood count, and electrolytes should be obtained. If a hepatobiliary or pancreatic source is suspected, liver enzymes and an amylase and lipase can be added [5]. Additional labs including those measuring end organ perfusion such as lactate and mixed venous oxygen saturation should be obtained if the patient is suspected of having severe sepsis or septic shock [1]. Further imaging studies should be obtained in patients with suspected intraabdominal infection, if feasible. Cross-sectional imaging with computed tomography (CT scan, Fig. 79.2) with intravenous contrast is the diagnostic modality of choice for most cases of intraabdominal infection such as appendicitis, diverticulitis and colitis. Enteral contrast is useful to differentiate the viscera for potentially pathologic fluid collections such as abscesses or anastomotic leaks. However, the utility of enteral contrast in the emergency situation is somewhat debatable, and should be utilized according to local protocols. Intravenous contrast permits optimal visualization of infectious processes, inflammation, ischemia, hemorrhage and solid organ assessment [3]. If a biliary source is suspected, ultrasound is the preferred imaging modality [6].

Resuscitation

Patients with intraabdominal infections become volume depleted by several mechanisms including decreased oral intake, increased sensible losses due to vomiting and diarrhea and increased insensible losses due to third spacing, fever and tachypnea [7]. Fluid resuscitation should begin as soon as a diagnosis of sepsis is suspected, following the Surviving Sepsis Campaign guidelines [1, 2, 7].

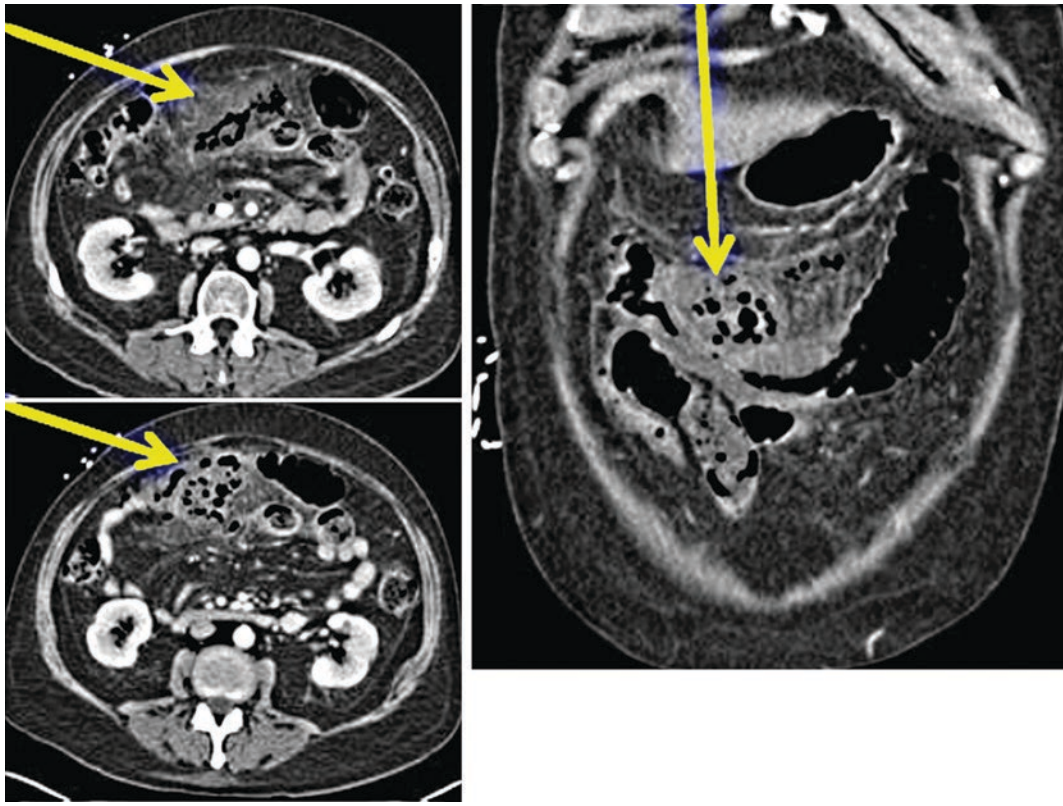


Fig. 79.2 CT scan imaging demonstrating inflammatory changes around the mid-transverse colon with extraluminal air and fluid in this area, consistent with a perforation of the transverse colon and peritonitis

To Be Completed Within 3 h of Time of Presentation[1]

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 ml/kg crystalloid for hypotension or lactate ≥4 mmol/L

To Be Completed Within 6 h of Time of Presentation

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mmHg
6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mmHg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion with either
   - Repeat focused exam (after initial fluid resuscitation) including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings
   - Or two of the following:

[1] "Time of presentation" is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.

- Measure CVP
- Measure ScvO2
- Bedside cardiovascular ultrasound
- Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

7. Re-measure lactate if initial lactate elevated.

[From: http://www.survivingsepsis.org/SiteCollectionDocuments/SSC_Bundle.pdf]

In patients with severe infections and ongoing contamination, resuscitation may not be successful until source control is achieved, and a necessary source control procedure should not be unduly delayed in an effort to achieve all goals of resuscitation. However, resuscitation efforts should continue intraoperatively and postoperatively in such patients.

Source Control

Source control is one of the fundamental treatment strategies for intraabdominal sepsis. The goal is to remove the infected fluid, debride infected solid tissue, remove infected devices or foreign bodies and gain control of ongoing enteric drainage by correcting anatomic derangements [8]. It may be obtained by either operative intervention or percutaneous drainage, depending on size and location of the infection and acuity of the patient [4].

Operative intervention, either open or laparoscopic, should be performed in patients with peritonitis, suspected bowel ischemia or necrosis, evidence of uncontrolled, on-going contamination or those who have failed percutaneous drainage [2, 4, 7, 9]. In unstable patients, damage control surgery may be performed. This concept has been adopted from its use in trauma patients. It is a multistep process, with the first stage being evacuation of infected material and control of gross contamination, including wide drainage [2, 7, 10, 11]. The abdomen is temporarily closed and the patient then undergoes further resuscitation to restore more normal physiologic functions. Once resuscitation is complete, re-laparotomy for definitive source control and reconstruction can be performed. If the patient's condition worsens during this resuscitative phase, earlier relaparotomy should be considered. The abdomen can be definitively closed once there are no concerns for ongoing ischemia, necrosis or infection [7].

Although planned re-laparotomy benefits some patients with severe peritonitis, its use should be restricted to patients who are physiologically unstable, are at risk for development of an abdominal compartment syndrome with early fascial closure, have a concern for ongoing bowel ischemia, or who will need further source control procedures to gain adequate control of the infection. The routine use of planned re-laparotomy for all patients with severe secondary peritonitis was not shown to be beneficial in a prospective randomized controlled trial [12]. Rather, on-demand re-laparotomy, employed in just those patients who manifested signs of ongoing infection, was found to be associated with shorter ICU and hospital lengths of stay and reduced expenses compared to planned re-laparotomy in all patients.

Percutaneous drainage is often the initial treatment for intraabdominal abscesses, as it as effective as surgical drainage and is less invasive, with resultant lower morbidity and mortality rates [2, 7, 13, 14]. It is also useful for patients who are poor surgical candidates [7]. It is also possible that it can serve as a temporizing measure in severely-ill patients, such as those with infected pancreatic necrosis.

Anti-Infective Therapy

Antimicrobial therapy should be started within one hour in patients with septic shock due to complicated intra-abdominal infections, and as soon as feasible in other patients who do not have evidence of hemodynamic or organ compromise [1, 2]. Therapy should be selected according to

Table 79.1 Agents and regimens that may be used for the initial empiric treatment of extra-biliary complicated intra-abdominal infection (community-acquired infection in adults)

Regimen	Mild to moderate severity: perforated or abscessed appendicitis and other infections of mild-to-moderate severity	High risk or severity: severe physiologic disturbance, advanced age, or immunocompromised state
Single agent	Cefoxitin, ertapenem, moxifloxacin, tigecycline, and ticarcillin-clavulanic acid	Imipenem-cilastatin, meropenem, doripenem, and piperacillin-tazobactam
Combination	Cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin, each in combination with metronidazole[a]	Cefepime, ceftazidime, ciprofloxacin, or levofloxacin, each in combination with metronidazole[a]

From Solomkin et al. [2]

[a]Because of increasing resistance of *Escherichia coli* to fluoroquinolones, local population susceptibility profiles and, if available, isolate susceptibility should be reviewed

the whether or not the patient as a community-acquired or a health-care-associated infection (Tables 79.1 and 79.2). It should also be based on local microbiologic data.

Empiric antibiotics should cover gram-negative aerobic and facultative bacilli and enteric anaerobic bacteria. Options include meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam or ceftazidime or cefepime in combination with metronidazole. If resistant gram negative bacteria are anticipated in a patient with a health-care-associated infection, an aminoglycoside or another gram negative agent may be required, based on local antibiograms. Empiric coverage for enterococci using ampicillin or vancomycin is recommended for patients with health care-associated intra-abdominal infection, if the selected regimen does not already provide such coverage. Vancomycin is also recommended for the treatment of the occasional intraabdominal infection suspected or proven to be due to methicillin-resistant Staphylococcus aureus [2]. If *Candida sp* is grown from intraabdominal cultures or is strongly suspected to be a component of the infection, antifungal therapy is recommended. An echinocandin is recommended for critically ill patients or those with fluconazole-resistant *Candida* species.

Evidence Contour

There are several areas of management of intraabdominal infections that are continuing to evolve.

Laparoscopic Peritoneal Lavage

Patients with purulent (Hinchey III) or feculent (Hinchey IV) peritonitis from perforated diverticulitis typically were treated with a sigmoid resection and colostomy (Table 79.3). There is new data that laparoscopic peritoneal lavage, in combination with antibiotics, may be a safe and effective alternative with low morbidity and mortality, and spares the patient a stoma [15]. A recent systematic review [16] of data from 871 patients who underwent laparoscopic peritoneal lavage for perforated diverticulitis reported that laparotomy conversion was required in only 1 % of patients with Hinchey stage III vs. 45 % in patients with Hinchey stage IV diverticulitis. Ongoing RCTs will better define the role of this technique in patients with complicated diverticulitis.

Minimally Invasive Approaches to Infected Pancreatic Necrosis

Pancreatic parenchymal and/or peripancreatic tissue necrosis (necrotizing pancreatitis) leads to additional morbidity and mortality in patients with acute pancreatitis. Approximately one third of patients with necrotizing pancreatitis will develop infected necrosis, and this also increases mortality due to sepsis and multisystem organ failure [17]. Patients with infected pancreatic necrosis often require intervention, and open surgical debridement, or necrosectomy, has been the traditional treatment. This invasive approach is associated with a high rate of complications and

Table 79.2 Recommendations for empiric antimicrobial therapy for health care – associated complicated intra-abdominal infection

	Regimen				
Organisms seen in health care-associated infection at the local institute	Carbapenem[a]	Piperacillin-tazobactam	Ceftazidime or cefepime, each with metronidazole	Aminoglycoside	Vancomycin
<20 % resistant *Pseudomonas aeruginosa*, ESBL-producing Enterobacteriaceae, *Acinetobacter*, or other MDR GNB	Recommended	Recommended	Recommended	Not recommended	Not recommended
ESBL-producing Enterobacteriaceae	Recommended	Recommended	Not recommended	Recommended	Not recommended
P. aeruginosa >20 % resistant to ceftazidime	Recommended	Recommended	Not recommended	Recommended	Not recommended
MRSA	Not recommended	Not recommended	Not recommended	Not recommended	Recommended

From Solomkin et al. [2]

ESBL extended-spectrum b-lactamase, *GNB* gram-negative bacilli, *MDR* multidrug resistant, *MRSA* methicillin-resistant *Staphylococcus aureus*

"Recommended" indicates that the listed agent or class is recommended for empiric use, before culture and susceptibility data are available, at institutions that encounter these isolates from other health care–associated infections. These may be unit- or hospital-specific

[a]Imipenem-cilastatin, meropenem, or doripenem

Table 79.3 Modified Hinchey classification for diverticulitis

Stage I	Pericolic abscess confined by the mesentery of the colon
Stage IIa	Distant pelvic abscess amenable to percutaneous drainage
Stage IIb	Complex abscess associated with or without fistula
Stage III	Generalized purulent peritonitis
Stage IV	Fecal peritonitis

death [18]. It is now acceptable for patients with infected pancreatic necrosis to initially be treated conservatively with antibiotics and supportive care. Patients who have clinical decompensation should then undergo more invasive treatments [19]. Alternative interventions including minimally invasive techniques such as percutaneous drainage, endoscopic drainage and minimally invasive retroperitoneal necrosectomy are being used more frequently when patients fail maximal medical therapy. In a large multicenter trial, the "step-up" approach (source control by percutaneous drainage followed by minimally invasive necrosectomy if the patient fails to improve) as compared to patients randomized to open necrosectomy, reduced the rate of the composite endpoint of major complications or death, decreased total costs and improved health care resource utilization [18]. Further data regarding the timing, cost and long term outcomes of these procedures still need to be obtained.

Procalcitonin

Procalcitonin is a biomarker that can be used as an adjunctive diagnostic tool for discriminating infection as the cause of fever or sepsis in critically ill patients [20]. In intraabdominal infections there are different cutoff levels and assays, leading to discordant findings. In addition, it is a nonspecific marker of bacterial infection and does not provide a source of sepsis. Further studies need to be performed with improved assay accuracy and standardization for it to be a useful adjunct in the treatment of intraabdominal infections [21].

References

1. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580–637.
2. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(2):133–64.
3. Crandall M, West MA. Evaluation of the abdomen in the critically ill patient: opening the black box. Curr Opin Crit Care. 2006;12(4):333–9.
4. Pieracci FM, Barie PS. Management of severe sepsis of abdominal origin. Scand J Surg. 2007;96(3):184–96.
5. Shirah GR, O'Neill PJ. Intra-abdominal infections. Surg Clin North Am. 2014;94(6):1319–33.
6. Noone TC, Semelka RC, Chaney DM, Reinhold C. Abdominal imaging studies: comparison of diagnostic accuracies resulting from ultrasound, computed tomography, and magnetic resonance imaging in the same individual. Magn Reson Imaging. 2004;22(1):19–24.
7. Lopez N, Kobayashi L, Coimbra R. A comprehensive review of abdominal infections. World J Emerg Surg. 2011;6:7.
8. Marshall JC, Maier RV, Jimenez M, Dellinger EP. Source control in the management of severe sepsis and septic shock: an evidence-based review. Crit Care Med. 2004;32(11 Suppl):S513–26.
9. Koperna T, Schulz F. Relaparotomy in peritonitis: prognosis and treatment of patients with persisting intraabdominal infection. World J Surg. 2000;24(1):32–7.
10. Waibel BH, Rotondo MF. Damage control for intra-abdominal sepsis. Surg Clin North Am. 2012;92(2):243–57.
11. Weber DG, Bendinelli C, Balogh ZJ. Damage control surgery for abdominal emergencies. Br J Surg. 2014;101(1):e109–18.
12. van Ruler O, Mahler CW, Boer KR, Reuland EA, Gooszen HG, Opmeer BC, et al. Comparison of on-demand vs planned relaparotomy strategy in patients with severe peritonitis; a randomized trial. JAMA. 2007;298(8):865–72.
13. Akinci D, Akhan O, Ozmen MN, Karabulut N, Ozkan O, Cil BE, et al. Percutaneous drainage of 300 intraperitoneal abscesses with long-term follow up. Cardiovasc Intervent Radiol. 2005;28(6):744–50.
14. Hemming A, Davis NL, Robins RE. Surgical versus percutaneous drainage of intra-abdominal abscesses. Am J Surg. 1991;161(5):593–5.
15. Toorenvliet BR, Swank H, Schoones JW, Hamming JF, Bemelman WA. Laparoscopic peritoneal lavage for perforated colonic diverticulitis: a systematic review. Colorectal Dis. 2010;12(9):862–7.

16. Cirocchi R, Trastulli S, Vettoretto N, Milani D, Cavaliere D, Renzi C, et al. Laparoscopic peritoneal lavage: a definitive treatment for diverticular peritonitis or a "bridge" to elective laparoscopic sigmoidectomy?: a systematic review. Medicine (Baltimore). 2015;94(1), e334.
17. Petrov MS, Shanbhag S, Chakraborty M, Phillips AR, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology. 2010;139(3):813–20.
18. van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med. 2010;362(16):1491–502.
19. Whitehead DA, Gardner TB. Evidence-based management of necrotizing pancreatitis. Curr Treat Options Gastroenterol. 2014;12(3):322–32.
20. O'Grady NP, Barie PS, Bartlett JG, Bleck T, Carroll K, Kalil AC, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. Crit Care Med. 2008;36(4):1330–49.
21. Watkins RR, Lemonovich TL. Serum procalcitonin in the diagnosis and management of intra-abdominal infections. Expert Rev Anti Infect Ther. 2012;10(2): 197–205.

Intestinal Obstruction: Small and Large Bowel

80

Joseph A. Posluszny Jr. and Fred A. Luchette

Case Presentation

A 76 year old male presented to the emergency room with 3 days of intermittent lower abdominal pain and nausea. He had not vomited but had not eaten or drank liquids in the past day. He was passing gas until 24 h ago. He has a past medical history of coronary artery disease requiring a coronary artery bypass, atrial fibrillation for which he was anticoagulated with warfarin and benign prostatic hypertrophy. He has a past surgical history of a right colectomy with primary anastomosis 10 years ago. He has never had a bowel obstruction. He was afebrile, heart rate was 85 and blood pressure was 130/80. On exam, he was not in any distress, his mucous membranes were dry, his abdomen was slightly distended with a midline scar and minimally tender. There was no evidence of ventral or inguinal hernias. Lab studies revealed a WBC count of 10, no bands, hematocrit of 50, creatinine of 1.3 (baseline 1.0), lactate 1.2 and INR of 2.0. A CT scan of the abdomen and pelvis (below) showed dilated, fluid filled small bowel with a tapering in the RLQ, a stool filled colon and was without pneumatosis, portal venous gas or significant mesenteric edema (Fig. 80.1).

Question How do you manage a patient with a small bowel obstruction?

Answer Since this patient had no signs of intestinal ischemia (fever, leukocytosis, tachycardia unresponsive to fluids, peritonitis), intestinal perforation (no pneumoperitoneum), a closed loop obstruction or hernia defect and had a history of prior abdominal surgery suggesting an etiology of adhesive small bowel disease, he was initially managed non-operatively with IVF resuscitation, NPO and nasogastric (NG) tube decompression. The NG tube initially evacuated 1.5 L of gastric and bilious fluid.

Over the course of the next 3 days, the NG tube output remained elevated but was more gastric in nature. He remained with only minimal abdominal tenderness but he was not passing gas per rectum or having bowel movements. As a result, laparotomy with lysis of adhesions was recommended for treatment of persistent small bowel obstruction and performed on hospital day 4. During the laparotomy, a combination of extensive moderate and dense adhesions was identified that twisted the bowel in a partially

J.A. Posluszny Jr. (✉)
Surgery, Loyola University Stritch School of Medicine, Maywood, IL, USA

Edward Hines Jr. Veterans Administration Medical Center, Maywood, IL, USA
e-mail: joseph.posluszny@lumc.edu

F.A. Luchette
Department of Surgery, Stritch School of Medicine, Loyola University of Chicago, Chicago, IL, USA

VA Affairs, Surgical Service Lines, Edward Hines Jr., Veterans Administration Medical Center, Maywood, IL, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_80

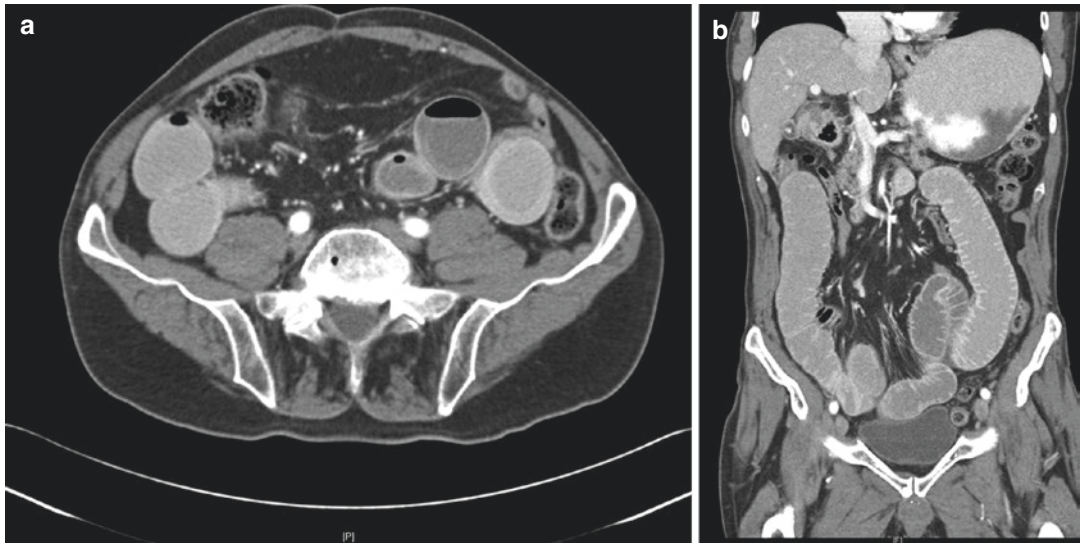


Fig. 80.1 CT scan images of small bowel obstruction. (**a**) Representative axial section of CT scan of the abdomen and pelvis with PO and IV contrast showing dilated, fluid filled small bowel. (**b**) Representative coronal section of CT scan for the same patient showing dilated, fluid filled small bowel consistent with small bowel obstruction

obstructed, but not ischemic, fashion. After lysis of adhesions, the small bowel was decompressed and its contents evacuated into the NG tube. The NG tube was removed on post-op day (POD) #1, diet started on POD#2, gas passed and bowel movement occurred on POD#3, and he was discharged to home on POD#5 once INR was therapeutic.

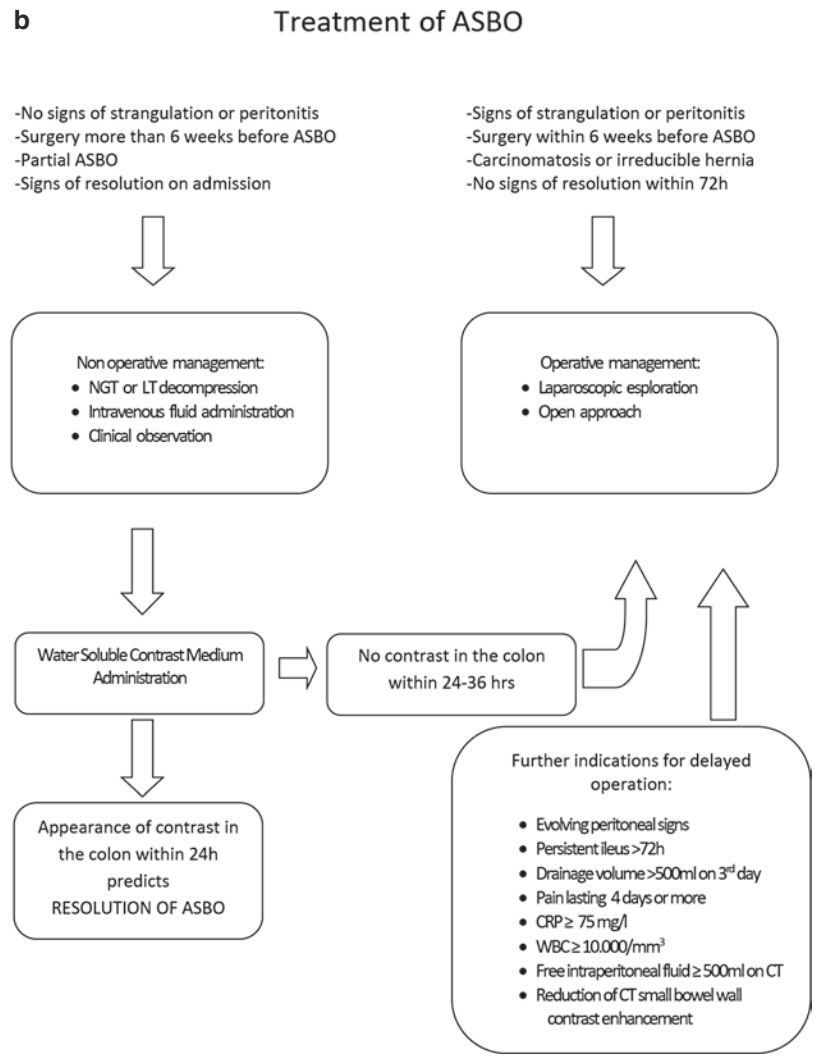
Standard Approach to Management

Small bowel obstruction (SBO) is most commonly due to adhesive disease, Crohn's disease, tumors or hernias [1]. The primary concern with SBO is bowel ischemia or necrosis. Since there are no physical exam findings, lab values or imaging tests that will confirm the presence of ischemia, it is a combination of these signs, symptoms and tests that must be evaluated to determine if laparotomy is necessary. As stated in the scenario above, leukocytosis, tachycardia unresponsive to fluid administration, acidosis and peritonitis are all concerning for intestinal ischemia [2, 3]. The presence of pneumoperitoneum on imaging signifies bowel necrosis and perforation and should prompt emergent exploration. A closed loop obstruction on CT imaging with focal peritonitis should prompt exploration as well. With the increased frequency of CT use, concerning imaging findings include portal venous gas, mesenteric edema and inflammatory stranding that may favor earlier rather than later exploration.

Patients with SBO more commonly present without an absolute indication for exploration (Fig. 80.2). In patients without immediate concern for bowel ischemia, bowel rest with NPO and NG tube decompression, fluid resuscitation, correction of electrolyte abnormalities and minimization of narcotics are trialed for a few days. Approximately 75 % of SBOs treated non-operatively will not require surgery during that admission [4]. Any evidence of worsened pain, tachycardia, acidosis or leukocytosis necessitates laparotomy. Otherwise, patients can be successfully managed non-operatively for 3–4 days until signs and symptoms of SBO resolve with restoration of intestinal function. Predictive models for the need for laparotomy using presenting symptoms, physical exam, lab values and CT imaging findings have been described but are not yet fully validated [5, 6].

Fig. 80.2 Evidence-based Algorithm for Diagnosis (**a**) and Treatment (**b**) of Adhesive SBO (ASBO) (From DiSaverio et al. [7]. © Di Saverio et al.; licensee BioMed Central Ltd. 2013 [Creative Commons Attribution License])

Fig. 80.2 (continued)



Evidence Contour

Timing of Operating for SBO

An old surgical dogma was to never let the sun set or sun rise on a SBO. This is no longer the case. However, when to operate for a SBO continues to challenge surgeons. For patients with prior abdominal surgery who most likely have an adhesive SBO, a trial of 48–72 h of non-operative management is successful in relieving the obstruction in ~75 % of cases [7].

Recently, the use of water-soluble contrast via NG tube or by mouth has been used to both treat and assess patients with adhesive small bowel disease [8, 9]. Essentially, patients are given a small volume of water-soluble contrast and serial abdominal plain films are obtained. Passage of contrast into the colon within 24 h of administration indicates resolution of the SBO and trials of a diet can ensue. This technique leads to shorter lengths of stay [10].

Management Differences Between Small and Large Bowel Obstruction

The case in this chapter illustrates the course of care for SBO. SBO is much more common than

large bowel obstruction (LBO). Although the presenting symptoms may be similar, the diagnostic work up and treatment are different. Adhesive disease does not normally lead to large bowel obstruction with the greatest concern with large bowel obstruction being cancer.

LBO is an emergency condition that requires early identification and intervention. Complete LBO, closed loop obstruction, evidence of colonic ischemia and volvulus commonly require emergency surgical intervention.

Other unique causes of large bowel obstruction include cecal or sigmoid volvulus, colonic ileus (Ogilvie's syndrome), toxic megacolon with *Clostridium difficile* infection, diverticular stricture and fecal impaction [11]. The clinical scenario for each of these potential causes of large bowel obstruction should help in delineating the cause and initial management steps. Also unique to patients with large bowel obstruction, especially in those who are debilitated and cannot undergo surgery [12] or who need to have an acute obstruction temporized [13], is the use of colonic stents to bypass an area of stricture or obstruction [14].

Management of Acute Small Bowel Obstruction in a Patient with No Prior Abdominal Surgery or Pathology

Less than 10 % of cases of small bowel obstruction will be present in patients without prior abdominal surgery. With the known etiologies of small bowel obstruction being adhesions, inflammatory bowel disease and hernias, an SBO in a virgin abdomen presents a clinical conundrum. Unfortunately, there is little evidence available to guide clinical management. Currently, unless the patient clearly has evidence of an infectious or inflammatory etiology for the obstruction, exploration with either laparoscopy or laparotomy is recommended given the concern for an underlying malignancy. However, recent data would suggest that up to 75 % of laparotomies for SBO in a virgin abdomen are due to adhesions [15]. Regardless, until more data is available, we recommend either laparoscopy or laparotomy for the evaluation of SBO in patients with a virgin abdomen and no obvious infectious or inflammatory source.

CT Imaging Findings Indicative of a Need for Exploration

With the frequent use of CT scanning in the emergency room for patients with abdominal pain or complaints consistent with bowel obstruction, the use of characteristic CT findings to predict the need for laparotomy has developed. An often identified CT finding for SBO is the "transition zone" or "transition point". While interesting for preoperative planning, a transition zone does not necessitate laparotomy nor does it decrease the chance that the SBO will resolve with non-operative management [16, 17].

Pneumatosis intestinalis identified on CT without either physical exam or laboratory values consistent with intestinal ischemia is no longer an absolute indication for exploratory laparotomy [18, 19]. Imaging findings that should contribute to a more heightened need for exploration include closed loop obstruction, mesenteric edema and reduced enhancement of mesenteric veins [20, 21]. In line with the theme of this chapter, one test alone, and in this case CT imaging, should not be used to determine the need for surgical intervention for a SBO. Rather, it is a combination of physical exam, clinical scenario, lab values and imaging that most appropriately identify those patients who need emergent laparotomy versus those who can trial a course of non-operative management.

References

1. Miller G, Boman J, Shrier I, Gordon PH. Etiology of small bowel obstruction. Am J Surg. 2000;180(1):33–6.
2. Maung AA, Johnson DC, Piper GL, Barbosa RR, Rowell SE, Bokhari F, Collins JN, Gordon JR, Ra JH, Kerwin AJ, Eastern Association for the Surgery of Trauma. Evaluation and management of small-bowel obstruction: an Eastern Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg. 2012;73(5 Suppl 4):S362–9.
3. Landercasper J, Cogbill TH, Merry WH, Stolee RT, Strutt PJ. Long-term outcome after hospitalization for

small-bowel obstruction. Arch Surg. 1993;128(7):765–70; discussion 770–1.
4. Foster NM, McGory ML, Zingmond DS, Ko CY. Small bowel obstruction: a population-based appraisal. J Am Coll Surg. 2006;203(2):170–6. Epub 2006 Jul 7.
5. Zielinski MD, Eiken PW, Bannon MP, Heller SF, Lohse CM, Huebner M, Sarr MG. Small bowel obstruction-who needs an operation? A multivariate prediction model. World J Surg. 2010;34(5):910–9.
6. O'Leary EA, Desale SY, Yi WS, Fujita KA, Hynes CF, Chandra SK, Sava JA. Letting the sun set on small bowel obstruction: can a simple risk score tell us when nonoperative care is inappropriate? Am Surg. 2014;80(6):572–9.
7. Di Saverio S, Coccolini F, Galati M, Smerieri N, Biffl WL, Ansaloni L, Tugnoli G, Velmahos GC, Sartelli M, Bendinelli C, Fraga GP, Kelly MD, Moore FA, Mandalà V, Mandalà S, Masetti M, Jovine E, Pinna AD, Peitzman AB, Leppaniemi A, Sugarbaker PH, Goor HV, Moore EE, Jeekel J, Catena F. Bologna guidelines for diagnosis and management of adhesive small bowel obstruction (ASBO): 2013 update of the evidence-based guidelines from the world society of emergency surgery ASBO working group. World J Emerg Surg. 2013;8(1):42.
8. Goussous N, Eiken PW, Bannon MP, Zielinski MD. Enhancement of a small bowel obstruction model using the gastrografin® challenge test. J Gastrointest Surg. 2013;17(1):110–6; discussion p. 116–7.
9. Di Saverio S, Catena F, Ansaloni L, Gavioli M, Valentino M, Pinna AD. Water-soluble contrast medium (gastrografin) value in adhesive small intestine obstruction (ASIO): a prospective, randomized, controlled, clinical trial. World J Surg. 2008;32(10):2293–304.
10. Loftus T, Moore F, VanZant E, Bala T, Brakenridge S, Croft C, Lottenberg L, Richards W, Mozingo D, Atteberry L, Mohr A, Jordan J. A protocol for the management of adhesive small bowel obstruction. J Trauma Acute Care Surg. 2015;78(1):13–9; discussion 19–21.
11. Sawai RS. Management of colonic obstruction: a review. Clin Colon Rectal Surg. 2012;25(4):200–3.
12. van den Berg MW, Ledeboer M, Dijkgraaf MG, Fockens P, Ter Borg F, van Hooft JE. Long-term results of palliative stent placement for acute malignant colonic obstruction. Surg Endosc. 2014; 29(6):1580–5.
13. van Hooft JE, van Halsema EE, Vanbiervliet G, Beets-Tan RG, DeWitt JM, Donnellan F, Dumonceau JM, Glynne-Jones RG, Hassan C, Jiménez-Perez J, Meisner S, Muthusamy VR, Parker MC, Regimbeau JM, Sabbagh C, Sagar J, Tanis PJ, Vandervoort J, Webster GJ, Manes G, Barthet MA, Repici A. Self-expandable metal stents for obstructing colonic and extracolonic cancer: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2014;46(11):990–1053.
14. Boyle DJ, Thorn C, Saini A, Elton C, Atkin GK, Mitchell IC, Lotzof K, Marcus A, Mathur P. Predictive factors for successful colonic stenting in acute large-bowel obstruction: a 15-year cohort analysis. Dis Colon Rectum. 2015;58(3):358–62.
15. Beardsley C, Furtado R, Mosse C, Gananadha S, Fergusson J, Jeans P, Beenen E. Small bowel obstruction in the virgin abdomen: the need for a mandatory laparotomy explored. Am J Surg. 2014;208(2):243–8.
16. Colon MJ, Telem DA, Wong D, Divino CM. The relevance of transition zones on computed tomography in the management of small bowel obstruction. Surgery. 2010;147(3):373–7.
17. Jones K, Mangram AJ, Lebron RA, Nadalo L, Dunn E. Can a computed tomography scoring system predict the need for surgery in small-bowel obstruction? Am J Surg. 2007;194(6):780–3; discussion 783–4.
18. Duron VP, Rutigliano S, Machan JT, Dupuy DE, Mazzaglia PJ. Computed tomographic diagnosis of pneumatosis intestinalis: clinical measures predictive of the need for surgical intervention. Arch Surg. 2011;146(5):506–10.
19. Morris MS, Gee AC, Cho SD, Limbaugh K, Underwood S, Ham B, Schreiber MA. Management and outcome of pneumatosis intestinalis. Am J Surg. 2008;195(5):679–82; discussion 682–3.
20. Nakashima K, Ishimaru H, Fujimoto T, Mizowaki T, Mitarai K, Nakashima K, Matsuoka Y, Uetani M. Diagnostic performance of CT findings for bowel ischemia and necrosis in closed-loop small-bowel obstruction. Abdom Imaging. 2014;40(5):1097–103.
21. Zalcman M, Sy M, Donckier V, Closset J, Gansbeke DV. Helical CT signs in the diagnosis of intestinal ischemia in small-bowel obstruction. AJR Am J Roentgenol. 2000;175(6):1601–7.

Management of Acute Compartment Syndrome

81

Ming-Jim Yang, Frederick A. Moore, and Janeen R. Jordan

Case Presentation

An 82 year old female with a history of liver cirrhosis secondary to hemochromatosis, coronary artery disease, CHF, and COPD was brought through the ED after a head-on motor vehicle collision. She complained initially of abdominal pain and right leg pain. Physical exam revealed a tender and distended abdomen in the right and left upper quadrants and a visible right lower leg deformity with a 4 cm wound over the lateral aspect of her thigh with exposed bone. A FAST exam was positive in the right upper quadrant. CT scan revealed a grade 2 liver laceration with active contrast extravasation (Fig. 81.1), a grade 3 splenic laceration, and a distal comminuted femur fracture (Fig. 81.2). An emergent hepatic and splenic artery embolization was performed followed by application of an tibial traction pin.

Postoperatively, she continued to have episodes of hypotension requiring continued resuscitation. Within the first 24 h, the patient received 6 L of crystalloid, 3U pRBC, and 500 cc of albumin. Despite the resuscitation, the patient developed acute renal failure requiring CVVH.

M.-J. Yang • F.A. Moore • J.R. Jordan (✉)
Department of Surgery, University of Florida, Gainesville, FL, USA
e-mail: jordanja29@gmail.com

Question What differential diagnoses should be considered?

Answer Abdominal and extremity compartment syndrome.

Old age, trauma and high volume resuscitation are risk factors for abdominal and extremity compartment syndromes. Since clinical exam is unreliable in predicting intra-abdominal pressures (IAP), surveillance of intra-abdominal pressures using transbladder pressure monitoring should be implemented. The fractured leg should be assessed with serial exams and intracompartmental pressure measurements. For this patient, transbladder pressures were monitored every 4 h.

Postinjury day 3, she presented with poor oxygenation while still on mechanical ventilation with peak pressures of 41. IAP was found to be 29. She was taken emergently to the operating room for a decompressive laparotomy. Her open abdomen was managed using a damage control technique employing a negative pressure therapy dressing. She continued to experience hypotensive episodes requiring cystalloid boluses.

On post-decompression day 2, her nurse noted increased swelling of her right lower extremity. On physical exam, passive movement of the leg seemed to cause her "agitation" that would not improve with normal doses of pain medication. Intracompartmental pressures in her right anterior compartment showed an absolute value of 40 mmHg with a diastolic blood pressure of 57 mmHg $(\Delta P = 17)$. An emergent 4

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_81

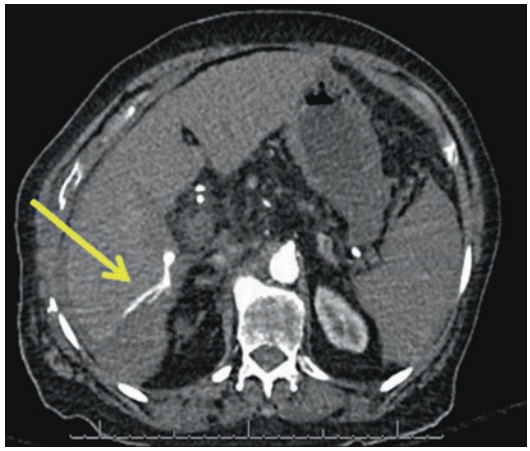


Fig. 81.1 CT Scan abdomen, Grade 2 liver laceration with active contrast extravasation

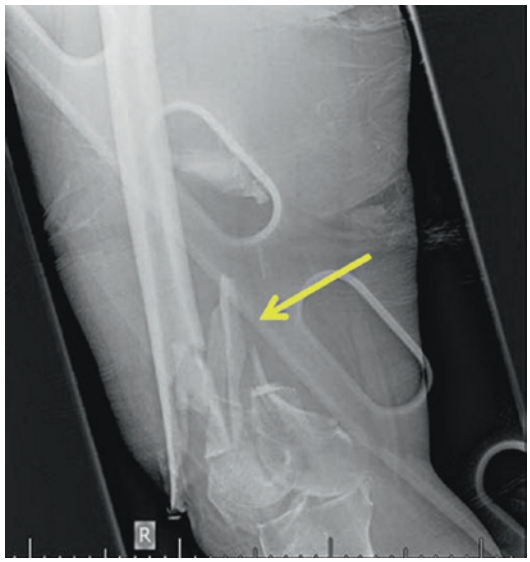


Fig. 81.2 Extremity radiograph with distal communited femur fracture

compartment fasciotomy was performed at the bedside. Muscle swelling without muscle necrosis was noted at the completion of the fasciotomy. Her fasciotomy wounds were initially managed with wet-to-dry gauze wraps with normal saline but were changed to a negative pressure therapy (NPT) dressing after 48 h. Her subsequent hospital course was notable only for a temporary abdominal coverage with a prosthetic mesh on postinjury day 10, followed by skin grafting on postinjury day 14. Delayed primary closure of her fasciotomy wound was achieved after 5 days of negative pressure therapy.

Principles of Management

Diagnosis

Compartment syndrome is a state of decreased tissue perfusion in a specific body compartment due to increased intracompartmental pressures from either interstitial edema, or increased intracompartmental contents or fluid. Early diagnosis is the key to successful management. Clinical exam alone has been shown to be inadequate for diagnosis of an acute compartment syndrome [1, 2]. Surveillance with a combination of serial clinical exams and intra-compartmental pressure monitoring is the most efficient approach to diagnosis in both the abdomen and extremity [3, 4].

Abdomen

Abdominal surgery, fluid resuscitation >3500 ml/24 h, ileus, pulmonary, renal, or liver dysfunction, hypothermia, acidosis, anemia, oliguria, and elevated GAP CO_2 (gastric mucosal CO_2 minus end-tidal CO_2 tension) have been identified as risk factors for abdominal compartment syndrome in three prospective trials [5–7]. Patients with at least 2 risk factors should be surveyed with intra-abdominal pressure measurments taken via transbladder catheter. The measurements should be taken by instilling 25 cc of normal saline through the catheter and connecting the catheter to a pressure monitor. The patient should be supine and the monitor should be zeroed at the midaxillary line at the iliac crest. Patients sometimes require sedation and neuromuscular blockade to obtain an accurate intra-abdominal pressure reading via urinary catheter, as activity and abdominal muscle tensing will falsely elevate bladder pressures.

Organ dysfunction has been detected with IAPs as low as 10–15 mmHg [8]. The World Society of the Abdominal Compartment Syndrome (WSACS) has defined intra-abdominal hypertension (IAH) as a pathological state where

Table 81.1 Intra-abdominal hypertension grading scale

Grade	IAP (mmHg)
1	12–15
2	16–20
3	21–25
4	25 +

Adapted from Malbrain et al. [8]

the IAP is persistently greater than 12 mmHg. The spectrum of IAH is broken into 4 categories of increasing severity (Table 81.1).

Abdominal compartment syndrome is defined as an abdominal compartment pressure of greater than 20 mmHg (class 3 or greater) that is associated with new organ dysfunction [8]. Common organ dysfunction associated with abdominal compartment syndrome include respiratory (high peak and plateau airway pressures, hypercarbia and hypoxemia) and renal (oliguria, increasing serum creatinine, acute kidney injury) dysfunction.

Extremity

Risk factors for extremity compartment syndrome can be separated into fracture vs. non-fracture factors. Fracture-related risk factors include tibial diaphyseal fractures, soft tissue injury, crush injury and distal radial fractures [9]. Non-fracture risk factors include older age, greater number of comorbidities, presence of a coagulopathy such as hemophilia A or warfarin therapy, an increased base deficit, lactate and pRBC transfusion [10, 11]. Patients with at least two risk factors should undergo surveillance via serial clinical exams and intracompartmental pressure monitoring.

Clinical presentation of acute extremity compartment syndrome is most notably characterized by pain out of proportion to exam and pain with passive stretch [4]. Paresthesias and paralysis are late signs. These clinical signs have a sensitivity of 14–16 % but a specificity of 97 % [2]. Intracompartmental pressures can be obtained via commercial monitoring devices or an arterial blood pressure assembly. The threshold for diagnosing an acute compartment syndrome is a dynamic threshold termed ΔP. It is defined as the difference between the diastolic blood pressure and the intracompartmental pressure. A threshold of less than 30 mmHg has generally been accepted as an indication for fasciotomy [12]. The sensitivity and specificity of continuous compartmental monitoring with a ΔP of less than 30 is 94 and 98 %, respectively [12].

Decompression

Definitive treatment of compartment syndrome involves surgical decompression of the compartment.

Abdomen

The gold standard for treatment of acute abdominal compartment syndrome is a decompressive laparotomy. Laparotomy is associated with a decrease in intra-abdominal pressure with improvement in cardiac, pulmonary and renal indices Despite these improvements, mortality still remains high at 46 % [13]. Temporizing measures have been developed to decrease intra-abdominal pressure in hopes of preventing an abdominal compartment syndrome such as sedation, supine positioning, and neuromuscular blockade [3]. Etiologies due to increased luminal or abdominal fluid collections could benefit from evacuation through nasogastric/orogastric suctioning and/or drainage of the fluid collections [3]. These measures should be implemented early before the development ofACS [3].

Extremity

Upon diagnosis of acute extremity compartment syndrome, emergent fasciotomy to release the compartment should be performed. The one exception is when there is suspicion that the compartment syndrome may have been ongoing for greater than 24 h. In a retrospective review of 336 combat veterans, delayed fasciotomy was associated with greater rates of muscle excision (25 vs. 11 %), amputation (31 vs. 15 %) and mortality (19 vs. 5 %) [14]. These results supported the findings of Finkelstein et al who described the clinical course in 5 patients who underwent delayed fasciotomy after 35 h of acute extremity compartment syndrome [15]. One patient died

from multi-organ failure and septicemia, and the remaining four patients required amputations to treat refractory infections, multi-organ failure and sepsis. They speculated that after 24 h most of the tissues in the leg had died and by exposing that dead tissue to the open air, it provided a substrate for bacterial infection [15]. Thus, after 24 h, patients suffering from acute compartment syndrome, should probably be considered for amputation rather than fasciotomy.

Wound Management

Once the compartment is released, it should remain open until the acute compartment syndrome has resolved. The patient then has an open wound that will require closure. Negative pressure therapy has been shown to help with wound closure in both the abdomen and extremity.

Abdomen

The WSACS has recommended negative pressure therapy (NPT) to help manage the open abdomen [3]. NPT has been shown to decrease bowel wall edema, remove cytokines, and reduce the incidence of intra-abdominal abscesses [16]. In their review of the literature, the WSACS showed that NPT significantly decreased mortality by 298 deaths per 1000 patients and increased primary closure by 350 per 1000 patients [3]. One potential complication of NPT is an entero-atmospheric fistula (EAF). With NPT, EAF incidence ranges in the literature from 2 to 20%, as compared to the rate of EAF formation with planned ventral hernia repair, 5–9% [17, 18]. As per the WSACS analysis, the calculated relative risk of EAF with NPT is 3.57 [3]. Following NPT, delayed primary closure should be attempted; but if that is unable to be achieved, a prosthetic mesh can be sewn in place, followed by skin grafting. The resulting ventral hernia can then be repaired electively after 6–12 months [19].

Extremity

Delayed primary closure is the goal for all fasciotomy wounds. If a fasciotomy cannot be closed primarily, a skin graft may be necessary for coverage. Negative pressure therapy has been studied as an adjunct to attain delayed primary closure. Zannis et al. retrospectively compared 458 patients who underwent fasciotomy in a 10-year period. They looked at rates of primary closure between NPT use and regular dressing changes and found that NPT use was associated with a greater percentage of primary closure as compared to traditional dressings changes (78.8 vs. 50.8%). Additionally, the fasciotomy wounds closed in fewer days with NPT use (7.1 vs. 9.6 days forprimary closure; 8.5 vs. 11.5 for secondary intention) [20].

Evidence Contour

Compartment syndrome is still being actively studied, and new management strategies for all aspects of acute compartment syndrome are still being discussed.

Abdomen

Abdominal Perfusion Pressure

Abdominal perfusion pressure has been suggested as a preferable means of diagnosing compartment syndrome over absolute pressure alone. Abdominal perfusion pressure is defined as the difference between the mean arterial pressure (MAP) and the IAP. In a retrospective study by Cheatham et al., they examined 149 patients with IAH or ACS who underwent IAP monitoring in a 25 month period [21]. Using ROC curve analysis, they found that APP as defined above was a better predictor of patient survival than either MAP or IAP alone.

Fluid Management

The WSACS has suggested that a damage – control resuscitation (DCR) protocol, ie. permissive hypotension, limited crystalloids and increased FFP:RBC ratio, may be beneficial during the initial resuscitation. This is supported by a prospective series of 141 trauma patients by Cotton et al who looked at providing blood products early in exsanguinating trauma. They found a decreased incidence of abdominal compartment syndrome and increased survival [22]. This was

subsequently supported by another retrospective series of 390 patients who either received DCR or not [23]. Both studies found that giving a greater FFP:RBC ratio earlier in a patient's resuscitation significantly reduces the amount of crystalloid administered and the incidence of ACS [22, 23]. Both studies are criticized for their use of historical controls and relatively small sample sizes. The WSACS has also recommended implementation of a fluid management protocol for at-risk patients to achieve an even or negative fluid balance once resuscitation is completed [3]. Currently, many ICU's use a combination of diuresis, albumin and continuous renal replacement therapies (CRRT) to achieve that balance. These modalities have not been studied specifically in the context of their effects on IAP though. A Belgium study is currently examining the effects of CRRT on intra-abdominal pressure.

Percutaneous Drainage

Percutaneous drainage has been studied as a possible alternative means of decompressing the abdomen in order to avoid the complications of decompressive laparotomy such as lateralization of the fascia, EAF and non-closure of the abdomen. The evidence for this practice lies mainly in case reports in burn patients and secondary ACS where there is a buildup of intraperitoneal fluid from massive resuscitation. A case control study of 62 patients by Cheatham et al comparing percutaneous drainage vs. open decompression for all etiologies showed that percutaneous drainage was not inferior to open decompression in regards to hospital stay (40 vs. 49, P = 0.4) and mortality (58 vs. 39 %, P = 0.2). They did see a non-statistically significant trend in recurrent ACS with percutaneous drainage (64 vs 48 %; $P = 0.39$) [24]. Several ongoing trials are looking at percutaneous drainage in the setting of acute pancreatitis, severe sepsis and managing IAH.

Extremity

Infared Spectroscopy

Near – infared spectroscopy (NIS) is an optical technique that measures the oxygenated state of hemoglobin within a tissue. It has been proposed as more direct means of assessing tissue perfusion in the context of extremity compartment syndrome. There are no clinical studies to support the use of near – infared spectroscopy in diagnosing an acute extremity compartment syndrome at this time, but an animal model of extremity compartment syndrome has shown a strong correlation between compartment pressures and spectroscopy readings [25]. There are currently 9 ongoing clinical trials at different stages of completion that are looking at near-infared spectroscopy as a diagnostic tool for extremity compartment syndrome.

Dermotraction

Split thickness skin grafts (STSG) are the gold standard for fasciotomy closure if delayed primary closure cannot be achieved. STSGs create a second wound, can cause pain at the donor site, cause numbness at the graft site, and is associated with weakness in the underlying muscle due to the lack of fascia [26]. For these reasons, many surgeons have explored other means of achieving delayed primary closure. Using either sutures or a commercial device, the concept is to apply gradual mechanical traction to the fascia over time to achieve closure. Most dermatotraction techniques are based on the "shoelace" technique [27] where vessel loops are criss-crossed from both sides of the wound and then stapled to the skin edge. The vessels are tightened every 48 h until closure is achieved. The evidence behind this technique and the devices are all reported in small case series ranging from 2 to 56 patients [26]. Larger comparative studies will have to be performed to assess non-inferiority of this technique with negative pressure therapy.

References

1. Kirkpatrick AW, Brenneman FD, McLean RF, Rapanos T, Boulanger BR. Is clinical examination an accurate indicator of raised intra-abdominal pressure in critically injured patients? Can J Surg. 2000;43:207–11.
2. Ulmer T. The clinical diagnosis of compartment syndrome of the lower leg: are clinical findings predictive of the disorder? J Orthop Trauma. 2002;16:572–7.

3. Kirkpatrick AW, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 2013;39:1190–206.
4. Garner MR, Taylor SA, Gausden E, Lyden JP. Compartment syndrome: diagnosis, management, and unique concerns in the twenty-first century. HSS J. 2014;10:143–52.
5. Balogh Z, et al. Both primary and secondary abdominal compartment syndrome can be predicted early and are harbingers of multiple organ failure. J Trauma. 2003;54:848–59; discussion 859–61.
6. Malbrain ML, et al. Prevalence of intra-abdominal hypertension in critically ill patients: a multicentre epidemiological study. Intensive Care Med. 2004; 30:822–9.
7. Malbrain ML, et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. Crit Care Med. 2005;33:315–22.
8. Malbrain ML, et al. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. I Definitions. Intensive Care Med. 2006;32:1722–32.
9. McQueen MM, Gaston P, Court-Brown CM. Acute compartment syndrome. who is at risk? J Bone Joint Surg Br. 2000;82:200–3.
10. Hope MJ, McQueen MM. Acute compartment syndrome in the absence of fracture. J Orthop Trauma. 2004;18:220–4.
11. Kosir R, et al. Acute lower extremity compartment syndrome (ALECS) screening protocol in critically ill trauma patients. J Trauma. 2007;63:268–75.
12. McQueen MM, Duckworth AD, Aitken SA, Court-Brown CM. The estimated sensitivity and specificity of compartment pressure monitoring for acute compartment syndrome. J Bone Joint Surg Am. 2013;95:673–7.
13. De Waele J, et al. Abdominal decompression for abdominal compartment syndrome in critically ill patients: a retrospective study. Acta Clin Belg. 2010;65:399–403.
14. Ritenour AE, et al. Complications after fasciotomy revision and delayed compartment release in combat patients. J Trauma. 2008;64:S153–161; discussion S161–152.
15. Finkelstein JA, Hunter GA, Hu RW. Lower limb compartment syndrome: course after delayed fasciotomy. J Trauma. 1996;40:342–4.
16. Batacchi S, et al. Vacuum-assisted closure device enhances recovery of critically ill patients following emergency surgical procedures. Crit Care. 2009; 13:R194.
17. Bee TK, et al. Temporary abdominal closure techniques: a prospective randomized trial comparing polyglactin 910 mesh and vacuum-assisted closure. J Trauma. 2008;65:337–42; discussion 342–34.
18. Dubose JJ, Lundy JB. Enterocutaneous fistulas in the setting of trauma and critical illness. Clin Colon Rectal Surg. 2010;23:182–9.
19. Fabian TC, et al. Planned ventral hernia. Staged management for acute abdominal wall defects. Ann Surg. 1994;219:643–50; discussion 651–43.
20. Zannis J, et al. Comparison of fasciotomy wound closures using traditional dressing changes and the vacuum-assisted closure device. Ann Plast Surg. 2009;62:407–9.
21. Cheatham ML, White MW, Sagraves SG, Johnson JL, Block EF. Abdominal perfusion pressure: a superior parameter in the assessment of intra-abdominal hypertension. J Trauma. 2000;49:621–6; discussion 626–7.
22. Cotton BA, et al. Damage control hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization. J Trauma. 2008;64:1177–82; discussion 1182–73.
23. Cotton BA, et al. Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. Ann Surg. 2011;254:598–605.
24. Cheatham ML, Safcsak K. Percutaneous catheter decompression in the treatment of elevated intraabdominal pressure. Chest. 2011;140:1428–35.
25. Cathcart CC, Shuler MS, Freedman BA, Reno LR, Budsberg SC. Correlation of near-infrared spectroscopy and direct pressure monitoring in an acute porcine compartmental syndrome model. J Orthop Trauma. 2014;28:365–9.
26. Kakagia D. How to close a limb fasciotomy wound: an overview of current techniques. Int J Low Extrem Wounds. 2014.
27. Kakagia D, et al. Wound closure of leg fasciotomy: comparison of vacuum-assisted closure versus shoelace technique. A randomised study. Injury. 2014; 45:890–3.

82 Extracorporeal Membrane Oxygenation (ECMO) and Extracorporeal CO_2 Removal ($ECCO_2R$)

Eric T. Chang and Lena M. Napolitano

Case Presentation

A 34 year old male presented to the outside hospital with a 2 day history of shortness of breath, chest pain, and syncope while walking. He had yellow sputum, a saturation of 85 % on room air, and a RLL infiltrate on CXR (Fig. 82.1). Blood cultures were negative. He was started on levofloxacin and only required 2 L of O_2 via nasal cannula. The next day, he had worsening shortness of breath and rapidly increasing oxygen requirements. He was intubated and started on vancomycin and piperacillin/tazobactam. CT showed bilateral lower lobe consolidation and enlarged mediastinal lymph nodes. His ABG with FiO_2 1.0 and PEEP 18 cm H_2O was 7.45/44/65. He was transferred to a quaternary care center. Oseltamivir and azithromycin were added. Influenza A PCR test returned positive. Neuromuscular blockade, recruitment maneuvers, proning, and inhaled nitric oxide as rescue strategies for severe hypoxemia improved his oxygenation initially, but PaO_2 then worsened to 45 and CXR demonstrated worsening bilateral infiltrates (Fig. 82.2). He also developed hypotension requiring multiple vasopressors and CRRT was initiated for acute anuric kidney injury.

Question What intervention would you consider next?

Answer Extracorporeal membrane oxygenation (ECMO) evaluation

This patient has severe ARDS (paO_2/FiO_2 ratio < 100) [1] and was initiated on lung protective ventilation measures per the ARDSnet

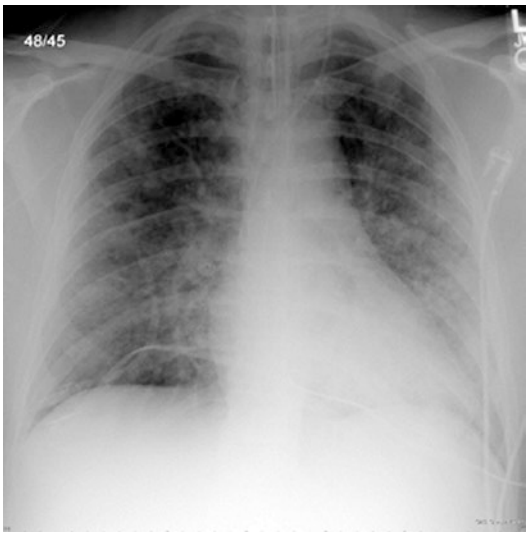


Fig. 82.1 Admission Chest Radiograph

E.T. Chang (✉)
General Surgery, University of Michigan,
Ann Arbor, MI, USA
e-mail: ericjang@med.umich.edu

L.M. Napolitano
Department of Surgery, Division of Acute Care Surgery, Trauma and Surgical Critical Care,
University of Michigan Health System,
Ann Arbor, MI, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_82

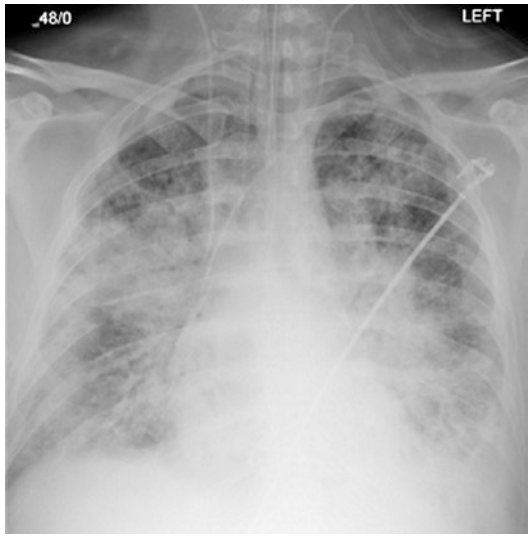


Fig. 82.2 Hospital day 2 Chest Radiograph

strategy [2]. With the development of severe hypoxemia, appropriate rescue strategies were implemented (proning, neuromuscular blockade, recruitment maneuvers, and inhaled nitric oxide). When severe refractory hypoxemia developed, he was evaluated for ECMO. A bicaval dual lumen ECMO cannula was placed via the right internal jugular vein under serial X-ray guidance [3] (Figs. 82.3 and 82.4).

A heparin bolus (100 u/kg IV) was administered and a 31 French bicaval dual-lumen cannula was advanced into position with the tip in the subdiaphragmatic, perihepatic inferior vena cava (Figs. 82.3, 82.4, and 82.5). Venovenous ECMO was initiated with a sweep of 2 L/min on a single oxygenator and a blood flow rate of 4 L/min on the centrifugal pump. His ABG on these settings were 7.38/42/75. Continuous heparin

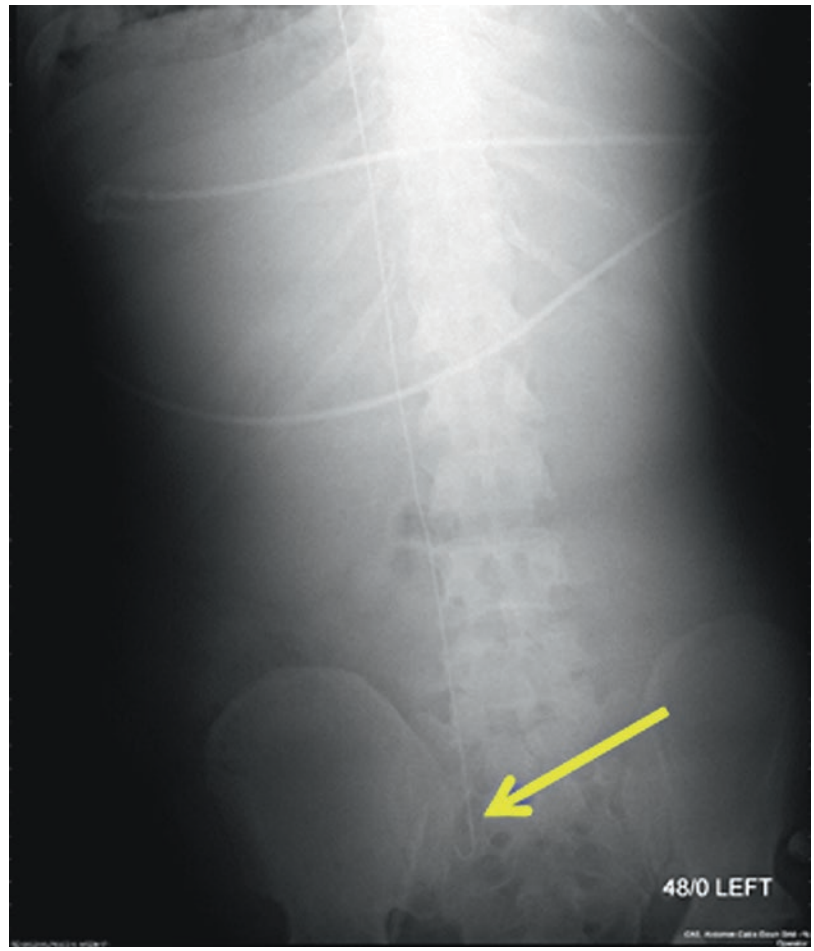


Fig. 82.3 Guidewire from right IJ to right iliac vein

infusion was initiated for systemic anticoagulation. FiO_2 was weaned to 50%, inhaled nitric oxide weaned off, neuromuscular blockade was discontinued, and spontaneous ventilation was initiated. VV-ECMO was weaned when native lung oxygenation improved.

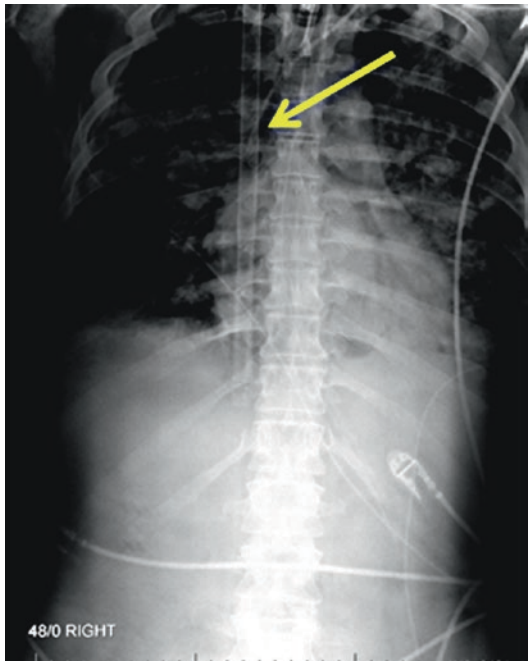


Fig. 82.4 31-French Bicaval Dual-lumen Cannula for VV-ECMO via right IJ vein

Principles of Management

ECMO Indications

ECMO should be considered for the most severe forms of acute respiratory failure, including severe hypoxemia and severe ARDS when other less costly strategies fail (Fig. 82.6). ECMO replaces pulmonary function, allows ultra-protective mechanical ventilation settings, and may facilitate lung healing.

ECMO should be considered in hypoxic respiratory failure from any cause when the risk of mortality is 50% or greater, and is indicated when the risk of mortality is 80% or greater. A 50% mortality risk is associated with a $PaO_2/FiO_2 < 150$ on $FiO_2 > 90\%$ and/or Murray score 2–3 (Table 82.1). An 80% mortality is associated with a PaO2/$FiO_2 < 100$ on $FiO_2 > 90\%$ and/or Murray score 3–4 despite optimal care for 6 h or more. Other indications include CO_2 retention on mechanical ventilation despite high $P_{plateau}$ (>30 cm H_2O), severe air leak syndromes, a need for intubation in a patient on the lung transplant list, and immediate cardiac or respiratory collapse (PE, blocked airway, unresponsive to optimal care).

ECMO survival in adults with severe respiratory failure has significantly improved. The ELSO registry report from 1986 to 2006 included 1473 patients with severe respiratory failure treated with ECMO and 50% survived to hospital discharge [4]. In the most recent study of adult

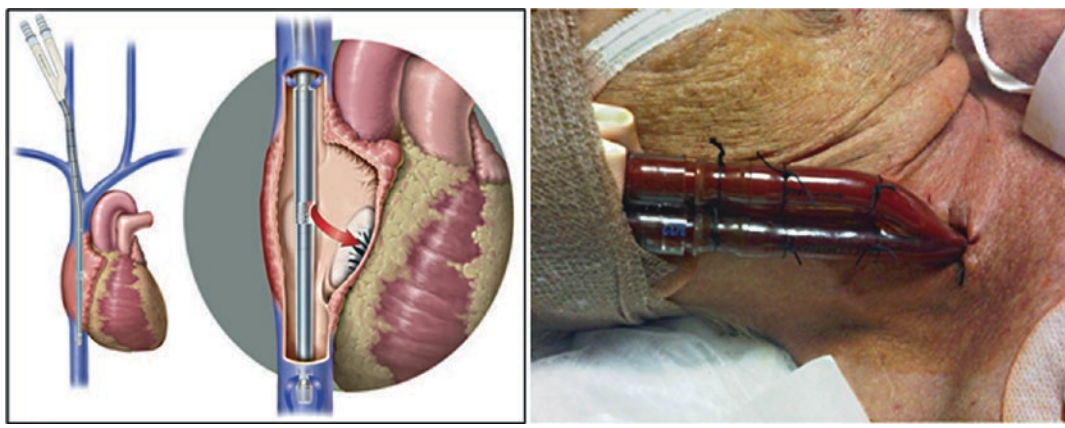


Fig. 82.5 Optimal position of the bicaval dual-lumen cannula with de-oxygenated blood outflow to ECMO circuit and oxygenated blood inflow to right atrium via medial infusion port

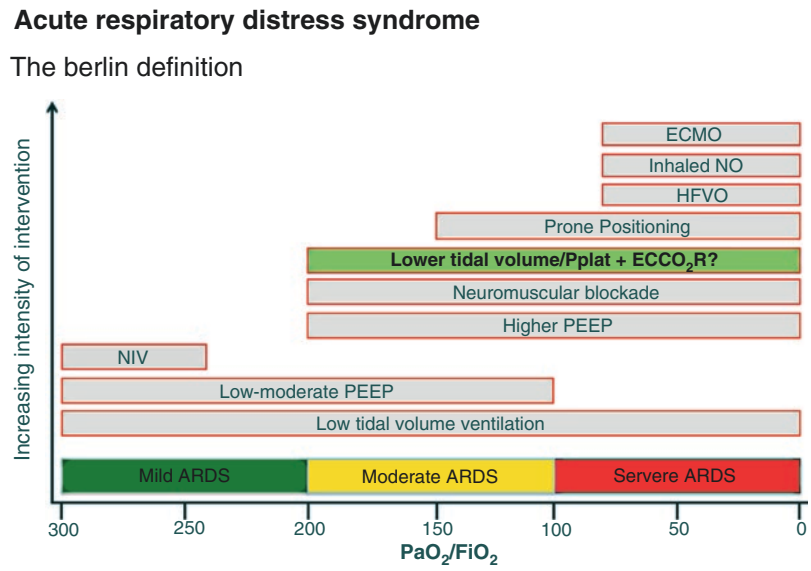


Fig. 82.6 Treatment and Rescue Strategies in ARDS (Definition Task Force ARDS [1])

Table 82.1 Murray Score for consideration of ECMO

Parameter/score	0	1	2	3	4
PaO_2/FiO_2 (On 100 % Oxygen)	≥300 mmHg ≥40 kPa	225–299 30–40	175–224 23–30	100–174 13–23	<100 <13
CXR	Normal	1 point per quadrant infiltrated			
PEEP (cmH_2O)	≤5	6–8	9–11	12–14	≥15
Compliance (ml/cmH_2O)	≥80	60–79	40–59	20–39	≤19

VV ECMO inclusion criteria – Murray score = average score of all 4 parameters

patients with severe acute respiratory failure treated with ECMO from 2000 to 2012 from the Extracorporeal Life Support Organization (ELSO) international registry, 1338 (57 %) of 2355 patients were discharged alive from hospital [5]. Hospital survival was 71 % in 2009 Influenza A (H1N1) ARDS patients treated with ECMO [6]. Referral to an ECMO Center was associated with significantly decreased mortality among patients with severe ARDS due to 2009 Influenza A (H1N1) viral pneumonia [7]. But it is recognized that data from retrospective series will never eliminate the bias of patient selection to receive ECMO.

Positive reports from the prospective randomized CESAR trial in 2009 (Conventional Ventilation or ECMO for Severe Adult Respiratory Failure trial) and from the H1N1 pandemic, in addition to reduced complexity and increased safety of ECMO have led to an increased use of ECMO for severe ARDS. The CESAR trial documented no death or severe disability in 63 % of patients randomized to the Leicester protocol, which included ECMO, compared to 47 % on conventional treatment [8]. The CESAR trial confirmed significant benefit for a strategy of referral to a single ECMO-capable hospital for ECMO assessment and management if criteria were met. Overall survival for adult respiratory ECMO is 57 % and since the H1N1 pandemic of 2009, and ECMO usage for adult respiratory failure remains above 400 cases per year [6, 9].

ECMO Contraindications

Although there are no absolute contraindications to ECMO, the following factors should be considered relative contraindications:

1. Mechanical ventilation at high settings ($FiO_2 > 0.9$, P-plat >30 cm H_2O) for 7 days or more (Lower likelihood of recovery if >5 days on the ventilator at these settings)
2. Major pharmacologic immunosuppression (absolute neutrophil count <400/mm^3)
3. Contraindications to systemic anticoagulation (includes recent or expanding CNS hemorrhage)
4. Increasing risk with advanced age

Initial ECMO Management

Venovenous ECMO access is adequate with either a bicaval dual-lumen cannula via the right internal jugular vein or two separate cannulas in the femoral and jugular veins (Fig. 82.7). Flow via the centrifugal pump should start at 50–80 cc/dry kg/min and then turned down to maintain SaO_2 >80–85 % at rest mechanical ventilation settings. The sweep gas flow should be titrated to a near-normal $PaCO_2$. Anticoagulation with heparin should maintain a PTT of 40–50 s. Ventilator pressures and FiO_2 are initially high during ECMO cannulation but should be decreased to FiO_2 0.4–0.5 with $P_{plateau} < 25$ cm H_2O and optimal P_{peep} (10–15 cm H_2O) to avoid damage but prevent atelectasis and total consolidation.

Weaning Off of ECMO

As native ventilation and oxygenation improve, incrementally decrease the sweep to maintain adequate ventilation and $SaO_2 > 95$ %. If the SaO_2 is stable on these settings, a trial off ECMO can be done by clamping the sweep gas while on lung protective ventilation settings. If $SaO_2 > 95$ % and $PaCO_2 < 50$ mmHg for an hour, consider discontinuing ECMO.

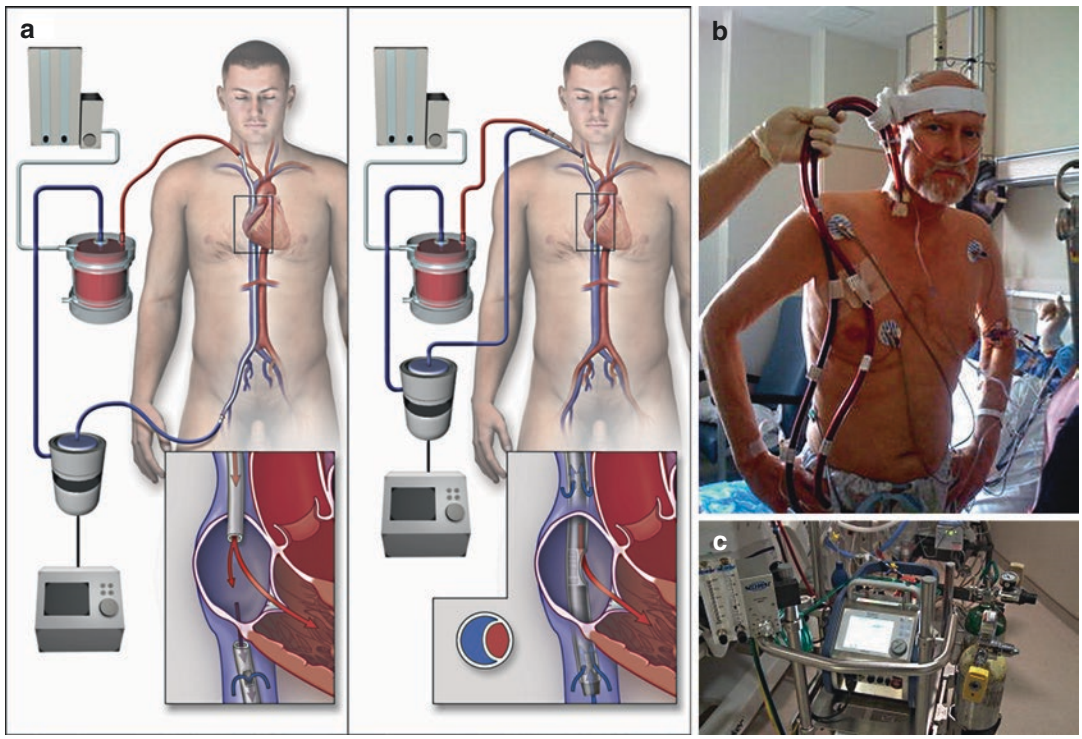


Fig. 82.7 (**a**) Traditional ECMO (right IJ/femoral vein) vs. dual lumen Avalon VV-ECMO (less mixing, no streaming, allows patient ambulation), (**b**) Patient on venovenous ECMO awaiting lung transplantation (Courtesy of Charles Hoopes, MD, with permission) and (**c**) ECMO circuit

Post-ECMO Considerations

The post-ECMO incidence of venous thrombus is common (particularly with femoral venous cannulae), with rates of pulmonary emboli found on post ECMO H1N1 confirmed cases as high as 50 % in a single center case report. Traditionally, IVC filters are placed after ECMO decannulation, however, a technique for guidewire exchange of the ECMO cannula to allow IVC filter placement using intravascular ultrasound has been described and successfully demonstrated [10].

Extracorporeal CO_2 Removal ($ECCO_2R$)

Extracorporeal CO_2 Removal ($ECCO_2R$) is a related technology that only addresses CO_2 exchange. The first clinical study of the safety and efficacy of using partial $ECCO_2R$ with a pump-less, arterio-venous gas exchange device to treat acute hypercapnic respiratory failure on non-invasive ventilation (NIV) was done in 2012 [11]. In the retrospective review, 14 of the 21 patients treated with $ECCO_2R$ had an acute exacerbation of COPD and 90 % of the 21 did not require intubation. No significant mortality difference was found. A subsequent pilot study was performed on COPD patients receiving partial $ECCO_2R$ and showed that all 9 patients with COPD requiring NIV avoided intubation. The group of 11 patients who were already intubated had a lesser degree of benefit, suggesting that $ECCO_2R$ may provide more clinical benefit if applied prior to ventilator dependence [12]. Additional pilot studies and randomized clinical trials for $ECCO_2R$ therapy as an adjunct to NIV in COPD are underway [13, 14].

Evidence Contour

ECMO

The use of adult ECMO in the setting of ARDS has increased dramatically since the H1N1 pandemic as well as the CESAR trial. Although the trial showed a significant mortality benefit in the group transferred for ECMO evaluation vs the conventional ventilation group, 25 % in the ECMO evaluation arm did not receive ECMO therapy and the control cohort did not receive standardized lung protective ventilation [8]. However, considering that transporting patients on ECMO can be done safely [15], the intervention of referring an eligible patient to a specialized center with ECMO capability resulted in a significant mortality benefit (31 % reduction in mortality in specialized center).

Prolonged ECMO

Since ECMO is now being used in severe ARDS patients who have failed other rescue strategies (neuromuscular blockade, prone position and inhaled nitric oxide), we have noted that more prolonged ECMO support is commonly required. A recent study of the Extracorporeal Life Support Organization (ELSO) registry confirmed that 974 patients had prolonged ECMO defined as ≥14 days ECMO support, with a mean ECMO duration of 25 days (range 15–208 days) [16]. Interestingly, hospital survival rate for prolonged ECMO for ARDS was 45.4 %, and prolonged ECMO survival increased in recent years since it has been used more frequently and ambulation is now possible with the dual-lumen cannulae.

ECMO Trial Data

A meta-analysis of the three ECMO randomized controlled trials documented a summary risk ratio of 0.93 (95 % CI 0.71–1.22), providing insufficient evidence to provide firm recommendations for ECMO [17]. The use of ECMO for severe ARDS thus remains controversial. However, clinicians consider ECMO within the context of other rescue strategies for severe hypoxemia and severe acute respiratory failure (Fig. 82.6).

Further evidence of the efficacy of venovenous ECMO in adult patients with severe ARDS from the ongoing **E**CM**O** to rescue **L**ung **I**njury in severe **A**RDS (EOLIA; ClinicalTrials.gov NCT01470703) [18] trial may lead to further

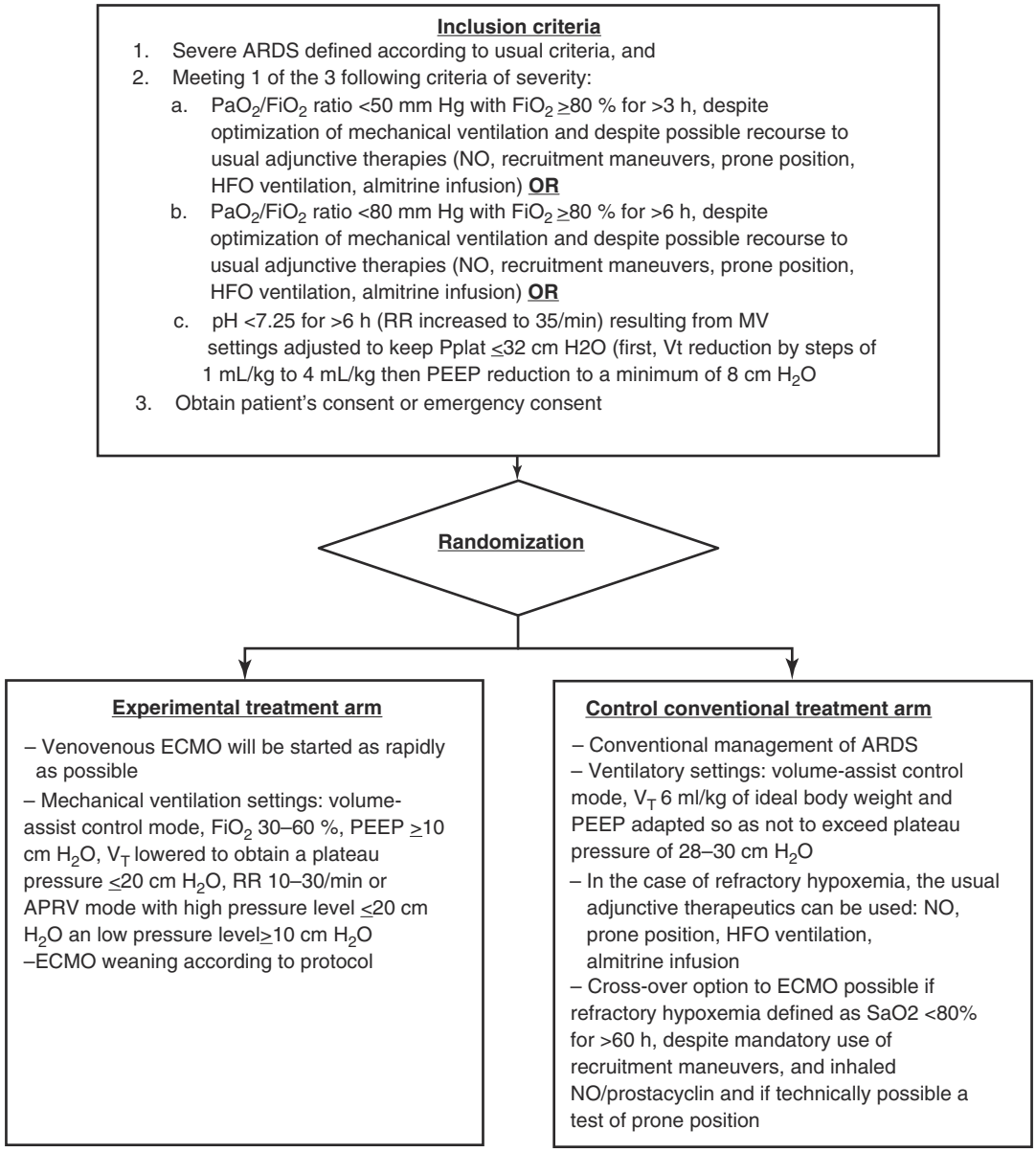


Fig. 82.8 EOLIA trial Inclusion Criteria and Randomization groups

expansion of ECMO use. This is a multicenter international RCT with best care possible in the ECMO arm with ECMO initiated in every patient randomized using the most recent ECMO technology (CardioHelp, Maquet, Inc.) and transport of randomized patients to the referral center under ECMO support. ECMO will be managed only in highly experienced centers. The control arm will be highly protective mechanical ventilation with plateau pressure limited to ≤24 cm H_2O and high PEEP, high recruitment strategy of the EXPRESS trial. An ethical cross-over option to ECMO is available if a control patient develops refractory hypoxemia.

The inclusion criteria for the EOLIA trial are provided in Fig. 82.8. The primary endpoint will be all-cause mortality at day 60.

ECMO Outcome Prediction

A number of prognostic scoring systems have been proposed for patients with ARDS supported with ECMO. The most recent is the Respiratory ECMO Survival Prediction (RESP) score which includes 12 simple variables that are readily available to clinicians and obtained from a large derivation cohort (n = 2355) [5, 19]. Future additional research is needed to validate these predictive scores and assist in determination of the optimal patients who would benefit from ECMO.

References

1. Definition Task Force ARDS, Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526–33. doi:10.1001/jama.2012.5669.
2. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with tranditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
3. Teman N, Haft J, Napolitano LM. Optimal endovascular methods for placement of bicaval dual-lumen cannulae for venovenous extracorporeal membrane oxygenation. ASAIO. 2013;442–447.
4. Brogan TV, Thiagarajan RR, Rycus PT, Bartlett RH, Bratton SL. Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multi-center database. Intensive Care Med. 2009;35(12):2105–14. doi:10.1007/s00134-009-1661-7.
5. Schmidt M, Bailey M, Sheldrake J, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure: The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. Am J Respir Crit Care Med. 2014;189(11):1374–82. doi:10.1164/rccm.201311-2023OC.
6. Davies A, Jones D, Bailey M, et al. Extracorporeal membrane oxygenation for 2009 influenza a(H1N1) acute respiratory distress syndrome. JAMA. 2009;302(17):1888–95. doi:10.1001/jama.2009.1535.
7. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). JAMA. 2011;306(15):1659–68. doi:10.1001/jama.2011.1471.
8. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009;374(9698):1351–63. doi:10.1016/S0140-6736(09)61069-2.
9. Paden ML, Conrad SA, Rycus PT, Thiagarajan RR. Extracorporeal life support organization registry report 2012. ASAIO J. 2013;59(June 2012):202–10. doi:10.1097/MAT.0b013e3182904a52.
10. Obi A, Park PK, Rectenwald J, et al. Inferior vena cava filter placement before ECMO decannulation. Am Soc Artif Intern Organs. 2012;622–625.
11. Kluge S, Braune SA, Engel M, et al. Avoiding invasive mechanical ventilation by extracorporeal carbon dioxide removal in patients failing noninvasive ventilation. Intensive Care Med. 2012;38(10):1632–9. doi:10.1007/s00134-012-2649-2.
12. Burki NK, Mani RK, Herth FJF, et al. A novel extracorporeal CO(2) removal system: results of a pilot study of hypercapnic respiratory failure in patients with COPD. Chest. 2013;143(3):678–86. doi:10.1378/chest.12-0228.
13. Abrams DC, Brenner K, Burkart KM, et al. Pilot study of extracorporeal carbon dioxide removal to facilitate extubation and ambulation in exacerbations of chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2013;10(4):307–14. doi:10.1513/AnnalsATS.201301-021OC.
14. Hermann A, Staudinger T, Bojic A, et al. First experience with a new miniaturized pump-driven venovenous extracorporeal CO2 removal system (iLA Activve): a retrospective data analysis. ASAIO J (Am Soc Artif Intern Organs 1992). 2014;60(3):342–7. doi:10.1097/MAT.0000000000000073.
15. Bryner B, Cooley E, Copenhaver W, et al. Two decades' experience with Interfacility transport on extracorporeal membrane oxygenation. Ann Thorac Surg. 2014;98(4):1363–70. doi:10.1016/j.athoracsur.2014.06.025.
16. Posluszny J, Rycus PT, Bartlett RH, Engoren M, Haft JW, Lynch WR, Park PK, Raghavendran K, Napolitano LM; ELSO Member Centers. Outcome of Adult Respiratory Failure Patients Receiving Prolonged (≥14 Days) ECMO. Ann Surg. 2015 Nov 24. [Epub ahead of print]
17. Mitchell MD, Mikkelsen ME, Umscheid CA, Lee I, Fuchs BD, Halpern SD. A systematic review to inform institutional decisions about the use of extracorporeal membrane oxygenation during the H1N1 influenza pandemic. Crit Care Med. 2010;38(6):1398–404. doi:10.1097/CCM.0b013e3181de45db.
18. Combes A. Extracorporeal membrane oxygenation to rescue lung injury in severe ARDS. Reanimation. 2011;20(1):49–61. doi:10.1007/s13546-010-0002-8.
19. Fan E, Pham T. Extracorporeal membrane oxygenation for severe acute respiratory failure. Crit Care. 2000;4(3):156–68. doi:10.1186/cc689.

Management of Acute Thermal Injury

83

Kavitha Ranganathan, Stewart C. Wang, and Benjamin Levi

Case Presentation

A 35 year old male with a history of alcohol and drug abuse is brought to the Emergency Department after sustaining partial and full thickness burns to his bilateral anterior upper extremities, chest, face, and neck. On physical exam, the patient has singed nasal hairs as well as soot in the perioral region. His extremities appear well perfused. He is mildly sedated but appropriately oriented (Fig. 83.1).

Question What is the most important first step in management?

Answer In the setting of thermal injury, a complete primary survey must be performed in accordance with ACLS guidelines to assess the exact nature of injuries [1, 2]. On presentation, the airway must be secured, breathing must be assessed and large bore IV access must be placed to facilitate aggressive fluid resuscitation [3]. Though it is preferred to obtain IV access in non-burned tissues, sometimes this is necessary. Despite higher infectious risk, central access might still be required. Prior to presentation, it is of utmost importance to isolate the patient from the cause of the injury, using aggressive irrigation of the tissues if necessary in the setting of chemical injury.

This patient presents with facial burns, and it is critical to assess airway patency immediately on arrival. Bronchoscopy is the definitive form of airway assessment. Although it is also important to take note of physical exam findings that can indicate potential injury to the airway such as singed nasal hairs or soot in the airway, these exam findings are not always accurate, and early protection of the airway is critical to the immediate survival of patients presenting with thermal injuries [4]. If there is even minor concern for inhalation injury, immediate intubation is required. Chest X-ray can be performed at this time to ensure appropriate placement of the endotracheal tube and to serve as a baseline given that pneumonia is the most common inpatient complication and cause of death for patients with burns. Importantly, succinyl choline must be avoided on induction of anesthesia in patients with long-standing thermal injury given the high risk for hyperkalemia due to upregulation of acetylcholine receptors post-injury.

Once the airway has been secured and the patient is hemodynamically stable, the extent of burn injury must be quantified. Total body surface area (TBSA) is a critical factor in this process (Table 83.1). TBSA impacts survival.

K. Ranganathan (✉) • B. Levi
Department of Surgery, University of Michigan Health Systems, Ann Arbor, MI, USA
e-mail: krangana@med.umich.edu

S.C. Wang
Burn Surgery, Department of Surgery, University of Michigan Health Systems, Ann Arbor, MI, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_83

Patients with greater than 10 % TBSA burns are commonly admitted to an intensive care unit for monitoring. Importantly, only deep partial and full thickness burns are included in the determination of TBSA; superficial injuries are not included (Table 83.2). This patient has approximately 36 % TBSA burns (9 % anterior bilateral upper extremities, 9 % head/neck). There are three zones of tissue injury: 1. zone of coagulation, 2. zone of stasis, 3. zone of hyperemia. The zone of coagulation is the site most severely and irreversibly injured by the initial injury. The zone of stasis however, can be salvaged with appropriate resuscitation. The zone of hyperemia although damaged, can heal on its own without required additional interventions. Thus, immediate, aggressive resuscitation is critical to maximize tissue viability and salvage of the zone of stasis [1]. After the primary survey, the next step is to promptly initiate aggressive fluid resuscitation.

Fig. 83.1 A 35 year old male presents with partial and full thickness burns as depicted as a result of severe trauma and thermal injury. There is significant soft tissue damage, and eminent airway compromise as a result of the injury

Table 83.1 Distribution of total body surface area

Anatomic surface	Percentage of total body surface area
Head and neck	9 %
Anterior trunk	18 %
Posterior trunk	18 %
Upper extremities	9 % each
Lower extremities	18 % each
Genitalia	1 %

Table 83.2 Lund and Browder chart

Age (years)	0–1	1–4	5–9	10–14	15	Adult
Head	9.5	8.5	6.5	5.5	4.5	3.5
Anterior or Posterior Thigh	2.75	3.25	4	4.5	4.5	4.75
Anterior or Posterior Leg	2.5	2.5	2.75	3	3.25	3.5
Arm	2	2	2	2	2	2
Forearm	1.5	1.5	1.5	1.5	1.5	1.5
Hand	1.5	1.5	1.5	1.5	1.5	1.5
Genitalia	1	1	1	1	1	1
Gluteus	5	5	5	5	5	5
Anterior or Posterior Thorax	13	13	13	13	13	13
Neck	1	1	1	1	1	1
Foot	1.75	1.75	1.75	1.75	1.75	1.75

Method of estimating surface area affected by the burn that accounts for age as a factor affecting growth [20]

Principles of Management

Diagnosis

Several factors must be considered on initial evaluation of a burn. The type of burn (scald, electrical, chemical, or flame), depth of the burn (superficial partial, deep partial, full thickness), mechanism of injury, comorbidities, and social situation must be thoroughly investigated [5]. Superficial partial thickness burns penetrate through the superficial dermis, and are associated with severe pain given the lack of complete injury to the adnexal structures (Fig. 83.2). These burns commonly heal without surgical intervention. Deep partial thickness burns extend to the reticular dermis, and may not be associated with pain. Compared to the mildly hyperemic tissues of superficial partial thickness injuries, deep partial thickness burns are lobster red in color. Due to complete loss of adnexal structures, the tissues become dry, non-tender, and commonly require surgical intervention to ensure appropriate healing. Full thickness burns extend beyond the dermis into the subcutaneous tissues. Immediate surgical intervention is critical to optimal healing of these burns, and significantly minimizes the risk for burn wound cellulitis and sepsis [6].

Question What are the three most common complications that occur in patients with burns?

Answer The most common complication and cause of death in patients with burns is pneumonia.

This can be decreased with early wake and extubate strategies as used in the general critical care population. The second and third most common complications are wound cellulitis and burn wound infection and urinary tract infections, respectively [6]. These complications can be decreased with early debridement and grafting and early removal of foley catheters when no longer needed to assess resuscitation.

Question What are appropriate options for local wound care?

Answer This patient received daily sulfamylon or silver nitrate soaks to his upper extremities. The facial burns were treated with bacitracin and xeroform dressings daily.

Wound Care

Proper wound care is the cornerstone of proper burn care [5]. Superficial partial thickness burns

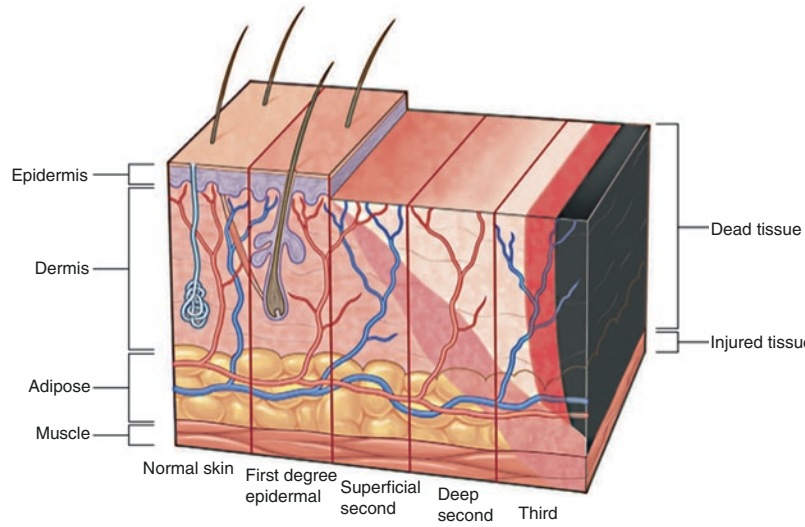


Fig. 83.2 Anatomy of the skin and subcutaneous tissue important in determining the percentage of total body surface area involved after thermal injury (From Nelingan et al. [1]. Reprinted with permission from Elsevier Limited)

Table 83.3 Commonly used topical ointments for local wound care

Topical agent	Targeted microorganisms	Complications
Bacitracin	Gram-positives and Gram-negatives	Allergic reaction (hyperemia)
Silvadene	Gram-positives and Gram-negatives	Leukopenia
Sulfamylon	Gram-positives	Metabolic acidosis
Silver nitrate	Staphylococcus, Gram-negative aerobes and fungal species	Hyponatremia, hypokalemia

can be treated with bacitracin and xeroform dressings. These dressings provide a moist environment to facilitate prompt reepithelialization of the traumatized tissues. Xenograft can also be used to treat painful superficial partial thickness burns. Burns on the face, especially over areas of exposed cartilage, are treated with sulfamylon ointment. It is important to obtain regular basic metabolic panels given the risk of metabolic acidosis that can occur with use of sulfamylon. Sulfamylon soaks can also be utilized over the whole body, and are performed two to three times daily given the broad-spectrum antimicrobial coverage. Importantly sulfamylon does not cover fungal species. Silver nitrate soaks are an alternative and have broad bacterial and fungal coverage and are cheaper than sulfamylon soaks. Silvadene is another commonly used ointment. Unlike sulfamylon, however, silvadene does not penetrate eschar and is associated with leukopenia. Silvadene can be mixed with nystatin to broaden coverage. Although known to have antimicrobial properties, the use of silver dressings in the setting of burn injury has not been shown to minimize wound infections [7] (Table 83.3).

Surgical Intervention

One of the most critical factors for improving mortality, decreasing morbidity, and minimizing the risk of complications including infection is prompt operative intervention. Deep partial thickness and full thickness burns should be treated as soon as possible with tangential excision to the level of healthy bleeding tissue followed by coverage with split thickness skin autografts if possible. Without immediate debridement, the incidence of cellulitis increases dramatically, and is a frequent cause of sepsis in patients with burns [6]. If immediate coverage with autograft is not possible, homograft or xenograft may be necessary [8]. Additionally, for extremity burns specifically, escharotomies or even fasciotomies may be necessary to ensure proper perfusion distally as in the case of this patient [1]. Additionally, if patients have large areas of chest or abdominal burns and a large resuscitation is expected, early escharotomies may mitigate difficulty ventilating and abdominal compartment syndrome respectively.

Fluid Management

Aggressive fluid resuscitation must be initiated immediately. For patients with greater than 20% TBSA burns, the Parkland formula is most commonly used to control fluid administration. According to this formula, the first 24 h post-injury are the most critical in preventing burn-induced shock. On presentation, fluid titration using Lactated Ringer's solution is performed according to TBSA and weight of the patient in kilograms [1].

Parkland Formula

$$4 \times \%\text{TBSA} \times \text{weight}\,(\text{kg}) = \text{total IV fluid to be administered over first 24 h}$$

$$\text{First half of IV fluid total administered 8 h post} - \text{injury} + \text{second half administered during next 16 h post} - \text{injury}$$

Supportive Care

1. Pneumonia is the most common cause of death in patients after thermal injury [1]. Thus, all intubated patients must receive prophylaxis with antiseptic oral rinses and regular spontaneous breathing trials. Broad-spectrum, properly dosed intravenous antibiotics must be initiated as soon as infection is suspected [9].
2. Significant metabolic demands are placed on the body during the process of wound healing. Thus, early use of enteral feeding with a high protein diet if possible is important [10].
3. Patients with burns are predisposed to developing joint contractures, especially at the elbows and axillary regions. Use of regular physical therapy and splinting is important to minimize the risk for severe joint contractures.
4. Given the prolonged immobility of patients with burn injury, pharmacologic deep venous thrombosis prophylaxis is required.

Evidence Contour

Several aspects of management in the patient with thermal injury remain without consensus in the face of available clinical trials.

Fluid Resuscitation Monitoring

Aggressive fluid resuscitation during the first 24–48 h post-injury improves outcomes in patients with burns. However, over-resuscitation can result in significant complications including abdominal compartment syndrome and respiratory failure due to pulmonary edema. Although numerous formulas exist to quantify the amount of fluid that should be administered, controversy exists as to how to adequately assess the overall fluid status of patients with thermal injuries. While some believe that a urine output of 0.5–1 mL/kg/h is adequate, others believe that the use of non-invasive hemodynamic indicators such as cardiac index, mean arterial pressure, central venous pressure, and lactate levels is more reliable. No consensus exists currently [11].

Scar Management

Although it is known that skin grafting performed within 3 weeks of the initial injury minimizes the risk for hypertrophic scarring and contracture, it remains unclear what the best method of chronic scar management is. Various modalities including silicone sheeting, steroid injections, scar massage, fat grafting, and laser treatments have been used in the past, but no consensus exists as to treatment duration, timing of initiation, and individualized indications for use [12–15]. More recently, fractionated CO_2 lasers have been shown to improve both aesthetic and functional outcomes in patients with hypertrophic scars after burn injury [16].

Conclusion

More than six million injuries and 400,000 deaths occur each year as a result of thermal trauma, and the mean cost per patient is approximately $88,218 [17–19]. Given the extent of these injuries, standardized protocols are required to provide uniform and systematic care. With prompt initiation of treatment protocols focused on aggressive resuscitation and recognition of common complications, it is possible to improve survival outcomes and minimize complications in this group of patients.

References

1. Neligan P, Steinstraesser L, Al-Benna S. Plastic surgery: acute management of burn/electrical injuries. 3 ed. Expert Consult; 2013.
2. Rousseau AF, Massion PB, Laungani A, Nizet JL, Damas P, Ledoux D. Toward targeted early burn care: lessons from a European survey. J Burn Care Res. 2014;35:e234–9.
3. Foster K. Clinical guidelines in the management of burn injury: a review and recommendations from the organization and delivery of burn care committee. J Burn Care Res. 2014;35:271–83.
4. Ching JA, Shah JL, Doran CJ, Chen H, Payne WG, Smith Jr DJ. The evaluation of physical exam findings in patients assessed for suspected burn inhalation injury. J Burn Care Res. 2015;36:197–202.
5. Brown D, Borschel G, Levi B. Michigan manual of plastic surgery. 2 ed. Lippincott Manual Series; 2014.

6. Heard JP, McDonald KM, Xing Y, Kluesner KM, Liao J, Wibbenmeyer LA. Regional and national review of factors associated with burn wound cellulitis. J Burn Care Res. 2015;36:23–32.
7. Rashaan ZM, Krijnen P, Klamer RR, Schipper IB, Dekkers OM, Breederveld RS. Nonsilver treatment vs. silver sulfadiazine in treatment of partial-thickness burn wounds in children: a systematic review and meta-analysis. Wound Repair Regeneration. 2014;22:473–82.
8. Greenhalgh DG. The use of dermal substitutes in burn surgery: acute phase. Wound Repair Regeneration. 2014;22:1–2.
9. Johnson BL, Damer KM, Walroth TA, Buening NR, Foster DR, Sood R. A Systematic Review of Vancomycin Dosing and Monitoring in Burn Patients. J Burn Care Res. 2014;36:641.
10. Lavrentieva A, Kontakiotis T, Bitzani M. Enteral nutrition intolerance in critically ill septic burn patients. J Burn Care Res. 2014;35:313–8.
11. Paratz JD, Stockton K, Paratz ED, Blot S, Muller M, Lipman J, Boots RJ. Burn resuscitation--hourly urine output versus alternative endpoints: a systematic review. Shock. 2014;42:295–306.
12. Ranganathan K, Wong VC, Krebsbach PH, Wang SC, Cederna PS, Levi B. Fat grafting for thermal injury: current state and future directions. J Burn Care Res. 2013;34:219–26.
13. Li X, Meng X, Wang X, Li Y, Li W, Lv X, Xu X, Lei Z, Li J. Human acellular dermal matrix allograft: a randomized, controlled human trial for the long-term evaluation of patients with extensive burns. Burns. 2015.
14. Loder S, Peterson JR, Agarwal S, Eboda O, Brownley C, DeLaRosa S, Ranganathan K, Cederna P, Wang SC, Levi B. Wound healing after thermal injury is improved by fat and adipose-derived stem cell isografts. J Burn Care Res. 2015;36:70–6.
15. Tredget EE, Levi B, Donelan MB. Biology and principles of scar management and burn reconstruction. Surg Clin North Am. 2014;94:793–815.
16. Hultman CS, Friedstat JS, Edkins RE, Cairns BA, Meyer AA. Laser resurfacing and remodeling of hypertrophic burn scars: the results of a large, prospective, before-after cohort study, with long-term follow-up. Ann Surg. 2014;260:519–29; discussion 29–32.
17. Hop MJ, Polinder S, van der Vlies CH, Middelkoop E, van Baar ME. Costs of burn care: a systematic review. Wound Repair Regeneration. 2014;22:436–50.
18. Stavrou D, Weissman O, Tessone A, Zilinsky I, Holloway S, Boyd J, Haik J. Health related quality of life in burn patients--a review of the literature. Burns. 2014;40:788–96.
19. Jackson PC, Hardwicke J, Bamford A, Nightingale P, Wilson Y, Papini R, Moiemen N. Revised estimates of mortality from the Birmingham Burn Centre, 2001-2010: a continuing analysis over 65 years. Ann Surg. 2014;259:979–84.
20. Miminas D. A critical evaluation of the Lund and Browder chart. Wounds. 2007;3:58–68.

Acute Arterial Ischemia

84

Danielle Horne and Jonathan L. Eliason

Case Presentation

A 30-year-old man sustained multiple gunshot wounds to the lower extremities and perineum following an altercation. On initial primary survey, he was found to have a loss of pulses in the left lower extremity with associated unstable femur fracture. Moderate bleeding occurred from the leg wound initially, but was not pulsatile. Representative images from the trauma computed tomography (CT) are shown below (Figs. 84.1, 84.2, 84.3, and 84.4).

Question What is the diagnosis and what is the next step in management?

Answer Acute limb ischemia secondary to high velocity penetrating trauma. Consider the merits of immediate bone fixation versus a revascularization first approach. Consultation to Vascular Surgery and Orthopedic Surgery at an early juncture may facilitate an optimal multidisciplinary approach in order appropriately sequence reperfusion and musculoskeletal fixation.

The CTA demonstrated a left SFA injury with segmental thrombosis but no active extravasation. Vascular Surgery and Orthopedic Surgery were consulted. In the operating room, the patient was hemodynamically stable. The ischemic time at operation was approximately 4.5 h. A decision was made to locally explore the wound, obtain proximal and distal vascular control, and then place an intraoperative vascular shunt while the orthopedic surgeons performed an external fixation of the femur (Fig. 84.5). After completion of the femur fixation, saphenous vein from the contralateral leg was harvested and reversed. An interposition reversed great saphenous vein reconstruction was then performed for definitive vascular reconstruction. Four compartment fasciotomies were next performed to limit potential for compartment syndrome given the ischemic time. The patient was subsequently admitted to the intensive care unit with hourly neurovascular checks ensuring that Doppler signals were present. The patient recovered and arterial brachial index (ABI) obtained prior to discharge was 1.09 on the right and 1.08 on the left.

Principles of Management

Initial Evaluation

When there are hard signs of vascular injury including active hemorrhage, rapidly expanding hematoma, absent pulses or a palpable thrill/bruit, immediate operative exploration is warranted. Patients who present without these signs, however, should undergo complete

D. Horne • J.L. Eliason (✉)
Section of Vascular Surgery, University of Michigan, Ann Arbor, MI, USA
e-mail: jonaelia@med.umich.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_84

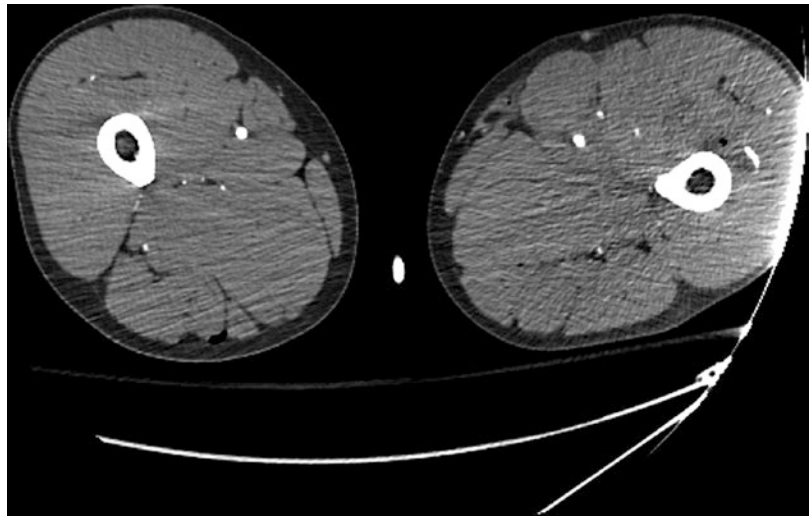


Fig. 84.1 Axial CT with arterial phase imaging demonstrates an intact left superficial femoral artery (SFA) without evidence of filling abnormality

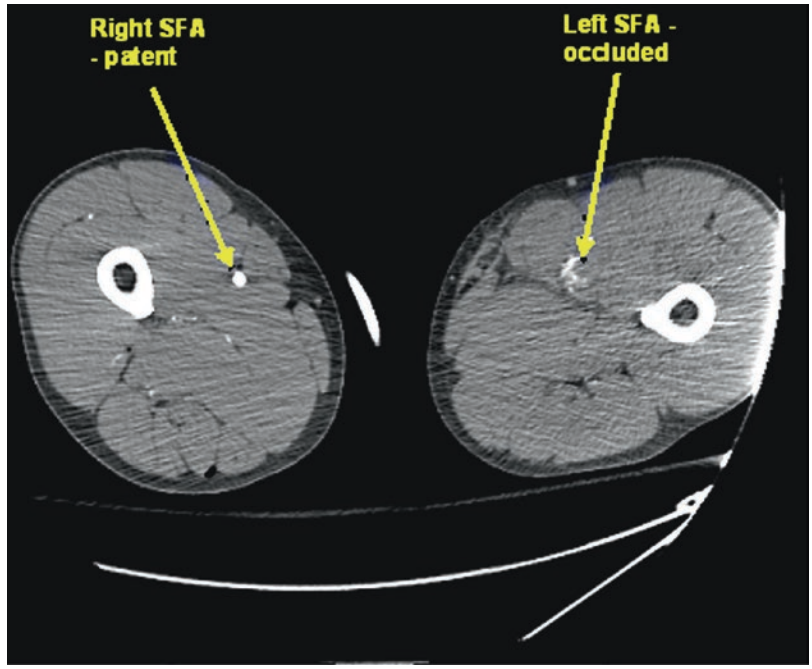


Fig. 84.2 Axial CT demonstrates occlusion of the left SFA in the more distal extremity. Note the normal, patent right SFA

physical exam with special attention to the vascular exam. Physical exam in conjunction with arterial pressure index measurement by Doppler has high sensitivity for injury [1, 2]. As such, patients with lower extremity trauma should also undergo arterial pressure indices in which the Doppler pressure for the affected extremity distal to the presumed injury site is indexed to the higher of the two upper extremity arterial Doppler pressures. In the setting of a normal physical exam and pressure index >0.9, patients may be observed and/or discharged home safely with follow up [3]. Those patients who have either an abnormal physical exam and/or ankle-brachial index (ABI) <0.9 should have further imaging.

Diagnostic Imaging

CT angiography (CTA) has mostly replaced catheter angiography for the primary modality of diagnostic imaging in lower extremity trauma.

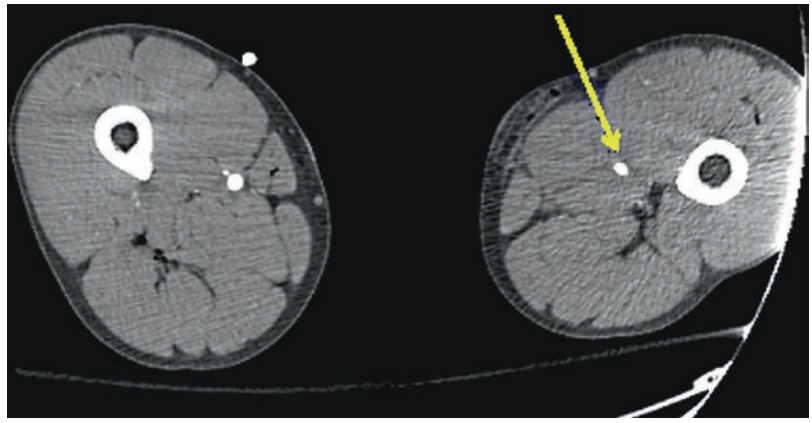


Fig. 84.3 Axial CT from the mid-distal thigh demonstrates an intact left SFA just caudal to the occluded segment without evidence of filling defect

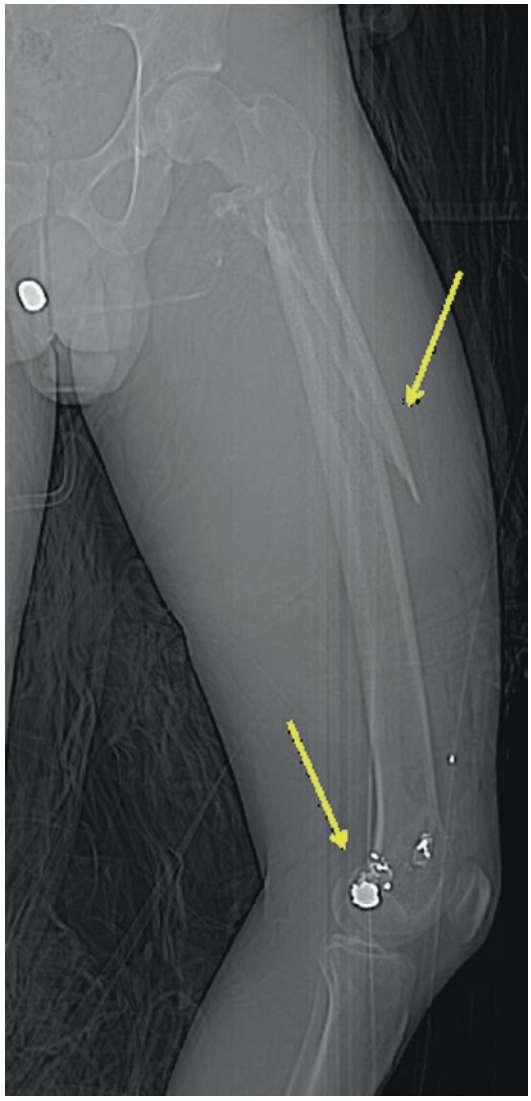


Fig. 84.4 Ballistic fracture of left femur with pelvic and knee foreign bodies

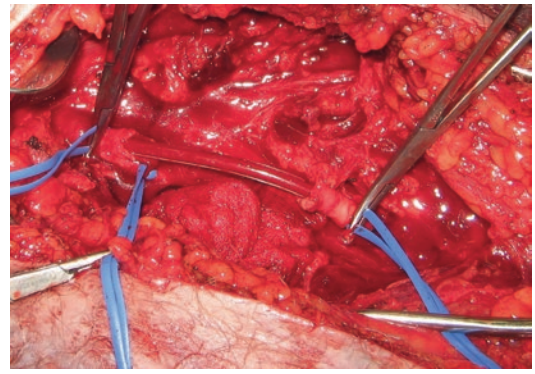


Fig. 84.5 This example of in-line arterial shunting using a 12 French carotid bypass shunt (Bard®) demonstrates tension on silastic loops for proximal and distal fixation of the shunt. This restores arterial inflow to the ischemia extremity immediately, and definitive vascular reconstruction can be performed after bony stabilization. The ballistic cavity is easily seen

Many recent studies have found the sensitivity and specificity of CTA approach 100% [4, 5]. Catheter angiography is still considered as an additional technique when the CTA is not diagnostic, when an overabundance of metal hardware renders image quality inferior due to scatter artifact, or when endovascular intervention is considered highly likely following the diagnostic portion of the procedure.

Intervention and Post-operative Management

Intervention includes open exploration of the wound after obtaining proximal and distal con-

trol. Temporary balloon occlusion for proximal control using endovascular techniques is more commonly employed in contemporary practice, especially for injuries approaching the junctional region (groin). It is important to prep both extremities in the operating room for potential vein harvest from the unaffected limb.

Management of displaced orthopedic injuries should take into account the complexity of the reduction/fixation procedure and duration of ischemia to the limb. If ischemic time is limited, orthopedic injuries should be addressed prior to definitive repair. If ischemic time is prolonged, however, vascular shunting can be used as an adjunct while the orthopedic repair occurs in order to quickly restore blood flow to the extremity.

Thorough irrigation should be employed if there is a large wound with contamination, and autologous conduit such as greater saphenous vein from the opposite, unaffected extremity should be considered as a preferred choice when suitable. If the patient has inadequate vein for conduit, prosthetic graft with muscular coverage or a tunnel avoiding the contaminated wound bed may be considered.

Fasciotomies should be considered if there is extensive trauma to the leg or if there has been prolonged ischemia time (i.e. > 4–6 h). If the decision is made not to perform fasciotomies it is important to have the patient in an ICU where hourly neurovascular checks and monitoring for a tense compartment may occur. The patient should undergo ankle-brachial index measurements prior to discharge and at follow-up.

Evidence Contour

Controversial Aspects of Management/Imaging

The modern era of vascular trauma has changed most significantly when it comes to diagnostic imaging modalities. As mentioned earlier, the gold standard for diagnostic imaging in lower extremity trauma has historically included catheter angiography. This paradigm is now changing, with improvements in CTA technology and software advancements making 3-dimensional reconstructions highly informative and diagnostic. In a recent study including 484 arterial injuries, CTA was used in 39.6% of the vascular trauma, whereas catheter angiography and open exploration occurred with frequencies of 11.4% and 29.7%, respectively [6]. Finally, a review of 9 studies representing 540 patients undergoing CTA to diagnose extremity arterial injuries had only seven missed injuries, resulting in a 1.3% false negative rate [7]. The follow up in the majority of these studies was limited. However, the new management guidelines for lower extremity trauma from the Eastern Association for the Surgery of Trauma recommend that CTA should be the primary diagnostic imaging modality for vascular trauma [3].

Endovascular Treatment Approach to Lower Extremity Vascular Trauma

Although open surgical intervention remains the gold standard approach for lower extremity vascular trauma, the era of endovascular surgical interventions has caused many to consider utilizing these techniques when appropriate in this trauma subset. Literature on the topic is limited, but continues to grow, and encompasses successful endovascular approaches to blunt and penetrating iliac artery, superficial femoral artery (SFA), popliteal artery and tibial arterial trauma [8–12]. Nearly all high level trauma hospitals in the United States include an endovascular suite or hybrid open/endovascular operating room in some form, making consideration of emergency endovascular interventions for trauma a possibility. At a minimum, high-quality C-arm technology with a vascular software package is available for use with a standard trauma operating room bed in which the pedestal has been configured to allow imaging of the lower extremities.

Patient selection for endovascular treatment of lower extremity trauma is imperative. Complex endovascular procedures may be time consuming and require systemic heparinization in the majority of cases except in cases of coil embolization for hemorrhage control. With this in mind, the trauma surgeon is best suited for decision making regarding risks related to anticoagulation. If patients have contraindications for heparinization

such as concomitant traumatic brain injury, endovascular techniques requiring this adjunct should be removed from the patient's treatment algorithm. Specialized endovascular procedures should also not increase the treatment times as prompt restoration of arterial inflow is the goal.

A readily available endovascular inventory for trauma and appropriately trained staff are also prerequisite for considering the utilization of these techniques. The inventory should include sheath sizes ranging between 5 and 11 French of varying lengths (10 cm standard length, 45–65 cm for distal lower extremity interventions using contralateral femoral approach), standard and exchange length wires (140–180 cm-long; 260–300 cm-long) of various types (hydrophilic, braided low stiffness, braided mid-high stiffness support wires), and appropriate therapeutic devises (percutaneous angioplasty balloons, stents, covered stents, embolization coils or plugs). Endovascular management of lower extremity vascular injury will be limited unless institutional mechanisms allow this degree of infrastructure to be present and available for use for the injured trauma patient.

References

1. Weaver FA, Yellin AE, Bauer M, et al. Is arterial proximity a valid indication for arteriography in penetrating extremity trauma? A prospective analysis. Arch Surg. 1990;125:1256–60.
2. Schwartz MR, Weaver FA, Bauer M, et al. Refining the indications for arteriography in penetrating extremity trauma: a prospective analysis. J Vasc Surg. 1993;17:116–22.
3. Fox N, Rajani RR, Bokhari F, et al. Evaluation and management of penetrating lower extremity arterial trauma: An Eastern Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg. 2012;73:S315–20.
4. Inaba K, Branco B, Reddy S, et al. Prospective evaluation of multidetector computed tomography for extremity vascular trauma. J Trauma. 2011;70:808–15.
5. Seamon MJ, Smoger D, Torres D, et al. A prospective validation of a current practice: the detection of extremity vascular injury with CT angiography. J Trauma. 2009;67:238–44.
6. DuBose JJ, Savage SA, Fabian TC, et al. The American Association for the Surgery of Trauma PROspective Observational Vascular Injury Treatment (PROOVIT) registry: multicenter data on modern vascular injury diagnosis, management, and outcomes. J Trauma Acute Care Surg. 2015;78:215–23.
7. Patterson BO, Hold PJ, Cleanthis M, et al. Imaging vascular trauma. Br J Surg. 2012;99:494–505.
8. Stewart DK, Brown PM, Tinsley EA Jr., et al. Use of stent grafts in lower extremity trauma. Ann Vasc Surg. 2011;25:264.e9–e13.
9. Arthurs ZM, Sohn VY, Starnes BW. Vascular trauma: endovascular management and techniques. Surg Clin North Am. 2007;87:1179–92.
10. Hutto JD, Reed AB. Endovascular repair of an acute blunt popliteal artery injury. J Vasc Surg. 2007;45:188–90.
11. Reuben BC, Whitten MG, Sarfati M, et al. Increasing use of endovascular therapy in acute arterial injuries: analysis of the National Trauma Data Bank. J Vasc Surg. 2007;46:1222–6.
12. Johnson CA. Endovascular management of peripheral vascular trauma. Sem Intervent Rad. 2010;27:39–43.

Management of Necrotizing Soft Tissue Infection

85

Heather Leigh Evans and Eileen M. Bulger

Case Presentation

A 50 year-old woman with history of congestive heart failure presented to the emergency room of her local community hospital complaining of progressive right elbow pain and swelling that developed after a minor fall at home 4 days prior. Her husband reported that she had profuse watery diarrhea 1 week prior, while continuing to take her home medications, which included Lasix. Since the fall, she had remained in bed with generalized weakness and poor PO intake. In the ED, her initial systolic blood pressure is 70 mmHg and the right forearm is noted to be swollen and tense, erythematous, warm and exquisitely painful to passive range of motion. Induration extends to the proximal posterior upper arm. WBC is 21, lactic acid 10.8, creatinine 11, sodium 119. She rapidly receives ceftriaxone and clindamycin, 3 L of crystalloid resuscitation and norepinephrine and vasopressin infusions are started.

The orthopedic surgeon on call takes her urgently to the operating room to treat what is strongly suspected to be a necrotizing soft tissue infection. The forearm skin is incised and the superficial volar compartment fascia released, the muscles are noted to be generally viable. No debridement is performed. A wound vacuum dressing is placed and she is transported to the ICU. Overnight, norepinephrine is discontinued, but her WBC increases to 36 and oliguria develops. She is transferred emergently to a tertiary care center, arriving in the emergency department intubated and sedated on mechanical ventilation, systolic blood pressure in the 80's despite ongoing treatment with vasopressin and sodium bicarbonate infusion for progressive metabolic acidosis (pH 7.09). Her sodium level is 131. The Gram stain from blood cultures obtained at the prior facility shows Gram positive cocci in chains.

Question What is the approach that should be applied to guide the management of this patient?

Answer Surgical source control

Norepinephrine is restarted, 3 L of lactated ringers fluid are administered immediately and additional antibiotics (vancomycin) are administered while the general surgeon on call evaluates the patient and arranges for emergent re-exploration. She is taken to the operating room where the wound vac dressing is removed. The wound is thoroughly evaluated, the incisions extended both proximally and distally to facilitate examination of the entire length of the forearm to the hand and the superficial and deep volar

H.L. Evans (✉)
Surgery, University of Washington/Harborview Medical Center, Seattle, WA, USA
e-mail: hlevans@u.washington.edu

E.M. Bulger
Surgery, University of Washington, Seattle, WA, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_85

compartments to the forearm are found to be nonviable (Fig. 85.1).

The general surgeon calls an emergent intraoperative consult to the on-call hand surgeon. Together, the two identify necrotic soft tissue throughout the forearm, with gray dishwasher fluid exuding from the soft tissues. There is dead muscle in both the volar and dorsal compartments and a transition zone of viability just proximal to the elbow; the biceps, triceps, and brachialis appear normal. The two surgeons agree that the forearm cannot be salvaged. Given the degree of swelling that extends through the elbow joint, a mid-humeral amputation is performed in order to gain proximal control and arrest the progressive infection. After achieving hemostasis, the wound is not closed, but is covered with a gauze dressing soaked in Dakin's solution. The patient is transported still intubated and mechanically ventilated to the critical care unit, with blood pressure still supported by norepinephrine and vasopressin. Post-operatively, her WBC remains in the 30's and her oliguria continues. The final cultures are reported as Group A beta-hemolytic *Streptococcus*. Given her ongoing shock and leukocytosis, the patient is taken back to the operating room the following day where additional sharp debridement of the mid-humeral amputation site is performed.

The patient is extubated the following day and vasopressin is discontinued. Antibiotics are narrowed to ceftriaxone. Over the next week, her WBC normalizes, she is weaned off norepinephrine, and her acute kidney injury resolves. On hospital day 8, the amputation site is revised with a formal myodesis and skin closure. She is discharged home on hospital day 10. Eight months later, the patient was fitted for a prosthetic arm.

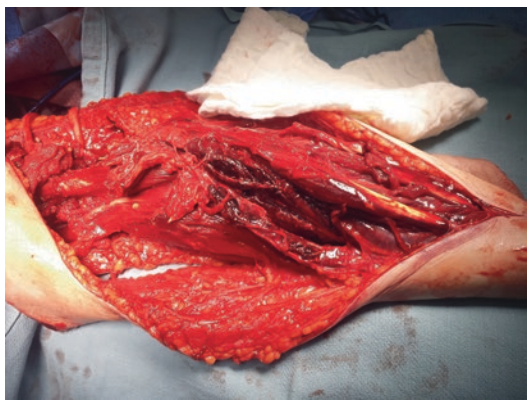


Fig. 85.1 Necrotic muscle visible in superficial and deep volar compartments to distal forearm (rightmost aspect of photo). Transition of viability is noted just below the elbow joint

Principles of Management

Rapid Diagnosis

While necrotizing soft tissue infections (NSTI) are very rare (estimated 1000 cases annually in the United States), because of the potential for rapid escalation to overwhelming septic shock with multisystem organ failure, early recognition of the possibility of necrotizing soft tissue infection is imperative. Even with optimal treatment, mortality ranges as high as 25–35 %. Unfortunately, the early signs and symptoms of NSTI can be identical to those seen with cellulitis or localized abscess. Generally, erythema, pain beyond the obvious margin of infection, swelling and fever are most common. More suggestive of NSTI are skin induration and pain disproportionate to examination findings. The most obvious "hard" clinical signs of skin bullae, ecchymosis and necrosis, cutaneous anesthesia, and gas on clinical or radiographic examination do not appear until much later in the course of the disease. NSTI can affect any region of the body, but the extremities and genito-perineal areas are most common. Inoculation of bacteria through the skin barrier is typically due to history of trauma, injection, insect bites or surgery, but may also occur via systemic dissemination from recent oropharyngeal or gastrointestinal infection.

After suspicion is established with history and physical exam features, laboratory data confirms metabolic derangement, generally with leukocytosis and other signs of acute inflammation (e.g., elevated CRP). Evidence of organ failure may be present on presentation as well, and the more deranged the laboratory values, the

higher the likelihood of a bad outcome. Radiography is seldom helpful in making the diagnosis, but computed tomography may help to define the extent of the disease on presentation. It should be recognized, however, that in the setting of high clinical suspicion, the gold standard for diagnosis of NSTI remains operative exploration *without delay*. In questionable cases, a skin incision carried down to the fascia allows evaluation of adherence of the fascia to other soft tissue layers. In classic necrotizing fasciitis, the diseased fascia is no longer adherent to the adjoining layers, allowing the surgeon to easily slide his or her finger along the fascial plane. Necrotizing adipositis or deep necrotizing myositis may also be diagnosed with local exploration for necrotic tissue.

Empiric Broad Spectrum Antibiotic Therapy and Resuscitation

Even prior to definitive diagnosis, patients with suspected NSTI should receive treatment appropriate for sepsis or septic shock, including empiric administration of broad spectrum antibiotics and fluid resuscitation. As definitive microbiology is not available until after blood and intra-operative tissue cultures are obtained, empiric antibiotics should cover Gram positive, Gram negative and anaerobic organisms. While the site and etiology of infection heavily influences the causative organism, with perineal infections tending to be polymicrobial NSTIs, antibiotics should cover both Type 1 polymicrobial infections (including *Clostridia* spp.) as well as Type 2 Group A Beta-hemolytic *Streptococcus* (GAS) infections. Type 3 infections, caused by marine organisms such as *Vibrio* spp., are more typically seen in warm-water coastal regions, or associated with the ingestion of shellfish. Empiric coverage against MRSA should be included for patients with history of colonization or recent healthcare exposure. Antibiotics may be tailored to final culture results, and generally, antibiotics are continued until operative debridement has been completed and the patient's immune response begins to resolve.

Surgical Source Control

The cornerstone of treatment for NSTI is early and wide surgical debridement of affected tissue, in order to obtain source control and arrest progression of disease. Delay from presentation to initial surgical debridement is associated with increased number of subsequent debridements and a higher incidence of septic shock and acute renal failure [1–5]. With a 24-h delay from presentation, there is an estimated ninefold increase in mortality [6]. As NSTI can continue and advance despite apparent initial adequate debridement, mandatory return to the operating room within 12–24 h is advisable in the most critically ill patients. Worsening of disease as measured by increased leukocytosis or progressive organ failure, or local spread of erythema and/or induration from the debridement site, should also prompt additional debridements until clinical improvement is established.

Evidence Contour

NSTI treatment is not without controversy. The preponderance of evidence available is from retrospective observational studies, and because of the relative rarity of this disease and its high mortality, randomized controlled trials of novel interventions are also challenging and rare.

Predicting NSTI Diagnosis and Outcome

Multiple scoring systems have been developed to facilitate diagnosis, but even the most widely used score, the laboratory risk indicator for necrotizing fasciitis (LRINEC) which uses level of C-reactive protein, white blood count, hemoglobin level, serum sodium level, serum creatinine level, and serum glucose level at admission, has never been validated prospectively [7]. While hyponatremia and extremes of WBC are also helpful in indicating severity of systematic derangement, and may portend poor outcome, these laboratory features are non-specific.

Magnetic resonance imaging has similarly been shown to be fairly sensitive, but lacks specificity as the tissue enhancement on T2-weighted imaging is frequently seen after trauma and other non-infectious inflammatory processes [8]. Finally, ultrasonography can be used to detect superficial abscesses but lacks sensitivity or specificity for NSTIs [9].

Early Amputation

The decision to perform an emergent extremity amputation is difficult, but when life-threatening infection is present, limb sacrifice may be warranted. For example, a 5-year review at our institution revealed that clostridial infection was an independent predictor for both limb loss and mortality [10]. The functional outcomes of early amputation and complex limb salvage have been demonstrated to be equivalent at 7 year follow up in a meta-analysis [11].

Adjunctive Therapies

Immunomodulatory Therapy

In infections caused by staphylococcal and streptococcal spp., exotoxins may engage the body in a especially robust immune response. Through activation of T cells, a polyclonal expansion and release of proinflammatory cytokines ensures that can lead to the combination of septic shock and multiple organ failure known as "toxic shock syndrome." While intravenous immunoglobulin has been used to neutralize antibodies against streptococcal superantigens, IVIG preparations vary, and success of its administration relies upon adequate antibodies from pooled human serum [12]. Two studies suggested a potential reduction in mortality, but these studies were limited by sample size and lack of randomization [13, 14]. A novel drug that selectively inhibits the direct binding of superantigen exotoxins to the CD28 costimulatory receptor on T-helper 1 lymphocytes was evaluated in a phase 2 randomized placebo controlled trial. This study established the drug's safety and pharmacokinetics in a population of patients with NSTI, and demonstrated promising results in decreasing the incidence of organ failure [15]. While not yet available for clinical use, the development of this therapy signals a new hope for targeting this mechanism of disease progression, and mitigation of the morbidity of NSTI.

Hyperbaric Oxygen

Hyperbaric oxygen (HBO) therapy is performed in a high-pressure chamber, resulting in delivery of oxygen at two to three times typical atmospheric pressure. This leads to substantially increased tissue oxygen tension as high as 300 mmHg, which based on animal and human studies, is thought to reduce tissue edema, stimulate fibroblast growth, increase the killing ability of leukocytes by augmenting the oxidative burst, have independent cytotoxic effects on some anaerobes, inhibit bacterial toxin elaboration and release, and enhance antibiotic efficacy. Multiple studies have examined the use of HBO in the treatment of NSTIs with mixed results. Early single-institution and small retrospective studies suggested a mortality benefit for patients with NSTI who were treated with HBO [16, 17]. Recent studies with larger sample sizes have failed to show a beneficial effect on mortality [18–20]. Due to lack of clear benefit, and to significant limitations on care delivery possible in hyperbaric chambers, HBO therapy should be limited to hemodynamically stable patients in whom HBO therapy will not delay surgical debridement.

References

1. Freischlag JA, Ajalat G, Busuttil RW. Treatment of necrotizing soft tissue infections. The need for a new approach. Am J Surg. 1985;149(6):751–5.
2. McHenry CR, Piotrowski JJ, Petrinic D, Malangoni MA. Determinants of mortality for necrotizing soft-tissue infections. Ann Surg. 1995;221(5):558–63; discussion 563–5.
3. Wall DB, de Virgilio C, Black S, Klein SR. Objective criteria may assist in distinguishing necrotizing fasciitis from nonnecrotizing soft tissue infection. Am J Surg. 2000;179(1):17–21.
4. Wong C-H, Chang H-C, Pasupathy S, Khin L-W, Tan J-L, Low C-O. Necrotizing fasciitis:

clinical presentation, microbiology, and determinants of mortality. J Bone Joint Surg Am Vol. 2003;85-A(8):1454–60.
5. Bilton BD, Zibari GB, McMillan RW, Aultman DF, Dunn G, McDonald JC. Aggressive surgical management of necrotizing fasciitis serves to decrease mortality: a retrospective study. Am Surg. 1998;64(5):397–400; discussion 400–1.
6. Kobayashi L, Konstantinidis A, Shackelford S, Chan LS, Talving P, Inaba K, et al. Necrotizing soft tissue infections: delayed surgical treatment is associated with increased number of surgical debridements and morbidity. J Trauma. 2011;71(5):1400–5.
7. Wong C, Khin L. Clinical relevance of the LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score for assessment of early necrotizing fasciitis. Crit Care Med. 2005;33(7):1677.
8. Arslan A, Pierre-Jerome C, Borthne A. Necrotizing fasciitis: unreliable MRI findings in the preoperative diagnosis. Eur J Radiol. 2000;36(3):139–43.
9. Loyer EM, DuBrow RA, David CL, Coan JD, Eftekhari F. Imaging of superficial soft-tissue infections: sonographic findings in cases of cellulitis and abscess. AJR Am J Roentgenol. 1996;166(1):149–52.
10. Anaya DA, Bulger EM, Kwon YS, Kao LS, Evans H, Nathens AB. Predicting death in necrotizing soft tissue infections: a clinical score. Surg Infect. 2009;10(6):517–22.
11. Busse JW, Jacobs CL, Swiontkowski MF, Bosse MJ, Bhandari M. Evidence-Based Orthopaedic Trauma Working Group. Complex limb salvage or early amputation for severe lower-limb injury: a meta-analysis of observational studies. J Orthop Trauma. 2007;21(1):70–6.
12. Kaul R, McGeer A, Norrby-Teglund A, Kotb M, Schwartz B, O'Rourke K, et al. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome--a comparative observational study. The Canadian Streptococcal Study Group. Clin Infect Dis. 1999;28(4):800–7.
13. Davies HD, McGeer A, Schwartz B, Green K, Cann D, Simor AE, et al. Invasive group A streptococcal infections in Ontario, Canada. Ontario Group A Streptococcal Study Group. N Engl J Med. 1996;335(8):547–54.
14. Linnér A, Darenberg J, Sjölin J, Henriques-Normark B, Norrby-Teglund A. Clinical efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal toxic shock syndrome: a comparative observational study. Clin Infect Dis. 2014; 59(6):851–7.
15. Bulger EM, Maier RV, Sperry J, Joshi M, Henry S, Moore FA, et al. A novel drug for treatment of necrotizing soft-tissue infections: a randomized clinical trial. JAMA Surg Am Med Assoc. 2014;149(6):528–36.
16. Riseman JA, Zamboni WA, Curtis A, Graham DR, Konrad HR, Ross DS. Hyperbaric oxygen therapy for necrotizing fasciitis reduces mortality and the need for debridements. Surgery. 1990;108(5):847–50.
17. Pizzorno R, Bonini F, Donelli A, Stubinski R, Medica M, Carmignani G. Hyperbaric oxygen therapy in the treatment of Fournier's disease in 11 male patients. J Urol. 1997;158(3 Pt 1):837–40.
18. George ME, Rueth NM, Skarda DE, Chipman JG, Quickel RR, Beilman GJ. Hyperbaric oxygen does not improve outcome in patients with necrotizing soft tissue infection. Surg Infect. 2009;10(1):21–8.
19. Massey PR, Sakran JV, Mills AM, Sarani B, Aufhauser DD, Sims CA, et al. Hyperbaric oxygen therapy in necrotizing soft tissue infections. J Surg Res. 2012;177(1):146–51.
20. Brown DR, Davis NL, Lepawsky M, Cunningham J, Kortbeek J. A multicenter review of the treatment of major truncal necrotizing infections with and without hyperbaric oxygen therapy. Am J Surg. 1994;167(5): 485–9.

Biliary Infections

86

Gregory A. Watson and Andrew B. Peitzman

Case Presentation

A 44 year-old morbidly obese male (470 lbs, BMI 55) with a history of type II diabetes mellitus developed fever (102.5 °C) and "shaking chills" 5 days earlier, followed 24 h later by nausea and vomiting. At that time, he presented to an urgent care center and was felt to have influenza and was discharged with a prescription for Tamiflu. His symptoms persisted, and 2 days prior to admission he developed right upper quadrant (RUQ) abdominal pain and worsening malaise. He was evaluated at an outlying emergency room, where he was noted to have jaundice with a temperature of 39.2 ° C, P 120 bpm, BP 96/60 mmHg, and marked RUQ tenderness. A RUQ ultrasound revealed numerous gallstones, a thickened gallbladder wall with pericholecystic fluid, and a common bile duct (CBD) measuring 8 mm. Pertinent labs included a white blood cell (WBC) count of 21,000/mm^3 with 20 % bands, creatinine mg/dL of 3.1, glucose 389 mg/dL, total bilirubin 5.4 mg/dL (direct 4.0), alkaline phosphatase (ALP) 227, aspartate aminotransferase (AST) 140, and alanine aminotransferase (ALT) 258. Appropriate initial care was instituted at the outlying hospital, and he was transferred to an intensive care unit (ICU) at a tertiary hospital for further management.

Question What is the diagnosis and how should this patient be managed?

Answer Acute cholecystitis, possible ascending cholangitis

The patient was admitted to the surgical ICU and was given 2 l of normal saline while central venous and arterial catheters were inserted. Blood cultures were obtained and the patient was started on piperacillin/tazobactam as empiric antibiotic coverage and norepinephrine to target a mean arterial pressure (MAP) of 65 mmHg, as well as an insulin infusion for treatment of hyperglycemia. Shortly thereafter, he required intubation for worsening mental status and progressive pulmonary failure. Both the surgery and gastroenterology services were consulted, and the patient was taken urgently to the operating room where an endoscopic retrograde cholangiopancreatography (ERCP) was performed initially. This revealed a non-dilated biliary tree with contrast filling the cystic duct (but not the gallbladder) and without filling defects (Fig. 86.1). There was a small amount of sludge present but no pus. The biliary tree was swept, a sphincterotomy was performed, and a stent was placed. The patient then underwent

G.A. Watson
Surgery & Critical Care, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

A.B. Peitzman (✉)
Department of Surgery, Trauma and Surgical Services, University of Pittsburgh School of Medicine, UPMC-Presbyterian, Pittsburgh, PA, USA
e-mail: peitzmanab@upmc.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_86

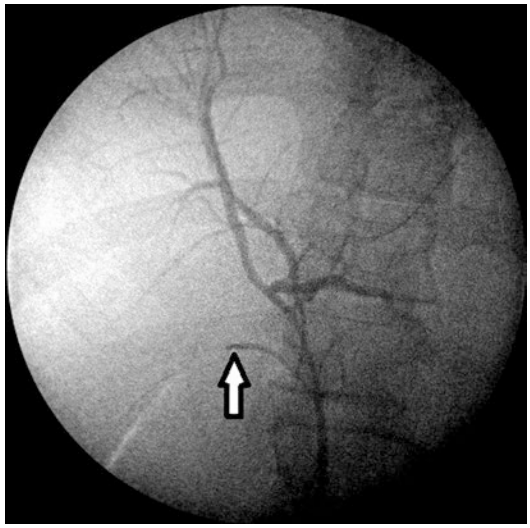


Fig. 86.1 Cholangiogram obtained during ERCP. Note the non-dilated biliary tree, absence of filling defects, and the patent cystic duct (*arrow*) but lack of gallbladder filling

laparoscopy, which revealed gallbladder necrosis. Laparoscopic cholecystectomy was attempted but was difficult given the patients large, fatty liver and bleeding. The procedure was converted to an open operation where a subtotal cholecystectomy was performed with placement of 2 closed-suction drains. Bile cultures were obtained. His immediate postoperative course was notable for worsening septic shock requiring the addition of vasopressin, renal failure necessitating continuous renal replacement therapy, and hyperglycemia. Blood and bile cultures grew *Escherichia coli* which were intermediately sensitive to piperacillin/tazobactam, and his antibiotics were changed to cefepime and metronidazole for a planned 14-day course. After 4 days, the patient weaned from all vasopressors and was able to tolerate intermittent hemodialysis. He was extubated uneventfully on postoperative day #8 but continued to require nocturnal biPAP upon discharge to a rehab facility.

Principles of Management

Diagnosis

The Tokyo Guidelines, first described in 2007 and revised in 2013, were developed to provide guidance for the management of acute cholecystitis and cholangitis. With respect to acute cholecystitis, the diagnosis is suspected when at least one local sign of inflammation (Murphy's sign, RUQ mass/pain/tenderness) is present with one (or more) systemic signs of inflammation (fever, elevated C-reactive protein (CRP), elevated WBC count) [1]. The diagnosis may be confirmed with supportive diagnostic imaging. Using these criteria, the sensitivity is 91.2 %, specificity 96.9 %, positive predictive value 96.7 %, and negative predictive value of 91.6 % with an overall accuracy rate of 94 % [1].

In the case of acute cholangitis, the diagnosis is suspected when one or more systemic signs of inflammation (fever and/or shaking chills, increased CRP, abnormal WBC count) is present with cholestasis, as evidenced by jaundice or abnormal liver function tests (LFT's) (ALP, gamma-glutamyl transferase (gGTP), AST, ALT >1.5× upper limit of normal) [2]. The diagnosis may be confirmed with imaging evidence of biliary dilatation or demonstration of the etiology (stricture, stone, etc.). These criteria are reasonably sensitive (91.8 %) but have moderate specificity (77.7 %). Importantly, 5.9 % of pathologically-proven cases of acute cholecystitis also fulfill these criteria, underscoring the difficulty with distinguishing these two entities at times [2].

Severity Assessment

In addition to standardizing diagnostic criteria, the Tokyo criteria also stratify both acute cholecystitis and cholangitis into varying degrees of severity with the intent of guiding management for each stage of the disease. For acute cholecystitis, three grades ranging from mild (grade I) to severe (grade III) have been described [1, 3]. Grade III acute cholecystitis is accompanied by dysfunction of either the cardiovascular, neurological, respiratory, renal, hepatic, or hematological systems. Grade II (moderate) is acute cholecystitis associated with marked leukocytosis (>18,000/mm^3), palpable tender RUQ mass, duration of symptoms >72 h, or marked local inflammation (gangrenous or emphysematous

cholecystitis, biliary peritonitis, or pericholecystic/hepatic abscess), and grade I (mild) does not meet either of the above criteria. In the case of acute cholangitis, three grades also exist which are similar to those described for acute cholecystitis [2, 3]. In grade III (severe), acute cholangitis is associated with dysfunction of at least one organ/system as described for cholecystitis above. For grade II (moderate) disease, acute cholangitis is associated with either high fever (≥39 °C), age ≥75, abnormal WBC (>12,000 or <4000/mm^3), hyperbilirubinemia (≥5 mg/dL), or hypoalbuminemia (<0.7× lower limit of normal). Grade I (mild) cholangitis does not meet criteria for either grade II or III disease (Tables 86.1 and 86.2).

Medical Management

Medical management should be initiated as soon as the diagnosis of acute cholecystitis or cholangitis is suspected [3]. This includes making the patient *nil per os* (NPO) and providing intravenous fluids, antibiotics, and analgesics, closely monitoring the patient's vital signs and urinary output, while simultaneously determining the disease severity. Antimicrobial therapy should be directed at the likely pathogens, which typically are of enteric origin (*Escherichia coli*, *Klebsiella*, *Enterococcus*, or anaerobic bacteria), and a sample of bile should be sent for culture and sensitivity testing when possible [4]. Selection of the appropriate empiric antibiotic also requires knowledge of disease severity, nosocomial or community-acquired nature of the infection, and patient factors such as recent antibiotic exposure, history of immunosuppression, or presence of a biliary-enteric anastomosis. Knowledge of the local susceptibility profile is also helpful.

The Surgical Infection Society has published guidelines for empiric treatment of biliary infection in adults [5] (Table 86.3). Data regarding duration of antimicrobial therapy are lacking. Most experts would agree that antibiotics can safely be discontinued within 24 h in mild disease (i.e., following cholecystectomy for grade I cholecystitis) but that longer courses are likely necessary in more severe disease. In cases of

Table 86.1 Severity assessment for acute cholecystitis according to the revised Tokyo Guidelines

Grade III (severe) acute cholecystitis is associated with dysfunction in any one of the following:	
1. Cardiovascular	Hypotension requiring treatment with dopamine ≥5 μg/kg per min, or any dose of norepinephrine
2. Neurologic	Decreased level of consciousness
3. Respiratory	PaO_2/FiO_2 ratio <300
4. Renal	Oliguria, creatinine >2.0 mg/dL
5. Hepatic	PT-INR >1.5
6. Hematologic	Platelet count <100,000/mm^3
Grade II (moderate) acute cholecystitis is associated with any one of the following:	
1. Elevated WBC count (>18,000/mm^3)	
2. Palpable tender mass in the RUQ	
3. Duration of symptoms >72 h	
4. Marked local inflammation (gangrenous or emphysematous cholecystitis, pericholecystic or hepatic abscess, biliary peritonitis)	
Grade I (mild) acute cholecystitis does not meet the criteria for grade II or III disease	

Adapted from Yokoe et al. [1]

Table 86.2 Severity assessment for acute cholangitis according to the revised Tokyo Guidelines

Grade III (severe) acute cholangitis is associated with dysfunction in any one of the following:	
1. Cardiovascular	Hypotension requiring treatment with dopamine ≥5 μg/kg per min, or any dose of norepinephrine
2. Neurologic	Disturbance of consciousness
3. Respiratory	PaO_2/FiO_2 ratio <300
4. Renal	Oliguria, creatinine >2.0 mg/dL
5. Hepatic	PT-INR >1.5
6. Hematologic	Platelet count <100,000/mm^3
Grade II (moderate) acute cholangitis is associated with any two of the following:	
1. Abnormal WBC count (>12,000/mm^3, <4000/mm^3)	
2. High fever (≥39 °C)	
3. Age ≥75 years	
4. Hyperbilirubinemia (total bilirubin ≥5 mg/dL)	
5. Hypoalbuminemia (<0.7 × lower limit of normal)	
Grade I (mild) acute cholangitis does not meet the criteria for grade II or III disease	

Adapted from Kiriyama et al. [2]

Table 86.3 Empiric treatment of biliary infection in adults

Infection	Regimen
Mild-moderate community-acquired acute cholecystitis	Cefazolin, cefuroxime, or ceftriaxone
Community-acquired acute cholecystitis of high severity or in the setting of advanced age or immunosuppression	Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam, ciprofloxacin, levofloxacin, or cefepime each in combination with metronidazole[a]
Acute cholangitis of any severity following bilio-enteric anastomosis	Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam, ciprofloxacin, levofloxacin, or cefepime each in combination with metronidazole[a]
Healthcare-associated biliary infection	Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam, ciprofloxacin, levofloxacin, or cefepime each in combination with metronidazole, vancomycin added to each regimen[a]

Adapted from Solomkin et al. [5]

[a]Given increasing resistance of *E. coli* to fluoroquinolones, local population susceptibility profiles and isolate susceptibility (if available) should be reviewed

severe disease, longer antimicrobial courses may be indicated. A recent randomized trial of 518 patients with complicated intra-abdominal infection and adequate source control confirmed that a fixed-duration antibiotic therapy (4 days) achieved similar outcomes (primary composite outcome of surgical site infection, recurrent intra-abdominal infection or death within 30 days after the index source control procedure) as a longer course of antibiotics (approximately 8 days) that extended until after the resolution of physiological abnormalities (fever, leukocytosis and ileus) [6].

Surgical and/or Interventional Management

In the case of acute cholecystitis, it is well-established that early (within 48 h of symptom onset) cholecystectomy is associated with several advantages including reduced healthcare costs and length of stay without increased morbidity or mortality. Furthermore, the laparoscopic approach has been shown to be safe when performed by skilled operators. According to the Tokyo Guidelines, early (within 72 h of symptom onset) laparoscopic cholecystectomy is the preferred procedure in cases of grade I and grade II disease [7, 8]. However, if severe inflammation is encountered or suspected, conversion to open cholecystectomy or percutaneous or open gallbladder drainage are safe and preferable options. Grade III acute cholecystitis is managed with supportive therapy and early gallbladder drainage. Cholecystectomy is performed at a later date if indicated (may not be necessary in some cases of cholecystitis) [9].

Biliary drainage is the most crucial component of therapy for acute cholangitis and may be performed by endoscopic, percutaneous interventional, or surgical means [3, 8]. Surgery is rarely utilized at present and is associated with the highest mortality rate. Endoscopic biliary drainage (ERCP) is currently the gold standard given the minimally invasive nature and high success rates. Percutaneous transhepatic cholangiographic (PTC) drainage, in general, is second-line therapy and is most useful in patients with an inaccessible papilla due to altered anatomy (i.e., Roux-en-Y anastomosis) or upper GI obstruction. According to the Tokyo Guidelines, once the diagnosis has been established, medical therapy is instituted as described above. For patients with grade I disease, an initial trial of medical management is acceptable for 24 h but if the patient fails to improve or worsens, biliary drainage should be pursued. In cases of grade II and III disease, urgent biliary decompression is recommended.

Evidence Contour

In general, the tenets of treatment for acute cholecystitis and cholangitis are well-established. However, uncertainty exists regarding the utility of certain diagnostic studies and consensus for duration of antimicrobial therapy are lacking. In

addition, the type and timing of intervention for both cholecystitis and cholangitis are debatable.

Diagnostic Studies

It is generally recommended that the initial diagnostic study for patients with RUQ abdominal pain is ultrasonography. The sensitivity of ultrasound for the diagnosis of acute cholecystitis is 81 % with specificity of 83 % [10, 11]. Though HIDA scan has superior sensitivity (96 %) and specificity (90 %), ultrasound generally is the first-line test as it is more widely available, faster, allows evaluation for gallstones, and allows assessment of the intra- and extrahepatic bile ducts. Furthermore, point-of-care ultrasonography performed by ED physicians for suspected cholecystitis has similar test characteristics to radiology-performed ultrasound and may have applicability in the ICU setting when performed by trained intensivists [12]. HIDA is probably best utilized in uncertain cases when the diagnosis could alter management plans and the patient can tolerate several hours in the radiology suite. Computed tomography (CT) is most useful in equivocal cases and can identify another etiology of the infection or complications of cholecystitis such as gangrene, abscess, perforation, and intraluminal hemorrhage [13]. As an initial test, CT suffers from low sensitivity (39 %) and positive predictive value (50 %). However, the negative predictive value (89 %) is acceptable so it is useful to exclude the diagnosis in patients with low clinical suspicion and nonspecific symptoms.

In the case of cholangitis, ultrasonography is helpful as it will demonstrate biliary dilatation and can also assess for cholecystitis. However, this study may not provide information on the nature of the obstruction. Common causes include choledocholithiasis and both benign and malignant strictures. In cases where urgent decompression is needed (grade III ± grade II), ERCP is both therapeutic and can provide diagnostic information. CT is not recommended as the primary imaging modality in patients with suspected cholangitis but may be obtained if the patient has sepsis of uncertain etiology. The gallstone detection rate is poor, but if choledocholithiasis is demonstrated there is no need for further imaging [11]. Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive method for detecting common bile duct (CBD) stones with a specificity of 96.6 % and a negative predictive value of nearly 100 % [14]. This test should not be ordered in patients in whom ERCP is required (grade III ± grade II cholangitis) but may be useful in milder cases of disease where a negative study would result in nonoperative therapy.

Duration of Antibiotics

As mentioned earlier, data regarding duration of antibiotic therapy in biliary infections are lacking. The 2009 Surgical Infection Society guidelines recommend discontinuation of antibiotics within 24 h of cholecystectomy in the case of mild disease (B-II) and suggest limiting therapy to 4–7 days in cases of more severe disease unless source control is difficult to achieve (B-III) [5]. A point of emphasis from these guidelines, however, was the need to study the appropriate duration of antibiotic therapy as the use of antibiotics in the absence of guidelines is erratic, costly, and without clear benefit [15].

A recent observational study examined the relationship between surgical site infections and duration of antibiotic therapy in 287 patients with grade II acute cholecystitis who underwent cholecystectomy within 72 h. Most patients (58.2 %) received >7 days of antibiotics, while 26.1 % received 5–7 days and 15.7 % had 0–4 days antibiotic therapy [16]. Interestingly, there were no significant differences in frequency of surgical site infection between the groups after risk adjustment, suggesting that a shorter course is reasonable. A larger Swiss database study went one step further, suggesting that antibiotic prophylaxis in acute cholecystectomy may not be beneficial. In this study, 13,911 patients who underwent acute cholecystectomies for gallstone-related complications (73.2 %) and uncomplicated gallstone disease (26.8 %) were reviewed and the relationship between antibiotic prophylaxis and the

development of a postoperative infection requiring antibiotics or abscess formation was reported. Of note, 59 % of patients (n = 8205) in this study had acute cholecystitis. Using multivariable logistic regression, no significant benefit was seen with antibiotic prophylaxis in terms of reduced incidence of postoperative infection requiring antibiotics or abscess formation [17].

Data regarding duration of therapy in acute cholangitis are even more scant. The Tokyo Guidelines recommend 5–7 days of antibiotics for patients with acute cholangitis [18] and the Surviving Sepsis Campaign recommends 7–10 days of antibiotics in patients with sepsis [19]. A recent small, prospective study reported on fever-based management of patients with grade II-III acute cholangitis treated with urgent biliary decompression [20]. Eighteen patients with grade II (n = 14) or III (n = 4) cholangitis underwent biliary decompression with a mean time to drainage of 6 h after diagnosis. Antibiotics were continued until the patient was afebrile (temperature < 37 °C) for a period of 24 h, and recurrence within 3 days and at 4 weeks was reported. Body temperature normalized after a median of 2 days and antibiotics were administered for a median of 3 days. Four patients required 5–7 days of antibiotics, and interestingly these patients were all found to have bacteria resistant to the initial antibiotic, underscoring the importance of obtaining cultures when feasible. No patients suffered a recurrence of cholangitis within 3 days of discontinuing antibiotics or at 4 weeks follow-up. Although the study was a small group of highly-selected patients, it suggests that a shorter course of antibiotics may suffice.

Type and Timing of Intervention

No randomized controlled trials have been completed stratifying the surgical management of cholecystitis by grade of disease. As mentioned above, it is well-accepted that early laparoscopic cholecystectomy is safe and is associated with lower morbidity and shorter postoperative stay relative to open cholecystectomy [21, 22]. Furthermore, early (preferably within 48 h) laparoscopic cholecystectomy is associated with decreased length of stay, decreased rates of readmission, and greater cost savings without an increase in morbidity or conversion to an open procedure when compared to delayed (>6 weeks) laparoscopic cholecystectomy [23].

Two types of patients warrant special mention; those with acute acalculous cholecystitis and those with a prolonged duration of symptoms or who present a prohibitive operative risk.

Acalculous cholecystitis often occurs in chronically ill patients who are more likely to already be in an ICU setting and on antibiotics for unexplained fever. For this reason, diagnosis is often delayed and may be difficult to establish as ultrasound and CT findings may be non-specific. Laparoscopic cholecystectomy may be attempted but conversion rates are high (28 %) [24]. Percutaneous cholecystostomy is probably preferable as the procedure is highly effective and has low morbidity [25–27].

For patients with a prolonged duration of symptoms (>72 h), the Tokyo Guidelines recommend either an attempt at laparoscopic cholecystectomy or gallbladder drainage. However, operative times are prolonged and conversion rates are higher when surgery is delayed beyond 48 h [28]. Antibiotics ± percutaneous cholecystostomy may be used in these patients and in those who present a prohibitive operative risk. The need for interval cholecystectomy remains controversial as there are no randomized controlled trials on the subject. Delayed interval cholecystectomy is typically recommended but recent studies cite a low rate of recurrence (0–16.7 %) following cholecystostomy alone in patients with both calculous [26, 27] and acalculous [25] cholecystitis. Similarly, treatment with antibiotics alone was associated with a low (13.7 %) recurrence rate in 226 patients followed for a median of 308 days [29].

Although biliary decompression is the most crucial component of therapy in the case of cholangitis, the optimal timing is still debated. A retrospective study of 90 patients at the Johns Hopkins Hospital showed that unsuccessful or delayed ERCP was associated with prolonged length of stay and increased costs. Furthermore, a delay in

ERCP was independently associated with increased risk of death, persistent organ failure, and/or ICU admission (OR 7.8, $p=0.04$) [30]. However, "delayed" ERCP was defined as being performed 72 h after admission, which is far later than what the Tokyo Guidelines recommend. A recent study by Mok et al. attempted to better define the optimal timing of biliary decompression. The authors retrospectively reviewed 250 patients who had undergone either ERCP (n = 228) or percutaneous biliary drainage (PBD; n = 22) and reported all-cause mortality with respect to time of intervention [31]. The risk for hospital mortality was significantly less in the earliest quartile (intervention within 11 h) when compared to the latest (>42 h) quartile (RR 0.34, 95 % CI 0.12–0.99, $p=0.049$), and the risk of hospital readmission was also less. Other secondary endpoints, such as multiple organ failure, sepsis, systemic inflammatory response syndrome, and length of stay showed no differences.

References

1. Yokoe M, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Gomi H, Pitt HA, Gouma DJ, Garden OJ, Büchler MW, Kiriyama S, Kimura Y, Tsuyuguchi T, Itoi T, Yoshida M, Miura F, Yamashita Y, Okamoto K, Gabata T, Hata J, Higuchi R, Windsor JA, Bornman PC, Fan ST, Singh H, de Santibanes E, Kusachi S, Murata A, Chen XP, Jagannath P, Lee S, Padbury R, Chen MF; Tokyo Guidelines Revision Committee. New diagnostic criteria and severity assessment of acute cholecystitis in revised Tokyo Guidelines. J Hepatobiliary Pancreat Sci. 2012;19(5):578–85.
2. Kiriyama S, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Pitt HA, Gouma DJ, Garden OJ, Büchler MW, Yokoe M, Kimura Y, Tsuyuguchi T, Itoi T, Yoshida M, Miura F, Yamashita Y, Okamoto K, Gabata T, Hata J, Higuchi R, Windsor JA, Bornman PC, Fan ST, Singh H, de Santibanes E, Gomi H, Kusachi S, Murata A, Chen XP, Jagannath P, Lee S, Padbury R, Chen MF; Tokyo Guidelines Revision Committee. New diagnostic criteria and severity assessment of acute cholangitis in revised Tokyo Guidelines. J Hepatobiliary Pancreat Sci. 2012;19(5):548–56.
3. Miura F, Takada T, Kawarada Y, Nimura Y, Wada K, Hirota M, Nagino M, Tsuyuguchi T, Mayumi T, Yoshida M, Strasberg SM, Pitt HA, Belghiti J, de Santibanes E, Gadacz TR, Gouma DJ, Fan ST, Chen MF, Padbury RT, Bornman PC, Kim SW, Liau KH, Belli G, Dervenis C. Flowcharts for the diagnosis and treatment of acute cholangitis and cholecystitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14(1):27–34.
4. Fuks D, Cossé C, Régimbeau JM. Antibiotic therapy in acute calculous cholecystitis. J Visc Surg. 2013;150(1):3–8.
5. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, O'Neill PJ, Chow AW, Dellinger EP, Eachempati SR, Gorbach S, Hilfiker M, May AK, Nathens AB, Sawyer RG, Bartlett JG. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect (Larchmt). 2010;11(1):79–109.
6. Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, Cook CH, O'Neill PJ, Mazuski JE, Askari R, Wilson MA, Napolitano LM, Namias N, Miller PR, Dellinger EP, Watson CM, Coimbra R, Dent DL, Lowry SF, Cocanour CS, West MA, Banton KL, Cheadle WG, Lipsett PA, Guidry CA, Popovsky K. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med. 2015;372(21):1996–2005.
7. Yamashita Y, Takada T, Strasberg SM, Pitt HA, Gouma DJ, Garden OJ, Büchler MW, Gomi H, Dervenis C, Windsor JA, Kim SW, de Santibanes E, Padbury R, Chen XP, Chan AC, Fan ST, Jagannath P, Mayumi T, Yoshida M, Miura F, Tsuyuguchi T, Itoi T, Supe AN, Tokyo Guideline Revision Committee. TG13 surgical management of acute cholecystitis. J Hepatobiliary Pancreat Sci. 2013;20(1):89–96.
8. Okamoto K, Takada T, Strasberg SM, Solomkin JS, Pitt HA, Garden OJ, Büchler MW, Yoshida M, Miura F, Kimura Y, Higuchi R, Yamashita Y, Mayumi T, Gomi H, Kusachi S, Kiriyama S, Yokoe M, Lau WY, Kim MH, Tokyo Guideline Revision Committee. TG13 management bundles for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2013;20(1):55–9.
9. Kirkegård J, Horn T, Christensen SD, Larsen LP, Knudsen AR, Mortensen FV. Percutaneous cholecystostomy is an effective definitive treatment option for acute acalculous cholecystitis. Scand J Surg. 2015. 104(4):238–43.
10. Kiewiet JJ, Leeuwenburgh MM, Bipat S, Bossuyt PM, Stoker J, Boermeester MA. 43. A systematic review and meta-analysis of diagnostic performance of imaging in acute cholecystitis. Radiology. 2012;264(3):708–20.
11. Yarmish GM, Smith MP, Rosen MP, Baker ME, Blake MA, Cash BD, Hindman NM, Kamel IR, Kaur H, Nelson RC, Piorkowski RJ, Qayyum A, Tulchinsky M. ACR appropriateness criteria right upper quadrant pain. J Am Coll Radiol. 2014;11(3):316–22.
12. Summers SM, Scruggs W, Menchine MD, Lahham S, Anderson C, Amr O, Lotfipour S, Cusick SS, Fox JC. A prospective evaluation of emergency department bedside ultrasonography for the detection of acute cholecystitis. Ann Emerg Med. 2010;56(2):114–22.

13. Patel NB, Oto A, Thomas S. Multidetector CT of emergent biliary pathologic conditions. Radiographics. 2013;33(7):1867–88.
14. Chang JH, Lee IS, Lim YS, Jung SH, Paik CN, Kim HK, Kim TH, Kim CW, Han SW, Choi MG, Jung IS. Role of magnetic resonance cholangiopancreatography for choledocholithiasis: analysis of patients with negative MRCP. Scand J Gastroenterol. 2012;47(2): 217–24.
15. Kanafani ZA, Khalifé N, Kanj SS, Araj GF, Khalifeh M, Sharara AI. Antibiotic use in acute cholecystitis: practice patterns in the absence of evidence-based guidelines. J Infect. 2005;51(2):128–34.
16. Rodríguez-Sanjuán JC, Casella G, Antolín F, Castillo F, Fernández-Santiago R, Riaño M, Herrera LA, Gómez-Fleitas M. How long is antibiotic therapy necessary after urgent cholecystectomy for acute cholecystitis? J Gastrointest Surg. 2013;17(11):1947–52.
17. Jaafar G, Persson G, Svennblad B, Sandblom G. Outcomes of antibiotic prophylaxis in acute cholecystectomy in a population-based gallstone surgery registry. Br J Surg. 2014;101(2):69–73.
18. Tokyo Guidelines for the management of acute cholangitis and cholecystitis. Proceedings of a consensus meeting, April 2006, Tokyo, Japan. J Hepatobiliary Pancreat Surg. 2007;14(1):1–121.
19. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008;36(1):296–327.
20. Kogure H, Tsujino T, Yamamoto K, Mizuno S, Yashima Y, Yagioka H, Kawakubo K, Sasaki T, Nakai Y, Hirano K, Sasahira N, Isayama H, Tada M, Kawabe T, Omata M, Harada S, Ota Y, Koike K. Fever-based antibiotic therapy for acute cholangitis following successful endoscopic biliary drainage. J Gastroenterol. 2011;46(12):1411–7.
21. Catena F, Ansaloni L, Bianchi E, Di Saverio S, Coccolini F, Vallicelli C, Lazzareschi D, Sartelli M, Amaduzzi A, Amaduzz A, Pinna AD. The ACTIVE (Acute Cholecystitis Trial Invasive Versus Endoscopic) Study: multicenter randomized, double-blind, controlled trial of laparoscopic versus open surgery for acute cholecystitis. Hepatogastroenterology. 2013;60(127):1552–6.
22. Pessaux P, Tuech JJ, Rouge C, Duplessis R, Cervi C, Arnaud JP. Laparoscopic cholecystectomy in acute cholecystitis. A prospective comparative study in patients with acute vs. chronic cholecystitis. Surg Endosc. 2000;14(4):358–61.
23. Gurusamy KS, Davidson C, Gluud C, Davidson BR. Early versus delayed laparoscopic cholecystectomy for people with acute cholecystitis. Cochrane Database Syst Rev. 2013;(6):CD005440.
24. Morse BC, Smith JB, Lawdahl RB, Roettger RH. Management of acute cholecystitis in critically ill patients: contemporary role for cholecystostomy and subsequent cholecystectomy. Am Surg. 2010;76(7):708–12.
25. Chung YH, Choi ER, Kim KM, Kim MJ, Lee JK, Lee KT, Lee KH, Choo SW, Do YS, Choo IW. Can percutaneous cholecystostomy be a definitive management for acute acalculous cholecystitis? J Clin Gastroenterol. 2012;46(3):216–9.
26. Cha BH, Song HH, Kim YN, Jeon WJ, Lee SJ, Kim JD, Lee HH, Lee BS, Lee SH. Percutaneous cholecystostomy is appropriate as definitive treatment for acute cholecystitis in critically ill patients: a single center, cross-sectional study. Korean J Gastroenterol. 2014;63(1):32–8.
27. Zerem E, Omerović S. Can percutaneous cholecystostomy be a definitive management for acute cholecystitis in high-risk patients? Surg Laparosc Endosc Percutan Tech. 2014;24(2):187–91.
28. Brooks KR, Scarborough JE, Vaslef SN, Shapiro ML. No need to wait: an analysis of the timing of cholecystectomy during admission for acute cholecystitis using the American College of Surgeons National Surgical Quality Improvement Program database. J Trauma Acute Care Surg. 2013;74(1):167–73. 173–4.
29. Wang CH, Chou HC, Liu KL, Lien WC, Wang HP, Wu YM. Long-term outcome of patients with acute cholecystitis receiving antibiotic treatment: a retrospective cohort study. World J Surg. 2014;38(2): 347–54.
30. Khashab MA, Tariq A, Tariq U, Kim K, Ponor L, Lennon AM, Canto MI, Gurakar A, Yu Q, Dunbar K, Hutfless S, Kalloo AN, Singh VK. Delayed and unsuccessful endoscopic retrograde cholangiopancreatography are associated with worse outcomes in patients with acute cholangitis. Clin Gastroenterol Hepatol. 2012;10(10):1157–61.
31. Mok SR, Mannino CL, Malin J, Drew ME, Henry P, Shivaprasad P, Milcarek B, Elfant AB, Judge TA. Does the urgency of endoscopic retrograde cholangiopancreatography (ercp)/percutaneous biliary drainage (pbd) impact mortality and disease related complications in ascending cholangitis? (deim-i study). J Interv Gastroenterol. 2012;2(4):161–7.

Part XI

Critical Care in Obstetrics

Marie R. Baldisseri

Peripartum Cardiomyopathy

87

Hayah Kassis, Maria Patarroyo Aponte, and Srinivas Murali

Case Presentation

A 28 year old African-American woman presented to her primary care physician 3 months postpartum with a chief complaint of progressive shortness of breath. She reported a progressive onset during the last month of gestation which was out of proportion compared to her previous pregnancy. At that time, the symptoms were attributed to normal physiologic changes of gravidity. However, her symptoms did not improve in the first few weeks after delivery and progressed to include orthopnea, nocturnal cough, and lower extremity swelling. A transthoracic echocardiogram revealed four chamber enlargement, severely reduced left ventricular systolic function with an ejection fraction of 5–10 %, right ventricular dysfunction, moderate mitral and tricuspid regurgitation, and an elevated pulmonary artery systolic pressure of 56 mmHg. Additionally, there was a left ventricular thrombus noted on the anteroseptal wall. A right heart catheterization revealed elevated filling pressures and low cardiac output consistent with acute decompensated heart failure with a reduced ejection fraction (HFrEF). She was given intravenous diuretics and intravenous heparin and dobutamine infusions were initiated.

On day 1 of her hospitalization, the patient developed acute mental status changes and right sided hemiplegia. She was emergently intubated for airway protection. CT imaging ruled out intracerebral hemorrhage, but CT angiography revealed a large area of left middle cerebral artery territory ischemia and distal left internal carotid artery occlusion. She underwent catheter embolectomy. Her medical course was further complicated by hemorrhagic conversion of cerebral ischemia and impending central brain herniation prompting emergent craniotomy. On day 4, she was extubated and the right sided paresis improved. Anticoagulation with intravenous heparin was continued throughout her hospitalization.

Inotropic therapy with dobutamine was also continued and she underwent aggressive intravenous diuresis. After her filling pressures and cardiac indices were optimized, the dobutamine infusion was weaned and discontinued. Therapy with an angiotensin converting enzyme inhibitor and a beta blocker was initiated. Given gestational hypertension, preeclampsia history, and an active 10 pack year history of tobacco use, the patient underwent a selective coronary angiogram which ruled out obstructive coronary artery disease. Cardiac MR was obtained for further

H. Kassis • M.P. Aponte
Cardiovascular Institute, Allegheny Health Network, Pittsburgh, PA, USA

S. Murali (✉)
Cardiovascular Institute, Allegheny Health Network, Pittsburgh, PA, USA

Cardiovascular Medicine, Allegheny General Hospital, Pittsburgh, PA, USA
e-mail: srinivas.murali@ahn.org

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_87

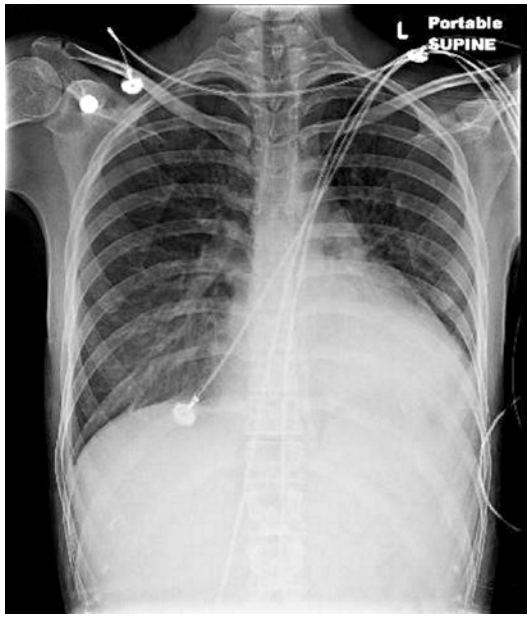


Fig. 87.1 Chest X-ray on admission showing cardiomegaly without significant pulmonary congestion

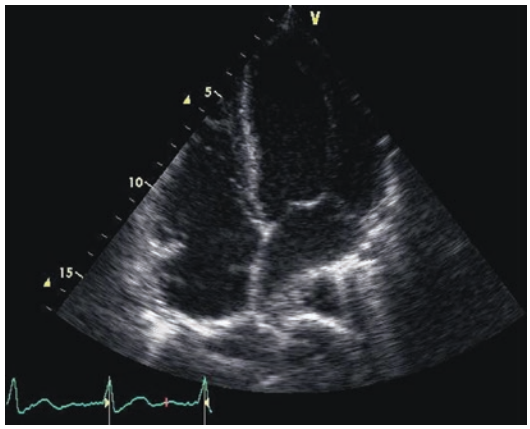


Fig. 87.2 Trans-thoracic echocardiogram 4-chamber view showing enlargement of both left and right ventricles consistent with a dilated cardiomyopathy

assessment of myocardial structure and function. This revealed dissipation of the left ventricular mural thrombus and viable myocardium. There was no late gadolinium enhancement indicative of infarction, inflammation or infiltration. The left ventricular ejection fraction had increased to 35 % (Figs. 87.1 and 87.2).

The patient was discharged to a skilled nursing facility. Guideline directed medical therapy was optimized as an outpatient as tolerated based on heart rate and blood pressure measurements. Transthoracic echocardiogram repeated 3 months post hospitalization revealed normal left ventricular dimensions, only mildly reduced left systolic function (LVEF 50 %), mildly reduced right ventricular systolic function, no significant valvular disease, and borderline elevated pulmonary pressures of 40 mmHg.

Question What is her diagnosis and her treatment regimen?

Answer Peripartum Cardiomyopathy

Peripartum cardiomyopathy (PPCM) is defined as (1) the new development of cardiomyopathy in a previously healthy woman in the final month of gestation or up to 5 months postpartum; (2) demonstration of left ventricular systolic dysfunction (ejection fraction < 45 %, and/or fractional shortening < 30 %, end-diastolic dimension > 2.7 cm/m^2) and; (3) the absence of an identifiable cause or any prior heart disease [1]. The overall incidence is relatively low, less than 0.1 % of pregnancies, and the majority of patients present in the first 4 months postpartum and are in the upper or lower end of the child bearing age. The etiology of PPCM may be multi-factorial and it remains a diagnosis of exclusion. A familial predisposition has been reported. Viral myocarditis has been proposed and supported by findings of myocyte edema, necrosis, fibrosis and lymphocytic infiltration on myocardial biopsy. A pathologic immune response to fetal cells in the maternal myocardium after delivery (micro-chimerism), exaggerated mal-adaptive hemodynamic response during pregnancy characterized by increased cardiac output, decreased afterload, left ventricular hypertrophy and dysfunction, excessive secretion of prolactin, increased pro-inflammatory cytokines, mal-nutrition and selenium deficiency, and prolonged use of tocolytic drugs have all been proposed as mechanisms contributing to the development of PPCM [2].

Symptoms of PPCM include progressive dyspnea, orthopnea, cough, unintentional weight

Table 87.1 Maternal risk factors and adverse events in PPCM

Maternal risk factors	Major adverse events	Long term effects of major adverse events
Advanced maternal age	Cardiopulmonary arrest	Death
African American race	Refractory heart failure	Permanent pacemaker
Non-Caucasian ethnicity	Atrial fibrillation or flutter	Implantable cardioverter defibrillator
Multiparity	Ventricular Arrhythmia	Temporary mechanical circulatory support
Multigravidity	Cerebrovascular accident	Left ventricular assist device
Twin pregnancy	Limb ischemia	Heart transplantation
Poor socioeconomic status		Neurologic deficits
Gestational Hypertension		
Pre-eclampsia		

gain or retention of weight post-partum, and peripheral edema. If mild, these same symptoms may be attributed to physiological changes of pregnancy resulting in a delay in the diagnosis. One series demonstrated a significant correlation between major adverse event rates and several weeks' delay in diagnosis; therefore heightened awareness is crucial [3]. Chest discomfort and palpitations are common and may be due to dysrhythmias. There is a higher incidence of systemic embolization in PPCM. Historical clues indicative of thromboembolic phenomena include transient loss of vision, aphasia, dysphagia, asymmetric lower extremity edema, digital cyanosis, abdominal pain and decreased urine output.

Risk factors associated with the development of PPCM include African American race, advanced maternal age, multiparity, multigravidity, tocolysis, gestational hypertension or preeclampsia [3, 4]. Major adverse events are more common in non-Caucasian women, initial left ventricular ejection fraction ≤25 % and delay in diagnosis, and are attributed to the development of left ventricular thrombus, ventricular arrhythmias, and refractory heart failure [3]. Complications and long term effects include cardiac arrest, thromboembolic events, limb ischemia, neurological deficits, and use of temporary or permanent mechanical circulatory support devices, death, and heart transplantation (Table 87.1). Patients who have suffered a neurological insult have residual long-term morbidity [3–5].

PPCM patients who recover their left ventricular systolic function have a good prognosis. Evidence suggests that 30–50 % of patients can fully recover left ventricular function on optimal medical therapy. There is a risk for recurrence of PPCM among these patients with subsequent pregnancies [6]. The precise risk is difficult to predict, and there are no guidelines on this issue. PPCM patients with persistent left ventricular dysfunction are clearly at risk for recurrence with subsequent pregnancies. They are also at high risk for premature births and spontaneous abortions. These patients should be strongly counseled against future pregnancies. Patients who fully recover their cardiac function have a 20 % risk of relapse with subsequent pregnancies. Patients who have a normal cardiac contractile reserve on an exercise echocardiogram may be at an even lower risk for relapse with subsequent pregnancy. These patients could undergo another pregnancy under careful monitoring with serial echocardiograms, and NT pro-BNP measurements without a relapse of PPCM. It is also not clear if women who fully recover their cardiac function can safely discontinue their heart failure therapy without the risk of decline in their LVEF. In the absence of guidelines, most physicians tend to continue medical therapy in recovered patients. Reported mortality worldwide in PPCM ranges between 5 and 32 % [7, 8]. Patients who present in severe heart failure or shock have a higher mortality. Mortality is also threefold higher in patients who have a fractional shortening of <20 % and a left ventricular end-diastolic dimension of >6 cm at initial presentation. Mortality rates have improved in recent years with early diagnosis and implementation of guideline based medical therapy.

Principles of Management

Diagnosis

Initially, the clinician must to perform a careful bedside clinical assessment looking for signs of hypoperfusion or signs of congestion that will help to identify the hemodynamic profile of the patient [9]. Signs of hypoperfusion include: cool extremities, altered mental status, decreased pulse pressure and renal insufficiency, while signs of congestion include: jugular venous distention, lower extremity edema, rales on auscultation. In most cases, the clinical evaluation will be enough to define the hemodynamic profile of the patient. However, sometimes invasive monitoring with pulmonary artery catheterization may be necessary to make the diagnosis and guide therapy, although there are no studies that compare invasive hemodynamic monitoring plus treatment versus standard of care alone in this population [10]. Once the hemodynamic profile of the patient has been established, the therapy will be guided to relieve congestion and/or improve cardiac output.

Initial assessment in PPCM should include transthoracic echocardiography to evaluate cardiac size and function, and investigate the presence of a left ventricular thrombus which is not uncommon [1]. Cardiac magnetic resonance (CMR) provides a more accurate measurement of both ventricular volumes, ejection fraction, and has a higher sensitivity for the detection of a left ventricular thrombus. Late gadolinium enhancement and T2 weighted imaging can provide important diagnostic information regarding inflammation or myocarditis and fibrosis. Depending on concomitant co-morbidities and maternal age, assessment for ischemia should be made with coronary angiography or stress testing.

Electrocardiogram findings include sinus tachycardia, left ventricular hypertrophy and ST-T wave repolarization abnormalities [11]. Patients may present with supraventricular or ventricular arrhythmias or cardiac arrest, as observed in patients with any form of cardiomyopathy. The electrocardiogram can help differentiate other causes of acute heart failure, including myocardial infarction or ischemia, cardiac tamponade, pulmonary embolus, mitral stenosis, or hemodynamically significant dysrhythmias.

Laboratory investigation includes measurement of NT-pro brain natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP). The median serum levels of NT-proBNP observed in the first week postpartum after a normal pregnancy is typically about 100 ng/mL but can reach levels up to 700 ng/mL. This is attributed to increased venous return and preload after decompression of the IVC at childbirth [12–14]. However, in peripartum cardiomyopathy NT-proBNP levels are significantly higher with levels in the range of nearly 1000–3000 ng/mL [14].

Differential diagnoses should guide other diagnostic investigations including left heart catheterization and cardiac biomarkers if there is a suspicion of pregnancy-associated myocardial ischemia or infarction, ventilation-perfusion scanning or CT pulmonary angiogram and D-dimer if pulmonary embolus is suspected, and checking HIV assays as a potential cause for non-dilated cardiomyopathy [5]. Ultimately imaging modalities and laboratory data are complementary to a thorough physical examination and invasive hemodynamic assessment may be needed for directed therapeutic approach (Table 87.2).

Table 87.2 Diagnosis of PPCM

Clinical suspicion	Symptoms and signs	Diagnostic studies
Previously healthy woman with new onset heart failure in the last month of gestation or first 4 months post-partum Risk factors for PPCM Family History	Dyspnea at rest or exertion Fatigue Exercise intolerance Edema Chest pain Palpitations Cough Weight gain Weakness Jugular venous distension Tachycardia S3 or S4 gallop	Complete blood count and differential Complete chemistry BNP or NT-proBNP Cardiac troponin-T (if needed) Chest X-ray (if needed) EKG Transthoracic echocardiogram CMR Endomyocardial biopsy (if indicated)

Standard Medical Therapy for Heart Failure

The medical therapy for acute decompensated heart failure in peripartum cardiomyopathy is the same as to those patients with acute systolic heart failure from other etiologies (Table 87.3). In general, oxygen should be administered to patients with oxygen saturations lower than 90%. If the patient is in distress, they should be promptly intubated and placed on mechanical ventilation to reduce the work of breathing. For patients with pulmonary congestion, especially those who present with pulmonary edema, the use of intravenous diuretics will help with immediate relief of the symptoms. Loop diuretics should be used cautiously in the antepartum period as precipitous decreases in blood pressure from a large diuresis can compromise placental blood flow. Thiazide diuretics may be a useful alternative in these patients. Vasodilators like, nitroglycerine, nitropusside and nesiritide can be used in combination with diuretic therapy and will help to decrease preload and afterload in those patients who present with elevated blood pressures. However, these medications should be avoided in patients with systolic blood pressure less than 100 mmHg. Inotropes like dobutamine and

Table 87.3 Pharmacologic therapy in PPCM

Clinical presentation	Medication	Dose	During pregnancy	During lactation
Acute decompensated heart failure				
Fetal monitoring in antepartum women	Furosemide Bumetanide	20–600 mg daily 0.5–10 mg daily	Compatible Compatible	Compatible Compatible
	If SBP ≥100 mmHg			
	Nitroglycerine	0.1–5.0 mcg/kg/min	Compatible	Compatible
	Nitroprusside	0.2–5 mcg/kg/min	Unknown	Unknown
	Milrinone	0.125–0.75mcg/kg/min	Compatible	Unknown
	Dobutamine	2–10 mcg/kg/min	Compatible	Unknown
	If SBP ≤80 mmHg			
	Norepinephrine	0.01–3 mcg/kg/min	Compatible	Unknown
	Epinephrine	0.01–2 mcg/kg/min	Compatible	Unknown
	Dopamine	2.5–20 mcg/kg/min	Compatible	Unknown
Chronic heart failure				
Angiotensin-converting enzyme inhibitor (ACE-I)	Lisinopril Enalapril Captopril losartan	2.5–40 mg daily 2.5–10 mg BID 6.25–50 mg TID 25–150 mg daily	Discontinue Discontinue Discontinue Discontinue	Discontinue Discontinue Discontinue Discontinue
Angiotensin II receptor blockers (ARBs)	Valsartan	40–160 mg BID	Discontinue	Discontinue
Alternative to ACE-I/ARBs	Hydralazine Isosorbide dinitrite	25–100 mg TID 10–30 mg TID or QID	Compatible Compatible	Compatible Compatible
Beta blockers	Carvedilol Metoprolol succinate	3.125–50 mg BID 12.5–200 mg daily	Discontinue Compatible	Discontinue Compatible
Aldosterone antagonists	Epleronone Spironolactone	25 mg daily 12.5–25 mg daily	Unknown Compatible	Unknown Discontinue
Digoxin		0.125–0.25 mg daily	Compatible	Compatible
Targeted therapies				
	Bromocriptine IV immunoglobulin Pentoxifylline	2.5 mg BID for 2 weeks, then 2.5 mg daily for 4–6 weeks 1 g/kg daily for 2 days 400 mg TID	Compatible Compatible Compatible Unknown	Discontinue Unknown Discontinue Unknown

milrinone are indicated in patients who present with decreased perfusion or in cardiogenic shock in order to improve the cardiac output and maintain adequate organ perfusion. Other inotropic drugs like levosimendan, although used extensively in other countries, are not approved in the United States [5]. The use of vasopressors like norepinephrine, epinephrine and dopamine is associated with an increase in afterload and a subsequent decrease in the cardiac output and their use should be restricted to patients with marked hypotension despite adequate filling pressures and cardiac output.

Chronic Medical Therapy

Once hemodynamic stabilization is achieved, the patients should be started on chronic therapy for heart failure with reduced ejection fraction in accordance with the AHA/ACC guidelines targeting goal doses, including angiotensin converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs), hydralazine-nitrate for those patients intolerant or with contraindications to the use of ACE-I or ARBs, and aldosterone antagonists. Beta blockers should be started once the patients are euvolemic and no longer requiring intravenous therapies [15]. It is important to remember that during pregnancy the use of ACE-I and ARBs is contraindicated due to fetal toxicity. Eplerenone, an aldosterone antagonist, is generally contraindicated during pregnancy due to lack of studies on fetal toxicity and beta blockers with B2 receptor antagonism should be avoided due to their anti-tocolytic action [5].

Anticoagulation

Acute and/or chronic anticoagulation is needed in patients with paroxysmal or persistent atrial arrhythmias, demonstrable left ventricular thrombus or clinical evidence for embolic event. The use of novel oral anti-coagulants is not recommended in PPCM.

Implantable Cardioverter Defibrillator

Patients with symptomatic, sustained ventricular tachycardia or survivors of cardiac arrest will need an implantable cardioverter defibrillator (ICD) prior to discharge from the hospital. Patients with LVEF <35 % should receive a wearable external defibrillator (Lifevest) at the time of discharge from the hospital. If the LVEF remains under 35 % despite 3 months of optimal guideline based medical therapy at goal doses, they should receive a prophylactic ICD for primary prevention against sudden cardiac death.

Mechanical Support

For those patients who remain unstable and in persistent heart failure despite optimal medical therapy or for those that are inotrope dependent, the use of temporary or durable mechanical circulatory support and heart transplantation evaluation should be considered. Mechanical support with a left ventricular assist device should be considered first in these patients due to the likelihood of full recovery of left ventricular function at 6 months in nearly half of the patients with PPCM [5]. The evidence for use of mechanical circulatory support in these patients is anecdotal and there are no studies comparing the different types of device therapies [10]. For some of these patients, IABP is adequate support as a temporary (up to 5–7 days) bridge to recovery or bridge to LVAD; other temporary support strategies like Centrimag extra-corporeal support system, Impella CP, and Tandemheart pVAD are also helpful for temporary support (2–4 weeks) as a bridge to recovery or LVAD; and finally durable LVADs can be use as a long term bridge to recovery or transplantation [16]. In an analysis from the INTERMACs registry, women with PPCM who received support with LVAD had a better survival than women with other forms of cardiomyopathy [17]. In the same analysis, just 48 % of the women with LVAD and a history of PPCM needed cardiac transplantation after 3 years on mechanical support. It should be noted that cardiac transplantation may carry a higher risk for allograft rejection in these patients.

Delivery

If the cardiomyopathy is diagnosed during gestation, there is no need for early delivery unless the

mother presents with hemodynamic instability [5]. Early delivery can often precipitate and worsen the signs and symptoms of heart failure. In that case, the primary objective is to achieve maternal cardiovascular benefit and vaginal delivery is preferred except in women requiring mechanical support or for obstetrical complications [5].

Postpartum Supportive Care

Women who are malnourished should undergo nutritional counseling and receive appropriate nutritional supplements. Many of the drugs used to treat HFrEF should be avoided if the patient is breast feeding. Perhaps, it is safest to avoid breast feeding in PPCM patients to avoid the risk of getting drugs ingested by the infant through breast milk. Breast feeding does not need to be interrupted for administration of gadolinium to obtain a cardiac MR for diagnostic purposes [5].

Evidence Contour

Several studies have suggested a role for inflammation in the pathogenesis of PPCM. There is an increase in inflammatory markers in PPCM patients, including tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), Interleukin-6 and interferon γ [18]. In addition, during pregnancy there is an increase in oxidative stress [19]. In animal models, this increase in oxidative stress leads to an overexpression of the signal transducer and activator of transcription 3 (Stat 3). Stat-3 increases cathepsin D, an enzyme that cleaves prolactin into its active form. This active form of prolactin has pro-apoptotic and anti-angiogenic properties that can lead to a destruction of cardiac myocytes, and cardiac dysfunction [20].

Immunotherapy and Anti-inflammatory Mediators

Based on these findings, some authors have suggested the use of targeted therapies such as intravenous immunoglobulin [21], pentoxifylline (that decreases action of TNF-α, CRP and fas/apoptosis antigen 1) [22] and bromocriptine (a dopamine agonist that decreases prolactin production) [23–26] based on promising results with improvement in mortality, LV function and functional capacity in small studies. Because of the lack of large, randomized clinical studies, these medications are not recommended as part of the routine therapy in PPCM. In addition, bromocriptine use has been associated with several reports of myocardial infarction and anticoagulation should be used routinely with this medication [27].

References

1. Pearson GD, Veille JC, Rahimtoola S, Hsia J, Oakley CM, Hosenpud JD, Ansari A, Baughman KL. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. JAMA. 2000;283:1183–8.
2. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. Am J Physiol. 1989;256(4 Pt 2):H1060–5.
3. Goland S, Modi K, Bitar F, Janmohamed M, Mirocha JM, Czer LSC, Illum S, Hatamizadeh P, Elkayam U. Clinical profile and predictors of complications in peripartum cardiomyopathy. J Card Fail. 2009;15:645–50.
4. Ntobeko BAN, Bongani MM. Aetiology and risk factors of peripartum cardiomyopathy: a systematic review. Int J Cardiol. 2009;131:168–79.
5. Sliwa K, Hilfiker-Kleiner D, Petri MC, Mebazaa A, Pieske B, Buchmann E, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, van Veldhuisen DJ, Watkins H, Shah AJ, Seferovic PM, Elkayam U, Pankuweit S, Papp Z, Mouquet F, McMurray JJV. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. Eur J Heart Fail. 2010;12:767–78.
6. Elkayam U. Risk of subsequent pregnancies in women with a history of peripartum cardiomyopathy. J Am Coll Cardiol. 2014;64:1629–36.
7. Elkayam U, Akhter MW, Singh H, Khan S, Bitar F, Hameed A, Shotan A. Pregnancy-associated cardiomyopathy: clinical characteristics and comparison between early and late presentation. Circulation. 2005;111:2050–5.
8. Johnson-Coyle L, Jenson L, Sobey A. Peripartum cardiomyopathy. Review and Practice Guidelines. Am J Crit Care. 2012;21:89–98.
9. Stevenson LW. Tailored therapy to hemodynamic goals for advanced heart failure. Eur J Heart Fail. 1999;1:251–7.

10. Carlin AJ, Alfirevic Z, Gyte GM. Interventions for treating peripartum cardiomyopathy to improve outcomes for women and babies. Cochrane Database Syst Rev. 2010;(9):CD008589.
11. Diao M, Diop IB, Kane A, Camara S, Kane A, Sarr M, Ba SA, Diouf SM. Electrocardiographic recording of long duration (Holter) of 24 hours during idiopathic cardiomyopathy of the peripartum. Arch Mal Coeur Vaiss. 2004;97:25–30.
12. Terata M, Nakai K, Fukushima A, Itoh M, Kikuchi A, Sugiyama T. Detection of peripartum myocardial burden by vector-projected 187 channel electrocardiography and serum NT-proBNP. Int Heart J. 2013;54: 140–5.
13. Forester O, Hilfiker-Kleiner D, Ansari A, Sundstrom J, Libhaber E, Tshani W, Becker A, Yip A, Klein G, Sliwa K. Reversal of IFN-γ, oxLDL and prolactin serum levels correlate with clinical improvement in patients with peripartum cardiomyopathy. Eur J Heart Fail. 2008;10:861–8.
14. Yamada T, Koyama T, Furuta I, Takeda M, Nishida R, Yamada T, Morikawa M, Minakami H. Effects of caesarean section on serum levels of NT-proBNP. Clin Endocrinol. 2013;78:460–5.
15. Yancy CW, Jessup M, Bozkurt B, Butler J, Case DE, Drazner MH, Fonarow GC, Geraci S, Horwich T, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240–327.
16. Gevaert S, Van Belleghem Y, Bouchez S, Herck I, De Somer F, De Block Y, Tromp F, Vandecasteele E, Martens F, De Pauw M. Acute and critically ill peripartum cardiomyopathy and 'bridge to' therapeutic options; a single center experience with intra-aortic balloon pump, extra corporeal membrane oxygenation and continuous-flow left ventricular assist devices. Crit Care. 2011;15:R93.
17. Loyaga-Rendon RY, Pamboukian SV, Tallaj TA, Acharya D, Cantor R, Starling RC, Naftel D, Kirklin J. Outcomes of patients with peripartum cardiomyopathy who received mechanical circulatory support. Data from the Interagency Registry for Mechanically Assisted Circulatory Support. Circ Heart Fail. 2014;7:300–9.
18. Sliwa K, Forster O, Libhaber E, Fett JD, Sundstrom JB, Hilfiker-Kleiner D, Ansari AA. Peripartum cardiomyopathy: inflammatory markers as predictors of outcome in 100 prospectively studied patients. Eur Heart J. 2006;27:441–6.
19. Burton GJ. Jauniaux. Oxidative stress. Best Pract Res Clin Obstet Gynaecol. 2011;25:28.
20. Hilfiker-Kleiner D, Kaminski K, Podewski E, Bonda T, Schaefer A, Sliwa K, Forster O, Quint A, Landmesser U, Doerries C, Luchtefeld M, Poli V, Schneider MD, Balligand JL, Desjardins F, Ansari A, Struman I, Nguyen NQ, Zschemisch NH, Klein G, Heusch G, Schulz R, Hilfiker A, Drexler H. A cathepsine D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. Cell. 2007;128:589–600.
21. Bozkurt B, Villaneuva FS, Holubkov R, Tokarczyk T, Alvarez RJ, MacGowan GA, Murali S, Roenblum WD, Feldman AM, McNamara DM. Intravenous immune globulin in the therapy of peripartum cardiomyopathy. J Am Coll Cardiol. 1999;34:177–80.
22. Sliwa K, Skudicky D, Candy G, Bergemann A, Hopley M, Sareli P. The addition of pentoxifylline to conventional therapy improves outcome in patients with peripartum cardiomyopathy. Eur J Heart Fail. 2002;4:305–9.
23. Sliwa K, Blauwet L, Tibazarwa K, Libhaber E, Smedema JP, Becker A, et al. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof-of-concept pilot study. Circulation. 2010;121(13):1465–73.
24. Forster O, Hilfiker-Kleiner D, Ansari AA, Sundstrom JB, Libhaber E, Tshani W, Becker A, Yip A, Klein G, Sliwa K. Reversal of IFN-gamma, oxLDL and prolactin serum levels correlate with clinical improvement in patients with peripartum cardiomyopathy. Eur J Heart Fail. 2008;10:861–8.
25. Hilfiker-Kleiner D, Meyer GP, Schieffer E, Goldmann B, Podewski E, Struman I, Fischer P, Drexler H. Recovery from postpartum cardiomyopathy in 2 patients by blocking prolactin release with bromocriptine. J Am Coll Cardiol. 2007;50:2354–5.
26. Habedank D, Kuhnle Y, Elgeti T, Dudenhausen JW, Haverkamp W, Dietz R. Recovery from peripartum cardiomyopathy after treatment with bromocriptine. Eur J Heart Fail. 2008;10:1149–51.
27. Hopp L, Haider B, Iffy L. Myocardial infarction postpartum in patients taking bromocriptine for the prevention of breast engorgement. Int J Cardiol. 1996;57:227–32.

Management of Amniotic Fluid Embolism

88

Susan H. Cheng and Marie R. Baldisseri

Case Presentation

A 45 year old obese, multiparous (G3P3), African American female with no other past medical history and an uncomplicated prenatal course, presents with twins at 40 weeks gestation. Her prior vaginal deliveries were uncomplicated. She experiences a tumultuous labor of many hours with delivery by Cesarean section because of fetal distress. Shortly after delivery, she suddenly complains of shortness of breath. Her oxygen saturation falls from 98 to 74 %, blood pressure falls to 86/50, and she suffers a generalized seizure. You also note oozing at her IV insertion sites and increased bloody vaginal discharge.

Question What diagnosis is suspected?

Answer Amniotic Fluid Embolism Syndrome (AFE) is a clinical diagnosis of exclusion, that is rare (estimated between 1.7 and 12 cases per 100,000 deliveries) [1–9] but with high mortality (most recent data estimates 11–43 %) [1–9] and morbidity (especially neurologic injury). It is unpredictable, unpreventable and usually occurs with an abrupt onset during pregnancy or shortly after delivery with a constellation of multi systemic symptoms [10].

She is intubated for airway protection and to improve oxygenation. Ativan is given to control seizure activity. A 500 cc crystalloid bolus results in minimal blood pressure improvement. Stat labs are ordered: ABG with PaO_2 of 60, Hgb of 7 (previously 14), platelet of 90, (PT, PTT, INR, D-dimer, fibrinogen levels consistent with DIC). Stat blood transfusion is ordered. Oxygenation improves to 96 % and blood pressure to 118/72. The patient is transferred to the ICU where an arterial line and central venous catheter are placed. Portable chest x-ray is obtained. Norepinephrine infusion is started.

Symptoms

1. Hypoxemia (most common) and respiratory failure
2. Hypotension from cardiogenic shock
3. Disseminated intravascular coagulation
4. Seizures or coma

Risk Factors

1. Precipitous or tumultuous labor [10]
2. Advanced maternal age [6, 7, 11, 12]
3. Cesarean [6–8, 11, 12] and instrumental delivery [10]
4. Placenta previa and abruption [6, 11]
5. Multiparity [12]
6. Multiple birth delivery [8, 11]
7. Cervical lacerations [10]
8. Fetal distress [8, 11]
9. Eclampsia [11]
10. Medical induction of labor [8, 11]

S.H. Cheng (✉) • M.R. Baldisseri
Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
e-mail: chengsh@upmc.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_88

Pathophysiology

The precise mechanism is unclear. It is proposed that amniotic fluid enters the maternal circulation through endocervical veins, placental insertion site, or a site of uterine trauma [13]. There is evidence of a biphasic pattern of cardiogenic shock. During the initial phase (15–30 min) there is acute pulmonary hypertension and right heart failure followed by a later phase of left ventricular dysfunction [14].

Hypoxemia is primarily due to severe ventilation/perfusion mismatching contributed to by acute pulmonary hypertension in the initial phase and cardiogenic pulmonary edema in the second phase [15]. Physical obstruction or vasoconstriction of pulmonary vasculature caused by amniotic fluid emboli may be the main mechanism of the brief phase of right ventricular failure [10], whereas, the second phase appears to be due to an anaphylactoid reaction mediated by immunologic factors such as complement activation [5, 16, 17]. These findings may explain why there are often few or no anatomical changes seen at autopsy in the pulmonary vasculature unlike the occlusive thrombi associated with pulmonary emboli.

Principles of Management

Diagnosis

The most important aspect of diagnosis is maintaining a high index of suspicion. There are currently variations in definitions of AFE among nations, but most diagnoses are based on clinical symptoms. All definitions include an acute onset of symptoms (hypoxia/respiratory distress, hypotension/cardiac arrest, DIC, and coma/seizure) in a pregnant or peripartum woman that requires intervention with no other clear alternative explanation.

There is a recent suggestion that there is more than one type of AFE. One type is characterized as AFE that starts with cardiopulmonary collapse and another type that presents initially with uterine atonic bleeding/DIC [5].

Management

There is no specific treatment of AFE. Management consists of supportive care with the main objectives to correct hypoxemia and hypotension to prevent ischemic sequelae such as hypoxic brain injury, acute kidney injury and to maintain oxygen delivery to any unborn fetus.

Initial Assessment

Initial assessment should include continuous cardiac/respiratory monitoring of maternal oxyhemoglobin saturation, heart rate, rhythm, respiratory rate, and non-invasive blood pressure, as well as fetal heart rate if applicable. Preparations should be made to insert both an arterial catheter and central venous catheter, but placement should not delay supportive therapies. The arterial catheter provides continuous invasive blood pressure monitoring and access for frequent arterial blood gases. A central venous catheter is used for infusion of fluids, medications, blood products, and access for venous blood testing [1].

Routine placement of a pulmonary arterial catheter for hemodynamic monitoring is usually not advised but may be useful in select patients with shock, pulmonary edema, and whose intravascular volume is uncertain.

Oxygenation

Provide supplemental oxygen with a goal maternal $PaO_2 > 65$. This goal is chosen because PaO_2 of 65 lies on the flat portion of the hemoglobin dissociation curve where small changes in PaO_2 do not cause large changes in oxyhemoglobin saturation and oxygen delivery. Oxygen should be provided through high flow supplemental oxygen via facemask or invasive mechanical ventilation if needed (with adjustment of fraction of inspired oxygen, positive end-expiratory oxygenation, and inspiratory to expiratory ratio).

Noninvasive positive pressure ventilation should be avoided due to high risk of aspiration during pregnancy. Intrapartum women may also need red blood cell transfusion and inotropic agents to increase maternal cardiac output and maintain oxygen delivery to the fetus [1].

Hemodynamic Support

Hypotensive patients require repletion of intravascular volume when they are clinically hypovolemic. In normovolemic or hypervolemic patients, a vasopressor is the treatment of choice. In patients whose intravascular status is unclear, treatment can either begin empirically with a vasopressor or hemodynamic monitoring with fluid repletion if indicated.

Norepinephine and dopamine are initial vasoactive agents of choice. Dobutamine can be added to increase cardiac output and decrease afterload in cardiogenic shock. Dobutamine should be added after vasopressors have increased blood pressure and to prevent hypotension when dobutamine is used alone.

There should be cautious use of intravenous fluids in patients with AFE since pulmonary edema is a common feature of AFE. Intravenous fluids should be given in small bolus with reassessment after each bolus and fluids discontinued once normovolemic or if there are signs of pulmonary edema.

In addition to intravenous fluids and vasoactive agents, blood transfusions are needed in cases of AFE with coagulopathy or DIC.

Delivery of Fetus

If AFE presents intrapartum, the decision for immediate delivery of the fetus is usually mandated to support maternal hemodynamics. Efforts should be made to correct coagulopathy prior to emergent cesarean; otherwise blood products (blood, fresh frozen plasma, platelets, and cryoprecipitate) should be available in the operating room.

Evidence Contour

Diagnosis

In 1926, the presence of amniotic fluid debris was first described in the pulmonary vasculature of a mother who died suddenly in labor [18], but the syndrome was not recognized until 1941 when an autopsy series revealed fetal mucin and squamous cells in the pulmonary vasculature of women who died suddenly of shock during labor [19]. Previously, amniotic fluid found in a blood sample from the distal port of a pulmonary artery catheter was pathognomonic for AFE. Amniotic fluid debris is also found in the circulation of healthy pregnant women without AFE [20] and there are cases of AFE that meet clinical criteria, but have no amniotic or fetal components detected in the lungs post mortem [5].

Several serum markers for an ancillary diagnosis of AFE have been proposed. Low levels of C3 and C4 had a sensitivity between 88 and 100 % and a specificity of 100 % for the diagnosis of AFE [21]. In a recent study of over 400 cases of AFE in Japan, levels of zinc coproporphyrin-1 and sialyl Tn antigen levels were increased in cases of AFE that presented mainly with cardiopulmonary collapse, and C3 and C4 levels were reduced in cases of AFE that mainly involved DIC and atonic bleeding [5].

Insulin-like growth factor binding protein-1 was also found to be higher in women with AFE in a case control study compared to women with post-partum hemorrhage, normal pregnancy, complicated pregnancy and nonpregnant women with pulmonary embolism [22], but this has not been fully validated for routine clinical practice.

C1 esterase inhibitor levels were decreased in patients with AFE, and many deceased patients from AFE had C1 esterase inhibitor levels far below 25 %. The suggested mechanism is that decreased levels of C1 esterase inhibitor uninhibit the complement system and contribute to uterine atony, DIC and the anaphylactoid reaction seen in AFE [5].

Adjunctive Therapies

Some adjunct therapies reported include the use of nitric oxide [23] and a right ventricular assist device [24] in patients with pulmonary hypertension and right ventricular failure.

Cardiopulmonary bypass with thromboembolectomy [25], intra-aortic balloon pump counterpulsation, and extracorporal membrane oxygenation (ECMO) [26, 27] have been used in patients with severe left ventricular failure and hypoxemia.

Recombinant human factor VIIa (rVIIa) has been used in patients with severe coagulopathy and bleeding, especially in those undergoing surgery to control postpartum hemorrhage. It is controversial in its use in AFE because rVIIa may be associated with thrombotic morbidity and mortality [24, 28]. Although in a recent case report, rVIIa was used in a case with AFE and resulted in clinical improvement of her coagulopathy and without apparent adverse thrombotic effect [29].

Low levels of C1 esterase inhibitor are associated with AFE and C1 esterase contained in fresh frozen plasma seems to contribute to improvement. This suggests that obtaining levels may be applicable for prognosis and supplemental C1 esterase inhibitor (indicated currently for hereditary angioedema) may be a potential treatment for AFE [5].

References

1. Baldisseri MR. Amniotic fluid embolism syndrome. www.uptodate.com. Accessed 19 Jan 15.
2. Moore J, Baldisseri MR. Amniotic fluid embolism. Crit Care Med. 2005;33(10):S279–85.
3. Conde-Agudelo A and Romero R. Amniotic fluid embolism: an evidence-based review. AJOG. 2009;201: 445.e1–13.
4. Fitzpatrick K, Tuffnell D, Kurinczuk J, Knight M. Incidence, risk factors, management and outcomes of amniotic-fluid embolism: a population based cohort and nested case control study. BJOG. 2015; doi:10.1111/1471-0528.13300.
5. Kanayama N, Tamura N. Amniotic fluid embolism: pathophysiology and new strategies for management. J Obstet Gynaecol Res. 2014;40(6):1507–17.
6. Abenhaim H, Azoulay L, Kramer M and Leduc L. Incidence and risk factors of amniotic fluid embolisms: a population-based study on 3 million births in the United States. AJOG. 2008;199:49.e1–49.e8.
7. Stein PD, Matta F, Yaekoub AY. Incidence of amniotic fluid embolism: relation to cesarean section and to age. J Womens Health. 2009;18(3):327–9.
8. Knight M, Tuffnell D, Brocklehurst P, Spark P, Kurinczuk JJ. Incidence and risk factors for amniotic-fluid embolism. Obstet Gynecol. 2010;115:910–7.
9. McDonnell NJ, Percival V, and Paech MJ. Amniotic fluid embolism: a leading cause of maternal death yet still a medical conundrum. Int J Obstet Anesth. 2013;22:329–36.
10. Morgan M. Amniotic fluid embolism. Anesthesia. 1979;30:20–6.
11. Kramer MS, Rouleau J, Baskett TF, Joseph KS. Amniotic fluid embolism and medication induction of labour; a restrospective, population-based cohort study. Lancet. 2006;368:1444–8.
12. Stolk KH, Zwart JJ, Van Roosmalen J. Severe maternal morbidity and mortality from amniotic fluid embolism in the Netherlands. Acta Obstet Gynecol Scand. 2012;91(8):991–5.
13. Courtney LD. Amniotic fluid embolism. Obstet Gynecol Surv. 1974;29:169–77.
14. Clark SL. New concepts of amniotic fluid embolism: a review. Obstet Gynecol Surv. 1990;45:360–8.
15. Gist RS, Stafford IP, Leibowitz AB, Beilin Y. Amniotic fluid embolism. Anesth Analg. 2009;108: 1599–602.
16. Benson MD. A hypothesis regarding complement activation and amniotic fluid embolism. Med Hypotheses. 2007;68:1019–25.
17. Benson MD. Current concepts of immunology and diagnosis in amniotic fluid embolism. Clin Dev Immunol. 2012;2012:946576.
18. Meyer JR. Embolia pulmonary amnio caseosa. Bras Med. 1926;2:301–3.
19. Steiner PE, Lushbaugh C. Maternal pulmonary embolism by amniotic fluid as a cause of obstetric shock and unexpected deaths in obstetrics. JAMA. 1941;117:1245–54. 1340–5.
20. Lee W, Ginsburg KA, Cotton DB, Kaufman RH. Squamous and trophoblastc cells in the maternal pulmonary circulation identified by invasive hemodynamic monitoring during the peripartum period. Am J Obstet Gynecol. 1986;155:999–1001.
21. Benson MD, Kobayashi H, Silver RK, Oi H, Greenberger PA, Terao T. Immunologic studies in presumed amniotic fluid embolism. Obstet Gynecol. 2001;97:510–4.
22. Legrand M, Rossignol M, Dreux S, Luton D, Ventre C, Barranger E, Laribi S, Payen D, Muller F. Diagnostic accuracy of insulin-like growth factor binding protein-1 for amniotic fluid embolism. Crit Care Med. 2012;40(7):2059–63.
23. McDonnell NJ, Chan BO, Frengley RW. Rapid reversal of critical haemodynamic cmpromis with nitric oxide in a parturient with amniotic fluid embolism. Int J Obstet Anesth. 2007;16:269–73.

24. Nagarsheth NP, Pinney S, Bassily-Marcus A, Anyanwu A, Friedman L, Beilin Y. Successful placement of a right ventricular assist device for treatment of a presumed amniotic fluid embolism. Anesth Analg. 2008;107(3):962–4.
25. Kumar S, Wong G, Maysky M, Shulman M, Olenchock S, Falzon-Kirby M, Oo TH. Amniotic fluid embolism complicated by paradoxical embolism and disseminated intravascular coagulation. Am J Crit Care. 2010;19(4):379–82.
26. Hsieh YY, Chang CC, Li PC, Tsai HD, Tsai CH. Successful application of extracorporeal membrane oxygenation and intra-aortic balloon counterpulsation as lifesaving therapy for a patient with amniotic fluid embolism. Am J Obstet Gynecol. 2000;183(2):496–7.
27. Shen HP, Chang WC, Yeh LS, Ho M. Amniotic fluid embolism treated with emergency extracorporeal membrane oxygenation: a case report. J Reprod Med. 2009;54(11-12):706–8.
28. Leighton BL, Wall MH. Lockhart EM, Phillips LE, Zatta AJ. Use of recombinant factor VIIa in patients with amniotic fluid embolism: a systematic review of case reports. Anesthesiology. 2011;115: 1201–8.
29. Rogers WK, Wernimont SA, Kumar GC, Bennett E, Chestnut DH. Acute hypotension associated with intraoperative cell salvage using a leukocyte depletion filter during management of obstetric hemorrhage due to amniotic fluid embolism. Anesth Analg. 2013;117(2):449–52.

Respiratory Diseases of Pregnancy

89

Nithya Menon and Mary Jane Reed

Case Presentation

A 26 year-old gravida 3 para 2 with no known prior medical history presents at 34 weeks gestation to the emergency room with shortness of breath that worsened in the last 24 h. She had been sick for the last week and had been to her primary care provider who treated her symptomatically. Vital signs are remarkable for an oxygen saturation of 88 % on room air and tachycardia. On exam she appears to be tachypneic, using accessory muscles of respiration. Coarse breath sounds are heard on auscultation. She has mild pedal edema. A rapid flu test comes back positive. Chest X-ray shows diffuse interstitial infiltrates (Fig. 89.1). She is admitted to the intensive care unit and started on supplemental oxygen and oseltamivir. A blood gas obtained an hour after admission shows a PCO_2 of 40 and a PaO_2 of 70 on an FIO_2 of 100 %.

Question What is her diagnosis?

Answer ARDS associated with Influenza pneumonia.

N. Menon
Pulmonary and Critical Care,
Geisinger Medical Center, Danville, PA, USA

M.J. Reed (✉)
Critical Care Medicine, Geisinger Medical Center,
Danville, PA, USA
e-mail: mreed@geisinger.edu

Question What will you do next?

Answer Intubate the patient with precautions for possible difficulty airway and initiate mechanical ventilation. Initiate empiric antibacterial therapy along with neuraminidase inhibitors.

Principles of Management

Physiologic Respiratory Changes Seen in Pregnancy

Dyspnea on exertion is a common complaint reported by gravid patients as the pregnancy progresses. The etiology is the increase in oxygen

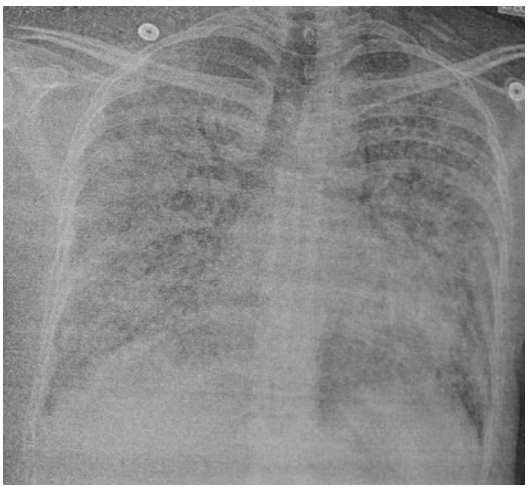


Fig. 89.1 Patient's chest x-ray

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_89

consumption by almost 20 %. However, the body compensates for this by increasing both respiratory rate and tidal volume, thereby increasing minute ventilation [1, 2]. These changes make the partial pressure of oxygen slightly higher than normal on a blood gas, and would range from 100 to 110 mmHg. The partial pressure of carbon dioxide would be lower than normal for a non-pregnant patient and ranges from 27 to 32 mmHg [3]. Low pulmonary reserves that arise from reductions in functional residual capacity and increased oxygen consumption make pregnant women develop hypoxemia more rapidly [4].

Differential Diagnosis of Pulmonary Conditions in Pregnancy

Conditions Unique to Pregnancy

Pulmonary edema

- Pre-eclampsia related
- Tocolytic induced pulmonary edema
- Peripartum cardiomyopathy
- Ovarian hyper stimulation syndrome
- Mendelson syndrome
- Amniotic emboli

Conditions not Unique to Pregnancy

Exacerbation of underlying pulmonary conditions

- Asthma
- Obstructive sleep apnea

Pulmonary infections

Pulmonary emboli

ARDS secondary to trauma, burns, sepsis

Pulmonary Edema

Pulmonary edema can be broadly classified as cardiogenic or non-cardiogenic. Cardiac output increases very early on and is the highest in the post-partum period. Plasma volume expands due to sodium and water retention, thereby increasing preload, but afterload reduces due to vasodilation systemically [5]. The most common causes of non-cardiogenic acute pulmonary edema in pregnancy are the use of tocolytic agents, fluid overload, preeclampsia, sepsis, trauma or following aspiration of gastric contents [6, 7].

Pre-eclampsia associated pulmonary edema – Pulmonary edema is a frequently encountered complication in patients with pre-eclampsia with most cases occurring after delivery. Initial management involves lowering the blood pressure urgently especially in patients who have severe elevations of blood pressure that persists longer than 15 min. Once pulmonary edema occurs, parenteral therapy is more effective, and nitroglycerine is the agent of choice as recommended by The European Society of Cardiology [8]. Diuretics should be instituted to promote pre load reduction recognizing that the preeclamptic patient may have complex fluid balance needs due to low oncotic pressure. When necessary, noninvasive ventilation is recommended, in patients with increased work of breathing or hypoxemia as it is known to improve these parameters and can decrease the need for invasive mechanical ventilation by [9].

Tocolytic induced pulmonary edema is relatively uncommon [10]. Tocolytics such as ritodrine and terbutaline are beta agonists that increase heart rate and stroke volume but cause peripheral vasodilation and decrease blood pressure. Management involves firstly stopping the tocolytic therapy and treating pulmonary edema with diuretics. These patients tend to recover well and reported mortality is low [11].

Peripartum cardiomyopathy – These patients usually have no known prior heart disease and present with congestive heart failure typically in the last month of pregnancy and up to 5 months post-partum. Unfortunately, the mortality can be as high as 20–50 % [12, 13].

Ovarian hyperstimulation syndrome (*OHSS*) is another uncommon cause of pulmonary edema with a prevalence of 1–10 %. Mechanisms are not entirely clear but involve increased vascular permeability. Treatment is supportive care [14].

Aspiration – Certain factors such as an incompetent lower esophageal sphincter coupled with a decrease in stomach motility can increase the risk for aspiration. One must have a high index of suspicion as not all events are witnessed. Treatment is usually supportive [15].

Airway Disease

Asthma is seen very frequently with prevalence in pregnancy ranging from 1 to 8 % [16]. Certain factors easily obtained by a good history can help you understand who is at increased risk of complications from asthma, these being history of exacerbations, intubations, and recent steroid use. Most exacerbations are characterized by cough, wheezing, and dyspnea. The National Asthma Education and Prevention (NAEP) group recommends obtaining a baseline peak expiratory flow in order to guide further management. If the patient is approaching less than half of what their baseline is, then treatment with supplemental oxygen to correct hypoxemia and bronchodilators such as a beta-agonist and anticholinergic agents are to be given. A target oxygen saturation above 90 % with consideration for invasive mechanical ventilation in those who are in impending respiratory failure. A partial pressure of carbon dioxide within the normal range of 36–40 on an arterial blood gas can be a early sign of imment respiratory failure in the gravid patient. Intravenous steroids also have to be instituted. Care should be taken during mechanical ventilation to avoid a short expiratory time that can cause auto peep [16]. Intravenous magnesium sulfate may be beneficial in acute severe asthma in addition to bronchodilators especially in patients with coexistent hypertension or preterm uterine contractions [16, 17].

Large airway obstruction mostly arises due to a difficult intubation and the incidence is anywhere between 0.4 and 5.5 %. Intubation may be difficult during pregnancy and the peripartum period due to upper airway edema, pharyngeal mucosal friability and diminished airway caliber, especially late in pregnancy. The gravid patient especially third trimester, should be considered a difficult airway patient with high risk of aspiration and decreased oxygen reserve. Other causes of airway obstruction such as tumors, hematoma and laryngeal edema are rarely encountered [18, 19].

Obstructive Sleep Apnea in Pregnancy

Increased upper airway resistance may occur in pregnancy as a result of pharyngeal edema and increased pharyngeal tone could potentially worsen OSA in pregnant women. Incidence of OSA is estimated to be between 8.4 % in the first trimester and 19.7 % in the third trimester [20]. Maternal risks include increased morbidity from conditions that have been associated with OSA and underlying obesity such as preeclampsia, eclampsia, gestational hypertension, cardiomyopathy and gestational diabetes [21]. These patients are at higher risk for hypoxemia during labor, and continuous monitoring is necessary. CPAP therapy remains the first line of therapy and women are instructed to bring in their device when they come during labor.

Pulmonary Infections in Pregnancy

Viral Pneumonia

Varicella and influenza are the most common pathogens associated with viral pneumonia in pregnancy [22].

Estimated mortality rate amongst the H1N1 pandemic ranged from 12.5 to 42.1 % [23]. The risk of hospitalization is highest in the third trimester. Mortality related to influenza is mostly due to secondary bacterial pneumonia, although the 2009 H1N1 pandemic differed in this aspect with more patients dying primarily from the effects of H1N1 virus. The most commonly implicated pathogens are *S. pneumonia* and *Staphylococcus aureus* followed by *H.* influenza and it is reasonable to start empiric antibacterial agents at the time of presentation [24].

Bacterial Pneumonia

Streptococcus pneumonia followed by *Hemophilus Influenza* are the most commonly encountered agents [22]. Some of the risk factors for pneumonia in pregnancy include anemia, asthma, antepartum corticosteroids given to enhance fetal lung maturity, and the use of tocolytic agents to induce labor [25].

Oxygen supplementation is necessary with a goal of keeping the partial pressure of oxygen above 70 mmHg. The penicillins, cephalosporins, and macrolides are considered safe to use in pregnancy [22]. A history of contact with farm animals should raise suspicion for Q fever and therapy with macrolides is preferred [26].

Neuromuscular Diseases and Central Causes

Central causes of respiratory failure such as drugs, tumors, hemorrhage, and infection should be treated for in a similar manner as the general population with treatment of the underlying cause and mechanical ventilation if necessary. Conditions such as kyphoscoliosis may precipitate hypercapnic respiratory failure in pregnancy [27]. These patients should be closely monitored with arterial blood gasses, vital capacity and maximal and minimal inspiratory pressures [28].

Magnesium sulfate which is used as a tocolytic and to prevent seizures in pre-eclampsia can cause respiratory depression at levels greater than 12, and respiratory arrest at levels of 16–18.

Careful monitoring of magnesium sulfate dosing and infusion rates and monitoring maternal deep tendon reflexes and urine output with serum magnesium levels with precise infusion rates is necessary.

Pneumothorax in Pregnancy

Pneumothorax may occur because of hyperemesis, pushing efforts in labor, underlying lung disease, and without obvious precipitating cause [29]. Hamman's syndrome of intrapartum subcutaneous emphysema, pneumomediastinum, or pneumothorax results from the forceful "pushing" efforts during labor and about 200 cases have been reported worldwide before [30]. The clinical presentation is usually chest pain with breathlessness and presence of crackles or 'Hamman's sign 'in the left lateral decubitus position in systole. Most cases resolve spontaneously, but emergent chest tube placement might be required in some cases.

Pulmonary Embolism in Pregnancy

Embolic events rank among the major causes of maternal mortality in modern obstetrics. Risk factors include venous stasis, advanced age, sepsis, obesity and cesarean section. Hypoxemia is common. With massive embolism, circulatory failure is more prominent. Diagnosis is made by compression ultrasonography and if negative they will need perfusion study. If the diagnosis of PE is strongly considered, then treatment with unfractionated heparin should be started immediately unless a high risk or contraindication is present for the use of any anticoagulants.

Unfractionated heparin and low-molecular weight heparin are safe to use during pregnancy because they do not cross the placenta. TPA has also been used during pregnancy although there are no controlled trials [31, 32].

Cystic Fibrosis

Cystic fibrosis is the most common congenital pulmonary disease encountered during pregnancy. It is a restrictive and obstructive disorder, with a predisposition to infection. Bronchodilators and chest physiotherapy should be recommended, and chest infections should be treated aggressively [33].

Evidence Contour

The critically ill pregnant patient requires a multidisciplinary approach and early inclusion of obstetrical expertise is paramount in managing these patients especially in the third trimester.

Ventilation Strategies in the Pregnant Patient

Challenges

Pregnant women have hypocapnia due to hyperventilation at baseline. Thus, the arterial carbon dioxide tension ($PaCO_2$) tends to be lower in a pregnant woman, and a normal $PaCO_2$ is a sign of impending respiratory failure. Intubation may be difficult during pregnancy and the peripartum period due to upper airway edema and diminished airway caliber, especially late in pregnancy.

Goals of Ventilation

The goal is to rest the fatigued respiratory muscles while providing suitable gas exchange. Respiratory muscle rest involves institution of invasive or noninvasive mechanical support, and the ventilator must overcome pressures related to airway resistance and elastic properties of the lung to allow adequate ventilation and gas exchange.

Non-invasive Ventilation

A trial of NIV can be instituted early on in patients with pulmonary edema. Favorable outcomes have been reported in case reports and series [34].

Mechanical Ventilation

Low tidal ventilation strategy is recommended [35]. PEEP improves oxygenation and should be used to provide a $PaO_2 > 65$ mmHg while administering the least FiO_2. The target $PaCO_2$ is 30–32 mmHg since this is the normal level during pregnancy. Marked respiratory alkalosis should be avoided because it may decrease uterine blood flow. Maternal permissive hypercapnia may also be deleterious to the fetus because of resultant fetal respiratory acidosis although this mode of ventilation has been used safely in pregnant women in small trials.

Propofol remains the first choice for sedation in these patients and if paralytics are clinically of cisatracurium would be the preferred agent [36].

Extra Corporeal Membrane Oxygenation (ECMO)

This technique has been used a rescue therapy for refractory ARDS with reported maternal and fetal survival rates between 80% and 70%, respectively [37, 38]. Most of the published literature is from the 2009 H1N1 influenza pandemic. Early institution with careful patient selection and judicial management of anticoagulation might improve successful outcomes [38, 39].

Prone Ventilation

Use of prone positioning in the third trimester has not been widely studied however case reports have appeared in the literature with apparently acceptable results. As in other severe ARDS patients, proning requires careful attention to inadvertent decannulation of lines or extubation. The pressure points especially eyes need to be protected and no hyperextension of joints. There needs to be adequate room for the abdomen to expand passively. This can be achieved by the use of appropriately sized bolsters at chest and hip level to help elevate the patient above the mattress. This also allows for anterior displacement of uterus off of the inferior vena cava which is necessary for adequate venous return after 20 weeks gestation. Close monitoring of mother and fetus including continuous fetal cardiotocography should be in place if fetus of viable age [40, 41].

Delivery

Delivery of the fetus can improve the maternal condition in several obstetrical disease states. In ARDS, it appears perhaps to improve oxygenation and management of the mother but does not definitively improve maternal survival [35, 42].

References

1. Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy. Clin Chest Med. 2011:32(1). doi:10.1016/j.ccm.2010.11.001.
2. Crapo RO. Normal cardiopulmonary physiology during pregnancy. Clin Obstet Gynecol. 1996;39(1):3–16.
3. Templeton A, Kelman GR. Maternal blood-gases, PAo2--Pao2), physiological shunt and VD/VT in normal pregnancy. Br J Anaesth. 1976;48(10):1001–4.
4. Archer GW, Marx GF. Arterial oxygen tension during apnoea in parturient women. Br J Anaesth. 1974; 46(5):358.
5. Benedetti TJ, Carlson RW. Studies of colloid osmotic pressure in pregnancy-induced hypertension. Am J Obstet Gynecol. 1979;135(3):308–11.
6. Bandi VD, Munnur U, Matthay MA. Acute lung injury and acute respiratory distress syndrome in pregnancy. Crit Care Clin. 2004;20:577–607.
7. Vasquez DN, Estenssoro E, Canales HS, et al. Clinical characteristics and outcomes of obstetric patients requiring icu admission. Chest. 2007;131(3):718–24.
8. Melchiorre K, Sharma R, Thilaganathan B. Cardiovascular implications in preeclampsia: an overview. Circulation. 2014;130(8):703–14.
9. Dennis AT, Solnordal CB. Acute pulmonary oedema in pregnant women. Anaesthesia. 2012;67:646–59.

10. Bowen RE, Dedhia HV, Beatty J, Schiebel F, Koss W, Granado J. ARDS associated with the use of sympathomimetics and glucocorticoids for the treatment of premature labor. Crit Care Med. 1983;11(8):671–2.
11. DiFederico EM, Burlingame JM, Kilpatrick SJ, Harrison M, Matthay MA. Pulmonary edema in obstetric patients is rapidly resolved except in the presence of infection or of nitroglycerin tocolysis after open fetal surgery. Am J Obstet Gynecol. 1998;179(4):925–33.
12. Pearson GD, Veille JC, Rahimtoola S, et al. Peripartum cardiomyopathy: National Heart, Lung and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. JAMA. 2000;283:1183.
13. Sciscione AC, Ivester T, Largoza M, Manley J, Shlossman P, Colmorgen GH. Acute pulmonary edema in pregnancy. Obstet Gynecol. 2003;101(3):511–5.
14. Brinsden PR, Wada I, Tan SL, et al. Diagnosis, prevention and management of ovarian hyperstimulation syndrome. Br J Obstet Gynaecol. 1995;102:767–72.
15. Ashe Jr JR. Pulmonary aspiration—a life-threatening complication in obstetrics. N C Med J. 1976; 37(12):655–7.
16. Murphy VE, Gibson PG, Smith R, Clifton VL. Asthma during pregnancy: mechanisms and treatment implications. Eur Respir J. 2005;25(4):731.
17. Clark SL. Asthma in pregnancy. National Asthma Education Program Working Group on Asthma and Pregnancy. National Institutes of Health, National Heart, Lung, and Blood Institute. Obstet Gynecol. 1993;82(6):1036–40.
18. McKeen DM, George RB, O'Connell CM, Allen VM, Yazer M, Wilson M, Phu TC. Difficult and failed intubation: Incident rates and maternal, obstetrical, and anesthetic predictors. Can J Anaesth. 2011;58(6):514–24.
19. Biro P. Difficult intubation in pregnancy. Curr Opin Anaethesiol. 2011;24(3):249–54.
20. Pien GW, Pack AI, Jackson N, Maislin G, Macones GA, Schwab RJ. Risk factors for sleep-disordered breathing in pregnancy. Thorax. 2014;69(4):371–7. Epub 2013 Nov 21.
21. Pamidi S, Pinto LM, Marc I, Benedetti A, Schwartzman K, Kimoff RJ. Maternal sleep-disordered breathing and adverse pregnancy outcomes: a systematic review and meta-analysis. Am J Obstet Gynecol. 2014; 210(1):52.e1–52.
22. Goodnight WH, Soper DE. Pneumonia in pregnancy. Crit Care Med. 2005;33(10(Suppl)). doi:10.1097/01.CCM.0000182483.24836.66.
23. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, Louie J, Doyle TJ, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA. 2010;303(15):1517–25. doi:10.1001/jama.2010.479.
24. Petersdorf RG, Fusco JJ, Harter DH, Albrink WS. Pulmonary infections complicating Asian influenza. AMA Arch Intern Med. 1959;103:262–72.
25. Lim WS, Macfarlane JT, Colthorpe CL. Pneumonia and pregnancy. Thorax. 2001;56:398–405. doi:10.1136/thorax.56.5.398.
26. Benedetti TJ, Valle R, Ledger WJ. Antepartum pneumonia in pregnancy. Am J Obstet Gynecol. 1982;144: 413–7.
27. Leighton B, Fish J. Pulmonary disease in pregnancy glob. Libr Women Med (ISSN: 1756-2228). 2008. doi:10.3843/GLOWM.10170.
28. Shneerson JM, Simonds AK. Noninvasive ventilation for chest wall and neuromuscular disorders. ERJ. 2002;20(2):480–7. Doi:10.1183/09031936.02.00404002.
29. Andrew McGregor A, Ogwu C, Uppal T, Wong GM. Spontaneous subcutaneous emphysema and pneumomediastinum during second stage of labour. BMJ Case Rep. 2011. doi:10.1136/bcr.04.2011.4067.
30. Heffner JE, Sahn SA. Pleural disease in pregnancy. Clin Chest Med. 1992;13(4):667–78.
31. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton 3rd LJ. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med. 2005;143(10):697–706.
32. Liu S, Rouleau J, Joseph KS, et al. Epidemiology of pregnancy-associated venous thromboembolism: a population-based study in Canada. J Obstet Gynaecol Can. 2009;31(7):611–20.
33. Bhatia P, Bhatia K. Pregnancy and the lungs. Postgrad Med J. 2000;76:683–9. doi:10.1136/pmj.76.901.683.
34. Allred CC, Esquinas AM, Caronia J, Mahdavi R, Mina BA. Successful use of noninvasive ventilation in pregnancy. Eur Respir Rev. 2014. doi:10.1183/09059180.00008113.
35. Campbell LA, Klocke RA. Implications for the pregnant patient. Am J Respir Crit Care Med. 2001; 163:1051–4.
36. Pacheco LD, Saade GR, Hankins GDV. Mechanical ventilation during pregnancy: sedation, analgesia, and paralysis. Clin Obstet Gynecol. 2014;57(4):844–50.
37. Afessa B, Green B, Delke I, Koch K. Systemic inflammatory response syndrome, organ failure, and outcome in critically ill obstetric patients treated in an icu. Chest. 2001;120(4):1271–7.
38. Nair P, Davies AR, Beca J, et al. Extracorporeal membrane oxygenation for severe ARDS in pregnant and postpartum women during the 2009 H1N1 pandemic. Intensive Care Med. 2011;37:648–54.
39. Nirmal S, Wille KM, Bellot SC, et al. Modern use of extracorporeal life support in pregnancy and postpartum. Sharma Am Soc Artif Int Organs. 2015; 61(1):110–4.
40. Kenn S, Weber-Carstens S, Weizsaecker K, Bercker S. Prone positioning for ARDS following blunt chest trauma in late pregnancy. Int J Obstet Anesth. 2009;18(3):268–71.
41. Samanta S, Samanta S, Wig J, Baronia AK. How safe is the prone position in acute respiratory distress syndrome at late pregnancy. Am J Emerg Med. 2014; 32(6):687.e1–3.
42. Tomlinson MW, Caruthers TJ, Whitty JE, Gonik B. Does delivery improve maternal condition in the respiratory-compromised gravida? Obstet Gynecol. 1998;91:108–11.

Preeclampsia, Eclampsia and HELLP Syndrome

90

Meike Schuster, Emmie Ruth Strassberg, and Mary Jane Reed

Case Presentation

A 36 year old primiparous woman at 32 weeks gestation with a past medical history of morbid obesity (BMI is 43 kg/m^2) and tobacco use presents to Labor and Delivery complaining of headache and abdominal pain. On arrival to Labor and Delivery her blood pressure is 160/92 mmHg, her pulse is 110 beats per minute (bpm), respirations are 20 breaths per minute and oxygen saturation is 96 % on room air. She feels occasional contractions but denies any vaginal bleeding or leakage of fluid and appreciates good fetal movement. Her abdominal pain is located on the right side under her ribcage, and she has had nausea and vomiting. The headache woke her from sleep; she had taken acetaminophen 1000 mg at home with no relief. On physical exam, she has tenderness in the right upper quadrant but no guarding or rebound. She has edema in her face, hands, and lower extremities. Her reflexes are +3/4 bilaterally, and clonus is present. A repeat blood pressure 15 min later is 155/90 mmHg. Fetal heart tracing shows minimal variability and a baseline of 130 beats per minute. Irregular contractions every 3–7 min are noted on tocometer. She reports that her headache is worse with accompanying "spots" in her vision. Laboratory tests including complete blood count and urinalysis were performed. Her protein/creatinine ratio results at 0.63, platelets are 90 K/uL, hemoglobin is 10 mg/dL, creatinine is 1.2 mg/dL, aspartate aminotransferase (AST) is 295 U/L and alanine aminotransferase (ALT) is 316 U/L. A bedside glucose is 82 mg/dL.

Question What initial therapy should be started in this patient?

Answer Magnesium Sulfate

This patient meets criteria for preeclampsia with severe features, and, therefore, her initial treatment should be intravenous magnesium sulfate for seizure prophylaxis. A 6 g bolus of intravenous magnesium sulfate over 30 min and then a maintenance dose of 2 g/h was ordered. Betamethasone 12 mg IM was given for fetal lung maturity development and a second dose was ordered for 24 h later. As her magnesium bolus is just being hung she appears agitated and begins to seize. The seizure last 30 s and the 6 g magnesium sulfate bolus is given over the next 20 min. Fetal monitoring demonstrates fetal heart rate deceleration down to 60 bpm lasting 4 min with a return to baseline at 120 bpm and minimal variability. She has no past medical history of seizures.

M. Schuster • E.R. Strassberg
Maternal Fetal Medicine, Geisinger Medical Center, Danville, PA, USA

M.J. Reed (✉)
Critical Care Medicine, Geisinger Medical Center, Danville, PA, USA
e-mail: mreed@geisinger.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_90

Question What is the diagnosis?

Answer Eclampsia

Eclampsia is diagnosed in a pregnant patient with new onset seizures that cannot be attributed to another cause in patients with hypertension or other signs or symptoms of preeclampsia. Magnesium sulfate remains the treatment of choice and has been shown to decrease the risk of seizure reoccurrence compared to other anticonvulsants [1]. Magnesium sulfate is continued and on postictal exam, the patient appears lethargic but responsive. With the diagnosis of eclampsia, the decision is made to move toward delivery. On cervical exam, her cervix is long, thick and closed, and the fetus is breech on bedside ultrasound. The decision is made to proceed with cesarean delivery secondary to breech presentation of the fetus. She is still complaining of headache and spots in her vision and blood pressure is 170/113. A repeat blood pressure 15 min later is 185/109.

Question While continuing to prepare for delivery, what is the next step in the management of this patient?

Answer Antihypertensive rescue therapy

Since she has had two severe-range blood pressures (greater than 160 mmHg diastolic or 110 mmHg diastolic) 15 min apart and antihypertensive therapy should be given to reduce the risk of cerebral hemorrhage and stroke [2, 3]. She is given Labetalol 20 mg IV slow-push over 2 min. A repeat blood pressure 10 min later is 155/117 mmHg and additional 40 mg IV labetalol is given over 2 min. Ten minutes after that her blood pressure is 158/95 mmHg. Coagulation studies are sent in preparation for delivery. A peripheral smear, haptoglobin and lactate dehydrogenase (LD) levels were sent earlier and have just resulted: Her LD level is 875 IU/L, haptoglobin is 20 mg/dL, and her peripheral smear shows schistocytes.

Question What additional diagnosis is made in light of these laboratory findings?

Answer HELLP syndrome

"HELLP" (Hemolysis, Elevated Liver Enzymes and Low Platelets) syndrome is characterized by microangiopathic hemolytic anemia (diagnosed by the presence of schistocytes on peripheral smear, anemia, lactate dehydrogenase grater than 600 U/L and haptoglobin less than or equal to 25 mg/dL), thrombocytopenia (platelets less than 100,000), and abnormal liver function (elevated transaminase levels) in a pregnant patient usually occurring in the setting of preeclampsia/eclampsia [4]. HELLP syndrome is progressive and can cause significant maternal and fetal morbidity and mortality. Delivery is recommended if HELLP syndrome is diagnosed after 34 weeks gestational age or sooner if there is disseminated intravascular coagulation, liver hemorrhage or infarction, pulmonary edema, renal failure, placental abruption, non-reassuring fetal status, eclampsia or other preeclampsia with severe features where expectant management is contraindicated such as uncontrolled severe hypertension [2, 5]. Antenatal steroids such as dexamethasone given in HELLP have not been shown to improve maternal outcomes [2, 6]. Our patient's coagulation studies resulted with fibrinogen level of 99 mg/dL, international normalized ration (INR) of 2.1 and activated partial thromboplastin time (APTT) of 68 s. On the way to the operating room she begins to have moderate vaginal bleeding. She is now complaining of severe diffuse abdominal pain and recurrent late decelerations are seen on fetal monitoring.

Question What new clinical diagnosis is now suspected in this patient?

Answer Placental Abruption.

Placental abruption occurs when the placenta prematurely separates from the uterus causing bleeding and fetal compromise from blood loss at the maternal-fetal interface. Placental abruption can lead to maternal disseminated intravascular coagulation and fetal demise. Placental abruption is a known complication of HELLP syndrome and has a strong association with development of disseminated intravascular coagulation (DIC) [4]. The clinical presentation of placental abruption is

abdominal pain and vaginal bleeding after 20 weeks gestation and fetal compromise [7]. Our patient is typed and crossed for six units of packed red blood cells, two units of platelets and two units of fresh frozen plasma. A Foley urinary catheter, an arterial line and a second large bore IV site are placed and one unit of fresh frozen plasma is administered. She is placed under general anesthesia and cesarean section is performed. A 1217 g male fetus is delivered with APGARs of 5 and 6. Estimated blood loss during the surgery is 3.5 l. She receives one unit of packed red blood cells and 2 units of fresh frozen plasma intra-operatively. In recovery her blood pressure is 155/97, heart rate is 110 bpm, oxygenation is 96% on room air and respiratory rate is 16 breaths per minute. Her latest laboratory values show fibrinogen of 150 mg/dL, INR of 1.5, platelets of 70 K/uL and hemoglobin of 8.0 mg/dL. Magnesium sulfate is continued for seizure prophylaxis for 24 h postpartum. She recovers well over the next few days, her laboratory values and blood pressures improve and she is discharged from the hospital in stable condition on post-operative day number four.

Principles of Management

Diagnosis

Diagnosis of preeclampsia is made when a patient has significant proteinuria of greater than 300 mg of protein in a 24 h urine collection or a protein/creatinine ratio of 0.3 mg/dL and blood pressure measurements of greater than 140 mmHg systolic or 90 mmHg diastolic on two instances 4 h. Preeclampsia with severe features is diagnosed when at least one of the following criteria is met:

- Blood pressure measurements of greater than or equal to 160 mmHg systolic or 110 mmHg diastolic on two occasions
- Thrombocytopenia with platelet count less than 100 K/uL
- Impaired liver function as indicated by AST or ALT to twice their normal concentration, severe persistent right upper quadrant pain or epigastric pain unresponsive to medication and not accounted for by alternative diagnosis
- Progressive renal insufficiency as indicated by serum creatinine of greater than 1.1 mg/dL or doubling of the serum creatinine in the absence of renal disease.
- Pulmonary edema
- New-onset cerebral or visual disturbances including worsening headache not relieved with medication or accounted for by alternative diagnosis and new onset seizures (eclampsia) [2].

Additional signs and symptoms of preeclampsia include systemic edema (hands, face, lower extremities), rapid weight gain, hyperreflexia, oliguria or anuria, fetal growth restriction, nausea and vomiting, chest pain and shortness of breath. In severe preeclampsia systemic endothelial dysfunction leads to end-organ damage secondary to inadequate vascular perfusion. Untreated, severe preeclampsia can lead coagulopathy, multi-organ failure and death [7].

Eclampsia is the development of new onset seizures that cannot be attributed to another cause occurring after 20 weeks gestation, usually in the setting of hypertension and proteinuria.

HELLP Syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets) is diagnosed in a pregnant patient after 20 weeks gestation with evidence of hemolysis from microangiopathic anemia (schistocytes on peripheral smear, anemia, lactate dehydrogenase greater than 600 U/L, total bilirubin greater than 1.2 mg/dL), thrombocytopenia (platelets less than 100 K U/L and elevated liver transaminases to at least twice their normal level often in the setting of preeclampsia, although hypertension and proteinuria do not always occur [8].

Preeclampsia, Eclampsia and HELLP are all considered part of the same disease spectrum that carries high rate of maternal and fetal morbidity and mortality. These are progressive conditions that warrant prompt evaluation and management. The primary disease process in these states is endothelial dysfunction and vasospasm. Thus can affect many organ systems in the body:

- **Neurological**: Cerebral edema, vascular occlusion, and cerebral hemorrhage have all been associated preeclampsia. Cerebral manifestations include scotomata, blindness, headache, tinnitus, dizziness, fever, mental

confusion and seizure. Hyperreflexia of deep tendon reflexes and clonus may be present.
- **Cardiovascular**: Hypertension, cardiomyopathy, heart failure
- **Pulmonary**: Pulmonary edema, aspiration from eclamptic seizure
- **Hematologic**: Disseminated Intravascular Coagulation, intravascular volume depletion, third spacing of fluid manifesting as edema of the face and extremities
- **Gastrointestinal**: Liver enlargement, liver capsule edema, intrahepatic hemorrhage, infarction. Aspartate aminotransferase (AST) and alanine aminotransferase may be elevated. Liver capsule rupture can occur and has an extremely high mortality rate.
- **Renal**: proteinuria, renal failure, oliguria, anuria, rhabdomyolysis from eclamptic seizure
- **Fetal**: Placental insufficiency, fetal demise, placental abruption [7]

Seizure Prophylaxis

Magnesium sulfate is first line therapy for seizure prophylaxis in patients with preeclampsia [2, 7]. Magnesium sulfate is a calcium channel blocker and smooth muscle antagonist; it also depresses central nervous system irritability. The initial dose for seizure prophylaxis is intravenous bolus of 4 or 6 g over 15–30 min followed by a maintenance dose of 2 g/h IV. Magnesium is renally cleared. In worsening renal function, magnesium levels should be drawn to titrate magnesium dose and the patient frequently checked for signs of magnesium toxicity (loss of deep tendon reflexes and respiratory depression). If magnesium toxicity occurs, calcium gluconate is the first line agent to reverse this complication. Magnesium should be continued at 2 g/h until 12–24 h postpartum, or until diuresis has occurred [7].

Treatment of Eclamptic Seizure

An actively seizing eclamptic patient should be placed in the left lateral recumbent position, given oxygen as needed and oral secretions should be suctioned to prevent aspiration. Magnesium sulfate is the treatment of choice for eclamptic seizures [1, 2, 9]. If seizures reoccur and magnesium is already being given a second IV bolus of 2 g of magnesium can be given over 3–5 min. If this does not work, other anticonvulsants such as diazepam or lorazepam should be given [7, 9, 10].

Antenatal Steroids and Delivery

Delivery is the definitive treatment for preeclampsia, eclampsia and HELLP syndrome although it can take a few days after delivery for the disease process to resolve fully. Additionally, postpartum preeclampsia and eclampsia can still develop weeks after delivery. Delivery is indicated when there are signs of maternal and/or fetal compromise. Delivery should occur after maternal stabilization in the setting of eclampsia or cardiovascular and/or hemodynamic instability if possible. In patients with preeclampsia without severe features delivery can be delayed until 37 weeks gestation. In patients with preeclampsia with severe features greater than 34 weeks gestation delivery should not be delayed. In patients with preeclampsia with severe features before 34 weeks gestation delivery should be delayed if possible until antenatal steroids are administered, and steroid benefit is achieved. In cases of unstable maternal or fetal conditions, this may not be possible. Cesarean section should be reserved for the usual obstetric indications but induction of labor should be carried out as swiftly as possible [2]. In patients with suspected liver hematoma cesarean section is indicated if vaginal delivery is not imminent as subcapsular liver hematomas are at risk of rupturing and this complication has a very high maternal and fetal mortality rate [11].

Anti-hypertensive Therapy

The use of anti-hypertensive therapy in a preeclamptic patient should be limited to preventing maternal intracranial bleeding or stroke. The risk of intracranial hemorrhage and stroke is increased when maternal blood pressures are above 160 mmHg diastolic and 110 mmHg systolic. There is no proven fetal benefit to lowering blood pressures lower than this cut off in preeclamptic

patients and no evidence that lower maternal blood pressure will decrease the risk of seizure. Lowering maternal blood pressure too aggressively could potentially lead to decreased placental perfusion and fetal compromise. Antihypertensive therapy should be initiated when two blood pressures taken 15 min apart are greater than 160 mmHg diastolic or 110 mmHg diastolic. First line antihypertensive treatment in pregnancy includes intravenous labetalol or hydralazine or oral nifedipine [2, 3, 7]. Labetalol is more commonly used since hydralazine can cause precipitous decreases in blood pressure in those patients who are volume depleted as often seen in preeclamptic patients. Nifedipine is a calcium channel blocker and caution is advised when using this medication concurrently with magnesium sulfate. Labetalol is given starting at 20 mg IV push over two minutes. The dose is increased to 40 mg, then 80 mg every 10 min if blood pressure has not improved to less than 160 mmHg systolic or 110 mmHg diastolic. If blood pressure is still not lowered after 80 mg labetalol, hydralazine 10 mg IV push over 2 min can be given. Alternatively antihypertensive therapy can be initiated with hydralazine 5–10 mg IV push over 2 min and repeated in 10 min if blood pressure is still not controlled. After two doses of hydralazine have not shown to control blood pressure, therapy with labetalol should be initiated. If these regimens are unable to control blood pressure, further management should be decided upon per maternal-fetal medicine or critical care specialist [2]. Sodium nitroprusside is not often used but may be considered in a hypertensive emergency if other medications fail. Diuretics should only be used to treat pulmonary edema in a pregnant preeclamptic patient. These patients are often intravascularly depleted, and diuretics are not recommended for blood pressure management [9].

Treatment of DIC

Disseminated intravascular coagulation (DIC) occurs in up to 10 % of patients with severe preeclampsia [7] and can present with severe bleeding, shock, hemoptysis, dyspnea and acute renal failure. The diagnosis is made with clinical presentation as well as laboratory findings consistent with coagulopathy such as low fibrinogen, thrombocytopenia, prolonged PT, prolonged APTT and elevated INR. Large bore intravenous access should be achieved. An arterial line should be considered for close monitoring. Fluid and product resuscitation should be begun. Most hospitals have a Massive Transfusion Protocol and this should be initiated. As in all cases of DIC, the underlying cause should be treated and in the pregnant patient with severe preeclampsia, eclampsia or HELLP definitive treatment is delivery. Cesarean delivery is preferred in a patient with hemodynamic instability and worsening DIC despite blood product replacement. An attempt should be made to improve clotting ability before surgery if possible. Surgeons with the experience to perform cesarean hysterectomy and manage intrapartum hemorrhage should attend the delivery. The patient should be cared for in the critical care unit postpartum with blood product replacement and hemodynamic monitoring as needed [12].

Evidence Contour

Magnesium Sulfate Therapy

Magnesium sulfate is the cornerstone of seizure prevention and treatment in patients with severe preeclampsia, eclampsia and HELLP syndrome. The Magpie Trial published in 2002 randomized 10,000 women with preeclampsia to magnesium or placebo for prevention of eclampsia and demonstrated that the women who received magnesium had a 58 % lower risk of seizure. The Collaborative Eclampsia Trial reported in the Lancet in 2003 an international multicenter trial comparing magnesium sulfate and diazepam and magnesium sulfate and phenytoin for the anticonvulsant treatment of eclampsia. Magnesium sulfate reduced the rate of recurrent seizure by greater than 50 % in this study [13].

Invasive Monitoring

The preeclamptic patient with refractory oliguria or anuria and pulmonary edema is a candidate for invasive monitoring. Invasive monitoring can

help determine the underlying etiology of the pulmonary edema and, therefore, guide treatment. A study of eight preeclamptic patients with severe preeclampsia and pulmonary edema postpartum monitored with pulmonary artery Swan-Ganz catheters showed that the etiology of the pulmonary edema is not the same for every preeclamptic patient: five patients had changes in colloid oncotic pressure, three patients had pulmonary capillary leak, two had left ventricular failure, and in three of the patients central venous pressure was significantly lower than simultaneously obtained pulmonary capillary wedge pressure [14]. A Cochrane review of pulmonary artery catheter use in pregnant women showed there are no randomized controlled trials of monitoring preeclamptic women with pulmonary artery catheters; further studies are needed and no firm recommendation can be made to use this form of monitoring over central venous monitoring [15].

Dexamethasone Therapy in HELLP Syndrome

Dexamethasone was used in the past for treatment of HELLP but a Cochrane review in 2010 showed that this therapy did significantly improve platelet counts in patients with HELLP syndrome but did not improve maternal outcomes or perinatal mortality [6]. The American College of Obstetricians and Gynecologist states in their task force statement on hypertension and pregnancy that dexamethasone therapy in patients with HELLP syndrome may be justified in situations where platelet improvement could be clinically valuable [2].

Differentiation from Acute Fatty Liver of Pregnancy (AFLP)

It is often difficult to distinguish AFLP from Preeclampsia with HELLP syndrome as it carries similar symptoms and laboratory findings. Symptoms include persistent nausea, vomiting and epigastric pain which are features of both diseases [16–20]. Laboratory findings include liver function abnormalities, elevated creatinine, coagulopathies and hypoglycemia. Some distinguishing features may be a higher level of bilirubin possibly causing jaundice, higher levels of creatinine contributing to renal failure with possible need for dialysis and higher levels of uric acid and neutrophils [17, 18, 20]. In contrast to HELLP coagulopathies, AFLP causes prolongation in prothrombin time, this is thought to be secondary to increased consumption and decreased production by the hepatocytes, and is associated with thrombocytopenia often <50,000 and a hypofibrinogenemia [20, 21]. AFLP also causes acidosis and hypoglycemia which are uncommon in HELLP syndrome. Laboratory values should reach their nadir 2 days postpartum while clinical improvement may not be until postpartum day 3–4, and return to normal values may take as long as 6–21 days [20]. Some more severe complications of AFLP include pancreatitis, acute renal failure, disseminated intravascular coagulopathy (DIC), gastrointestinal bleeding, pulmonary edema, encephalopathy, diabetes insipidus [22] and intractable hypoglycemia [16, 18]. Most common period for the diagnosis of AFLP is during the third trimester.

References

1. The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. Lancet. 1995;345:1455–63.
2. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122:1122–31.
3. American College of Obstetricians and Gynecologists, Committee Opinion no. 623: Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period. Obstet Gynecol. 2015;125(2):521–5.
4. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Obstet Gynecol. 1993;169:1000–6.
5. Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes,

and low platelet count. Obstet Gynecol. 2004;103: 981–91.
6. Woudstra DM, Chandra S, Hofmeyr JG, Dowswell T. Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy. Cochrane Database Syst Rev. 2010;(9):CD008148.
7. Creasy RK, Resnik R, Iams JD. Creasy and Resnik's maternal-fetal medicine: principles and practice. 7th ed. Philadelphia: Elsevier Health Sciences; 2013.
8. Egerman RS, Sibai BM. HELLP syndrome. Clin Obstet Gynecol. 1999;42:381–9.
9. Sibai BM. Diagnosis, prevention, and management of eclampsia. Obstet Gynecol. 2005;105:402–10.
10. Prasad K, Krishnan PR, Al-Roomi K, Sequeira R. Anticonvulsant therapy for status epilepticus. Br J Clin Pharmacol Engl: Blackwell Publishing. 2007; 63:640–7.
11. Araujo ACPF, Leao MD, Nobrega MH, et al. Characteristics and treatment of hepatic rupture caused by HELLP syndrome. Obstet Gynecol. 2006; 195:129–33.
12. Ramin SM, Ramin KD. Disseminated intravascular coagulation during pregnancy. UpToDate. Accessed 4/9/15.
13. Altman D, Carroli G, Duley L, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet. 2002;359: 1877–90.
14. Benedetti TJ, Kates R, Williams V. Hemodynamic observations in severe preeclampsia complicated by pulmonary edema. Obstet Gynecol. 1985;152:330.
15. Li YH, Novikova N. Pulmonary artery flow catheters for directing management in pre-eclampsia. Cochrane Database Syst Rev. 2012;(6):CD008882.
16. Holub K, Camune Barbara. Caring for the woman with acute fatty liver of pregnancy. J Perinat Neonatal Nurs. 2015;29(1):32–40. doi:10.1097/JPN.0000000000000076.
17. Creasy RK, Resnik R, Iams JD, Lockwood CJ, Moore TR, Greene MF, editors. Creasy & Resnik's maternal fetal medicine principles and practice. 7th ed. Philadelphia: Elsevier; 2014.
18. Papafragkakis H, Singhal S, Anand S. Acute fatty liver of pregnancy. South Med J. 2013;106(10):588–93. Accessed 20131007. doi:http://dx.doi.org/10.1097/SMJ.0000000000000007.
19. Chu Y, Meng M, Zeng J, et al. Effectiveness of combining plasma exchange with continuous hemodiafiltration on acute fatty liver of pregnancy complicated by multiple organ dysfunction. Artif Organs. 2012;36(6):530–4. doi:10.1111/j.1525-1594.2011.01424.x.
20. Nelson DB, Yost NP, Cunningham FG. Acute fatty liver of pregnancy: clinical outcomes and expected duration of recovery. Obstet Anesth Digest. 2014;34(3):176. doi:10.1097/01.aoa.0000452194.00769.2a.
21. Nelson DB, Yost NP, Cunningham F. Hemostatic dysfunction with acute fatty liver of pregnancy. Obstet Gynecol. 2014;124(1):40–6. doi:10.1097/AOG.0000000000000296.
22. Lee L, Conn J, Nankervis A. A case series of acute fatty liver of pregnancy complicated by diabetes insipidus: experience at The Royal Women's Hospital, Parkville. Intern Med J. 2012;42(Suppl 2):8.

Part XII

Other Conditions

Robert C. Hyzy

Management of Severe Skin Eruptions

91

Jad Harb, Andrew Hankinson, and Garth W. Garrison

Case Presentation

A 24 year old man with a medical history significant for epilepsy, treated for years with levetiracetam, who had lamotrigine added to his medication regimen. He presents 3 weeks afterwards with a 5-day history of a tingling erythematous rash on both palms, that spread to involve his face, neck, chest, abdomen, back, upper and lower extremities over the next 4 days. Within 1 day of developing the palmar rash, he developed sore throat, oral pain, and widespread ulcerations of the lips and oral mucosa, as well as fever and generalized fatigue. He also developed an ulceration of the urethral meatus with significant dysuria.

His examination revealed multiple, scattered 5–15 mm erythematous macules with dusky purple centers, some of which had a targetoid appearance involving the face, trunk, limbs, hands, penile shaft and the peri-inguinal areas.

The lips were cracked and dry with widespread erythematous erosions involving the buccal mucosa, soft and hard palate, and beneath the tongue. There was a discrete erythematous erosion of the glans penis extending into the urethral meatus (Fig. 91.1).

Question What is the most likely diagnosis for this patient's skin eruption?

Answer Stevens-Johnson syndrome

Stevens-Johnson syndrome and the more severe toxic epidermal necrolysis (TEN) encompass a spectrum of potentially life threatening cutaneous diseases with systemic manifestations [1]. It presents typically with a prodrome of fever, anorexia, pharyngitis and headaches, followed by extensive detachment of the epidermis, in a widespread erythematous or confluent purpuric macules or atypical flat targetoid lesions, which evolve into vesicles or bullae. Skin sloughing follows, and can occur in sheets during the acute phase. Lateral pressure on the skin can produce sloughing of the epidermis and exposure of the dermis, known as Nikolsky sign, characteristic of the syndrome but seen in other severe skin eruptions.

Mucosal involvement is almost universal, occurring in more than 95 % of cases of SJS/TEN, and usually precedes the skin manifestations by a few days. It is characterized by painful, hemorrhagic erosions that can be widespread and commonly involve the eyes, oropharyngeal, anal and genital mucosae. Ulcers and crusts form on

J. Harb • G.W. Garrison (✉)
Division of Pulmonary and Critical Care Medicine, University of Vermont Medical Center, Burlington, VT, USA
e-mail: Garth.garrison@uvmhealth.org

A. Hankinson
Division of Dermatology, University of Vermont Medical Center, Burlington, VT, USA

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_91

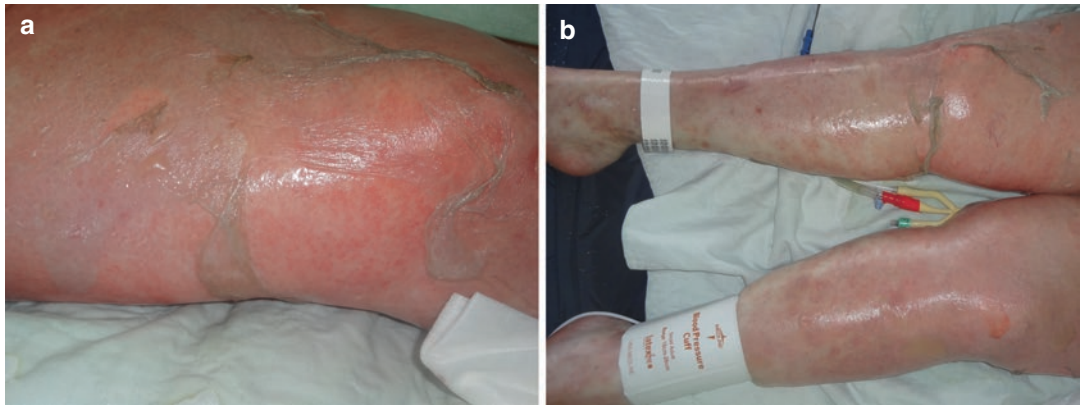


Fig. 91.1 (**a**, **b**) Large loose flaccid bullae which quickly desquamate leaving behind moist erosions. Nikolsky sign was positive with gentle pressure on non-bullous skin causing sloughing. Asboe-Hansen sign was positive with gentle pressure on bullae causing advancement of bullae. Both indicate epidermal necrosis and are sensitive signs for SJS/TEN

the affected mucosal sites and can result in bleeding or infection.

Ocular involvement occurs in more than 60 % of SJS/TEN cases, and can range from mild conjunctivitis, to the more severe membranous or pseudomembranous conjunctivitis, with goblet cell and lachrymal gland loss leading to alterations in the amount and consistency of the tear film, with resultant photophobia, eye dryness and severe pain, prompting an ophthalmologic evaluation early in the course of the disease [2].

The severity of the SJS/TEN syndrome is based on the percentage of epidermal detachment of the body surface area (BSA). It ranges from a BSA of less than 10 % in SJS, to 10–30 % of BSA involvement in the SJS/TEN overlap, to more than 30 % of BSA involved in TEN. The mortality can range from 9 % for SJS to 48 % for TEN [3].

It remains a rare disease, with an incidence of 2–7 cases per million per year, and SJS incidence is almost 3 times that of TEN [4]. It can affect virtually any age group, even occurring in newborns, with an average age of presentation in the sixth decade. It is more prevalent in women and the elderly.

The SCORTEN score was developed to predict the risk of death early in the course of the disease (Table 91.1). It contains seven clinical criteria and laboratory values, with one point given for the worse of each criterion, and a maximal score of seven predicting the expected highest mortality [5].

Table 91.1 Scorten Score

Clinical		Score
Age	≥40 years	1
BSA involved[a]	≥10 %	1
Malignancy	yes	1
Tachycardia	≥120 BPM	1
BUN	≥27 mg/dL[b]	1
Serum glucose	≥250 mg/dL[c]	1
Serum bicarbonate	≤20 mEq/L	1
Total		0–7

A SCORTEN score of 0–1 predicts a mortality rate is 3.2 %. A score of 2 predicts a mortality rate of 12.2 %, a score of 3 predicts a mortality rate of 35.3 %, a score of 4 predicts a mortality rate of 58.3 %, and a score of ≥5 predicts a mortality rate of 90.0 %

[a]Skin detachment on day 1

[b]10 mmol/L

[c]14 mmol/L

In most instances, SJS/TEN is caused by drugs, emphasizing the need for obtaining a detailed history focusing on patterns of drug intake, and on any new added drugs and their association with the onset of the disease [6]. Drugs most associated with SJS include anti-infective agents such as nevirapine, sulfonamide antibiotics, allopurinol, anti-epileptics such as carbamazepine, lamotrigine, phenytoin, phenobarbital, cyclooxygenase inhibitors including NSAIDs.

Fewer cases of SJS/TEN are due to infections, especially Mycoplasma pneumonia [7] or

viruses, such as coxsakie, Epstein–Barr, human herpes virus 6 and 7, cytomegalovirus, especially in children [8].

SJS, and more commonly TEN, can have systemic manifestations by involving the epithelial linings of internal organs, which include acute renal failure with micro albuminuria, as a result of glomerular and tubular epithelial involvement. Pulmonary manifestations such as adult respiratory distress syndrome, bronchiolitis obliterans and infectious pneumonitis, can lead to respiratory failure and death [9]. Gastrointestinal manifestations present with oral and pharyngeal mucosal lesions that can evolve into painful crusts from ruptured vesicles, leading to dysphagia. In the severe cases, it can result in inadequate nutritional and fluid intake. Extension to the entire gastrointestinal tract has been reported [10] leading to diarrhea, gastrointestinal bleeding, cholestatic hepatitis [11] and intestinal necrosis [12].

Pathogenesis

SJS/TEN syndrome is considered a delayed, type IV hypersensitivity reaction to an offending agent, usually a drug. It has been recently established that certain drugs can bind non-covalently to peptide grooves on human leukocyte antigen (HLA) proteins in susceptible individuals. The drug-HLA complex is then presented on keratinocyte cell surface and recognized by the TCR of CD8+ cells, leading to activation of these cells into cytotoxic T lymphocytes, (CTLs) and NK cells, which triggers the secretion of effector chemokines such as granulysin, a cationic cytolytic protein with direct cytotoxic effects leading to extensive keratinocyte apoptosis [13].

SJS/TEN has been linked to certain HLA alleles, such as the association of Carbamazepine-induced SJS to the HLA-B 15:02 allele, found in Han ethnic Chinese with the US Food and Drug Administration to recommending screening for HLA-B 15:02 prior to starting carbamazepine therapy for patients of Southeast Asian ancestry [14]. Other associations include Abacavir, linked to the HLA-B 57:01 allele, or Allopurinol, linked to HLA-b 58:01 [15].

Principles of Management

Supportive Care

The key aspects of treatment for SJS/TEN consists of removal of any suspected offending drug agent with supportive care, and prompt transfer to preferentially a burn unit or a skilled intensive care unit with experience in treating these patients. Adjuvant systemic therapies have shown equivocal outcomes across the literature [16–19].

Supportive therapy is aimed at limiting associated complications. Burn units have experience in handling patients with extensive epidermal damage and sloughing as seen in SJS/TEN. Prompt identification of SJS/TEN via skin biopsy is critical, since minimizing the time between the onset of skin symptoms and transfer to a burn unit has been shown to directly influence survival [16]. Supportive care is focused on fluid and electrolyte replacement, preserving the barrier function of the skin, promoting re-epithelialization of denuded areas, prevention and treatment of infection, and prevention of ocular damage. Volume status, protein and electrolyte replacement is crucial due to significant losses of fluid and protein. This contributes to an overall catabolic state which can lead to mortality. Administration of large volumes of fluids, electrolytes, crystalloids, and TPN are often needed. Venous access sites should be obtained away from involved areas [17]. Gentle and meticulous daily wound care is essential and dermatology consult is necessary when available.

Intact areas of skin should be left dry. Blistered and detached skin surfaces should have vaseline gauze applied until re-epithelialization, as it provides a low friction coverage to these areas [17]. Silicone dressings can also be applied to more eroded areas and left in place until re-epithelialization has occurred. Topical antibiotics such as mupirocin should be applied to the most affected areas, especially to facial mucosal areas such as the nares, mouth and ears [19], but silver sulfadiazine should be avoided if sulfa was suspected offending agent [18]. Systemic antibiotic prophylactic therapy, which used to be the standard of care, is no longer practiced

routinely because of risk of cross reactivity with prescribed antibiotics [18]. Damage to the eye and ocular structures is a significant risk and an ophthalmology consult is essential, for frequent evaluation during the disease course but also for follow up and to treat any sequelae that may have occurred. Damage can be minimized by topical antibiotic use, frequent lubrication, and lysis of adhesions by an ophthalmologist [20]. Oral cleaning should be done frequently with antiseptic spray and removal of any oral crusting should be done as needed [20].

Evidence Contour

Several aspects of management in the patient with SJS and TEN are without consensus in the face of high quality clinical trials. The evidence of systemic therapy for SJS and TEN patients remains conflicting, without any convincing role for adjuvant therapies. There have been no prospective controlled trials for treatment of SJS and TEN, and given the low incidence of the disease, larger controlled trials are very difficult to perform.

Systemic Corticosteroids

Systemic corticosteroids have been frequently used for treatment of patients with TEN despite theoretical increase in infection risk. Prior studies have suggested an increase in mortality with steroid use [21] although newer evidence does not corroborate this [22]. Their use remains controversial with no general consensus on the therapy [17].

Intravenous Immunoglobulins (IVIG)

IVIG has been used for treatment of TEN for the past 15 years given early case reports and series demonstrating potential mortality benefit. Larger follow-up studies demonstrated less convincing benefit or no improvement in mortality. A 2012 meta-analysis of IVIG for TEN did not find a clinical benefit from IVIG [23]. The earlier studies demonstrating efficacy suffered from a lack of control group, heterogeneity of hospital supportive care, and heterogeneity of patients' population [17, 24, 28].

Cyclosporine

Cyclosporine has showed promising results for treatment of SJS/TEN [25–27]. A European pilot study of 29 patients with SJS/TEN demonstrated cyclosporine therapy to be well tolerated without increased risk of infection. Of these 29 patients, the expected death rate was 2.75 % per the SCORTEN score, and the actual death rate was 0 % [25]. Another study showed direct mortality benefit from cyclosporine compared to IVIG in a total 71 patients [27]. These results did not reach a statistical significance because of the small sample size, and thus, larger follow-up studies for confirmation are needed.

TNF Alpha Inhibitors

TNF alpha inhibitors from recent studies are showing possible mortality benefit, with one such study form Italy showing improvement in 10/10 patients treated with a single dose of etanercept (50 mg) without significant side effects [30, 31].

Thalidomide

Thalidomide has been shown to increase mortality in SJS/TEN, and a randomized control trial was discontinued due to increased mortality in 10/12 patients on thalidomide therapy vs 3/10 in the control arm [29].

Summary

In summary, the mainstay of treatment for SJS/TEN involves prompt withdrawal of any offending agents, supportive care with transfer to a burn or intensive care unit. The evidence for use of systemic therapies are not yet conclusive [17, 20], at this point, and their role is at best equivocal.

References

1. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol. 1993;129:92–6.
2. Yip LW, Thong BY, Lim J, et al. Ocular manifestations and complications of Stevens-Johnson syndrome and toxic epidermal necrolysis: an Asian series. Allergy. 2007;62:527–31.
3. Mockenhaupt M. Severe cutaneous adverse reactions. In: Burgdorf WHC, Plewig G, Wolff HH, Landthaler M, editors. Braun-Falco's dermatology. 3rd ed. Heidelberg: Springer Medizin Verlag; 2009. p. 473–84.
4. Lissia M, Mulas P, Bulla A, Rubino C. Toxic epidermal necrolysis (Lyell's disease). Burns. 2010;36:152–63.
5. Bastuji-Garin S, Fouchard N, Bertocchi M, et al. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000;115:149–53.
6. Sassolas B, Haddad C, Mockenhaupt M, et al. ALDEN an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clin Pharmacol Ther. 2010;88(1):60–8.
7. Fournier S, Bastuji-Garin S, Mentec H, Revuz J, Roujeau JC. Toxic epi- dermal necrolysis associated with Mycoplasma pneumoniae infection. Eur J Clin Microbiol Infect Dis. 1995;14:558–9.
8. Sotelo-Cruz N. Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Gac Med Mex. 2012;148:265–75.
9. Lebargy F, Wolkenstein P, Gisselbrecht M, Lange F, Fleury-Feith J, Delclaux C, et al. Pulmonary complications in toxic epidermal necrolysis: a prospective clinical study. Intensive Care Med. 1997;23:1237–44.
10. Boe J, Dalgaard JB, Scott D. Mucocutaneous-ocular syndrome with intestinal involvement. Am J Med. 1958;25:857–67.
11. Morelli MS, O'Brien FX. CASE REPORT: Stevens-Johnson syndrome and cholestatic hepatitis. Dig Dis Sci. 2001;46:2385–8.
12. Carter FM, Mitchell CK. Toxic epidermal necolysis, an unusual cause of colonic perforation: report of a case. Dis Colon Rectum. 1993;36:773–7.
13. Illing PT, et al. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. Nature. 2012;486(7404):554–8.
14. Leckband SG, Kelsoe JR, Dunnenberger HM, et al. Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and carbamazepine dosing. Clin Pharmacol Therap. 2013;94(3):324–8.
15. Hung SI, Chung WH, Liou LB, et al. HLA-B *5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A. 2005;102:4134–9.
16. Palmieri TL, et al. A multicenter review of toxic epidermal necrolysis treated in US burn centers at the end of the twentieth century. J Burn Care Res. 2002;23(2):87–96.
17. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. J Am Acad Dermatol. 2013;69(2):187–e1.
18. Fine J-D. Management of acquired bullous skin diseases. N Engl J Med. 1995;333(22):1475–84.
19. French LE, Prins C. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. In: Bolognia JL, Jorizzo JJ, Schaffer JV, editors. Dermatology. Philadelphia: Saunders; 2012. p. 319–34.
20. Hazin R, Ibrahimi OA, Hazin MI, Kimyai-Asadi A. Stevens-Johnson syndrome: pathogenesis diagnosis, and management. Ann Med. 2008;40:129–38.
21. Halebian PH, Corder VJ, Madden MR, Finklestein JL, Shires GT. Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. Ann Surg. 1986;204:503–12.
22. Law EH, Leung M. Corticosteroids in Stevens-Johnson Syndrome/toxic epidermal necrolysis: current evidence and implications for future research. Ann Pharmacother. 2015;49(3):335–42.
23. Huang YC, Li YC, Chen TJ. The efficacy of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systemic review and meta-analysis. Br J Dermatol. 2012;167:424–32.
24. Gerull R, Nelle M, Schaible T. Toxic epidermal necrolysis and Stevens-Johnson syndrome: a review. Crit Care Med. 2011;139:1521.
25. Valeyrie-Allanore L, et al. Open trial of cyclosporin treatment for Stevens–Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol. 2010;163(4):847–53.
26. Singh GK, Chatterjee M, Verma R. Cyclosporine in Stevens Johnson syndrome and toxic epidermal necrolysis and retrospective comparison with systemic corticosteroid. Indian J Dermatol Venereol Leprol. 2013;79(5):686.
27. Kirchhof MG, et al. Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine. J Am Acad Dermatol. 2014;71(5):941–7.
28. Lalosevic J, et al. Stevens–Johnson syndrome and toxic epidermal necrolysis: a 20-year single-center experience. Int J Dermatol. 2014;54(8):978–84.
29. Wolkenstein P, et al. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. Lancet. 1998;352(9140):1586–9.
30. Paradisi A, et al. Etanercept therapy for toxic epidermal necrolysis. J Am Acad Dermatol. 2014;71(2):278–83.
31. Famularo G, et al. Etanercept for toxic epidermal necrolysis. Ann Pharmacother. 2007;41(6):1083–4.

Management of Alcohol Withdrawal Syndromes

92

Lucas A. Mikulic and Garth W. Garrison

Case Presentation

A 53 year-old man with a history of alcohol abuse, presented to the emergency department with altered mental status, agitation, tremors and visual hallucinations. His family members recall the patient drinking 1 pint of vodka and 2 cases of beer a day, which he had stopped in preparation for a screening colonoscopy. His vital signs were notable for a BP 230/120 mmHg, pulse 160 bpm, temperature 101 F, respiratory rate 27/min, and pulse oximetry 82 % on room air. Laboratory data was significant for WBC 27,000, Creatinine 1.5, Potassium 2.6 and CK 17,000. Capillary glucose levels was 160 mg/dL, and computed tomography of the brain showed cortical atrophy, which was more than expected for patient's age. The patient was admitted to the intensive care unit for further management.

Question What is the most likely diagnosis on this patient?

Answer Alcohol Withdrawal Delirium (AWD) – Delirium tremens (DTs)

L.A. Mikulic (✉) • G.W. Garrison
Division of Pulmonary and Critical Care Medicine,
University of Vermont Medical Center,
Burlington, VT, USA
e-mail: Garth.garrison@uvmhealth.org

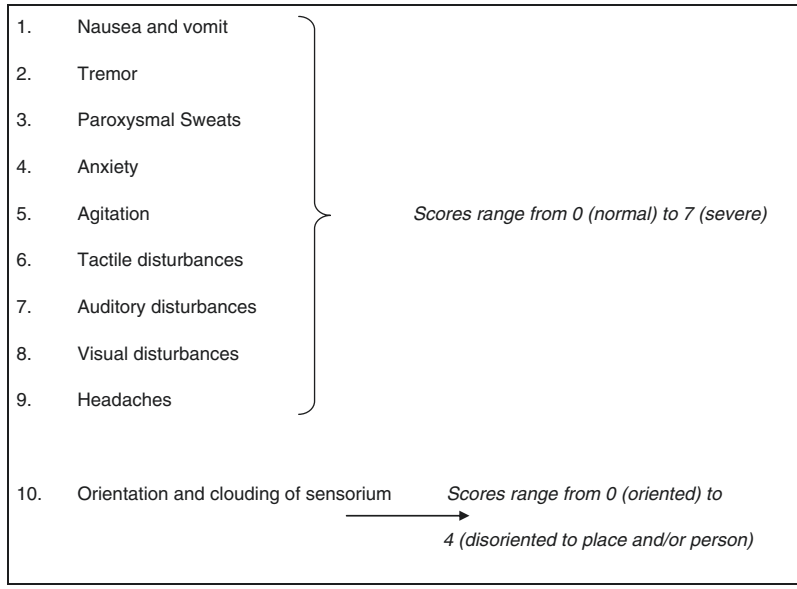
DTs is defined as alcohol withdrawal and clouding of the sensorium (delirium) [1, 3] (Table 92.1). This patient was admitted to the medical intensive care unit (ICU), where his Clinical Institute Withdrawal Assessment scale for Alcohol, Revised (CIWA-Ar) score was calculated to be 19 (Table 92.2). The patient was given IV thiamine, and then started on intravenous fluids. Serum electrolytes were closely monitored and any deficits corrected. Subsequent testing including urinalysis, urine toxicology, chest x-ray and electrocardiogram were normal. The patient was started on intravenous lorazepam 1–5 mg IV every 5–15 min as needed and adjusted for patient's somnolence. As his agitation and hallucinations were not well controlled, haloperidol was started (0.5–5 mg intravenously every hour, not exceeding 20 mg/h). Electrocardiograms were closely monitored for any QT prolongation. As the patient's symptoms continued to progress, he was electively intubated and started on IV propofol with benzodiazepines and haloperidol continued on as-needed bases and titrated according to the Richmond Agitation Severity Scale (RASS). After 72 h, the patient's symptoms were better controlled and he was extubated. His sedatives were then administered on as needed bases according to CIWA-Ar protocol. He was eventually transferred to a medical floor in improved condition.

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_92

Table 92.1 Delirium tremens DSM V criteria [27]

Alcohol withdrawal:	**Delirium**:
A. Discontinuation of prolonged heavy alcohol intake *B. At least two of the following symptoms*: Autonomic hyperactivity Hand tremors Insomnia Nausea or vomit Transient hallucinations or illusions Psychomotor agitation Anxiety Generalized tonic clonic seizures	Decreased attention or awareness Disturbance in attention, awareness, memory, orientation, language, Visuospatial ability, perception, or all of these abilities that is a change from the normal level and fluctuates in severity during the day Disturbances in memory, orientation, language, visuospatial ability, or perception No evidence of coma or other evolving neurocognitive disorders
Predictors of delirium tremens: [1]	
CIWA-AR scores > 15	
Tachycardia (heart rate > 100 bpm)	
Hypertension (systolic blood pressure > 150 mmHg)	
Older age	
Recent or prior seizures/AWS	
Recent misuse of other depressant drugs	
Electrolyte abnormalities	
Other comorbidities (cardiac, pulmonary, gastrointestinal)	

Table 92.2 The revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar) [4]



A score greater than 10 indicates the need for admission to the hospital, with higher scores correlating with severity of withdrawal and probability of seizures [5, 6]

Principles of Management

Diagnosis

Alcohol withdrawal is a clinical diagnosis based on appropriate patient history and symptoms, with reasonable exclusion of other etiologies (e.g. infectious workup if patient presents with fever). Patients should have a history of chronic alcohol abuse with a recent abrupt reduction in intake. The symptoms of alcohol withdrawal can be divided into three broad categories: CNS

excitation, autonomic hyperactivity, and psychosis. CNS excitation occurs 12–48 h following alcohol cessation, and is due to decreased inhibitory tone of the γ-amino butyric acid (GABA) receptor, and increased excitatory activity of the N-methyl-aspartate glutamate receptor (previously suppressed by alcohol intake). The patient may present with anxiety, agitation and restlessness, which, if left untreated, can progress to seizures. Most of the seizures are self- limited but can progress to status epilepticus. Autonomic hyperactivity typically occurs 24–48 h following alcohol cessation and is related to increased noradrenergic response. The patient may experience fevers, tachycardia, hypertension, diaphoresis and fevers. Psychosis occurs due to excess dopamine release through the mesolimbic tract. The patient will show confusion, hallucinations, and paranoia [3, 7].

Initial Phase of Care

The management of alcohol withdrawal is directed towards alleviating symptoms of withdrawal and avoiding its progression into seizures or DTs. For patients with marked alteration in mentation, hemodynamic instability, or those requiring frequent nursing assessment and intervention, ICU admission is suggested. Due to disease and medication related alterations in mentation; patients may require endotracheal intubation for airway protection. Benzodiazepines (e.g. lorazepam, diazepam) remain the first line of treatment, and are typically given intravenously to patients requiring ICU monitoring. Initially, a symptom-triggered escalating dose strategy has been shown to reduce the duration of therapy and the total dose of the medication given [8]. The goal of this protocol is to rapidly increase the doses until a desired level of sedation is achieved, before severe agitation occurs (Table 92.3). In cases of DTs, continuous benzodiazepine infusion may be required to alleviate symptoms [1, 7, 9, 10]. As propylene glycol toxicity may occur with high doses of IV lorazepam, it is recommend to check serum osmolarity (Osm) and the osmolar gap in these patients, and to stop the infusion if serum osm >350 mOsm/kg or serum osmol gap >10 [10, 11].

The goal of care must also include nutritional supplementation and hydration, with emphasis in avoiding excessive fluid administration. Blood glucose and electrolytes must be monitored closely. Thiamine (500 mg IV once or twice a day for 3 days) is recommended to prevent the development of Wernicke encephalopathy, and it's particularly important to be given before the administration of IV dextrose, as the latter can precipitate acute thiamine efficiency [1, 9, 10].

Table 92.3 Pharmacologic treatment of alcohol withdrawal delirium [9, 12]

Drug	Loading dose	Repeated dosing regimen if ineffective
Diazepam	5 mg IV	1. Repeat dose of 2.5 mg IV in 10 min, then 2. Administer additional 2.5 mg dose, then 3. Repeat dosing every 10 min increasing to 5 mg, then 10 mg, then 20 mg as is needed
Lorazepam	1–4 mg IV	1–4 mg IV every 5–15 min, can repeat hourly
	1–40 mg IM	Repeat 1–40 mg IM
Phenobarbital	260 mg IV	130–260 mg IV every 15–20 min
The following drugs must be utilized as adjunct therapy or in combination with benzodiazepines for the treatment of DT's [12–16]		
Propofol	Can be bolused and/or administered as an infusion (5–80 ug/kg/min)	
Haloperidol	0.5–5 mg IV/IM every 30–60 min	
Dexmedetomidine	Infusion: 0.2–0.7 ug/kg/h, with no bolus.	

Note: phenobarbital and propofol must be administered in an ICU. Phenobarbital may be administered as monotherapy or in combination with benzodiazepines for refractory DTs. In the ICU, medications are titrated according to the Richmond Agitation Severity Score (RASS)

Evidence Contour

Several aspects of management in the patient with alcohol withdrawal remain without consensus in the face of available clinical trials.

Patient Disposition

ICU admission is frequent in patients admitted to the hospital with acute alcohol withdrawal; studies have described between a 20–30% risk of ICU admission [15]. In patients admitted to the intensive care unit, many will ultimately require mechanical ventilation [11]. Early identification and treatment with symptom-triggered benzodiazepine dose strategy, done on the floor, can reduce ICU admissions. A phenobarbital protocol, given outside the ICU, has also been described to reduce ICU admission [12]. However adjuvant/alternate therapies including propofol and dexmedetomidine infusions require ICU transfer for their administration. Whether there is a benefit for admission to ICU level care in patients with moderate withdrawal symptoms prior to decompensation is currently unknown. Likewise, outcomes with early or delayed intubation have not been prospectively evaluated [11]. However given risk of ultimate ICU need overall, a low threshold for ICU transfer is advised.

Propofol

In patients requiring mechanical ventilation, propofol may be used for the treatment of alcohol withdrawal. In a retrospective cohort analysis, no significant difference was found in length of hospital stay, ICU stay, or mechanical ventilation when patients were treated with benzodiazepine monotherapy, propofol monotherapy, or benzodiazepine plus propofol [17].

Phenobarbital

Traditionally, benzodiazepines have been recommended as the first line of treatment in AWS, as barbiturates have a narrower therapeutic window, a higher likelihood for respiratory depression, and greater potential for interaction with other medications.

The use of phenobarbital in alcohol withdrawal has been typically reserved for those cases resistant to conventional therapy with benzodiazepines, which is defined as a patient requiring more than 40 mg diazepam (or 10 m lorazepam) in 1 h. In these cases, barbiturates have been proven to be effective. As demonstrated by Gold et Al in a retrospective study performed in patients admitted to a medical ICU for severe AWS, higher doses of diazepam in combination with barbiturates were associated with a twofold decrease in mechanical ventilation [18].

In Denmark, barbiturates have been used in the treatment of DTs for decades. In a prospective study performed by Kramp and Rafaelsen, diazepam and phenobarbital were compared in the treatment of DTs. No difference was found between the two drugs in cases of mild- moderate AWS, nevertheless phenobarbital was found to be superior to diazepam in the treatment of DTs [19].

In a recent prospective study, a single use of IV phenobarbital, together with a symptom guided lorazepam regimen, resulted in decreased ICU admission rate in emergency department patients with AWS, and was not associated with increased adverse events [12].

This evidence supports the use of phenobarbital in severe cases of AWS or DTs. In mild to moderate cases, benzodiazepines still remain the standard of care, at least until further prospective studies confirm safety and efficacy of phenobarbital.

Central Alpha 2 Agonists

Stimulation of the presynaptic alpha 2 receptors decreases the release of norepinephrine and activation of the autonomous nervous system, with anxiolytic, analgesic, anesthetic and sympatholytic effects [20]. Both clonidine and dexmedetomidine are alpha 2 agonists, nevertheless the latter is administered IV, has a

shorter half-life (approximately 2 h), and is eight times more potent [20, 21]. These medications cannot be utilized solely for AWS but in conjunction with benzodiazepines [22]. Several small retrospective trials have shown that the addition of dexmedetomidine to benzodiazepine treatment decreases the total use of benzodiazepines. The most common side effects observed were hypotension and bradycardia [14, 20, 23, 24]. Since no randomized control trials have evaluated the use of dexmedetomidine in the intensive care unit, neither proven its efficacy to prevent seizures or DTs, this drug should be used with care.

Antipsychotics

Intravenous antipsychotics may be utilized for the treatment of psychosis when patients fail to respond to the usual care with benzodiazepines. These medications should be used with caution, as they can lower the seizure threshold, cause neuroleptic malignant syndrome, or prolong the QT interval [9]. If utilized, close monitoring of QTc and electrolytes is recommended [1, 7].

Anticonvulsants

Benzodiazepines (alone or in conjunction with propofol or phenobarbital) are the gold standard for the treatment of alcohol withdrawal seizures. The use of phenytoin has been proven to be nonbeneficial in preventing recurrences of seizures [6, 25]. Carbamazepine has been utilized with success in the treatment of AWS, and when compared to oxazepam, at least two studies have shown the efficacy of this medication to reduce withdrawal symptoms [26]. Its use in the ICU still requires further research.

Other Agents

Gabapentin, valproic acid, and baclofen have shown promising results in small studies in the treatment of AWS. Still, larger studies are needed to assess safety and efficacy [26].

References

1. Schuckit MA. Recognition and management of withdrawal delirium (delirium tremens). N Engl J Med. 2014;371(22):2109–13.
2. Young GP, Rores C, Murphy C, Dailey RH. Intravenous phenobarbital for alcohol withdrawal and convulsions. Ann Emerg Med. 1987;16(8):847–50.
3. Hall W, Zador D. The alcohol withdrawal syndrome. Lancet. 1997;349:1897–900.
4. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict. 1989;84(11):1353–7.
5. Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. N Engl J Med. 2003;348:1786–95.
6. Chance JF. Emergency department treatment of alcohol withdrawal seizures with phenytoin. Ann Emerg Med. 1991;20(5):520–2.
7. Nejad SH, et al. Case 39-2012: A 55 year old man with alcoholism, recurrent seizures, and agitation. N Engl J Med. 2012;367;2428–34.
8. Yahwak JA, Riker RR, Fraser GL, Subak-Sharpe S. Determination of a lorazepam dose threshold for using the osmol gap to monitor for propylene glycol toxicity. Pharmacotherapy. 2008;28(8):984–91.
9. Mayo-Smith MF, Beecher LH, Fischer TL, Gorelick DA, Guillaume JL, Hill A, Jara G, Kasser C, Melbourne J. Management of alcohol withdrawal delirium. An evidence-based practice guideline. Arch Intern Med. 2004;164(13):1405–12.
10. DeCarolis DD, Rice KL, Ho L, Willenbring ML, Cassaro S. Symptom-driven lorazepam protocol for treatment of severe alcohol withdrawal delirium in the intensive care unit. Pharmacotherapy. 2007;27(4):510–8.
11. Stewart R, Perez R, Musial B, Lukens C, Adjepong YA, Manthous C. Outcomes of patients with alcohol withdrawal syndrome treated with high-dose sedatives and deferred intubation. Ann Am Thorac Soc. 2016;13(2):248–52.
12. Rosenson J, Clements C, Simon B, Vieaux J, Graffman S, Vahidnia F, Cisse B, Lam J, Alter H. Phenobarbital for acute alcohol withdrawal: a prospective randomized double-blind placebo-controlled study. J Emerg Med. 2013;44(3):592–8.e2.
13. Frazee EN, Personett HA, Leung JG, Nelson S, Dierkhising RA, Bauer PR. Influence of dexmedetomidine therapy on the management of severe alcohol withdrawal syndrome in critically ill patients. J Crit Care. 2014;29(2):298–302.
14. Rayner SG, Weinert CR, Peng H, Jepsen S, Broccard AF; Study Institution. Dexmedetomidine as adjunct treatment for severe alcohol withdrawal in the ICU. Ann Intens Care. 2012;2(1):12.

15. Carlson RW, Kumar NN, Wong-Mckinstry E, et al. Alcohol withdrawal syndrome. Crit Care Clin. 2012; 28(4):549–85.
16. Jean-Bernard Daeppen MD, Pascal Gache MD, Ulrika Landry BA, Eva Sekera MD, Verena Schweizer MD, Stéphane Gloor PD, Bertrand Yersin MD. Symptom-triggered vs fixed-schedule doses of benzodiazepine for alcohol withdrawal: a randomized treatment trial. Arch Intern Med. 2002;162(10):1117–21.
17. Sohraby R, Attridge RL, Hughes DW. Use of propofol-containing versus benzodiazepine regimens for alcohol withdrawal requiring mechanical ventilation. Ann Pharmacother. 2014;48(4):456–61.
18. Gold JA, Rimal B, Nolan A, Nelson LS. A strategy of escalating doses of benzodiazepines and phenobarbital administration reduces the need for mechanical ventilation in delirium tremens. Crit Care Med. 2007;35(3):724–30.
19. Kramp P, Rafaelsen OJ. Delirium tremens: a double-blind comparison of diazepam and barbital treatment. Acta Psychiatr Scand. 1978;58(2):174–90.
20. DeMuro JP, Botros DG, Wirkowski E, Hanna AF. Use of dexmedetomidine for the treatment of alcohol withdrawal syndrome in critically ill patients: a retrospective case series. J Anesth. 2012;26(4):601–5.
21. Lizotte RJ, Kappes JA, Bartel BJ, Hayes KM, Lesselyoung VL. Evaluating the effects of dexmedetomidine compared to propofol as adjunctive therapy in patients with alcohol withdrawal. Clin Pharmacol. 2014;6:171–7.
22. Muzyk AJ, Fowler JA, Norwood DK, Chilipko A. Role of α2-agonists in the treatment of acute alcohol withdrawal. Ann Pharmacother. 2011; 45(5):649–57.
23. Dailey RW, Leatherman JW, Sprenkle MD. Dexmedetomidine in the management of alcohol withdrawal and alcohol withdrawal delirium. Am J Respir Crit Care Med. 2011;183:A3164.
24. Muzyk AJ, Revollo JY, Rivelli SK. The use of dexmedetomidine in alcohol withdrawal. J Neuropsychiatry Clin Neurosci. 2012;24:3.
25. Alldredge BK, Lowenstein DH, Simon RP. Placebo-controlled trial of intravenous diphenylhydantoin for short-term treatment of alcohol withdrawal seizures. Am J Med. 1989;87(6):645–8.
26. Leggio L, Kenna GA, Swift RM. Newdevelopments for the pharmacological treatment of alcohol withdrawal syndrome. A focus on non-benzodiazepine GABAergic medications. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(5):1106–17.
27. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. DSM-V. Washington, DC: American Psychiatric Publishing; 2013.

Part XIII

Medical Ethics

Robert C. Hyzy

End of Life Care in the ICU

93

Sameer Shah and Nicholas S. Ward

Case Presentation

An 85 year old man was admitted to the ICU for acute respiratory failure from pneumonia and hypotension and altered mental status. He was known to have lung cancer and CT scan obtained in ER showed what appeared to be metastases in his brain.

After stabilizing the patient the ICU, the team met with the family who were composed of a grandson who lives in another state, an elderly sister with dementia and a daughter-in-law who has been intermittently looking in on him for years. At that point the patient was unable to participate in the discussion because he is obtunded.

After telling the family about his acute and chronic illnesses and the treatments he has been receiving the team began a discussion about goals of care. The family stated that he did not have a written advance directive nor had he documented a healthcare proxy. In the course of these discussions, the grandson said that he wants "everything done", the sister only nodded, and the daughter-in-law disagreed saying that the patient did not like hospitals, was lonely, and wanted to die. She favored minimal medical interventions and a focus on comfort. They asked questions about his prognosis such as whether he will live and what he will be like afterward.

After more discussion the topic of Do Not Resuscitate (DNR) was raised. The family did not want him to suffer but worried if he is DNR he would not get antibiotics and would be ignored by the ICU team. Eventually, a consensus decision with the ICU team was made. The goals of care would be to focus on comfort with some medical care such as fluids and antibiotics and oxygen for limited period of time to see if he could easily recover from the acute event. By the second day the patient was in renal failure and still hypotensive.

Question Based on the discussion of goals of care should additional life support measures, such as dialysis, now be provided?

Answer According to the current understanding of the goals of care the answer would be no. However, current management with antibiotics, fluids and oxygen would continue.

Given the deterioration in the patient's clinical condition a continued dialog with the patient's family to inform them of this change is important. When the family was made aware of the deterioration in the patient's clinical condition the patient's goals of care were subsequently changed to comfort measures only (CMO). Palliative care

S. Shah • N.S. Ward (✉)
Division of Pulmonary, Critical Care, and Sleep Medicine Medicine, Alpert/Brown Medical School, Providence, RI, USA
e-mail: Nicholas_Ward@brown.edu

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7_93

was then consulted and additional medical interventions were withheld. The patient expired a day later.

Principles of Management

Making Decisions in the ICU

The manner in which important medical decisions are made has changed throughout the history of medicine. For much of the time, almost all decisions were made by physicians in a manner often referred to as *medical paternalism*. In the later twentieth century, however, cultural views changed and the pendulum swung to a more patient-centered model and the idea of *medical autonomy* became key tenet of medical decision making. New medical technologies drove much of this change as increasingly complex decisions needed be made on life-or-death issues. These decisions often encompassed elements of both medical care as well as personal views on how and when a person dies. In the last several decades, the problems of using either a predominantly paternalistic or autonomy-based decision model have become clear. Put succinctly, paternalism often fails to consider patients' values and autonomy can often lead to decisions made that fail to recognize medical realities and may place heavy burdens on families. Increasingly, the medical community is advocating for a model of decision making referred to as a *shared-decision model* that seeks to incorporate elements of both models. This will be discussed in more detail later in the chapter.

Unfortunately, as in the case described here, ICU patients are often unable to participate in these shared-decisions, and as a result, physicians must rely heavily upon surrogate decision making [1]. There are numerous challenges that exist when using surrogate decision makers. As this case illustrates, sometimes it is not clear who should be used as a surrogate and often surrogates propose differing views. As a matter of convention, physicians often look to family but sometimes there are family characteristics that make them less than optimal decision makers. When a patient cannot speak for him or herself and does not have a clear written directive the team then looks for a *healthcare proxy*, or someone legally designated as a decision maker. In the absence of that they look to a surrogate. A surrogate is someone who (ideally): (1) knows what the patient would want and (2) has the patient's best interests in mind. Choosing a surrogate can be challenging. In as case such as this, two key principles should be applied. One is that ICU team should work to create some consensus among the family and the second is that weight should be given to the surrogate who would know what the patient would want. In some cases, where no family is available, close friends or neighbors can be used to help guide the goals of care if the team feels they are fulfilling the principles of surrogacy.

More problems exist with surrogate decision making. Studies have shown that even close relatives are not always able to guess what complex or life determining treatments their loved one would want or not want [2]. Surrogates and physicians are thus often left with questions regarding decisions they have made. Additionally, it is clear that putting the burden of such critical decisions on family can impose a tremendous emotional burden, in some cases leading to long-term psychiatric morbidity. Psychiatric morbidity, manifesting as symptoms of post-traumatic stress disorder (PTSD) in surrogates at 90 days, has been associated with shared decision making. Nearly 1/3 of surrogates will have these symptoms, and the risk is higher in patients involved in shared decision making regarding end-of-life (EOL) decisions [3]. Despite the limitations of shared decision making, particularly the use of surrogates, it is accepted as striking the appropriate balance between autonomy and paternalism.

Prognostication

Another big challenge facing ICU physicians when engaging families in discussions regarding EOL care is identifying who is at the end of life. Failure to predict may prevent timely discussions and over prediction of mortality can lead to family

mistrust of the medical staff. There are many tools available for prognostication, including published data for mortality in certain diseases, mortality scoring tools, and physician experience. Published data is often hard to use for a particular patient, as each patient may or may not fit within the specific entry criteria in those studies. Also, medical therapies for a particular disease state can change rapidly making studies that are only a couple years old irrelevant. Many severity scoring systems have been to help with prognostication (APACHE, SAPS, SOFA) but predictions are at best 90% accurate [4] and only can give predications based on a few components of physiology making them accurate for groups but less helpful for specific individuals. Physicians and ICU staff are much less accurate, predicting incorrectly as much as 44% of the time [5]. In the case of this ICU patient, family is also concerned with morbidity and after care which can be even harder to predict. Nevertheless, the team should include discussion of post-treatment morbidity in goals of care discussions and they should be transparent about the difficulties in accurately predicting outcomes. Additionally, this case illustrates that the effect of uncertainty at the time of admission can be ameliorated by changing goals of care as the time makes the prognosis more clear.

What Constitutes Good End of Life Care?

Given how many people now die in ICUs, there has been increasing emphasis placed on improving this element of patient care. Problems arise, however, when one tries to determine what elements of care are good. The Institute of Medicine, in 1998, proposed "that people should be able to expect and achieve a decent or good death—*one that is free from avoidable distress and suffering for patients*, *families*, *and caregivers*; *in general accord with patients' and families*, *wishes*; *and reasonably consistent with clinical*, *cultural*, *and ethical standards*." [6] A good death is the goal for all patients, but the manner in which that arrives is an area where the medical community continues to struggle.

There are clearly things that have been shown to improve EOL care. Tools like the Quality of Dying and Death (QODD) questionnaire have helped identify key components of EOL care that improve family outcomes and experiences. Support for the family, family presence at time of dying, perceived nursing skill, decision-making support, and documentation of patient wishes regarding EOL care were all associated with improved QODD scores. Lower QODD scores were seen when patients had CPR within the last hour of life [7–9]. Communication is the cornerstone of effective EOL care. Particular factors in family meetings have been shown to improve family outcomes, including higher proportion of family speech, increased empathic statements ensuring non-abandonment, symptom control and decision-making. Interestingly, the length of family conferences was not associated with improved satisfaction [10–12].

Access to spiritual care at family request, including the presence of a spiritual advisor in the last day of life, can also improve satisfaction [13]. Shared decision-making, evaluating the patient's end-of-life wishes, a physician recommendation to withdraw life-prolonging interventions, and death after these interventions have been withdrawn have all improved family satisfaction with end of life care. Patients that died on full support have family members with worse satisfaction [14, 15]. Finally, withdrawal of life-sustaining therapies is often a key component of EOL care. Family understanding of the withdrawal process, proceeding as expected and management of symptoms was also associated with improved satisfaction [16].

Evidence Contour

Code Status and the ICU Patient

The Do-not-resuscitate (DNR) order and related treatment decisions remain some of the most controversial topics in medicine and especially ICU care. The underlying concept is that patients may reach a state of poor health such that they do not want to be revived when dying or the treating

physician feels that such resuscitation would be ineffective. The modern iteration of this rose to prominence after cardiopulmonary resuscitation (CPR) was invented, an intervention that literally allowed doctors to revive someone who would normally have been considered dead (i.e. pulseless). The main controversies arose from several elements of this decision such as: who decides, what constitutes "resuscitation" and how does this decision impact other elements of care.

Background

In the 1960s the technique of closed cardiac massage for resuscitating patients who were pulseless was popularized and began to be used commonly in hospitals. Not long after that the medical literature began to detail a number of adverse complications that could occur [17] as well as stories of patients who received it unwanted while dying. In a famous letter to the British Medical Journal a physician wrote of a colleague's agonizing death from untreatable gastric cancer. He was repeatedly resuscitated over the course of days despite pleas to be left to die [18]. The ensuing years were chaotic in terms of defining who should decide when not to administer CPR and the process by which that should occur. In the early years, the doctors made such decisions almost unilaterally and often without the patient's knowledge. Other publicized cases from the 1970s drew attention to the lack of disclosure and a confused process by which these decisions were being made in hospitals. Finally, in the 1980s and 1990s several major professional societies and journals began publishing consensus-based guidelines which helped to unify, somewhat, the process [19–22]. Despite these efforts, DNR other code status designations remain a source of controversy and confusion.

Problems with DNR

One major problem is defining what the term means. To some, DNR designates only that CPR and/or the Advanced Cardiac Life Support (ACLS) protocols will not be performed. This may or may not include respiratory support, electrical cardioversion, chemical cardioversion, and other acute interventions meant to save a life. In many cases it is clear that either the patient or physician is using the term to go beyond CPR and denote a general limitation of aggressive, life-saving procedures that could include things like hemodialysis, blood transfusions, surgery and many other interventions. At the very least, physicians and other healthcare providers should understand that there is lack of consensus as to what DNR means for any given patient and care should be taken among all providers and families to clarify.

Some efforts to customize or better define a given patient's code status have resulted in improvements but new problems as well. Many institutions have tried using complex, menu-like systems that list a variety of life supporting interventions. It is now possible to see a patient who wishes to be resuscitated but not intubated (DNI), or intubated but not resuscitated. These designations start from the best intentions but often end up creating more confusion or creating situations that are medically futile or impossible to carry-out. Hospitals can find themselves confronted with situations where a patient is refusing one form of therapy that may lead to cardiac arrest but still wishes to have ACLS. Additionally, many physicians feel that asking patients to decide on specific complex interventions violates principles of good informed consent since the indications, risks, and benefits are too complex for them to fully understand.

Who Should Make Decisions About Life Support?

Two important principles involved in DNR orders are the concepts of futility and patient autonomy. Modern western medical ethics values a patient's right to determine which treatments he or she wishes to receive and this principle was the primary driver of much of the evolution of DNR orders. As mentioned earlier, for many years physicians had the sole ability to decide when aggressive care should not be offered based on perceived futility. It was not until the later part of the twentieth century that it became acceptable for patients to make these decisions. During this time medical culture changed on many fronts with much more emphasis placed on the patient's right

to determine their care. This was largely a positive change that led to more personalized care that was in keeping with personal values.

There was a downside to this focus on autonomy, unfortunately. By asking patients or their families to make decisions on acute, complex, life-saving interventions we may burden them with guilt, stress, and the potential to make poor decisions based on limited understanding of the medical benefits and risks. As an example, the physicians may feel they are being nice when asking this family if they want CPR or ACLS performed on the patient but by doing so they have given them a life-or-death decision that must often be made with little time, in a time of great stress and emotion and with insufficient medical knowledge to fully comprehend the benefits. Because of this, medical culture in the United States has been evolving towards a shared-decision model care plans.

Going Forward with Life-Sustaining Treatment Decisions

In light of the experience and knowledge learned in the last several decades, new ideas for life sustaining care decisions are being discussed and advocated. These seek to preserve the good elements of patient autonomy and the ability to limit or refuse life prolonging treatments but reduce the guilt, stress, and poor decisions that may result from current paradigms. The following elements describe key features of the process of making these decisions currently.

- Care limitation decisions should be made in Shared Decision model that includes input from both the patient (or surrogates) and the physicians. Treatments that are felt to be useless should not be offered by the physician team as this will only introduce confusion and the opportunity for poor decisions. Physicians have the responsibility to be transparent about their decision making process and to give as much weight as possible to the wishes of the patient.
- Physicians should recognize that prognostication is often difficult and inaccurate, especially when predicting morbidity. Their decisions and discussions with patients should acknowledge this.
- Physicians should recognize that there is considerable variation in the use of the term DNR and recognize that even among their team there may be differing understandings of the term. Efforts should be made to clarify, among all groups, the specifics of the care plan.
- In many cases, it is better to avoid such specific designations as DNR or DNI and to solicit more general goals from families and patients and then tailor medical interventions based on those stated goals. Communication and transparency of these decisions is important.

It is important for physicians to make it clear to patients and family that decisions to limit some aspects of life sustaining care does not necessarily limit any other aspects of care.

Futility and Requests for Inappropriate Treatments

Defining Futility

Owing to ongoing advances in medical care, any definition of medical futility is situational and subject to ongoing reconsideration. There have been many definitions put forth of the term "medically futile" but most prove inadequate for practical use. For much of the last century, the term was used to describe either a patient who simply could not be kept alive (i.e. refractory shock) or a patient in whom death was inevitable in the near future (i.e. advanced cancer). The term, "terminally ill" probably better describes the second situation. Nevertheless, these concepts have often been invoked as a justification for limiting life-saving interventions yet both are problematic. With modern medical interventions such as extracorporeal membrane oxygenation (ECMO) and others that can support vital organ functions, there are fewer times when physicians cannot keep a patient alive. Additionally, as patients with advanced illnesses are increasingly treated in ICUs with the goal of only a few more weeks or days of life, it becomes clear that one person's definition of "terminally ill" may not be anoth-

er's. In the most recent joint statement from some of the key professional societies addressing such issues the authors chose avoid using the word futility whenever possible given its subjective nature.

As mentioned, in 2015, several professional societies (American Thoracic Society, American Association of Critical Care Nurses, American College of Chest Physicians, European Society for Intensive Care Medicine, and Society of Critical Care Medicine) jointly produced and published a statement addressing conflicts of this nature. The statement makes several points that sum up the key components of addressing requests for potentially inappropriate care in ICUs.

- Institutions should implement strategies to prevent intractable treatment conflicts, including proactive communication and early involvement of expert consultants.
- The term "potentially inappropriate" should be used, rather than futile, to describe treatments that have at least some chance of accomplishing the effect sought by the patient, but clinicians believe that competing ethical considerations justify not providing them. Clinicians should explain and advocate for the treatment plan they believe is appropriate.
- Conflicts regarding potentially inappropriate treatments that remain intractable despite intensive communication and negotiation should be managed by a fair process of conflict resolution; this process should include hospital review, attempts to find a willing provider at another institution, and opportunity for external review of decisions. When time pressures make it infeasible to complete all steps of the conflict resolution process and clinicians have a high degree of certainty that the requested treatment is outside accepted practice, they should seek procedural oversight to the extent allowed by the clinical situation and need not provide the requested treatment.
- Use of the term "futile" should be restricted to the rare situations in which surrogates request interventions that simply cannot accomplish their intended physiologic goal. Clinicians should not provide futile interventions.
- The medical profession should lead public engagement efforts and advocate for policies and legislation about when life-prolonging technologies should not be used [7].

This statement acknowledges that it is increasingly difficult to label a patient as medically futile or terminally ill but also recognizes that it is common for situations to arise in which the patient or surrogates are requesting therapies that are felt to be inappropriate.

References

1. Heyland DK, Cook DJ, Rocker GM, Dodek PM, Kutsogiannis DJ, Peters S, Tranmer JE, O'Callaghan CJ. Decision-making in the ICU: perspectives of the substitute decision-maker. Intensive Care Med. 2003 ;29:75–82.
2. Johnson SK, Bautista CA, Hong SY, Weissfeld L, White DB. An empirical study of surrogates' preferred level of control over value-laden life sup-port decisions in intensive care units. Am J Respir Crit Care Med. 2011;183:915–21.
3. Azoulay E, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. Am J Respir Crit Care Med. 2005;171:987–94.
4. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA. 2001;286:1754–8.
5. Meadow W, Pohlman A, Reynolds D, et al. Power and limitations of daily prognostications of death in the medical ICU for outcomes in the following 6 months. Crit Care Med. 2014;42:2387–92.
6. Field MJ, Cassel CK, editors. Approaching death: improving care at the end of life. Washington, DC: National Academy Press;1997:14–32.
7. Mularski RA, Heine CE, Osborne ML, Ganzini L, Curtis JR. Quality of dying in the ICU: ratings by family members. Chest. 2005;128(1):280–7.
8. Osborn TR, Curtis JR, Nielsen EL, Back AL, Shannon SE, Engelberg RA. Identifying elements of ICU care that families report as important but unsatisfactory: decision-making, control, and ICU atmosphere. Chest. 2012;142(5):1185–92.
9. Glavan BJ, Engelberg RA, Downey L, Curtis JR. Using the medical record to evaluate the quality of end-of-life care in the intensive care unit. Crit Care Med. 2008;36(4):1138–46.
10. McDonagh JR, Elliott TB, Engelberg RA, et al. Family satisfaction with family conferences about end-of-life care in the intensive care unit: Increased proportion of

family speech is associated with increased satisfaction. Crit Care Med. 2004;32(7):1484–8.
11. Selph RB, Shiang J, Engelberg R, Curtis JR, White DB. Empathy and life support decisions in intensive care units. J Gen Intern Med. 2008;23(9):1311–7.
12. Stapleton RD, Engelberg RA, Wenrich MD, Goss CH, Curtis JR. Clinician statements and family satisfaction with family conferences in the intensive care unit. Crit Care Med. 2006;34(6):1679–85.
13. Wall RJ, Engelberg RA, Gries CJ, Glavan B, Curtis JR. Spiritual care of families in intensive care unit. Crit Care Med. 2007;35(4):1084–90.
14. Gries CJ, Curtis JR, Wall RJ, Engelberg RA. Family member satisfaction with end-of-life decision making in the ICU. Chest. 2008;133(3):704–12.
15. White DB, Braddock III CH, Bereknyei S, Curtis JR. Toward shared decision making at the end of life in intensive care units: opportunities for improvement. Arch Intern Med. 2007;167(5):461–7.
16. Keenan SP, Mawdsley C, Plotkin D, Webster GK, Priestap F. Withdrawal of life support: how the family feels, and why. J Palliat Care. 2000;16(Suppl):S40–44.
17. Clark DT. Complications following closed-chest cardiac massage. JAMA. 1962;181:337–8.
18. Symmers Sr WS. Not allowed to die. Br Med J. 1968;1:442.
19. Bedell SE, Pelle D, Maher PL, Cleary PD. Do-not-resuscitate orders for critically ill patients in the hospital. How are they used and what is their impact? JAMA. 1986;256:233–7.
20. Paris JJ, Reardon FE. The AMA's guidelines on DNR policy: conflict over patient autonomy, family consent and physician responsibility. Clin Ethics Rep. 1991;5:1–7.
21. Barnes TA. Clinical practice guidelines for resuscitation in acute care hospitals. Respir Care. 1995;40:346–59; discussion 59–63.
22. Layon AJ, Dirk L. Resuscitation and DNR: ethical aspects for anaesthetists. Can J Anaesth. 1995;42:134–40.

Index

A
ABCDEF bundle, 252, 282
  components of, 283–284
  sepsis and septic shock, 467
Abdominal compartment syndrome, 688, 689
Abdominal perfusion pressure, 690
Acalculous cholecystitis, 724
Accidental hypothermia. *See* Hypothermia
Acetaminophen
  acute liver failure, 554, 556
  toxin-induced hyperthermia, 350
Acidemia, 466
Acidosis
  anion gap metabolic, 420
  bicarbonate infusion in lactic, 466
  metabolic, 466, 536
ACS. *See* Acute coronary syndrome (ACS)
Activated partial thromboplastin time (aPTT), 531
Acute alcoholic hepatitis, 599
Acute aortic syndromes
  case study, 163–164
  complications, 168
  DeBakey classification, 165
  definition, 164–166
  diagnosis, 166
  esmolol, 166
  evidence contour, 168–170
  medical management, 166–168
  risk factors for, 166
  surgical intervention for, 168–170
Acute arterial ischemia
  case study, 707
  controversial aspects of management/imaging, 710
  diagnostic imaging, 708–709
  initial evaluation, 707–708
  intervention and post-operative management, 709–710
Acute cholangitis, 720, 721
Acute cholecystitis, 720, 721
Acute coagulopathy, 620, 622
Acute compartment syndrome, 687–691
  abdominal, 688, 689
  extremity, 689–690
Acute coronary syndrome (ACS)
  anti-ischemic therapy, 114–115
  antiplatelet therapy, 115–116
  anti-thrombotic therapy, 115
  assessment, 112–114
  case study, 111
  DAPT, 119
  diagnosis, 111–112
  evidence contour, 118–119
  ezetimibe in, 119
  NSTE-ACS, 117–118
  post-cardiac arrest syndrome, 17
  risk stratification, 112–114
  STEMI, 117–119
Acute Decompensated Heart Failure National Registry (ADHERE), 105, 107
Acute exacerbation of COPD, 199–200
  antibiotics, 201
  bronchodilators, 200
  diagnosis, 199–200
  evidence contour, 202
  ICU admission, indications, 200
  NIPPV, 199, 201–202
  symptoms, 199
  systemic corticosteroids, 200–201
Acute exacerbation of IPF (AE-IPF)
  anticoagulation, 268
  anti-fibrotic medications, 269–270
  case study, 265–266
  corticosteroids, 267
  cyclophosphamide, 268–269
  cyclosporin A, 269
  diagnosis, 267
  extracorporeal life support, 269
  high flow nasal cannula, 268
  incidence and prognosis, 266
  noninvasive ventilation, 268
  palliative care, 267
  pulmonary transplantation, 269
  restrictive operative fluid balance, 269
  supportive care, 267
  during surgical procedures, 267–268
  ventilator settings, 268
Acute fatty liver of pregnancy (AFLP), 754

R.C. Hyzy (ed.), *Evidence-Based Critical Care*, DOI 10.1007/978-3-319-43341-7

Acute heart failure (AHF)
case study, 103–104
diagnosis, 104–105
diuretic dosing, 107
diuretic therapy, 105
emergent mechanical circulatory support, 106
etiologies, 105
inotropic agents, 106–107
intravenous vasodilators, 105
nesiritide, 107–108
nitroglycerin, 105
pulmonary artery catheters, 106
renal-dose dopamine, 108
ultrafiltration, 107
Acute hyponatremia *vs.* chronic hyponatremia, 407
Acute ischemic stroke (AIS)
acute cerebral artery dissection, 310
anticoagulation, 308–310
antiplatelets, 310
atrial fibrillation, 308–309
AVERT randomized controlled trial, 310
basilar artery thrombosis, 311
blood pressure strategy, 310
CAPRIE study, 312
CARESS trial, 312
case study, 303–304
CHANCE trial, 312
CREST trial, 312
diagnosis, 304–305
dual-antiplatelet therapy, 312
ECAS, 312
endovascular therapy without IV tPA, 311
endovascular thrombectomy, 306–308
FLAME study, 311
heart failure, 308–309
hemicraniectomy, 310
ICAS, 311–312
imaging, 304–305
MATCH trial, 312
POINT trial, 312
supportive care, 308
tPA administration, 305–306
"wake-up" strokes, 309
Acute kidney injury (AKI), 395, 600
biomarkers, 378–380
case study, 375–376, 383
and CKD, 377–378
complications of, 384
crystalloid and colloid solutions, 389
diagnosis, 379
dialysis, early initiation, 389–390
diuretics, 385–386
etiology of, 385
intravenous fluids, 384–385, 387–389
life-threatening complications, 389
medical management, 385–387
nutrition in, 389
prevention, 385
renal replacement therapy, 387, 388
RIFLE, 376
RRT for prevention of, 399
serum creatinine, 376–379
stage-based management, 386
tight glycemic control, 389
with TLS, 644
treatments for, 385
urine output, 376–377
vasodilators and growth factor interventions, 389
vasopressors, 384–385
Acute limb ischemia, 707
Acute liver failure (ALF)
acetaminophen overdose, 554
adverse outcomes in, 555
bioartificial hepatic support systems, 559
case study, 551–553
cerebral edema in, 556, 558
coagulopathy, 554
diagnostic evaluation, 555
etiology, 553–554
hemodynamic support, 554–556
hepatic encephalopathy, 556
infection, 556
intracranial hypertension in ALF patients, 557
liver transplantation, 559
neurologic complications, 556–558
recombinant factor VIIa
to correct coagulopathy, 558
infusion protocol, 557
renal insufficiency, 556
serial NH_3 levels in ALF patients, 559
targeted temperature management, 559
Acute lower gastrointestinal bleeding (LGIB)
appropriate patient disposition, 564
blood transfusion goals, 566
case study, 561–562
definition, 562
diagnostic imaging modalities, 567
differential diagnosis, 563
initial evaluation, 562–563
initial resuscitation and management, 563–564
management, 565
massive transfusions, 566–567
mesenteric angiography, 565–566
nasogastric tube lavage, 564
predicting severity and outcomes of, 566
provocation testing, 567
surgery, 566
urgent colonoscopy, 564–565
Acute lung injury (ALI), 190
Acute lymphoblastic leukemia (ALL), 650
Acute myelogenous leukemia (AML), 647, 650, 652
Acute myeloid leukemia (AML), 615, 650, 652
diagnosis, 616
treatment, 617
Acute myocardial infarction (AMI). *See* Myocardial infarction
Acute pancreatitis
ACG recommendations for ERCP in, 548

antibiotics, 547
BISAP criteria, 546
case study, 545–546
diagnosis, 546
etiology, 547
intravenous fluids, 546–547
nutritional support, 548–549
pain control, 547
Acute promyelocytic leukemia (APML), 615, 618
Acute renal failure (ARF), 398, 644
Acute respiratory distress syndrome (ARDS), 659, 695
Berlin criteria, 190–191
case study, 189–190
chest x-ray, 190
corticosteroids, 195
diagnosis, 190
driving pressure, 192
ECMO, 195
evidence contour, 193
fluid management, 193
helmet ventilation, 194
HFOV, 195
inhaled vasodilators, 196
lung protective ventilation, 191–192
mechanical ventilation, 274
negative pressure ventilation, 52–53
neuromuscular blockade, 194–195
open lung ventilation, 192
oxygenation, 191
PEEP, 189, 191–194
P/F ratio, 190
pressure limited mechanical ventilation, 194
prone ventilation, 192–193
risk factors, 190, 193
subgroups and subphenotypes, 193–194
supportive care, 193
transpulmonary pressure, 194
ventilatory considerations in face of, 292
Acute respiratory failure, 694, 695, 698
clinical settings, 51
definition, 49–51
high-flow nasal cannula, 53–54
indications and contraindications, 51
negative pressure ventilation, 50–53
palliative care indications, 53
pneumonia, 52
predictors, 51–52
Acute stroke management
acute cerebral artery dissection, 310
anticoagulation, 308–310
antiplatelets, 310
atrial fibrillation, 308–309
AVERT randomized controlled trial, 310
basilar artery thrombosis, 311
blood pressure strategy, 310
CAPRIE study, 312
CARESS trial, 312
case study, 303–304
CHANCE trial, 312
CREST trial, 312
diagnosis, 304–305
dual-antiplatelet therapy, 312
ECAS, 312
endovascular therapy without IV tPA, 311
endovascular thrombectomy, 306–308
FLAME study, 311
heart failure, 308–309
hemicraniectomy, 310
ICAS, 311–312
imaging, 304–305
MATCH trial, 312
POINT trial, 312
supportive care, 308
tPA administration, 305–306
“wake-up” strokes, 309
Acute Study of the Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF), 107–108
Acute tubular necrosis (ATN), 556, 600
Acute tumor lysis syndrome. *See* Tumor lysis syndrome (TLS)
Acute viral illness, 521
ADAMTS-13, 620
activity level, 606, 607
deficiency, 606
Addisonian crisis, 434–436
Addison’s disease. *See* Adrenal insufficiency
Adhesion, 681–682, 685
Adhesive SBO (ASBO)
diagnosis, 683
treatment, 684
Adjunctive dexamethasone, 321
Adrenal deficiency, 407
Adrenal insufficiency
absolute, 434–435
ACTH stimulation test, 435–436, 438
case study, 433–434
diagnostic criteria, 436
etomidate and opiates role in development of, 439
primary, 434
random cortisol, 436
relative, 435
salivary cortisol testing, 438
secondary, 434
serum cortisol measurement, 435
steroid replacement
additional testing, 437–438
concurrent fluid management, 437
dose and duration, 436–437
in septic shock, 438
steroid selection, 436
tertiary, 434
test results, 435
Adrenocorticotropic hormone (ACTH), 434
stimulation test, 435–436, 438
test, 465
Adult respiratory distress syndrome, 261
Advanced cardiac life support (ACLS), 87, 776

Advanced Trauma Life Support (ATLS) guidelines, 665
AFLP. *See* Acute fatty liver of pregnancy (AFLP)
AH. *See* Alcoholic hepatitis (AH)
Airway disease, 745
Airway obstruction, 745
Airway pressure release ventilation (APRV), 194, 292
Alberta Stroke Program Early CT Score (ASPECTS), 303, 308
Albumin, 585
  hypovolemic shock, 43
Alcoholic cirrhosis, 593
  decompensated, 592
Alcoholic hepatitis (AH), 590
  acute, 599
  prognosis in, 591–593
Alcoholic liver disease (ALD)
  case study, 589–590
  classification, 590–591
  intubation for EGD, 601
  management, 597
  nutritional and micronutrient supplementation, 597
  spectrum of, 591–592
  upper GI bleeding in patients with, 597–600
Alcoholic pancreatitis, 545
Alcohol intoxication, accidental hypothermia, 88
Alcohol scale, clinical institute withdrawal assessment of, 594
Alcohol use disorders (AUD), 590
  diagnostic criteria for, 593
  ICU management of, 595–596
  intubation for EGD, 601
  management, 597
  nutritional and micronutrient supplementation, 597
Alcohol withdrawal delirium, 767
Alcohol withdrawal syndrome (AWS), 590
  antipsychotics, 769
  case study, 765–766
  central alpha 2 agonists, 768–769
  diagnosis, 766–767
  diagnostic criteria for, 593
  ICU management of, 595–596
  initial phase of care, 767
  optimal medications for, 600
  patient disposition, 768
  phenobarbital, 768
  propofol, 768
ALD. *See* Alcoholic liver disease (ALD)
Aldehyde dehydrogenase (ADH) blockade, 77–79
ALF. *See* Acute liver failure (ALF)
Alkalinization, urine, 79, 398
ALL. *See* Acute lymphoblastic leukemia (ALL)
Allopurinol, 643
All-*trans*-retinoic acid (ATRA), 616, 617
Altered mental status (AMS), 53, 201, 341, 631
American Academy of Neurology, 368
American Heart Association (AHA), 87, 367
American Thoracic Society (ATS), 258–260
Amiodarone, ventricular arrhythmias, 157–158
Amniotic fluid debris, 739
Amniotic fluid embolism syndrome (AFE)
  anaphylactoid reaction, 738, 739
  case study, 737
  complement activation, 738
  diagnosis, 737–739
  fetus delivery, 739
  hemodynamic support, 739
  initial assessment, 738
  management, 738, 740
  oxygenation, 738–739
  pathophysiology, 738
  ventilation/perfusion mismatching, 738
ANCA. *See* Antineutrophil cytoplasic antibody (ANCA)
Anemia, 504–505
  microangiopathic hemolytic, 608
Anesthetics, status asthmaticus, 212
Angiodysplasias, 563
Angioectasia, 563
Angioembolization
  for blunt solid organ injury, 668
  of hepatic injury, 668
Angiography, mesenteric, 562, 565–566
Angiotensin converting enzyme inhibitors (ACE-I), 734
Angiotensin II receptor blockers (ARBs), 734
Anion gap, 73–76
  metabolic acidosis, 420
Anoxic brain injury
  AAN guidelines, 369
  case study, 363
  diagnosis, 365
  neurologic prognostication, 368–369
  normothermia, 366, 368
  supportive care, 366–367
  therapeutic hypothermia, 365–368
Anti-arrhythmic drug therapy
  TCA toxicity, 62
  ventricular arrhythmias, 159
Antibiotics
  bacterial meningitis, 319–321
  COPD exacerbation, 201
  prophylaxis, 359–360
Anticoagulant, 227, 445, 531–532, 734
  ACS, 116
  acute stroke management, 308–310
  IPF, 268
  prophylactic, 222
Anticonvulsants, 769
Antidiuretic hormone (ADH), 414
  syndrome of inappropriate, 406–407
Anti-epileptic drugs (AEDs)
  prophylactic use, 358–359
  status epilepticus, 336–338, 340–342, 367
Antifibrinolytics, hemorrhagic shock, 42–43
Antigen rapid detection test (RDT), 506
Antihypertensive therapy, 750
Anti-ischemic therapy, acute coronary syndrome, 114–115
Antimicrobial therapy, endocarditis, 174
Antineutrophil cytoplasic antibody (ANCA), 297, 299, 394
Antiplatelet therapy, 611

for acute coronary syndrome, 115–116
acute stroke management, 310
Antipsychotics, 769
delirium, 247
Antithrombin III (ATIII), 618, 623
Anti-thrombotic therapy, 115
Anuria, 753
Aortic arch dissections
diagnosis of, 168
management of patients with, 169
surgical intervention for, 168–170
types of, 167
aPCC, 531
ARDS. *See* Acute respiratory distress syndrome (ARDS)
ARF. *See* Acute renal failure (ARF)
Arrhythmias, cardiac, 643–644
Arterial blood gases, monitoring of, 208
Arterial blood pressure, 4
Arterial brachial index (ABI), 707, 708
Arterial extravasation (AE), 669
Arterial ischemia, acute. *See* Acute arterial ischemia
Arthralgias, 513–515
ASBO. *See* Adhesive SBO (ASBO)
Ascitic fluid, 582
infections, 583
Aspergillosis, 218
invasive
antifungal resistance, 475
antifungal therapy, 474
combination therapy, 475
monotherapy, 474–475
risk factors, 473
Aspergillus, invasive
antifungal resistance, 475
case study, 471–472
diagnostic approach, 472–473
evidence contour, 475–476
Aspiration, 744
Aspirin, ACS, 115
Asthma, 745. *See also* Status asthmaticus
and bronchodilators, 207, 211
exacerbation, 52
life-threatening, 207, 211
Asymptomatic hepatic steatosis, 591
Atrial fibrillation
acute stroke management, 308–309
case study, 145–146
diagnosis, 146
management challenges, 150–151
physiologic effects, 146–147
treatment, 147–149
Atropine, 67–68
AUD. *See* Alcohol use disorders (AUD)
Autoimmune disease, 434
Automated external defibrillator (AED), 3
Autonomic dysfunction, NMS, 350
Autonomy, 774, 776, 777
Autopsy, 395
AWS. *See* Alcohol withdrawal syndrome (AWS)

B

Bacterascites, non-neutrocytic, 586
Bacterial meningitis
antibiotic therapy, 319–321
case study, 317–318
CSF shunts, 323–324
diagnosis, 319
epidemiology, 319
GNB meningitis, 323
gram stain appearance, 321
hypothermia, 323
intracranial pressure, 323
Kernig's and Brudzinski's signs, 318
long term neurologic complications, 321–322
meningococcemia, 322–323
post exposure prophylaxis, 324
steroids, 320–321
Bacterial peritonitis, secondary, 582, 583
Bacterial pneumonia, 745
BAE. *See* Bronchial artery embolization (BAE)
BAL. *See* Bronchoalveolar lavage (BAL)
Balloon-occluded retrograde transvenous obliteration (BRTO), 540–541
Barotrauma, 194–195, 207, 210–211
Basilar artery thrombosis, 311
Benzodiazepines, 600, 765, 767
NMS, 351
with sedation, 245–246
Beta-adrenergic agonists, side effects of, 200
Beta-adrenergic blockers, ACS, 114
Beta blockers, 428
therapy, 466
ventricular arrhythmias, 157
Bicarbonate infusion
in lactic acidosis, 466
rhabdomyolysis, 398
Bilevel positive airway pressure (BPAP), 50, 201
Bi-level ventilation, 194
Biliary infections
case study, 719–720
diagnosis, 720, 723
duration of antibiotics, 723–724
intervention, 722, 724–725
medical management, 721–722
severity assessment, 720–721
surgical management, 722
treatment, 722
Bioartificial hepatic support system, ALF, 559
Biomarkers
acute kidney injury, 378–380
hemophagocytic lymphohistiocytosis, 628–629
Bivalirudin, 116
Blackwater fever, 495
Bleeding, 511
gum, 509, 510
Blood chemical values, 394
Blood pressure control
acute ischemic stroke, 310
hypertensive crises, 142
septic shock, 466

Blood urea nitrogen (BUN), 375, 376
Blunt abdominal trauma
  balanced resuscitation, 667
  blunt solid organ injury
    angioembolization, 668
    nonoperative management, 667–668
  case study, 665
  follow-up imaging, 669–670
  imaging and diagnosis, 667
  nonoperative management, 669
  post-splenectomy vaccinations, 668
  unstable *vs.* stable, 666–667
  venous thromboembolism prophylaxis, 670
Blunt chest trauma, 659
Blunt hollow viscus injury, 667
Blunt solid organ injury
  angioembolization for, 668
  nonoperative management of, 667–668
BO. *See* Bronchiolitis obliterans (BO)
Body cavity lavage, 86
Bolus therapy, hyponatremia, 403
Bone marrow biopsy, 625, 647
BOS. *See* Bronchiolitis obliterans syndrome (BOS)
Bowel ischemia, 682
BPAP. *See* Bilevel positive airway pressure (BPAP)
Brain edema, 401, 403, 407
Brain natriuretic peptide (BNP), 732
Brain tissue oxygen ($PbtO_2$), 355, 359
Brincidofovir, 493
Bromocriptine, NMS, 345, 352
Bronchial artery embolization (BAE), 236, 238–239
Bronchiolitis obliterans (BO), 637
Bronchiolitis obliterans syndrome (BOS), 631, 633, 634
Bronchoalveolar lavage (BAL), 265–266, 297, 635
  community acquired pneumonia, 181, 183
Bronchodilators
  asthma and, 207, 211
  COPD exacerbation, 200
Bronchoscopy, 625
  hemoptysis, 237, 238
  status asthmaticus, 212
BRTO. *See* Balloon-occluded retrograde transvenous obliteration (BRTO)
Brudzinski's signs, 318
B-type natriuretic peptide (BNP), 107
Burch and Wartofsky scoring system, 429
Burkitt's lymphoma, 642

C

Calcium channel blocker poisonings
  atropine, 67–68
  calcium salts, 67
  case study, 66
  extracorporeal albumin dialysis, 70
  gastrointestinal decontamination, 66–67
  glucagon, 67
  high-dose insulin therapy, 68
  intravenous lipid emulsions, 69–70
  invasive circulatory support, 68–69
  methylene blue, 70
  sodium bicarbonate, 70
  vasopressor support, 68
Caloric goals, in critical illness, 577
CALORIES Trial, 577
CAM-ICU. *See* Confusion Assessment Method for the ICU (CAM-ICU)
Cane-cutter fever. *See* Leptospirosis
Canicola fever. *See* Leptospirosis
CAP. *See* Community acquired pneumonia (CAP)
Capnography, 4
Cardiac arrest
  case study, 4–5
  causes, 6–7
  chest compressions, 4–5
  defibrillation, 6
  hemodynamic directed resuscitation, 9
  hypothermia and, 365–369
  mechanical and manual compressions, 7–9
  oxygen and ventilation, 5–6
  quality assurance, 4, 7
  recognition, of sudden cardiac arrest, 5
  resuscitation, 4–7
Cardiac arrhythmias, prevention, 643–644
Cardiac Intensive Care Unit (CICU), 95
Cardiac MR, 729–730
Cardiac pump theory, 7
Cardiac tamponade, 121, 124
  case study, 129–131
  clinical findings, 131
  closed pericardiocentesis, 133
  ECG, 130
  ECP, 133–134
  hemodynamic derangements, 131
  invasive diagnostic testing, 132–133
  non-invasive diagnostic testing, 131–132
  surgical drainage, 133
Cardiac transplantation, 734
Cardiogenic pulmonary edema, 738
Cardiogenic shock, 26, 28–29, 738, 739
  case study, 95–96
  diagnosis, 96
  early revascularization, 96–97
  mechanical circulatory support, 99–101
    percutaneous, 97–98
    temporary surgical, 98–99
  multivessel revascularization, 99
  myocardial infarction, 123–127
  vasopressors/inotropes, 97
Cardiopulmonary bypass (CPB), 84
Cardiopulmonary collapse, 738–739
Cardiopulmonary resuscitation (CPR), 5–6, 776
  quality assurance, 4, 7
Cardiorenal syndrome, 385, 386
CARESS trial, AIS, 312
CAS. *See* Central anticholinergic syndrome (CAS)
CDI. *See* Clostridium difficile infection (CDI)
Ceftriaxone, 535

Central alpha 2 agonists, 768–769
Central anticholinergic syndrome (CAS), 347, 350
Central venous catheter (CVC) placement, 490
Central venous pressure (CVP), 460
  RV dysfunction, 289–290
Cerebral contusion, 356, 357
Cerebral edema, 366, 367, 414, 415, 422, 444, 556, 558
Cerebral malaria, 504
Cerebral microdialysis, 359
Cerebral perfusion pressure (CPP), 46
Cerebral salt wasting (CSW), 414
Cerebrospinal fluid (CSF)
  bacterial meningitis, 319, 324
  shunts, 323–324
  status epilepticus, 336, 337
Cerebrovascular accidents (CVAs), 147
C1 esterase inhibitor, 739, 740
CHADS2-Vasc score, 147, 148
CHANCE trial, AIS, 312
Chemical injury, 703
Chest compressions, 4–5
Chest CTA, 163, 164, 166
Chest pain, 166, 167
Chest x-ray (CXR), 50
  acute heart failure, 103
  acute thermal injury, 701
  ARDS, 190
  bilateral infiltrates, 648
  diffuse alveolar hemorrhage, 296, 298
  immunocompromised pneumonia, 216
  lateral, 458
  PA, 457
  peripartum cardiomyopathy, 730
  pulmonary edema, 163, 172
  respiratory diseases of pregnancy, 743
  thoracic trauma, 658, 660
  weaning from mechanical ventilation, 274
Chikungunya, 509
  case study, 513–514
  diagnosis, 514–515
  epidemiology, 515, 516
  treatment, 515
  volume management, 515
Cholangitis, acute, 720, 721
Cholecystectomy, delayed interval, 724
Cholecystitis
  acalculous, 724
  acute, 720, 721
Cholecystostomy, percutaneous, 724
Chronic hyponatremia, *vs.* acute hyponatremia, 407
Chronic kidney disease (CKD), 377–378
Chronic lymphocytic leukemia (CLL), 641, 650
Chronic obstructive pulmonary disease (COPD), 471, 697
  acute exacerbation of, 199–200
CIRCI. *See* Critical-illness related corticosteroid insufficiency (CIRCI)
Cirrhosis, 539, 598
  alcoholic, 593
Clevidipine, hypertensive crises, 138, 139
Clinical Institute Withdrawal Assessment scale for Alcohol, Revised (CIWA-Ar), 765, 766
Clinical pulmonary infection score (CPIS), 259, 260
CLL. *See* Chronic lymphocytic leukemia (CLL)
Clostridium difficile infection (CDI)
  capsulized frozen fecal microbiota, 572
  case study, 569
  diagnosis, 570
  epidemiology and infection control, 571–572
  fecal microbiota transplant, 572
  investigational antibiotics, 572
  medical therapies, 571
  monoclonal antibodies and vaccines, 572
  probiotics, 572
  risk factors, 570
  severity of disease, 570
  spores, nontoxogenic, 572
  surgical intervention, 571
  symptoms, 569–570
  treatment recommendations, 571
Coagulopathy, 504–505, 531, 554
  acute, management of, 620–622
Cognitive impairment, 282, 284, 285
Cognitive rehabilitation, 284–285
Colorectal cancer, 563
Community-acquired MRSA (CA-MRSA), 186
Community acquired pneumonia (CAP)
  case study, 181
  community-acquired MRSA, 186
  corticosteroids, 186
  diagnostic testing, 182–183
  empirical *vs.* pathogen-directed therapy, 183–185
  epidemiologic conditions, 184
  IDSA/ATS minor criteria, 182
  microbial culprits, 183
  multidrug resistant pathogens, 185
  parapneumonic effusions, 185
  procalcitonin, 186
  risk factors, 184
  site-of-care decisions, 181–182
Compartment syndrome, 398
  abdominal, 688, 689
  abdominal perfusion pressure, 690
  case study, 687–688
  decompression, 689
  dermotraction, 691
  diagnosis, 688
  extremity, 689–690
  fluid management, 690–691
  infraed spectroscopy, 691
  percutaneous drainage, 691
  wound management, 690
Complicated parapneumonic effusion (CPPE), 185
Computed tomographic pulmonary angiography (CTPA), 223–226
  RV failure, 287–289

Computed tomography (CT)
acute ischemic stroke, 304
anoxic brain injury, 363, 364, 366, 369
aspergillosis, 218
of cerebrum, 401, 402
diffuse alveolar hemorrhage, 296, 297
endocarditis, 175
ICH, 328, 329
immunocompromised pneumonia, 216, 217
IPF, 267
pneumonia, 287
TBI, 355–358
Confusion Assessment Method for the ICU (CAM-ICU), 241, 242, 244
Congenital disease, 434
Conjunctival suffusion, 519–521
Conjunctivitis, 514
Consumptive coagulopathy, 619
Continuous arteriovenous rewarming (CAVR), 86–87
Continuous electroencephalographic (cEEG) monitoring, 369
Continuous positive airway pressure (CPAP), 50
Continuous venovenous hemofiltration (CVVH), 556
Continuous venovenous rewarming (CVVR), 86–87
Contrast-enhanced ultrasonography (CEUS), 379
Convalescent plasma, 493
Convulsive status epilepticus (CSE), 337
Coronary angiography, post-cardiac arrest syndrome, 14, 19–20
Coronary perfusion pressure (CPP), 4
Corticosteroids, 599
ARDS, 195
community acquired pneumonia, 186
COPD exacerbation, 200–201
IPF, 267
replacement, 449
role, 522–523
status asthmaticus, 207
systemic, 762
CORTICUS trial, 465
CPIS. *See* Clinical pulmonary infection score (CPIS)
CPR. *See* Cardiopulmonary resuscitation (CPR)
C-reactive protein (CRP), 720
Creatine kinase (CK), 346, 350, 395
CREST trial, AIS, 312
Critical illness, PICS, 281–285
Critical-illness related corticosteroid insufficiency (CIRCI), 435
decision tree for investigation, 437
CRP. *See* C-reactive protein (CRP)
Crystalloids, 667
CSE. *See* Convulsive status epilepticus (CSE)
CT angiography (CTA), 707–709
hemoptysis, 236
pulmonary angiogram, 266
Cuff leak test, 275
CURB-65 Score, 182
CVC placement. *See* Central venous catheter (CVC) placement
CVVH. *See* Continuous venovenous hemofiltration (CVVH)
Cyclophosphamide
diffuse alveolar hemorrhage, 296, 299
IPF, 268–269
Cyclosporin A, 269
Cystic fibrosis, 746
Cytomegalovirus (CMV), 193, 636
Cytoxan. *See* Cyclophosphamide

D
Dabigatran, 531
DAH. *See* Diffuse alveolar hemorrhage (DAH)
Damage–control resuscitation (DCR) protocol, 690
Dantrolene, NMS, 345, 351–352
Decision making, life support, 776–777
Decontamination, 487
Deep venous thrombosis (DVT), 222–223
De-escalate antimicrobial therapy, 259
Defibrillation, 6
Dehydration, 442–443
Delayed interval cholecystectomy, 724
Delirium
antipsychotics, 247
case study, 241–242
component, 243
long-term outcomes, 247
monitoring, 242
prevention of, 247
risk factors for, 242–244
sedation and, 246–247
Delirium tremens (DTs), 595–596, 765–767
Demyelination, osmotic, 407
Dengue
aspects of care, 511
case study, 509–510
classification, 510
illness and diagnosis, 510–511
management, principles, 510
supportive treatment, 511
volume replacement, 511
Dengue hemorrhagic fever (DHF), 510
Dengue shock syndrome (DSS), 510
Descending thoracic aorta (DTA), 234–235
Desmopressin, 402, 405
Dexamethasone, bacterial meningitis, 320–321
Dexmedetomidine, 246, 601, 768, 769
DHF. *See* Dengue hemorrhagic fever (DHF)
Diabetes mellitus, 441, 442
Diabetic ketoacidosis (DKA)
bicarbonate infusion, 422
case study, 419–420
complications, 422
diagnosis, 420
electrolyte repletion, 421
euglycemic, 422, 424
fluid replacement therapy, 420–421
fluid resuscitation, 419, 421, 422

vs. HHS, 443
insulin therapy, 421, 422
management algorithm, 423
potassium and, 419, 421
precipitating condition, treatment, 421–422
site of care, 422
Diagnostic peritoneal aspiration (DPA), 666
Diagnostic peritoneal lavage (DPL), 666
Dialysis, initiation of, 389–390
Diarrhea, watery, 569
DIC. *See* Disseminated intravascular coagulation (DIC)
Diffuse alveolar hemorrhage (DAH), 635
case study, 295–296
classification, 298
diagnosis, 298–299
differential diagnosis, 296–298
recombinant Factor VII, 299
Rituximab, 299
treatment, 299
Digoxin, ventricular arrhythmias, 159
Dihydropyridine, 65
Dilated cardiomyopathy, 730
Direct current cardioversion (DCCV), 148
Direct factor Xa and thrombin inhibitors, 230
Disseminated intravascular coagulation (DIC), 322, 398, 750
antithrombin III, 618, 623
case study, 615–616, 619–620
causes of, 617, 620
diagnosis, 620
differential diagnosis, 616
heparin therapy, 617, 622
laboratory profile of, 616–617
peripheral smear of, 620
recombinant factor VIIa, 618
rhabdomyolysis, 398
supportive care/blood product transfusion for, 617
thrombomodulin-α, 623
thrombotic predominant, 622
treatment, 617, 620, 753
Disseminated strongyloides infection, 480
Distributive shock, 26, 28
DITMA. *See* Drug-induced thrombotic microangiopathy (DITMA)
Diuretic dosing
acute heart failure, 105, 107
AKI, 385–386
Diuretic Optimization Strategies Evaluation (DOSE), 107
Diverticulitis, Hinchey classification for, 679
Diverticulosis, 563
Do-not-intubate (DNI) orders, 202
Do Not Resuscitate (DNR), 773, 776
Dopamine, 108, 461
DPA. *See* Diagnostic peritoneal aspiration (DPA)
DPL. *See* Diagnostic peritoneal lavage (DPL)
Driving pressure, ARDS, 192
Drug-eluting stents (DES), 119
Drug-induced thrombotic microangiopathy (DITMA), 611
Drug-resistant pathogens (DRP), 185
DSS. *See* Dengue shock syndrome (DSS)
DTA. *See* Descending thoracic aorta (DTA)
DTs. *See* Delirium tremens (DTs)
Dual antiplatelet therapy (DAPT), 312
acute coronary syndrome, 119
acute stroke management, 312
Dual-lumen endotracheal tubes, 237–238
DVT. *See* Deep venous thrombosis (DVT)
Dysautonomia, in NMS, 351
Dysmotility, 577
Dyspnea, 743

E
Early goal directed therapy (EGDT), 463
Ebola virus disease (EVD)
active screening, 486
case study, 485
clinical care, 488
bedside assessments, 489
monitoring, 489
team structure, 488–489
CVC placement, 490
decontamination, 487
diagnostic evaluation, 491–492
diagnostic testing
blood analysis, 489
imaging, 489
invasive procedures, 489
emergency response teams, 490
endotracheal intubation, 490
establishing likelihood of, 491
evidence contour, 492
fluid and electrolytes, 491–492
infection control, 485–486
isolation, 485–486
mechanical ventilation, 492
modality, 490
nutrition, 492
personal protective equipment (PPE), 485–490
protocols and policies, 486
provisions of care, 493
renal replacement therapy, 492
specimen collection and handling, 486–487
staffing model, 493
supportive therapy, 491
targeted therapy, 493
testing for, 491
waste management, 487–488
Ecchymosis, 518
from thrombocytopenia, 497
Echinocandins, 475
Eclampsia, 750, 751
antenatal steroids and delivery, 752
magnesium sulfate therapy, 753
treatment of, 752

ECLS. *See* Extracorporeal life support (ECLS)
ECMO. *See* Extracorporeal membrane oxygenation (ECMO)
Edema
  origin of, 190
  pulmonary (*see* Pulmonary edema)
Effusive-constrictive pericarditis (ECP), 133–134
EGDT. *See* Early goal directed therapy (EGDT)
Ehrlichiosis, 521
Electrical injury, 703
Electroconvulsive therapy (ECT), 342, 345, 352
Electroencephalogram (EEG)
  anoxic brain injury, 369
  status epilepticus, 335–338, 341
Electrolyte-free water clearance (EFWC), 402
Elevated intracranial pressure, 319, 324, 356
ELISA IgM test, 509–510, 514
Embolic stroke, 175
Embolization, 238–239, 565
Emergency coronary angiography, 19–20
Emergency department (ED)
  neuroleptic malignant syndrome, 345
  status epilepticus, 335, 337
  TBI, 356
Enalaprilat, hypertensive crises, 140, 141
Encephalopathy, hepatic, 556
Endocarditis
  antimicrobial therapy, 174
  cardiac device related, 176
  case study, 171–172
  diagnosis, 173–174
  epidemiology, 172–173
  follow-up evaluation, 174
  indications for surgery, 174
  microorganism, 173
  Modified Duke criteria, 173, 176
  neuroimaging in, 175
  non-emergent surgery, timing of, 175
  septic cerebral embolic stroke, 175
  valve repair *vs.* replacement, 175–176
End of life (EOL) care, 774, 775
End-organ perfusion, 289
Endoscopic biliary drainage, 722
Endoscopic retrograde cholangiopancreatography (ERCP), 719, 720, 724–725
Endovascular rewarming, hypothermia, 89
Endovascular therapy, without IV tPA, 311
Endovascular thrombectomy, 306–308
Engraftment syndrome, 636
Enteral feeding, 548, 575–576
Enteral nutrition (EN), 575, 577
Entero-atmospheric fistula (EAF), 690
EOLIA trial, 699
Eosinophilic granulomatosis with polyangiitis (EGPA), 298
Epidural hematoma, 357–358
Erythromycin, 535
Esmolol
  acute aortic syndromes, 166
  hypertensive crises, 137, 140
Esophageal varix, 537
Esophagogastroduodenoscopy (EGD), 535, 537, 539
  intubation for, 601
Ethylene glycol ingestion
  aldehyde dehydrogenase blockade, 77–79
  case study, 73–74
  cofactor supplementation, 79
  diagnosis, 74–76
  fomepizole *vs.* ethanol, 78
  gastric decontamination/lavage/charcoal, 77
  hemodialysis, 78
  methanol, 79–80
  serum and urine alkalization, 79
  ventilator and circulatory support, 77
Etomidate, 439
Etoposide, 626, 628
Euglycemic DKA, 422, 424
European Hypothermia after Cardiac Arrest (HACA), 365
EVD. *See* Ebola virus disease (EVD)
Extended Focused Assessment with Ultrasound in Trauma (E-FAST), 39, 40
Extracorporeal cardiopulmonary resuscitation (ECPR), 84
Extracorporeal CO_2 Removal ($ECCO_2R$), 697
Extracorporeal life support (ECLS)
  IPF, 269
  status asthmaticus, 212
Extracorporeal membrane oxygenation (ECMO), 84, 292, 747
  ARDS, 195
  case study, 693–694
  contraindications, 696
  $ECCO_2R$, 697
  indications, 694–696
  management, 696
  Murray score for consideration of, 696
  outcome prediction, 698–699
  post-ECMO considerations, 697
  prolonged, 698
  trial data, 698
  weaning off of, 696
Extracorporeal plasmapheresis, 430
Extracorporeal rewarming, hypothermia, 86–87
Extracranial arterial stenosis (ECAS), 312
Extremity compartment syndrome, 689
Ezetimibe, in ACS, 119

F
Falciparum malaria. *See* Malaria
FAM therapy, 637
Fasciotomy, 688–690, 710
FAST. *See* Focused assessment with sonography in trauma (FAST)
Fecal microbiota transplant, 572

Feedings
enteral, 548, 575–576
in pancreatitis, 548
trophic, 576
Fenestrated tracheostomy tube, 253, 255
Fenoldopam, hypertensive crises, 139, 141
Fever. *See also* Leptospirosis
Blackwater, 495
NMS, 345, 347, 350
Fibrinolysis, 111, 114, 116
Fibrosis
cystic, 746
IPF (*see* Idiopathic pulmonary fibrosis (IPF))
Fidaxomicin, 571
Flexible bronchoscopy, 237
Fluid management
ARDS, 193
rhabdomyolysis, 396, 398
Focused assessment with sonography in trauma (FAST), 355, 665, 666
Foley urinary catheter, 751
Folic acid, methanol ingestion, 80
Fomepizole, 77
aldehyde dehydrogenase blockade, 78
Fondaparinux, 116
Free T3 (triiodothyronine), 426, 427
Free T4 (thyroxine), 426, 427
Fresh frozen plasma (FFP), 531, 606, 609–611, 617, 622
Frisen Scale, 136, 137
Futility, ICU, 777–778

G
Gallstone pancreatitis, 545, 547
Gastric decontamination, 77
Gastric residuals, 576–577
Gastrointestinal bleed (GIB)
anticoagulant, reversal, 531–532
blood transfusion, 529
case study, 527
clinical factors, 528
coagulopathy, reversal, 531
diagnosis, 527–528
nasogastric lavage, 529–530
proton pump inhibitor therapy, 529, 530
risk stratification, 528–529
salvage therapy, 530–531
thrombocytopenia, 531
warfarin, reversal, 531
Gastrointestinal decontamination, 66–67
Geneva Score, pulmonary embolism, 223–224
German Registry for Acute Aortic Dissection Type A (GERAADA) study, 170
GIB. *See* Gastrointestinal bleed (GIB)
Glasgow-Blatchford Score (GBS), 528
Glasgow Coma Scale/Score (GCS), 39, 83
ICH, 330
TBI, 355–358
Glasgow Motor Score (GMS), 19
Glomerulonephritis, 298, 299
Glucagon, calcium channel blocker poisonings, 67
Glucocorticoids, 428
Glycoprotein IIb/IIIa inhibitors, ACS, 116
Graft versus host disease (GVHD), 631, 633–634
Gram negative bacilli (GNB) meningitis, 323
Granulocyte colony-stimulating factor (G-CSF), 476
Granulomatosis with polyangiitis (GPA), 298

H
Hamman's syndrome, 746
Hantavirus, 521
HAS-BLED score, 147, 148
HCT. *See* Hematopoietic stem cell transplantation (HCT)
Healthcare-associated pneumonia (HCAP), 182
Heart failure. *See also* Acute heart failure (AHF)
acute stroke management, 308–309
medical therapy for, 733–734
Heart failure with preserved ejection fraction (HFpEF), 104
Heart failure with reduced ejection fraction (HFrEF), 104, 729
Heart rate control, in septic shock, 466–467
Heliox, status asthmaticus, 211
HELLP syndrome, 750–752
antenatal steroids and delivery, 752
dexamethasone therapy in, 754
magnesium sulfate therapy, 753
Helmet ventilation, ARDS, 194
Hematochezia, 561, 562, 564
Hematologic values, 394
Hematopoietic stem cell transplantation (HCT)
case study, 631–632
etiology, 632
GVHD, 633–634
infectious complications, 635
primer on, 632–633
prognosis, 638
pulmonary complications, 634–637
recovery from, 634–635
respiratory failure, 634, 637–638
Hemicraniectomy, 310
Hemodialysis, ethylene glycol ingestion, 78
Hemodynamics, 288, 290–292
directed resuscitation, 9
Hemoglobinuria, 518
Hemolysis, 504
Hemolytic anemia, microangiopathic, 608
Hemolytic uremic syndrome, 606, 607
Hemophagocytic lymphohistiocytosis (HLH)
biomarker testing, 628–629
case study, 625–627
diagnosis, 627, 628
presentation, 627
prognosis, 628
treatment, 627–628

Hemoptysis, 295, 296, 298, 299
  approach to managing life threatening, 236–237
  assessment, 237
  case study, 233
  causes of, 236
  clinical algorithm to, 235
  computed tomography, 234
  CT angiography, 236
  diseases associated with, 236
  dual lumen *vs.* unilateral airway intubation, 237–238
  epidemiology, 234
  plain radiographs, 236
  recurrent bleeding, 238–239
  rigid *vs.* flexible bronchoscopy, 237
  sources of hemorrhage, 234–236
  systemic treatments for, 238
Hemorrhage, 238
  active *vs.* non-active, 237
  acute coagulopathy, 620–622
  intracerebral (*see* Intracerebral hemorrhage (ICH))
  intraretinal, 648
  sources of, 234–236
  stable *vs.* unstable, 237
  variceal (*see* Variceal hemorrhage)
Hemorrhagic shock
  antifibrinolytics, 42–43
  coagulopathy and, 41–42
  crystalloid administration, 42
  damage control surgery, 41
  expedite anatomic control of bleeding, 41
  hemostatic resuscitation, 46
  invasive non-surgical hemorrhage control, 45–46
  ionized calcium repletion, 44–45
  massive transfusion protocol, 44
  permissive hypotension, 41
  point-of-care monitor, 45
  transfusion therapy, 43
  vasopressors, 46
Hemorrhoids, 563
Hemostasis, 535, 536
  interventions, 536–537
Hemostatic resuscitation, 41, 46
Hemothorax, 658, 660–661
Heparin. *See* Unfractionated heparin (UFH)
Hepatic encephalopathy, 556
Hepatic injury
  angioembolization of, 668
  blunt, 668, 669
Hepatic steatosis, asymptomatic, 591
Hepatic support system, 559
Hepatitis, 590–593
Hepatorenal syndrome (HRS), 384–385
  clinical diagnosis of, 585
  management, 599–600
Hernia, 681, 682, 685
Herpesviruses (HSV), 635
HHS. *See* Hyperosmolar hyperglycemic syndrome (HHS)
HIDA scan, 723
High-flow nasal cannula (HFNC), 50, 53–54, 268
High frequency oscillatory ventilation (HFOV), 195
HLH. *See* Hemophagocytic lymphohistiocytosis (HLH)
HRS. *See* Hepatorenal syndrome (HRS)
Human leukocyte-associated antigens (HLA), 632–633
HVS. *See* Hyperviscosity syndrome (HVS)
Hydralazine, hypertensive crises, 138, 140
Hydrocortisone, 435, 437
Hyperbaric oxygen (HBO) therapy, 716
Hypercalcemia, 427
Hypercapnia, permissive, 208–209
Hyperferritinemia, 627
Hyperglycemia, 88, 443
Hyperglycemic crisis, 443
Hyperinflation, status asthmaticus, 209–210
Hyperkalemia, 398, 642, 643
Hyperleukocytosis, 649
Hyperosmolar hyperglycemic syndrome (HHS)
  anticoagulation, 445
  case study, 441–442
  diagnosis, 442–443
  vs. DKA, 443
  electrolytes correction
    magnesium, 444
    phosphate, 444
    potassium, 444
    sodium, 444
  fluid therapy, 443
  insulin therapy, 443–444
  type of IV fluid, 444–445
Hyperosmolar therapy, ICH, 330–331
Hyperosmotic agents, 330
Hyperphosphatemia, 387, 398, 616, 642, 644, 645
Hypertension, 332, 750, 751
Hypertensive crises
  case study, 135–136
  diagnosis, 136–137
  physical examination, 135
  secondary causes, 141, 142
  treatment, 137
    beta blockers, 142
    blood pressure control, 142
    drugs and clinical scenarios, 139–141
    pharmacotherapy, 137–141
Hyperthermia, neuroleptic malignant syndrome, 347, 350
Hypertonic saline, 402, 407, 414
  ICH, 330, 331
Hypertriglyceridemia, 547
Hyperviscosity syndrome (HVS)
  case study, 647–648
  clinical symptoms, 649, 650
  diagnosis, 649–650
  lack of procedural standardization, 652
  management, 650–651
  pathophysiology, 648–649
  plasma viscosity measurement, 652
Hypocalcaemia, 398, 643–644
Hypoglycemia, 444, 505
Hypoinsulinemia, 66

Hypokalemia, 444
Hypomagnesaemia, 444
Hyponatremia, 520
  acute *vs.* chronic, 407
  adrenal deficiency, 407
  and association with mortality, 407–408
  avoidance of overcorrection, 403–405
  bolus therapy, 403
  case study, 401–402, 413–414
  causes of, 415
  correction rate monitoring, 415
  despite suppressed ADH, 406
  diagnosis, 402–403
  drugs associated with, 405
  evaluation, 414
  hypotonic, 402
  hypovolemic, 415
  with increased extracellular volume/sodium, 406
  lasting correction, 405
  novel treatments, 416
  with reduced ECV/sodium, 405–406
  risk stratification, 414
  serum sodium correction, 414–415
  treatment algorithm, 403
Hypotension
  ethylene glycol ingestion, 77
  tricyclic antidepressant toxicity due to, 60–61
Hypothermia, 342, 536
  adjunctive testing, 85–86
  anoxic brain injury, 365–366
  bacterial meningitis, 323
  case study, 83–84
  classification and staging, 85
  clinical findings, 86
  core afterdrop, 90
  diagnosis, 85
  disposition, 88
  endovascular rewarming, 89
  extracorporeal support, 89
  ICH, 332
  patient monitoring, 85
  pediatric patients, 88
  post-cardiac arrest management, 18
  rewarming, 86–87
    active and passive, 86
    in cardiac arrest, 89
    extracorporeal, 86–87
  TBI, 359
  transcutaneous pacing, 89
  withholding CPR, 88–89
  without pulse, 87–88
Hypothermic targeted temperature management (HTTM), 14, 17–18, 20–21
Hypothyroidism, 447, 449
Hypotonic fluids, 404
Hypotonic hyponatremia, 402
Hypoventilation, status asthmaticus, 208–209
Hypovolemia, 27, 414
  hyponatremia, 415
Hypovolemic shock
  albumin role in, 43
  IV access, 40
  normal saline *vs.* balanced solutions, 43
  physiologic reserve, 40–41
  pressors, 43
  resuscitation, 41
  volume responsiveness monitor, 41
Hypoxemia, 499, 738
Hypoxic-ischemic encephalopathy, 365, 369

I

IABP. *See* Intra-aortic balloon pump (IABP)
Ideal body weight (IBW), calculation, 192
Idiopathic pneumonia syndrome (IPS), 636
Idiopathic pulmonary fibrosis (IPF)
  anticoagulation, 268
  anti-fibrotic medications, 269–270
  case study, 265–266
  corticosteroids, 267
  CT scan, 267
  cyclophosphamide, 268–269
  cyclosporin A, 269
  diagnosis, 267
  exacerbation during surgical procedures, 267–268
  extracorporeal life support, 269
  high flow nasal cannula, 268
  incidence and prognosis, 266
  noninvasive ventilation, 268
  palliative care, 267
  pulmonary transplantation, 269
  restrictive operative fluid balance, 269
  supportive care, 267
  ventilator settings, 268
IE. *See* Infective endocarditis (IE)
ILCOR. *See* International Liaison Committee on Resuscitation (ILCOR)
ILD. *See* Interstitial lung disease (ILD)
Ileus, hyperinfection associated with paralytic, 483
Immune dysregulation, 629
Immunocompromised pneumonia
  antimicrobial therapy, 217
  case study, 215
  chest X-ray, 216
  CT scan, 216, 217
  diagnosis, 216–218
  empiric treatment, 217
  etiology, 216
  noninvasive ventilation, 219
  presentation, 215–216
  serologic tests, 217
  serum tests for, 218–219
  supportive care, 218
  utility of invasive testing, 218
Immunonutrition, 576
Immunosuppressive agents, 610, 611
Impella, 98
Impella Device™, 22

Implantable cardioverter defibrillator (ICD), 734
Infectious Diseases Society of America (IDSA), 259–260, 262, 321
Infective endocarditis (IE)
  antimicrobial therapy, 174
  cardiac device related, 176
  case study, 171–172
  diagnosis, 173–174
  epidemiology, 172–173
  follow-up evaluation, 174
  indications for surgery, 174
  Modified Duke criteria, 173
  neuroimaging in, 175
  non-emergent surgery, timing of, 175
  septic cerebral embolic stroke, 175
  valve repair *vs.* replacement, 175–176
Inferior vena cava (IVC), 460, 461
  filter placement, 229–230
Inflammation and Host Response to Injury Project, 667
Inflammatory bowel disease, 563
Inhaled nitric oxide (iNO), 292
Inhibitors, TNF alpha, 762
Inotropes
  cardiogenic shock, 97
  therapy, 729
Inotropes agents, 291
  acute heart failure, 106–107
Insulin-like growth factor binding protein-1, 739
Insulin therapy
  calcium channel blocker poisonings, 68
  diabetic ketoacidosis, 421, 422
  HHS, 443–444
Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT2), 332
Intensive Care Delirium Screening Checklist (ICDSC), 242
Intensive care unit (ICU)
  admission, indications for, 200
  code status and ICU patient, 775–776
  with COPD exacerbations, 200
  decision making, 774
    life support, 776–777
  decompensated RV failure in, 287–292
  end of life care, 775
  futility, 777–778
  hemoptysis, 234, 238
  life-sustaining treatment decisions, 777
  problems with DNR, 776
  prognostication, 774–775
  venous thromboembolism in
    case study, 221–222
    clinical presentation, 223–224
    diagnosis, 226
    epidemiology, 222–223
    evidence contour, 228–230
    pulmonary embolism severity, 224–226
    risk factors, 222
    treatment, 226–228
International Liaison Committee on Resuscitation (ILCOR), 367, 368
Interstitial lung disease (ILD), 267
Interventional Radiology (IR), 238
Intra-abdominal hypertension (IAH), 688–689
Intraabdominal infections, 677, 679
  anti-infective therapy, 676–677
  case study, 673
  diagnosis, 673–674
  empiric antimicrobial therapy for health care, 678
  laparoscopic peritoneal lavage, 677
  procalcitonin, 679
  resuscitation, 674–676
  source control, 676
  treatment of extra-biliary complicated, 677
Intra-abdominal pressure (IAP), 687
Intra-aortic balloon pump (IABP), 98, 104
  myocardial infarction, 127
Intracerebral hemorrhage (ICH)
  acute management, 328–330
  calculation, 329
  case study, 327
  clinical presentation, 328
  complications, 330
  CT, 328, 329
  diagnosis, 328
  hyperosmolar therapy, 330–331
  hypertension management, 332
  hypothermia, 332
  natural history, 330
  score, 330–331
  seizure prophylaxis, 331
  spot sign, 328, 329
Intra-compartmental pressure, 688
Intracranial arterial stenosis (ICAS), 311–312
Intracranial hypertension, in ALF, 557
Intracranial pressure (ICP), 46, 329–332, 403
  indication of, 358
  management, 323
  traumatic brain injury, 358, 359, 367
Intramural hematomas (IMH), 164, 167
Intraparenchymal hematoma, 358
Intraretinal hemorrhage, 648
Intravenous fluids, AKI, 384–385, 387–389
Intravenous immunoglobulins (IVIG), 762
Intravenous lipid emulsions, 69–70
Intravenous vasodilators, 105
Invasive mechanical ventilation (IMV)
  indications for, 201, 202
  status asthmaticus, 208–209
Iodinated radiocontrast agents, 429–430
Ionized calcium repletion, hemorrhagic shock, 44–45
IPF. *See* Idiopathic pulmonary fibrosis (IPF)
IPS. *See* Idiopathic pneumonia syndrome (IPS)
Ischemia. *See also* Acute arterial ischemia
  acute limb, 707
  bowel, 682
  post-cardiac arrest syndrome, 16
Ischemic colitis, 563

Ischemic-hypoxic encephalopathy. *See* Anoxic brain injury
Isopropyl alcohol, 80
Itraconazole, 475
IVIG. *See* Intravenous immunoglobulins (IVIG)

J
Jarisch-Herxheimer reaction, 522
Jaundice, 518
Jugular bulb oximetry, 359
Jugular venous distention (JVD), 124

K
Kernig's signs, 318
Ketogenic diet, 336, 342
Kidney Disease Improving Global Outcomes (KDIGO), 385, 387, 389
Kidney injury, acute. *See* Acute kidney injury (AKI)

L
Labetalol, 753
  hypertensive crises, 137, 140
Laboratory risk indicator for necrotizing fasciitis (LRINEC), 715
Lactated Ringer's, 388–389
Lactic acidosis
  from beta agonist, 211
  bicarbonate infusion in, 466
Laparotomy, 689
Large bowel obstruction (LBO), 684–685
LC. *See* Lung contusion (LC)
L-Carnitine, 430
Left ventricular assist devices (LVADs), 100
Left ventricular failure (LVF), 25, 122, 123, 125, 266
Left ventricular function, 731, 734
Left ventricular thrombus, 729, 731, 732
Leptospirosis, 514, 517
  antibiotic administration, 521–522
  case study, 517–518
  clinical presentation, 520
  corticosteroids role, 522–523
  diagnostic tools
    culture, 522
    molecular tests, 522
    reference standard, 522
    serology, 522
  differential diagnosis, 521
  drug resistance, 522
  epidemiology, 518–519
  laboratory presentation, 520–521
  microbiology, 519–520
  prevention, 523
  risk factors, 519
Leucopenia, 513
Leukapheresis, in AML, 652
Leukocyte larceny, 651
Leukostasis, 649
LGIB. *See* Lower gastrointestinal bleeding (LGIB)
Lidocaine
  arrhythmias, 62
  ventricular arrhythmias, 158–159
Life-threatening asthma, 207, 211
Limb ischemia, acute, 707
Linezolid, 181, 184–186
Lipase, 546
Lipid, in tube feeds, 577–578
LIPS. *See* Lung injury prediction score (LIPS)
Listeria monocytogenes, 318, 319, 584, 585
Liver failure, acute. *See* Acute liver failure (ALF)
Liver injury scale, 668
Liver transplantation, 559
Long-term acute care hospital (LTAC), 252, 254
Loop diuretics, 385
Lower extremity trauma, 708, 710
  vascular, endovascular treatment approach, 710–711
Lower gastrointestinal bleeding (LGIB), 528–530
  appropriate patient disposition, 564
  blood transfusion goals, 566
  case study, 561–562
  definition, 562
  diagnostic imaging modalities, 567
  differential diagnosis, 563
  initial evaluation, 562–563
  initial resuscitation and management, 563–564
  management, 565
  massive transfusions, 566–567
  mesenteric angiography, 565–566
  nasogastric tube lavage, 564
  predicting severity and outcomes of, 566
  provocation testing, 567
  surgery, 566
  urgent colonoscopy, 564–565
Low molecular weight heparin (LMWH), 116, 222–223, 227, 622–623, 670
LTAC. *See* Long-term acute care hospital (LTAC)
Lumbar puncture (LP), 317–319
Lung contusion (LC), 659–660
Lung injury prediction score (LIPS), 190, 191
Lung Open Ventilation Study (LOVS), 192
Lung protective ventilation (LPV), ARDS, 189–192
Lymphopenia, 513

M
Maculopapular rash, 514
Magnesium
  status asthmaticus, 211
  for ventricular arrhythmias, 62
Magnesium sulfate therapy, 750–753
Magnetic resonance imaging (MRI)
  acute aortic syndromes, 166
  anoxic brain injury, 364, 369
  pituitary and hypothalamus, 438
  status epilepticus, 337

MAHA. *See* Microangiopathic hemolytic anemia (MAHA)
Malaria
  anemia and coagulopathy, 504–505
  antigen rapid detection test, 506
  bacterial infection, 506
  blood products, 505
  case study, 495
  cerebral, 504
  clinical management principles, 497–499
  definition, 496
  diagnosis, 496–497
  diagnostic modalities, 506
  exchange transfusion, 507
  fever, 505–506
  hypoglycemia, 505
  management, principles, 495–496
  molecular methods, 507
  monitoring parasite density, 499
  neurologic involvement, 504
  nutrition, 505
  quantitative buffy coat, 506
  respiratory system, 499
  retina in patient with, 499
  seizure management, 504
  serology, 506
  treatment, 500–503
  volume management, 505
Malignant hyperthermia (MH), 347, 350, 351
Mannitol, 330, 356
Massive hemoptysis. *See* Hemoptysis
Massive transfusion protocol, hemorrhagic shock, 44
MAT. *See* Microscopic agglutination test (MAT)
MATCH trial, AIS, 312
MDCT. *See* Multidetector Computed Tomography (MDCT)
Mechanical chest compressions, 7–9
Mechanical circulatory support, 731, 734
  acute heart failure, 106
  cardiogenic shock, 99–101
    percutaneous, 97–98
    temporary surgical, 98–99
  ventricular arrhythmias
    ECMO, 159–160
    IABP, 159
Mechanical intubation, IPF, 268
Mechanical ventilation
  ARDS, 274
  prolonged (*see* Prolonged mechanical ventilation (PMV))
  TBI, 356–357
  weaning from, 273–279
Medical paternalism, 774
Medication-induced movement disorder, 348–349
MELD score, 592
Meningococcemia, 322–323
Mental health, 282, 489
Mesenteric angiography, 562, 565–566
Metabolic acidosis, 420, 466, 536
Methanol, ethylene glycol ingestion, 79–80
Methicillin-resistant *Staphylococcus aureus* (MRSA), 184–185
  community-acquired, 186
  drugs to suppress toxin with, 186
Methicillin-sensitive *Staphylococcus aureus,* 258
Methimazole, 428
Methylene blue, calcium channel blocker poisonings, 70
Michigan alcohol withdrawal severity (MAWS) scoring system, 596
Microangiopathic hemolytic anemia (MAHA), 605, 606, 608, 619
Microdialysis, cerebral, 359
Micronutrient goals, 577
Microscopic agglutination test (MAT), 517, 522
Microscopic polyangiitis (MPA), 296, 298
Microvascular thrombosis, 607
Mitral valve repair, 175
Modification of Diet in Renal Disease (MDRD) formula, 378
Modified Rankin score, 33, 308
Montreal Cognitive Assessment (MoCA), 282
Morphine, ACS, 114
MPA. *See* Microscopic polyangiitis (MPA)
MRI with diffusion-weighted imaging (MRI-DWI), 304–305
Mud fever. *See* Leptospirosis
Multidetector Computed Tomography (MDCT), 237, 238
Multidrug resistant (MDR)
  community acquired pneumonia, 185
  pathogens, 257, 258, 260
  risk factors, 258
  VAP, 258
Multivessel revascularization, cardiogenic shock, 99
Muscle biopsy, 396
Muscle damage, 398
Muscle injury, 395, 398
Muscular rigidity, NMS, 350–351
Mycoplasma pneumonia, 760
Myelinolysis, 415
Myocardial dysfunction, in post-cardiac arrest syndrome, 15–16
Myocardial infarction
  case study, 121–122
  diagnosis, 123–125
  epidemiology, 123
  intra-aortic balloon pump, 127
  Killip Class definition, 122, 123
  LV failure, 125
  mechanical complications, 125–126
  VSR, 126
Myocarditis, viral, 730
Myoglobin, 395
Myxedema coma (myxedema)
  case study, 447–448
  corticosteroid replacement, 449
  diagnosis, 448–449
  supportive care, 449–450
  symptoms and signs, 449
  thyroid hormone replacement, 450
  thyroxine replacement, 449

N
Nanukayami fever. *See* Leptospirosis
National Acute Brain Injury Study: Hypothermia II, 332
National Health Safety Network, 261
National Institutes of Health Stroke Scale (NIHSS) score, 303–307
NCSE. *See* Non-convulsive status epilepticus (NCSE)
Necrosis, 682
  pancreatic, 677, 679
Necrotizing fasciitis, 715
Necrotizing soft tissue infection (NSTI)
  antibiotic therapy and resuscitation, 715
  case study, 713–714
  debridement, 714, 715
  diagnosis and outcome, 715–716
  early amputation, 716
  hyperbaric oxygen therapy, 716
  immunomodulatory therapy, 716
  rapid diagnosis, 714–715
  surgical source control, 715
Negative pressure therapy (NPT), 690
Negative pressure ventilation (NIV)
  altered mental status, 53
  ARDS, 52–53
  asthma exacerbation, 52
  full face mask, 50
  hi-flow nasal cannula, 50
  indications and contraindications, 51
  pneumonia patients, 52
  predictors of failure, 51–52
Neisseria meningitidis, 318–319, 322, 324
Nephrostomy, 453, 456
Nesiritide, acute heart failure, 107–108
Neurocritical Care Society (NCS), 335
Neurointensive care, 336
Neuroleptic malignant syndrome (NMS)
  altered mental status, 350
  autonomic dysfunction, 351
  benzodiazepines, 351
  bromocriptine, 345, 352
  case study, 345–346
  dantrolene, 345, 351–352
  diagnosis, 346–347
  differential diagnosis for, 348–349
  ECT, 345, 352
  hyperthermia, 350
  medication history and temporal clues, 347
  muscular rigidity, 350–351
Neurologic outcome, 366–369, 506
Neuromuscular blockade, ARDS, 194–195
Neuromuscular diseases, 746
Neuromuscular paralysis, TBI, 357
Neuroprognostication, 368, 369
  post-cardiac arrest syndrome, 18–19
Neuroprotective agents, TBI, 360
Nicardipine, hypertensive crises, 138, 139
NICE-SUGAR trial, 463
Nifedipine, 753
NIPPV. *See* Noninvasive positive pressure ventilation (NIPPV)
Nitrates, ACS, 114
Nitroglycerin
  acute heart failure, 105
  hypertensive crises, 138, 139
NMS. *See* Neuroleptic malignant syndrome (NMS)
Non-cardiogenic acute pulmonary edema, 744
Non-convulsive status epilepticus (NCSE), 335–337, 340, 341, 366, 367, 369
Non-dihydropyridines, 65
Non-Hodgkin's lymphoma, 642
Noninvasive mechanical ventilation, 202
Noninvasive positive pressure ventilation (NIPPV), 199, 201–202, 268
  after extubation, 202
  DNI orders, 202
  immunocompromised pneumonia, 218, 219
  status asthmaticus, 211–212
Non-neutrocytic bacterascites, 586
Nonoperative management (NOM), 667–668
Nonselective beta blockers (NSBB), 585
Non-steroidal anti-inflammatory drugs (NSAIDs), 114, 350, 760
Non-ST segment elevation ACS (NSTE-ACS), 115, 117–118
Non-ST segment elevation MI (NSTEMI), 112, 114, 116
Norepinephrine, 461, 555
  decompensated RV failure, 291
Normal saline, 413
Normoglycemia, 505
Normothermia, 366, 368
Novel oral anticoagulants (NOAC), 309
NSBB. *See* Nonselective beta blockers (NSBB)
NSTEMI. *See* Non-ST segment elevation MI (NSTEMI)
NSTI. *See* Necrotizing soft tissue infection (NSTI)
NT-pro brain natriuretic peptide (NT-proBNP), 732
Nuchal rigidity, 317, 318, 324
Nutrition
  in AKI, 389
  in critically Ill patient, 575–578

O
Obesity, 578
Obstructive shock, 28
Obstructive sleep apnea, in pregnancy, 745
OD. *See* Osmotic demyelination (OD)
ODS. *See* Osmotic demyelination syndrome (ODS)
OHSS. *See* Ovarian hyperstimulation syndrome (OHSS)
Oliguria, refractory, 753
OMEGA trial, 578
Ommaya reservoir, 323
Open lung ventilation, 192
Opiate, 439
Organizing pneumonia (OP), 637
Osmotic demyelination (OD), 401, 404, 407
Osmotic demyelination syndrome (ODS), 415
  outcomes, 416
  prevention, 416
Osmotic diuresis, 331, 420, 442
Out-of-hospital cardiac arrests (OHCA), 3

Ovarian hyperstimulation syndrome (OHSS), 744
Overwhelming post-splenectomy infection (OPSI), 668
Oxygenation, ARDS, 191
Oxygen therapy, ACS, 114

P
Palliative care, IPF, 267
Pancreatic necrosis, 677, 679
Pancreatic pseudocyst, 546
Pancreatitis
  acute (*see* Acute pancreatitis)
  alcoholic, 545, 547
  feeding in, 548
  gallstone, 545, 547
Panton-Valentine leukocidin (PVL), 186
Papillary muscle rupture, 121, 123–125
Paralytic ileus, hyperinfection associated with, 483
Parapneumonic effusions, 185
Paraproteinemias, 649–651
Parasitemia, 499
Parenteral nutrition (PN), 576, 577
  CALORIES Trial, 577
Partial thromboplastin time (PTT), 620, 622
PASP. *See* Pulmonary artery systolic pressure (PASP)
Passy-Muir® speaking valve, 253, 254
Pathogen-directed therapy, community acquired pneumonia, 183–185
PCC. *See* Prothrombin complex concentrate (PCC)
PDS. *See* Pericardial decompression syndrome (PDS)
PE. *See* Pulmonary embolism (PE)
PEEP. *See* Positive end-expiratory pressure (PEEP)
PEITHO trial, pulmonary embolism, 221, 228
Penetrating aortic ulcers (PAU), 164, 165, 167
Percutaneous cholecystostomy, 724
Percutaneous coronary intervention (PCI), 14, 15, 118, 119
Percutaneous dilational tracheostomy, 252, 253
Percutaneous transhepatic cholangiographic (PTC) drainage, 722
Perforated diverticulitis, 674
Pericardial decompression syndrome (PDS), 133
Pericardial effusion, 129–133
Pericardiocentesis, 133
Peripartum cardiomyopathy (PPCM), 744
  anticoagulation, 734
  anti-inflammatory mediators, 735
  case study, 729–731
  chronic medical therapy, 734
  delivery, 734–735
  diagnosis, 732
  immunotherapy, 735
  implantable cardioverter defibrillator, 734
  maternal risk factors and adverse events in, 731
  mechanical support, 734
  pharmacologic therapy in, 733
  postpartum supportive care, 735
  symptoms, 730–731
Peripheral intravenous (PIV) catheters, 564
Permissive hypercapnia, 208–209
Personal protective equipment (PPE), 485–490
PESI. *See* Pulmonary Embolism Severity Index (PESI)
Petechiae, 510, 605
Phenobarbital, 768
Phentolamine, hypertensive crises, 140, 141
Phosphate binders, in TLS, 644
Phosphodiesterase 5 (PDE5) inhibitors, 292
Physical impairment, PICS, 282–284
PICS-F. *See* Post-Intensive Care Syndrome-Family (PICS-F)
Placental abruption, 750
Plain radiographs, hemoptysis, 236
Plasmapheresis, 299, 651
  extracorporeal, 430
Plasmodium falciparum, 495–498
Plateau airway pressure, 189, 192, 194
Platelet transfusion, 617
Plethysmography variation index (PVI), 29
PMV. *See* Prolonged mechanical ventilation (PMV)
PN. *See* Parenteral nutrition (PN)
Pneumonia
  bacterial, 745
  case study, 215
  chest X-ray, 216
  community acquired (*see* Community acquired pneumonia (CAP))
  CT scan, 216, 217, 287
  diagnosis, 216–217
  empiric treatment, 217
  etiology, 216
  immunocompromised, 215–219
  immunosuppressed, 216, 217, 219
  mycoplasma, 760
  negative pressure ventilation, 52
  noninvasive ventilation, 219
  presentation, 215–216
  serum tests for, 218–219
  supportive care, 218
  utility of invasive testing, 218
  viral, 745
Pneumonia Severity Index (PSI), 182
Pneumonitis, 635
Pneumothorax, 658, 660
  in pregnancy, 746
Point-of-care ultrasound, RV failure, 287, 289
POINT trial, AIS, 312
Polyenes, 475
Polymerase chain reaction (PCR), *Pneumocystis,* 215
Posaconazole, 475
Positive end-expiratory pressure (PEEP)
  ARDS, 189, 191–194
  IPF, 268
  RV dysfunction, 290, 292
Post-cardiac arrest syndrome (PCAS)
  brain injury, 15
  case study, 13–14
  emergency coronary angiography, 19–20
  glucose control, 18

hemodynamic optimization, 16–17
hypothermic TTM, 17–18, 20–21
myocardial dysfunction, 15–16
neuroprognostication, 18–19
organ donation, 19
patient selection, 19–21
persistent precipitating pathology, 16
with refractory cardiogenic shock, 21–22
seizures, 18
STEMI and ACS, 17
systemic ischemia/reperfusion response, 16
ventilation and oxygenation, 17
Post exposure prophylaxis, 324
Post-intensive care syndrome (PICS), 254, 638
ABCDEF bundle, 283–284
case study, 281
cognitive rehabilitation, 284–285
diagnosis, 281–282
ICU follow up clinic, 284
physical impairment, 282–284
prevention, 282
rehabilitation, 282
Post-Intensive Care Syndrome-Family (PICS-F), 284
Post-pyloric feed, 577
Post-traumatic seizures, 358–359
Post-traumatic stress disorder (PTSD), 774
PPE. *See* Personal protective equipment (PPE)
PPI. *See* Proton pump inhibitor (PPI)
Preeclampsia, 744
antenatal steroids and delivery, 752
anti-hypertensive therapy, 752–753
diagnosis, 751–752
invasive monitoring, 753–754
magnesium sulfate therapy, 753
seizure prophylaxis, 752
treatment, 753
Pregnancy, 730, 731
airway disease, 745
bacterial pneumonia, 745
cystic fibrosis, 746
differential diagnosis of pulmonary conditions in, 744
neuromuscular diseases and central causes, 746
obstructive sleep apnea in, 745
physiologic respiratory changes in, 743–744
pneumothorax in, 746
pulmonary edema, 744
pulmonary embolism in, 746
pulmonary infections in, 745
ventilation strategies in
challenges, 746
delivery of fetus, 747
ECMO, 747
goals of ventilation, 747
mechanical ventilation, 747
non-invasive ventilation, 747
prone ventilation, 747
viral pneumonia, 745
Pressors, hypovolemic shock, 43
Procalcitonin (PCT), 186, 679
Prokinetic agents, 577
Prolonged mechanical ventilation (PMV)
assess expected survival, 251–252
case study, 251
daily tracheostomy collar trials, 252
diagnosis, 251
early mobility, 252
place tracheostomy, 252, 253
Provent14 score, 251, 252
speaking valve trials, 253
survivorship clinics, 254–255
symptom burden, 254–255
timing of tracheostomy, 253–254
tracheostomy removal, 253
transfer benefit to LTAC, 254
weaning from, 275
Prone ventilation, ARDS, 192–193
Prophylactic dialysis, 389
Prophylaxis
antibiotics, 359–360
post exposure, 324
seizure, 331, 752
Propofol, 768
Propranolol, 425, 426, 428
Propylthiouracil (PTU), 428
PROTECT trial, pulmonary embolism, 222–223
Prothrombin complex concentrate (PCC), 531
Protocolized Care for Early Septic Shock (ProCESS) trial, 463, 466
Proton pump inhibitor (PPI), 529, 530, 540
Pseudocyst, pancreatic, 546
Pseudomonas, 183, 184
PTSD. *See* Post-traumatic stress disorder (PTSD)
Pulmonary artery catheterization (PAC), 106, 291
Pulmonary artery pressure, 288, 289, 291
Pulmonary artery systolic pressure (PASP), 288–289
Pulmonary complications, HCT patient, 634–637
Pulmonary edema, 636, 744, 753
cardiogenic, 738
chest x-ray, 163, 172
non-cardiogenic acute, 744
pre-eclampsia associated, 744
tocolytic induced, 744
Pulmonary embolism (PE), 222
clinical presentation, 223–224
diagnosis, 226
Geneva Score, 223–224
hemodynamically stable, 228–229
IVC filter placement, 229–230
in PEITHO trial, 221, 228
in pregnancy, 746
in PROTECT trial, 222–223
severity, 224–226
treatment, 226–228
Wells criteria, 223–224
Pulmonary Embolism Severity Index (PESI), 225–226
Pulmonary hypertension, 288–289, 292
Pulmonary infections, in pregnancy, 745
Pulmonary transplantation, IPF, 269

Pulmonary vascular resistance (PVR), 290
Pulmonary vasculature, 289
Pulseless electrical activity (PEA), 6–7
Pulse pressure variation (PPV), 29, 289
Pulsus paradoxus, 124, 129, 131
Purpura, 605
Purpura fulminans, 322, 622
P2Y12 receptor inhibitors, ACS, 116, 119
Pyuria, 454

Q
Quality of Dying and Death (QODD) questionnaire, 775
Quantitative buffy coat (QBC), 506
Quick Sepsis Organ Failure Assessment Score (qSOFA), 459

R
Radiocontrast agents, iodinated, 429–430
Radiofrequency catheter ablation, ventricular arrhythmias, 160
Randomized controlled trial (RCT)
  acute exacerbation of COPD, 200, 201
  AKI, 388
  diuretics, 385
  status epilepticus, 337, 339
  VAP, 260
Rapid detection test (RDT), antigen, 506
Rasburicase, 643
Rash
  maculopapular, 514
  petechial, 510
RASS. *See* Richmond Agitation-Sedation Scale (RASS)
RCT. *See* Randomized controlled trial (RCT)
Recombinant Factor VII, 299
Recombinant Factor VIIa (rFVIIa), 618
  to correct coagulopathy, 558
  infusion protocol, 557
Recombinant human factor VIIa (rVIIa), 740
Recurrent bleeding, hemoptysis, 238–239
Refractory cardiogenic shock, PCAS, 21–22
Refractory oliguria, 753
Refractory status epilepticus (RSE), 338–341
Rehabilitation, PICS, 282, 284–285
Relative adrenal insufficiency, 435
Renal-dose dopamine, 108
Renal failure, 295, 296. *See also* Acute renal failure (ARF)
  in rhabdomyolysis, 395, 396, 398
Renal replacement therapy (RRT), 387, 388, 390, 399, 492, 644–645
Renin-angiotensin-aldosterone system (RAAS), 406
Reperfusion therapy, 228–229, 399
Respiratory failure
  acute, 694, 695, 698
  causes of, 746
  in HCT patient, 634, 637–638
Resuscitation
  cardiac arrest management, 5–6
    hemodynamic directed, 9
    quality assurance, 4, 7
  ECPR, 84
  for hemorrhagic shock, 41, 46
  hypovolemic shock, 41
Return of spontaneous circulation (ROSC), 13, 363, 364
Revascularization, cardiogenic shock, 96–97
Rewarming, for hypothermia, 86–87
  active and passive, 86
  in cardiac arrest, 89
  extracorporeal, 86–87
Rhabdomyolysis
  antioxidants, 399
  bicarbonate therapy, 398
  case study, 393–395
  causes of, 396–397
  complications, management, 398
  diagnosis, 395–396
  diuretics, 398–399
  fluid therapy, 396, 398
  free radical scavengers, 399
  management, principles, 395
  mannitol, 398–399
  renal failure in, 395, 396, 398
  in skeletal muscle, 395
Rice-field fever. *See* Leptospirosis
Richmond Agitation-Sedation Scale (RASS), 241–243
Richmond Agitation Severity Scale (RASS), 765
Rickettsial disease, 521
Right ventricular failure, decompensation, 287–292
Rigid bronchoscopy, 237
Rituximab, 611
  diffuse alveolar hemorrhage, 299
Rivaroxaban, 532
Rockall score, 528
RRT. *See* Renal replacement therapy (RRT)
RSE. *See* Refractory status epilepticus (RSE)
Rumack-Matthew nomogram, 553

S
Saline *vs.* Albumin Fluid Evaluation (SAFE) trial, 460
Salivary cortisol testing, 438
SAS. *See* Sedation-Agitation Scale (SAS)
SATs. *See* Spontaneous awakening trials (SATs)
SBO. *See* Small bowel obstruction (SBO)
SBP. *See* Spontaneous bacterial peritonitis (SBP)
Scar management, 705
SCCM. *See* Society of Critical Care Medicine (SCCM)
Sclerotherapy, 537
Sclerotic skin lesion, 633
Scrub typhus, 521
SE. *See* Status epilepticus (SE)
Secondary bacterial peritonitis, 582, 583
Sedation
  anoxic brain injury, 363, 365, 366
  benzodiazepines with, 245–246

case study, 241–242
choice, 244–246
and delirium, 246–247
monitoring, 242
spontaneous awakening trials, 246
TBI, 357
Sedation-Agitation Scale (SAS), 242, 243
Seizure management, 767
eclamptic, 752
malaria, 504
PCAS, 18
post-traumatic, 358–359
prophylaxis, 331, 752
TCA toxicity, 61
Sengstaken-Blakemore tube, 540, 541
Sepsis, 193, 453–455. *See also* Urosepsis
AKI, 383, 384, 388
antimicrobial therapy, 462
case study, 457–458
definition and recognition, 458–459
EGDT, 463
fluid management, 459–460
glycemic control and nutrition, 463
hemodynamic response, 460–461
sequella after surviving severe, 467
SIRS criteria in, 466
surviving sepsis campaign bundle, 459, 464
treatment, 462, 464–465
ventilator management, 463
Septic shock, 714–716
antimicrobial therapy, 462
blood pressure target in, 466
case study, 457–458
definition and recognition, 458–459
EGDT, 463
fluid management, 459–460
fluid resuscitation in, 466
glycemic control and nutrition, 463
heart rate control in, 466–467
sequella after surviving severe, 467
steroid replacement in, 438
tissue perfusion, 461
treatment, 462, 464–465
vasopressors, 461–462
ventilator management, 463
Serotonin syndrome (SS), 347, 350
Serum cortisol measurement, 435
Serum creatinine, 376–379
Serum myoglobin, 395
SFA. *See* Superficial femoral artery (SFA)
Shared decision making, 774, 775
SHEA. *See* Society for Healthcare Epidemiology of America (SHEA)
Shivering, 363, 365, 366
Shock, 510, 511
bedside echocardiography, 25–26, 32–36
cardiogenic, 26, 28–29
case study, 25–26
definition, 26
differential diagnosis, 25
distributive, 26, 28
hypovolemia, 27
types, 26–29, 36
volume responsiveness assessment, 29–32
Short acting anti-cholinergic agents, 200
SIADH. *See* Syndrome of inappropriate antidiuretic hormone activity (SIADH)
SIRS. *See* Systemic inflammatory response syndrome (SIRS)
Site-of-care decisions, CAP, 181–182
SJS. *See* Stevens-Johnson syndrome (SJS)
Skeletal muscle, rhabdomyolysis in, 395
Skin eruption, 759–762
Skin mottling, 460, 461
SLE. *See* Systemic lupus erythematosus (SLE)
Sleep apnea, in pregnancy, 745
Small bowel obstruction (SBO)
acute, 685
CT imaging findings, 685
management, 684–685
standard approach to management, 682
timing of operating for, 684
Society for Healthcare Epidemiology of America (SHEA), 262
Society of Critical Care Medicine (SCCM), 242, 244, 247
Sodium bicarbonate, calcium channel blocker poisonings, 70
Sodium nitroprusside, hypertensive crises, 138, 139
Solid organ injury, blunt. *See* Blunt solid organ injury
Somatosensory evoked potentials (SSEPs), 369
SPA. *See* Splenic artery pseudoaneurysm (SPA)
Spleen injury scale, 667
Splenectomy vaccinations, 668
Splenic artery pseudoaneurysm (SPA), 669
Splenic injury, blunt, 668, 669
Split thickness skin grafts (STSG), 691
Spontaneous awakening trials (SATs), 242, 246, 283
Spontaneous bacterial peritonitis (SBP)
albumin, 585
antibiotic prophylaxis, 585–586
antibiotics, 584–586
case study, 581–582
diagnosis, 582–583
duration of therapy, 586
management, 584
microbiologic etiology, 583–584
NSBB, 585
patient with non-neutrocytic bacterascites, 586
treatment, 584
Spontaneous breathing trial (SBT), 242, 273, 275, 277, 283
Spot sign, 328, 329
SRSE. *See* Super-refractory status epilepticus (SRSE)
SS. *See* Serotonin syndrome (SS)
Statin therapy, ACS, 114–115

Status asthmaticus
adjuvant pharmacologic treatments, 211
anesthetics, 212
arterial blood gases, monitoring of, 208
barotrauma, recognizing, 210–211
bronchoscopy, 212
case study, 206
corticosteroids, 207
ECLS, 212
heliox, 211
hyperinflation, 209–210
hypoventilation, 208–209
inhaled bronchodilators, 207
intravenous bronchodilators, 211
lactic acidosis from beta agonist, 211
magnesium, 211
noninvasive positive pressure ventilation, 211–212
permissive hypercapnia, 208–209
ventilator strategies, 208
Status epilepticus (SE), 340–341
case study, 335
cerebrospinal fluid, 337
complications, 342
diagnosis of, 337
EEG, 335–338, 341
electroconvulsive therapy, 342
etiology, 337
goals of treatment, 340–341
medical management, 339
medications, 338
multidisciplinary care, 339
non-convulsive, 341
pharmacologic therapy, 337–338
refractory, 338–339
second-line therapy, 337
systemic complication, 340
treatment options in, 341–342
STE-ACS. *See* ST-segment elevation ACS (STE-ACS)
STEMI. *See* ST-segment elevation myocardial infarction (STEMI)
Stent-retriever device, 304, 306, 311
Steroid replacement
additional testing, 437–438
concurrent fluid management, 437
dose and duration, 436–437
in septic shock, 438
steroid selection, 436
Steroids
bacterial meningitis, 320–321
TBI, 360
Stevens-Johnson syndrome (SJS), 759–761
cyclosporine, 762
pathogenesis, 761
supportive care, 761–762
thalidomide, 762
STOPAH trial, 599
Streptococcus pneumonia, 317–319
Strokes. *See also* Acute stroke management
rehabilitation in, 310–311
"wake-up," 309
Stroke volume (SV), 29, 30
Stroke volume variation (SVV), 29, 289
Strongyloides hyperinfection syndrome
anti-parasitics, 482–483
case study, 479–480
diagnosis, 482
disseminated infection and hyperinfection, 482
epidemiology, 481
hyperinfection associated with paralytic ileus, 483
life cycle, 481–482
management, principles, 480
severe infections, 483
supportive care and follow up, 483
Strongyloides stercoralis, 481
ST-segment elevation ACS (STE-ACS), 111, 112
ST-segment elevation myocardial infarction (STEMI), 116, 117
complete revascularization in, 118–119
fibrinolytic regimens for, 118
manual thrombectomy during primary PCI in, 119
PCI after successful thrombolysis in, 118
post-cardiac arrest syndrome, 17
STSG. *See* Split thickness skin grafts (STSG)
Stuttgart disease. *See* Leptospirosis
Subdural hematoma, 358
Superficial femoral artery (SFA), 708, 709
Super-refractory status epilepticus (SRSE), 336, 338, 340–342
Superselective embolization, 565
Supraventricular tachycardias, 150
Surgical Trial in Intracerebral Haemorrahage (STICH), 327
Surrogate decision making, 774
Swamp fever. *See* Leptospirosis
Swan-ganz catheter, 104
Swineherd's disease. *See* Leptospirosis
Syndrome of inappropriate antidiuretic hormone activity (SIADH), 406, 413
causes of, 415
diagnostics, 416
Systemic inflammatory response syndrome (SIRS), 459, 625
criteria in sepsis, 466
Systemic lupus erythematosus (SLE), 393
Systolic pressure variation (SPV), 462

T

TandemHeart®, 96–98
Tandem Heart pump™, 21
TAPSE. *See* Tricuspid annular plane systolic excursion (TAPSE)
Targeted temperature management (TTM), 363–364, 366–368
TBI. *See* Traumatic brain injury (TBI)
TBSA. *See* Total body surface area (TBSA)
T-cell function, 634

TEE. *See* Transesophageal echocardiogram (TEE)
Therapeutic hypothermia. *See* Hypothermia
Therapeutic plasma exchange (TPE), 606, 609, 610
Thermal injury, 702
  case study, 701–702
  diagnosis, 703
  fluid management, 704
  fluid resuscitation monitoring, 705
  scar management, 705
  supportive care, 705
  surgical intervention, 704
  wound care, 703–704
Thionamides, 428
Thoracic pump theory, 7
Thoracic trauma
  case study, 657–658
  hemothorax, 658, 660–661
  lung contusion, 659–660
  pneumothorax, 658, 660
  rib fractures, 658–659, 661
Thoratec Device™, 21
Thrombectomy
  endovascular, 306–308
  with PCI, 119
Thrombocytopenia, 513, 531, 605
  causes of, 616
  differential diagnosis, 608
  ecchymosis from, 497
Thrombocytosis, 650
Thromboembolism, prophylaxis, 611
Thrombolysis
  catheter-directed, 227–228, 230
  contraindications to, 229, 230
  in hemodynamically stable acute PE, 229
  hemodynamic benefits, 228
Thrombomodulin-α, 623
Thrombosis, microvascular, 607
Thrombotic microangiopathy, drug-induced, 611, 612
Thrombotic thrombocytopenic purpura (TTP)
  ADAMTS13 activity level and autoantibody testing, 606, 607
  anti-platelet agents, 611
  case study, 605–606
  diagnosis, 606–607
  drug-induced thrombotic microangiopathy, 611
  FFP, 609–612
  immunosuppressive agents, 610, 611
  prevention, 611
  TPE, 609
  treatment algorithm, 610
  venous thromboembolism prophylaxis, 611
Thyroid hormone, 426, 428, 430
  replacement, 450
Thyroid stimulating hormone (TSH), 425, 427
Thyroid storm, 426–427
  case study, 425–426
  diagnosis, 427
    clinical tools, 429
    criteria, 429
  etiology, 426
  incidence, 426
  iodinated radiocontrast agents, 429–430
  medication dosing guide, 427
    beta-blockers, 428
    glucocorticoids, 428
    iodine solutions, 428
    thionamides, 428
  treatment, 427
  triggers of, 426
Thyroxine replacement, 449
Tight glycemic control, AKI, 389
Tissue plasminogen activator (tPA), 221, 228
  acute stroke management, 305–306
  community acquired pneumonia, 185
TKM-Ebola, 493
TLS. *See* Tumor lysis syndrome (TLS)
TNF alpha inhibitors, 762
Tocolytic induced pulmonary edema, 744
Total body irradiation (TBI), 633
Total body surface area (TBSA), 701–702
Tourniquet test, 511
Toxic epidermal necrolysis (TEN) syndrome, 759–761
  cyclosporine, 762
  intravenous immunoglobulins, 762
  pathogenesis, 761
  supportive care, 761–762
  systemic corticosteroids, 762
  thalidomide, 762
Toxic shock syndrome, 716
tPA. *See* Tissue plasminogen activator (tPA)
TPE. *See* Therapeutic plasma exchange (TPE)
Tracheostomy
  collar trials, 252
  Passy-Muir® speaking valve, 253, 254
  placement of, 252, 253
  for prolonged transition, 278–279
  removal, 253
  timing of, 253–254
Trans-arterial embolization (TAE), 530
Transcoronary ethanol ablation, ventricular arrhythmias, 160
Transesophageal echocardiogram (TEE), 226
  acute aortic syndromes, 164, 166
  endocarditis, 173–174
  myocardial infarction, 122, 123, 125
Transfusion therapy, hemorrhagic shock, 43
Transjugular intrahepatic portosystemic shunt (TIPS) placement, 536–538, 540
Transpulmonary pressure, ARDS, 194
Transthoracic echocardiogram (TTE), 729
  acute aortic syndromes, 164, 166
  cardiac tamponade, 130–132
  endocarditis, 172–174
  myocardial infarction, 124
  PASP, 288–289
Trauma, 396, 702
  vascular, 710

Traumatic brain injury (TBI)
analgesia, 357
case study, 355
invasive intracranial pressure monitoring, 358
mechanical ventilation, 356–357
neuromonitoring, 359
neuromuscular paralysis, 357
neuroprotective agents, 360
post-traumatic seizures, 358–359
prehospital and emergency department, 356
primary and secondary, 356
prophylactic antibiotics, 359–360
sedation, 357
severity of, 356, 357
steroids, 360
surgical treatment, 357–358
therapeutic hypothermia, 359
Traumatic cerebral contusion, 358
Triazoles, 474–475
Tricuspid annular plane systolic excursion (TAPSE), 288–289
Tricyclic antidepressant (TCA) toxicity
antiarrhythmic drugs, 62
case studies, 57–58
diagnosis, 58–59
EKG finding, 59
extracorporeal elimination, 61
gastrointestinal decontamination, 59–60
hypertonic saline, 61–62
hypotension and vasopressor support, 60–61
intravenous lipid emulsion, 61
plasma alkalinization, 60
seizure management, 61
sodium channel blockade, 58
Triiodothyronine (T3), 450
Trophic feedings, 576
TTP. *See* Thrombotic thrombocytopenic purpura (TTP)
Tumor lysis syndrome (TLS)
acute renal failure, 644
with AKI, 644
case study, 641
clinical classifications, 642
clinical outcomes, 644
hypouricemic agents, 643
low intensity chemotherapy, 642
monitoring, 643
phosphate binders in, 644
prevention and treatment, 642–643
renal replacement therapy, 644–645
risk stratification for development of clinical, 642
Type A dissections, 166, 168
Type B dissections, 166, 170

U
UGIB. *See* Upper gastrointestinal bleed (UGIB)
Ultrafiltration (UF), 107
Ultrasound
cardiac arrest management, 7
hypertensive crises, 135
Undifferentiated shock
bedside echocardiography, 25–26, 32–36
case study, 25–26
types, 26–29, 36
volume responsiveness assessment, 29–32
Unfractionated heparin (UFH), 222–223, 227, 622–623
Unstable angina (UA), 112, 114, 116
Upper gastrointestinal bleed (UGIB), 528–530
Urea, 416
Uremic syndrome, hemolytic, 606, 607
Ureteral stent, 454–456
Uric acid, reduction of, 643
Urinary alkalization, 642, 643
Urinary tract
infection, 454, 455
obstruction, 454
Urine
alkalinization of, 79, 398
output, 376–377
Urosepsis
case study, 453
diagnosis, 453–454
empiric anitbiotic choice, 455
empiric antimicrobial administration, 454
indications for imaging, 455
intervention method, 455–456
procedures/surgery, 454

V
VAE. *See* Ventilator Associated Event (VAE)
VALI. *See* Ventilator associated lung injury (VALI)
VAP. *See* Ventilator-associated pneumonia (VAP)
Vaptans, 416
Variceal bleeding, 590, 597, 598
Variceal hemorrhage
acid suppression, 540
antibiotic prophylaxis, 537–538
balloon tamponade, 540
BRTO, 540–541
case study, 535–536
correction of coagulopathy, 539
endotracheal intubation, 539–540
hemostasis interventions, 536–537
initial resuscitation, 536
red blood cell transfusion, 538–539
surgery, 541
TIPS placement, 536–538, 540
vasoactive medications, 536
vasoconstrictor agents for, 537
Vascular ectasias, 563
Vascular injury, 707, 710–711
Vasculitides, ANCA-ssociated, 298–299
Vasoconstrictor, agents for variceal hemorrhage, 537
Vasodilation
acute heart failure, 105
AKI, 389
ARDS, 196
Vasopressin, 536, 555
Vasopressin V2 receptor antagonist (vaptan), 416

Vasopressors, 461–462
AKI, 384–385
calcium channel blocker poisonings, 68
cardiogenic shock, 97
hemorrhagic shock, 46
tricyclic antidepressant toxicity, 60–61
VATS. *See* Video-assisted thoracoscopic surgery (VATS)
Venoarterial Extracorporeal Membrane Oxygenation (v-a ECMO), 98
Venous thromboembolism (VTE), in ICU
case study, 221–222
clinical presentation, 223–224
diagnosis, 226
epidemiology, 222–223
evidence contour, 228–230
PROTECT trial, 222–223
pulmonary embolism severity, 224–226
risk factors, 222
treatment, 226–228
Venous thromboembolism (VTE) prophylaxis, 611, 670
Ventilator Associated Event (VAE), 261
Ventilator associated lung injury (VALI), 189, 194
Ventilator-associated pneumonia (VAP), 576
ATS/IDSA guidelines, 258–260
case study, 257
CDC surveillance definition, 261–262
de-escalate antimicrobial therapy, 259
diagnosis and treatment, 258
duration of antimicrobial therapy, 258–259
invasive *vs.* noninvasive sampling strategies, 259–260
MRSA, 260
multidrug resistant organisms, 258
new and old strategies to prevent, 262
RCT, 260
Ventricular arrhythmias
amiodarone, 157–158
anti-arrhythmic drug therapy, 159
beta blockers, 157
cardiac sympathetic denervation, 160
case study, 153–154
diagnosis, 154–156
digoxin immune fab, 159
general measures, 156–157
lidocaine, 158–159
mechanical circulatory support
ECMO, 159–160
IABP, 159
radiofrequency catheter ablation, 160
transcoronary ethanol ablation, 160
Ventricular assist devices, 21–22
Ventricular septal rupture (VSR)
percutaneous closure, 126
timing of surgery, 126
Ventriculoperitoneal (VP) shunts, 323
Ventriculostomy catheter, 323, 358
Video-assisted thoracoscopic surgery (VATS), 185, 472, 658, 660–661
Viral hemorrhagic fever. *See* Ebola virus disease (EVD)
Viral illness, acute, 521
Viral myocarditis, 730
Viral pneumonia, 745
Virchow's triad, 222
Vitamin D supplementation, 193
Volume responsiveness
dynamic measures, 29
end-expiratory occlusion, 30
hypovolemic shock, 41
passive leg raising, 31–32
predictors of, 31
static filling pressure, 29
Voriconazole, 474–475
VSR. *See* Ventricular septal rupture (VSR)

W
"Wake-up" strokes, 309
Waldenstroms macrogloulinemia, 649
Warfarin, 531
Waterborne fever. *See* Leptospirosis
Watery diarrhea, 569
Weaning from mechanical ventilation
case study, 273
evidence contour, 275–279
management, principles, 274–275
pressure support *vs.* T-tube, 278
protocols, 275–277
telemetry monitoring, 274
Weil's disease. *See* Leptospirosis
Weil-Vasilyev disease. *See* Leptospirosis
Wells criteria, for PE, 223–224
Wernicke-Korsakoff syndrome, 597
World Society of the Abdominal Compartment Syndrome (WSACS), 688, 690, 691

Z
ZMapp, 493
Zoonosis, 517