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FIFTH EDITION

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# **GI/LIVER SECRETS Plus**

**FIFTH EDITION**

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**PETER R. McNALLY, DO, MSRF, MACG**

Chief, GI/Hepatology  
Evans Army Hospital  
Colorado Springs, Colorado

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1600 John F. Kennedy Blvd.  
Ste 1800  
Philadelphia, PA 19103-2899

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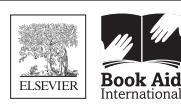
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*The editor dedicates this book to his wife, Cynthia; to his children, Alex, Meghan, Amanda, Genevieve, and Bridgette; to his grandchildren Charlotte and Xavier; and to his parents, Jeanette and Russel.*

# CONTRIBUTORS

## **Daphne Antillon, MPH**

Touro University Nevada  
Henderson, Nevada

## **Mainor Antillon, MD, MBA, MPH**

Chairman  
Gastroenterology and Hepatology  
Ochsner Clinic Foundation  
New Orleans, Louisiana

## **Fehmi Ates, MD**

Research Fellow Gastroenterology  
Hepatology and Nutrition  
Vanderbilt University  
Nashville, Tennessee

## **Mary A. Atia, MD**

Physician Gastroenterology  
Mayo Clinic Arizona  
Scottsdale, Arizona

## **Marianne Augustine, MD**

Fellow Pediatric Gastroenterology  
Hepatology and Nutrition  
The Children's Hospital of Philadelphia  
Philadelphia, Pennsylvania

## **Bruce R. Bacon, MD**

James F. King MD  
Endowed Chair in Gastroenterology  
Professor of Internal Medicine  
Division of Gastroenterology and Hepatology  
Saint Louis University School of Medicine  
St. Louis, Missouri

## **Ji Young Bang, MD, MPH**

Fellow in Gastroenterology-Hepatology  
Indiana University Medical Center  
Indianapolis, Indiana

## **Jamie S. Barkin, MD**

Professor of Medicine  
University of Miami  
Miami, Florida;  
Gastroenterology  
Mt. Sinai Medical Center  
Miami Beach, Florida

## **Devina Bhasin, MD**

Transplant Hepatologist  
Piedmont Transplant Institute  
Piedmont Hospital  
Atlanta, Georgia

## **Harikrishna Bhatt, MD**

Assistant Professor of Medicine  
Medicine, Endocrinology  
Brown University  
Providence, Rhode Island

## **Herbert L. Bonkovsky, MD**

Professor and Senior Advisor for Research  
Internal Medicine  
Carolinas Medical Center  
Charlotte, North Carolina;  
Professor Internal Medicine  
University of North Carolina  
Chapel Hill and Charlotte, North Carolina;  
Professor Internal Medicine  
University of Connecticut Health Sciences Center  
Farmington, Connecticut

## **Aaron Brzezinski, MD**

Gastroenterologist  
Center for Inflammatory Bowel Disease  
Cleveland Clinic  
Cleveland, Ohio

## **Carol Ann Burke, MD**

Director, Center for Colon Polyp and Cancer  
Prevention  
Department of Gastroenterology and Hepatology  
Cleveland Clinic  
Cleveland, Ohio

## **Wesley R. Campbell, MD**

Fellow in infectious diseases  
Walter Reed National Military Medical Center  
Bethesda, MD

## **Mitchell S. Cappell, MD, PhD**

Chief, Division of Gastroenterology and Hepatology  
William Beaumont Hospital  
Royal Oak, Michigan;  
Professor Medicine  
Oakland University William Beaumont School of  
Medicine  
Royal Oak, Michigan

## **Emily Carey, DO**

Clinical Associate  
Gastroenterology and Hepatology  
Cleveland Clinic  
Cleveland, Ohio

**William D. Carey, MD, MACG**

Professor of Medicine  
Cleveland Clinic Lerner College of Medicine  
Cleveland, Ohio;  
Staff Hepatologist  
Cleveland Clinic  
Cleveland, Ohio  
Ohio

**Joseph G. Cheatham, MD**

Assistant Professor of Medicine  
Uniformed Services University of the Health Sciences  
Bethesda, Maryland

**Vivian Cheng, MD**

Gastroenterology Division  
Beth Israel Deaconess Medical Center  
Boston, Massachusetts

**Reena V. Chokshi, MD**

Assistant Professor of Medicine  
Department of Medicine  
Division of Gastroenterology and Hepatology  
University of Connecticut Health Center  
Farmington, Connecticut

**Vito V. Cirigliano, DO, CPT(P), MC**

Fellow Gastroenterology  
Walter Reed National Military Medical Center  
Bethesda, Maryland

**John O. Clarke, MD**

Assistant Professor Medicine  
Johns Hopkins University  
Baltimore, Maryland

**Elizabeth Coss, MD, MSc**

Fellow Gastroenterology  
University of Texas Southwestern  
Dallas, Texas

**Byron Cryer, MD**

Professor of Medicine  
Digestive Diseases  
University of Texas Southwestern Medical School  
Dallas, Texas

**Scott E. Cunningham, MD, CPT(P), MC**

USA Gastroenterology Fellow National Capital  
Consortium  
Bethesda, Maryland

**Albert J. Czaja, MD**

Professor Emeritus of Medicine  
Gastroenterology and Hepatology  
Mayo Clinic College of Medicine  
Rochester, Minnesota

**Amar R. Deshpande, MD**

Associate Professor of Medicine  
Division of Gastroenterology  
Department of Medicine  
University of Miami Miller School of Medicine  
Miami, Florida

**John C. Deutsch, MD**

Staff Gastroenterologist  
Medicine  
Essential Health  
Duluth, Minnesota

**Jack A. Di Palma, MD**

Professor of Medicine and Director  
Division of Gastroenterology  
University of South Alabama  
Mobile, Alabama

**John E. Eaton, MD**

Instructor of Medicine  
Department of Internal Medicine. Division of  
Gastroenterology and Hepatology  
Mayo Clinic  
Rochester, Minnesota

**Shahan Fernando, MD**

Fellow Pediatric Gastroenterology  
Hepatology and Nutrition  
Digestive Health Institute  
Children's Hospital Colorado  
Aurora, Colorado

**James E. Fitzpatrick, MD**

Professor, Department of Dermatology  
University of Colorado Denver  
Aurora, Colorado

**Michael G. Fox, MD**

Associate Professor  
Radiology and Medical Imaging  
University of Virginia  
Charlottesville, Virginia

**Joshua Friedman, MD, PhD**

Assistant Professor, Pediatrics  
Perelman School of Medicine at the University of  
Pennsylvania  
The Children's Hospital of Philadelphia  
Philadelphia, Pennsylvania

**Glenn T. Furuta, MD**

Professor, Pediatrics  
University of Colorado School of Medicine  
Aurora, Colorado;  
Digestive Health Institute  
Children's Hospital Colorado  
Aurora, Colorado

**Phillip S. Ge, MD**

Fellow in Gastroenterology  
Division of Digestive Diseases David Geffen School  
of Medicine at UCLA  
Los Angeles, California

***John S. Goff, MD***

Rocky Mountain Gastroenterology  
Lakewood, Colorado

***Stevan A. Gonzalez, MD, MS***

Attending Physician Hepatology  
Annette C. and Harold C. Simmons  
Transplant Institute  
Fort Worth, Texas

***Geetha Gopalakrishnan, MD***

Program Director, Clinical Fellowship in Endocrinology  
Diabetes and Metabolism  
Brown University  
Hallett Center for Diabetes and Endocrinology  
East Providence, Rhode Island

***Carlos Guarner, MD, PhD***

Director, Liver Unit  
Hospital de la Santa Creu i Sant Pau  
Autonomous University of Barcelona  
Barcelona, Spain

***Ramiro L. Gutiérrez, MD, MPH, CDR, MC (UMO), USN***

Deputy Head  
Enterics Diseases Department  
Naval Medical Research Center  
Silver Spring, Maryland;  
Assistant Professor of Medicine  
Uniformed Services University of the Health Sciences  
Bethesda, Maryland

***Christina Hanson, NP-C***

South Denver Gastroenterology  
Englewood, Colorado

***Stephen A. Harrison, MD***

Chief of Hepatology  
Medicine  
Division of Gastroenterology  
Brooke Army Medical Center  
Fort Sam Houston, Texas

***Jorge L. Herrera, MD***

Professor of Medicine  
Division of Gastroenterology  
University of South Alabama College of Medicine  
Mobile, Alabama

***Brenda Hoffman, MD***

Professor of Medicine  
Division of Gastroenterology and Hepatology  
Medical University of South Carolina  
Charleston, SC

***Henry A. Horton, MD***

Staff Physician  
Department of Internal Medicine  
Cedars-Sinai Medical Center  
Los Angeles, CA

***John D. Horwhat, MD***

Assistant Professor of Medicine  
Uniformed Services  
University of the Health Sciences  
Bethesda, MD

***David P. Jones, DO, FACP, FACG, FASGE***

Gastroenterology Consultants of San Antonio,  
Private Practice San Antonio, Texas;  
Associate Professor of Medicine  
Medicine/Gastroenterology  
University of Texas Health Sciences Center  
San Antonio, Texas

***Bonnie Jortberg, PhD, RD, CDE***

Assistant Professor, Family Medicine  
University of Colorado School of Medicine  
Aurora, Colorado

***Ryan Kaliney, MD***

Radiologist  
Jefferson Radiology  
Hartford, CT

***Hayoon Kim, MD***

Resident  
VCU-St. Francis Family Medicine Program

***Christopher D. Knudsen, DO***

Clinical Instructor, Gastroenterology  
University of South Alabama College of Medicine  
Mobile, Alabama

***Cynthia W. Ko, MD, MS***

Associate Professor of Medicine  
University of Washington  
Seattle, WA

***Georgios Kokosis, MD***

Surgical Resident  
Department of Surgery  
Duke University Medical Center  
Durham, North Carolina

***Kimi L. Kondo, DO***

Associate Professor  
Department of Radiology  
Division of Interventional Radiology  
University of Colorado Anschutz Medical Campus  
Aurora, Colorado

***Burton I. Korelitz, MD, MACG***

Emeritus Chief  
Director Clinical Research  
Division of Gastroenterology  
Department of Medicine  
Lenox Hill Hospital  
New York, New York

***Marcelo Kugelmas, MD***

Gastroenterologist and Hepatologist  
South Denver Gastroenterology  
Englewood, Colorado

***Clark Kulig, MD***

Director, Porter Center for Liver Care  
Transplant Service  
Porter Adventist Hospital  
Denver, Colorado

**Ryan M. Kwok, MD**

Gastroenterology Fellow  
Department of Medicine  
Gastroenterology  
Walter Reed National Military Medical Center  
Bethesda, Maryland;  
Teaching Fellow, Internal Medicine  
Uniformed Service University of the Health Sciences  
Bethesda, Maryland

**Anthony J. LaPorta, MD, FACS**

Clinical Professor of Surgery  
University of Colorado Health Sciences Center  
Aurora, Colorado

**Nicholas F. LaRusso, MD**

Medical Director, Center for Connected Care  
Mayo Clinic  
Rochester, Minnesota;  
Charles H. Weinman Professor of Medicine  
Biochemistry and Molecular Biology  
Mayo Clinic College of Medicine  
Rochester, Minnesota;  
Distinguished Investigator  
Mayo Foundation  
Rochester, Minnesota

**Bret A. Lashner, MD**

Professor of Medicine  
Gastroenterology and Hepatology  
Cleveland Clinic  
Cleveland, Ohio

**Sum P. Lee, MD, PhD**

Professor & Dean of Medicine  
Li Ka Shing Faculty of Medicine  
University of Hong Kong  
Professor Emeritus  
Division of Gastroenterology  
University of Washington  
School of Medicine  
Seattle, Washington

**Linda S. Lee, MD**

Assistant Professor of Medicine  
Harvard Medical School  
Director, Endoscopic Education, Women's Health in  
GI, IMPACT (Interdisciplinary Management of  
Pancreatic Cystic Tumors)  
Clinic Brigham and Women's Hospital  
Boston, Massachusetts

**Daniel A. Leffler, MD, MS**

Director of Clinical Research  
Celiac Center  
Beth Israel Deaconess Medical Center  
Boston, Massachusetts;  
Director of Quality Assurance  
Gastroenterology  
Beth Israel Deaconess Medical Center  
Boston, Massachusetts;  
Associate Professor  
Medicine Harvard Medical School  
Boston, Massachusetts

**Anthony Lembo, MD**

Director of GI Motility Center  
Beth Israel Deaconess Medical Center  
Boston, Massachusetts;  
Associate Professor  
Medicine Harvard Medical School  
Boston, Massachusetts

**Carole Macaron, MD**

Cleveland Clinic  
Gastroenterology and Hepatology  
Digestive Disease Institute  
Cleveland, Ohio

**Catherine S. Manolakis, MD**

Fellow Gastroenterology  
University of South Alabama College of Medicine  
Mobile, Alabama

**Richard W. McCallum, MD, FACP, FRACP (Aust), FACG**

Professor and Founding Chair of Medicine  
Department of Internal Medicine  
Director  
Center for Neurogastroenterology and GI Motility  
Texas Tech University Health Sciences Center  
Paul L. Foster School of Medicine  
El Paso, Texas

**Martin D. McCarter, MD**

Professor GI, Tumor, and Endocrine Surgery  
University of Colorado School of Medicine  
Aurora, Colorado

**Peter R. McNally, DO, MSRF, MACG**

Chief, Gastroenterology/Hepatology  
Evans Army Hospital  
Colorado Springs, Colorado;  
Center for Human Simulation  
University of Colorado School of Medicine  
Aurora, Colorado

**Gil Y. Melmed, MD, MS**

Director, Clinical Inflammatory Bowel Disease  
Department of Medicine  
Cedars-Sinai Medical Center  
Los Angeles, California

**Fouad Joseph Moawad, MD, FACC**

Director of Motility and Reflux Testing Lab  
Walter Reed National Military Medical Center  
Bethesda, Maryland

**Enrique Molina, MD**

Gastroenterologist and Hepatologist  
Gastroenterology Consultants  
Memorial Healthcare System  
Hollywood, Florida

**Klaus E. Mönkemüller, MD, PhD**

Director Hirschowitz Endoscopy Center  
Division of Gastroenterology & Hepatology  
Professor of Medicine, University of Alabama  
Birmingham, Alabama

***Francis C. Okeke, MD, MPH***

Postdoctoral Clinical Fellow  
Gastroenterology (Neurogastroenterology)  
Johns Hopkins University  
Baltimore, Maryland

***Kiyoko Oshima, MD***

Associate Professor  
Pathology  
Medical College of Wisconsin  
Milwaukee, Wisconsin

***Theodore N. Pappas, MD***

Professor of Surgery  
Chief, Division of General & Advanced GI Surgery  
Duke University Medical Center  
Durham, North Carolina

***Angelo H. Paredes, MD***

Gastroenterology, Internal Medicine  
Walter Reed Army Medical Center  
Bethesda, Maryland

***Gail Pearson, FNP-C***

Nurse Practitioner  
South Denver Gastroenterology  
Englewood, Colorado

***Shajan Peter, MD***

Associate Professor of Medicine  
Division of Gastroenterology-Hepatology  
University of Alabama School of Medicine  
Birmingham, Alabama

***Lori D. Prok, MD***

Assistant Professor  
Pediatric Dermatology and Dermatopathology  
University of Colorado Denver  
Aurora, Colorado

***Siobhan Proksell, BS, MD***

Resident, Internal Medicine  
Post Graduate Year 3  
University of Pittsburgh Medical Center  
Pittsburgh, Pennsylvania

***Ramona O. Rajapakse, MD, FRCP(UK)***

Associate Professor of Clinical Medicine  
Medicine  
Division of Gastroenterology  
Stony Brook University Hospital  
Stony Brook, New York

***Francisco C. Ramirez, MD***

Professor of Medicine  
Gastroenterology  
Mayo Clinic  
Scottsdale, Arizona

***Michael Reiter, DO***

Associate Professor of Clinical Radiology  
Stony Brook University Hospital  
Stony Brook, New York

***Joel E. Richter, MD, FACP, MACG***

Professor and Director  
Division of Digestive Diseases and Nutrition

University of South Florida

Tampa, Florida;  
Director Joy McCann Culverhouse Center for  
Swallowing Disorders  
University of South Florida  
Tampa, Florida

***Mark S. Riddle, MD, MPH&TM, DrPH***

Enteric Diseases Department  
Naval Medical Research Center  
Silver Spring, Maryland

***Jason R. Roberts, MD***

Assistant Professor, Gastroenterology  
Hepatology and Nutrition  
University of Louisville School of Medicine  
Louisville, Kentucky

***Arvey I. Rogers, MD, FACP, MACG***

Professor Emeritus, Internal Medicine  
Gastroenterology  
Miller School of Medicine  
University of Miami  
Miami, Florida  
USA

***Suzanne Rose, MD, MSEd***

Senior Associate Dean for Education  
Professor of Medicine  
University of Connecticut School of Medicine  
Farmington, Connecticut

***Kevin Rothchild, MD***

Assistant Professor  
GI, Tumor, and Endocrine Surgery  
University of Colorado Hospital  
Aurora, Colorado

***Bruce A. Runyon, MD***

Director of Hepatology  
Santa Monica-UCLA Medical Center  
Clinical Professor of Medicine  
Division of Digestive Diseases David Geffen School of  
Medicine at UCLA  
Los Angeles, California

***Paul D. Russ, MD***

Professor Radiology  
University of Colorado School of Medicine  
Aurora, CO

***Mark W. Russo, MD, MPH, FACP***

Medical Director of Liver Transplantation  
Hepatology  
Carolinas Medical Center  
Charlotte, North Carolina

***Travis J. Rutland, MD***

Digestive Health Specialists  
Dothan, Alabama

***Davinder Sandhu, MBBCh, FRCP***

Fellow Division of Gastroenterology  
University of Washington  
Seattle, WA

**Lawrence R. Schiller, MD**

Attending Physician  
Digestive Health Associates of Texas  
Baylor University Medical Center  
Dallas, Texas

**Jonathan A. Schoen, MD**

Assistant Professor of Surgery  
GI, Tumor, and Endocrine Surgery  
University of Colorado Hospital  
Aurora, CO

**Raj J. Shah, MD, FASGE, AGAF**

Associate Professor of Medicine  
Gastroenterology  
University of Colorado School of Medicine  
Aurora, Colorado;  
Director Pancreaticobiliary Endoscopy and Medical  
Co-Director Digestive Health Center  
Gastroenterology  
University of Colorado Anschutz Medical Campus  
Aurora, Colorado

**Roshan Shrestha, MD**

Chairman, Department of Transplantation  
Medical Director of Liver Transplantation  
Piedmont Transplant Institute, Atlanta, GA  
Clinical Professor of Medicine  
Mercer University School of Medicine  
Savannah, Georgia

**Won S. Song, MD**

Chief, Nuclear Medicine Service  
Department of Radiology  
Womack Army Medical Center  
Fort Bragg, North Carolina

**Luca Stocchi, MD**

Staff Surgeon  
The Story-Garschina Chair in Colorectal  
Surgery  
Colorectal Surgery  
Digestive Disease Institute  
Cleveland Clinic  
Cleveland, Ohio

**Lisa Strate, MD, MPH**

Associate Professor of Medicine  
Department of Medicine  
Division of Gastroenterology  
University of Washington School of Medicine  
Seattle, Washington

**Joseph K. Sunny, Jr., MD**

Senior Fellow  
Division of Gastroenterology, Hepatology and Nutrition,  
Texas Tech University Health Sciences Center  
Paul L. Foster School of Medicine  
El Paso, Texas

**Christina M. Surawicz, MD**

Professor Medicine  
Division of Gastroenterology  
University of Washington  
Seattle, Washington

**Jayant A. Talwalkar, MD, MPH**

Professor of Medicine  
Gastroenterology/Hepatology  
Mayo Clinic  
Rochester, Minnesota

**Shalini Tayal, MD**

Associate Professor  
Department of Pathology  
Denver Health Medical Center  
Denver, Colorado  
University of Colorado School of Medicine  
Aurora, Colorado

**John J. Tiedeken, MD**

General Surgeon  
Tiedeken General Surgery  
Sacramento, California

**Dawn M. Torres, MD**

Chief Hepatology, Walter Reed National Military  
Medical Center  
Bethesda, Maryland

**George Triadafilopoulos, MD, DSc**

Clinical Professor of Medicine  
Division of Gastroenterology and Hepatology  
Stanford University School of Medicine  
Stanford, California

**James F. Trotter, MD**

Medical Director of Transplant  
Hepatology  
Baylor University Medical Center  
Dallas, Texas

**Michael F. Vaezi, MD, PhD, MS**

Professor of Medicine  
Clinical Director  
Division of Gastroenterology and Hepatology  
Vanderbilt University Medical Center  
Director, Center for Swallowing and Esophageal  
Disorders  
Director, Clinical Research  
Vanderbilt University Medical Center  
Nashville, Tennessee

**Nimish B. Vakil, MD, FACP, FACG, AGAF, FASGE**

Clinical Professor of Medicine  
University of Wisconsin School of Medicine  
and Public Health  
Madison, Wisconsin

**Rohini R. Vanga, MBBS, MD**

Fellow Gastroenterology  
Baylor College of Medicine  
Houston, Texas

**Shyam Varadarajulu, MD**

Medical Director, Center for Interventional Endoscopy  
Florida Hospital Orlando, Florida;  
Professor of Medicine  
University of Central Florida College of Medicine  
Orlando, Florida

**Stephen M. Vindigni, MD, MPH**

Fellow of Gastroenterology  
University of Washington School of Medicine  
Seattle, Washington

**Jill M. Watanabe, MD, MPH**

Associate Professor of Medicine  
Division on General Internal Medicine  
University of Washington School of Medicine;  
Harborview Medical Center  
Seattle, Washington

**Sterling G. West, MD, MACP, FACP**

Professor of Medicine  
Department of Medicine

**Division of Rheumatology**

University of Colorado School of Medicine  
Aurora, Colorado

**C. Mel Wilcox, MD, MSPH**

Professor of Medicine  
Division of Gastroenterology and Hepatology  
University of Alabama at Birmingham  
Birmingham, Alabama

**Cemal Yazici, MD**

Fellow in Gastroenterology and Hepatology  
Division of GI-Hepatology  
Department of Medicine  
University of Illinois at Chicago  
Chicago, Illinois

**Patrick E. Young, MD**

Fellowship Program Director Gastroenterology  
Walter Reed National Military Medical Center  
Bethesda, Maryland;  
Associate Professor Medicine  
Uniformed Services University of Health Sciences  
Bethesda, Maryland

# PREFACE

To practice the art of medicine, one must learn the secrets of pathophysiology, diagnosis and therapy. In this text, you will find the answers to many questions about the hepatic and digestive diseases. We hope that medical students, residents, fellows, and, yes, even attending physicians will find the fifth edition of *GI/Liver Secrets Plus* instructive and insightful.

As editor, I wish to thank James Merritt, Kelly McGowan and the staff at Elsevier for their wonderful support of this project and their courage and determination to make this book available on the web. I am most appreciative of all my contributing authors who have shared their invaluable secrets and made this book an enjoyable, as well as an educational, experience.

**Peter R. McNally, DO, MSRF, MACG**

# TOP 100 SECRETS

Peter R. McNally, DO, MSRF, MACG

1. **Runyon criteria** for diagnosis of secondary bacterial peritonitis (based on presence of two the following three ascitic fluid criteria):
  - Total protein more than 1 g/dL
  - Glucose less than 50 mg/dL
  - Lactate dehydrogenase (LDH) more than 225 mU/mL (or > upper limit of normal [ULN] for serum)

It is important to differentiate spontaneous bacterial peritonitis (SBP) from *secondary bacterial peritonitis* in cirrhotic patients, because treatment for SBP is medical, whereas treatment for *secondary bacterial peritonitis* is usually surgical. Patients with Runyon criteria for *secondary bacterial peritonitis* must be evaluated promptly by abdominal computed tomography imaging and early surgical consultation.
2. In Central and South America, Chagas disease is a multisystem infectious disease caused by the protozoan *Trypanosoma cruzi* and transmitted by bites from the Reduvid (kissing) bug. Ganglion cells are destroyed throughout the body, resulting in megaesophagus, duodenum, colon, and rectum. Esophageal Chagas disease is identical to idiopathic achalasia.
3. ALL individuals born in between 1945 and 1965 should have a once in a lifetime test for hepatitis C virus (HCV) exposure, regardless of risk factors (HCV Cohort Screening).
4. Suspected variceal bleeding requires additional preendoscopic medical therapy with antibiotics and octreotide.
5. Eighty-five percent of cases of lower gastrointestinal bleeding are self-limited and uncomplicated, and urgent colonoscopy versus elective colonoscopy has not been proven to change clinical or cost outcomes.
6. Dysphagia is common after a stroke (at least 25% of patients) and is a risk factor for pneumonia and aspiration. In most stroke patients dysphagia will improve and percutaneous gastrostomy should be avoided for at least the first 2 weeks.
7. Aspiration of amebic abscess should be considered under the following circumstances:
  - When pyogenic abscess or secondary infection of an amebic abscess cannot be excluded
  - When the patient does not respond to 5 to 7 days of adequate therapy
  - When the abscess is very large, usually greater than 5 cm, or in the left lobe, which are risk factors for rupture and causes severe pain
8. The combination of ulcerative colitis (UC) and primary sclerosing cholangitis (PSC) is more often associated with pancolitis, less endoscopic activity, backwash ileitis, rectal sparing, an increased risk of pouchitis, peristomal varices after proctocolectomy with ileostomy, and colon cancer when compared with chronic UC not associated with PSC.
9. Symptoms of esophageal obstructive dysphagia have been shown to correlate with luminal diameter smaller than 13 mm, and symptoms are unlikely at luminal diameter larger than 20 mm.
10. Vertical transmission of HCV occurs in 2% to 10% for infants born of HCV-RNA positive mothers. The risk for vertical transmission increases dramatically with mothers coinfecte with HCV and human immunodeficiency virus and those with HCV RNA of more than 1 million copies. There is no evidence that HCV is transmitted in breast milk.
11. Scleroderma is associated with esophageal motility disorders in greater than 90% of patients.
12. Colonoscopy colon cancer screening recommendations, by risk group:  
*Patients with average risk and asymptomatic screening:*
  - All men and women 50 years or older
  - Exception: African Americans 45 years or older
  - Repeat colonoscopy every 10 years, after a negative examination*For patients found to have multiple or large polyps:*
  - Colonoscopy at the time of initial polyp diagnosis.
  - If 1 to 2 small adenomatous polyps with low grade abnormality, repeat in 5 to 10 years.

- If 3 to 10 adenomatous polyps or 1 adenomatous polyp greater than 1 cm, repeat colonoscopy within 3 years after polyp removal.
- With certain types of polyps or with high-grade abnormality, repeat colonoscopy within 3 years. If normal, repeat again in 5 years.
- If more than 10 adenomatous polyps, repeat in less than 3 years.
- If polyps are permanently attached and not on a stem and are removed in portions, repeat colonoscopy in 2 to 6 months to verify complete polyp removal.

*Patients with prior surgery for colorectal cancer:*

- Colonoscopy within 1 year after surgery; if normal, repeat in 3 years; if still normal, repeat in 5 years.

*Persons with family history of colon cancer:*

- Colonoscopy at age 40 or 10 years before the age that the index family member was diagnosed with cancer or colon adenomatous polyps, whichever is earlier; if normal, repeat every 5 years.

*Persons with a family history of familial adenomatous polyposis:*

- At age 10 to 12, annual flexible sigmoidoscopy.
- If positive genetic test, colon removal should be considered because of very high risk of colorectal cancer.

*People with a family history of hereditary nonpolyposis colon cancer (Lynch syndrome):*

- Colonoscopy every 1 to 2 years, starting at age 20 to 25 or 10 years before age that immediate family member had cancer, whichever is earlier.
- Genetic testing should be offered to first-degree family members.

*Persons with inflammatory bowel disease (IBD):*

- Colonoscopy every 1 to 2 years, starting 8 years after the start of pancolitis (involvement of the entire colon) or 12 to 15 years after the start of left-sided colitis.

13. Antimitochondrial antibodies (AMA) are highly specific (95%-98%) for primary biliary cirrhosis (PBC). When clinical suspicion for PBC is high and AMA is negative, a liver biopsy should be performed to establish the diagnosis of AMA (-) PBC.
14. Autoimmune pancreatitis is associated with other autoimmune disorders such as autoimmune hepatitis, PSC, PBC, Sjögren's syndrome, and scleroderma. It is characterized by the presence of autoantibodies, increased serum immunoglobulin (Ig) levels, elevated IgG4 levels in the serum (usually above 140 mg/dL), and a response to administration of corticosteroids. There is a recurrence rate of approximately 41% upon discontinuation of steroids.
15. Acetaminophen hepatotoxicity is the most common cause of acute liver failure in the United States. Risk factors for poor prognosis associated with acetaminophen hepatotoxicity include pH of less than 7.3 or international normalized ratio of more than 6.5, creatinine of more than 3.4, and grade 3 or higher encephalopathy. The N-acetylcysteine antidote should be given in all cases of potential acetaminophen overdose.
16. Vedolizumab is a highly selective monoclonal antibody targeting the α4β7 integrin receptor found on the surface of T-cell homing to the lymphoid tissues of the gastrointestinal tract. It has been shown to be effective in inducing response and remission of ulcerative colitis.
17. A combined esophageal pH/impedance catheter performed off proton pump inhibitors can help distinguish acid reflux from non-acid reflux and esophageal hypersensitivity from functional heartburn.
18. The diagnosis of achalasia should be entertained in young women with suspected eating disorders and patients with intractable gastroesophageal reflux disease (GERD) symptoms and a stricture not responding to dilation.
19. Metastatic carcinoma to the esophagus is unusual, but melanoma and breast cancer are the most common.
20. Liver transplantation will definitively cure an underlying hypercoagulable state caused by protein C, protein S, or antithrombin deficiency. Patients with other underlying hypercoagulable states require long-term anticoagulation.
21. Endoscopic ultrasound (EUS) fine-needle aspiration should **not** be performed with suspected pheochromocytomas because of the risk of hypertensive crisis, and possible hepatic carcinoid metastases should not be sampled, because of the risk of profound hypotension.
22. Avoid antibiotics when *Escherichia coli* such as O157:H7 infection is suspected because of the risk of hemolytic uremic syndrome.
23. The diagnosis of insulinoma is suggested by the presence of Whipple's triad (i.e., symptoms of hypoglycemia, blood sugar levels of less than 70 mg/dL, and resolution of symptoms with food).

24. The risk of cancer in Barrett's esophagus is 0.5% per year, which means that approximately 1 in 200 patients with Barrett's esophagus will develop esophageal cancer each year.
25. The central scar in focal nodular hyperplasia is hyperintense on T2-weighted (T2-w) images, but in fibrolamellar hepatocellular carcinoma (HCC), it is hypointense on T2-w images.
26. Magnetic resonance imaging is accurate in differentiating HCC from dysplastic nodules, with HCC usually having increased T2-w signal and dysplastic nodules having decreased T2-w signal.
27. Hallmarks of ischemic hepatitis (shock liver) include marked elevations in aspartate transferase (AST), alanine aminotransferase (ALT) (10 times the ULN), bilirubin, prothrombin time (PT), and LDH levels after an episode of systemic hypotension or decreased cardiac output.
28. A patient presenting with chest pain and crepitus after an episode of persistent vomiting and retching should prompt a diagnosis of Boerhaave's syndrome.
29. Evaluate for HCC in cirrhotic patients with a new diagnosis of portal vein thrombosis.
30. The two most common causes of acute cholestatic hepatitis are hepatitis A and drug-induced liver injury.
31. Plummer-Vinson syndrome is a triad of an esophageal web, iron deficiency anemia, and glossitis.
32. The most important studies to order on ascitic fluid are cell count and differential, gram stain and bacterial culture, albumin, total protein, and cytologic examination (only when peritoneal carcinomatosis is suspected).
33. Combination therapy with Ledipasvir and Sofosbuvir has been shown to be extremely effective in the treatment of chronic hepatitis C. Sustained virologic response rates of 99% have been reported after 12 weeks of treatment with this combination of NS5A and NS5B inhibitors.
34. EUS fine needle aspiration should not be performed with suspected pheochromocytomas because of the risk of hypertensive crisis, and possible hepatic carcinoid metastases should not be sampled because of the risk of profound hypotension.
35. Patients with cirrhosis who consumed raw oysters were 80 times more likely to develop *Vibrio vulnificus* infection and 200 times more likely to die of the infection.
36. Women with IBD have higher rates of cervical dysplasia and cancer-causing human papillomavirus (HPV) serotypes, particularly if on immunosuppression for longer than 6 months. The HPV vaccine is recommended for women and men ages 9 to 26 years.
37. In patients with acute severe (fulminant) autoimmune hepatitis, treat with prednisolone alone because prednisone is a prodrug and azathioprine has a slow onset of action.
38. Acute onset diarrhea during hospitalization is most likely due to *Clostridium difficile*.
39. Patients should be considered for liver transplantation if they have a Model of End-Stage Liver Disease score of 15 or more, or life-threatening complications such as ascites, encephalopathy, portal hypertensive bleeding, jaundice, weight loss, or HCC.
40. Frontline therapy with budesonide in combination with azathioprine has the strongest rationale in asymptomatic, noncirrhotic patients with mild autoimmune hepatitis disease and no concurrent immune diseases or in older adults with osteopenia.
41. Endoscopy is the most valuable procedure for evaluation of upper and lower gastrointestinal symptoms in patients with acquired immune deficiency syndrome.
42. The serum-ascites albumin gradient (SAAG) is calculated by:

$$\text{SAAG} = \text{albumin}_{\text{serum}} - \text{albumin}_{\text{ascites}}$$

The SAAG is a useful tool in the classification of ascites. Patients with gradients of 1.1 g/dL or more have portal hypertension, whereas patients with gradients less than 1.1 g/dL do not have portal hypertension.

43. A leiomyoma is benign proliferation of spindled smooth muscle cells that strongly react with smooth muscle actin (SMA) and desmin, but are negative for CD117. A gastrointestinal stromal tumor (GIST) is composed of a proliferation of spindle cells that react strongly with CD117 and CD34. Malignant potential for GIST depends on the extent of mitotic activity, necrosis, and cytological atypia.
44. The treatment of vasculitis caused by hepatitis B or C infection must include antiviral therapy to eliminate the antigenemia.

45. The most common causes of acute liver failure in the United States are acetaminophen (46%), indeterminate (14%), drug-induced (11%), hepatitis B (6%), autoimmune hepatitis (6%), ischemia (4%), hepatitis A (3%), and other (9%).
46. All patients with an inflammatory small joint arthritis, positive rheumatoid factor, and elevated liver-associated transaminase levels should have chronic hepatitis C infection ruled out before receiving the diagnosis of rheumatoid arthritis.
47. *Helicobacter pylori* infection is believed to be acquired during childhood and is associated with low socioeconomic status. The presence of the *H. pylori* cagA gene is associated with more severe gastroduodenal disease (i.e., ulcers).
48. Type I hepatorenal syndrome is characterized by a rapid and progressive reduction of renal function, defined by a doubling of the initial serum creatinine to a level greater than 2.5 mg/dL or a 50% reduction in the initial 24-hour creatinine clearance to a level less than 20 mL/min in less than 2 weeks. Clinical presentation is acute renal failure.
49. Elevated gastrin level and a gastric carcinoid suggest that achlorhydria is likely. Check a vitamin B<sub>12</sub> level.
50. The ascitic fluid neutrophil count is the single most important test for detecting bacterial infection of peritoneal fluid. An absolute neutrophil count of 250 cells/mm<sup>3</sup> or more warrants empiric antibiotic treatment with cefotaxime.
51. Refractory celiac disease (RCD) is defined by persistent or recurrent malabsorptive symptoms and signs with villous atrophy despite a strict gluten-free diet for more than 12 months. RCD is uncommon, affecting 1% to 2% of patients with celiac disease (CD). Type I RCD is identified by polyclonal intraepithelial lymphocyte infiltration in the small intestinal mucosa similar to that seen in untreated CD. Type II RCD is recognized by monoclonal aberrant CD3 positive T lymphocytes that lack expression of CD8. Traditional treatment for both type I and II RCD, consists of systemic corticosteroids, budesonide or azathioprine. Type II RCD carries a less favorable prognosis because of the risk for malignant transformation to enteropathy-associated T-cell lymphoma.
52. Essential mixed cryoglobulinemia is due to chronic hepatitis C infection in more than 90% of patients.
53. All patients with a systemic medium or small vessel vasculitis should be evaluated for chronic hepatitis B and C infection.
54. Antibiotic therapy for *H. pylori* can cure a large proportion of patients with MALT lymphoma, even in the absence of documented *Helicobacter* infection.
55. JAK2 mutations are strongly implicated in the pathogenesis of myeloproliferative disorders and hypercoagulability. Anywhere from 30% to 50% of patients with Budd Chiari syndrome exhibit JAK2 mutation.
56. Botox therapy for achalasia can provide clinical improvement within 1 month in more than 80% of patients, but less than 60% are in remission at 1 year.
57. Hepatitis A virus (HAV) and hepatitis B virus (HBV) vaccines are strongly recommended in patients with cirrhosis as concomitant infection dramatically increases morbidity and mortality.
58. Key predictors of the malignant potential for GISTS are size larger than 3 cm and more than 10 mitotic figures per high powered field.
59. *Herpes simplex* hepatitis can be fulminant during pregnancy and associated with high mortality rates. Patients present in the third trimester with fever, systemic symptoms, and possibly vesicular cutaneous rash. Associated pneumonitis or encephalitis may be present. Liver biopsy is characteristic, showing necrosis and inclusion bodies in viable hepatocytes, along with few or no inflammatory infiltrates. Response to acyclovir therapy is prompt; there is no need for immediate delivery of the baby.
60. Sixty percent of patients with gastroparesis have concomitant small intestinal bacterial overgrowth (SIBO) based on breath testing data. Some symptoms of postprandial bloating in gastroparesis may be explained by SIBO and responsive to therapy with antibiotics, probiotics, and promotility agents.
61. Gilbert's syndrome is common benign disorder seen in the United States ( $\approx$ 5% white population). It is characterized by elevations of unconjugated bilirubin (2-7 mg/dL), which is often more pronounced after fasting or illness. There is no increased risk for liver disease with Gilbert's Syndrome.
62. Chronic pancreatitis may lead to splenic vein thrombosis in approximately 12% of patients.
63. Kayser-Fleischer (KF) rings are virtually always present when there are neurologic features of Wilson disease. Demonstration of KF rings often requires a slit lamp examination. The absence of KF rings does not exclude Wilsonian liver disease and KF rings have rarely been reported in other conditions (e.g., PBC).

64. Hereditary hemochromatosis gene testing should be done to evaluate unexplained elevations in ferritin ( $>300 \text{ ng/mL}$ ) and transferrin saturation ( $>45\%$ ).
65. UC and Crohn's colitis are present in at least 70% to 80% of patients with PSC. In contrast, only 5% of patients with IBD will have concurrent PSC.
66. The ZZ phenotype of  $\alpha 1$ -antitrypsin deficiency is the most likely to cause liver disease.
67. Nonepidermolytic palmoplantar keratoderma (Tylosis) is a rare autosomal-dominant disorder defined by a genetic abnormality at chromosome 17q25, that confers 95% lifetime risk of squamous cell esophageal carcinoma. It is characterized by hyperkeratosis of the palms and soles, as well as by thickening of the oral mucosa.
68. Wilson disease is diagnosed with a ceruloplasmin less than 20 mg/dL, KF rings, urine copper of more than 40 mcg/24 h, and most precisely by hepatic copper levels of more than 250 mcg/g dry weight.
69. Autoimmune hepatitis should be considered with the presence of antinuclear antibodies, SMA, liver-kidney microsomal 1 titers greater than 1:80 and AST and ALT elevations (5-10 times the ULN).
70. The reported incidence of malignancy within a congenital bile duct cyst ranges from 10% to 30%.
71. Consider testing for HBV exposure in most individuals born outside of the United States.
72. The risk for acute HBV to become chronic hepatitis varies inversely by the age at which acute infection occurs: 90% HBV chronicity for perinatal (vertical) acquired infection, 20% to 50% HBV chronicity for infection during the ages of 1 to 5 years, and 5% chronicity for adult-acquired HBV infection.
73. Celiac Disease (CD) evaluation is divided into diagnostic and confirmatory testing:

### **Diagnostic Testing**

- Preferred test IgA anti-tissue transglutaminase (TTG)
  - If IgA is normal: 95% sensitive and specific
  - Poor test, if IgA deficient
- If IgA deficient: deamidated gliadin peptides (DGPs)
  - Alternative test IgG TTG
- DQ2 and HLA-DQ8 is an excellent negative predictive test
- In children younger than 2 years, IgG TTG alone or with DGP
- All patients should be on gluten-containing diet before antibody testing

**Confirmatory Testing** Duodenal biopsy ( $\geq 2$  duodenal bulb and  $\geq 4$  from second and third duodenum)  
Histologic findings consistent with Marsh or Corazza criteria

74. All patients about to start immunosuppressive therapy should be tested for hepatitis B infection. If positive for the hepatitis B surface antigen antiviral therapy should be started even if ALT levels are normal and levels of hepatitis B DNA are low or nondetectable.
75. Vertical transmission of HBV is common. Mothers who are e-antigen positive and have a viral load exceeding 200,000 IU/mL have a 7% to 9% risk of transmitting the infection despite passive and active immunization of the newborn.
76. Extraintestinal manifestations of IBD occur in approximately 30% of patients and include uveitis, scleritis, episcleritis, pyoderma gangrenosum, erythema nodosum, peripheral arthritis, axial arthritis, PSC, aphthous stomatitis, thromboembolic events, and oxalate-nephrolithiasis.
77. PSC is associated with malignancies that include cholangiocarcinoma, gallbladder cancer, colorectal cancer (when associated with IBD), and HCC (when cirrhosis is present).
78. Ursodeoxycholic acid is the treatment of choice for PBC, but response is less likely in men, those diagnosed at an earlier age, patients with cirrhosis, and individuals who do not demonstrate biochemical improvement.
79. Eosinophilic esophagitis is the most common cause for acute food impaction.
80. Minocycline and nitrofurantoin account for 90% of all drug-induced autoimmune-like hepatitis.
81. If traveling within 4 weeks to an endemic area for HAV, one should receive immunoprophylaxis with anti-HAV Ig as it takes 4 weeks after vaccination to develop adequate immunity.
82. Hereditary pancreatitis genetic abnormalities include mutations in the cationic trypsinogen gene (PRSS1), pancreatic secretory trypsin inhibitor (SPINK1), and cystic fibrosis transmembrane conductance regulator (CFTR) genes have been confirmed as major risk factors for chronic pancreatitis.

83. Prednisolone 40 mg daily for 28 days improves survival for alcohol hepatitis, if the **Maddrey discriminant function** (**Formula:  $4.6 \times (\text{PT} - \text{Control PT}) + \text{Tbili}$** ) is 32 or more. Contraindications to treatment of alcoholic hepatitis with prednisolone include renal failure, gastrointestinal bleeding, and active infection.
84. Drugs can cause gallbladder stones. Remember, ceftriaxone is excreted into bile and may precipitate with calcium sludge in the gallbladder, and progestins, oral contraceptives, and octreotide (somatostatin) impair gallbladder emptying and promote gallbladder sludge and stone formation.
85. Any cause of cirrhosis is an indication to screen for esophageal varices and HCC.
86. Individuals with more than 6 months of abstinence from alcohol and decompensated alcohol cirrhosis do well with liver transplantation. Unfortunately, alcohol recidivism still remains common after liver transplantation.
87. Suspect Budd-Chiari Syndrome among females on oral contraceptives or who are pregnant, with chronic dull abdominal pain, new-onset ascites, edema of lower extremities, and elevated liver enzymes.
88. The combination of octreotide and midodrine has also been demonstrated to be an important treatment for type 1 hepatorenal syndrome.
89. The probability of survival after the first onset of ascites has been estimated at 50% and 20%, after 1 and 5 years of follow-up, respectively. The prognosis is even worse in patients with diuretic-resistant ascites; the 1-year survival rate is 25%. Because the 1-year survival rate after liver transplantation is greater than 75%, patients with cirrhosis who develop ascites should be considered for liver transplantation.
90. In type II hepatorenal syndrome, renal failure does not have such a rapidly progressive course. These patients develop a clinical picture of refractory ascites.
91. Treatment of amebic abscess consists of metronidazole followed by an intraluminal amebicide.
92. Management of suspected SBP includes paracentesis: send ascitic fluid for cell count and differential, albumin, protein, gram stain, and culture. If ascitic fluid neutrophils are  $250 \text{ cells/mm}^3$  or more, or high clinical suspicion exists for SBP, then *immediately* start cefotaxime 2 g intravenously, dosed every 8 hours. If nosocomial or cephalosporin-resistant SBP is suspected, then consider starting a carbapenem.
93. Diagnostic liver biopsy findings for PBC and PSC:
  - PBC: a florid bile duct lesion (nonsuppurative destructive cholangitis), characterized by biliary epithelial damage, basement membrane destruction and lymphoplasmacytic infiltrate. Noncaseating granulomas are seen in up to 25% of cases.
  - PSC: findings of onion skin fibrosis and reduced number of bile ducts is diagnostic, but present in less than 40% of the liver biopsies.
94. Clinical signs in pancreatic carcinoma (PC) include:
*Courvoisier sign:* A palpable, distended, gallbladder in the right upper quadrant in a patient with jaundice resulting from bile duct obstruction secondary to PC. However, this finding is not specific to PC. Patients with distal cholangiocarcinoma or an ampullary mass may present similarly.
*Trousseau's syndrome:* Manifestation of pancreatic cancer as superficial or deep vein thrombosis.
95. Small Intestinal Bacterial Overgrowth (SIBO) is common and should be considered in any case of unexplained diarrhea.
96. *H. pylori* infection does not have an important role in the pathogenesis of gastroesophageal reflux disease.
97. The most common mechanism of GERD is transient lower esophageal sphincter relaxation (TLESR). These TLESRs permit reflux of the “acid pocket,” a layer of unbuffered acidic gastric juice that sits on top of a meal, to reflux in the postprandial period.
98. Transarterial chemoembolization (TACE) with drug-eluting beads is commonly used to control HCC tumor burden in patients considered for liver transplantation.
99. Selective internal radiation therapy with Yttrium-90 microspheres for colorectal liver metastases or HCC requires prior embolization of the gastroduodenal artery and other feeding celiac and SMA branches to prevent posttreatment ulceration of the stomach and duodenum.
100. Hepatic hydrothorax is defined as the accumulation of ascitic fluid in the pleural space in a patient with cirrhosis, in whom cardiac, pulmonary, or pleural causes have been excluded. Approximately 5% to 10% of patients with cirrhotic ascites develop hepatic hydrothorax (70% right sided). Approximately 10% of patients with cirrhosis admitted to the hospital with hepatic hydrothorax have a spontaneous bacterial empyema and 40% of these episodes are not associated with SBP. A diagnostic thoracocentesis in these patients is useful to evaluate for other causes of pleural effusion and to diagnose spontaneous bacterial empyema. Chest tube insertion is contraindicated in patients with simple hepatic hydrothorax and can lead to rapid clinical deterioration.

# SWALLOWING DISORDERS AND DYSPHAGIA

Francis C. Okeke, MD, MPH, and John O. Clarke, MD

## 1. What is the definition of *dysphagia*?

*Dysphagia* derives from the Greek words *dys* (which means difficult) and *phagia* (which means “eating”), and refers to a subjective difficulty or abnormality in swallowing, or passage of food or liquid from the mouth to stomach.

## 2. What is the definition of *odynophagia*?

*Odynophagia* derives from the Greek roots *odyno* (which means pain) and *phagia* (which means “eating”), and refers to pain with swallowing. *Odynophagia* can accompany *dysphagia* or exist independently.

## 3. What is the definition of *globus sensation*?

*Globus sensation* is defined as an intermittent or persistent sensation of a foreign body or lump in the throat between meals and in the absence of *dysphagia* or *odynophagia*. This was previously referred to as *globus hystericus* because of erroneous suspicion by prior generations of physicians that the cause may stem from factors produced by the uterus.

## 4. What are the different phases of normal swallowing?

Swallowing can be separated into three distinct phases. The *oral preparatory/transfer phase* occurs when food is voluntarily chewed, mixed with saliva, and transferred to the back of the tongue. The *pharyngeal phase* occurs when the bolus is propelled from the pharynx across the relaxed upper esophageal sphincter. The *esophageal phase* occurs when the bolus is transferred by peristalsis through the esophagus and across the lower esophageal sphincter into the stomach. The pharyngeal and esophageal phases are mediated by reflexes and are involuntary.

## 5. Is *dysphagia* an alarm symptom?

Yes. The presence of *dysphagia* suggests an organic abnormality and mandates additional evaluation. Although *dysphagia* may occur because of benign processes, it is neither a natural phenomenon nor a result of aging, and always requires additional evaluation.

## 6. How is *dysphagia* classified clinically?

*Dysphagia* can be clinically classified based on either location or etiologic factors. If classified by location, *dysphagia* can generally be separated into either *oropharyngeal dysphagia* (also referred to as *transfer dysphagia*) or *esophageal dysphagia*. If classified by etiologic factors, *dysphagia* can be separated into a mechanical disorder (often characterized by *dysphagia* to solid foods only) or a motility disorder (generally characterized by *dysphagia* to both solids and liquids).

## 7. What are the clinical features of *oropharyngeal dysphagia*?

*Oropharyngeal dysphagia* results in difficulty transferring food from the mouth to the posterior pharynx. This can lead to symptoms of subjective obstruction in the neck, coughing, choking, regurgitation with either solids or liquids (including nasal regurgitation), drooling, dysphonia, and aspiration pneumonia. Specific physical maneuvers may aid oropharyngeal function and may be used to compensate for deficits.

## 8. What is the differential diagnosis for *oropharyngeal dysphagia*?

*Oropharyngeal dysphagia* can result from coordination, weak propulsion, or structural abnormalities. Although the differential diagnosis is broad, neurologic or muscular etiologic factors are most commonly seen in practice and account for approximately 80% of cases in older adults. Of that group, cerebrovascular accidents account for the vast majority. See Table 1-1 for a more extensive differential.

## 9. When is it appropriate to evaluate *dysphagia* related to a cerebrovascular accident?

*Dysphagia* is common after a stroke (at least 25% of patients) and is a risk factor for pneumonia and aspiration. Although early evaluation is reasonable to minimize these complications, and most patients with *dysphagia* after a cerebrovascular accident will note improvement within the first 2 weeks. Because of this, invasive procedures such as percutaneous gastrostomy should be avoided for at least the first 2 weeks after a cerebrovascular accident, with the hopes that there will be improvement in the interim.

## 10. Do patients accurately localize the site of *dysphagia*?

Patients with *oropharyngeal dysphagia* generally recognize that their dysfunction is in the *oropharynx* and often point to the cervical region when asked to localize the source of their symptoms. For patients with *esophageal dysphagia*, however, symptoms may not be a reliable predictor of location. Localization of *dysphagia* to the distal esophagus (near the xiphoid process) is generally viewed as specific for a distal esophageal process; however, suprasternal (or upper chest) localization can be referred from a distal process in approximately one third of cases and is viewed as less specific.

**Table 1-1.** Differential Diagnosis for Oropharyngeal Dysphagia

Iatrogenic	Metabolic	Myopathic
Corrosive (pill injury or ingestion)	Amyloidosis	Connective tissue disease (scleroderma, Sjögren's syndrome, systemic lupus erythematosus)
Functional dysphagia	Cushing's syndrome	Dermatomyositis
Medication side effects (chemotherapy, neuroleptics, anticholinergics, antihistamines, antihypertensives, steroids, others less common)	Hypothyroidism with myxedema	Myotonic dystrophy
Postsurgical	Thyrotoxicosis	Myasthenia gravis
Radiation	Wilson disease	Metabolic myopathy
		Oculopharyngeal dystrophy
		Polymyositis
		Paraneoplastic syndromes
		Sarcoidosis
Infectious	Neurologic	Structural
AIDS (CNS involvement)	Amyotrophic lateral sclerosis	Cervical webs
Botulism	Brainstem tumors	Congenital disorders (cleft palate for example)
Diphtheria	Cranial nerve palsies	Cricopharyngeal bar
Lyme disease	Cerebrovascular accident	Dental anomalies
Mucosal inflammation (abscess, candida, CMV, HSV, pharyngitis, tuberculosis)	Dementia	Extrinsic compression (goiter, lymphadenopathy, neoplasm)
Rabies	Guillain-Barré syndrome	Oropharyngeal neoplasm
Syphilis	Head trauma	Prosthetics
	Huntington disease	Skeletal abnormalities and osteophytes
	Metabolic encephalopathies	Xerostomia
	Multiple sclerosis	Zenker diverticulum
	Parkinson disease	
	Poliomyelitis (bulbar)	
	Postpolio syndrome	
	Tardive dyskinesia	

AIDS, Acquired immune deficiency syndrome; CMV, cytomegalovirus; CNS, central nervous system; HSV, herpes simplex virus.

## 11. What is the best test to evaluate oropharyngeal dysphagia?

A careful history and detailed physical examination are essential first steps, and most patients with oropharyngeal dysphagia will require radiographic imaging. Because of the rapid sequence of events that comprise a swallow, static barium studies are often not adequate to evaluate the oropharynx. The preferred initial study is video fluoroscopy or modified barium swallow. Some centers may also perform a fiberoptic endoscopic evaluation of swallowing or nasoendoscopy, which allows direct imaging for structural abnormalities and acquisition of biopsies if required. Routine esophagogastroduodenoscopy and esophageal manometry have a limited and complementary role in this population.

## 12. What is the differential diagnosis of esophageal dysphagia?

Esophageal dysphagia is generally related to either a motility disorder (such as achalasia, spasm, nutcracker esophagus, scleroderma) or a mechanical disorder (stricture, rings, web, diverticulum, cancer). A motility disorder is suggested by dysphagia to solids and liquids, whereas a mechanical disorder is suggested by dysphagia to solids only. See Table 1-2 for a more extensive differential diagnosis.

**Table 1-2.** Differential Diagnosis for Esophageal Dysphagia

Mechanical	Motor
Caustic of NG tube stricture	Achalasia
Cardiovascular compromise (dysphagia lusoria)	Diffuse esophageal spasm
Diverticulum	Esophagogastric junction outflow obstruction
Eosinophilic esophagitis	Functional dysphagia
Esophageal rings or webs	Ineffective esophageal motility
Infectious esophagitis	Jackhammer esophagus
Medication-induced injury	Nutcracker esophagus
Peptic stricture	Scleroderma
Radiation injury	
Tumor (benign or malignant)	

NG, Nasogastric.

### 13. What are the key questions to ask of a patient with suspected esophageal dysphagia?

A careful history can often clarify the etiologic factors of esophageal dysphagia. The key points to clarify on initial evaluation are as follows:

- **Chronology:** How long have symptoms been present? How often does it occur? Is it progressing with time?
- **Dysphagia:** What type of foods cause problems (solids, liquids, both)? Where does the food become stuck? How long does it stick for?
- **Regurgitation:** Does food or liquid come back up to the throat or mouth? Does this occur when eating, soon after the meal is over, or at a much later time? Can this occur hours after the meal is complete? Is it more likely to occur when lying down or sitting up? Does it taste sour or bitter?
- **Cough:** Is there coughing or choking during or after eating? Does this occur with swallows, soon after swallowing, or after the meal is over?
- **Pain:** Is there throat or chest pain either while eating or afterward? Where is the pain located? Does it radiate anywhere else?

### 14. At what luminal diameter will most patients experience symptoms of dysphagia?

This exact issue was evaluated by radiologist Richard Schatzki in the 1950s and 1960s. He reported that for patients with a distal esophageal ring (now named the Schatzki ring), *dysphagia was almost universal if the diameter of the lumen was less than 13 mm. If the diameter was greater than 20 mm, no one was symptomatic.* Intermittent symptoms could be seen in some people at ranges in between. It is because of these seminal studies that most barium tablets used in a traditional radiographic dysphagia evaluation are 13 mm in diameter.

### 15. What diagnostic studies are available to evaluate a patient with esophageal dysphagia?

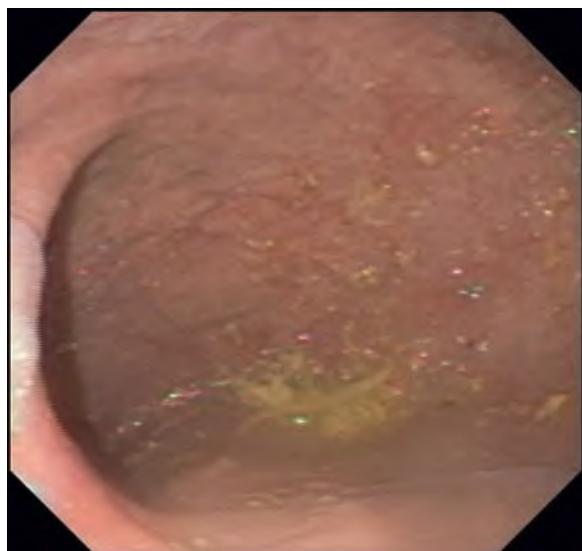
Much can be deciphered by a careful history; however, diagnostic studies are usually necessary to arrive at a diagnosis and optimize therapy. To evaluate dysphagia, three main diagnostic modalities are currently employed, plus other emerging studies. The key studies appear in the following list. [Figure 1-1](#), [E-Figure 1-2](#), and [E-Figure 1-3](#) show a representative example of achalasia using fluoroscopy, endoscopy, and manometry, respectively.

- **Fluoroscopy:** The classic fluoroscopic study employed is a barium esophagram, in which contrast is ingested while serial x-rays are obtained. This allows visualization of structural lesions such as rings, webs, bars,

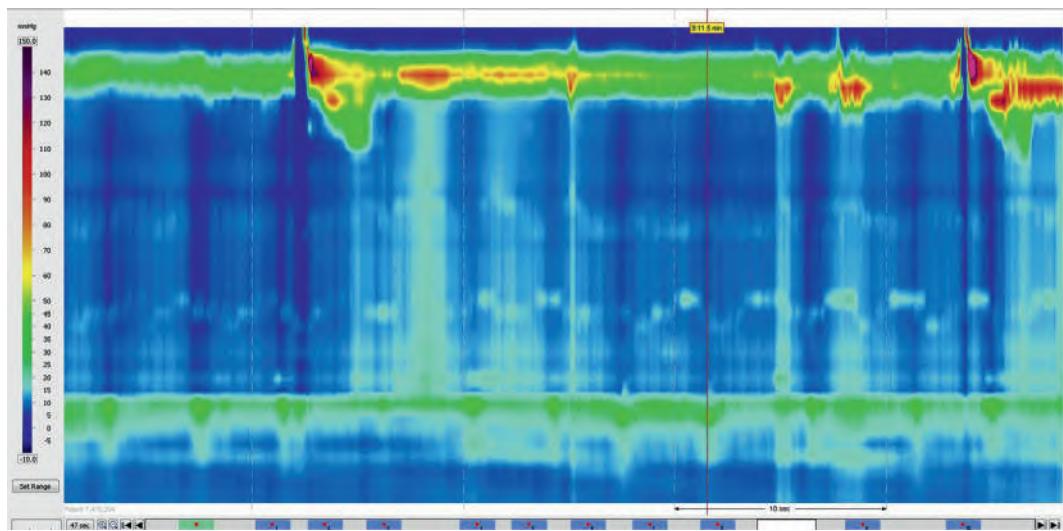
**Figure 1-1.** A representative fluoroscopic image of a patient with established achalasia. Note the dilated esophagus and classic bird's beak appearance (representing the tonically contracted lower esophageal sphincter).



**9.e1 SWALLOWING DISORDERS AND DYSPHAGIA**



**E-Figure 1-2.** An extreme endoscopic image of a patient with advanced achalasia. Note the dilated esophagus, atonic mucosa, and scant retained food particles.



**E-Figure 1-3.** A representative high-resolution esophageal manometry showing a patient with achalasia (type II pattern). Note the absence of any esophageal peristaltic waves in this patient with achalasia, as compared with normal peristalsis shown in [E-Figure 1-5](#). Manometry is the most sensitive test for detection of achalasia and may detect abnormalities before either radiographic or endoscopic changes are noted.

## **10 SWALLOWING DISORDERS AND DYSPHAGIA**

strictures, masses, diverticula, and fistulas. It also may detect any gross motility abnormalities such as spasm and achalasia.

- **Endoscopy:** A flexible fiberoptic tube is passed from the mouth to small bowel and allows direct visualization, biopsy acquisition, and potential therapeutic options (such as dilatation). This can also be combined with endoscopic ultrasound if available to evaluate for possible extrinsic compression or submucosal processes.
- **Manometry:** A catheter with numerous pressure sensors is placed, allowing measurement of the upper esophageal sphincter, esophageal body, and lower esophageal sphincter. This study evaluates intraluminal pressure and coordination of pressure activity. This is the most sensitive study for detection of an esophageal motility disorder but is usually reserved for those cases in which the diagnosis is not readily apparent with the tests detailed previously.
- **Impedance:** Impedance allows direct measurement of bolus flow and can be a useful adjunct to manometry. It is mainly used for detection of nonacid reflux, but can be employed if needed in the work-up of dysphagia.
- **Impedance planimetry:** This is a new technology recently approved by the Food and Drug Administration. It can be used to evaluate esophageal compliance and has been shown in recent papers to have benefit in predicting prognosis for patients with achalasia and eosinophilic esophagitis. This is limited to tertiary referral centers at present and the role for this technology in evaluation of dysphagia remains unclear to a certain extent.

### **16. What is the best initial test for a patient with esophageal dysphagia?**

This is a controversial area and there is a debate as to whether a barium esophagram or endoscopy should be the initial test of choice. Endoscopy offers diagnostic value as well as the ability to obtain biopsies to clarify etiologic factors and the ability to perform therapeutic intervention, such as dilatation. Barium studies may provide more information in patients with proximal lesions or motility disorders. There are no official guidelines recommending one approach versus the other, and the initial test of choice is often based on local practice patterns and regional expertise.

### **17. What is the most common cause of dysphagia in young patients today?**

Eosinophilic esophagitis is the most common cause of dysphagia in young patients today and is increasing in both incidence and recognition. Although the etiologic impetus is not clear, it is believed to be an allergic diathesis in which eosinophilic tissue deposition leads to remodeling of the esophagus and decreased distensibility, characterized by development of rings and strictures. The diagnosis is made by esophageal biopsy demonstrating more than 15 eosinophils per high-powered field. Typical endoscopic findings include circumferential rings, longitudinal furrows, and white plaques (representing eosinophilic microabscesses), although up to 20% of endoscopies may appear normal on gross appearance. For this reason, biopsies of the esophagus should be taken during endoscopy for all patients with dysphagia.

### **18. What is the preferred treatment for patients with documented esophageal eosinophilia?**

Approximately 25% of patients with esophageal eosinophilia will have marked improvement or resolution of their symptoms with proton pump inhibitors. For this reason, the term *eosinophilic esophagitis* is reserved for those patients with continued eosinophilic tissue deposition despite acid suppressive therapy. For these patients, there is data to support the use of steroids (both topical and systemic), dietary modification, and intermittent endoscopic dilatation. There is no clear consensus as to what the optimal initial therapy should be and no good head-to-head trials at present. Most authorities initiate treatment with topical steroids, usually either swallowed fluticasone (220-440 mcg twice daily) or viscous budesonide (1 mg twice daily).

### **19. Is it safe to perform endoscopic dilatation for patients with eosinophilic esophagitis?**

Early reports of dilatation for patients with eosinophilic esophagitis suggested deep mucosal tears and an increased risk of perforation, prompting the medical establishment to recommend against dilatation unless medical therapy had failed and a clear stricture was present. However, more recent studies have suggested that the rate of perforation in expert hands is much lower than previously reported (approximately 0.3% in the largest series to date) and may be a safe treatment option if performed with care. Of note, although dilatation is effective for relieving dysphagia, it has no effect on the underlying inflammation and therapeutic relief will likely be transient.

### **20. What is a Schatzki ring?**

A Schatzki ring is a thin membrane found at the squamo-columnar junction (separating the esophagus and stomach), composed of mucosa and submucosa. There is debate as to whether it is a vestigial structure or a result of reflux and inflammation. It is seen in approximately 15% of adults older than the age of 50 and is a benign process. It can cause intermittent dysphagia to solids and is treated with dilatation. There is data to suggest that acid suppressive therapy may decrease recurrence of the ring after dilatation. The classic clinical scenario is the “steakhouse syndrome” wherein a businessperson is eating dinner at a steakhouse, socializing and taking larger bites than normal, and subsequently develops food impaction from a piece of meat lodging at the ring.

### **21. What is Plummer-Vinson syndrome?**

Plummer-Vinson syndrome is a rare condition characterized by the presence of an esophageal web, dysphagia, and iron-deficiency anemia. An esophageal web is a thin, horizontal membrane of stratified squamous

epithelium, which typically is eccentric and does not circle the entire lumen. Treatment consists of iron repletion and dilatation and rupture of the esophageal web. Patients with Plummer-Vinson syndrome have a higher risk of developing esophageal squamous carcinoma.

## 22. What is a Zenker diverticulum?

A Zenker diverticulum is a mucosal outpouching (or diverticulum) in the hypopharynx. This is immediately proximal to the cricopharyngeus and often is a result of relative obstruction in this region. Symptoms consist of dysphagia and regurgitation, often delayed. The best study to identify a Zenker diverticulum is a barium swallow. Treatment consists of surgical diverticulectomy with or without myotomy, rigid endoscopic myotomy, and flexible endoscopic cricopharyngeal myotomy.

## 23. What is the difference between conventional manometry and high-resolution esophageal manometry?

Manometry uses pressure sensors arranged via a catheter to measure intraluminal esophageal pressure and assess coordination of contractions. The fundamental difference between conventional manometry and high-resolution manometry is the number of sensors and the space between them. Conventional manometry uses sensors spaced at approximately 5-cm intervals, whereas high-resolution manometry uses sensors spaced no more than 1 cm apart throughout the length of the esophagus. This allows more detailed analysis of esophageal pressure patterns, may increase sensitivity of the study, and may provide prognostic information for disorders such as achalasia. Because of the increased data obtained with high-resolution manometry, the data is displayed as an esophageal pressure topography map to make visualization more intuitive. A characteristic conventional and high-resolution manometry image for a patient with a normal manometry swallow is detailed in [E-Figure 1-4](#) and [E-Figure 1-5](#).

## 24. What is the Chicago classification of esophageal motility?

Because of the increased data presented with high-resolution esophageal manometry, new classification schemes have been proposed to guide use of results. The Chicago classification is currently the main system in use for classification of esophageal motility disorders via high-resolution esophageal manometry. The main steps of the Chicago classification are (1) assessment of the gastroesophageal junction, and (2) assessment of esophageal contractility. Based on these two parameters, studies can be divided into disorders that are clearly abnormal and not seen in normal individuals, as compared with borderline abnormalities of uncertain clinical significance. The main classification categories of the Chicago classification are listed in [Box 1-1](#).

### Box 1-1. Chicago Classification of Esophageal Motility: High-Resolution Manometry

Achalasia	Borderline motor function
EGJ outflow obstruction	Frequent failed peristalsis
Abnormal motor function	Weak peristalsis
Esophageal spasm	Rapid contraction
Hypercontractile (jackhammer) esophagus	Hypertensive (nutcracker) esophagus
Absent peristalsis	Normal

EGJ, Esophagogastric junction.

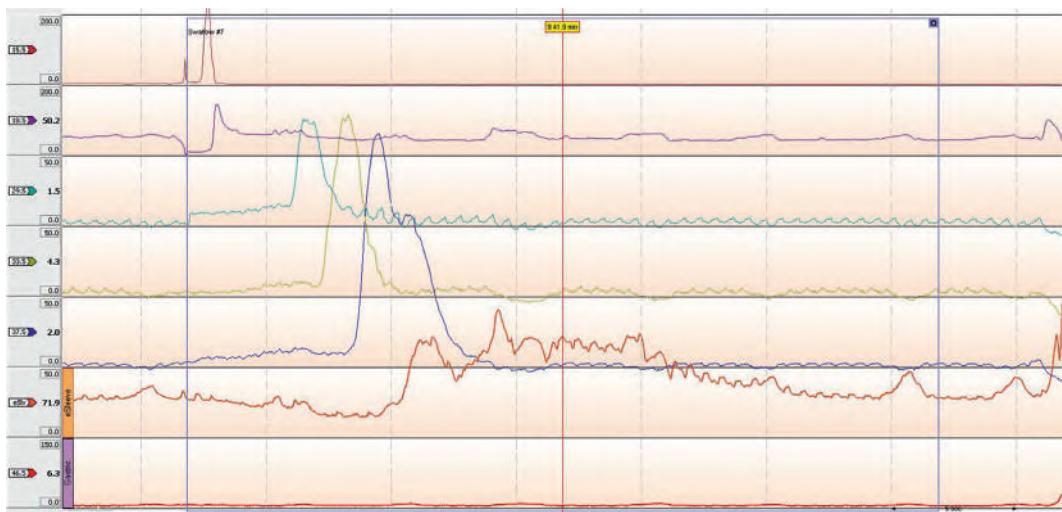
## 25. What is nutcracker esophagus?

The phrase *nutcracker esophagus* was coined by Dr. Donald Castell, who is perhaps the world's foremost authority on esophageal motility. The term was used to describe a condition in which the esophageal pressures are so high that they could perhaps crack a nut (hence the name). The normal amplitude of esophageal contractions is between 30 mm Hg and 180 mm Hg, and nutcracker esophagus was defined as an average esophageal amplitude of more than 180 mm Hg. Symptoms of chest pain and dysphagia have both been reported with this condition, although it remains unclear whether the high amplitude is a direct cause of symptoms or a result of some other process. Treatment consists of reflux therapy (if appropriate) and smooth muscle relaxants (such as calcium channel blockers or nitrates).

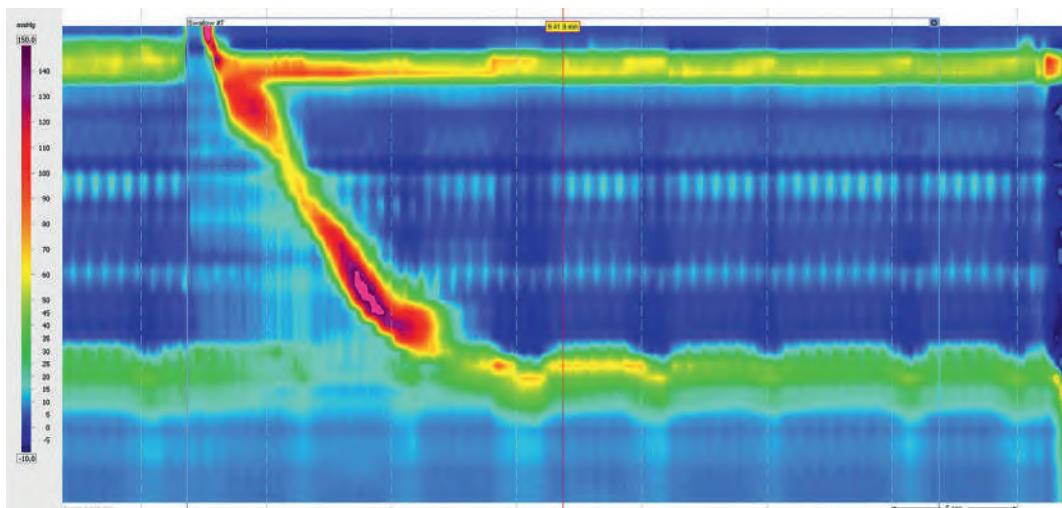
## 26. How common is esophageal spasm?

Esophageal spasm has been defined as uncoordinated or rapid contraction in association with symptoms such as chest pain and dysphagia. Although this is commonly cited as the source of unexplained chest pain and dysphagia, several large studies suggest that this is actually uncommon, with one large study suggesting spasm is present in only 3% of patients with unexplained chest pain or dysphagia. The gold standard for diagnosis is esophageal manometry, although barium radiography can also be highly suggestive. Treatment consists of reflux therapy (if appropriate) and smooth muscle relaxants (such as calcium channel blockers or nitrates).

**11.e1 SWALLOWING DISORDERS AND DYSPHAGIA**



**E-Figure 1-4.** A normal manometry study using a conventional catheter.



**E-Figure 1-5.** A normal manometry study using a high-resolution manometry catheter.

### 27. What is a scleroderma esophagus?

Scleroderma is associated with esophageal motility disorders in greater than 90% of patients.

The characteristic pattern is a hypotensive lower esophageal sphincter and either aperistalsis or weak peristalsis; however, multiple variations can be seen and not all patients with scleroderma have this pattern. Colloquially, a manometry pattern of aperistalsis with a hypotensive lower esophageal sphincter has been referred to as a *scleroderma pattern*, or as *scleroderma esophagus*. However, it should be noted that this pattern is not pathognomonic for scleroderma and can be seen in other conditions.

### 28. Can cardiovascular abnormalities cause dysphagia?

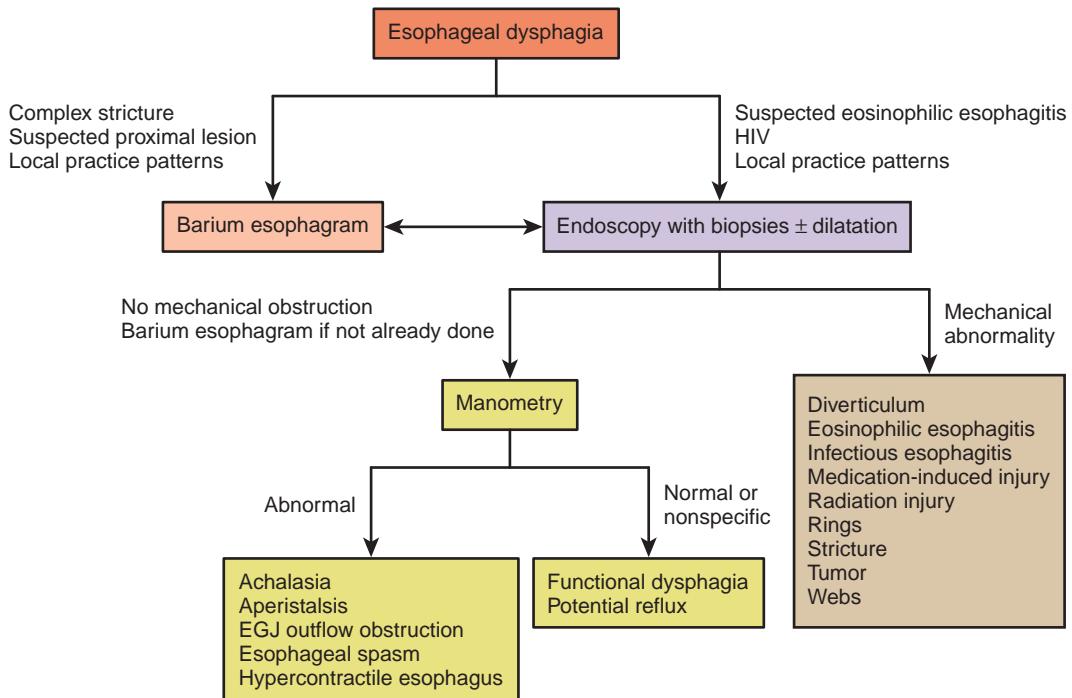
Occasionally, vascular anomalies can cause dysphagia by compressing the esophagus. This is referred to as *dysphagia lusoria*, but is relatively rare. The diagnosis can be suggested by barium esophagram and can be confirmed by endoscopic ultrasound or CT. In our experience, treatment is usually conservative. In older adults, a large aneurysm of the thoracic aorta or severe atherosclerosis can result in impingement of the esophagus and is referred to as *dysphagia aortica*.

### 29. What is functional dysphagia?

Functional dysphagia is defined by the Rome III criteria as a sense of solid or liquid food lodging or passing abnormally through the esophagus in the absence of gastroesophageal reflux, a structural disorder, or a defined motility disorder. Although the cause is not known, this is believed to be a manifestation of visceral hypersensitivity. Patients should be reassured and instructed to avoid any known precipitants. Treatment is largely supportive.

### 30. How should I approach a patient with esophageal dysphagia?

The evaluation of dysphagia is not standardized and variation can exist based on local practice patterns. Societal guidelines have not been updated in more than a decade and it remains controversial whether an upper endoscopy or barium esophagram should be the initial study. A suggested algorithm is detailed in Figure 1-6.



**Figure 1-6.** A suggested approach to esophageal dysphagia. EGJ, Esophagogastric junction; HIV, human immunodeficiency virus.

Please access ExpertConsult to view the E-Figures and **Clinical Vignette** for this chapter.

#### BIBLIOGRAPHY

1. Bredenoord AG, Fox M, Kahrilas PJ, et al. Chicago classification criteria of esophageal motility disorders defined in high resolution esophageal pressure topography. *Neurogastroenterol Motil* 2012;24(Supp 1):57–65.
2. Cook IJ. Diagnostic evaluation of dysphagia. *Nat Clin Pract Gastroenterol Hepatol* 2008;5:393–403.
3. Cook IJ, Kahrilas PJ. AGA technical review on management of oropharyngeal dysphagia. *Gastroenterology* 1999;116:455–78.
4. Dellow ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis. *Am J Gastroenterol* 2013;108:679–92.
5. Liacouras CA, Furuta GA, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3–20.
6. Spechler SJ. American gastroenterological association medical position statement on treatment of patients with dysphagia caused by benign disorders of the distal esophagus. *Gastroenterology* 1999;117:229–33.

#### Websites

Goyal and Shaker GI Motility Online. [www.nature.com/gimo/](http://www.nature.com/gimo/) [Accessed September 22, 2014].

American Neurogastroenterology and Motility Society. [www.motilitysociety.org](http://www.motilitysociety.org) [Accessed September 22, 2014].

American Partnership for Eosinophilic Disorders. [www.apfed.org](http://www.apfed.org) [Accessed September 22, 2014].

# GASTROESOPHAGEAL REFLUX DISEASE

Fehmi Ates, MD, and Michael F. Vaezi, MD, PhD, MS

## 1. What is gastroesophageal reflux disease (GERD)?

GERD develops when the reflux of stomach contents causes troublesome symptoms or complications. This means that GERD is defined by a constellation of both symptoms or objective findings such as esophageal erosions or Barrett's esophagus.

## 2. Is GERD a common disease?

GERD is one of the most common disorders of the gastrointestinal tract. In developed countries, the prevalence of GERD (defined by symptoms of heartburn, acid regurgitation, or both, at least once a week) is 10% to 20%, whereas in Asia the prevalence is roughly less than 5%. In the United States, this disease is the most common gastrointestinal diagnosis to prompt an outpatient clinic visit (8.9 million visits in 2009). The rising prevalence of GERD seems to be related to the rapidly increasing prevalence of obesity, which includes increasing abdominal girth and the resulting pressure-induced relaxation of the lower esophageal sphincter (LES), causing reflux.

## 3. Is GERD an important public health problem?

GERD has become an important public health problem because it impairs quality of life, creates a considerable economic burden, reduces productivity, and requires medications and consultations. The cost of treating typical GERD in the United States is \$9 to \$12 billion; treating extraesophageal reflux is four to five times as expensive as treating typical GERD and is estimated to be near \$50 billion.

## 4. What are the most typical symptoms of GERD?

The two most typical symptoms of GERD are heartburn (pyrosis) and regurgitation. Heartburn is characterized by a painful retrosternal burning sensation of fairly short duration (several minutes). Regurgitation is defined as backflow of gastric content into the mouth, not associated with nausea or retching. Some patients perceive their reflux episodes as angina-like chest pain, but this symptom requires thorough evaluation for a cardiac cause before GERD is considered.

## 5. What are the other typical symptoms of GERD?

Water brash, dysphagia, and odynophagia are considered other typical symptoms of GERD.

**Water brash** is the sudden appearance in the mouth of a slightly sour or salty fluid. It is not regurgitated fluid, but rather vagally mediated secretions from the salivary glands in response to acid reflux.

**Dysphagia** (difficulty swallowing) is seen in up to 40% of patients with long-standing GERD and may herald the presence of an esophageal stricture, esophageal dysmotility, ring, or even esophageal carcinoma. Dysphagia is an alarm symptom or warning sign and an indication for early endoscopy to rule out a GERD complication.

**Odynophagia** (painful swallowing) is usually described as a sharp or lancinating pain located behind the sternum. Although severe erosive esophagitis or esophageal ulceration from reflux can cause painful swallowing, both are uncommon causes of odynophagia. Its presence should raise the suspicion of an alternative cause of esophagitis, especially infections or injury from impacted pills.

## 6. What are the extraesophageal manifestations of GERD?

Chronic cough, asthma, chronic laryngitis, dental erosion, chronic obstructive pulmonary disease, hoarseness, globus, postnasal drip disease, sinusitis, otitis media, recurrent pneumonia, and laryngeal cancer are the extraesophageal manifestations of GERD. These symptoms may occur concomitantly with typical symptoms or in isolation. The latter results in delayed diagnosis of reflux as a potential contributing factor to patients' symptoms.

## 7. What other diseases should be considered in the differential diagnosis of GERD?

GERD needs to be distinguished from infectious esophagitis, pill esophagitis, eosinophilic esophagitis, peptic ulcer disease, nonulcer dyspepsia, biliary tract disease, coronary artery disease, and esophageal motor disorders. Symptoms alone do not reliably distinguish among these disorders. Similarly, the severity and duration of symptoms correlate poorly with the severity of esophagitis. However, because many patients with the diseases listed previously share symptoms with GERD, it is important that these diagnoses be ruled out in a patient who is not responsive to acid-suppressive therapy.

## 8. Which mechanisms are involved in the pathophysiologic findings of GERD?

Dysfunction of the esophagogastric junction, esophageal body dysfunction, delayed gastric emptying, increased intragastric pressure, acid pocket, and esophageal hypersensitivity are involved in the pathophysiologic findings of GERD. The two most common pathophysiologic mechanisms include transient lower esophageal relaxation (TLESR), which is the most common cause, and reduced LES pressure caused by hiatal hernia, which

is more common in patients with Barrett's esophagus. TLESR events are the result of a vagally mediated reflex that is triggered by gastric distention and serves to enable gas venting from the stomach. On average, a TLESR persists for approximately 20 seconds, which is significantly longer than the typical swallow-induced relaxation. In patients with scleroderma or Sjögren's disease, alteration in esophageal peristalsis and saliva are important contributing factors.

#### **9. What are the components of the esophagogastric junction?**

Three components make up the esophagogastric junction: the LES, the crural diaphragm, and the anatomic flap valve. This complex functions as an antireflux barrier, which, when competent, prevents reflux of gastroduodenal contents into the esophagus but when incompetent may result in symptoms or esophageal erosions.

#### **10. Where is the LES? What is the function of the LES?**

The LES involves the distal 3 to 4 cm of the esophagus and at rest is tonically contracted. It is the major component of the antireflux barrier, being capable of preventing reflux even when completely displaced from the diaphragmatic crura by a hiatal hernia. The proximal portion of the LES is normally 1.5 to 2 cm above the squamocolumnar junction, whereas the distal segment, approximately 2 cm in length, lies within the abdominal cavity. This location maintains gastroesophageal competence during intraabdominal pressure excursions. Resting LES pressure ranges from 10 to 35 mm Hg with a generous reserve capacity because only a pressure of 5 to 10 mm Hg is necessary to prevent GERD.

#### **11. What is the anatomic flap valve?**

In healthy people, an anatomic flap valve is present at the esophagogastric junction, which functions to keep the distal part of the LES in the abdomen and to maintain the angle of His (i.e., the acute angle between the entrance to the stomach and the esophagus). As the flap valve disrupts and the LES moves above the crural canal, the high-pressure zone loses its synergistic configuration and both sphincters (LES and diaphragm) become appreciably weaker.

#### **12. What is the role of the esophageal body dysfunction in the development of GERD?**

Acid clearance begins with peristalsis, which empties the refluxed fluid from the esophagus, and is completed by titration of the residual acid by swallowed saliva. Thus peristaltic function is an important defense mechanism against GERD. Of particular importance are failed peristalsis and hypotensive peristaltic contractions (<30 mm Hg), which result in incomplete emptying. This may result in the development of esophagitis or symptoms of dysphagia resulting from poor esophageal clearance of bolus.

#### **13. Is delayed gastric emptying a contributory factor in gastroesophageal reflux activity?**

Postprandial relaxation of the proximal stomach is augmented or prolonged in GERD, and this abnormality is associated with extended presence of the meal in the proximal stomach. A positive correlation was noted between slow proximal—but not distal or total—gastric emptying and esophageal acid exposure. Patients who only partially respond to acid suppressive therapy or continue to have epigastric discomfort or early satiety should be suspected of harboring this diagnosis.

#### **14. What is the importance of obesity in the development of GERD?**

Obesity augments the risk of reflux symptoms, prolonged esophageal acid exposure, esophagitis, and Barrett's esophagus, and that increased abdominal pressure is the pivotal mechanistic factor. Obesity results in an increased incidence of TLESR, which in turn results in increasing acid reflux and predisposes patients to complications of GERD such as esophagitis, Barrett's esophagus, and even adenocarcinoma.

#### **15. What is the acid pocket?**

In the postprandial period, a layer of unbuffered acidic gastric juice sits on top of the meal, close to the cardia, ready to reflux. This occurrence has become known as the *acid pocket* and is facilitated by an absence of peristaltic contractions in the proximal stomach. In patients with GERD, the acid pocket is located more proximally with respect to the squamocolumnar junction, and it could even extend above the manometrically defined LES.

#### **16. Does esophageal hypersensitivity to acid occur only in people with erosive esophagitis?**

Hypersensitivity to acid occurs both in people with erosive esophagitis and in those with a macroscopically normal mucosa. Experiments in which acid is infused in the esophagus indicate that the threshold to development of heartburn and pain is lower in patients with either erosive esophagitis or nonerosive reflux disease than in controls. Factors contributing to the noted increased esophageal sensitivity are impaired mucosal barrier function, upregulation of peripheral nociceptors, and central sensitization.

#### **17. Is there any relationship between *Helicobacter pylori* and GERD?**

*Helicobacter pylori* does not have an important role in the pathogenesis of GERD. Eradication of the microorganism does not lead to an increased chance of development of the disorder. Patients with *H. pylori* should be treated to eradicate the organism, which is important in the development and recurrence of peptic ulcer disease and gastric malignancy.

**18. What are the diagnostic methods for GERD?**

The diagnosis of GERD is made using a combination of symptom presentation, objective testing with endoscopy, ambulatory reflux monitoring, and response to antisecretory therapy. The symptoms of heartburn and regurgitation are the most reliable for making a presumptive diagnosis based on history alone. Empiric therapy with acid suppressive therapy and response to such therapy is considered an important indication for presence of GERD. Diagnostic testing with endoscopy and pH monitoring are typically reserved for those who are either unresponsive or suboptimally responsive to acid suppressive therapy.

**19. What is the most reasonable approach to confirm the diagnosis of GERD?**

Empiric proton pump inhibitor (PPI) therapy (termed PPI trial) is a reasonable approach to confirm GERD when it is suspected in patients with typical symptoms. However, the PPI trial might also be positive in other acid-related disorders, such as peptic ulcer disease and functional dyspepsia, and an important placebo effect has been seen. Therefore the specificity of the test is poor (24%-65%) and is not higher than that of testing with placebo (38%-41%). Nonetheless, in primary care, a short trial of a PPI is deemed useful, because the combination of a favorable response and absence of alarm symptoms makes additional diagnostic testing unnecessary.

**20. Are barium radiograph and esophageal manometry used in the diagnosis of GERD?**

Barium radiographs should not be performed to diagnose GERD without dysphagia. Esophageal manometry is recommended for preoperative evaluation, but has no role in the diagnosis of GERD. Both tests have low sensitivity to make a diagnosis of GERD and are reserved for patients with dysphagia in whom motility disorder is considered likely.

**21. Is upper endoscopy required for the initial diagnosis of GERD?**

Upper endoscopy is not required in the presence of typical GERD symptoms. Endoscopy is recommended in the presence of alarm symptoms (dysphagia, gastrointestinal bleeding, weight loss, anemia, recurrent vomiting, etc.) and for screening patients at high risk for complications. Repeat endoscopy is not indicated in patients without Barrett's esophagus in the absence of new symptoms.

**22. Is there a benefit of histologic analysis for diagnosis of GERD?**

Routine biopsies from the distal esophagus are not recommended specifically to diagnose GERD. A large interobserver variation, low sensitivity, and low specificity strongly limit the value of histologic analysis as a diagnostic method for GERD. Biopsy samples should therefore only be taken when other causes of esophagitis are being considered. In young patients with suspected eosinophilic esophagitis, biopsies should be taken for confirmation of the diagnosis.

**23. Why is upper endoscopy performed in patients with GERD?**

Upper endoscopy should be performed in refractory patients with typical or dyspeptic symptoms principally to exclude non-GERD etiologic factors. For example, the test serves to rule out alternative diagnoses, such as eosinophilic esophagitis, infection, and pill injury; furthermore, an observation of typical reflux esophagitis confirms the diagnosis of GERD. However, erosive esophagitis is only found in *approximately 30% of untreated GERD patients*.

**24. How is the severity of endoscopic reflux esophagitis classified?**

GERD can be classified as the presence of symptoms without erosions on endoscopic examination (nonerosive reflux disease [NERD]) or GERD symptoms with erosions present (erosive reflux disease). The severity of endoscopically observed reflux esophagitis is graded with the Los Angeles classification ([Figure 2-1](#)).

**Grade A:** One or more mucosal breaks confined to folds, 5 mm or smaller.

**Grade B:** One or more mucosal breaks larger than 5 mm confined to folds but not continuous between tops of mucosal folds.

**Grade C:** Mucosal breaks continuous between tops of two or more mucosal folds but less than 75% of esophageal circumference is involved.

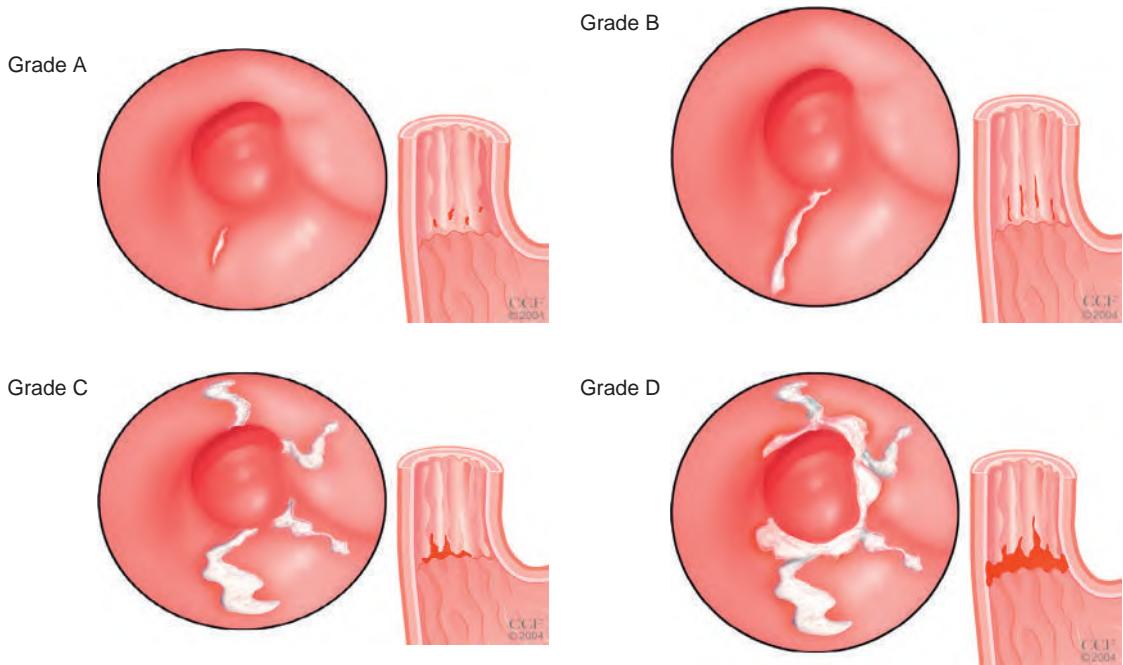
**Grade D:** Mucosal breaks encompass more than 75% of esophageal circumference.

**25. What are the indications of ambulatory esophageal reflux monitoring?**

Ambulatory esophageal reflux monitoring is indicated before consideration of endoscopic or surgical therapy in patients with NERD, as part of the evaluation of patients refractory to PPI therapy, and in situations in which the diagnosis of GERD is in question. It may also be performed in those who have undergone surgical fundoplication whose symptoms have returned to assess if the wrap is loosened.

**26. What are the advantages of ambulatory esophageal reflux monitoring?**

Ambulatory reflux monitoring (pH or impedance-pH) is the only test that allows for determining the presence of abnormal esophageal acid exposure, reflux frequency, and symptoms associated with reflux episodes. Performed with either a telemetry capsule (usually 48 h) or transnasal catheter (24 h), pH monitoring has excellent sensitivity (77%-100%) and specificity (85%-100%) in patients with erosive esophagitis; however, the



**Figure 2-1.** Los Angeles classification of grades A–D esophagitis.

sensitivity is lower in those with endoscopy-negative reflux symptoms (<71%) when a diagnostic test is more likely to be needed.

**27. What is the esophageal impedance? What are the advantages of the combination of impedance-pH monitoring?**

Esophageal impedance measurement allows detection of reflux independent of the pH of the refluxate. This method uses a catheter with circular electrodes that measure the electrical impedance of the esophageal contents at multiple levels along the longitudinal axis of the esophagus. Impedance and pH monitoring are usually done in combination, and a distinction can be made between acid ( $\text{pH} < 4$ ), weakly acidic ( $\text{pH } 4\text{--}7$ ), and alkaline ( $\text{pH} > 7$ ) reflux episodes. This combined technique is debated, as is whether to test on or off therapy. As a true diagnostic test to determine whether abnormal acid exposure is present and for evaluation before considering surgery in a patient with NERD, an off-therapy test is recommended. Testing while on PPI therapy can help determine if the patient's continued symptoms on therapy are due to persistent reflux. Combined impedance and pH monitoring has a higher diagnostic yield than pH monitoring alone.

**28. What is the effectiveness of the dietary modifications for GERD patients?**

The effectiveness of dietary modifications has not been shown, and in view of this absence of evidence, limitation of dietary advice seems wise. Thus cessation of fatty foods, chocolate, caffeine, spicy foods, peppermint, citrus, and carbonated beverages is not routinely recommended for GERD patients. Selective elimination could be considered if patients note correlation with GERD symptoms and improvement with elimination.

**29. Is lifestyle modification helpful for GERD patients?**

Cessation of tobacco smoking and alcohol drinking is a sensible recommendation in general, but no data show that stopping smoking and alcohol drinking leads to a reduction in reflux symptoms. By contrast, much evidence indicates the effectiveness of weight reduction, at least in patients who are overweight or obese. The frequent advice to elevate the head of the bed is only rational for patients with GERD who have reflux episodes at night.

**30. What are the medical options for patients failing dietary and lifestyle interventions?**

Medical options for patients failing lifestyle interventions include antacids, histamine-receptor antagonists ( $\text{H}_2\text{RAs}$ ), or PPI. In the past step-up therapy was recommended in which patients were first treated with antacids and lifestyle modifications followed by  $\text{H}_2\text{RAs}$  and PPIs. However, current recommendations are in favor of step-down therapy in which PPI therapy is the first option followed by tapering to  $\text{H}_2\text{RAs}$  and antacids if possible.

**31. How should we treat patients with moderate to severe symptoms of GERD or severe erosive esophagitis?**

In patients with moderate to severe symptoms of GERD or severe erosive esophagitis, 8 week treatment with PPIs should be regarded as first-line treatment. Findings of many studies show a clear advantage of PPIs (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, and dexlansoprazole) over H<sub>2</sub> blockers for both healing of esophagitis and maintenance of healing. There are no major differences in efficacy between the different PPIs. Patients with severe esophagitis may need lifelong therapy with acid suppressive medications because recurrence of esophagitis is common off therapy.

**32. Is PPI treatment safe?**

PPI treatment is very safe. However, over the years, some concerns about the effects of prolonged acid suppression have been raised, including a high risk of infection, enhanced propensity to develop atrophic gastritis, increased risk of *Clostridium difficile*-associated diarrhea, greater risk of fractures, hypomagnesemia, deficiencies of vitamin B<sub>12</sub> and iron, and the potential for a transient increase in acid secretion after discontinuation. Clinically important drug interactions are rare. The platelet aggregation inhibitor clopidogrel is less active in conjunction with PPI treatment because of decreased activation. However, recent work suggests that this interaction is not clinically relevant. Overall, we must be selective on the use of PPI therapy and limit it to those who need it and who cannot be tapered off therapy because of recurrence of symptoms or esophagitis.

**33. Are the currently available prokinetics effective for treatment of GERD?**

The currently available prokinetics metoclopramide and domperidone (not available in the United States) are not effective for treatment of this disease. Cisapride was an effective drug but is no longer available. New prokinetics are in development today. The main role of this class of agents is in those with gastroparesis.

**34. What are the techniques for endoscopic treatment of GERD? What is the effectiveness of these treatments?**

Currently available techniques for endoscopic treatment of GERD include suturing devices, transmural fasteners and staplers, and radiofrequency ablation. Although the techniques all seem feasible and have safety profiles similar to those of antireflux surgery, they are not as effective as surgery for returning acid exposure to normal, healing of esophagitis, and resolution of symptoms. Long-term results with endoscopic therapies may not be as good as the gold standard of surgical fundoplication.

**35. What are the indications for surgery in patients with GERD?**

Reasons to refer GERD patients for surgery may include desire to discontinue medical therapy, noncompliance, side effects associated with medical therapy, the presence of a large hiatal hernia, esophagitis refractory to medical therapy, or persistent symptoms documented to be caused by refractory GERD (mainly caused by continued regurgitations). Fundoplication has also proven effective in patients for whom nonacid reflux (regurgitation) is an important determinant of symptoms. Preoperative ambulatory pH monitoring is mandatory in patients without evidence of erosive esophagitis. All patients should undergo preoperative manometry to rule out achalasia or scleroderma-like esophagus. Surgical therapy is as effective as medical therapy for carefully selected patients with chronic GERD when performed by an experienced surgeon.

**36. What is the management algorithm for GERD patients with alarm or refractory symptoms?**

After endoscopy, patients undergo a trial of single-dose PPI, but when this approach has already been tried, twice-daily PPI therapy (off-label indication) is started. When the response to PPI is satisfactory, patients with severe esophagitis and Barrett's esophagus should continue with daily PPI (maintenance treatment), whereas those with no or mild esophagitis can use a PPI on demand or taper acid-suppressive therapy to H<sub>2</sub>RAs. When symptoms persist despite a sufficiently long period with high-dose PPI, the next step is to investigate whether symptoms are truly the result of reflux, using ambulatory reflux monitoring. The outcomes are either that the patient's symptoms are not related to reflux, that symptoms are the result of insufficient reflux therapy, or more commonly that they are caused by non-GERD-related causes (Figure 2-2).

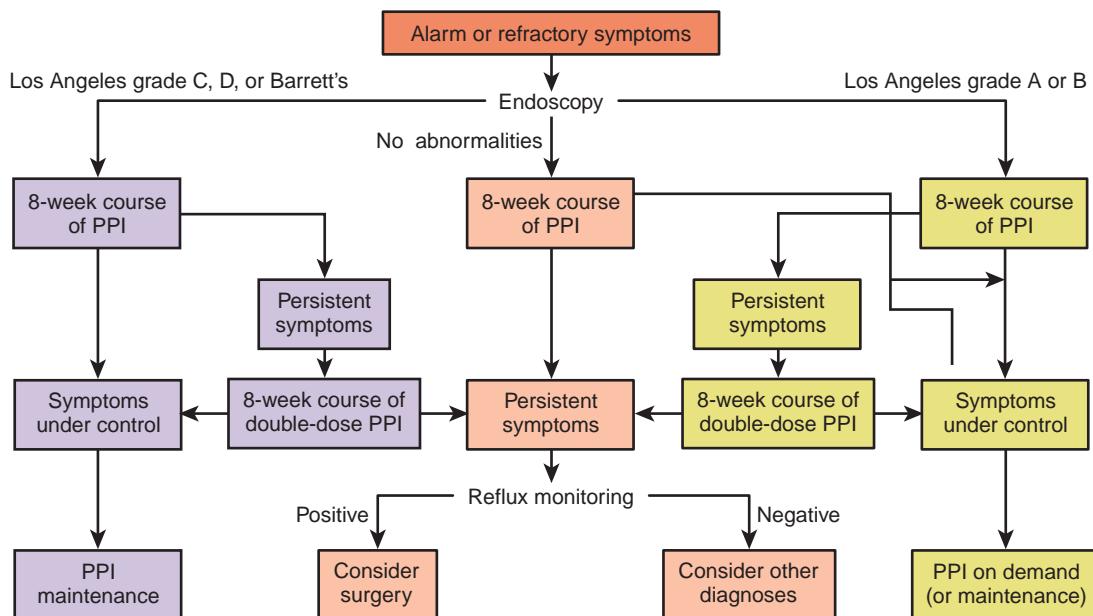
**37. What is the treatment of extraesophageal reflux manifestations?**

A PPI trial is recommended to treat extraesophageal symptoms in patients who also have typical symptoms of GERD. Esophageal pH and impedance monitoring are usually reserved for those who continue to be symptomatic despite initial empiric trial of PPI therapy. The reason behind the lower response rate for extraesophageal symptoms could be that many patients have an alternative diagnosis, and reflux is not the cause of their symptoms. Surgery should generally not be performed to treat extraesophageal symptoms of GERD in patients who do not respond to acid suppression with a PPI.

**38. What are the complications associated with GERD?**

The complications of GERD can be broadly divided into three categories:

- Esophagitis, which can be associated with a variety of symptoms, including heartburn, regurgitation, and dysphagia
- Consequences of the reparative process of esophagitis (peptic stricture and Barrett's metaplasia)
- Extraesophageal manifestations of reflux, such as asthma, laryngitis, and cough



**Figure 2-2.** Management algorithm for symptoms of refractory reflux. PPI, Proton pump inhibitor.

### 39. What is the approach to treatment of peptic stricture?

The approach to treatment depends on the cause and characteristics of the stricture and usually includes acid suppression, with at least daily PPI, and dilation therapy. The choice of dilator (bougie or balloon) depends on the experience of the endoscopist; most strictures can be managed with either. Complicated strictures might need a combination of approaches and repeated sessions. Refractory strictures are those not responding to repeated sessions (usually three). An intralesional steroid injection or placement of an endoprosthesis might be needed in such cases; however, data for these techniques are limited.

### 40. What is Barrett's esophagus? How is Barrett's esophagus managed?

Barrett's esophagus is a complication of GERD in which potentially precancerous metaplastic columnar cells replace the normal squamous mucosa. Barrett's can be found in 5% to 15% of patients who have endoscopy for symptoms of GERD and tends to be seen at the higher end of this range in patients with long duration of symptoms who are white men older than 50. The American Gastroenterology Association supports intervals of 3–5 years if no evidence of dysplasia is seen and a shorter interval for low-grade dysplasia (6 months) and high-grade dysplasia (3 months or intervention). The endoscopic ablation is a viable option for some patients with high-grade dysplasia. However, data for endoscopic ablation in Barrett's esophagus without dysplasia are not supported by evidence. Patients with Barrett's esophagus with no dysplasia should be treated with once-daily PPI therapy for life.

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### BIBLIOGRAPHY

- Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation* 2010;122:2619–33.
- Bredenoord AJ, Pandolfino JE, Smout AJ. Gastro-oesophageal reflux disease. *Lancet* 2013;381:1933–42.
- Derakhshan MH, Robertson EV, Fletcher J, et al. Mechanism of association between BMI and dysfunction of the gastro-oesophageal barrier in patients with normal endoscopy. *Gut* 2012;61:337–43.
- El-Serag H, Hill C, Jones R. Systematic review: the epidemiology of gastro-oesophageal reflux disease in primary care, using the UK General Practice Research Database. *Aliment Pharmacol Ther* 2009;29:470–80.
- Francis DO, Rymer JA, Slaughter JC, et al. High economic burden of caring for patients with suspected extraesophageal reflux. *Am J Gastroenterol* 2013;108:905–11.
- Grande L, Lacima G, Ros E, et al. Lack of effect of metoclopramide and domperidone on esophageal peristalsis and esophageal acid clearance in reflux esophagitis. A randomized, double-blind study. *Dig Dis Sci* 1992;37:583–8.
- Guardino JM, Khandwala F, Lopez R, et al. Barrett's esophagus at a tertiary care center: association of age on incidence and prevalence of dysplasia and adenocarcinoma. *Am J Gastroenterol* 2006;101:2187–93.

8. Hemmink GJ, Bredenoord AJ, Weusten BL, et al. Does acute psychological stress increase perception of oesophageal acid? *Neurogastroenterol Motil* 2009;21:1055–e86.
9. Hemmink GJ, Bredenoord AJ, Weusten BL, et al. Esophageal pH-impedance monitoring in patients with therapy-resistant reflux symptoms: “on” or “off” proton pump inhibitor? *Am J Gastroenterol* 2008;103:2446–53.
10. Hirano I, Richter JE. ACG practice guidelines: esophageal reflux testing. *Am J Gastroenterol* 2007;102:668–85.
11. Johnsson F, Hatlebakk JG, Klintenberg AC, et al. One-week esomeprazole treatment: an effective confirmatory test in patients with suspected gastroesophageal reflux disease. *Scand J Gastroenterol* 2003;38:354–9.
12. Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. *Arch Intern Med* 2006;166:965–71.
13. Lind T, Havelund T, Carlsson R, et al. Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. *Scand J Gastroenterol* 1997;32:974–9.
14. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999;45:172–80.
15. Mainie I, Tutuian R, Agrawal A, et al. Combined multichannel intraluminal impedance-pH monitoring to select patients with persistent gastro-oesophageal reflux for laparoscopic Nissen fundoplication. *Br J Surg* 2006;93:1483–7.
16. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection—the Maastricht IV/Florence Consensus Report. *Gut* 2012;61:646–64.
17. Miner P, Jr., Katz PO, Chen Y, et al. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. *Am J Gastroenterol* 2003;98:2616–20.
18. Peery AF, Dellar ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterol* 2012;143:1179–87, e1–e3.
19. Singh M, Lee J, Gupta N, et al. Weight loss can lead to resolution of gastroesophageal reflux disease symptoms: a prospective intervention trial. *Obesity (Silver Spring)* 2012;284–90.
20. Stacher G, Lenglinger J, Bergmann H, et al. Gastric emptying: a contributory factor in gastro-oesophageal reflux activity? *Gut* 2000;47:661–6.

# ESOPHAGEAL CAUSES OF CHEST PAIN

Vito V. Cirigliano, DO, CPT(P), MC, and Fouad J. Moawad, MD, FACG

## 1. What are the epidemiologic factors of noncardiac chest pain (NCCP)?

Chest pain is one of the most ubiquitous chief complaints presenting to outpatient clinics and is currently the second most common reason for a visit to the emergency department. Population-based studies from several countries have estimated the prevalence of NCCP to be between 13% and 33%, with an equal gender distribution. There is an inverse relationship between age and prevalence of NCCP.

## 2. Does a cardiac etiologic factor need to be excluded before starting an evaluation for esophageal chest pain?

Yes. It is important to recognize that a patient's history does not reliably distinguish cardiac from esophageal causes. As cardiac etiologic factors are potentially life-threatening, these should generally be evaluated first. Patients should be risk stratified based on age, cardiac comorbidities and other risk factors, with a referral to a cardiologist as appropriate. For example, a 20-year-old otherwise healthy woman probably does not require an extensive cardiac evaluation. Conversely, a 65-year-old man with hypertension and typical angina should be thoroughly evaluated for coronary artery disease before considering esophageal causes.

## 3. Once a cardiac cause is excluded, what are the causes of NCCP?

The source of NCCP can be *pulmonary, musculoskeletal, dermatologic, rheumatologic, or psychiatric*. A careful history and physical examination can often eliminate many of these potential sources. Among esophageal sources of chest pain, gastroesophageal reflux disease (GERD) is the most common cause, accounting for up to 60% of cases.

## 4. How is esophageal chest pain transmitted?

Esophageal hypersensitivity results from a combination of peripheral and central sensitization. Although GERD is the most common cause of esophageal chest pain, acid in the esophagus does not induce symptoms in all individuals, which suggests alternate pain pathways. Mechanoreceptors are sensitive to esophageal distention and therefore may be a potential source of pain. The challenge of identifying the underlying pathophysiologic condition is compounded by the significant overlap between esophageal, intrathoracic, and psychiatric disease states. Interestingly, not only is there shared innervation between the esophagus and the heart, but distal esophageal acid exposure has also been documented to reduce coronary blood flow.

## 5. Is a proton pump inhibitor (PPI) test a reasonable first-line approach for diagnosis of GERD?

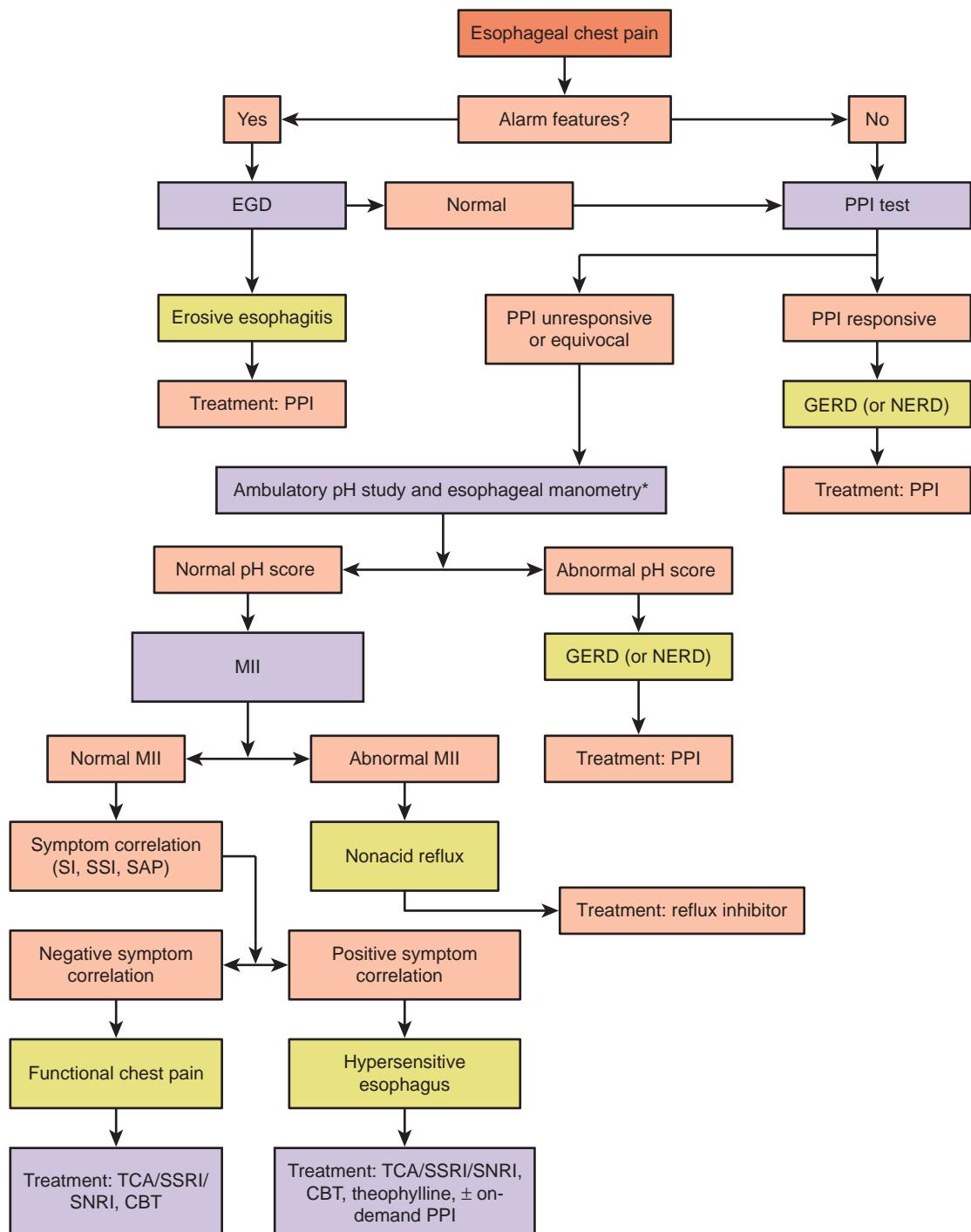
Yes. Because GERD is the most common cause of esophageal chest pain, it is reasonable to give a trial of a PPI for both diagnostic and therapeutic intent. The "PPI trial" is readily available to all physicians, and offers sensitivity and specificity rates comparable to more invasive and expensive tests (endoscopy, ambulatory pH studies), thus reducing health care costs and unnecessary referrals to subspecialty clinics (Figure 3-1).

## 6. What PPI dosing strategies are used during a PPI test?

One dosing strategy for GERD associated NCCP is high-dose acid suppression for 1 to 2 weeks (e.g., omeprazole 40 mg by mouth twice daily or its equivalent) using symptom improvement as a measure of responsiveness. Longer courses (2–3 months) have been more commonly used, but this strategy can be more costly and time consuming, and can delay diagnosis without much increase in sensitivity or specificity. Typically, patients with increased acid exposure or those with erosive esophagitis tend to have greater response and higher diagnostic yield. It is important to ensure a patient does not remain on a high-dose PPI regimen indefinitely. Rather, the PPI should be titrated to the lowest effective dose or discontinued if there is no symptom improvement.

## 7. Is there a role for endoscopy in the evaluation of esophageal chest pain?

The answer depends on the patient's risk factors. Esophagogastroduodenoscopy (EGD) should be reserved for those patients with high risk features or "red flags" that should prompt evaluation for erosive esophagitis, Barrett's esophagus, or malignancy. Patients at risk include men older than 50 years, particularly those with central adiposity or with symptoms of dysphagia or odynophagia, or in the setting of unintentional weight loss. Otherwise, the sensitivity of EGD in patients with typical reflux symptoms is 30% to 50% and should not be the initial diagnostic tool in these patients.



\*Esophageal manometry performed at the same time as a pH study for both accurate catheter placement and to rule out motility disorders causing chest pain.

**Figure 3-1.** Algorithm for esophageal causes of chest pain. CBT, Cognitive behavioral therapy; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; MMI, multichannel intraluminal impedance; NERD, nonerosive reflux disease; PPI, proton pump inhibitor; SAP, symptom association probability; SI, symptom index; SSI, symptom severity index; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective-serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

### 8. Can esophageal motility disorders induce chest pain?

Yes. Sir William Osler described “pseudo angina” more than a century ago, which he attributed to esophageal dysmotility. In patients with esophageal chest pain, abnormal manometry can be encountered in up to 50% of patients. The most common motility disorder presenting as esophageal chest pain is nutcracker esophagus (hypertensive peristaltic contractions), accounting for nearly half of all cases. Other dysmotility causes include jackhammer esophagus (hypercontractile esophagus with repetitive high-amplitude contractions), ineffective esophageal motility, diffuse esophageal spasm, achalasia, and hypertensive lower esophageal sphincter (Table 3-1).

**Table 3-1.** Diagnostic Criteria of Esophageal Motility Disorders Adopted from the Chicago Classification

DIAGNOSIS	DIAGNOSTIC CRITERIA
Nutcracker esophagus (hypertensive peristalsis)	Extremely high pressures during peristalsis with an average DCI >5000
Jackhammer esophagus (hypercontractile esophagus)	Diagnosed with a DCI >8000 on any one swallow during the study
Ineffective esophageal motility	Weak peristalsis or peristaltic defects, characterized by “breaks” in the peristaltic wave
Diffuse esophageal spasm	Premature or simultaneous contractions in ≥20% of swallows
Achalasia	Failed peristalsis and incomplete LES relaxation

DCI, Distal contractile integral; LES, lower esophageal sphincter.

### 9. How is esophageal motility evaluated?

Recent advances in high-resolution manometry (HRM) have improved both the diagnostic and prognostic data. Whereas standard manometry graphically displays esophageal pressure changes in three to eight locations of the esophagus, HRM uses up to 30 sensors spaced at 1-cm intervals and provides a detailed mapping of esophageal pressures, which are displayed in graded color fields to visually distinguish changes in intraluminal pressures. This information can also be reformatted into a three-dimensional display, where areas of high pressure appear to have spikes or peaks as the swallow propagates through the esophagus. Figure 3-2 demonstrates propagation of a swallow in a normal esophagus. Figure 3-3 gives an example of two of the more common motility disorders, nutcracker esophagus and diffuse esophageal spasm.

### 10. What is the treatment for esophageal motility disorders?

Treatment of esophageal motility disorders can be challenging, and often requires trials of medications both within the same class and across different classes to uncover the most efficacious treatment. Medications that have been employed with success include calcium channel antagonists, nitrates, and anticholinergics. In small clinical trials, trazodone and selective-serotonin reuptake inhibitors have demonstrated symptomatic improvement without inducing manometric changes.

### 11. Is barium esophagogram a useful test in the evaluation of esophageal chest pain?

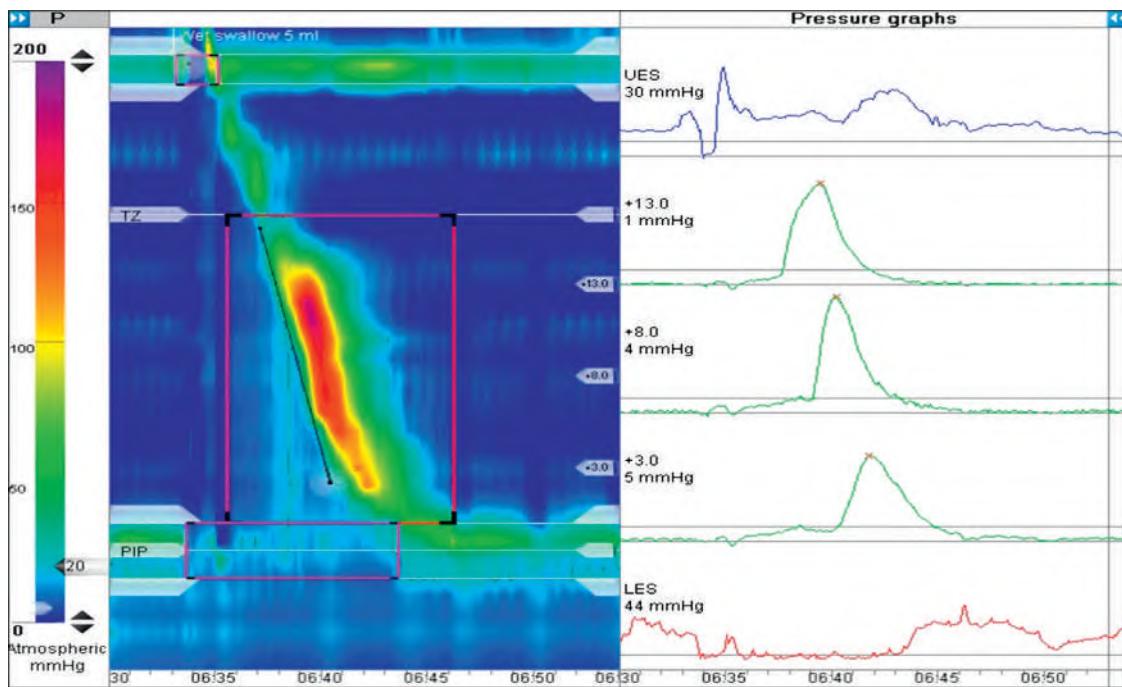
Not usually. Although acid reflux may be a cause of esophageal chest pain, a barium esophagogram has low sensitivity for diagnosing GERD and should be reserved for patients with concomitant dysphagia. Barium esophagogram studies can demonstrate reflux in up to 20% of healthy individuals, and therefore should not be used as a substitute for other higher yield diagnostic modalities for GERD (i.e., PPI test, ambulatory pH study). Barium esophagogram is useful in cases of suspected achalasia, which can demonstrate a dilated esophagus with distal narrowing and a characteristic “bird’s beak” sign.

### 12. What is the next best test in someone who is partially responsive or unresponsive to PPI?

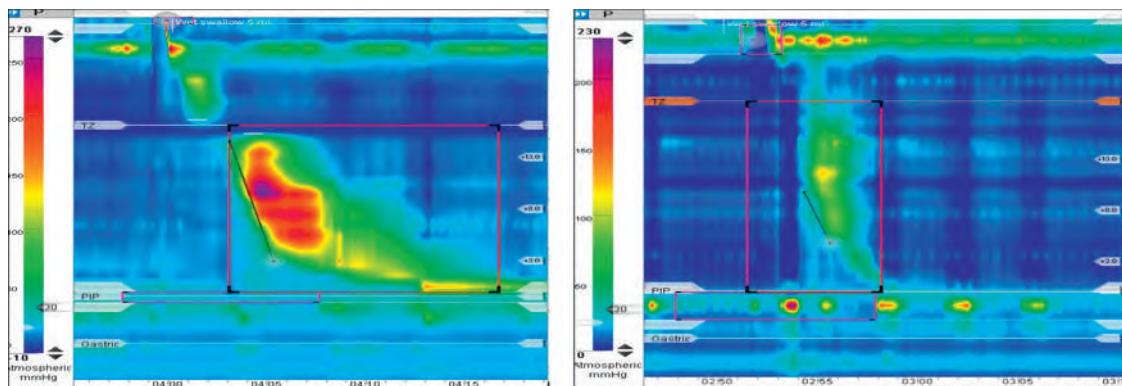
An ambulatory pH test measures the degree and duration of esophageal acid exposure with the degree of severity of reflux expressed as a scoring index (i.e., the Johnson-DeMeester score, DeMeester score, or percent time pH < 4). With a sensitivity similar to the PPI test, ambulatory pH testing is usually reserved for those who are PPI unresponsive or partially responsive. Additionally, this test can be used when objective evidence of reflux is needed (i.e., prior to antireflux surgery). Ambulatory pH testing not only provides objective evidence of abnormal esophageal acid exposure, but it can assess the temporal relationship of chest pain and acid reflux events in up to 50% of cases.

### 13. How is pH monitoring performed?

Ambulatory pH testing can be performed using transnasal catheter-based probes or via wireless capsule monitoring systems. Data can be collected over 24 to 48 hours. Figure 3-4 is an example of acid reflux on pH testing.



**Figure 3-2.** Normal manometric tracings obtained on high-resolution manometry and standard two-dimensional manometry.



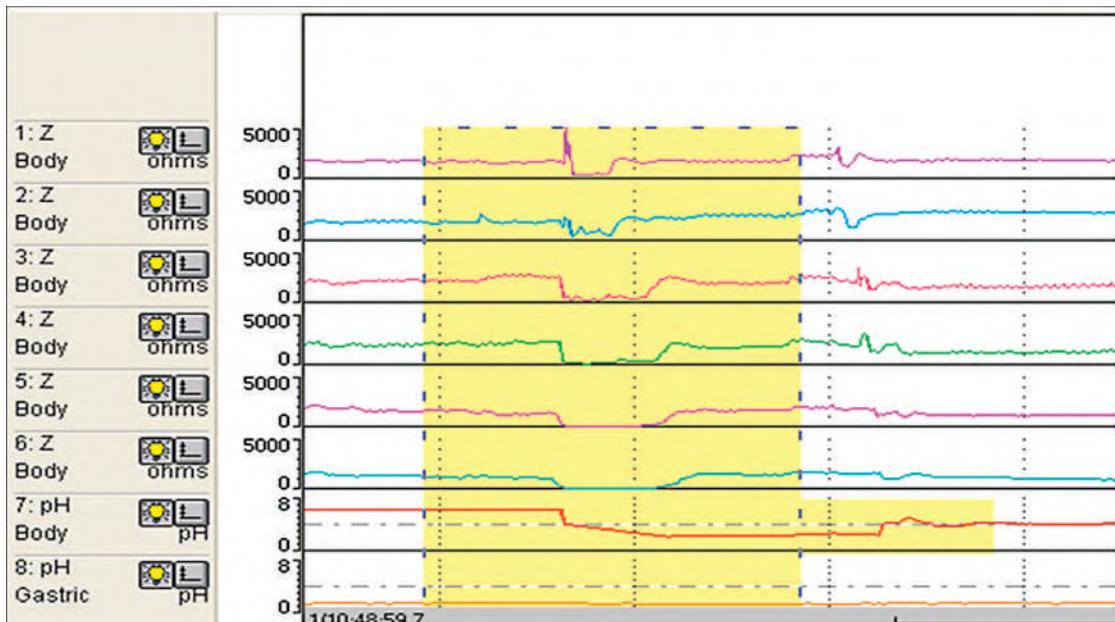
**Figure 3-3.** Right: High-resolution manometry and pressure graph tracing in a patient with nutcracker esophagus. The vigor of the esophageal contraction is measured using the distal contractile integral (DCI), which is a three-dimensional measurement of the segment spanning from the proximal to distal pressure trough or gastroesophageal junction (amplitude  $\times$  duration  $\times$  length). Left: Diffuse esophageal spasm. Note the simultaneous contraction of the swallow.

#### 14. What are some advantages and disadvantages of the transnasal catheter?

The procedure to place a transnasal catheter can be performed in the office without sedation and can usually be combined with impedance monitors to provide additional information regarding reflux. The catheter, which is placed 5 cm proximal to the lower esophageal sphincter, can have one or more pH sensors that will measure acid exposure in different locations of the esophagus. The disadvantage of this system is that they can be cumbersome and uncomfortable for patients, and data recording is typically limited to 24 hours. Patient discomfort may lead to altered dietary intake and decreased daily activity, which can adversely affect the accuracy of the test.

#### 15. What are some advantages and disadvantages of the wireless pH monitor?

An endoscopically placed capsule is temporarily fixed to the esophageal mucosa, located 6 cm proximal to the gastroesophageal junction, and information regarding esophageal acid exposure is transmitted to a receiver



**Figure 3-4.** Note the change in impedance in sensors 1–6 with a prolonged drop in pH less than 4, indicating an acid reflux episode.

over 48 hours. This system tends to be better tolerated by patients and therefore patients are more likely to resume normal dietary intake and daily activities. Disadvantages include the need for endoscopy with sedation and a reported premature detachment of the capsule in up to 12% of cases. Additionally, wireless pH may not be optimal in the evaluation of chest pain as these patients may report worsening symptoms with capsule placement. Endoscopic removal for chest pain has been reported in up to 2%.

#### 16. In a patient with a normal pH score, what is the next step in evaluating for reflux?

Multichannel intraluminal impedance (MII) is useful in detecting nonacid or weak-acid ( $\text{pH} > 4$ ) reflux episodes that are undetected by conventional pH monitoring systems. Patients who have a normal pH study but abnormal MII are diagnosed with nonacid reflux, which can occur in up to *one third of patients* with GERD symptoms that persist despite a PPI trial.

#### 17. How does MII work?

MII allows detection of both acid and nonacid reflux contents. Multiple sensors embedded in a transnasal catheter measure changes in intraluminal resistance to alternating current. Because air has poor electrical conductivity and solids conduct well, MII can differentiate between the presence of liquid and gas. Additionally, the multiple sensors, acting in concert, can determine the direction of flow of gas or solid material, thus differentiating between aerophagia versus belch and food bolus versus reflux. [Figure 3-5](#) is an example of nonacid reflux.

#### 18. Can any other data be obtained from a 24-hour pH/MII catheter?

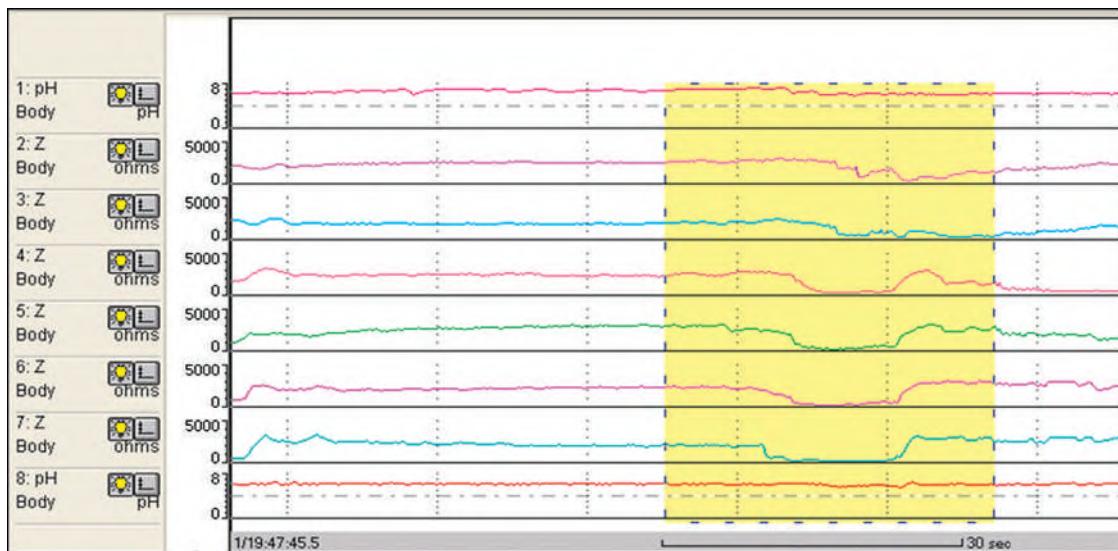
Yes. Symptom correlation is an integral piece of information in the interpretation of data from a 24-hour pH/MII study. Patients are connected to an ambulatory monitoring device that allows them to press a button when they experience their index symptoms. Symptom episodes are then compared with the pH/MII data to establish a correlation between symptoms and reflux events, either acid or nonacid.

#### 19. How is functional esophageal chest pain defined?

According to the ROME III criteria, functional chest pain of esophageal origin must meet all of the following diagnostic criteria:

1. Midline chest pain or discomfort that is not of burning quality (to distinguish from functional heartburn)
2. Absence of evidence that gastroesophageal acid reflux is the cause of the symptom
3. Absence of histopathologic-based esophageal motility disorders

Additionally, symptoms must be present for the preceding 3 months, with onset more than 6 months prior to the diagnosis.



**Figure 3-5.** Note the change in impedance in sensors 2–7 without a concomitant drop in esophageal pH (sensor 8), indicating nonacid reflux.

## 20. What does a positive symptom correlation mean?

Three indices express the correlation between symptoms and reflux. Symptom index and symptom severity index provide data on the strength of the association between symptoms and reflux events, whereas symptom association probability evaluates the statistical probability that a symptom is due to a reflux event rather than chance alone (Table 3-2). One weakness of any of these associations is that often there are too few episodes of chest pain experienced in a 24 to 48 hour period to make an accurate assessment. Also, a chest pain episode may be prolonged and a reflux episode may have occurred during that time by chance. Of note, none of these methods can reliably predict response to treatment and are therefore viewed as complementary data to support findings on the pH/MII study and clinical suspicions.

**Table 3-2.** Modalities for Calculating the Association of Symptoms and Reflux Events

SYMPOTMS SCORING MODALITY	CALCULATION	POSITIVE SCORE
SI	$\frac{\text{Symptomatic episodes associated with reflux events}}{\text{Total number of symptomatic episodes}} \times 100$	$\geq 50\%$
SSI	$\frac{\text{Number of symptomatic episodes with pH } < 4}{\text{Total number of reflux episodes}} \times 100$	$\geq 10\%$
SAP	Chi square: Total 24-hour pH recording data divided into 2-minute segments. Each segment is interpreted for reflux events and reported symptoms. The data is summarized into a $2 \times 2$ table and a probability that an association exists is calculated using the Fisher's exact test.	$\geq 95\%$

SAP, Symptom association probability; SI, symptom index; SSI, symptom severity index.

## 21. How do you treat esophageal hypersensitivity?

Treating esophageal hypersensitivity can be challenging and currently there are no uniformly recommended treatments. Diagnosis can be with a normal endoscopy and normal pH/MII study but positive symptom correlation. If a trial of acid suppressants has failed, pain modulators can be considered. Several medications have been studied for esophageal pain in clinical trials. These include tricyclic antidepressants (imipramine), selective-serotonin reuptake inhibitors (sertraline, citalopram, or paroxetine), or serotonin-norepinephrine reuptake inhibitors (venlafaxine). Additionally, theophylline has been successful in increasing pain thresholds in distention-induced esophageal chest pain. Finally, there may be a role for cognitive behavioral therapy in patients with esophageal hypersensitivity.

## 22. How do you treat functional chest pain?

Although less robust data exists regarding treatment of functional chest pain, anecdotal and expert recommendations are similar to treatment of esophageal hypersensitivity. Patients with functional chest pain tend to have other concomitant functional gastrointestinal disorders, which may similarly benefit from neurotransmitter modulation.

## 23. Are there any provocative tests that can be done?

Yes, but these tests are rarely used outside of research settings because of difficulties in standardization and increased diagnostic yields of newer modalities (e.g., ambulatory pH studies, PPI test, etc.). Of the tests designed to evaluate esophageal sensitivity, only esophageal balloon distention test continues to have some clinical implications. Otherwise, tests designed to evaluate for response to acid exposure (Bernstein test) or esophageal dysmotility (bethanechol test, edrophonium test, ergonovine test, and pentagastrin test) are either not readily available or have low diagnostic utility.

## 24. How is the esophageal balloon distention test performed?

Using serial inflations of an esophageal balloon, subjects are monitored for the degree of distention required to induce index symptoms. A positive study is defined as reproducing symptoms at a volume that does not induce pain in normal subjects. This study may have to be coupled with other provocative tests, such as acid instillation and electrical stimulation, to unravel the complicated interplay between mechanoreceptors, chemoreceptors, and nociceptors that govern the perception of esophageal pain. Using these methods, future research in this area can potentially provide adequate medications to either increase the pain threshold or blunt neurotransmitters in debilitating cases of esophageal chest pain.

## 25. What are the treatment options for reflux-related esophageal chest pain with a negative endoscopy?

For nonerosive reflux disease, PPIs should be titrated to the lowest effective dose. For nonacid reflux documented on 24 pH/MII while on PPI therapy, reflux inhibitors (e.g., baclofen) can be used to reduce transient lower esophageal sphincter relaxations.

## 26. Are there any emerging treatments or diagnostic modalities for esophageal chest pain?

Some receptors that have gained attention in clinical trials include:

- N-methyl-D-aspartate receptor antagonist (ketamine) increases sensory threshold without a change in esophageal motility and reduces secondary hyperalgesia. There are considerable adverse drug reactions (central nervous system depression, arrhythmia, respiratory depression) and it requires intramuscular or intravenous administration.
- Alpha-2-delta ligand (pregabalin) reduces centrally acting pain modulators, glutamate, and substance P.

## 27. Are any psychiatric diagnoses associated with esophageal chest pain?

Yes. Psychiatric comorbidities, most commonly anxiety disorder, frequently present with esophageal chest pain. Additional comorbid conditions include major depression, panic disorder, and somatization, and can occur in up to 33% of patients with esophageal chest pain. The exact pathophysiologic factors linking these disorders to pain is not clear, which makes treatment difficult. Cognitive behavioral therapy has been used with some success, but treatment of the underlying psychiatric illness remains key to resolution of symptoms.

## 28. What is the long-term prognosis of NCCP?

Although there is no increase in overall mortality above the general population, several long-term, outcome-based studies have demonstrated increased morbidity, as well as impaired quality of life in patients with NCCP. As many as two thirds of patients will continue to experience their index symptoms up to 11 years later. Although providing an exact diagnosis may not decrease the frequency or severity of symptoms, patients who understand their pain to be esophageal in origin tend to feel less impaired and use less medical resources for ongoing symptoms.

*The authors would like to acknowledge the contributions of Dr. Amit Agrawal and Dr. Donald O. Castell, who were the authors of this chapter in the previous edition.*

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## BIBLIOGRAPHY

1. Bredenoord AJ, Fox M, Kahrilas PJ, et al. Chicago classification criteria of esophageal motility disorders defined in high-resolution esophageal pressure topography (EPT). *Neurogastroenterol Motil* 2012;24(Suppl. 1):57–65.
2. Cossentino MJ, Mann K, Armbruster SP, et al. Randomized clinical trial: the effect of baclofen in patients with gastro-oesophageal reflux—a randomized prospective study. *Aliment Pharmacol Therapeut* 2012;35:1036–44.
3. Eslick GD. Classification, natural history, epidemiology, and risk factors of noncardiac chest pain. *Dis Mon* 2008;54:593–603.
4. Fass R, Achem SR. Noncardiac chest pain: diagnostic evaluation. *Dis Esophagus* 2012;25:89–101.
5. Fass R, Hershcovici T. Non-cardiac chest pain. the esophagus. 5th ed. Malden, MA: Wiley-Blackwell; 2012. p. 14–41.
6. Flook NW, Moayyedi P, Dent J, et al. Acid-suppressive therapy with esomeprazole for relief of unexplained chest pain in primary care: a randomized, double-blind, placebo-controlled trial. *Am J Gastroenterol* 2013;108:56–64.
7. Gasiorowska A, Fass R. The proton pump inhibitor test in GERD: does it still have a role? *J Clin Gastroenterol* 2008;42:867–74.
8. Hershcovici T, Achem SR, Jha LK, Fass R. Systematic review: the treatment of noncardiac chest pain. *Aliment Pharmacol Ther* 2012;35:5–14.

9. Moawad FJ, Betteridge JD, Boger JA, et al. Reflux episodes detected by impedance in patients on and off esomeprazole: a randomized double-blinded placebo-controlled crossover study. *Aliment Pharmacol Ther* 2013;37(10):1011–8.
10. Nguyen TMT, Eslick GD. Systematic review: the treatment of noncardiac chest pain with antidepressants. *Aliment Pharmacol Ther* 2012;35:493–500.
11. Rao SSC. Diagnosis and management of esophageal chest pain. *Gastroenterol Hep* 2011;7(1):50–2.
12. ROME III Diagnostic criteria for functional gastrointestinal disorders. Available online at <http://www.romecriteria.org/criteria> [Accessed September 22, 2014].
13. Wang WH, Huang JQ, Zheng GF, et al. Is proton pump inhibitor testing an effective approach to diagnose gastroesophageal reflux disease in patients with noncardiac chest pain?: a meta-analysis. *Arch Intern Med* 2005;165(11):1222–8.

# ACHALASIA

Joel E. Richter, MD, FACP, MACG

## 1. Define achalasia.

Achalasia is the most well-recognized esophageal motility disorder and the only primary motility disorder with established pathologic findings. The term is Greek for “failure to relax” and describes the predominant feature of this disorder: a poorly relaxing lower esophageal sphincter (LES). The second cardinal feature is aperistalsis of the esophagus. The first case of achalasia was reported more than 300 years ago by Sir Thomas Willis. The patient’s esophageal obstruction responded to dilation with a whale’s bone.

## 2. How common is achalasia?

Achalasia is a rare disorder that affects all races equally with a mean age at diagnosis of 50 years. The mean incidence of new diagnosis is approximately 0.5 to 1.5 cases per year per 100,000 population. The prevalence of achalasia is much higher, between 8.7 and 10.8 cases per 100,000 population, owing to the fact that achalasia is a chronic disease with a low disease-related mortality rate.

## 3. Where is the pathologic lesion in achalasia?

The pathologic changes identified at autopsy or from myotomy specimens are seen in the esophageal myenteric (Auerbach’s) plexus and include a prominent but patchy inflammatory response consisting primarily of T lymphocytes, loss of ganglion cells, and some degree of myenteric neurofibrosis. The end result of this chronic inflammation is *a selective loss of postganglionic inhibitory neurons containing nitric oxide and vasoactive intestinal polypeptide*. Postganglionic excitatory neurons are spared; therefore cholinergic stimulation continues unopposed, leading sometimes to high resting LES pressure. The loss of inhibitory neurons results in incomplete LES relaxation and aperistalsis is caused by a loss of the latency gradient that permits sequential contractions along the esophageal body, a process mediated by nitric oxide.

## 4. What is the suspected cause of achalasia?

The exact cause is unknown, but evidence is accumulating that an autoimmune response targets the neurons, possibly triggered by an infectious agent. Reports indicate a significant association with specific human leukocyte antigen genotypes (DQA1\*0103 and DQB1\*0603 alleles) and achalasia. Recently, herpes simplex virus type 1 (HSV-1) DNA was demonstrated in esophageal tissue and shown to trigger a persistent immunologic cascade consisting of infiltration of the ganglion cells with cytotoxic CD8 T cells and circulating antineuronal antibodies. As HSV-1 is a neurotrophic virus with a predilection for squamous epithelium, this helps to explain the selective loss of neurons in the esophagus.

## 5. What is the most common complaint in the patient suspected of having achalasia?

**Dysphagia** is reported by most patients with achalasia. Dysphagia is initially more for solids than liquids, but by the time of presentation as many as 70% to 97% of patients have troubling dysphagia for liquids. The onset of dysphagia is usually gradual, being described initially as an infrequent “fullness” in the chest or “sticking” sensation, but usually occurs daily or with every meal by the time of presentation to the physician. Some patients correctly locate their dysphagia to the subxiphoid area, but many complain of dysphagia referred to the cervical esophagus. Patients cut their food up well, chew thoroughly, drink plenty of liquids, and usually are the last to leave the table. Over the years they have learned to accommodate their dysphagia using various maneuvers, including throwing their shoulders back, lifting the neck, or using the head-back position and simultaneously using the Valsalva maneuver in the upright position to help empty the esophagus.

## 6. Are other symptoms commonly associated with achalasia?

**Regurgitation** of undigested retained food or accumulated saliva occurs in approximately 75% of patients with achalasia. The food regurgitated is usually undigested, eaten several hours before, and does not have an acid taste. Unprovoked regurgitation often occurs during or shortly after a meal. It is not unusual for patients to induce vomiting manually to relieve chest discomfort. Other patients complain of thick white phlegm in their mouth, which is the result of regurgitated swallowed saliva. Nocturnal regurgitation can be annoying and quite severe. Regurgitated food or saliva may end up on the pillow case, cause audible gurgling sounds, or may sometimes be aspirated in the trachea, producing bouts of coughing, choking, and rarely aspiration pneumonia. In young women, the symptoms of regurgitation may be confused with an eating disorder.

Less common complaints include chest pain, heartburn, and weight loss. Chest pain is reported by nearly 40% of patients with achalasia, usually younger patients whose esophagi are not very dilated. Symptoms often have no relationship to meals and frequently awaken the patient from a deep sleep. Prominent pain usually occurs early in the course of achalasia when the esophagus is minimally dilated and over time pain usually lessens and sometimes resolves. Surprisingly, heartburn can be seen in up to 50% of patients with achalasia and many times these patients are initially misdiagnosed as having gastroesophageal reflux disease (GERD). Occasionally the heartburn is related to true acid reflux but more frequently it is due to retention of acid-rich beverages or, in patients with very large esophagi, retention of food. In the latter situation, the food may undergo fermentation and the acid sensation is caused by lactic acid rather than hydrochloric acid. These patients typically do not respond to antacids or proton pump inhibitors. More than half the patients with achalasia report weight loss, on average approximately 10 to 20 pounds. However, morbidly obese patients have been described with achalasia.

## **7. What is the best initial test for diagnosing achalasia?**

When achalasia is suspected, a barium esophagram with fluoroscopy is the best initial test. The esophagus is usually dilated and sometimes tortuous, and does not empty barium in the upright position. Retained food and saliva produces an air-fluid level at the top of the barium column. Some patients' esophagus are markedly dilated, resembling a sigmoid colon. The distal esophagus is characterized by a smooth tapering leading to the closed LES that resembles a bird beak. Fluoroscopy always shows a lack of peristalsis replaced by to-and-fro movement in the supine position. Early cases may be misdiagnosed because screening barium x-ray studies fail to reveal esophageal dilation and peristalsis is not evaluated.

## **8. What are the classic manometric features of achalasia?**

Esophageal manometry is required to establish the diagnosis of achalasia and should be done on any patient for whom invasive therapies are planned. Because achalasia only involves the smooth muscle of the esophagus, manometry abnormalities are confined to the distal two thirds of the esophagus. *All patients have at least two manometric abnormalities: aperistalsis and abnormal LES relaxation.* Other abnormalities include elevated LES pressure in up to 50% of patients and an increase in esophageal baseline pressure, often greater than gastric pressure resulting from retention of food and saliva.

## **9. What is high-resolution manometry and how has it improved our ability to diagnosis achalasia?**

High-resolution manometry (HRM) is now the gold standard for diagnosing achalasia. In this procedure, a transnasal catheter incorporating 36 pressure transducers approximately 1 cm apart is passed into the stomach (the old system used five pressure sensors). HRM allows a detailed, colored pressure recording from the pharynx to stomach. For the first time LES relaxation can be accurately measured, introducing a new manometric term: *integrated relaxation pressure (IRP)*. This parameter is automatically calculated to assess the postswallow LES pressure during a 4-second period in between crural diaphragm contractions. Normal IRP in healthy controls is less than 15 mm Hg; therefore values higher than this are the best predictor of impaired LES relaxation in achalasia patients.

With the emergence of HRM, achalasia can now be subclassified into three clinically relevant groups based on the contractile pattern in the esophagus (*Figure 4-1*). In **Type I** (classic achalasia) there is impaired relaxation but no significant pressurization within the esophageal body. In **Type II** achalasia, swallowing of water causes rapid panesophageal pressurization, usually exceeding 30 mm Hg. This may exceed LES pressure, causing the esophagus to empty. **Type III** achalasia (formerly *vigorous achalasia*) is associated with rapidly propagated pressurization; however, these are attributable to normal lumen obliterating contractions as seen with spasm.

## **10. Do any manometric features of achalasia predict response to therapy or direct therapy?**

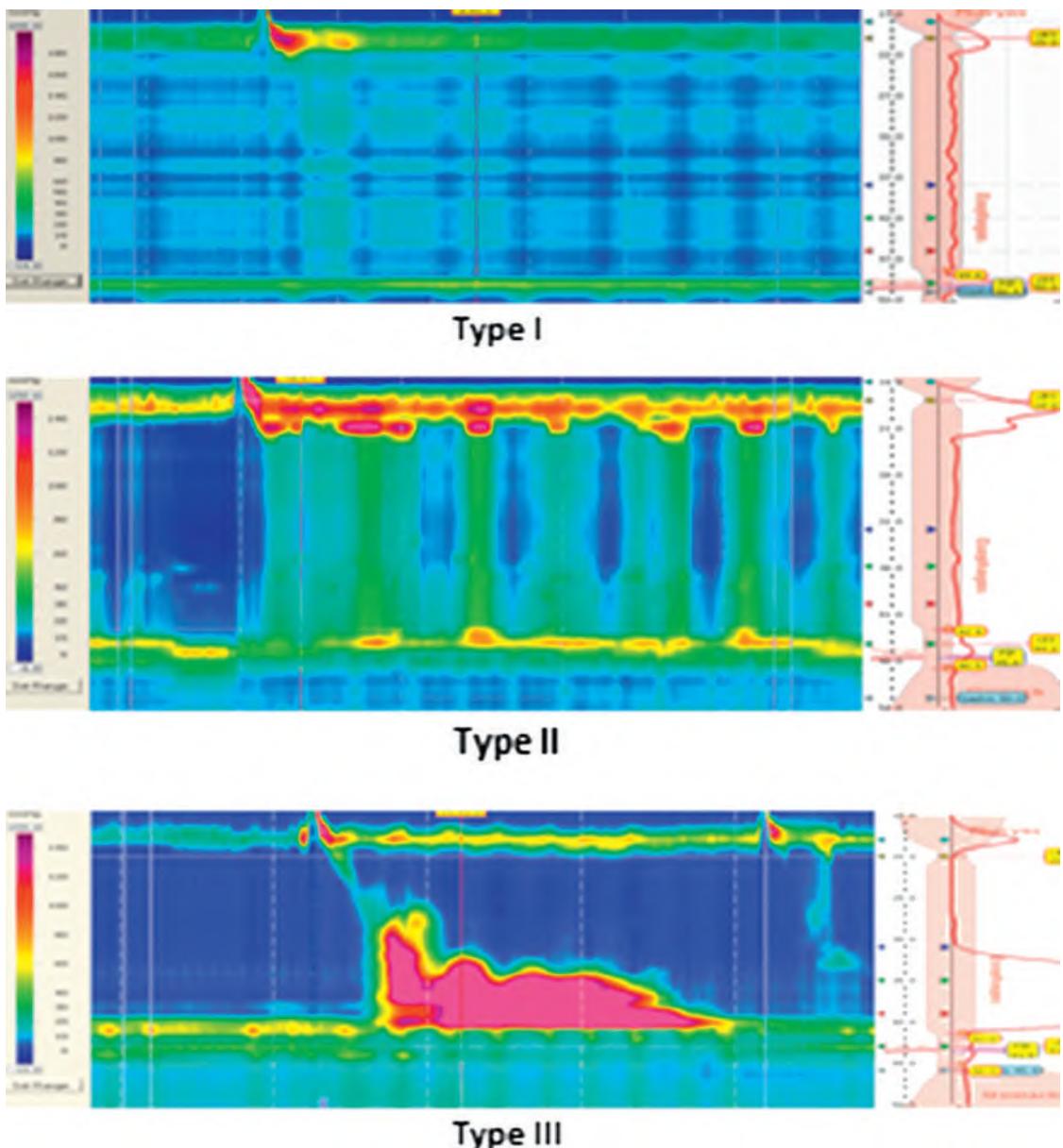
Until the advent of HRM, the answer was no. However, for the first time, the esophageal patterns defined by HRM can be used to predict response to various treatments. **Type I** and especially **Type II** achalasia patients (60%-100%) respond well to pneumatic dilation, Heller myotomy, or botulinum toxin. **Type III** responds less well (approximately 30%) and may do best with surgical myotomy.

## **11. Is there a role for endoscopy in the evaluation of achalasia?**

Endoscopy may be reported as normal in a surprising number of patients in whom achalasia is not suspected before the procedure. In more obvious cases, the esophagus is dilated and contains a variable amount of clear fluid; saliva; or retained, macerated food. With long-standing disease, the esophagus can be very tortuous and sometimes it is difficult to intubate the LES. The esophageal mucosa demonstrate a variety of changes from mild erythema to frank erosions or even ulcerations. The LES appears puckered and remains closed with air insufflation; however the endoscope usually passes into the stomach with gentle pressure. In some patients a "pop" is noted, but this is uncommon. If excessive pressure is required, the presence of pseudoachalasia should be highly suspected. Retroflex view of the cardia should always be done and biopsy samples obtained from suspicious areas to exclude a malignancy before treatment.

## **12. What are the two most common diseases mimicking achalasia?**

In Central and South America, Chagas disease is a multisystem infectious disease caused by the protozoan *Trypanosoma cruzi* and transmitted by bites from the reduviid (kissing) bugs. Ganglion cells are destroyed



**Figure 4-1.** High-resolution manometry examples of the three types of achalasia proposed by Pandolfino and colleagues (2008). Type I is characterized by the absence of esophageal pressurization to more than 30 mm Hg. Type II is associated with panesophageal pressurization to greater than 30 mm Hg observed after at least 2 of 10 water swallows. Type III has spastic contractions caused by abnormal lumen, obliterating contractions with or without periods of panesophageal pressurization.

throughout the body, resulting in megaesophagus, duodenum, colon, and rectum damage. The esophageal disease is identical to idiopathic achalasia. Many patients have cardiac disease, which is the leading cause of death in Chagas patients.

In other regions, “pseudoachalasia” secondary to malignancies represent approximately 3% of all achalasia patients and approximately 10% of achalasia patients older than 60 years of age. It should be suspected in older adult patients with rapidly progressing dysphagia and weight loss, but it can be seen in much younger individuals. The most common cancers are adenocarcinoma of the esophagus and stomach, but rare tumors such as *breast, prostate, lung, and lymphoma* have been reported. The diagnosis usually can be made at endoscopy with multiple biopsies. Sometimes endoscopic ultrasound with directed biopsies may be helpful.

### 13. Are we seeing more secondary cases of achalasia?

Rare causes of secondary achalasia include *amyloidosis, eosinophilic esophagitis, sarcoidosis, and pancreatic pseudocysts*. Increasingly, secondary achalasia is being recognized after laparoscopic fundoplication and especially gastric banding. In these situations, the fundoplication is too tight around the distal esophagus or the gastric band has been misplaced too high near the esophagogastric junction (EGJ), impairing esophageal emptying. These patients complain of dysphagia and the esophagus dilates. Usually, correction of these surgical problems results in return of peristalsis and resolution of the dysphagia.

### 14. What are the goals for the treatment of achalasia?

No treatment can restore muscle activity to the denervated esophagus. Treatment is directed at reducing the gradient across the LES with three goals:

1. Relieve the primary symptoms of dysphagia and regurgitation.
2. Improve esophageal emptying.
3. Prevent the development of megaesophagus over time.

Overall, using single or multiple modalities of treatment, more than 90% of achalasia patients do well. However, the disease is never “cured” and touch-up treatments are required over longer periods of follow up.

### 15. Are oral drugs available for treating achalasia?

The two most common oral agents for treating achalasia are nitrates and calcium channel blockers. Nitrates increase nitric oxide concentration in smooth muscle cells, promoting muscle relaxation. Channel blockers inhibit cellular calcium uptake and lower LES pressure by approximately 50%. Nitrates in the form of isosorbide dinitrate (5 mg) or nifedipine (10–30 mg) are given sublingually approximately 15 to 30 min before meals and at bedtime. A significant drawback is the occurrence of side effects such as hypotension, headaches, and dizziness in approximately 30% of patients; drug tolerance develops over time.

### 16. How does botulinum toxin work in achalasia?

Botulinum toxin A injected directly into the LES is the most common drug used in treating achalasia. It is a neurotoxin that blocks the release of acetylcholine from the nerve terminals. The effect is temporary as the cholinergic synapses eventually regenerate. Although there are five commercial formulations of botulinum toxin with variable potencies, most studies have used Botox (Allergan Inc., Irvine, CA) or Dysport (Ipsen Pharmaceutical, Bologne-Billancourt, France). Botox is available in vials containing 100 units of the lyophilized powder. For use in achalasia, this can be diluted in 5 mL of normal saline to yield a solution containing 20 units/mL. Flexible upper endoscopy is performed and the toxin injected via a 5-mm sclerotherapy needle into the LES region, piercing the mucosa approximately 1 cm above the Z line and slanting the needle approximately 45 degrees. The injections are administered in 5 aliquots (total of 100 units) distributed circumferentially around the closed LES.

### 17. What are the results of Botox therapy?

Using doses of 80 to 100 units of Botox, there is clinical improvement within 1 month in more than 80% of patients, but fewer than 60% are in remission at 1 year. Older patients and those patients with vigorous achalasia have a more favorable response to Botox. Of those responding to the first injection, 75% respond to a second Botox injection, but some report a decreased response to further injections, probably from antibody production to the foreign protein. Five randomized trials comparing botulinum toxin to pneumatic dilation and one to laparoscopic myotomy found comparable dysphagia relief initially, but rapid deterioration in the drug-treated group over 6 to 12 months.

### 18. Does Botox have any side effects or short comings?

Botox should not be given to patients with an egg allergy. Otherwise, the drug is safe and simple to administer. Reported complications have included transient chest pain and heartburn. The major drawback is its cost (approximately \$500/vial) coupled with the need for multiple injections. Some surgical reports suggest that repeated injections of Botox make surgical planes between tissue more difficult to dissect. However, the outcomes after surgery appear not to be affected, whether or not Botox has been previously administered.

### 19. Where do botulinum toxin injections have greatest utility in the treatment of achalasia?

In the United States, botulinum toxin injections tend to be the first line of treatment for older adult patients or those with severe comorbid illnesses because it is safe and improves symptoms, and because older patients generally require treatments no more frequently than once a year. It should not be used in healthy younger patients, as more definitive treatments are available. Botulinum toxin treatment may be cost effective for achalasia patients living less than 2 years.

### 20. How is pneumatic dilation of the LES performed?

Pneumatic dilation tears the LES by partially stretching the muscle using air-filled balloons. The procedure has been markedly simplified using the Microvasive Rigiflex balloon system (Boston Scientific Corp, Massachusetts USA). These noncompliant polyethylene balloons come in three diameters (30, 35, 40 mm) mounted on a flexible catheter placed over a guidewire at endoscopy. The procedure adds approximately 5 minutes to initial endoscopy. The achalasia balloon is positioned across the LES with the location determined by fluoroscopy. The “waist,” caused by the nonrelaxing LES, is gradually flattened using 7 to 15 psi of air held for 15 to 60 seconds.

Most procedures are done in an outpatient setting, with the patient observed for 2 to 4 hours before returning to normal activities the next day. Dilatations are usually started with the smallest balloon (30 mm) and then repeated at 2- to 4-week intervals, with serially larger balloons if symptom relief and improved esophageal emptying does not occur.

## **21. What are the results of pneumatic dilation?**

In a recent review of nearly 1200 patients across 24 studies with an average follow up of 3 years, Rigiflex pneumatic dilation resulted in good to excellent symptom relief in 74%, 86%, and 90% of patients with 30-, 35-, and 40-mm balloons, respectively. Over 5 years, nearly one third of patients have symptom relapses; however, long-term remission can be achieved in most patients by repeat dilations “on demand” based on symptom recurrence. If the patient fails three serial balloon dilations, most authorities then recommend surgery. Pneumatic dilation is the most cost-effective treatment for achalasia during a 5- to 10-year postprocedure window.

## **22. Are there subsets of patients who do better with pneumatic dilation?**

Patients with the best outcomes following pneumatic dilation are older (older than 40 years), women, and those with Type II pattern confirmed by HRM. Nevertheless, pneumatic dilation can be done on almost any patient. Some authorities recommend beginning with the 35 mm balloon when treating young men and those who have undergone a previous Heller myotomy.

## **23. What are the complications associated with pneumatic dilation?**

Poor cardiopulmonary status or other comorbid illnesses preventing surgery, should a perforation occur, are absolute contraindications to pneumatic dilations. Up to 33% of patients have complications after pneumatic dilation, but most complications are minor, with chest pains being most common. Esophageal perforations are the most serious complications with an overall rate in experienced hands of 2% (range, 0%-16%) of which 50% will require surgery. Severe complications of GERD are rare after pneumatic dilatation, but 15% to 35% of patients have heartburn responding to proton pump inhibitors.

## **24. What are the critical elements of the laparoscopic myotomy for treating achalasia?**

From a surgical point of view, minimally invasive myotomy through the abdomen has become the gold standard for treating achalasia. Patients are usually hospitalized for less than 48 hours and return to work within 2 weeks. Recent surgical improvements include extending the myotomy 2 to 3 cm onto the proximal stomach to cut the gastric sling fibers thereby nearly obliterating LES resting pressure and the addition of an incomplete fundoplication (Dor or Toupet) to decrease complications of severe acid reflux.

## **25. How successful is surgical myotomy for achalasia?**

Clinical success rates after laparoscopic myotomy are very high, on average 89% (ranging from 75% to 100%) after an average follow up of nearly 3 years. However, the success rate drops to 65% to 85% after 5 years, probably as a result of progression of the disease and GERD complications. Patients failing pneumatic dilatation or botulinum toxin treatment can be successfully treated with surgical myotomy, although some studies suggest a lower success rate.

## **26. Are there predictors of surgical success for myotomy?**

Positive predictive factors for successful myotomy include younger patients (<40 years), men, LES pressure more than 30 mm Hg, and a straight esophagus. As with pneumatic dilatation, the Type II HRM achalasia pattern has the best outcome after surgery. However, recent data suggest that surgery is superior in Type III patients, probably because of the more extensive proximal disruption of the esophageal muscle.

## **27. What are the major problems with surgery?**

Laparoscopic myotomy is very safe, with a mortality rate approximately 0.1%. The most common complication is perforation of the esophageal or gastric mucosa (range, 0%-35%) during myotomy, which is usually recognized during the procedure and repaired without clinical consequences. Recurrence of dysphagia, if it occurs after myotomy, usually develops within 12 to 18 months. The most common cause is an incomplete myotomy, usually on a gastric side where the dissection is more complicated, late scarring of the myotomy, and an obstructing antireflux wrap. Recurrent dysphagia after myotomy can be treated with pneumatic dilatation or repeat myotomy. GERD can be a severe complication after myotomy with a reported rate approaching 50%. Approximately 25% of patients will have moderate to severe esophagitis and 7% to 10% of patients may develop Barrett's esophagus and occasionally a secondary adenocarcinoma.

## **28. Which is the best treatment for the healthy patient with achalasia?**

Until recently, addressing this question has been difficult because large prospective randomized studies were not available. This changed in 2011 with the publication of the European Achalasia Trial from five countries randomizing 94 patients to Rigiflex pneumatic dilation (30 and 35 mm with up to three repeat dilations) and 106 to laparoscopic myotomy with Dor fundoplication performed by physicians highly skilled in both procedures. Over 2 years, both treatments had comparable success in relieving symptoms (92% for dilation versus 87% for myotomy), improving barium emptying, and decreasing LES pressure. Although longer follow up is planned, this study indicates that both treatments are equally effective at least over 2 to 3 years.

### 29. What is the new endoscopic treatment for achalasia?

Developed in Japan, peroral esophageal myotomy is the most exciting new treatment for achalasia being widely studied in the United States and Europe. An endoscopic myotomy is performed using a submucosal tunnel; the circular muscles are divided over a minimum of 6 cm in the distal esophagus and 2 cm onto the cardia, and the mucosal entry side is closed with standard endoscopic clips. Small studies usually involving fewer than 20 patients report success rates on average of 90% with decreases in LES pressure and improved esophageal emptying. However, the procedure is technically demanding; many patients get mediastinal air leaks and purulent mediastinitis is a possible complication; and follow-up is still short, on average 6 months. More importantly, an antireflux procedure is not included in this procedure and the risk of GERD may be considerable (up to 45% in one study), which may represent a serious drawback.

### 30. What is the follow-up treatment for the patient with treated achalasia?

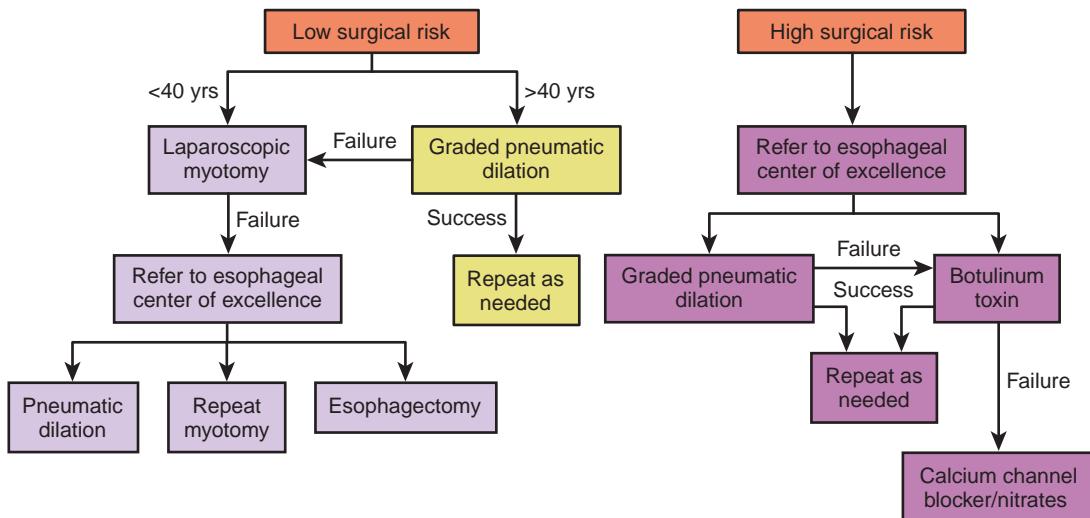
Because achalasia is never cured, all patients regardless of treatment or symptoms need physiologic follow up of their achalasia. Previously, the preferred physiologic test was repeat measurements of the LES; however, a recent study suggests an upright timed barium esophagram gives better information. In this test, the patient is given 8 ounces of thin barium to drink in the upright position and esophageal emptying is assessed at 1 and 5 minutes. In the recent European Achalasia Trial, the timed barium esophagram was more predictive of 2-year outcome (88%) than postprocedure LES pressure. Newer testing suggests that barium emptying correlates well with EGJ distensibility. Those patients with normal distensibility usually have complete upright emptying by 5 minutes, whereas those with persistent impaired esophageal opening have an average barium column height of 5 to 8 cm at 5 minutes. Patients with symptom relief and good esophageal emptying do well in the long term, and should be checked every 2 to 3 years. Those with persistent symptoms or poor esophageal emptying warrant further treatment or close follow up in 1 year.

### 31. Is achalasia a premalignant condition?

The risk of developing esophageal cancer, particularly squamous cell cancer, is increased by ten- to fiftyfold in achalasia. However, incidence of cancer is rare overall, endoscopic surveillance is difficult, and there are no recommendations for routine follow up by gastroenterology societies. If considered, it seems most reasonable in those patients with a very large esophagus and poor draining, as the cancer is most related to chronic stasis and inflammation in the esophageal body.

### 32. What is a good algorithm for treating the patient with achalasia?

A treatment algorithm is determined by the skills of the surgeon and gastroenterologists in your community. Figure 4-2 depicts an algorithm commonly used at centers seeing a large volume of achalasia patients.



**Figure 4-2.** Suggested algorithm for the treatment of achalasia. (From Boeckxstaens GE, Zanitto G, Richter JE: Achalasia, Lancet 2014;383:83–93.)

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

1. Boeckstaens GE, Annese V, des Varannes SB, et al. Pneumatic dilation vs laparoscopic Heller myotomy for idiopathic achalasia. *N Engl J Med* 2011;364:1807–16.
2. Boeckxstaens GE, Zanitto G, Richter JE. Achalasia. *Lancet* 2014;383:83–93.
3. Bresadola V, Feo CV. Minimally invasive myotomy for the treatment of esophageal achalasia: evolution of the surgical procedure and the therapeutic algorithm. *Surg Laparosc Endosc Percutan Tech* 2012;22:83–7.
4. Facco M, Brun P, Baesso I, et al. T cells in the myenteric plexus of achalasia patients show a skewed TCR repertoire and react to HSV-1 antigens. *Am J Gastroenterol* 2008;103:1598–609.
5. Ghosh SK, Pandolfino JE, Rice J, et al. Impaired degllutitive EGJ relaxation in clinical esophageal manometry: a quantitative analysis of 400 patients and 75 controls. *Am J Physiol Gastrointest Liver Physiol* 2007;293:G878–85.
6. Katzka DA, Castell DO. Review article: an analysis of the efficacy, perforate rates and methods used in pneumatic dilation for achalasia. *Aliment Pharmacol Ther* 2011;34:832–9.
7. Leeuwenburgh I, Scholten P, Alderliestein J, et al. Long-term esophageal cancer risk in patients with primary achalasia: a prospective study. *Am J Gastroenterol* 2010;105:2144–9.
8. Lynch KL, Pandolfino JE, Howden CW, Kahrilas PJ. Major complications of pneumatic dilation and Heller myotomy for achalasia. Single-center experience and systematic review of the literature. *Am J Gastroenterol* 2012;107:1817–25.
9. Naeff M, Mouton WG, Naeff U, et al. Esophageal dysmotility disorders after laparoscopic gastric banding—an underestimated complication. *Ann Surg* 2011;253:285–90.
10. Pandolfino JE, Kwiattek MA, Nealis T, et al. Achalasia: a new clinically relevant classification by high-resolution manometry. *Gastroenterology* 2008;135:1526–33.
11. Ramzan Z, Nassri AB. The role of Botulinum toxin injection in the management of achalasia. *Curr Opin Gastroenterol* 2013;29:468–73.
12. Richter JE, Boeckstaens GE. Management of achalasia: surgery or pneumatic dilation. *Gut* 2011;60:869–76.
13. Rohof WO, Hirsch DP, Kassing BF, Boeckstaens GE. Efficacy of treatment for patients with achalasia depends on the distensibility of the esophagogastric junction. *Gastroenterology* 2012;143:328–35.
14. Rohof WO, Salvador R, Annese V, et al. Outcomes of treatment of achalasia depend on manometric subtype. *Gastroenterology* 2013;718–25.
15. Sandowski DC, Ackah F, Jiang B, Svenson LW. Achalasia: incidences, prevalence and survival. A population-based study. *Neurogastroenterol Motil* 2010;22(9):256–61.
16. Swanstrom LL, Kurian A, Dunst CM, et al. Long-term outcomes of an endoscopic myotomy for achalasia. The POEM procedure. *Ann Surg* 2012;256:659–67.
17. Vaezi MF, Baker ME, Achkar E, Richter JE. Timed barium oesophagram: better predictor of long-term success after pneumatic dilation in achalasia than symptom assessment. *Gut* 2002;50:765–70.
18. Vela MF, Richter JE, Wachberger D, et al. Complexities of managing achalasia at a tertiary center: use of pneumatic dilation, Heller myotomy and botulinum toxins injection. *Am J Gastroenterol* 2004;99:1029–36.
19. Wen ZH, Gardner E, Wang YP. Nitrates for achalasia. *Cochrane Database Syst Rev* 2004;(1), CD002299.
20. Zerbib F, Thetiot V, Richy F, et al. Repeated pneumatic dilations as long-term maintenance therapy for esophageal achalasia. *Am J Gastroenterol* 2006;101:692–7.

## Websites

- Cleveland Clinic. Treatments and procedures: achalasia overview. [http://my.clevelandclinic.org/disorders/achalasia/ts\\_overview.aspx](http://my.clevelandclinic.org/disorders/achalasia/ts_overview.aspx) [Accessed September 22, 2014].
- [MedicineNet.com](http://www.medicinenet.com/achalasia/patient-comments-284.htm). Patient comments: achalasia—describe your experience. <http://www.medicinenet.com/achalasia/patient-comments-284.htm> [Accessed September 22, 2014].

# ESOPHAGEAL CANCER

Peter R. McNally, DO, MSRF, MACG, Nimish B. Vakil, MD, FACP, FACG, AGAF, FASGE, and John C. Deutsch, MD

## 1. How common is esophageal cancer?

Cancer of the esophagus accounts for 1% of all newly diagnosed cancers in the United States. In 2013, approximately 17,990 new esophageal cancer cases were diagnosed (14,440 in men and 3550 in women) and there were approximately 15,210 deaths from esophageal cancer (12,220 in men and 2990 in women). This disease is three to four times more common among men than among women. The lifetime risk of esophageal cancer in the United States is approximately 1 in 125 in men and 1 in 435 in women.

## 2. Is the incidence of esophageal cancer increasing?

No, the incidence of esophageal carcinoma in the United States has plateaued for the last decade. However, significant changes have been observed in the cell types of esophageal cancer seen. Forty years ago squamous cell carcinoma (SCCA) was the most common form of esophageal cancer in the United States; now adenocarcinoma (AdenoCA) is the most common form of esophageal carcinoma ([E-Figure 5-1](#)).

Esophageal cancer was once much more common in black patients than in whites, but it is now about equally as common, as rates have fallen in blacks and increased slightly in whites during the past few decades. SCCA is the most common type of cancer of the esophagus among blacks, whereas AdenoCA is more common in whites.

## 3. Are there geographical variations in the incidence of esophageal cancer?

Yes. The incidence of esophageal cancer varies internationally nearly sixteenfold. For example, esophageal cancer rates in the “esophageal cancer belt” (Iran, Northern China, India, and parts of Africa) are 10 to 100 times higher than in the United States. Exposure to tobacco, low levels of soil selenium, high ingestion of nitrosamines and hot liquids, and low intake of fruits and vegetables are thought to be causative factors.

## 4. What are the most common types of esophageal cancer?

Worldwide the most common type of esophageal cancer is SCCA (90%-95% of all esophageal cancers), whereas in the United States the incidence of SCCA has dwindled during the last 40 years. Prior to 1970, SCCA was the most common cell type in the United States, but in recent years AdenoCA has become the most common type of esophageal cancer (see [E-Figure 5-1](#)). A decline in tobacco use and smoking is thought to be responsible for the decline in SCCA, whereas the epidemic of obesity and gastroesophageal reflux disease (GERD) are responsible for the increase in AdenoCA.

## 5. What is the association between bisphosphonates and esophageal cancer?

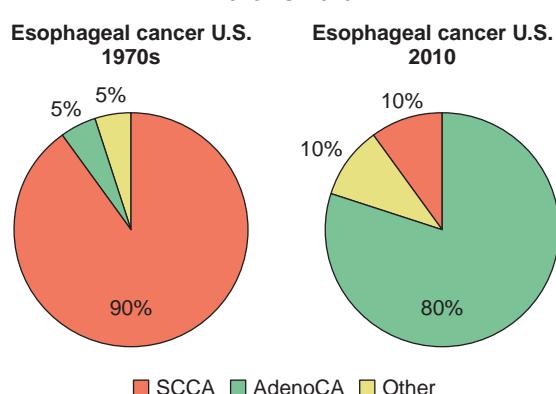
Use of bisphosphonates has been linked to esophageal AdenoCA and SCCA in postmarketing surveillance. As a result, the Food and Drug Administration has recommended that oral bisphosphonates not be used in patients with BE.

## 6. What are the current recommendations for screening of esophageal cancer in the United States?

Currently, there is no cost-effective method of screening for esophageal cancer in the United States. Several patient subgroups are at increased risk for esophageal cancer and should be independently considered for endoscopic screening. These are patients with:

- Achalasia
- Lye ingestion
- Plummer-Vinson syndrome
- Tylosis

There are no strict guidelines for endoscopic cancer screening for patients with achalasia or previous lye ingestion, but some experts suggest endoscopic examination and biopsy at the 15-year mark and the need for a low threshold to investigate dyspeptic and dysphagia symptoms. Dysphagia symptoms associated with Plummer-Vinson syndrome should be investigated with endoscopy and biopsy and iron deficiency corrected. Patients with tylosis should begin endoscopic surveillance at the age of 30. Most cases of esophageal cancer in these patients have been noted in the distal esophagus, so attention should be focused in this area during the examination. BE is associated with increased risk for AdenoCA of the esophagus. However, optimal cost-effective screening for the identification of BE is debated. The American College of Gastroenterology guidelines suggest that patients with chronic GERD are most likely to have BE and should undergo endoscopy. The highest yield for BE is in white men older than 50 years of age who have a long history of reflux symptoms. Once BE is

TRENDS IN ESOPHAGEAL CANCER CELL TYPE  
1970 VS. 2010

**E-Figure 5-1.** Comparison of esophageal cancer cell types: 1970 versus 2010 demonstrating a shift from squamous cell carcinoma (SCCA) as the predominant esophageal cancer cell type in the 1970s to adenocarcinoma (AdenoCA) cell type in 2010.

identified, periodic esophagogastroduodenoscopy (EGD) and biopsy is recommended. The reader is referred to Chapters 7 and 62, "Barrett's Esophagus" and "Endoscopic Cancer Screening and Surveillance," respectively, for additional information.

### 7. What gastrointestinal disorders are associated with increased risk for esophageal cancer?

- Achalasia: SCCA
- Plummer-Vinson syndrome: SCCA
- BE: AdenoCA
- Celiac disease: SCCA
- Prior gastrectomy: SCCA

### 8. What are the typical clinical features of esophageal cancer?

Although SCCA typically occurs in the upper and middle esophagus and AdenoCA typically occurs in the distal esophagus, both have similar clinical presentations. The most common age of onset for esophageal cancer is 65 to 74 years. Typical clinical features of esophageal cancer are shown in Table 5-1.

**Table 5-1.** Clinical Features of Esophageal Cancer

CLINICAL FEATURE	FREQUENCY (%)	SIGNIFICANCE
Peak age at onset	65-75	Comorbidities often preclude operability
Gender (♂ : ♀)	4:1	Much more common in men
Race (black: white)	50:50	SCCA > black men AdenoCA > white men
Dysphagia	90	Often advanced disease
Anorexia and weight loss	75	
Odynophagia	50	Suggests tumor ulceration
Chest pain, often radiates to back	Less frequent	Implies invasion of neuromediastinal structures
Vocal cord paralysis	Less frequent	Suggests invasion more typical of SCCA
Cough and pneumonia	Less frequent	Esophageal obstruction, aspiration, fistula
Hoarseness	Less frequent	High GERD, coincident ENT malignancy, SCCA invasion
Hiccups	Less frequent	Diaphragmatic involvement

AdenoCA, Adenocarcinoma; ENT, ear, nose, and throat; GERD, gastroesophageal reflux disease; SCCA, squamous cell carcinoma.

### 9. What are the risk factors for esophageal cancer?

Risk factors for esophageal cancer vary according to cell type and are outlined in Table 5-2. Tobacco and alcohol are the most commonly identified risk factors, but obesity has recently been identified as an important

**Table 5-2.** Risk Factors for Esophageal Cancer

RISK FACTOR	SQUAMOUS CELL CARCINOMA	ADENOCARCINOMA
Tobacco use	+	+
Alcohol use	+	-
Barrett's esophagus	-	+
Frequent gastroesophageal reflux	-	+
Body mass index > 30	-	+
Low socioeconomic status	+	-
Prior caustic lye ingestion	+	-
Diet: high N-nitroso compounds, pickled vegetables, toxic fungi, areca nuts or betel quid, hot beverages, low selenium and zinc	+	-
Human papilloma virus	+	?

independent risk factor. Barrett's esophagus (BE) is an acquired condition associated with metaplastic replacement of normal squamous epithelium with a columnar lining caused by chronic gastroesophageal reflux. The incidence of AdenoCA increases nearly fortyfold in patients with BE and is the most significant risk factor for esophageal cancer. It is estimated that 5% of patients with BE will eventually develop invasive cancer, and patients with histologically proven BE require lifelong surveillance because of this risk. It is generally believed that disease progresses from Barrett's metaplasia to low-grade dysplasia to high-grade dysplasia to AdenoCA.

#### **10. Is there a link between current or past history of ear, nose, and throat (ENT) conditions and esophageal cancer?**

Yes. This probably reflects exposure to common SCCA risk factors, such as smoking and alcohol. Although some studies have suggested the incidence of synchronous or metachronous SCCA to be between 3% and 14%, there are no accepted guidelines for periodic surveillance. The American Society of Gastrointestinal Endoscopy does recommend a single EGD to evaluate for synchronous esophageal cancer in patients with ENT malignancy. It is prudent for caregivers to have a low threshold for investigation of aerodigestive symptoms among these patients and to engage in a regular, directed inquiry about symptoms of dysphagia.

#### **11. What genetic condition is highly associated with SCCA of the esophagus?**

Nonepidermolytic palmoplantar keratoderma (tylosis) is a rare autosomal-dominant disorder defined by a genetic abnormality at chromosome 17q25 and is the only recognized familial syndrome that predisposes patients to SCCA of the esophagus. It is characterized by hyperkeratosis of the palms and soles, as well as by thickening of the oral mucosa, and in affected families it confers up to a 95% risk of SCCA of the esophagus by the age of 70 years.

#### **12. What type of cancers have been reported to metastasize to the esophagus?**

Metastatic carcinoma to the esophagus is unusual, but melanoma and breast cancer are the most common.

#### **13. What is the prognosis for esophageal cancer presenting with dysphagia?**

Prognosis is poor; 50% to 60% of patients presenting with dysphagia have incurable locally advanced disease or metastasis. Two factors seem to be responsible for this: tumors are usually far advanced before sufficient luminal narrowing occurs to cause obstructive symptoms, and the lack of an outer esophageal serosa reduces the resistance to local spread.

#### **14. Is infection with *Helicobacter pylori* associated with increased risk for esophageal cancer?**

No. There is actually an inverse relationship between *H. pylori* infection and the risk for development of AdenoCA of the esophagus. The prevalence of the more virulent cagA+ strain of *H. pylori* is lower in patients with more severe complications of GERD. Also, the odds of having BE complicated by dysplasia or cancer is reduced more than twofold in patients infected with cagA+ strains.

#### **15. How is esophageal cancer diagnosed and staged?**

Endoscopy and biopsy are necessary for the diagnosis of esophageal cancer. Precise cancer staging is of critical importance in the management of patients with esophageal cancer. Accurate staging helps to determine the choice of treatment and is an important determinant of prognosis. Staging should include a clinical examination, blood counts, endoscopy (including bronchoscopy in patients with SCCA) and a computed tomography scan of the chest and abdomen. In patients who are candidates for surgery, high-resolution endoscopic ultrasound is essential to assess the depth of invasion (T stage) and lymph node (N stage). Positron emission tomography (PET) can be helpful in identifying otherwise undetected distant metastases. The strengths and weaknesses of these staging modalities are outlined in [E-Table 5-3](#).

#### **16. What are the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging criteria for esophageal cancer?**

The AJCC TNM staging criteria for esophageal cancer are outlined in [Table 5-4](#).

#### **17. What are the general principles that guide the management of esophageal cancer?**

Interdisciplinary planning is essential in the management of patients with esophageal cancer. Interventions are based on operability ("fitness" to tolerate surgery), stage of disease, and cell type. An algorithm defining the pathway for patients with limited (stage I) and locally advanced (stage II-III) esophageal cancer is demonstrated in [Figure 5-2](#) and [Figure 5-3](#).

#### **18. What AJCC stage of esophageal cancer is considered amenable to endoscopic treatment?**

Consideration of endoscopic resection (ER) for early esophageal cancer (T1a) requires precise staging and the use of high-frequency endoscopic ultrasound. A more comprehensive subclassification scheme has been

**E-Table 5-3.** Methods of Esophageal Cancer Staging

METHOD	STRENGTH	WEAKNESS
Endoscopy	Tissue sampling Location (cervical, thoracic, abdominal) Tumor >5 cm, poor prognosis	No N or M staging
CT chest and abdomen	Readily identified significant metastasis	Limited value for celiac axis nodal involvement Limited for small metastasis
EUS	Best for T and N staging	Limited for M staging Limited by obstructing tumors (30% of esophageal cancers)
FDG-PET PET scan +/- integrated CT	Complements EUS and CT Most cost effective for detecting occult metastasis	FDG uptake by primary esophageal tumor may obscure local N Poor spatial resolution
Bronchoscopy	Esophageal cancers of the proximal esophagus, at or above the carina	

CT, Computed tomography; EUS, endoscopic ultrasound; FDG, (18 F)-2-deoxy-D-glucose; M, metastasis; N, node; PET, positron emission tomography; T, tumor.

**Table 5-4.** American Joint Committee on Cancer Esophageal Cancer Staging Guidelines

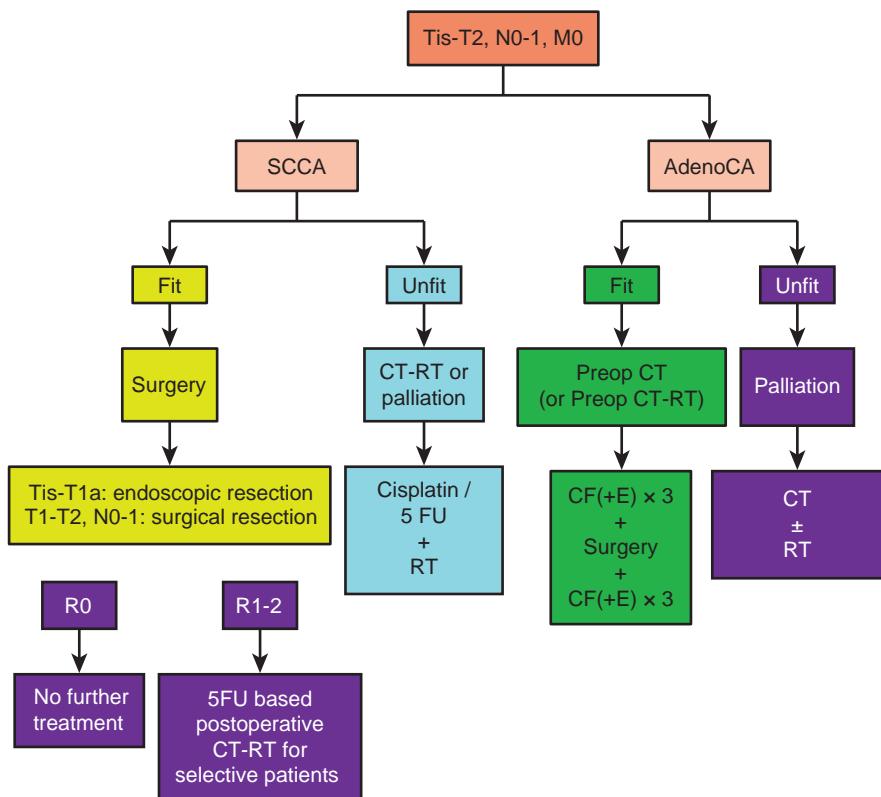
<b>Primary Tumor (T-Stage)</b>	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia (Note: this includes <i>carcinoma in situ</i> , a term no longer used)
T1	Tumor invades lamina propria, muscularis mucosa, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosa
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures: aorta, vertebrae, trachea
<b>Regional Lymph Nodes (N)</b>	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in $\geq 7$ regional lymph nodes
Note: 2010 TNM staging no longer classifies (+) celiac axis lymph node M1a; it is just N (+).	
<b>Distant Metastasis (M)</b>	
M0	No distant metastasis
M1	Distant metastasis
<b>Histologic Grade (G)</b>	
GX	Grade cannot be assessed—stage in grouping as G1
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated—stage in grouping G3
<b>Stage</b>	
Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
Stage IIA	T2, N0, M0; T3, N0, M0
Stage IIB	T1, N1, M0; T2, N1, M0
Stage III	T3, N1, M0; T4, any N, M0
Stage IVA	Any T, any N, M1a
Stage IV B	Any T, any N, M1b

TNM, Tumor, node, metastasis.

Edge SB, Byrd DR, Compton CC, et al: American Joint Committee on Cancer staging manual, ed 7, New York, 2010, Springer, p 103.

proposed for early esophageal cancers and is useful in deciding on ER. According to this classification, mucosal tumors are divided into three types based on the depth of invasion:

- M1: limited to the epithelial layer
- M2: invades the lamina propria
- M3: invades into, but not through, the muscularis mucosa



**Figure 5-2.** Esophageal cancer treatment algorithm for limited disease (stage I). AdenoCA, Adenocarcinoma; C, cisplatin; CT, chemotherapy; E, epirubicin; F, fluorouracil; R0, complete resection; R1-2, incomplete resection; RT, radiation therapy; SCCA, squamous cell carcinoma.

Lymph node metastasis with M1 and M2 lesions is uniformly 0, but among M3 lesions LN (+) has been seen consistently in approximately 8% to 12%. Identification of lymphovascular invasion seems to portend significant additional risk for nodal metastasis. For M3 esophageal cancers treated with ER, the 5-year rate of metastasis with and without lymphovascular invasion was 47% versus 7%, respectively.

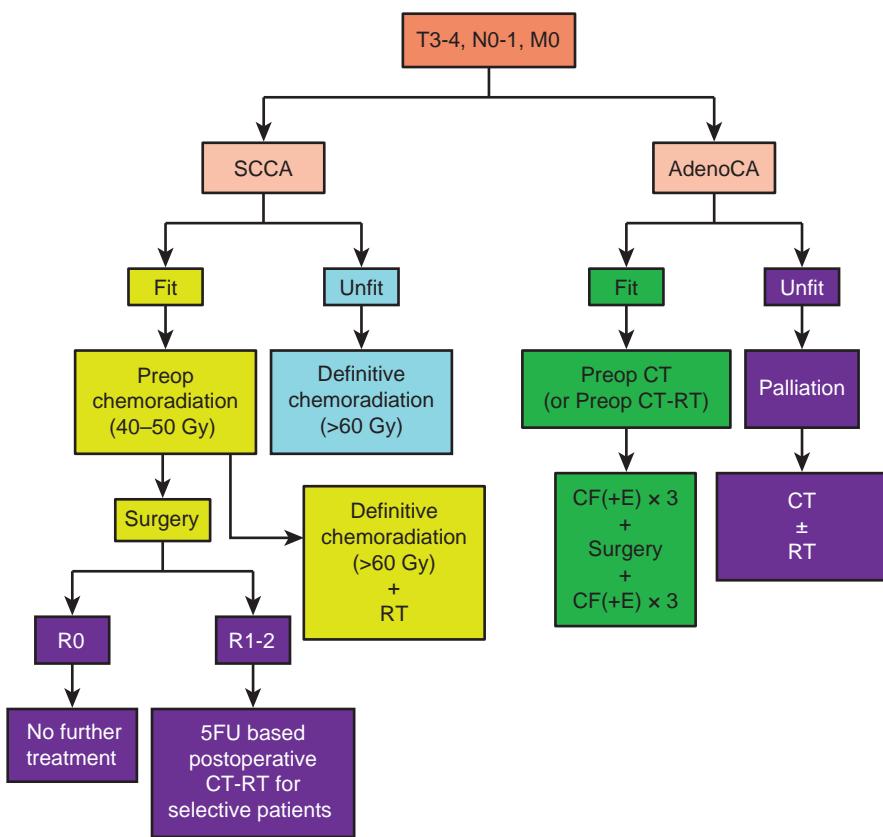
ER techniques include endoscopic mucosal resection (EMR) and endoscopic submucosal dissection. Both techniques require specialized skill and equipment, and do carry potential procedural risk (postresection bleeding [10%), perforation rates [2%-5%], and stricture [5%-17%]) that need to be thoroughly discussed with the patient. Description of these ER techniques and other evolving ablative therapies is beyond the scope of this chapter; please see the referenced websites for video demonstration and further description.

#### 19. What is the standard of care for “fit” patients with localized tumors?

Surgical resection is still the standard of care for local disease. In expert surgical hands, patients with stage I disease have 5-year survival of 40% to 50%. The reader is referred to Chapter 73 for details about surgical options. Radiation therapy alone can cure a minority of patients with SCCA and has been supplanted by combination therapy. Preoperative chemotherapy is of benefit in patients with AdenoCA. Preoperative chemoradiation has been shown to confer a survival benefit, and a meta analysis supports the use of chemoradiation preoperatively. However postoperative mortality may be increased and the exact population that benefits is not clear. Chemotherapy alone is now increasingly used as an induction therapy prior to surgery. Stage-directed therapy is evolving as new endoscopic and minimally invasive surgical modalities become available.

#### 20. What are the treatment options for limited disease (stage I)?

Patients with early stage disease generally are treated with curative surgery alone or in conjunction with preoperative chemotherapy. Surgery is the treatment of choice for localized SCCA and AdenoCA, particularly if the submucosa or muscularis are involved (T1[M3]-2 N0-1). Although controversial, many experts believe that esophagectomy is the preferred treatment for intramucosal superficial cancers as well. Chemotherapy and radiation are not used as adjuvants for early mucosal cancers (Tis [M1 or M2], N0). Surgical therapy consists of resection of the tumor with anastomosis of the stomach with the cervical esophagus (gastric pull-up).



**Figure 5-3.** Esophageal cancer treatment algorithm for locally advanced disease (stage II-III). AdenoCA, Adenocarcinoma; C, cisplatin; CT, chemotherapy; E, epirubicin; F, fluorouracil; R0, complete resection; R1-2, incomplete resection; RT, radiation therapy; SCCA, squamous cell carcinoma.

or interposition of the colon to reestablish gastrointestinal continuity (see Chapter 73). Results are better in hospitals that perform this surgery frequently and poorer in small hospitals that perform the surgery infrequently.

## 21. What are the treatment options for locally advanced disease (stages II-III)?

Surgery alone is not a standard treatment in these patients because complete tumor resection is not possible in a substantial number of patients and even when resection is apparently complete, survival rarely exceeds 20%. A recent metaanalysis has shown that a multimodality approach consisting of chemotherapy and radiation followed by surgery (triple therapy) offers the best likelihood of cure. Triple therapy is aggressive and expensive and has a high side-effect rate. Patients who are in poor general condition may elect to have palliative therapy after balancing the low probability of cure against the morbidity of treatment. Combined modality therapy using chemoradiation followed by surgery or definitive chemoradiation in patients who cannot or will not undergo surgery are the currently recommended treatments.

## 22. What are the treatment options for distant metastases (stage IV)?

Distant metastases make esophageal cancer incurable and therapy is palliative. External beam irradiation (EBRT), radiation therapy, and chemotherapy are frequently used and may offer small increases in survival rates with the trade-off of systemic side effects. In patients with dysphagia, a number of palliative measures are possible but do not prolong survival.

Endoscopic options for palliation of malignant dysphagia include:

- Esophageal dilation—transient relief
- Endoscopic laser (ND:YAG)
- Endoscopic injection (absolute alcohol)
- Argon plasma coagulation
- EMR
- Photodynamic therapy (PDT)
- Placement of prosthetic self-expanding plastic stent or self-expanding metal stent

### 23. What does the future hold for patients at risk for development of esophageal cancer?

Prevention of esophageal cancer by lifestyle modification is a goal, but the U.S. epidemic of obesity and resurgence in the popularity of tobacco and alcohol among young adults is cause for pessimism that we will achieve this goal. Early detection (selective screening of at-risk groups), refinement of endoscopic and minimally invasive surgical techniques complemented with targeted radio- and chemotherapy offers great optimism for improved survival and decreased morbidity caused by this devastating disease. Advances in chemoprevention of esophageal cancer holds great promise. Although definitive proof is lacking, there is a significant amount of suggestive evidence that aspirin, nonsteroidal antiinflammatory drugs, COX-2 inhibitors, proton pump inhibitors, and even statins may have a beneficial role in chemoprevention for selected patients.

Please access ExpertConsult to view the [E-Figure](#) and [E-Table](#) for this chapter.

### BIBLIOGRAPHY

1. American Society for Gastrointestinal Endoscopy Standards of Practice Committee. The role of endoscopy in the assessment and treatment of esophageal cancer. *Gastointest Endosc* 2013;77:328–34.
2. Choia SE, Hura C. Screening and surveillance for Barrett's esophagus: current issues and future directions. *Curr Opin Gastroenterol* 2012;28(4):377–81.
3. Edge SB, Byrd DR, Compton CC, et al. American Joint Committee on cancer staging manual. ed 7 New York: Springer; 2010 p. 103.
4. El-Serag HB, Mason AC, Petersen N, et al. Epidemiological differences between adenocarcinoma of the oesophagus and adenocarcinoma of the gastric cardia in the USA. *Gut* 2002;50(3):368–72.
5. McLoughlin JM, Lewis JM, Meredith KL. The impact of age on morbidity and mortality following esophagectomy for esophageal cancer. *Cancer Control* 2013;20:144–50.
6. Rajendra S, Wang B, Snow ET, Sharma P, Pavey D, Merrett N, et al. Transcriptionally active human papillomavirus is strongly associated with Barrett's dysplasia and esophageal adenocarcinoma. *Am J Gastroenterol* 2013;108:1082–93.
7. Risk JM, Mills HS, Garde J, et al. The tylosis esophageal cancer (TOC) locus: more than just a familial cancer gene. *Dis Esophagus* 1999;12:173–6.
8. Shridhar R, Almhanha K, Meredith KL, Biagioli MC, et al. Radiation therapy and esophageal cancer. *Cancer Control* 2013;20:97–110.
9. Siegel R, Neishadham D, Jamal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013;63(1):11–30.
10. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association technical review on the management of Barrett's esophagus. *Gastroenterology* 2011;140:1084–91.
11. Stahl M, Budach W, Meyer HJ, Cervantes A, European Society for Medical Oncology (ESMO). Esophageal cancer: clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21:v46–47.
12. Turati F, Tramacere I, La Vecchia C, Negri E. A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. *Ann Oncol* 2013;24:609.
13. Wang K, Sampliner R. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol* 2008;103:788–97.
14. Winberg H, Lindblad M, Lagergren J, Dahlstrand H. Risk factors and chemoprevention in Barrett's esophagus—an update. *Scand J Gastroenterol* 2012;47(4):397–406.
15. Yamashina T, Ishihara R, Nagai K, et al. Long-term outcome and metastatic risk after endoscopic resection of superficial esophageal squamous cell cancer. *Am J Gastroenterol* 2013;108:544.

### Websites

- Barrett's esophagus and its link to esophageal cancer. YouTube. <https://www.youtube.com/watch?v=i5OJQtpF2C0> [Accessed September 22, 2014].
- Ralph's story: footage from the endoscopic mucosal resection of esophageal cancer. Surgery Theater. <http://www.surgerytheater.com/video/7097/Ralphs-Story-Footage-from-the-Endoscopic-Mucosal-Resection-of-Esophageal-Cancer-> [Accessed September 22, 2014].

# ESOPHAGEAL ANOMALIES, INFECTIONS, AND NONACID INJURIES

Mary A. Atia, MD, and Francisco C. Ramirez, MD

## 1. What is the difference between a ring and a web? Name the three different types of rings.

A ring is a *concentric* thin (2-5 mm) extension of tissue most commonly located in the *distal* esophagus, whereas a web is a thin (<2 mm) *eccentric* membrane mostly located in the *proximal* esophagus ([Table 6-1](#)).

**Table 6-1.** Types of Esophageal Rings

TYPE	LOCATION	SYMPTOMATIC?
A	1.5 cm proximal to squamocolumnar junction	Rare
B (Schatzki ring)	At the squamocolumnar junction or proximal border of a hiatal hernia	Often
C	Indentation caused by the diaphragmatic crura	Never

## 2. What is the clinical presentation of a Schatzki ring?

Patients classically have intermittent solid-food dysphagia caused mainly by bread and meat—the “steakhouse syndrome.” Dysphagia is either followed by regurgitation or passage of the food bolus. Occasionally, the patient requires endoscopic intervention.

## 3. How is a Schatzki ring diagnosed?

A history of intermittent solid-food dysphagia can be followed by a barium esophagram with a solid food bolus (i.e., marshmallow or barium tablet). Patients note dysphagia at 13 mm or less. Therefore per the “Schatzki rule,” mucosal rings less than 13 mm almost always produce symptoms, whereas rings more than 20 mm rarely cause dysphagia. Endoscopy is less sensitive to detect esophageal rings, but may be used with therapeutic purposes, such as food bolus disimpaction or dilation ([Figure 6-1](#)).



**Figure 6-1.** Barium esophagram displaying a Schatzki ring.

**4. What are treatment options for patients with a Schatzki ring (or esophageal web)?**

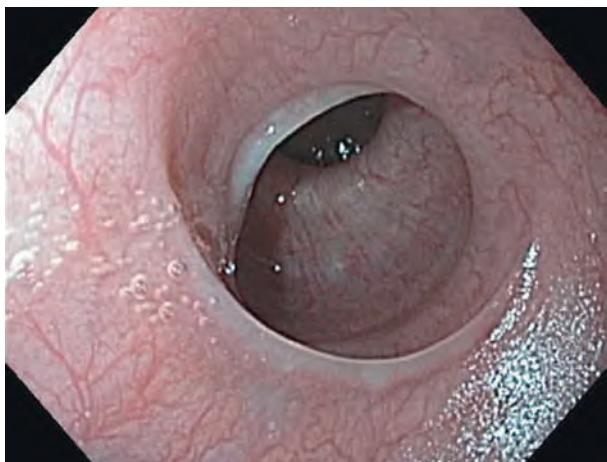
Patients should adhere to lifestyle modifications such as cutting and chewing food more carefully, eating more slowly, and drinking plenty of fluids with meals. Because there might be a correlation with gastroesophageal reflux disease, patients could be evaluated with pH monitoring and treated with chronic proton pump inhibitor therapy if increased acid levels are present. If these measures are unsuccessful, esophageal dilation with a large bougie or balloon (45-60 French) is required and aimed at fracturing the ring.

**5. What is Plummer-Vinson syndrome?**

Plummer-Vinson syndrome is a proximal esophageal web associated with microcytic iron deficiency anemia, glossitis, angular cheilitis, and koilonychia. It is also known as *Paterson-Kelly* or *sideropenic dysphagia*. Patients typically have chronic intermittent painless dysphagia. They describe a choking sensation or difficulty swallowing solid foods.

**6. What other diseases are associated with esophageal webs?**

Thyroid disease, Zenker diverticulum, esophageal duplication cyst, inlet patch, squamous cell carcinoma of the esophagus, and chronic graft-versus-host disease are all associated with esophageal webs. Patients with blistering skin diseases such as bullous pemphigoid, epidermolysis bullosa, and Stevens-Johnson syndrome may also develop webs (Figure 6-2).



**Figure 6-2.** Endoscopic view of an esophageal web.  
(Courtesy John DiBaise.)

**7. How are esophageal webs diagnosed?**

As with esophageal rings, radiographic techniques are the most sensitive method. Because of the proximal location, videoradiography is the preferred modality with lateral and anteroposterior views. Endoscopy must be pursued with caution via direct visualization of the upper esophageal sphincter to avoid piercing the web before its presence can be appreciated.

**8. What are the treatment options for a cricopharyngeal (CP) bar?**

The first step is to ensure that other potential etiologic factors for oropharyngeal dysphagia have been excluded, as it can be an incidental finding (prevalence is up to 20% of radiologic imaging).

Reflux has been associated with CP hypertrophy; therefore one may consider starting acid-suppressing therapy. Endoscopic treatment options include bougie dilation or injection with botulinum toxin. A surgical option is CP myotomy (Figure 6-3).

**9. Describe the different types of esophageal diverticula.**

See Table 6-2.

**Table 6-2.** Types of Esophageal Diverticula

NAME	LOCATION	PATHOGENESIS
Cervical (Zenker diverticulum)	Cricopharyngeus muscle	Abnormally high pressures during swallowing lead to protrusion of mucosa through an area of anatomic weakness in the pharynx
Midesophageal (traction diverticula)	Middle third, bifurcation of the trachea	Mediastinal inflammation secondary to infections such as tuberculosis or histoplasmosis or lymphadenopathy
Epiphrenic	Distal esophagus	Associated with motility disorders



**Figure 6-3.** Barium swallow of cricopharyngeal bar.

#### 10. What is the cause of Zenker diverticulum?

Zenker diverticulum is an acquired condition resulting from abnormally high pressures occurring during swallowing leading to protrusion of mucosa through an area of anatomic weakness in the pharynx known as Killian's triangle. Killian's triangle is located where the transverse fibers of the CP sphincter intersect with the oblique fibers of the inferior pharyngeal constrictor muscle ([Figure 6-4](#)).



**Figure 6-4.** Videoradiography with large (7.5 cm) Zenker diverticulum.

**11. What are the presenting symptoms in patients with a Zenker diverticulum?**

Patients present with slowly progressive upper esophageal dysphagia. As the condition worsens, patients note regurgitation, choking, aspiration, voice changes, and halitosis. Approximately one third of patients eventually develop weight loss. (Access ExpertConsult to see Video 6-1.)

**12. What is the pathogenesis of diverticula of the esophageal body?**

Midesophageal diverticula, also known as *traction diverticula*, are often related to mediastinal inflammation secondary to infections such as tuberculosis or histoplasmosis. Enlarged mediastinal lymph nodes from lung malignancies can also cause traction diverticula. Epiphrenic diverticula are also acquired and nearly 80% are associated with motility disorders (E-Figure 6-5).

**13. What are treatment options for patients with esophageal diverticula?**

Patients without symptoms require no intervention. Symptomatic patients should be treated given the almost certain progression in size, symptoms, and potential for respiratory complications. Preoperative endoscopy and manometry should be pursued. Surgery involves inversion or resection of the diverticula and myotomy (given the high probability of associated motility disorder).

**14. What is the common term for heterotopic gastric mucosal patch?**

The common term is *inlet patch*. It is an island of ectopic gastric mucosa that is salmon colored and located in the proximal esophagus. The true pathogenesis is unknown, but it is believed to be a congenital anomaly. Another theory proposes a phenomenon similar to Barrett's esophagus (i.e., an adaptation secondary to chronic acid injury) (E-Figure 6-6).

**15. What is the clinical significance of an inlet patch?**

The majority of these lesions are found incidentally on endoscopy with no associated symptoms. However, laryngopharyngeal reflux symptoms, such as regurgitation, dysphagia, hoarseness, globus sensation, and cough, are the most frequently reported. Biopsies should be obtained to assess for metaplasia or dysplasia. If found, surveillance for malignancy should be considered.

**16. Name the etiologic factors for the development of an acquired tracheoesophageal fistula (TEF).**

Malignancy accounts for more than 50% of TEFs; the primary tumor is usually esophageal, but can also arise from the lung, trachea, thyroid, larynx, and lymph nodes. Nonmalignant TEFs are frequently a complication of mechanical ventilation. Other causes include a history of trauma, granulomatous mediastinal disease, prior esophageal or tracheal surgery, and acquired immune deficiency syndrome (AIDS). Coughing while swallowing (Ono's sign) is a key symptom among those with a TEF.

## INFECTIONS

**17. What are the presenting symptoms for those with infectious esophagitis?**

Patients commonly have odynophagia or dysphagia. Other symptoms include chest pain, heartburn, and bleeding. The discomfort may be so severe that it results in weight loss.

**18. What subset of patients typically has esophagitis secondary to infection?**

Esophageal opportunistic infections are most common in the immunocompromised patients such as those infected with human immunodeficiency virus or AIDS. Also, patients with malignancies or following organ transplantation or autoimmune diseases who require chemotherapy or immunosuppressive therapy are also affected. Infections in the immunocompetent patient usually occur in the setting of an underlying motility disorder causing prolonged stasis of luminal contents. Patients using local (and systemic) steroids may also develop opportunistic infections.

**19. What is the most common pathogen for infectious esophagitis?**

*Candida albicans* is the most common pathogen causing infectious esophagitis. *Candida* species are normal oral flora but can become pathogenic. Typically patients have a predisposing condition such as immunodeficiency, diabetes, adrenal insufficiency, alcoholism, or use of antibiotics. Oral thrush may be absent.

**20. What is seen endoscopically in patients with *Candida* esophagitis?**

Endoscopy shows small, yellow-white raised plaques with surrounding erythema in mild disease. Confluent linear and nodular plaques reflect extensive disease. Confirmation is made by brushing the lesion followed by cytologic examination or biopsy in which inflammation, hyphae, and masses of budding yeast are seen (E-Figure 6-7; access ExpertConsult to see Video 6-2).

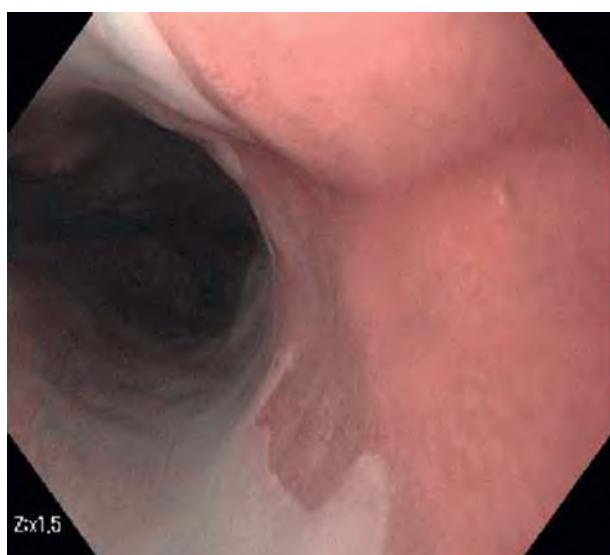
**21. What is the treatment for *Candida* esophagitis?**

Initial therapy is fluconazole 100 mg daily for 10 to 14 days. Patients with resistant disease may require itraconazole 200 mg/day for 10 to 14 days. If patients cannot tolerate oral medications, the echinocandins (i.e., caspofungin, micafungin) or amphotericin B (0.3-0.5 mg/kg/day) should be used.

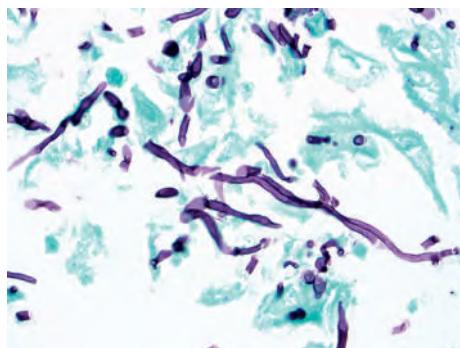
**E-Figure 6-5.** Endoscopic view of midesophageal diverticula. (Courtesy John DiBaise.)



**46.e2** ESOPHAGEAL ANOMALIES, INFECTIONS, AND NONACID INJURIES



**E-Figure 6-6.** Gastric heterotopia (inlet patch).



**E-Figure 6-7.** Histologic examination of *Candida esophagitis* (Grocott's methenamine silver stain). (Courtesy Dora Lam-Himlin.)

**22. What are the most common types of viral esophagitis among the immunocompetent host and the immunocompromised host?**

Herpes simplex virus (HSV) is the most common among the immunocompetent. It can represent either primary infection or, more commonly, a reactivation of a latent virus. Oropharyngeal lesions are found in only one of five cases. Severe odynophagia, heartburn, and fever are the principal symptoms. Cytomegalovirus (CMV) is the most common opportunistic virus of the esophagus among the immunocompromised.

**23. What are the differentiating features of HSV and CMV esophagitis on endoscopic and histologic examination?**

HSV often presents with multiple small superficial ulcers or erosive esophagitis with diffuse friability in the distal esophagus. Vesicles are rarely visualized. Biopsies should be obtained from the edge of the ulcer as HSV affects the epithelium. On histologic examination, ground-glass nuclei, eosinophilic Cowdry type A intranuclear inclusions, and multinucleated cells are found.

CMV typically creates large shallow or serpiginous ulcers in the middle to distal third of the esophagus. Biopsies should be taken from the base of the ulcer as CMV affects the vessels and endothelium. Cytopathic changes include intranuclear inclusions, perinuclear halo, and cytoplasmic inclusions ([Table 6-3](#), [E-Figure 6-8](#), and [E-Figure 6-9](#)).

**Table 6-3.** Distinguishing Features of Viral Esophagitis

	HSV	CMV
Endoscopic features	Multiple small superficial ulcers	Large serpiginous ulcers
Location	Distal third	Middle to distal third
Biopsy	Edge	Center
Histologic findings	Ground-glass nuclei Eosinophilic Cowdry type A Multinucleated giant cells	Intranuclear inclusions Perinuclear halo Cytoplasmic inclusions
Treatment	IV acyclovir 250 mg/m <sup>2</sup> every 8 hours Oral valacyclovir 100 mg three times daily for 7-10 days	IV ganciclovir 5 mg/kg for 14 days Oral valacyclovir

CMV, Cytomegalovirus; HSV, herpes simplex virus; IV, intravenous.

**24. What is the most common parasitic infection of the esophagus?**

*Trypanosoma cruzi* causing Chagas disease is the most common parasitic infection of the esophagus. This parasite is endemic in South America. The pathologic condition is due to progressive destruction of mesenchymal tissues and nerve ganglion cells throughout the body. Esophageal manifestations develop approximately 20 years after acute infection. Symptoms mimic achalasia with dysphagia, cough, regurgitation, nocturnal aspiration, and chest pain.

**25. How is Chagas disease diagnosed?**

A *trypanosoma cruzi* serologic test should be ordered. On manometry, the esophagus findings are similar to achalasia but the lower esophageal sphincter pressure is less with Chagas disease. Other organ involvement manifests as dilated cardiomyopathy, megacolon, and neuritis.

**26. What are treatment options for patients with Chagas disease?**

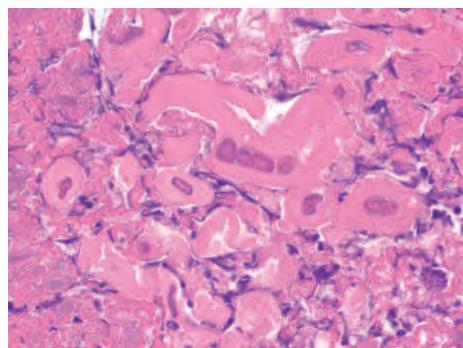
The first line of treatment is nitrates. If symptoms persist, balloon dilation is pursued. Refractory cases may require myotomy at the gastroesophageal junction. Intractable symptoms or pulmonary complications are candidates for esophagectomy.

## PILL AND NONACID INJURY

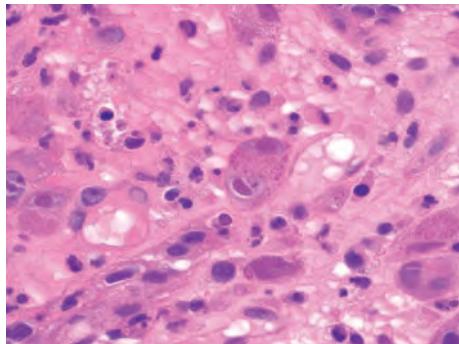
**27. What risk factors predispose patients to pill-induced esophagitis?**

- Decreased salivary flow (age, sicca syndrome, anticholinergic medications)
- Disorders of esophageal motility (achalasia, scleroderma)
- Disordered local anatomy (esophageal diverticula, aortic aneurysms, enlarged left atrium, strictures)
- Medication formulations (sustained-release, large tablets)
- Medications that affect the tone of the lower esophageal sphincter (benzodiazepines, opioid analgesics, calcium channel blockers)
- Bedridden, older adult patients

**47.e1** ESOPHAGEAL ANOMALIES, INFECTIONS, AND NONACID INJURIES



**E-Figure 6-8.** Histology of herpes simplex virus esophagitis with evidence of multinucleation, margination of chromatin, and molding of nuclei. (Courtesy Dora Lam-Himlin.)



**E-Figure 6-9.** Histologic examination of cytomegalovirus esophagitis with eosinophilic Cowdry-type A and B nuclear and cytoplasmic inclusions. (Courtesy Dora Lam-Himlin.)

**28. What is the classic clinical presentation of pill-induced esophagitis?**

The typical patient has no antecedent history of esophageal disease, but presents with sudden onset of odynophagia with or without dysphagia. Patients also have retrosternal chest pain that may be confused with an acute cardiopulmonary process such as a myocardial infarction or pulmonary embolism. An astute clinician must elicit the finding that, although the pain may be constant, swallowing exacerbates it.

**29. What is the mechanism of injury in pill esophagitis?**

There are four potential mechanisms:

- Production of a caustic acidic solution (ascorbic acid, ferrous sulfate)
- Production of a caustic alkaline solution (alendronate)
- Creation of a hyperosmolar solution in contact with the mucosa (potassium chloride)
- Direct drug toxicity to the mucosa (tetracycline)

**30. Name some medications commonly associated with esophageal injury.**

Nearly 100 different medications have been reported in the literature. Table 6-4 lists the more common offending agents.

**Table 6-4. Common Medications Causing Pill Esophagitis**

Antibiotics	Bisphosphonates
Doxycycline	Etidronate
Penicillin	Pamidronate
Rifampin	Nonsteroidal Antiinflammatory Drugs
Tetracycline	Aspirin
Antiviral Agents	Ibuprofen
Nelfinavir	Naproxen
Zalcitabine	Other Medications
Zidovudine	Ascorbic acid
Chemotherapeutic Agents	Ferrous sulfate
Bleomycin	Lansoprazole
Cytarabine	Multivitamins
Dactinomycin	Potassium chloride
Daunorubicin	Quinidine
5-Fluorouracil	Theophylline
Methotrexate	
Vincristine	

**31. How is pill esophagitis diagnosed?**

In uncomplicated cases with classic history, diagnostic evaluation is not required as it is usually a self-limiting disease. Endoscopy is indicated when the symptoms continue to progress, when hemorrhage is present, when dysphagia predominates, or when the pill-taking history is not elicited.

On endoscopy, there commonly are one or more discrete ulcers with normal surrounding mucosa. Biopsies help exclude infection and neoplasia. Diffuse, severe esophagitis with pseudomembranes has also been observed in the setting of bisphosphonates.

**32. What portion of the esophagus is most likely to be affected by pill esophagitis?**

The junction at the proximal and middle third of the esophagus is a common location. This is due to a combination of esophageal compression by the aortic arch and the relatively low amplitude of peristaltic contraction. Strictures are also prone to be affected by pill-induced esophagitis.

**33. How should patients be advised to reduce the risk of pill-induced esophagitis?**

- Drink at least 4 ounces of fluid with any pill, and twice this amount with pills such as alendronate, potassium chloride, or quinidine, which are more prone to esophageal injury.
- Take all pills in the upright position.

- Remain upright for at least 10 minutes after taking pills and for at least 30 minutes after taking pills that have the potential to cause serious injury.
- Pills implicated in esophagitis should be avoided in bedridden patients or patients with esophageal dysmotility.

#### **34. What are the pathophysiologic findings of an alkali injury and subsequent complications?**

Agents with a pH higher than 12 are extremely corrosive. These include drain, toilet, and oven cleaners; lye; and disc batteries. Alkaline ingestion causes a liquefactive necrosis that rapidly extends through the mucosa, submucosa, and muscularis of the esophagus. Vascular thrombosis occurs following the necrosis. Because of transmural injury, perforation, mediastinitis, and peritonitis can occur. After a few days, the esophagus develops ulcerations. Subsequently, granulation tissue, fibroblastic activity, and collagen deposition develop, leading to stricture formation ([E-Figure 6-10](#)).

#### **35. What is the initial management for caustic ingestion?**

As in all emergency situations, airway, breathing, and circulation should be addressed immediately. Imaging of the chest and abdomen with plain films or computed tomography should then be obtained to assess for perforation evidenced by pneumomediastinum, pneumothorax, or pneumoperitoneum. Patients with perforation should be evaluated for surgical intervention.

Inducing emesis or nasogastric lavage is contraindicated to avoid reexposure of the caustic substance to the esophagus. Moreover, induced retching may increase the risk for perforation. Neutralizing agents are not used, as they have not been shown to be effective. Empiric use of steroids and antibiotics are not recommended.

#### **36. What is the role of endoscopy in caustic ingestion?**

Once perforation has been excluded, patients should have an upper endoscopy within 24 to 48 hours for diagnostic and prognostic purposes. It should be noted that a patient with a normal physical examination should still undergo esophagogastroduodenoscopy as severe esophageal injury was observed in approximately 20% of patients who did not have symptoms. Conversely, approximately 60% of patients with clinical symptoms had minimal esophageal injury.

Endoscopic grading is quite accurate in predicting the onset of complications. Strictures develop in 55% to 100% of patients with grade IIB or above. Grade IV injury has a mortality of 65% ([Table 6-5](#)).

**Table 6-5. Endoscopic Grading of Caustic Ingestions**

GRADE	ENDOSCOPIC FINDINGS
I	Edema and erythema
IIA	Hemorrhage, erosions, blisters, ulcers with exudate
IIB	Circumferential ulceration
III	Multiple deep ulcers with brown, black, or gray discoloration
IV	Perforation

#### **37. How are late complications of caustic injury managed?**

Primary treatment of esophageal strictures is frequent dilation. Unfortunately, caustic stricture formation is more resistant to endoscopic dilation. As many as 10% to 50% of patients require surgical intervention.

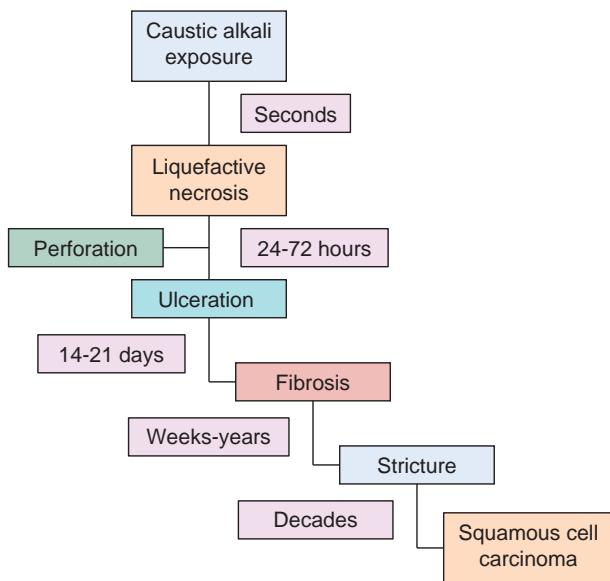
*Alkaline ingestion also increases one's risk of squamous cell carcinoma 1000-fold.* As a result, endoscopic surveillance for malignancy is recommended 15 to 20 years after ingestion and every 1 to 3 years thereafter.

#### **38. How do patients with a Mallory-Weiss tear classically present?**

Patients typically have a history of recent nonbloody emesis or frequent retching followed by hematemesis or coffee-ground emesis. However, a Mallory-Weiss tear can occur with the first episode of vomiting. The tear is secondary to increased intraabdominal pressure, which causes a shearing effect at the gastroesophageal junction as it herniates through the diaphragm.

#### **39. Name the eponym of a transmural esophageal tear.**

Boerhaave's syndrome is the eponym used to describe a transmural esophageal tear. Similar to a Mallory-Weiss tear, preceding symptoms are related to an abrupt increase in intraabdominal pressure by vomiting, retching, abdominal straining, or coughing. Symptoms include severe chest pain and subcutaneous emphysema with crepitus, with the possibility of shock and sepsis. On chest imaging, pneumomediastinum and a left pleural effusion are present.



**E-Figure 6-10.** Pathophysiologic findings of alkali injury.

**40. What are the early manifestations of radiation injury to the esophagus and when do they occur?**

Acute radiation esophagitis occurs 2 to 3 weeks following initiation of therapy. Clinically, patients report dysphagia and odynophagia. Chest discomfort not related to swallowing is also present. Severe symptoms lead to dehydration and weight loss. *Candida* esophagitis has identical symptoms and is common in this patient population; therefore endoscopy is often necessary to differentiate.

**41. Describe the late complications associated with radiation therapy.**

Late complications include strictures, ulceration, altered motility, and fistula formation. They may occur months to years (median 6 months) after treatment secondary to inflammation and subsequent fibrosis. Development of late complications is dose dependent with the upper limit at 60 Gy. Because recurrence of malignancy might present similarly, endoscopic evaluation is recommended.

*The authors would like to acknowledge the contributions of Dr. Hunt, Dr. Meier, Dr. Davis, Dr. Bachinski, and Dr. James, who were the authors of this chapter in the previous edition.*

Please access ExpertConsult to view the **E-Figures**, Videos, and **Clinical Vignette** for this chapter.

**BIBLIOGRAPHY**

1. Antoine Geagea CC. Scope of drug-induced, infectious and allergic esophageal injury. *Curr Opin Gastroenterol* 2008;24:496–501.
2. Baehr PH, McDonald GB. Esophageal infections: risk factors, presentation, diagnosis, and treatment. *Gastroenterology* 1994;106(2):509–32.
3. Chong VH. Clinical significance of heterotopic gastric mucosal patch of the proximal esophagus. *World J Gastroenterol* 2013;19(3):331–8.
4. Ginsberg GG, Pfau PR. Foreign bodies, bezoars, and caustic ingestions. In: Feldman M, Brandt LJ, Friedman LS, editors. 9th ed. *Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management*, vol. 1. Philadelphia: Saunders, Elsevier; 2010. p. 406–8.
5. Hirota WK, Zuckerman MJ, Adler DG, et al. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc* 2006;63(4):570–80.
6. Hoffman RM, Jaffe PE. Plummer-Vinson syndrome: a case report and literature review. *Arch Intern Med* 1995;155(18):2008–11.
7. Katzka DA. Esophageal disorders caused by medications, trauma, and infection. In: Feldman M, Brandt LJ, Friedman LS, editors. 9th ed. *Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management*, vol. 1. Philadelphia: Saunders, Elsevier; 2010. p. 735–43.
8. Kelly J. Management of upper esophageal sphincter disorders: indications and complications of myotomy. *Am J Med* 2000;108(4A):43–6.
9. Kikendall JW. Pill esophagitis. *J Clin Gastroenterol* 1999;28(4):298–305.
10. Mario Costantini GZ, Rizzetto C, Narne S, Ancona E. Oesophageal diverticula. *Best Pract Res Clin Gastroenterol* 2004;18(1):3–17.
11. Pace F, Antinori S, Repici A. What is new in esophageal injury (infection, drug-induced, caustic, stricture, perforation)? *Curr Opin Gastroenterol* 2009;25:372–9.
12. Reed MF, Mathisen DJ. Tracheoesophageal fistula. *Chest Surg Clin N Am* 2003;13(2):271–89.
13. Sajid Jalil DOC. Schatzki's ring: a benign cause of dysphagia in adults. *J Clin Gastroenterol* 2002;35(4):295–8.
14. Spechler SJ. American Gastroenterological Association medical position statement on treatment of patients with dysphagia caused by benign disorders of the distal esophagus. *Gastroenterology* 1999;117:229–32.
15. Temiz A, Oguzkurt P, Ezer SS, et al. Predictability of outcome of caustic ingestion by esophagogastroduodenoscopy in children. *World J Gastroenterol* 2012;18(10):1098–103.
16. Tobin RW. Esophageal rings, webs, and diverticula. *J Clin Gastroenterol* 1998;27(4):285–95.
17. Wang AY, Kadkade R, Kahrlas PJ, et al. Effectiveness of esophageal dilation for symptomatic cricopharyngeal bar. *Gastrointest Endosc* 2005;61(1):148–52.
18. Harford Jr W, Jeyarajah R. Diverticula of the pharynx, esophagus, stomach, and small intestine. In: Feldman M, Brandt LJ, Friedman LS, editors. 9th ed. *Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management*, vol. 1. Philadelphia: Saunders, Elsevier; 2010. p. 371–5.

# BARRETT'S ESOPHAGUS

Nimish B. Vakil, MD, FACP, FACG, AGAF, FASGE

## 1. How is Barrett's esophagus defined?

Barrett's esophagus may be simply defined as the presence of columnar metaplasia of the anatomic esophagus. It is a complication of chronic gastroesophageal reflux disease (GERD). The current American Gastroenterological Association guideline defines Barrett's esophagus as a condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus. This is consistent with an international consensus definition of Barrett's esophagus that defines Barrett's esophagus as the partial replacement, from the gastroesophageal junction proximally, of esophageal squamous epithelium with metaplastic columnar epithelium. It is important to realize that both these definitions depart from the traditional view that the presence of intestinal metaplasia is a prerequisite for the diagnosis of Barrett's esophagus.

## 2. Why is Barrett's esophagus important?

Barrett's esophagus is a precancerous lesion. Identification of dysplasia in Barrett's esophagus allows intervention at an early stage with good outcomes. On the other hand, advanced esophageal cancer has a poor prognosis. Surveillance using endoscopy is the cornerstone of management and allows patients to be detected at an early stage.

## 3. What are the risk factors for Barrett's esophagus?

Established risk factors for Barrett's esophagus include:

- Age older than 50 years
- Male gender
- White race
- Chronic GERD
- Hiatal hernia
- High body mass index
- Truncal obesity

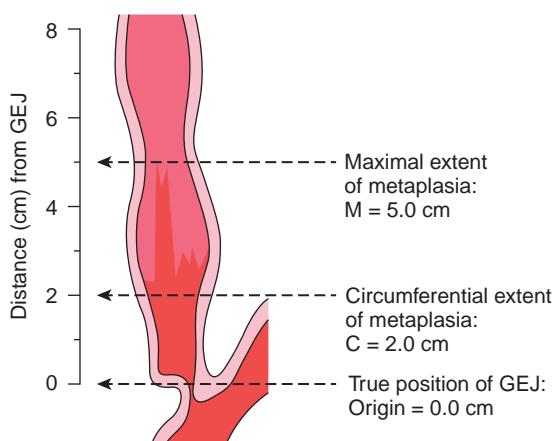
## 4. What is the endoscopic appearance and characterization of Barrett's esophagus?

Barrett's esophagus has a typical endoscopic appearance. It is generally described as a salmon or pink color within the tubular esophagus, in contrast to the light gray appearance of esophageal squamous mucosa (Figure 7-1). It should be emphasized that histologic examination of esophageal biopsy samples is required to confirm the diagnosis of Barrett's esophagus. The Prague Classification is a standardized method of reporting the extent of



**Figure 7-1.** Barrett's esophagus seen at conventional endoscopy. Note the salmon-colored epithelium that contrasts with the normal gray epithelial lining of the esophagus.

Barrett's esophagus and is recommended for routine endoscopy. The vertical extent of Barrett's epithelium that is circumferential is measured from the top of the gastric folds and designated as the C length. Longitudinal columns of Barrett's epithelium are designated by the letter M, followed by the vertical length. For example, a patient with a circumferential change of 2 cm and 1 cm tongues of Barrett's epithelium extending upward from the circumferential segment is designated as C2M1 based on the Prague Classification (Figure 7-2). Short-segment Barrett's esophagus is defined by the presence of intestinal metaplasia identified in biopsies obtained from the esophagus with an endoscopic appearance suggestive of Barrett's that extends less than 3 cm into the esophagus. Long-segment Barrett's esophagus is defined by segments of abnormal epithelium longer than 3 cm.



**Figure 7-2.** Diagrammatic representation of endoscopic Barrett's esophagus showing an area classified as C2M5. C, extent of circumferential metaplasia; GEJ, gastroesophageal junction; M, maximal extent of the metaplasia (C plus a distal "tongue" of 3 cm). (With permission, Sharma P, et al: The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M Criteria, Gastroenterology 131:1392-1399, 2006.)

## 5. What is the risk of cancer in Barrett's esophagus?

The generally quoted figure for the risk of cancer is 0.5% per year, which means that approximately 1 in 200 patients with Barrett's esophagus will develop esophageal cancer each year. Recent studies, however, suggest that the risk may be substantially lower than originally estimated. Further data are needed to clarify this issue. Until then, it may be reasonable to offer a range from 0.3% to 0.5% per year.

## 6. What are the risk factors for the development of dysplasia and cancer in Barrett's esophagus?

It is uncertain if the risk increases or decreases with the passage of time, but dysplasia and cancer are typically found after the age of 50. There is good evidence to suggest a higher risk for patients with long-segment Barrett's esophagus and a greater risk in men compared with women. Obesity (particularly truncal obesity) is a major risk factor that is amenable to intervention. Smoking increases the risk in some studies but not in others.

## 7. Does medical therapy prevent the risk of dysplasia or cancer?

There is no high-level evidence to tell us with certainty. Treatment with proton pump inhibitors has been shown to reduce the risk of dysplasia and cancer in observational studies. Epidemiologic studies suggest a decrease in the risk of cancer in users of low-dose aspirin or statins but these await confirmation in ongoing trials.

## 8. Is there a role for screening upper endoscopy to identify Barrett's esophagus?

There is no consensus on whether screening should be recommended and at what age and what intervals. Despite the absence of evidence or cost-effectiveness data, the concept of a "once in a lifetime" endoscopy to look for Barrett's esophagus has gained popularity and is widely followed in the United States. If this is done, the yield is probably greatest at or about the age of 50 years.

## 9. What is the goal of medical treatment in Barrett's esophagus?

The goal of medical treatment is to (1) treat the symptoms of GERD commonly associated with Barrett's esophagus, (2) to prevent complications by decreasing mucosal inflammation in the esophagus, and (3) to monitor the patient for the development of dysplasia or cancer of the esophagus so that early intervention may be offered to the patient.

## 10. What is the recommendation for surveillance in Barrett's esophagus (Table 7-1)?

Surveillance of dysplastic Barrett's esophagus should not be considered a definitive treatment and ablative therapies should be considered when dysplasia is identified.

**Table 7-1.** Recommended Surveillance Intervals for Barrett's Esophagus

No dysplasia	3-5 years
Low-grade dysplasia	6-12 months
High-grade dysplasia	3 months (in the absence of ablation therapy)

### 11. What is the recommended biopsy protocol for Barrett's esophagus?

Endoscopic evaluation is recommended using white light endoscopy. High-definition endoscopes and narrow band imaging can help identify surface abnormalities that require targeted biopsies. Current recommendations are that four-quadrant biopsy specimens be taken every 2 cm from the Barrett's epithelium. Chromoendoscopy is a technique using dye (Methylene blue or Indigo Carmine) sprayed over the Barrett's epithelium to identify surface abnormalities. Narrow-band imaging uses a narrow spectrum of light that achieves the same effect (Figure 7-3).



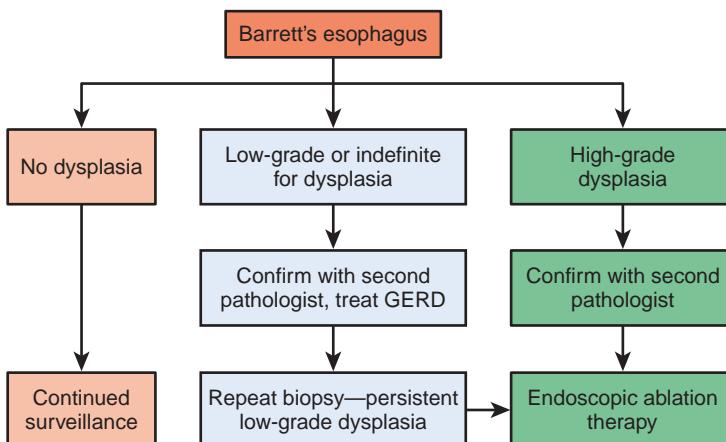
**Figure 7-3.** Narrow band imaging of Barrett's esophagus. Using a narrow spectrum of light enhances detail and allows clearer visualization of the surface characteristics. It allows sharp demarcation from the normal squamous epithelium.

### 12. How reliable is the pathologic diagnosis of high-grade dysplasia?

It has long been recognized that there is interobserver variability between pathologists in identifying high-grade dysplasia and early cancer. At least two experienced gastrointestinal pathologists should evaluate all Barrett's biopsies when a diagnosis of dysplasia is considered.

### 13. What is the management of high-grade dysplasia in Barrett's esophagus?

Endoscopic treatment should be preferred over endoscopic surveillance for management of most patients with Barrett's esophagus who have high-grade dysplasia or intramucosal cancer in the esophagus (Figure 7-4).



**Figure 7-4.** Algorithm for the management of Barrett's esophagus based on dysplasia identified at histopathologic examination. GERD, Gastroesophageal reflux disease.

Endoscopic therapy is also preferred to surgical intervention in this setting. The commonly used options for endoscopic therapy are radiofrequency ablation and photodynamic therapy. Both have shown a high degree of success in ablating the dysplastic epithelium and preventing recurrence.

#### **14. What is the management of early esophageal cancer in Barrett's esophagus?**

Endoscopic resection of early esophageal cancer is the preferred treatment when the lesion is confined to the T1 without vascular or lymphatic spread. Expert guidance and endoscopic ultrasound to stage the lesion are mandatory.

#### **15. How reliable is the pathologic diagnosis of low-grade dysplasia in Barrett's esophagus?**

The criteria for the definition of low-grade dysplasia are not well defined and vary in different regions of the world. There is a tendency to over-diagnose low-grade dysplasia as a result of misinterpretation of regenerative changes. Confirmation of the diagnosis with two pathologists is essential.

#### **16. What is the risk of progression in low-grade dysplasia?**

Low-grade dysplasia is a risk factor for malignancy. The risk for progression may have been under estimated in the past. A recent study showed that many patients with low-grade dysplasia were down-graded to no dysplasia after further pathologic review. In patients in whom low-grade dysplasia was confirmed by pathologic review, the rate of progression was very high (85%). The incidence rate of high-grade dysplasia or cancer was 13.4% per patient per year for patients in whom the diagnosis of low-grade dysplasia was confirmed.

#### **17. How should low-grade dysplasia be managed?**

As regenerative changes can be misinterpreted as dysplastic changes, confirmation of the diagnosis by a second pathologist is essential. In patients who have not been adequately treated for reflux disease, treatment with proton pump inhibitors followed by repeated biopsy is recommended (see [Figure 7-3](#)). The confounding effects of inflammation and regeneration are removed. Persistent low-grade dysplasia needs careful monitoring for progression. Many experts believe that, because of the high rate of progression when low-grade dysplasia is persistent and confirmed, ablative therapy should be offered to these patients.

#### **18. What future developments are anticipated?**

The areas in which progress may be anticipated are (1) better diagnosis of dysplasia using cellular markers and endoscopic biopsy techniques, (2) better identification of individuals at risk for progression using genetics and cellular markers from Barrett's epithelium, (3) noninvasive markers for progression such as serum tests, (4) further endoscopic innovations for the management of dysplasia or cancer, and (5) pharmacotherapy to decrease the risk of progression or to prevent the development of Barrett's esophagus.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

#### **BIBLIOGRAPHY**

1. American Gastroenterological Association, Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology* 2011;140(3):1084–91.
2. ASGE Standards of Practice Committee. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. *Gastrointest Endosc* 2012;76(6):1087–94.
3. Bennett C, Vakil N, Bergman J, et al. Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a Delphi process. *Gastroenterology* 2012;143(2):336–46.
4. Sharma P, Dent J, Armstrong D, et al. The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. *Gastroenterology* 2006;131:1392–9.

#### **Websites**

Barrett's Oesophagus Campaign. <http://www.barrettscampaign.org.uk/> [Accessed September 22, 2014].

National Cancer Institute at the National Institutes of Health. Esophageal cancer treatment. <http://www.cancer.gov/cancertopics/pdq/treatment/esophageal/Patient/page1> [Accessed September 22, 2014].

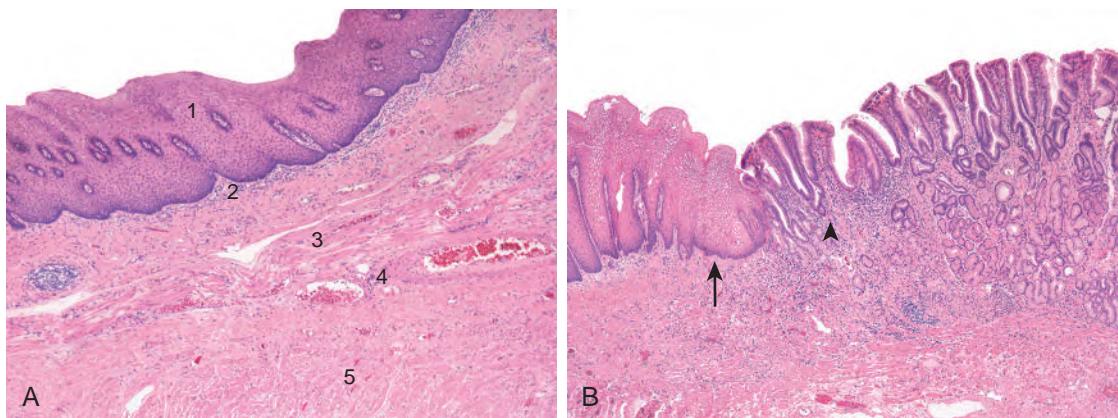
# ESOPHAGEAL AND STOMACH PATHOLOGY

Shalini Taval, MD

## ESOPHAGUS

### 1. Describe a normal esophagus lining.

- Esophagus consists of mucosa, lamina propria, muscularis mucosae, submucosa, muscularis propria, and adventitia (lacks serosa) (Figure 8-1A).
- Sebaceous glands can be seen normally in the submucosa.
- Normal gastroesophageal (GE) junction (see Figure 8-1B) shows squamous and columnar epithelium.



**Figure 8-1.** Photomicrographs of A, Normal esophagus lining: 1, mucosa; 2, lamina propria; 3, muscularis mucosae; 4, submucosa; 5, muscularis propria (adventitia is not shown) (hematoxylin and eosin [H&E] stain). B, Normal gastroesophageal junction showing squamous mucosa (arrow) and columnar mucosa (arrowhead) (H&E stain).

### 2. What are the histologic features of gastroesophageal reflux disease (GERD) and eosinophilic esophagitis (EE)?

Histologic Features of GERD include the following (Figure 8-2A):

- Distal esophagus is more severe than proximal esophagus.
- Basilar hyperplasia is present.
- Elongation of vascular papillae occurs.
- Intraepithelial neutrophils and eosinophils increase ( $\approx 8$  eosinophils per high power field [HPF]).
- Balloon cells (enlarged squamous cells with abundant accumulation of plasma proteins) indicate chemical injury.

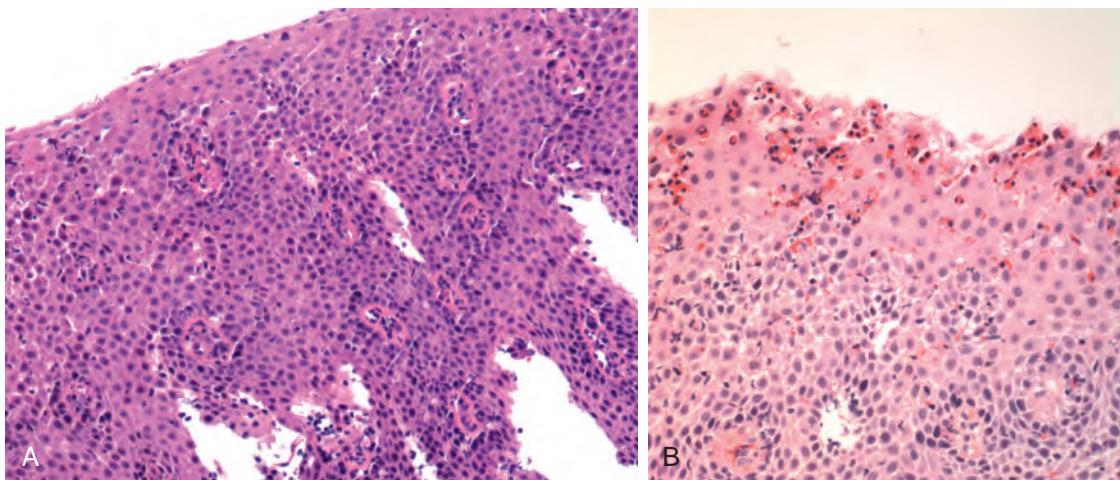
Histologic features of EE are the following (see Figure 8-2B):

- Proximal esophagus is more common than distal esophagus. Distribution can be patchy. Obtain biopsy samples from upper, mid, and distal esophagus.
- Intraepithelial eosinophils in upper layers of epithelium are increased ( $>15-20$  eosinophils/HPF).
- Eosinophilic microabscesses appear in superficial layers of epithelium.
- Extensive degranulation of eosinophils is more common.
- GERD can coexist in 30% of cases and is difficult to distinguish histologically.

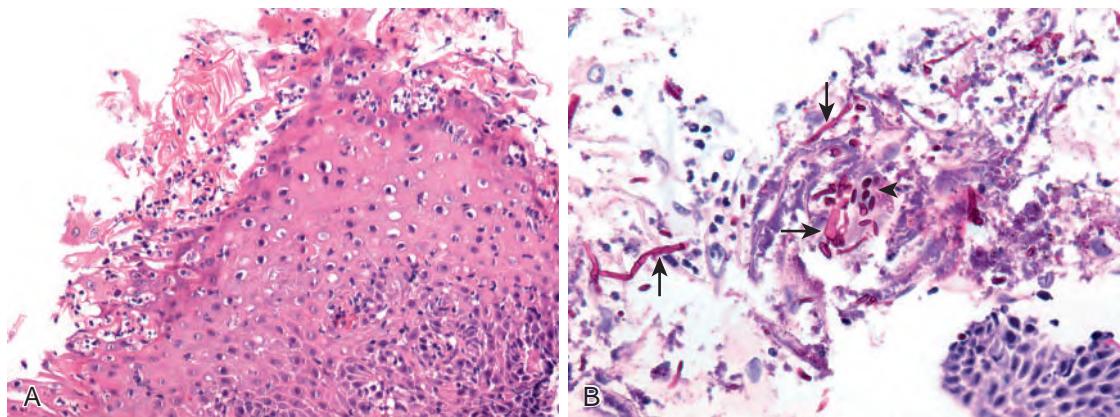
### 3. Discuss the infectious causes of esophagitis.

The infectious causes of fungal esophagitis are the following:

- *Candida esophagitis* (Figure 8-3A and B): *C. albicans* is the most common of the *Candida* species. Others include *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*. Endoscopy shows whitish, raised plaques with erosions or ulcerations. Histologic examination reveals erosion of superficial layers of squamous epithelium or ulceration with yeast and pseudohyphal forms (highlighted by special stains such as Grocott methenamine silver or periodic acid-Schiff [PAS]). The key to diagnosis is presence of pseudohyphal forms which indicates infection. The presence of yeast forms alone suggests oral contamination.



**Figure 8-2.** Photomicrographs of **A**, Reflux esophagitis (gastroesophageal reflux disease). Basilar hyperplasia and elongated vascular papillae (hematoxylin and eosin [H&E] stain). **B**, Eosinophilic esophagitis. Note the increased intraepithelial eosinophils in this biopsy sample from the midesophagus (H&E stain).



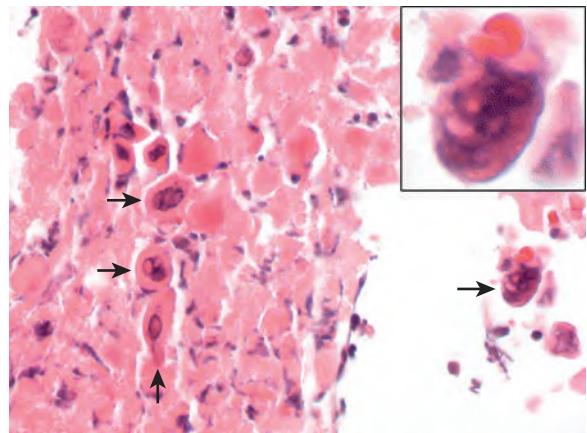
**Figure 8-3.** Photomicrographs of **A**, Candida esophagitis. Note the erosion in the upper layers of squamous mucosa with neutrophilic infiltrate forming microabscesses (hematoxylin and eosin stain). **B**, Yeast (arrowhead) and pseudohyphae (arrows) highlighted by periodic acid-Schiff stain.

- **Histoplasma:** In the United States, *Histoplasma* is endemic around Mississippi and Ohio River valleys. It is also endemic to Central and South America and the Caribbean islands. Endoscopy may appear normal. Histologic examination reveals subepithelial necrotizing granulomas with giant cells that contain organisms of 2 to 4 µm in diameter.
  - **Aspergillus:** The most common species are *Aspergillus fumigatus* and *A. flavus*. Seen as branching (at 45 degrees) septate hyphae 4 µm in diameter.
  - **Mucormycosis:** *Mucormycosis* can be seen in immunocompromised hosts as nonseptate parallel hyphae (10 to 15 µm in diameter) that branch at right angles.
- The infections causes of *viral esophagitis* are the following:
- **Herpes esophagitis (Figure 8-4):** *H. esophagitis* is seen in immunocompromised patients. Endoscopic examination may reveal vesicles or coalesced shallow ulcers. Histologic examination will reveal infected epithelial cells that show multinucleation with molding and smudged intranuclear inclusions.
  - **Cytomegalovirus:** *Cytomegalovirus* is seen in immunocompromised patients. The viral cytopathic effect includes intracytoplasmic and intranuclear inclusions seen in endothelial cells, histiocytes, or fibroblasts.

#### 4. What is the most important differential to be considered in biopsy samples to evaluate graft-versus-host disease (GVHD)?

Infectious etiologic factors must be ruled out with the use of special stains (fungal and viral) and with serologic and tissue culture examinations. In general, the upper esophagus is usually affected. Histologic examination

**Figure 8-4.** Photomicrograph of herpes esophagitis. Note the multinucleated cells with molding (arrows) and smudged eosinophilic viral inclusions (inset) (hematoxylin and eosin stain).



grades GVHD as mild, moderate, or severe based on the degree of damage seen. Apoptotic bodies are seen in the squamous epithelium; there are intraepithelial lymphocytes and basal vacuolization and, in severe cases, ulceration and necrosis.

#### 5. What is the histologic prevalence of esophageal Crohn's disease in endoscopically normal studies?

Histologic prevalence varies from 5% to 42% and does not correlate with endoscopic findings. Crohn's esophagitis may be seen with severe cases of ileocolic disease. Histologic features vary from mild inflammation with epithelioid nonnecrotizing granulomas in the lamina propria to ulcerations and transmural involvement with fistula formation.

#### 6. What are other miscellaneous esophageal conditions?

- **Glycogen acanthosis:** Endoscopic examination reveals small, white-gray plaques in the midesophagus. There is an association with Cowden syndrome. Histologic findings include squamous cells distended with increased intracellular glycogen.
- **Gastric inlet patch:** Endoscopic examination reveals a patch (2 mm to 3 cm) of gastric-appearance mucosa located just below the cricopharyngeus muscle. Histologic findings consist of oxytic (parietal)-type mucosa. Intestinal metaplasia may be found.
- **Pancreatic heterotopia:** Endoscopic findings are often not apparent to the eye. This tissue is often seen in biopsy samples at the GE junction or distal esophagus. It may represent metaplasia or ectopic foci of pancreatic tissue. Histologic examination reveals acinar cells with dense, coarse eosinophilic granules are seen.
- **Melanosis:** Endoscopic findings include tiny 1- to 2-mm brown-black spots. Melanocytes may be seen in the basal layer of squamous epithelium. The differential diagnosis is malignant melanoma. The melanocytes in melanosis are benign-looking and mature. Pigment can be seen in upper layers of mucosa and in the adjacent lamina propria.

#### 7. List the dermatologic conditions that can affect the esophagus.

Dermatologic conditions that affect the esophagus are pemphigus vulgaris, bullous pemphigoid, erythema multiforme, Behcet syndrome, lichen planus, dermatitis herpetiformis, scleroderma, and toxic epidermolysis necrosis.

#### 8. Discuss the histologic characteristics of Barrett's esophagus and the grading of dysplasia.

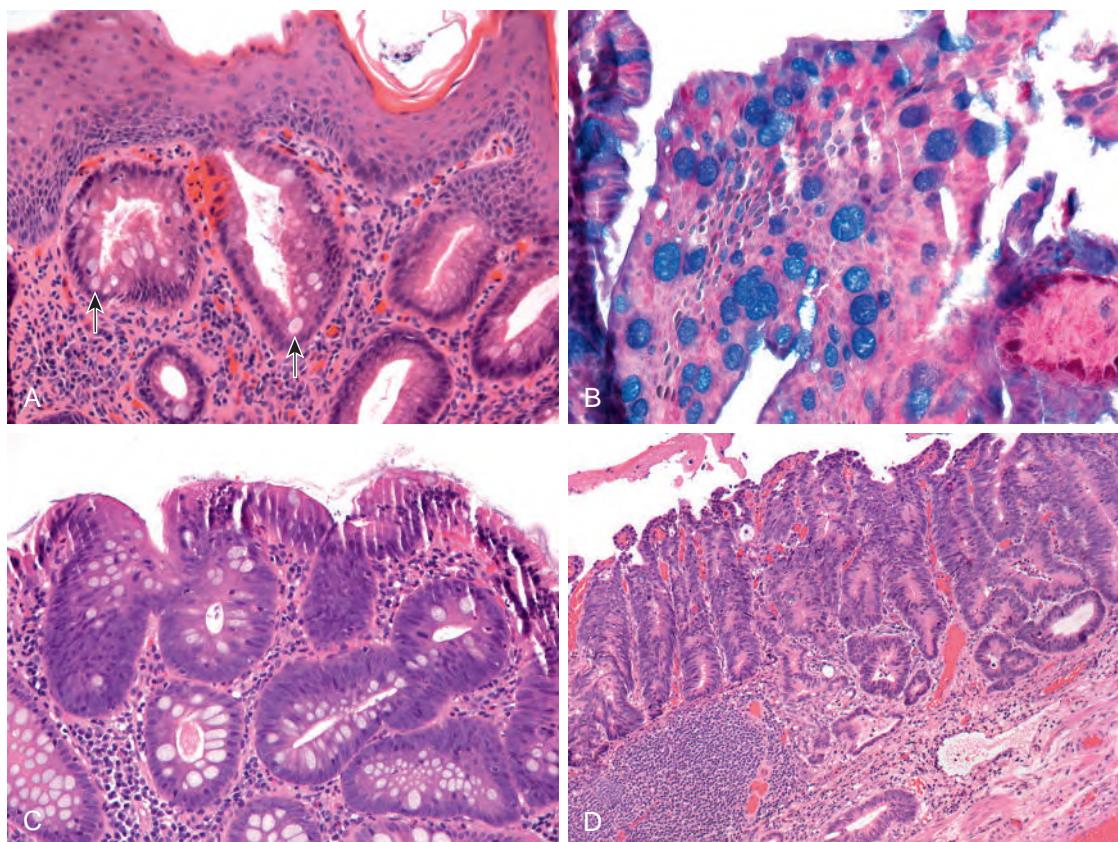
Barrett's esophagus is an endoscopic change in esophageal epithelium of any length, confirmed to have intestinal metaplasia at biopsy. Histologic findings include squamocolumnar junctional mucosa with intestinal metaplasia recognized by the presence of goblet cells (Figure 8-5A), which stain blue with Alcian blue stain at pH 2.5 (see Figure 8-5B).

Dysplasia in Barrett's esophagus is graded as follows:

*None:* There is no evidence of dysplasia.

*Indefinite for dysplasia:* This grading is assigned when distinction cannot be made between low-grade dysplasia and inflammatory changes. The surface epithelium shows maturation, but the deeper glands show architectural crowding, nuclear hyperchromasia, and occasionally increased mitotic activity.

*Low-grade dysplasia* (see Figure 8-5C): Lack of surface maturation and glandular epithelium shows amphophilic cytoplasm with mucin depletion and nuclear hyperchromasia. Architectural crowding is similar to that seen in colonic tubular adenomas.



**Figure 8-5.** Photomicrographs of Barrett's esophagus. **A**, Intestinal metaplasia is recognized by the presence of goblet cells (arrows) in the glandular epithelium (hematoxylin and eosin [H&E] stain). **B**, Alcian blue stain at pH 2.5 stains the acidic mucin of goblet cells blue. **C**, Barrett's esophagus with low-grade dysplasia. There is lack of surface maturation and the glandular epithelium shows nuclear stratification with hyperchromasia (H&E stain). **D**, Barrett's esophagus with high-grade dysplasia and invasion into the lamina propria (intramucosal carcinoma) seen next to the lymphoid aggregate (H&E stain).

**High-grade dysplasia:** Lack of surface maturation with cells shows marked cytologic atypia characterized by loss of polarity, high nuclear-to-cytoplasm ratio, irregular nuclear contours, and prominent large nucleoli. The architecture becomes complex with focal areas of cribriforming. Cytologic abnormalities supersede architectural complexity in diagnosing high-grade dysplasia.

**High-grade dysplasia with invasion or intramucosal carcinoma—T1** (see Figure 8-5D): Invasion into the lamina propria or muscularis mucosae has prognostic implications in the esophagus, unlike in the colon, because of the presence of lymphatics in the former. Lymph node metastasis has been reported in 13% of T1 tumors. Duplication of muscularis mucosae can at times be present and should not be mistaken for invasion into the submucosa.

#### 9. What histologic patterns can be seen in the biopsy samples from the GE junction that do not show typical endoscopic findings of Barrett's esophagus?

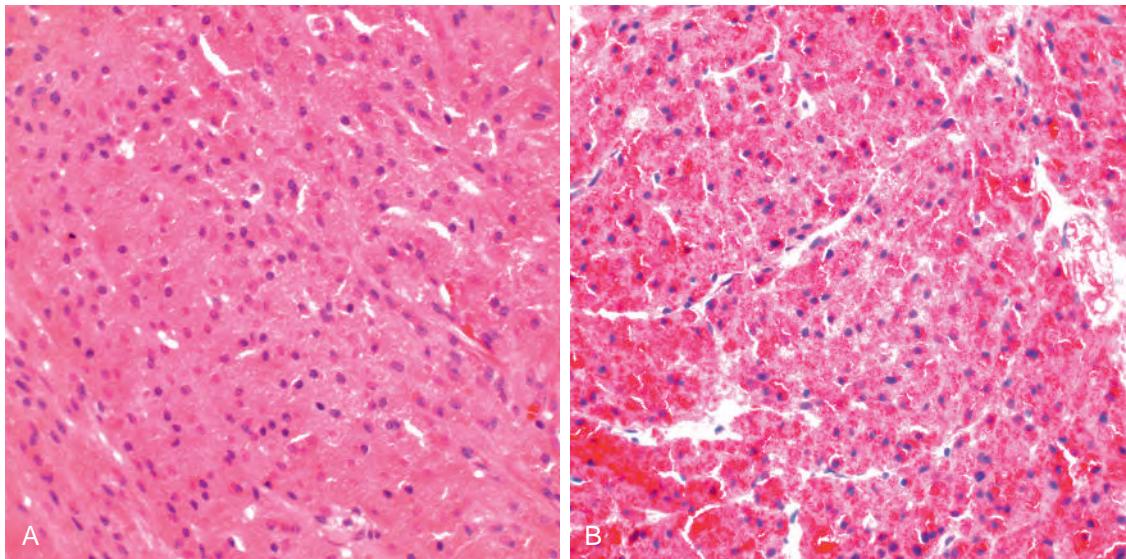
- Gastric-type mucosa without goblet cells—Gastric cardiac mucosa, mostly associated with inflammation (gastric carditis)
- Prominent Z-line showing gastric-cardiac mucosa with goblet cells
- In endoscopically uncertain cases, presence of goblet cells may suggest either Barrett's mucosa or gastric cardia with goblet cells.

#### 10. What is the differential diagnosis of esophageal polypoid lesions?

The differential diagnoses for nonneoplastic lesions are the following:

- *Pancreatic heterotopia/metaplasia* is usually seen at distal esophagus. On histologic examination, pancreatic acinar cells are seen, rarely associated with ductal structures.
- *Fibrovascular polyps* are benign, submucosal (fibrovascular and adipose) tissue surrounded by squamous epithelium. Occasionally, atypical stromal cells may be seen.

- *Squamous papilloma* is not uncommon in the esophagus. Histologic examination reveals lobulated squamous epithelium with fibrovascular cores. Squamous papilloma is seen in less than 0.1% of endoscopic examinations. Dysplasia is not usually seen. These have been related to human papilloma virus (HPV); however, reports also show that most are seen as a result of acid reflux and are not associated with HPV.
- The differential diagnoses for neoplasms are the following:
- *Granular cell tumor* of the gastrointestinal (GI) tract occurs most commonly in the esophagus, whereas the most common site in the body is the lingual dorsum. Endoscopic evaluation reveals submucosal nodules that are mostly solitary (multifocal in 10%). Histologic examination reveals pseudoepitheliomatous hyperplasia of overlying squamous mucosa with submucosal collection of neoplastic granular cells with granular eosinophilic cytoplasm ([Figure 8-6A](#)), which are PAS and S100 reactive (see [Figure 8-6B](#)). Most are benign; rare cases of malignant metastasis have been reported.
- *Leiomyoma* is submucosal benign proliferation of spindled smooth muscle cells. Leiomyoma strongly reacts with muscle markers like smooth muscle actin (SMA) and desmin, and is negative for CD117. Its malignant counterpart, leiomyosarcoma, is rare in the esophagus.
- *Gastrointestinal stromal tumor (GIST)* is rare in the esophagus. Histologic examination shows proliferation of spindle cells that react strongly with CD117 and CD34. Malignant potential depends on the extent of mitotic activity, necrosis, and cytologic atypia.
- *Squamous cell carcinoma* ([E-Figure 8-7](#)) is most common in the midesophagus. Histologic examination demonstrates neoplastic squamous cells with intercellular bridges, and keratin overproduction with keratin pearl formation. Involvement of mediastinal structures is common because of a lack of serosal barrier. Subtypes include basaloid squamous cell carcinoma, verrucous carcinoma, and adenosquamous carcinoma.
- *Adenocarcinoma* ([Figure 8-8](#)) is most common in the distal esophagus; if found in the midesophagus, it is usually as a result of Barrett's esophagus. Variants include mucinous and signet ring cell type. The depth of tumor (superficial versus deep) invasion correlates with tumor stage and prognosis. Lymph node metastasis has been reported in 13% of T1 tumors. The presence of lymphovascular invasion predicts worse overall survival and more tumor recurrence, and is an independent prognostic factor.
- *Malignant melanomas* are rare in the esophagus and are often larger polypoid lesions involving the distal esophagus. Marked cytologic atypia with prominent nucleoli and increased mitotic figures are seen. Malignant cells may show reactivity with one or more of the following antibodies: S100, Melan A, KBA-62, and HMB-45.
- Other malignant tumors include metastatic small cell and sarcomatoid carcinomas; these are rare.



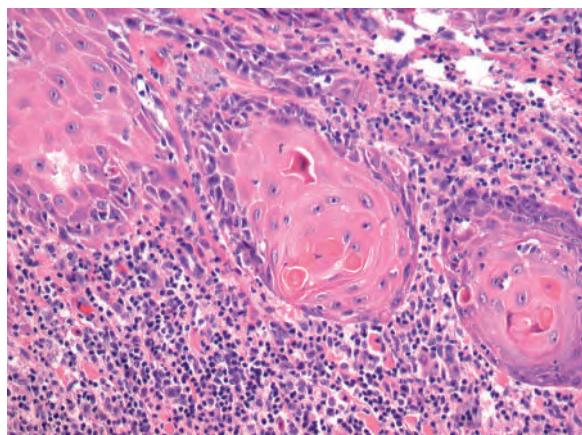
**Figure 8-6.** Photomicrographs of granular cell tumor. **A**, Note the abundant granular cytoplasm and small round nuclei hematoxylin and eosin stain, and **B**, S100 staining in the cytoplasm.

## STOMACH

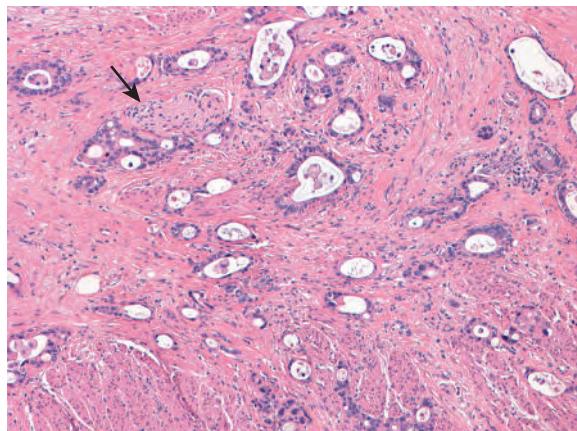
### 11. What are the histologic features of the mucosal lining in different parts of the stomach?

The five layers of the stomach are the:

- Mucosa
- Muscularis mucosae



**E-Figure 8-7.** Photomicrograph of squamous cell carcinoma. Note the infiltrating markedly atypical squamous cell nests, stromal response, and focal keratin pearl formation (hematoxylin and eosin stain).



**Figure 8-8.** Photomicrograph of esophageal adenocarcinoma showing infiltrating neoplastic glands with perineural invasion (arrow) (hematoxylin and eosin stain).

- Submucosa
- Muscularis propria (innermost oblique, inner circular, and outermost longitudinal layer)
- Serosa

The mucosa has three zones that vary by function in different locations of the stomach.

**Superficial layer of neutral mucin** secretes foveolar epithelium and lines the entire luminal surface of the stomach, followed by the isthmus (neck) and deep glandular layer.

**Fundus** and **body mucosa** have similar features and contain pyramid-shaped parietal or oxyntic (acid-secreting and intrinsic factor-producing) cells and the chief cells (enzyme-producing) in the isthmus and base with scattered endocrine cells. The lining foveolar layer is short. The isthmus also contains mucus-secreting cells.

**Cardia** and **antrum** have similar features and have a broad, superficial zone of foveolar epithelial cells. The gastric antrum also contains gastrin-secreting G cells. The other enteroendocrine cells have been shown to secrete serotonin, somatostatin (D cells), and vasoactive polypeptide-like substance.

#### 12. What are the histologic patterns of gastritis?

The two major histologic patterns of gastritis are the following:

- **Acute gastritis:** Onset is acute. Neutrophilic inflammation, edema, and hemorrhage may all be seen. Acute gastritis is associated with hemorrhage or erosions and ulcerations.
- **Chronic gastritis with or without activity:** Mixed inflammation with predominant mononuclear cell infiltration and foveolar hyperplasia occurs, with or without intestinal metaplasia and atrophy. Activity can be graded based on the extent of acute inflammation present (mild, moderate, or severe).

#### 13. What are the various histologic manifestations of *Helicobacter pylori*-associated gastritis?

Changes may vary from acute to chronic injury patterns: chronic gastritis, chronic active gastritis, multifocal atrophic gastritis, follicular gastritis, ulcers, adenocarcinoma, and mucosa-associated lymphoid tissue (MALT) lymphoma. *H. pylori* organisms are gram-negative, urease-producing, seagull-shaped, curved organisms ([E-Figure 8-9](#)) that adhere to the superficial foveolar epithelium, and are entangled in the mucus. These are also seen in the lumens lined by parietal cells. Warthin-Starry (silver stain), Giemsa, Thiazine B, and Diff-Quick are special stains that highlight *H. pylori*. The immunohistochemistry may be helpful in detecting coccoid forms seen in treated gastritis and differentiating it from other causes of gastritis.

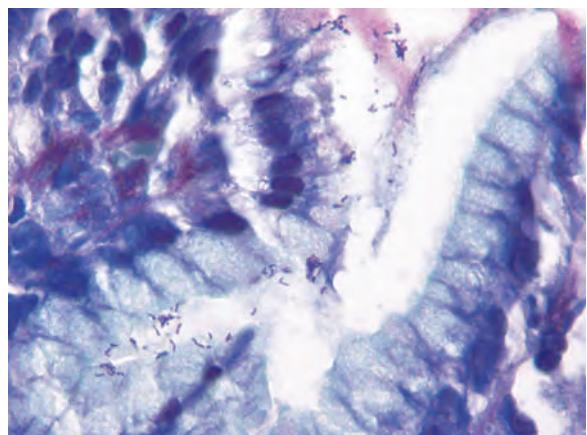
#### 14. What is *Helicobacter heilmannii*-associated gastritis?

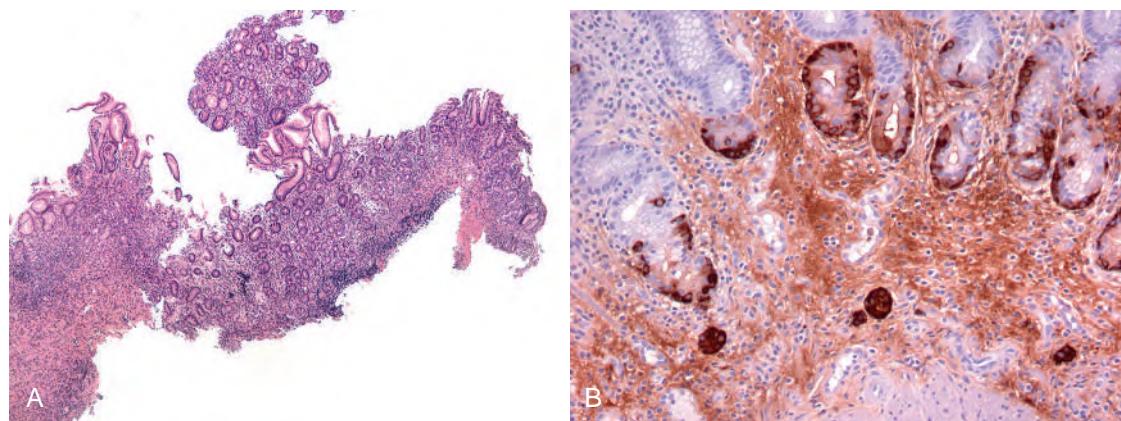
*H. heilmannii* (*Gastrospirillum hominis*) is a rare, long, tightly coiled gram-negative, urease-producing bacteria that causes gastritis of mild severity.

#### 15. What are the types of chronic atrophic gastritis, and how do these differ histologically?

- **Autoimmune gastritis** is also called type A gastritis. Endoscopic examination typically finds that the body or fundus is affected. Histologic examination of advanced disease shows gastric body or fundus mucosa with full-thickness, intense, chronic inflammation; loss of oxyntic glands with intestinal metaplasia ([E-Figure 8-10A](#)); and hyperplasia (linear or nodular) of enterochromaffin cell-like (ECL) cell (chromogranin stain; see [E-Figure 8-10B](#)). Pyloric antrum shows G-cell hyperplasia. Early disease is difficult to diagnose histologically and is indicated by inflammation in the deep glandular layer with antral metaplasia and ECL cell hyperplasia.

**E-Figure 8-9.** Photomicrograph of *Helicobacter pylori*. Note the curved, seagull-shaped forms on the epithelial surface (Giemsa stain).





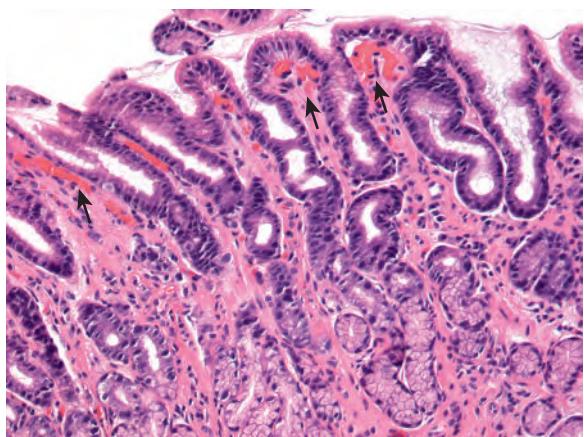
**E-Figure 8-10.** Photomicrographs of **A**, Chronic atrophic gastritis. Dense chronic inflammatory infiltrate in the lamina propria and with surface erosions. This biopsy from fundus shows *antral-type* epithelium. There is a loss of parietal cells (hematoxylin and eosin stain). **B**, Chronic atrophic gastritis, chromogranin stain, highlights the enterochromaffin cell–like cell hyperplasia, both linear and nodular.

- *Environmental gastritis* is also called *type B gastritis*. Endoscopic evaluation typically reveals involvement of antrum, and the body of the stomach if severe. In the initial stage, histologic examination finds chronic inflammatory infiltrate in the superficial zone; the later stages are marked with atrophy and metaplasia. Etiologic factors include *H. pylori*, lack of vitamin C, nitrosamines, and increased salt intake.

#### 16. What are the salient histologic features of chemical and reactive gastropathy?

- Histologic examination reveals foveolar hyperplasia with glandular tortuosity, edema in lamina propria, dilated superficial vessels, vertical muscle fibers in lamina propria, and minimal inflammation (Figure 8-11).
- Etiologic factors include nonsteroidal antiinflammatory drugs (NSAIDs), alcohol, and alkaline reflux (bile).

**Figure 8-11.** Photomicrograph of chemical-reactive gastropathy. Note the foveolar hyperplasia, glandular tortuosity, ectatic vessels in the lamina propria (arrow), and minimal inflammation (hematoxylin and eosin stain).



#### 17. What is lymphocytic gastritis, and with which disease processes is it associated?

- Lymphocytic gastritis occurs in the fundus and body of stomach, but the antrum is affected in celiac disease.
- Histologic examination demonstrates chronic gastritis pattern with increased intraepithelial lymphocytes.
- Etiologic factors most commonly include celiac disease and *H. pylori* infection. Less common etiologic factors include varioliform gastritis, lymphocytic gastroenterocolitis, human immunodeficiency virus infection, and lymphoma.

#### 18. What is the differential diagnosis of granulomatous gastritis?

- Histologic examination reveals granulomas that may be necrotizing or nonnecrotizing.
- Etiologic factors include infectious (tuberculous, fungal), Crohn's disease, sarcoid, drug reaction, vasculitis, or idiopathic (isolated granulomatous gastritis) causes.

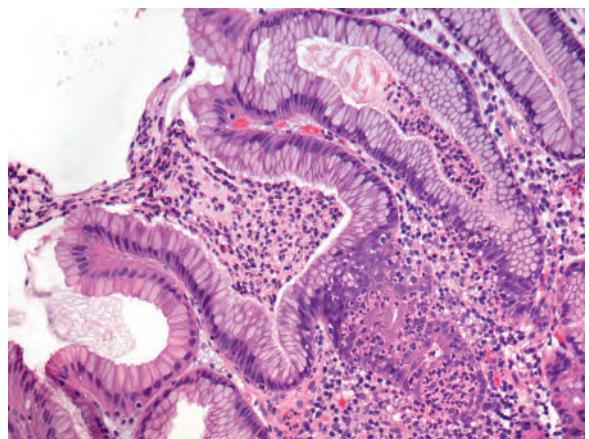
#### 19. What are the histologic features suggestive of gastric Crohn's disease?

The biopsies show patchy involvement of gastric mucosa by acute and chronic inflammation and pit abscesses (focally active gastritis) with intervening areas of normal mucosa (E-Figure 8-12). Occasionally, granulomas can be seen. Although difficult to diagnose in the absence of granulomas, these histologic features may suggest Crohn's disease.

#### 20. Histologically, how are gastric antral vascular ectasia (GAVE), portal hypertensive gastropathy, Dieulafoy lesion, and radiation injury differentiated?

- GAVE on endoscopic evaluation demonstrates red longitudinal stripes usually located in the antrum of the stomach; this is often referred to as "watermelon stomach." Histologic examination reveals dilated, congested vessels; fibrin thrombi and reactive changes like foveolar hyperplasia; and strands of muscle fibers in the lamina propria.
- *Portal hypertensive gastropathy* on endoscopic evaluation demonstrates the "tiger skin" pattern of dilated mucosal vessels in the body and fundus of the stomach. Histologic biopsy is not recommended. Histologic features include dilated ectatic vessels, foveolar hyperplasia, and fibrosis in the lamina propria with minimal inflammation. The lack of fibrin thrombi can distinguish this from GAVE.
- *Dieulafoy lesion* on endoscopic evaluation usually reveals a *pigmented protuberant vessel* in the proximal stomach without mucosal ulceration. Histologic examination finds abnormal large artery in superficial submucosa, which may erode and cause massive hemorrhage. The histologic features include erosion with fibrin and hemorrhage, and a large vessel in the submucosa.

**E-Figure 8-12.** Photomicrograph of gastric Crohn's disease. Note the neutrophilic infiltrate within the crypt lumens (focally active gastritis) (hematoxylin and eosin stain).



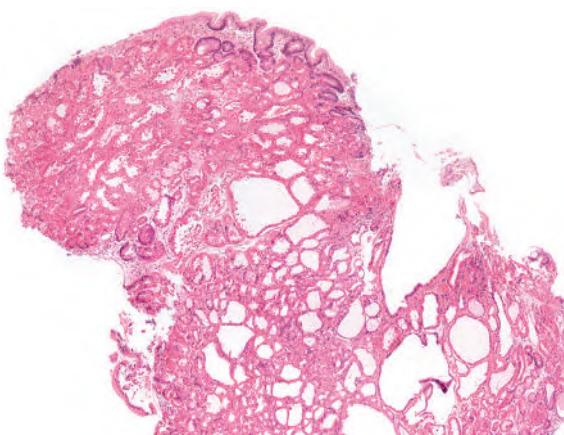
- Radiation injury on endoscopic evaluation demonstrates numerous mucosal red vascular ectasias located in the radiation port. Histologic examination demonstrates dilated vessels with hyalinized walls. The epithelial and stromal cells show marked atypia, raising the suspicion of dysplasia. Clinical history is important to rule out other causes of angiectasias like GAVE and portal hypertensive gastropathy.

**21. What are the histologic features of giant mucosal folds seen in Ménétrier's disease and Zollinger-Ellison syndrome?**

- Endoscopic examination finds enlarged gastric folds greater than 8 mm.
- Histologic examination demonstrates that the giant folds are due to hyperplasia of foveolar epithelium or oxyntic epithelium. Ménétrier's disease resembles hyperplastic polyp and shows elongated hyperplastic foveolar epithelium with loss of oxyntic glands in the gastric mucosa. Expansion of oxyntic glandular zone resulting in hypertrophic gastropathy is seen in Zollinger-Ellison syndrome. Large folds can also be seen in *H. pylori*-associated gastritis.

**22. What are the histologic features of gastric polyps and polypoid lesions?**

- *Fundic gland polyp*: On endoscopic evaluation, polyps are located in the fundus and body of the stomach. They can be sporadic or seen with familial adenomatous polyposis. Histologic examination reveals dilated oxyntic glands (Figure 8-13). The overlying foveolar epithelium is normal or occasionally shows hyperplastic change. Dysplasia is extremely rare in sporadic ones.

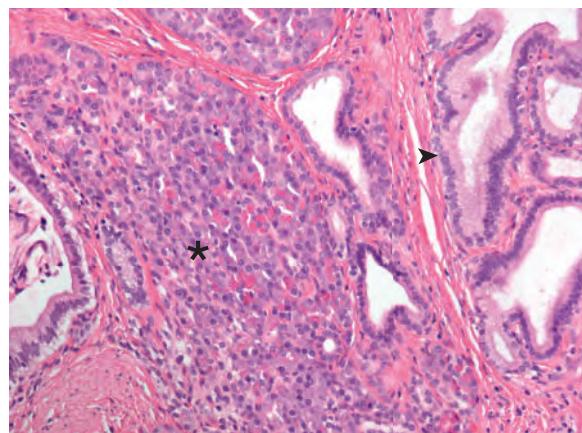


**Figure 8-13.** Photomicrograph of fundic gland polyp showing dilated oxyntic glands (hematoxylin and eosin stain).

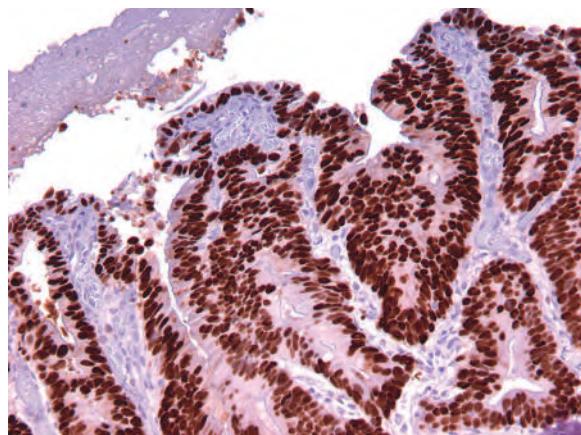
- *Hyperplastic polyp*: On endoscopic evaluation, usually a sessile polyp is located in the antrum. Histologic examination reveals hyperplastic, dilated foveolar glands within inflamed and edematous lamina propria, often with surface erosions or ulceration. The adjacent mucosa generally shows chronic gastritis. Rarely, dysplasia may be seen in these polyps, and rarely these may be present next to an adenocarcinoma. Hyperplastic morphologic characteristics are seen in the polyps of Cronkhite-Canada syndrome, Ménétrier's disease, juvenile polyps, and gastritis cystica profunda (in the postgastrectomy stomach). Isolated gastric hyperplastic polyps are not associated with polyps in the small intestine or colon.
- *Peutz-Jegher polyp*: Endoscopic evaluation reveals polyps throughout the upper GI tract; they are more common in the small intestine. Histologic evaluation reveals prominent foveolar hyperplasia in the stomach with minimal or no inflammation in the lamina propria. Arborizing smooth muscle pattern in the lamina propria is less common at this site.
- *Pancreatic heterotopia and metaplasia*: On endoscopic evaluation, pancreatic heterotopia and metaplasia are most commonly located in the antrum; their appearance is that of a submucosal nodule with a central depression ("volcano" lesion). Histologic examination shows ectopic pancreatic acini, ducts, and occasionally islet cells (30%) in varying proportions (E-Figure 8-14).
- *Gastric xanthoma*: On endoscopic evaluation, a flat yellow lesion is discovered as an incidental finding. Histologic examination reveals a benign collection of lipid-containing macrophages in the lamina propria. These have been associated with bile reflux, postgastrectomy stomach, and patients with cholestasis. Gastric adenoma is discussed next.

**23. Compare gastric dysplasia and adenoma.**

Gastric dysplasia refers to a flat lesion showing dysplasia (*flat adenoma*). A similar lesion with a polypoid appearance is referred to as an *adenoma*, which consists of tubular, or tubulovillous, architecture. Figure 8-15 depicts a gastric adenoma showing strong immunoreactivity with p53 antibody. The flat



**E-Figure 8-14.** Photomicrograph of pancreatic heterotopia. Note the acinar cells with dense eosinophilic zymogen granules (*asterisk*) and small ducts lined by cuboidal cells (*arrowhead*) (hematoxylin and eosin stain).



**Figure 8-15.** Photomicrograph of gastric adenoma showing strong nuclear immunoreactivity with p53 antibody (immunohistochemical stain).

lesion is more likely to be multifocal and associated with high-grade dysplasia. Mapping biopsies are required to rule out invasive carcinoma in both. The adenomas can have morphologic characteristics of the intestinal type (goblet or Paneth cells) or gastric type. Adenocarcinoma is more commonly associated with intestinal-type morphologic characteristics. **Table 8-1** depicts the Vienna classification of GI epithelial neoplasia.

**Table 8-1.** Vienna Classification of Gastrointestinal Epithelial Neoplasia

Category 1	Negative for neoplasia and dysplasia
Category 2	Indefinite for neoplasia and dysplasia
Category 3	Noninvasive low-grade neoplasia (low-grade adenoma and dysplasia)
Category 4	Noninvasive high-grade neoplasia 4.1 High-grade adenoma/dysplasia 4.2 Noninvasive carcinoma (carcinoma in situ) 4.3 Suspicion of invasive carcinoma
Category 5	Invasive neoplasia 5.1 Intramucosal carcinoma* 5.2 Submucosal carcinoma or beyond

\*Intramucosal carcinoma implies invasion into the lamina propria or muscularis mucosae.

(From Schlemper RJ et al: *The Vienna classification of gastrointestinal epithelial neoplasia*, Gut 47:251–255, 2000.)

#### 24. What are the histologic types of gastric adenocarcinoma?

The World Health Organization classification describes four histologic patterns:

- A. Tubular
- B. Papillary
- C. Mucinous
- D. Signet ring cell carcinoma

The Laurén system classifies gastric carcinomas into two subtypes:

- A. Intestinal type (arising in the background of intestinal metaplasia)
- B. Diffuse type (includes signet ring cell type) (Figure 8-16)

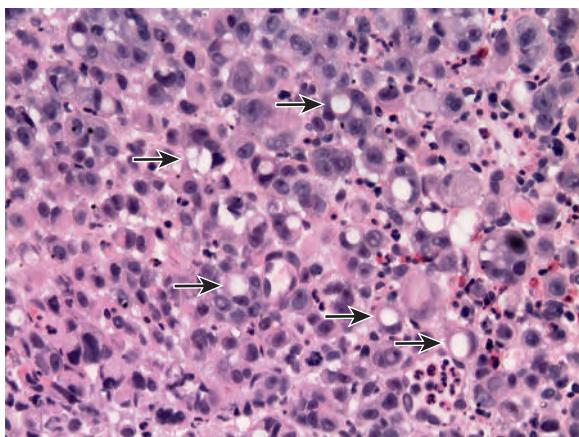
Rare variants include adenosquamous carcinoma, squamous cell carcinoma, and undifferentiated carcinoma.

#### 25. What is the histologic classification of neuroendocrine neoplasms of the stomach?

- Carcinoid (well-differentiated neuroendocrine neoplasm)
- Small-cell carcinoma (poorly differentiated neuroendocrine neoplasm)
- Large-cell neuroendocrine neoplasm

The carcinoids can further be subclassified as:

1. ECL cell carcinoid associated with autoimmune chronic atrophic gastritis; hypergastrinemia caused by increased gastrin production in the antrum



**Figure 8-16.** Photomicrograph of gastric adenocarcinoma with signet ring cell morphology (arrows) (hematoxylin and eosin stain).

2. Carcinoid tumors associated with MEN I or Zollinger-Ellison syndrome
3. Sporadic tumors not associated with hypergastrinemia or autoimmune chronic atrophic gastritis  
Aggressive behavior in carcinoids is associated with size greater than 1 cm, invasion of muscularis propria, increased mitotic activity, and angioinvasion.

#### 26. What is the differential diagnosis of gastric stromal tumors?

Gastric stromal tumors are seen as submucosal masses, and the differential diagnosis includes schwannoma, leiomyoma, GIST, and inflammatory fibroid polyps. The morphologic characteristics are similar to those seen in other sites.

GI stromal tumors are most commonly seen in the stomach (50%), followed by the small bowel (25%), the colon and rectum (10%), and the esophagus (5%). Histologically, these can be spindled or epithelioid and show strong reactivity with CD117 (95%), and positive staining with CD34 (60% to 70%). These also stain positive with DOG 1 (Discovered On GIST) antibody (including some of *kit* negative tumors). Approximately one third can also show reactivity with smooth muscle markers (SMA). These arise from interstitial cells of Cajal, and *kit* mutations are seen in 85% to 90% of GISTs. Approximately 5% show mutation within the PDGFRA gene, and these are seen in gastric GISTs and have epithelioid morphologic features and a less aggressive clinical course. All the GISTs are potentially aggressive. The clinical behavior can be predicted on the basis of size, mitotic figures, and site. Gastric GISTs have a better prognosis than the small bowel GISTs. The GISTs with exon 11 mutation have a low risk for progressive disease (as opposed to exon 9 mutation) and respond better to imatinib mesylate in the metastatic disease setting.

Inflammatory fibroid polyps are bland spindle cells accentuated around vessels, and accompanied by a mixed inflammatory infiltrate in the stroma. These are negative for CD117 and may show immunoreactivity with CD34.

#### 27. What are the different types of gastric lymphomas?

MALT lymphomas (also known as extramarginal zone B-cell lymphoma) are low-grade and show lymphoepithelial lesions (lymphoma cells infiltrating the gland epithelium). They extend deep into the muscularis mucosae, unlike reactive lymphoid hyperplasia, which is generally more superficial and a major differential diagnosis in these cases. These cells are CD20 (B-cell marker) positive; may coexpress CD43; and are CD5 negative, CD10 negative, and positive for bcl-2 protein. *Helicobacter* organisms may be seen. Distinction between reactive infiltrate versus neoplastic can be difficult in small biopsy specimens. Flow cytometry and cytogenetics are other useful studies. Gene rearrangement studies generally help determine the clonality in atypical lymphoid aggregates.

The other lymphomas that can involve the GI tract include mantle cell lymphoma, large B-cell lymphoma, enteropathy-like T-cell lymphoma, and Burkitt lymphoma.

Special thanks are given to Lisa Litzenberger for her superb photographic technical assistance.

Please access ExpertConsult to view the E-Figures for this chapter.

#### BIBLIOGRAPHY

1. Abraham SC, Krasinskas AM, Correa AM, et al. Duplication of muscularis mucosae in Barrett's esophagus: an underrecognized feature and its implications for staging of adenocarcinoma. Am J Surg Pathol 2007;31:1719-25.
2. Carr NJ, Monihan JM, Sabin LH. Squamous cell papilloma of the esophagus: a clinicopathologic and follow-up study of 25 cases. Am J Gastroenterol 1994;98:245.
3. Choudhry U, Boyce Jr HW, Coppola D. Proton pump inhibitor-associated gastric polyps: a retrospective analysis of their frequency, and endoscopic, histologic, and ultrastructural characteristics. Am J Clin Pathol 1998;110:615.

4. Demetri GD, Benjamin RS, Blanke CD, et al. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)—Update of the NCCN clinical practice guidelines. *J Natl Compr Canc Netw* 2007;5(Suppl. 2):S1–S29.
  5. Fenoglio-Presiser C, Carneiro F, Correa P, et al. WHO classification of tumors: pathology and genetics of the digestive system. Lyon, France: IARC Press; 2000, pp 43–49.
  6. Issacson PG, Muller-Hermelink HK, Piris MA, et al. WHO classification of tumors: tumors of hematopoietic and lymphoid tissues. Lyon: IARC Press; 2001, pp 157–160.
  7. Liu L, Hofsetter WL, Rashid A, et al. Significance of depth of tumor invasion and lymph node metastases in superficially invasive esophageal adenocarcinoma. *Am J Surg Pathol* 2005;29:1079–85.
  8. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol* 2006;23:111–9.
  9. Montgomery EA. Biopsy interpretation of the gastrointestinal tract mucosa. Philadelphia: Lippincott Williams & Wilkins; 2006.
  10. Mosca S, Manes G, Monaco R, et al. Squamous papilloma of the esophagus: long-term follow up. *J Gastroenterol Hepatol* 2001;16:857.
  11. Noffsinger A, Fenoglio-Presiser C, Maru D, et al. Gastrointestinal diseases—atlas of nontumor pathology, first series. Washington DC: American Registry of Pathology in collaboration with Armed Forces Institute of Pathology; 2007 104–111.138–51.
  12. Oberhuber G, Puspok A, Oesterreicher C, et al. Focally enhanced gastritis: a frequent type of gastritis in patients with Crohn's disease. *Gastroenterology* 1997;112:698–706.
  13. Prasad GA, Buttar NS, Wongkeesong LM, et al. Significance of neoplastic involvement of margins obtained by endoscopic mucosal resection in Barrett's esophagus. *Am J Gastroenterol* 2007;102:2380–6.
  14. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000;47:251–5.
- Websites**
- Akhtar I, Bhajee F, Poonam S, Weisenberg E, editors. Esophagus chapter. [PathologyOutlines.com](http://www.pathologyoutlines.com/esophagusp.html). <http://www.pathologyoutlines.com/esophagusp.html> [Accessed September 22, 2014].
- Mercer University School of Medicine. The internet pathology laboratory for medical education. <http://library.med.utah.edu/WebPath/webpath.html#MENU> [Accessed September 22, 2014].

# GASTRITIS, PEPTIC ULCER DISEASE, NSAIDS, AND *HELICOBACTER PYLORI* INFECTION

Elizabeth Coss, MD, MSc, and Byron Cryer, MD

## 1. What is gastritis?

Patients typically refer to the symptom of dyspepsia as *gastritis*. Gastroenterologists use the term *gastritis* to describe endoscopic observations. Pathologists refer to a histologic finding. Most would agree that gastritis requires a mucosal biopsy as it is a histopathologic diagnosis. Inflammation of the gastric mucosa can be classified into two types: *gastritis* or *gastropathy*. The gastric mucosa can have injury to its epithelium and regeneration without having significant inflammation. When this happens, it is referred to as *gastropathy*. *Gastritis*, however, refers to inflammation of the gastric mucosa with an associated inflammatory infiltrate. Although gastritis can be either acute or chronic, most cases of gastritis are truly chronic as acute gastritis is infrequently diagnosed soon after initiation of the inflammatory process.

## 2. What are the endoscopic findings associated with gastritis?

There is not one particular endoscopic entity that defines gastritis. Both gastroenterologists and pathologists have come to realize that endoscopic appearance frequently does not predict changes in histology (i.e., the presence of inflammation). Endoscopists use the word *gastritis* to describe an array of findings, including erythema, edema, enlarged gastric folds, polyps, the presence of erosions or ulcers, mucosal bleeding, or atrophy. The most common endoscopic finding associated with histologically diagnosed gastritis is a normal endoscopic appearance.

## 3. What is the Sydney system for diagnosis of gastritis?

The Sydney system is a gastric biopsy protocol indicating where gastric mucosal biopsies should be obtained to optimize diagnosis of gastritis including *Helicobacter pylori*. Five biopsy specimens are taken: two from the antrum within 2 to 3 cm from the pylorus (one from the distal lesser curvature and one from the distal greater curvature), two from the corpus approximately 8 cm from the cardia (one from the lesser and the other from the greater curvature), and one from the incisura angularis. Samples from the antrum, corpus, and incisura angularis should be separately identified. Duodenal biopsies may be useful in certain settings (e.g., suspected celiac disease and lymphocytic gastritis, or duodenal Crohn's disease and granulomatous gastritis).

## 4. What are common causes of chronic gastritis?

The most common cause of chronic gastritis is *H. pylori* infection. Autoimmune gastritis (atrophic gastritis) accounts for the most common cause of *H. pylori*-negative chronic gastritis (roughly 5%); less common causes include infections, eosinophilic gastritis, lymphocytic gastritis, granulomatous gastritis, graft-versus-host disease, and inflammatory bowel disease (Table 9-1). As mentioned previously, most cases of gastritis are "chronic" because patients with acute gastritis are rarely diagnosed.

## 5. What are common etiologic factors of reactive gastropathy?

Medications (particularly nonsteroidal antiinflammatory drugs [NSAIDs]), toxins, tobacco, alcohol, portal hypertensive gastropathy, cocaine, stress, radiation, bile reflux, ischemia, mechanical injury from gastric cardia prolapsing to the esophageal lumen during retching or vomiting, aging, and certain infections are commonly associated with reactive gastropathy.

## 6. What medications are frequently associated with gastropathy?

- Acetylsalicylic acid (even low-dose) and NSAIDs
- Oral iron
- Potassium chloride
- Bisphosphonate
- Fluoride
- Systemic chemotherapy
- Hepatic arterial infusion of chemotherapy
- Toxic ingestion of heavy metals

## 7. How does the gastric mucosa normally protect itself from injury given its acidic environment?

The stomach has epithelial defense mechanisms that serve to maintain its mucosal integrity. These protective mechanisms are often characterized into three components: preepithelial, epithelial, and postepithelial, all of which are prostaglandin dependent. See Box 9-1 and Figure 9-1.

**Table 9-1.** Types of Gastritis

PATHOLOGIC DIAGNOSIS	HISTOLOGIC FINDINGS	ETIOLOGIC FACTORS	ENDOSCOPIC FINDINGS	CLINICAL ASSOCIATIONS
Acute suppurative gastritis	Neutrophilic inflammation	Acute <i>H. pylori</i> and Streptococcal gastritis or other bacteria	May be normal or have mucosal fold swelling; dark red, distended stomach; pus	Acute gastroenteritis-like illness, perforation, gangrene
Chronic and chronic active gastritis	Mixed inflammatory infiltrates (neutrophils, plasma cells, eosinophils) with or without foveolar hyperplasia, lymphoid aggregates, erosions, ulcers, intestinal metaplasia, atrophy (late stages)	Chronic <i>H. pylori</i> gastritis	Typically normal; may present with erythema, friability, nodularity, or in some cases erosions or ulcerations	Varies; most may be asymptomatic; can present with duodenal ulcer, gastric ulcer, gastric adenocarcinoma; some association with functional dyspepsia
Lymphocytic gastritis	Chronic active inflammation with increased intraepithelial lymphocytes with or without foveolar hyperplasia, erosions, ulcers	Hypersensitivity to gliadin, hypersensitivity to unknown agents, autoimmune	Varioliform or chronic erosive gastritis (nodules with central ulceration); picture of Ménétrier's disease	Celiac sprue; Ménétrier's disease
Granulomatous gastritis	Multifocal (frequently necrotizing) active chronic inflammation with epithelioid granulomas	Idiopathic isolated granulomatous gastritis; Crohn's disease; fungal, mycobacterial, and spirochetal infections; sarcoidosis; vasculitis; drug reactions	Variable, including thickened folds and ulcerations	Depends on underlying disease
Eosinophilic gastritis	Sheets of eosinophils	Idiopathic food allergy, drug allergy, parasitic disease	Prominent folds, hyperemia, nodularity, ulcer, or may be normal	Pain; nausea, vomiting; early satiety; weight loss, anemia
Hypertrophic lymphocytic gastritis	Lymphocytic gastritis with extreme foveolar hyperplasia	Clinical syndrome identical to Ménétrier's gastropathy; etiologic factors presumed different	Same as hypertrophic gastropathy	Same as hypertrophic gastropathy

Adapted from Carpenter HA et al. Gastroenterol 108(3): p. 917-24, 1995.

## 8. What are common causes of gastric or duodenal ulcers?

Very common (>95%):

*H. pylori* infection

NSAIDs

**Box 9-1. Gastric Epithelial Defense Mechanisms****Preepithelial**

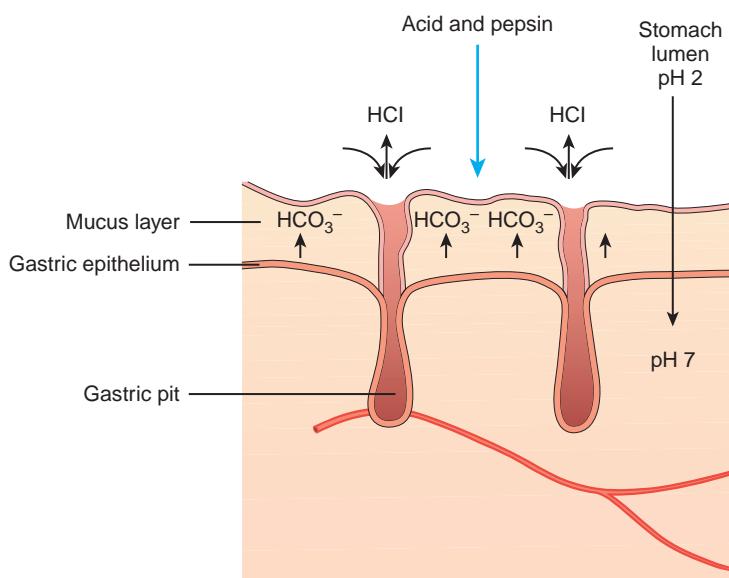
Mucus barrier forms a continuous gel into which bicarbonate-rich fluid is secreted, forming a protective pH gradient by maintaining a neutral pH.

**Epithelial**

Surface epithelial cells can withstand acidic environments as low as pH 2.5 and are designed to rapidly repair themselves through a process known as *mucosal restitution*.

**Postepithelial**

Rich vascular anatomy within the gastric mucosa that ensure delivery of the newly released bicarbonate by parietal cells to the gastric epithelium to neutralize neutrons.



**Figure 9-1.** Gastric mucosa protective mechanisms include mucus layer thickness, pH gradient, cell membrane hydrophobicity, bicarbonate secretion, and mucosal blood flow. These mechanisms are mostly mediated by prostaglandins.  $\text{HCO}_3^-$ , bicarbonate;  $\text{HCl}$ , hydrochloric acid.

Less common ( $\approx 5\%$ ):

- Gastric malignancy (adenocarcinoma or lymphoma)
- Stress ulceration (central nervous system trauma and burn patients)
- Viral infection (herpes simplex virus type 1 or cytomegalovirus)

Uncommon or rare (<1%):

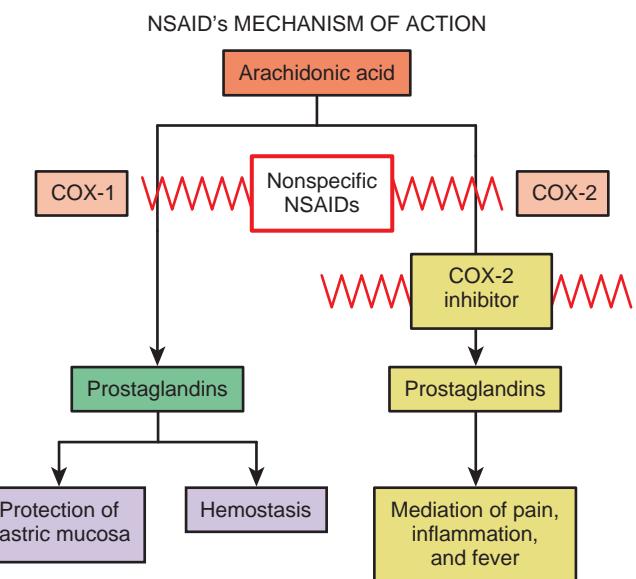
- Zollinger-Ellison syndrome
- Cocaine use
- Crohn's disease
- Systemic mastocytosis
- Myeloproliferative disorders with basophilia
- Idiopathic (non-*H. pylori*) hypersecretory duodenal ulcer
- Abdominal radiotherapy
- Hepatic artery infusion of 5-fluorouracil

## 9. What is the role of NSAIDs in the pathogenesis of gastroduodenal ulcers?

There are two principal pathogenic mechanisms by which NSAIDs cause ulceration (Figure 9-2).

- Reduction of gastrointestinal mucosal prostaglandins
  - Prostaglandins protect against injury in the gastrointestinal tract. NSAIDs inhibit cyclooxygenase (COX), the rate-limiting enzyme in prostaglandin synthesis, leading to a reduction in prostaglandin concentrations resulting in the loss of a major mechanism of protection and predisposing to injury. There are two COX isoforms: COX-1 and COX-2. COX-1 is the predominant isoform present in the gastrointestinal tract. COX-2 is primarily present at sites of inflammation; NSAIDs that inhibit primarily COX-2 cause less reduction in gastrointestinal prostaglandins and thus lower rates of NSAID-induced ulcers.
- Local, topical injury to surface epithelial cells

**Figure 9-2.** Nonsteroidal antiinflammatory drug's (NSAID) mechanism of action. NSAID's main mechanism of mucosal injury is via local irritation of gastric mucosa and by inhibition of cyclooxygenase, which subsequently leads to a reduction in prostaglandins. COX, Cyclooxygenase.



## 10. What are NSAID-related gastrointestinal complications?

The most common gastrointestinal finding associated with NSAID use is symptomatic ulcers. However, most of these ulcers have a benign course and most do not progress to complications. Among the possible complications of NSAID-related ulcers, gastrointestinal bleeding, perforation, or gastrointestinal obstruction are the most frequent occurrences. The most common gastrointestinal complication of NSAID use is bleeding from peptic ulcer disease, mostly in the stomach.

## 11. What are risk factors for developing NSAID-related complications?

- Older age
- Previous gastrointestinal event (e.g., previous ulcer or gastrointestinal bleeding)
- Concomitant use of anticoagulants
- Corticosteroids
- Other NSAIDs including low-dose aspirin, high-dose NSAID therapy
- Chronic debilitating disorders such as cardiovascular disease

*H. pylori* infection also increases the risk of NSAID-related ulcers. Treatment of *H. pylori* reduces the risk of rebleeding.

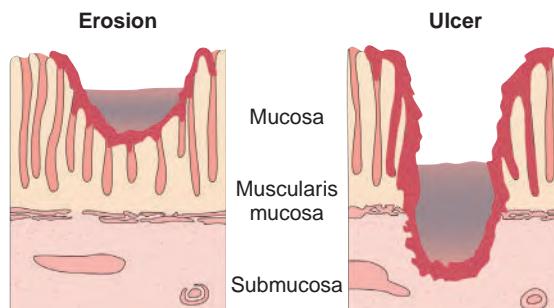
Selective serotonin reuptake inhibitors increases the risk of upper gastrointestinal bleeding threefold.

Concurrent use of NSAIDs potentiates this effect.

Concurrent use of clopidogrel (Plavix) with aspirin increases the risk of upper gastrointestinal bleeding. The need for antiplatelet agents should be reviewed. In patients with established cardiovascular disease who require antiplatelet therapy, proton pump inhibitor (PPI) co-therapy should be provided long-term.

## 12. How is an erosion different from an ulcer?

An erosion is differentiated from an ulcer according to the depth of the mucosal injury. Erosions do not extend into or below the muscularis mucosae, whereas ulcers do. See Figure 9-3 and Box 9-2.



**Figure 9-3.** The difference between an erosion and an ulcer mainly involves depth of mucosal injury.

**Box 9-2. Difference between Erosion and Ulcer**

Erosion	Well-defined hemorrhagic lesions 1 to 2 mm in size; superficial lamina necrosis—endoscopically defined as < 3 mm in diameter
Ulcer	Extends to the muscularis mucosa

Unlike erosions, ulcers extend to the muscularis mucosa and submucosa; therefore healing of an ulcer requires tissue, whereas a superficial erosion heals with the neighboring mucosa.

**13. What is the typical presentation of uncomplicated ulcer disease?**

- Burning, sharp, deep epigastric pain that usually arises 1 to 3 hours after eating
- Vague abdominal discomfort or nausea rather than pain
- Relief of symptoms by eating or taking antacids
- Occurrence of symptoms when the stomach is empty or at night
- History of self-treatment with antacids, frequent and longstanding use of H<sub>2</sub>-receptor antagonists or cigarette smoking
- Symptoms recurring over months or years
- Epigastric tenderness on palpation (with active symptomatic ulcers)

**14. How is the endoscopic diagnosis of an ulcer made?**

It is important to differentiate between an erosion and an ulcer. Whereas an erosion involves only the superficial mucosa, an ulcer generally extends to the submucosa where vessels reside. According to the most current guidelines from the American College of Gastroenterology (ACG), although the diagnosis of an ulcer requires histologic depth, we rely on the endoscopist to interpret the depth of the ulcer and to provide clues about the endoscopic appearance of the ulcer to help guide its management.

**15. What is *H. pylori* infection?**

*H. pylori* is a major pathogen in humans. *H. pylori* is a small, curved, microaerophilic, gram-negative, rod-shaped bacterium that can infect the human gastric mucosa and become persistent. Although many people infected with *H. pylori* may be asymptomatic, infection may lead to complications such as gastric and duodenal ulcers, multifocal atrophic gastritis, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer.

**16. How is *H. pylori* transmitted?**

Transmission of *H. pylori* appears to occur by direct, person-to-person contact especially gastro-oral. Fecal-oral, oral-oral, and salivary routes of transmission have been reported.

**17. What is cagA<sup>+</sup> *H. pylori*?**

*H. pylori* strains that possess the *cagA* gene are associated with severe forms of gastroduodenal disease. *CagA* is a gene that codes for an immunodominant antigen. The genetic locus that contains *cagA* (*cag*) is part of a 40-kb DNA insertion that likely is acquired horizontally.

**18. What is the prevalence of *H. pylori*?**

The prevalence of *H. pylori* varies worldwide. According to the Centers for Disease Control and Prevention, close to 50% of the world's population are infected with *H. pylori*. Although the prevalence of *H. pylori* in the United States has not been studied since the early 2000s, it is believed that in certain populations of the United States the prevalence of *H. pylori* may be as high as 50%.

**19. What are typical pathologic findings associated with *H. pylori* infection?**

*H. pylori* is usually found in the antrum, although it may be found in the corpus. An inflammatory infiltrate consisting of neutrophils within the lamina propria can be seen crossing the basement membrane. Intraepithelial neutrophils and subepithelial plasma cells are pathognomonic for *H. pylori* infection. Lymphoid aggregates are frequently present.

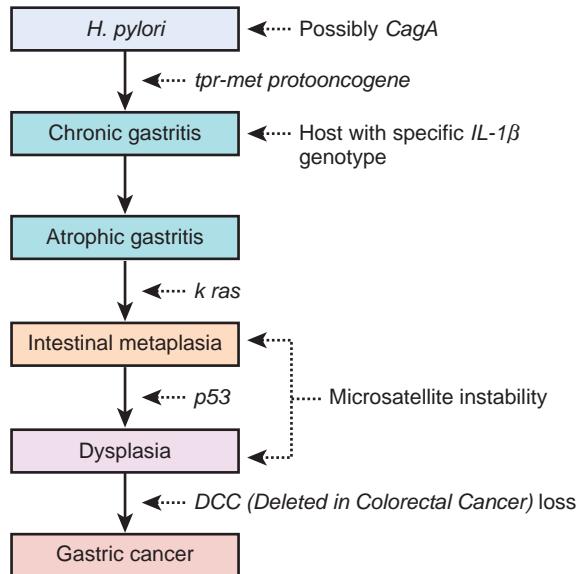
**20. How does *H. pylori* infection lead to gastric atrophy or atrophic gastritis?**

Long-standing *H. pylori* infection can lead to progressive depletion of native gastric mucosal structures in scattered patches throughout the stomach. This is often referred to as *multifocal atrophic gastritis*. It tends to be characterized by antrum-predominant gastritis or pangastritis, where the normal mucosa is subsequently replaced by mucosa that is not normally there (metaplasia). In the setting of *H. pylori* infection, atrophy and intestinal metaplasia invariably involve the antrum and could involve the corpus as well.

**21. How does *H. pylori* infection lead to gastric cancer?**

See Figure 9-4.

***H. pylori* INFECTION AND GASTRIC CANCER:  
THE CORREA CASCADE**



**Figure 9-4.** The Correa cascade in *Helicobacter pylori* infection and gastric cancer. Well-defined precancerous sequential stages initiated by *H. pylori* infection: chronic active gastritis → chronic atrophic gastritis → intestinal metaplasia → dysplasia (also called intraepithelial neoplasia) and carcinoma.

**Table 9-2.** Comparison of Diagnostic Tests for *Helicobacter pylori*

DIAGNOSTIC TEST	SENSITIVITY (%)	SPECIFICITY (%)
<b>Invasive (Endoscopy)</b>		
Gastric biopsies, histologic examination	93-99	95-99
Clo-test (rapid urease assay)	89-98	93-98
Culture	58	100
<b>Noninvasive (Nonendoscopic)</b>		
Serologic evaluation	88-99	93-98
Urea-breath test	90-97	90-100
Stool antigen	90-96	97-98

Adapted from the GI/Liver Secrets, ed 4, and Kanna S, et al. Diagnostic tests for *Helicobacter pylori*, in Gastroenterology and Endoscopy News, August 2013, McMahon Publishing.

**22. What diagnostic tests are available for testing for *H. pylori* and what is their sensitivity and specificity?**

See Table 9-2.

**23. Who should be tested and treated for *H. pylori* infection?**

A test-and-treat strategy for *H. pylori* is encouraged. According to the ACG, those with active peptic ulcer disease (gastric or duodenal ulcer), those with a confirmed history of peptic ulcer disease (not previously treated), those with gastric MALT lymphoma, those who have had resections of early gastric cancer, and those with uninvestigated dyspepsia who live in areas of high *H. pylori* prevalence should be tested for *H. pylori* and treated.

**24. What is the recommended treatment for *H. pylori* infection?**

Triple therapy has been the mainstay of treatment for *H. pylori* during the preceding decade. Triple therapy consists of amoxicillin 1000 mg orally twice daily, clarithromycin 500 mg orally twice daily, and the standard

**Table 9-3.** First-line Treatment Regimens for *Helicobacter pylori* Infection

REGIMEN (ORAL)	DURATION	ERADICATION RATES	COMMENTS
<b>First-line Therapy</b>			
<b>Standard Therapy</b>			
Standard dose PPI* twice daily, clarithromycin 500 mg twice daily, amoxicillin 1000 mg twice daily orally	10-14 days	70%-85%	Nonpenicillin allergic
Standard dose PPI* twice daily, clarithromycin 500 mg twice daily, metronidazole 500 mg twice daily orally	10-14 days	70%-85%	Penicillin allergic patients or patients unable to tolerate quadruple therapy
<b>Sequential Therapy</b>			
Amoxicillin 1000 mg twice daily and standard dose PPI* orally for 5-7 days, then clarithromycin 500 mg twice daily, standard dose of PPI orally for 5-7 days	5-7 days 5-7 days Total 10-14 days	>85%	First-line therapy per European guidelines based on patterns of clarithromycin resistance; has not been studied in the United States
<b>Quadruple Therapy</b>			
Bismuth subsalicylate 525 mg four times a day, metronidazole 250 mg four times a day, tetracycline 500 mg four times a day and standard dose of PPI*	10-14 days	75%-90%	Sold as Pylera in the United States given the tetracycline shortage; difficult for patients to take given pill burden

PPI, Proton pump inhibitor.

\*Standard dose varies depending on the PPI.

Adapted from Chey et al., Am J Gastroenterol 102(8):1808-1825, 2007.

dosing of a PPI (e.g., pantoprazole, omeprazole) for 14 days. In recent years, treatment of *H. pylori* has been challenging, given issues with antibiotic resistance leading to lower eradication rates. *H. pylori* is one of the only infections for which patients are treated without isolation or identification of the individual strain's susceptibility patterns. The last time resistance patterns were evaluated in the United States was in 1999, and at the time clarithromycin resistance appeared to be the factor most compromising for effective treatment response; in Europe sequential therapy is used to address issues with clarithromycin resistance.

## 25. What are the treatment regimens for *H. pylori* eradication per ACG guidelines?

See Table 9-3.

## 26. What is autoimmune atrophic gastritis?

*Autoimmune gastritis* refers to an autoimmune process that progressively destroys the normal parietal cells in the stomach, also referred to as *oxytic cells*, and leads to gastric atrophy.

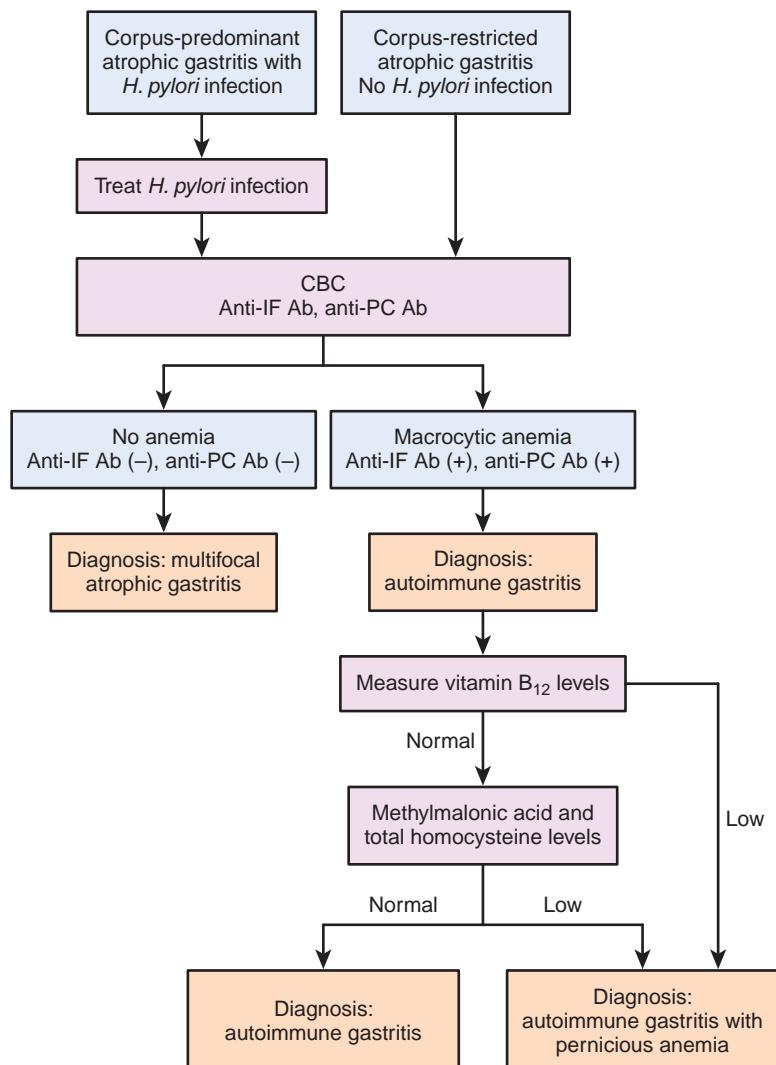
## 27. How is autoimmune atrophic gastritis different from multifocal atrophic gastritis?

Autoimmune atrophic gastritis tends to be restricted to the corpus whereas *H. pylori* multifocal atrophic gastritis involves the antrum. Autoimmune atrophic gastritis can be associated in its severe form with vitamin B<sub>12</sub> deficiency anemia, also known as *pernicious anemia*.

## 28. How is autoimmune atrophic gastritis diagnosed?

Patients with autoimmune atrophic gastritis often present with vague clinical symptoms, including fatigue, or symptoms related to iron-deficiency anemia, which is what prompts an endoscopic evaluation, usually with endoscopy and colonoscopy. The diagnosis of autoimmune atrophic gastritis relies on biopsies, but can be substantiated by demonstrating autoantibodies against intrinsic factor and parietal cells. Figure 9-5 is a diagram with a proposed algorithm for a treatment approach for a patient with a suspected autoimmune atrophic gastritis.

**Figure 9-5.** Proposed algorithm for diagnosis of autoimmune gastritis. Ab, Antibody; CBC, complete blood count; IF, Intrinsic factor; PC, Parietal cell. (From Neumann WL, et al: Autoimmune atrophic gastritis—pathogenesis, pathology and management. *Nat Rev Gastroenterol Hepatol*, 10(9):529-541, 2013 Sep.)



## BIBLIOGRAPHY

- Carpenter HA, Talley NJ. Gastroscopy is incomplete without biopsy: clinical relevance of distinguishing gastropathy from gastritis. *Gastroenterology* 1995;108(3):917-24.
- Chey WD, Wong BC. Practice Parameters Committee of the American College of Gastroenterology: American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol* 2007;102(8):1808-25.
- Correa P. Human gastric carcinogenesis: a multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer. *Cancer Res* 1992;52(24):6735-40.
- Dalton SO, Johansen C, Mellemkjaer L, Nørgård B, Sørensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. *Arch Intern Med* 2003;163(1):59-64.
- Dixon MF, et al. Classification and grading of gastritis. The updated Sydney System International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J Surg Pathol* 1996;20(10):1161-81.
- Feldman ML, Feldman E. Sleisenger and Fordtran's gastrointestinal and liver disease. ed 9. W.B. Saunders, Maryland Heights, MO; 2010.
- Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol* 2012;107(3):345-60.
- Nardone G. Review article: molecular basis of gastric carcinogenesis. *Aliment Pharmacol Ther* 2003;17(Suppl 2):75-81.
- Neumann WL, et al. Autoimmune atrophic gastritis-pathogenesis, pathology and management. *Nat Rev Gastroenterol Hepatol* 2013 Sep;10(9):529-41.
- Scheiman JM. NSAIDs, gastrointestinal injury, and cytoprotection. *Gastroenterol Clin North Am* 1996;25(2):279-98.

# GASTRIC CANCER

*John C. Deutsch, MD*

## **1. What determines whether a cancer at the gastroesophageal (GE) junction is gastric or esophageal?**

A cancer that arises more than 5 cm distal to the GE junction is considered gastric whether or not it involves the distal esophagus (Figure 10-1). A cancer that arises less than 5 cm distal to the GE junction but does not involve the GE junction is also considered gastric in origin.

## **2. What are the histologic types of gastric cancer?**

More than 80% of gastric cancers are adenocarcinomas. Less common types include lymphomas (both low grade and high grade), endocrine tumors such as carcinoid or small cell cancers, mesenchymal tumors, and metastatic tumors (e.g., melanoma, breast cancer).

## **3. What are mesenchymal tumors of the stomach?**

The mesenchyme is the loosely packed, unspecialized cells from which connective tissue, bone, cartilage, and the circulatory and lymphatic systems develop. These tissues can undergo transformation or dysregulated growth. In the stomach, these tumors appear to be subepithelial. The histologic findings can be varied and the final identification often relies on immunohistochemistry. For example, leiomyoma and leiomyosarcomas stain for muscle markers such as desmin and smooth muscle actin. Schwannomas stain for neural markers such as S-100 and calretinin. The most common mesenchymal tumor of the stomach is the gastrointestinal stromal tumor (GIST), which stains for c-kit/CD 117 and CD34.

## **4. What is a signet ring cell carcinoma?**

Signet ring carcinomas are adenocarcinomas in which more than 50% of the malignant cells in a tumor have intracytoplasmic mucin, which pushes the nucleus off to the side. Signet ring cell carcinoma tends to infiltrate and produce a desmoplastic (fibrous stromal) reaction. In general, signet ring carcinoma is an aggressive subtype.

## **5. What is linitis plastica?**

Linitis plastica is a form of gastric adenocarcinoma in which the tumor infiltrates along the stomach wall causing an associated desmoplastic reaction. The stomach becomes poorly distendable and resembles a “leather bottle.” This presentation generally has a poor prognosis.

## **6. What is the ethnic and geographic distribution of gastric adenocarcinoma?**

Adenocarcinoma of the stomach is one of the most common malignancies worldwide, resulting in approximately 600,000 deaths per year. There is a high incidence in Asia and South America. Scandinavian countries have a higher incidence than the United States.

## **7. How common is gastric cancer in the United States?**

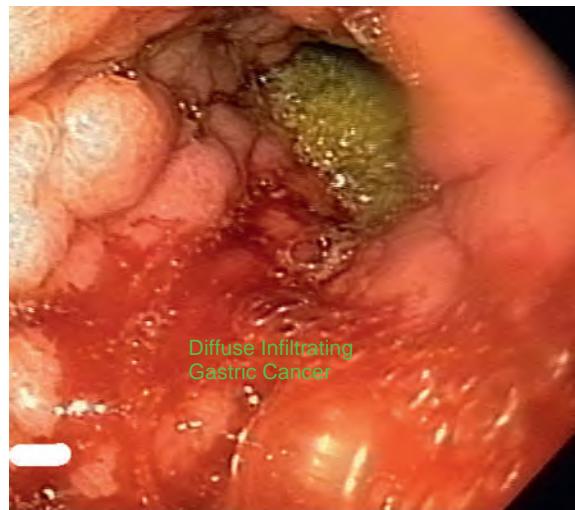
The American Cancer Society estimates that there were 21,000 new cases of stomach cancer (with 10,000 deaths) in the United States in 2012. In contrast, the same organization estimates there were 144,000 new cases of colorectal cancer in the same period.

## **8. How is the incidence of gastric adenocarcinoma changing?**

Gastric adenocarcinoma has two major sites of presentation—either proximally in the stomach near the esophagogastric junction, or distally in the antrum of the stomach. Worldwide, adenocarcinoma of the distal stomach is most common. In the United States, however, this presentation has markedly decreased during the past several decades. Conversely, proximal gastric adenocarcinoma has been increasing rapidly, probably related to reflux of gastric contents.

## **9. What is the role of diet in the development of gastric cancer?**

Dietary factors appear to be important in the development of gastric cancer. In general, the incidence of gastric cancer is higher when a higher proportion of the diet is obtained from salted or smoked meats or fish. Fruits and vegetables appear to be protective. Dietary factors are thought to explain a large part of the variation in gastric cancer occurrence from country to country and may be responsible for the decrease in gastric cancer incidence seen when subjects migrate from high-incidence to low-incidence areas.



**Figure 10-1.** Endoscopic view of infiltrating gastric adenocarcinoma.

#### 10. What inherited genetic syndromes are associated with gastric adenocarcinoma?

Approximately 10% of gastric cancer appears to be familial, independent of *Helicobacter pylori* status. Familial adenomatous polyposis patients have a tenfold increase in gastric cancer over the population at large. Gastric cancer is one of the tumors found in hereditary nonpolyposis colon cancer (HNPCC) syndrome, and approximately 10% of patients with HNPCC develop gastric cancer.

Families with specific mutations in the E-cadherin gene (CDH1) have been reported to have a 100% chance of developing diffuse gastric cancer.

An autosomal dominant syndrome has been described and is known as *gastric adenocarcinoma and proximal polyposis of the stomach*. This syndrome is characterized by fundic gland polyposis (a condition previously believed to be benign) and intestinal-type proximal gastric cancer.

#### 11. What is the role of *H. pylori* in gastric adenocarcinoma?

The medical literature generally supports the notion that *H. pylori* infection appears to increase the lifetime risk of gastric cancer. Infected persons have approximately a twofold increase in the risk of acquiring gastric adenocarcinoma. However, the chance of an *H. pylori*-infected person contracting cancer is very low.

#### 12. What mechanism is proposed for *H. pylori* causing an increased risk of gastric cancer?

*H. pylori* infection results in a rather marked inflammatory state in the stomach, which can eventually lead to atrophic gastritis and achlorhydria. Some reports suggest that host factors, including a proinflammatory host genotype, lead to both achlorhydria and gastric cancer development.

#### 13. What is the role of achlorhydria in gastric cancer?

Achlorhydria is caused by destruction of the parietal cells. Immune destruction is associated with antiparietal cell antibodies and elevated gastrin levels in the serum. These patients often have associated cobalamin ( $B_{12}$ ) deficiency. Other causes include parietal cell destruction after long bouts of infection with *H. pylori*. People with achlorhydria independent of *H. pylori* have a significant increase in the incidence of gastric cancers, possibly related to the associated elevation in gastrin levels, as well as the inflammation that leads to the parietal cell destruction.

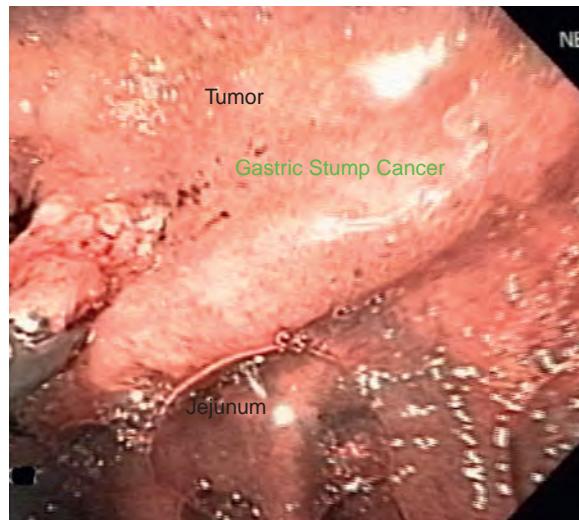
#### 14. Should *H. pylori* infection be eradicated to prevent gastric cancer from occurring?

Despite the epidemiologic link between *H. pylori* infection and gastric cancer, the data do not appear to support *H. pylori* eradication as a cancer preventive strategy at this time in the United States. A metaanalysis weighted toward higher-incidence countries raised the possibility that *H. pylori* eradication could decrease gastric cancer incidence.

The reasons *H. pylori* eradication might not show a decrease in gastric cancer rates include the relatively low incidence of cancer development in *H. pylori*-infected individuals and the variety of other factors related to cancer development, including the host's genetic propensity and the genetic makeup of different *H. pylori* strains. Furthermore, there seem to be important environmental factors such as tobacco use and diet that modulate the potential carcinogenic effects of *H. pylori*.

#### 15. Who should be screened for gastric cancer?

In Japan, where gastric cancer is the leading cause of cancer death, annual screening is recommended after the age of 40 years. There are no screening recommendations for distal gastric adenocarcinoma in the United States,



**Figure 10-2.** Endoscopic view of gastric stump cancer using narrow band imaging. The anastomosis is at a gastrojejunostomy.

and no recommendations are widely accepted for the screening of immigrants from high-risk areas. Screening for proximal gastric or GE junction cancer is probably warranted in people with a longstanding history of reflux symptoms. More details regarding screening are available at <http://www.uptodate.com/contents/screening-and-prevention-of-gastric-cancer> (accessed September 22, 2014).

#### 16. What is gastric stump cancer?

After partial gastric resection, the incidence of gastric cancers at the site of the intestinal-gastric anastomosis (Figure 10-2) appears to be increased by approximately twofold. However, this increase is not apparent until at least 15 years after surgery. In the initial 5 years after partial gastrectomy, there may be an actual decrease in cancer risk. These data suggest a certain background rate of gastric cancer formation. If part of the stomach is removed, less mucosa is at risk for malignant transformation. However, the surgery then imparts a procarcer effect, and over time more and more cancers start to form in the remaining mucosa. Although there are no firm recommendations, if surveillance is being considered, it should be instituted 15-20 years after the original gastric surgery.

#### 17. What is early gastric cancer?

Early gastric cancer is a gastric adenocarcinoma in which the primary tumor is confined to the mucosa or submucosa, independent of nodal status.

#### 18. What is the staging scheme for gastric adenocarcinoma?

Tumor-node-metastasis (TNM) staging is generally used. T stage is primarily determined by the relation of the tumor to the muscularis propria (above = T1, into = T2, or through = T3). T4a is through serosa and T4b is into adjacent structures (Figure 10-3). N stage is determined by the number and location of affected nodes (local versus distant). M stage is determined by whether distant metastases are present.

#### 19. How does staging help in treating gastric cancer?

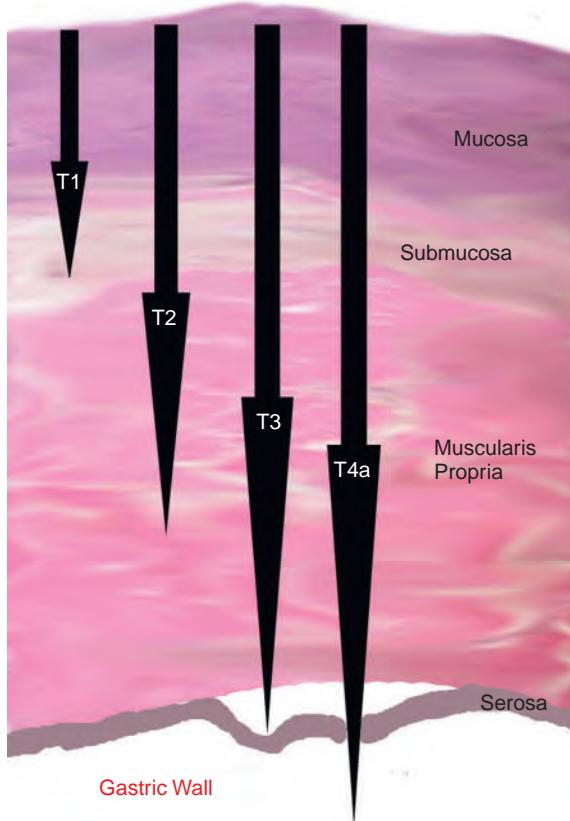
Survival after gastrectomy for gastric cancer is directly correlated with stage as reported in Surveillance, Epidemiology, and End Results data. For instance, stage-stratified 5-year/10-year relative survival rates in a study of more than 50,000 cases of gastric cancer in the United States were as follows:

- Stage IA 78%/65%
- Stage IB 58%/42%
- Stage II 34%/26%
- Stage IIIA 20%/14%
- Stage IIIB 8%/3%
- Stage IV 7%/5%

Therapy, prognosis, and follow up can be tailored based on the initial staging.

#### 20. What is the role of endoscopic ultrasonography (EUS) in staging gastric cancer?

EUS is a technique in which an ultrasound probe is attached to an endoscope. As a rule, it is the most accurate method of T and N staging gastrointestinal tumors and has the advantage of biopsy capability. EUS can detect small amounts of ascites in staging gastric cancer, which suggests unresectability. However, the accuracy of EUS compared with surgery in staging gastric cancer is still relatively low for certain presentations such as T2 lesions, which tend to be overstaged by EUS. Lymph node staging is approximately 80% accurate in most



**Figure 10-3.** T staging scheme for gastric adenocarcinoma.

studies and may be lower with the general application of EUS in the medical community. EUS imaging can provide a roadmap but surgical and pathologic staging is more definitive than image-based staging.

**21. What is the role of endoscopy in the treatment of early gastric cancer?**

Early gastric cancer that has a surface diameter less than 2 cm is amenable to endoscopic removal. The cure rate with endoscopic resection is higher than 95% if the tumor shows no evidence of lymphovascular invasion, is confined to the mucosa, and has intestinal histologic characteristics. EUS is a valuable adjunct to endoscopic resection, because detection of nodal involvement precludes definitive endoscopic management of the tumor.

**22. What are gastric endoscopic mucosal resection (EMR) and gastric endoscopic submucosal dissection (ESD)?**

Both methods generally employ the injection of a fluid between the mucosa and the gastric wall to separate the lesion from deeper structures. EMR often uses suction devices and a snare to remove the tumor, whereas ESD employs an endoscopic cautery knife to dissect the lesion free from underlying tissue. EMR is easier to perform and has a lesser complication rate, but ESD can be used for en-bloc resection of larger lesions.

**23. What is the extent of surgery used when trying to remove locally advanced gastric adenocarcinoma?**

Surgery is a potential curative therapy for localized gastric adenocarcinoma. The prognosis is based on TNM staging. The extent of resection is somewhat controversial. Japanese literature suggests that an extended lymphadenectomy plus omentectomy (D2 operation) is superior to a limited lymphadenectomy with omentectomy (D1 procedure) or limited lymphadenectomy (D0 procedure). In a randomized European study, patients undergoing D2 resection had twice the operative mortality as those undergoing D1 resection and there was no survival benefit.

**24. What is the role of neoadjuvant therapy in gastric adenocarcinoma?**

Neoadjuvant therapy is treatment given before an attempt at curative surgical resection. The hypothesis is that this therapy makes the primary tumor smaller and possibly treats small foci of disease outside the operative field. There are studies that suggest neoadjuvant chemotherapy is beneficial for proximal gastric cancer of a more advanced local stage.

**25. What is the role of adjuvant therapy in gastric adenocarcinoma?**

Adjuvant therapy is additional treatment given to patients after attempted curative surgery. Adjuvant treatment is given if there is no evidence of remaining disease. Studies (such as the randomized Intergroup trial 0116) have shown that adjuvant radiochemotherapy improves outcome in treating gastric cancer.

A metaanalysis has also suggested that adjuvant chemotherapy without radiation therapy provides benefit after curative-intent surgery.

**26. What is the usual therapy for metastatic gastric adenocarcinoma?**

Chemotherapy can be used in advanced gastric cancer with modest benefits. Several regimens have activity in gastric adenocarcinoma, using drugs such as 5-fluorouracil, etoposide, platinum-containing drugs, and taxanes. Trastuzumab, a monoclonal antibody directed against the HER2/neu receptor, has also been shown to be of some benefit.

**27. What is a mucosal-associated lymphoid tissue (MALT) lymphoma?**

MALT lymphomas are also referred to as *extranodal marginal zone B cell lymphomas*. They can occur in any mucosal location, both within and outside the gastrointestinal tract, but are most common in the stomach. MALT lymphomas are often low-grade B-cell lymphomas ([E-Figure 10-4](#)), but they also may be high-grade aggressive tumors. They can be associated with specific genetic alterations such as the 11:18, 14:18, or 1:14 translocation.

**28. What is unique about gastric MALT lymphomas?**

Gastric MALT lymphomas, unlike MALT lymphomas in other locations, often are associated with infection by *H. pylori*. Lymphoid tissue is not a normal part of gastric epithelium, and infection with *H. pylori* seems to drive lymphoid proliferation and tumor development.

**29. What is the role of antibiotic therapy in gastric MALT lymphomas?**

Treatment of *H. pylori* infection usually leads to regression and cure of low-grade B-cell gastric MALT lymphomas. It is believed that the low-grade tumors retain responsiveness to *H. pylori* antigen stimulation. Complete responses can take up to 18 months after antibiotic therapy. In general, high-grade gastric MALT lymphomas and those with more acquired chromosomal abnormalities do not respond well to antibacterial therapy.

**30. Describe the staging scheme for gastric lymphoma.**

Several staging systems are used for gastric lymphoma, including TNM staging (as for gastric adenocarcinoma). A clinical staging system used for non-Hodgkin's lymphoma (the Ann Arbor classification) is also available. The Ann Arbor system identifies the primary site of lymphoma as nodal or extranodal and assesses extent of disease based on number of sites involved, relation of the tumor to the diaphragm, and whether disease has metastasized to nonlymphoid organs. In the Ann Arbor system, a lymphoma involving both the stomach and a lymph node may be stage 2E (two sites with extranodal primary) or stage 4 (nodal primary with metastasis to the stomach). A new staging system that combines TNM staging with Ann Arbor criteria has recently been recommended for gastrointestinal lymphomas.

**31. What is the best therapy for high-grade gastric lymphoma?**

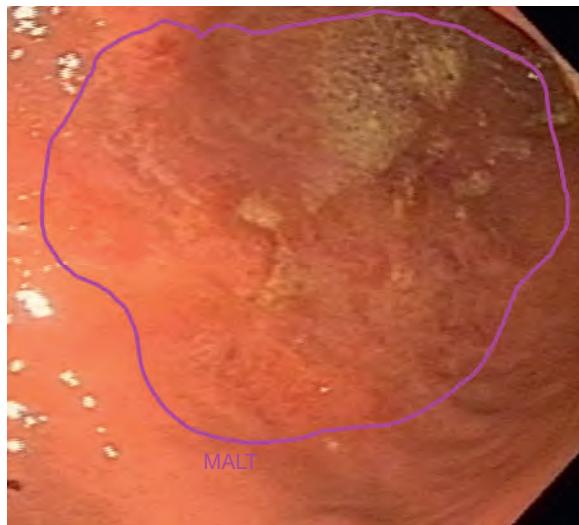
Therapy is determined somewhat by stage. For most cases of Ann Arbor stages I and II, surgery can be curative. However, recent data suggest that chemotherapy with or without radiation therapy can be equally effective and is becoming the standard of care. T stage may be important in the decision of whether or not to use a surgical approach because of the possibility of perforation when chemotherapy is used for T3 or T4 tumors. However, the trend is away from surgery for all stages.

**32. What are gastric carcinoid tumors?**

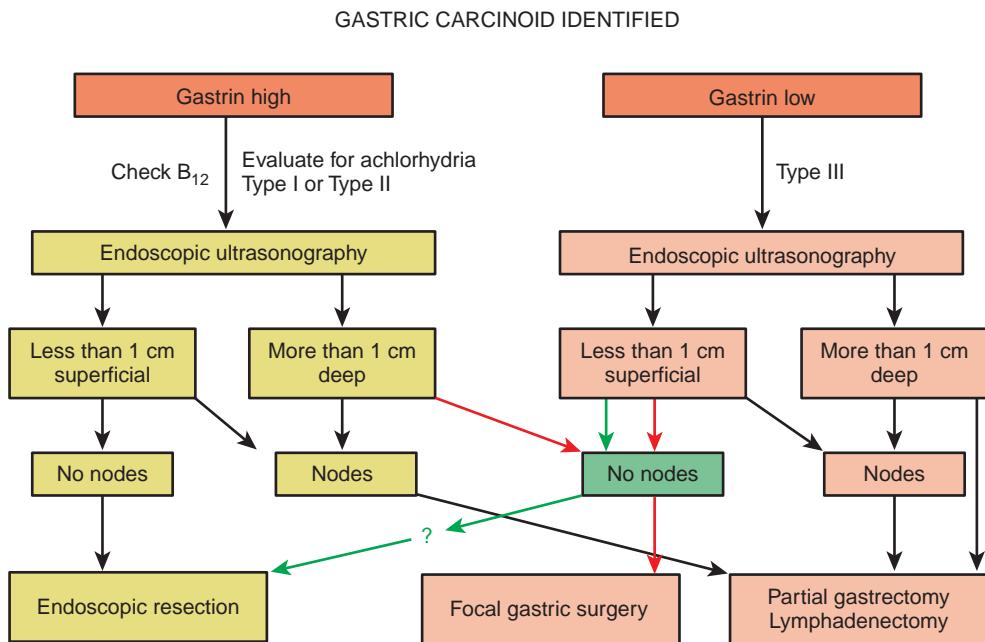
Gastric carcinoid tumors are growths of neuroendocrine cells that may be benign or malignant. They stain for chromogranin. As a rule, even the malignant tumors are slow growing. Tumors greater than 1 cm in diameter are generally more dangerous, whereas smaller tumors are not and may represent endochromagraffin cell hyperplasia. Tumors larger than 2 cm often have metastasized. As a rule, large tumors often require partial gastrectomy, whereas smaller tumors can be managed endoscopically or with localized surgery ([Figure 10-5](#)).

Two processes appear to lead to gastric carcinoid—de novo malignant transformation and loss of normal growth regulation in response to chronic elevation of serum gastrin levels. Tumors arising from de novo malignant (type III) ([Figure 10-6](#)) transformation are usually single, larger, and more aggressive, whereas those arising from elevated gastrin levels (types I and II) are often multiple and smaller. It is important to distinguish between those with and without elevated gastrin levels.

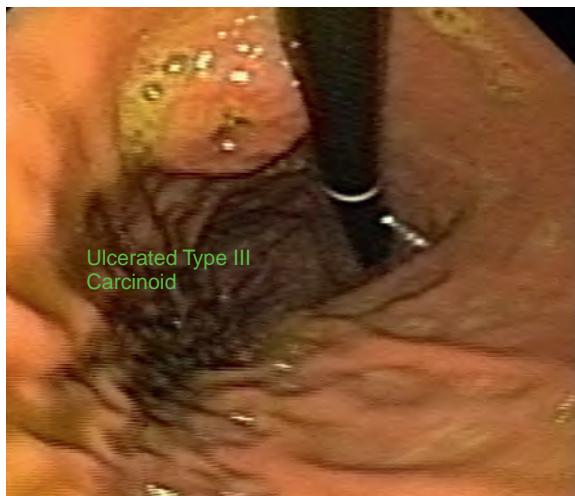
Patients in whom a gastric carcinoid has been found should have a gastrin level checked to see if the carcinoid tumor is associated with hypergastrinemia. If the gastrin level is elevated, evaluation for atrophic gastritis should be carried out, with assessment for vitamin B<sub>12</sub> levels, consideration of gastric biopsy to look for the presence of parietal cells. Serum antiparietal cell antibodies can be obtained to demonstrate an immune cause for the atrophic gastritis. If gastrin is elevated, and the patient does not appear to have atrophic gastritis, an evaluation for Zollinger-Ellison syndrome (gastrinoma) should be carried out.



**E-Figure 10-4.** Endoscopic view of superficial low-grade mucosal-associated lymphoid tissue.



**Figure 10-5.** Algorithm for the management of gastric carcinoid tumors. The majority are small and associated with an elevated gastrin level from atrophic gastritis. Endoscopic removal is sufficient for lesions less than 1 cm. Larger lesions are usually managed surgically, but endoscopic removal could be attempted in selected cases. Lesions not associated with elevated gastrin levels are usually more aggressive and tend to metastasize. These should be treated with more extensive removal.



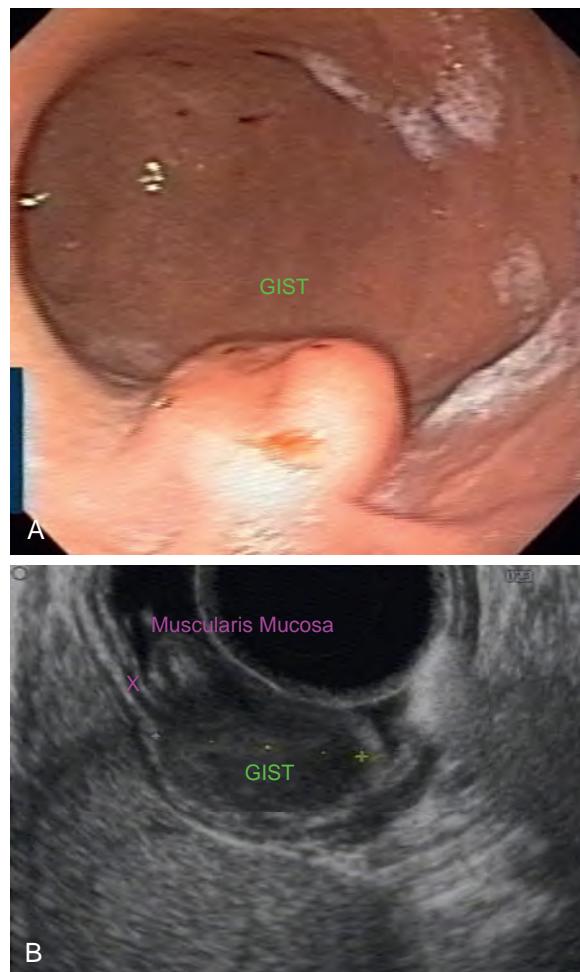
**Figure 10-6.** Endoscopic view of ulcerated type III carcinoid. (This patient is described in the video for the Clinical Vignette, found online on ExpertConsult.)

### 33. How are gastric carcinoid tumors staged?

TNM staging for gastric carcinoid tumors differs from gastric adenocarcinoma in that diameter of the primary tumor is considered as well as depth of invasion to separate early stages of disease. Superficial tumors more than 1 cm in size are considered to be T2 lesions, which is the same stage as smaller tumors that penetrate the muscularis propria.

### 34. What is a GIST?

A GIST is a tumor that develops in the gastric wall from the interstitial cells of Cajal (E-Figure 10-7). The tumor can be benign or malignant. Generally, malignancy correlates with size (greater than 3 to 5 cm in cross-section) and histologic features, such as the number of mitoses per 10 high-power fields. Histologically, these tumors



**E-Figure 10-7.** A, Endoscopic view of small gastrointestinal stromal tumor (GIST). B, Endoscopic ultrasonogram image of the same GIST, arising from the muscularis mucosa.

resemble leiomyomas, and the distinction between gastric leiomyomas and GIST can be difficult without histocytochemistry. Most GIST marks with an antibody against surface KIT, which is a tyrosine kinase. KIT is otherwise known as CD117. Approximately 70% to 80% have mutations in the KIT gene. Another 10% have mutations in the closely related platelet-derived growth factor receptor alpha (PDGFR $\alpha$ ) gene.

### **35. What is a wild type GIST?**

GISTs without mutations in KIT or PDGFR $\alpha$  are known as *wild type GISTs*. They express high levels of KIT and occur throughout the gastrointestinal tract. Like GISTs with the common mutations, wild type GISTs do not mark with neural or muscle stains. These tumors are heterogeneous and may have mutations in RAS, BRAF, or succinate dehydrogenase.

### **36. How are gastric GISTs staged?**

The staging system for gastric GISTs is unusual in that tumor size and histologic findings (mitosis per 50 high-powered fields) play major roles in staging. Tumors smaller than 5 cm are staged differently than tumors from 5 to 10 cm, and are different than tumors greater than 10 cm. For example, a 1-cm tumor with a high mitotic rate is the same stage as a 12-cm tumor with a low mitotic rate. Furthermore, nodal metastases are quite rare with GISTs and if no nodes are identified, the stage is considered N0 rather than Nx.

### **37. How are gastric GISTs treated?**

Small gastric GISTs are common and can be found in up to 35% of stomachs, depending on the case series. Smaller gastric GISTs, such as those smaller than 3 cm, without ulcerations, and normal homogeneous internal echoes, can be followed. Larger GISTs are removed surgically.

High-risk GISTs that have been removed, those that can't be removed, or those that have metastasized can be treated with drugs that bind to KIT and place it into the inactive conformation. The prototype drug is imatinib mesylate (Gleevec). Resistance seems to eventually develop and other drugs are then used in imatinib-resistant patients. Although most drugs in use inhibit KIT and PDGFR $\alpha$ , some compounds are being developed that inhibit other pathways such as HSP90, mTOR, and vascular endothelial growth factor receptor.

Please access ExpertConsult to view the E-Figures and [Clinical Vignette](#) for this chapter.

### **BIBLIOGRAPHY**

1. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastroint Endo* 2006;63:570–80.
2. Bonequi P, Meneses-González F, Correa P, Rabkin CS, et al. Risk factors for gastric cancer in Latin America: a meta-analysis. *Cancer Causes Control* 2013 Feb;24(2):217–31.
3. Crew KD, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006;12(3):354–62.
4. Dong QJ, Zhan SH, Wang LL, et al. Relatedness of *Helicobacter pylori* populations to gastric carcinogenesis. *World J Gastroenterol* 2012;18(45):6571–6.
5. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC cancer staging manual. ed 7. New York: Springer; 2010.
6. Fuccio L, Zagari RM, Eusebi LH, et al. Meta-analysis: can *Helicobacter pylori* eradication treatment reduce the risk for gastric cancer? *Ann Intern Med* 2009;151(2):121–8.
7. Gylling A, Abdel-Rahmen WM, Juhola M, et al. Is gastric cancer part of the tumour spectrum of hereditary non-polyposis colorectal cancer? A molecular genetic study. *Gut* 2007;56:926–33.
8. Humar B, Toro T, Graziano F, et al. Novel germline CDH1 mutations in hereditary diffuse gastric cancer families. *Hum Mutat* 2002;19:518–25.
9. Mocellin S, Marchet A, Nitti D. EUS for the staging of gastric cancer: a meta-analysis. *Gastrointest Endosc* 2011;73 (6):1122–34.
10. Worthley DL, Phillips KD, Wayte N, et al. Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): a new autosomal dominant syndrome. *Gut* 2012;61(5):774–9.

11. Bonenkamp JJ, Hermans J, Sasako M, et al. Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999;340(12):908–14.
12. Cunningham D, Allum WH, Stenning SP, et al. MAGIC trial participants: perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355(1):11.
13. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Paoletti X, Oba K, Burzykowski T, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *JAMA* 2010;303(17):1729.
14. Inoue H, Ikeda H, Hosoya T, et al. Endoscopic mucosal resection, endoscopic submucosal dissection, and beyond: full-layer resection for gastric cancer with nonexposure technique (CLEAN-NET). *Surg Oncol Clin N Am* 2012;21(1):129–40.
15. Lamba G, Gupta R, Lee B, et al. Current management and prognostic features for gastrointestinal stromal tumor (GIST). *Exp Hematol Oncol* 2012;1(1):14.
16. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345(10):725.
17. Oda I, Saito D, Tada M, et al. A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006;9:262–70.
18. Streubel B, Seitz G, Stolte M, et al. MALT lymphoma associated genetic aberrations occur at different frequencies in primary and secondary intestinal MALT lymphomas. *Gut* 2006;55(11):1581–5.
19. Yoon SS, Coit DG, Portlock CS, Karpeh MS. The diminishing role of surgery in the treatment of gastric lymphoma. *Ann Surg* 2004;240(1):28–37.
20. Zhang L, Ozao J, Warner R, Divino C. Review of the pathogenesis, diagnosis, and management of type I gastric carcinoid tumor. *World J Surg* 2011;35(8):1879–86.

# THICKENED GASTRIC FOLDS

Ryan M. Kwok, MD, and Patrick E. Young, MD

## 1. What is meant by thickened gastric folds?

Although *thickened gastric folds* is a somewhat ambiguous term, it generally refers to abnormally large gastric folds (generally >1 cm) that do not flatten on insufflation at upper endoscopy (Figure 11-1).



**Figure 11-1.** Thickened gastric folds in a patient with Ménétrier's disease.

## 2. Describe the differential diagnosis for thickened gastric folds.

The differential diagnosis includes Ménétrier's disease (MD), chronic gastritis (*Helicobacter pylori*-associated, eosinophilic, etc.), gastric malignancy (lymphoma, scirrous gastric adenocarcinoma), and Zollinger-Ellison syndrome.

## 3. What are the clinical features of MD?

Patients with MD may present with a combination of local and systemic symptoms. Local symptoms include epigastric pain, nausea, vomiting, gastrointestinal (GI) bleeding, and diarrhea. Systemic symptoms generally stem from substantial protein loss and include weight loss and peripheral edema.

## 4. How is MD diagnosed?

Full-thickness mucosal biopsy, via suction technique or snare resection, will reveal the characteristic foveolar hyperplasia, tortuous and dilated glands, inversion of the pit-gland ratio, and marked parietal cell loss. The lack of inflammatory cells in MD is a key differentiating factor between MD and its mimics (*Helicobacter*-associated hypertrophy, allergic hypertrophic gastritis). Laboratory findings that support the diagnosis include low basal and stimulated acid output and low albumin. Serologic testing for cytomegalovirus (CMV) is also a reasonable test to obtain, particularly in pediatric cases in which up to 1/3 of cases are CMV associated.

## 5. List the treatment options for MD.

Historically, supportive care, including a high-protein diet, albumin infusions, and pain medications, was the cornerstone of therapy. When these conservative options failed, gastrectomy was required. We now know that MD in adults is often related to local overproduction of transforming growth factor-alpha, leading to an increase in epidermal growth factor (EGF), which acts on the tyrosine kinase receptor. Cefitinimab, a monoclonal antibody that blocks EGF receptor binding, has proven an effective treatment for MD in recent small trials.

## 6. What are the key features of gastric mucosa-associated lymphoid tissue (MALT) lymphoma?

MALT lymphoma is a type of non-Hodgkin's lymphoma that represents 3% of gastric malignancies. Like gastric adenocarcinoma, MALT is highly associated with *H. pylori* infection. Diagnosis is made via tissue histologic examination in conjunction with immunohistochemical testing of B lymphocyte markers. Tumors with more than 20% large blast cells are considered high grade.

**7. Describe the treatment of gastric MALT lymphoma.**

First-line therapy for gastric MALT lymphoma is antibiotic therapy directed at *H. pylori*, followed by documentation of eradication. The success of this regimen to induce remission correlates with disease stage, with 80% of low-grade lymphomas regressing compared to only 50% of high-grade lymphomas. Even after successful bacterial eradication, complete remission may take more than a year. Several studies show residual clonal B-cells, even after histologic regression. Watchful waiting is advised in these cases, withholding further treatment unless there is evidence of histologic recurrence. In cases in which antibiotic therapy fails to induce remission, external-beam radiation (with or without systemic chemotherapy) is indicated.

**8. If no *H. pylori* is detected, should you still treat gastric MALT lymphoma with antibiotics?**

Yes, although this is certainly not intuitive. There are data showing that even *H. pylori*-negative cases of MALT lymphoma may respond to antibiotic therapy, so treatment is indicated whether or not *H. pylori* is detected.

**GASTRIC POLYPS****9. What are the types of gastric polyps and what is the relative prevalence of each type?**

There are essentially three types of gastric polyps: fundic gland ( $\approx 50\%$ ), hyperplastic ( $\approx 40\%$ ), and adenomatous ( $\approx 10\%$ ). In areas with higher *H. pylori* infection rates, hyperplastic polyps (HPs) and adenomas are correspondingly more prevalent.

**10. Describe the relationship of proton pump inhibitors (PPIs) to fundic gland polyps (FGPs).**

Prolonged PPI therapy is associated with the formation of FGPs. In a Chinese study of 599 patients, patients on PPI for greater than 5 years were at fourfold increased risk of FGP formation relative to those on PPI therapy for less than 1 year. The regression of FGPs after PPI cessation also supports their role in polyp formation.

**11. What is the relationship between medical conditions and FGPs?**

FGPs can occur in association with polyposis syndromes including familial adenomatous polyposis (FAP), Gardner's syndrome, MUTYH-associated polyposis (MAP), and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). In one series of 75 subjects with FAP, 88% were found to have FGPs. Additionally, FGPs have been reported in 11% of MAP patients. GAPPS is an autosomal-dominant syndrome characterized by formation of dysplastic FGP formation in the proximal stomach and an increased risk of gastric adenocarcinoma. Surveillance with upper endoscopy should be considered in patients with these conditions.

**12. How likely is it that a gastric adenoma will progress to adenocarcinoma?**

It depends. Much like adenomas of the colon, gastric adenomas are known precursors of adenocarcinoma. Both size and histologic characteristics influence the malignancy potential of a given lesion. For instance, progression occurs in 30% to 40% of adenomas with villous features and is likewise increased in adenomas larger than 2 cm. The overall incidence of gastric adenomas to progress to adenocarcinoma is approximately 5%. As such, complete removal should be performed whenever possible.

**13. Describe the management of gastric HPs.**

HPs have a lower risk of malignant transformation than adenomas but often occur in settings where the overall risk of malignancy in the gastric mucosa is elevated (pernicious anemia, *H. pylori*-associated gastritis, chronic gastritis, etc.). Reported rates of adenocarcinoma arising in an HP range from 0.6% to 2.1%. As the cancer risk increases with size, most experts recommend removing HPs greater than 1 cm in diameter.

**SUBEPITHELIAL TUMORS****14. What are the endosonographic layers of the stomach?**

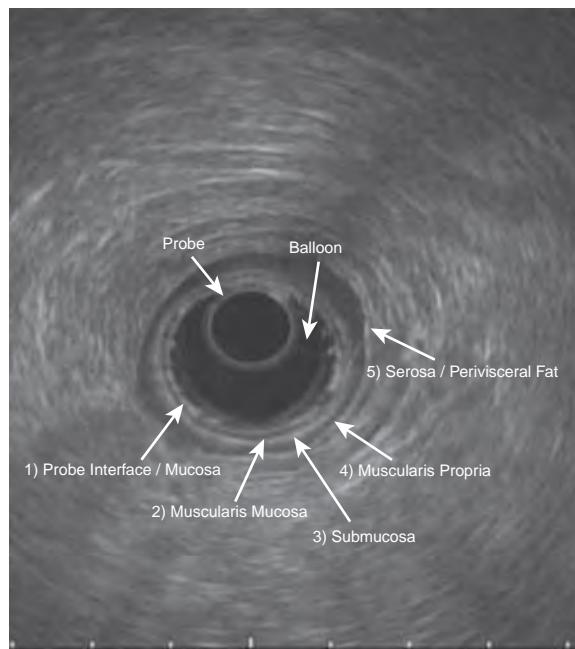
The stomach has five endosonographic layers that correspond to the histologic layers of the stomach. The first (most superficial) layer is hyperechoic (white on endoscopic ultrasonography [EUS]) and represents the interface between the ultrasound probe and the superficial mucosa. The second layer is hypoechoic (dark on EUS) and represents the deep mucosa including the muscularis mucosa. This layer distinguishes erosions from ulcers (i.e., if a lesion does not penetrate the second layer, it is considered an erosion). The third layer is hyperechoic and corresponds to the submucosa. Layer four is hypoechoic, correlates to the muscularis propria, and is the layer from which most subepithelial gastric tumors arise. Layer five is the serosa or perivisceral fat and is hyperechoic (Figure 11-2).

**15. What is the differential diagnosis for gastric subepithelial tumor (SET) (Table 11-1)?**

The differential diagnosis for a SET can be divided into intrinsic versus extramural lesions. Extramural lesions most often arise from the spleen and its associated vessels, although other perigastric organs such as the liver, gallbladder, pancreas, and colon may also create indentations on the luminal wall. Less commonly, extraluminal compression may arise from abscesses, enlarged lymph nodes, renal cysts, pancreatic pseudocysts, or aneurysms.

**16. Describe the common methods of making a tissue diagnosis of a SET.**

Symptomatic or large SETs may not require a preoperative histologic diagnosis prior to surgical resection. In cases in which tissue sampling is required, several modalities are available. Stacked or “bite-on-bite” jumbo



**Figure 11-2.** Endosonographic image of the gastric wall layers.

**Table 11-1.** Types of Gastric Subepithelial Tumors and Their Characteristics

SUBEPITHELIAL LESION	EUS LAYER	MALIGNANT POTENTIAL	ENDOSONOGRAPHIC FEATURES	IMPORTANT FACTS
Leiomyoma	2, 3, or 4 (4th is most common)	None	Hypoechoic	Rare in the stomach CD 117 (-), smooth muscle actin (+)
Neural origin tumors (schwannoma, neuroma, neurofibroma)	3 or 4	None	Hypoechoic	Schwannoma = 4th layer, S-100 (+)
Lipoma	3	None	Intensely hyperechoic	Yellow hue “pillow sign” when probed with closed forceps
Duplication cyst	Any/ extramural	None	Anechoic	Embryonic remnant lined with GI epithelium that can enlarge and lead to mass effect, rupture, or bleeding
Pancreatic rest	2 or 3		Hypoechoic/mixed	Endoscopy = characteristic central umbilication
Inflammatory fibroid polyp	3 or 4		Hyperechoic	Histologic findings = unencapsulated fibrous tissue, eosinophilic infiltrate, and small blood vessels
Granular cell tumor	2 or 3		Hypoechoic	
Varices	2 or 3		Hypo- or anechoic	Blue hue Suspect with findings of portal hypertension or splenic vein thrombosis

*Continued on following page*

**Table 11-1.** Types of Gastric Subepithelial Tumors and Their Characteristics (Continued)

SUBEPITHELIAL LESION	EUS LAYER	MALIGNANT POTENTIAL	ENDOSONOGRAPHIC FEATURES	IMPORTANT FACTS
GIST	4 (rarely 2)	See below (Question 20)	Hypoechoic, homogenous	GIST = 4th layer + CD117 (+)/ c-kit protein
Lymphoma	2, 3, or 4		Hypoechoic	Usually DLBCL or B cell-associated MALT lymphoma Typically require deep-tissue sampling for diagnosis
Carcinoid	2 or 3	See subtypes below*	Hypoechoic	Arise from ECL cells
Metastatic carcinoma	Any		Hypoechoic	Rare Associated with melanoma, breast, lung, kidney, ovaries
Glomus tumor	3 or 4	Typically benign, but can have malignant potential	Hypoechoic	CD117 (-), vimentin (+), smooth muscle actin (+)

DLBCL, Diffuse large B-cell lymphoma; ECL, enterochromaffin-like; EUS, endoscopic ultrasound; GI, gastrointestinal; GIST, gastrointestinal stromal tumor; MALT, mucosa-associated lymphoid tissue.

\*Types of carcinoid tumors:

Type 1: associated with hypergastrinemia from chronic atrophic gastritis

Type 2: associated with Zollinger-Ellison syndrome

Type 3: sporadic; associated with normal gastrin levels; can become malignant or metastatic and should be resected irrespective of size

forceps biopsies are the simplest technique, requiring no special training, but provide a definitive diagnosis in fewer than 50% of cases. EUS-guided fine-needle aspiration can be used in the evaluation of SET, lymph nodes, and lesions adjacent to the GI tract. EUS-guided core needle biopsy provides a larger sample of tissue that can be used for histologic evaluation. This is of particular value in cases, such as lymphoma, in which tissue architecture—as opposed to the mere cell type—is vital to diagnosis. Immunohistochemistry, in addition to standard cytologic analysis, is often helpful.

## 17. Do endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) have a role in the management of SET?

EMR and ESD are emerging modalities for sampling and resecting SET. Complications related to these procedures can include perforation and bleeding, and they should only be performed by endoscopists who are highly experienced in their use. In the United States, these techniques are generally limited to intramural lesions in the third layer or above.

## 18. How is a GI stromal tumor (GIST) differentiated from other mesenchymal SETs?

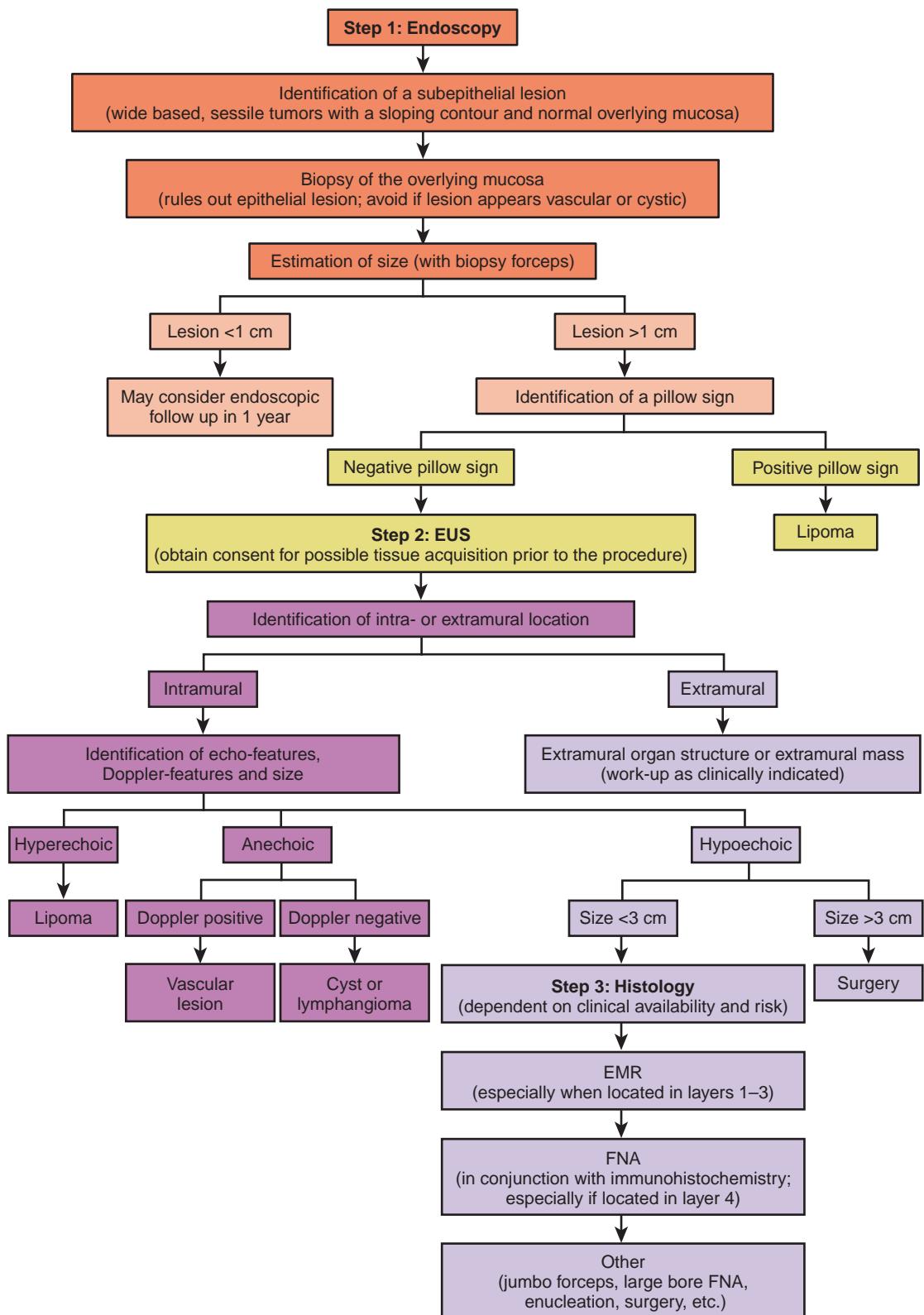
GI mesenchymal SETs can be classified into four types: schwannoma, leiomyoma, leiomyosarcoma, and GIST. All are spindle cell tumors and thus they are difficult to distinguish on histologic examination alone. Immunohistochemical stains are vital to distinguish among them (Table 11-2).

**Table 11-2.** Characteristics of Gastric Spindle Cell Tumors

TYPE	CD117	CD34	SMA	S100 PROTEIN	DESMIN
GISTs	+ (>95%)	+ (60-70%)	+/- (30-40%)	- (5% +)	Very rare
Leiomyoma	-	+ (10-15%)	+	-	+
Leiomyosarcoma	-	-	+	-	+
Schwannoma	-	-	-	+	-

GIST, Gastrointestinal stromal tumor; SMA, smooth muscle actin.

From Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. *Int J Surg Pathol* 2002;10(2):81-9; and Miettinen M, Sobin LH, Sartomo-rikala M. Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with respect to CD117 (KIT). *Mod Path* 2000;13(10):1134-42.



**Figure 11-3.** Diagnostic and treatment algorithm of subepithelial tumors. EMR, Endoscopic mucosal resection; EUS, endoscopic ultrasound; FNA, fine-needle aspiration. (Adapted from Eckardt AJ, Wassef W: Diagnosis of subepithelial tumors in the GI tract: endoscopy, EUS, and histology: bronze, silver, and gold, Gastrointest Endosc 62:209, 2005.)

**19. What is the cell of origin for a GIST?**

The cells of origin are interstitial cells of Cajal and the pacemaker cells of the stomach.

**20. How does one decide when surgery is required for a gastric GIST?**

Because GISTs have malignant potential, risk stratification is crucial in determining management.

In gastric GISTs, it is generally agreed that tumors larger than 2 cm should be resected, whereas those smaller than 1 cm and lacking worrisome EUS features can be followed endoscopically. EUS findings suggestive of malignancy include irregular extraluminal margins, cystic spaces, echogenic foci (heterogenous echotexture), and adjacent malignant-appearing lymph nodes. Management of GISTs between 1 and 2 cm remains controversial. Mitotic rate also helps predict tumor aggressiveness, with small tumors (<2 cm) that exhibit fewer than 5 mitoses per high-power field (HPF) having the lowest risk and larger tumors that have more than 10 per HPF having the highest risk. Calculation of the mitotic index requires a tissue block for histologic examination and cannot be performed on cytologic specimens alone.

**21. What medical options are available for GISTs?**

Imatinib mesylate, a tyrosine kinase receptor inhibitor, can be used as adjuvant therapy after resection of GISTs 3 cm or larger to minimize chance for recurrence. In cases of borderline tumor resectability or cases in which there may be significant organ disruption, neoadjuvant therapy may be used prior to resection ([Figure 11-3](#)).

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**BIBLIOGRAPHY**

1. Bianchi LK, Burke CA, Bennett AE, et al. Fundic gland polyp dysplasia is common in familial adenomatous polyposis. *Clin Gastroenterol Hepatol* 2008;6(2):180.
2. Goddard AF, Badreldin R, Pritchard DM, et al. The management of gastric polyps. *Gut* 2010;59(9):1270–6.
3. Hwang JH, Rulyak SD, Kimmey MB. American Gastroenterological Association Institute technical review on the management of gastric subepithelial masses. *Gastroenterology* 2006;130:2217–28.
4. Hwang JH, Saunders MD, Rulyak SJ, et al. A prospective study comparing endoscopy and EUS in the evaluation of GI subepithelial masses. *Gastrointest Endosc* 2005;62:202–8.
5. Jalving M, Koornstra JJ, Wesseling J, et al. Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. *Aliment Pharmacol Ther* 2006;24(9):1341.
6. Lambrecht NWG. Ménétrier's disease of the stomach: a clinical challenge. *Curr Gastroenterol Rep* 2011;13:513–7.
7. Polkowski M, Butruk E. Submucosal lesions. *Gastrointest Clin N Am* 2005;15:33–54.

# GASTROPARESIS

Richard W. McCallum, MD, FACP, FRACP (Aust), FACG, and Joseph K. Sunny, Jr., MD

## 1. Define gastroparesis.

Gastroparesis is a disorder defined by delayed gastric emptying in the absence of mechanical obstruction of the stomach or proximal small bowel. The spectrum of symptoms include nausea, vomiting, early satiety, postprandial fullness, epigastric discomfort and pain, bloating, and heartburn. Vomiting does not have to be present. Patients may only present with chronic nausea because they have learned how to remain below the vomiting threshold by modifying their diet by eating smaller meals or progressing to a liquid diet. Epigastric pain has traditionally been underestimated and it could even be the dominant complaint. It is reported to be present in up to 90% of gastroparesis patients.

## 2. How should gastroparesis be diagnosed?

Gastroparesis is a challenging clinical diagnosis that has to be confirmed by objective testing. The 4-hour gastric emptying scintigraphic method with a standardized low-fat, egg-white meal is the “gold standard.” Values greater than 60% retention at 2 hours and 10% retention at 4 hours indicate delayed gastric emptying. Severity can be defined by the degree of isotope retention at 4 hours: grade 1 as 11% to 20%, grade 2 as 21% to 35%, grade 3 as 36% to 50%, and grade 4 with greater than 50%. There has been poor correlation between the severity of symptoms and the grading of gastric retention as well as between symptom improvement and gastric emptying changes in treatment trials.

## 3. How can a wireless motility capsule (WMC) diagnose gastroparesis?

A WMC (SmartPill) is the same size as the small-bowel endoscopic camera and measures pH, pressure, and temperature. It is ingested together with a 250-calorie energy bar to initiate the onset of the fed pattern in the stomach. The gastric emptying time of this nondigestible solid, which empties after the digestible solids, is identified by an abrupt and sustained increase in pH to an alkaline level of pH 6 or 7 as it enters the duodenum. In a trial comparing WMC to the scintigraphic egg beater standard, a 5-hour cut-off for gastric emptying time for the WMC had a sensitivity of 65% and specificity of 87%. A major attraction of WMC is that abnormalities in the small bowel and colon transit that may also be contributing to the patient’s symptoms can also be identified.

## 4. Describe the normal physiology of the stomach.

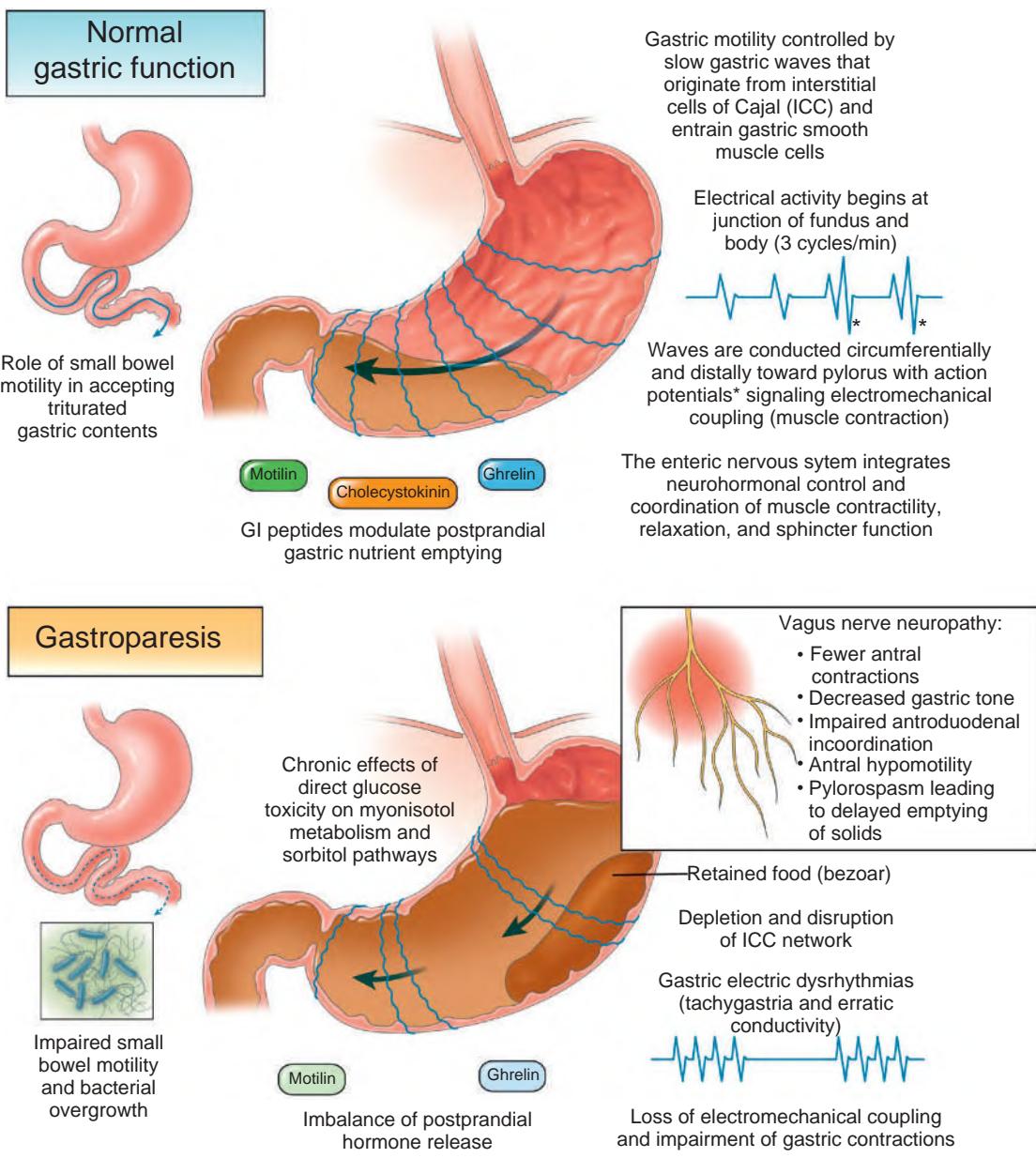
The stomach initially receives and stores food by relaxation of the fundus, which is mediated by vagal efferent fibers and nitric oxide pathways. This period termed the *lag phase* can vary from 15 to 40 minutes and is followed by the trituration process, which relies on the contractile and myoelectrical activities of the stomach. The gastric pacemaker cells, termed the *interstitial cells of Cajal* (ICC), initiate the gastric slow wave, which has a frequency of three cycles per minute. After a meal, depolarization of smooth muscle cells leads to electromechanical coupling, permitting gastric contractions to be initiated in association with release of neurotransmitters from the enteric neurons. Trituration of food to particle sizes less than 6 mm allows passage through a relaxed pylorus.

## 5. What are the pathophysiologic characteristics of gastroparesis?

The three main etiologic factors of gastroparesis are diabetes, idiopathic and post vagotomy produce the following pathophysiologic characteristics: (1) decreased accommodation of the stomach caused by loss of gastric inhibitory neurons or vagus nerve damage; (2) depletion of the ICCs in diabetes and postinfection injury results in dysrhythmias (e.g., tachygastria and ectopic pacemakers, associated with nausea and vomiting); (3) defective smooth muscle contractions resulting from impaired enteric neuronal function; (4) smooth muscle atrophy or fibrosis; (5) impaired release of gastrointestinal peptides (e.g., motilin, ghrelin, and pancreatic polypeptide, which facilitate gastric motility); (6) pyloric sphincter dysfunction and concept of “pyloric spasm” (Figure 12-1).

## 6. What are the ICCs in health and in gastroparesis?

The ICCs generate spontaneous electrical slow wave activity, which is conducted to the smooth muscle cells of the stomach and referred to as the “gastric slow wave.” In humans, this varies from two to four cycles per minute with an average of three. There are two ICC networks: one in the myenteric plexus region and the other in the deeper muscularis propria of the gastric corpus and antrum controlling propagation of the slow waves and hence the maximum frequency and aboral peristaltic direction of gastric contractions. Reduced ICC



**Figure 12-1.** Pathophysiologic characteristics of gastroparesis. GI, Gastrointestinal; ICC, interstitial cells of Cajal. (From Reddymasu SC: Severe gastroparesis: medical therapy or gastric electrical stimulation, *Clin Gastroenterol Hepatol* 8:117–124, 2010.)

numbers have been reported in up to 40% of gastroparetic patients of diabetic and idiopathic origin and are correlated with an electrical dysrhythmia as demonstrated by an abnormal electrogastrogram, which is the cutaneous recording of the electrical slow wave by electrodes on the abdominal surface overlying the stomach.

## 7. How can bloating be explained in gastroparesis?

Sixty percent of patients with gastroparesis have concomitant small intestinal bacterial overgrowth (SIBO) based on breath testing data. Explanations are impaired small bowel motility accompanying gastroparesis of diabetic and idiopathic etiologic factors; loss of the migrating motor complex, a sequelae of vagal nerve damage; gastric hypochlorhydria, which could be primary or secondary to the chronic use of proton pump inhibitors; and atrophy of small bowel smooth muscle as in scleroderma. The take home is that the symptom of postprandial bloating in gastroparesis may be explained by SIBO, and implications for therapy include antibiotics and probiotics in addition to promotility agents.

## 8. What is the estimated prevalence of gastroparesis?

Approximately 10 million individuals (3%) in the United States have gastroparesis. Of these, 75% are women averaging 34 years of age. Approximately 16,000 admissions annually in the United States have gastroparesis as a primary diagnosis. During a 10-year period, the risk of a patient with type 1 diabetes mellitus (T1DM) developing gastroparesis is 5.2% and 1% with diabetes mellitus type 2 (T2DM), compared with 0.2% in the general population. Based on a national sample survey, approximately 165,000 T1DM patients (14% of U.S. patients with T1DM) and 2.1 million T2DM patients (9.4%) are currently seeking treatment for diabetic gastroparesis (DGP) symptoms. To put this in gastroenterologic perspective, if celiac sprue is approaching an incidence of 1% of the U.S. population and hepatitis C is 2% to 3%, gastroparesis is more common than these entities.

## 9. What is idiopathic gastroparesis?

There are no clear etiologic factors for idiopathic gastroparesis. At least 80% of patients are female and a substantial percentage have a history of an infectious-like prodrome of viral or bacterial origin for which such agents as rotavirus and norovirus (Norwalk agent), Epstein-Barr virus, cytomegalovirus, herpes virus, and Lyme disease have been suspected. This data is based on findings of white cell infiltrate, macrophages, and neuronal loss in the enteric neurons from biopsies of gastric muscularis propria smooth muscle. Idiopathic gastroparesis patients who develop delayed gastric emptying after an infectious prodrome may be able to recover their neuromuscular and electrical functions at varying times, with a later unexpected return to normal gastric emptying. Other “idiopathics” remain chronically symptomatic and need careful investigation to exclude underlying connective tissue disease; central nervous system (CNS) disorders (e.g., multiple sclerosis); eating disorders (anorexia and bulimia nervosa); and the entity median arcuate ligament syndrome, which compresses the celiac ganglion.

## 10. What are some causes of gastroparesis that can be easily treated and reversed if identified?

Potentially reversible causes of gastroparesis can be broadly categorized as pharmacological, mechanical, metabolic and endocrine, CNS disorders, and paraneoplastic. Specific treatments can be initiated (Table 12-1). Narcotic use dominates the pharmacologic subgroup and modest success has been achieved with the  $\mu$ -opioid receptor antagonist methylnaltrexone subcutaneously four times a day. These entities need to be considered when patients present with symptomatic gastroparesis and are labeled *idiopathic*.

## 11. Describe metoclopramide's mechanism of action.

Metoclopramide, the only gastric prokinetic registered in the United States, blocks dopamine D<sub>2</sub> inhibitory receptors in the upper gastrointestinal tract and stimulates 5-HT<sub>4</sub> receptors, resulting in augmented acetylcholine release leading to increased gastric tone and intragastric pressure, coordination of antroduodenal motility with relaxation of the pylorus, and net acceleration in gastric emptying. Metoclopramide also provides

**Table 12-1.** Reversible Causes of Gastroparesis

ETIOLOGIC FACTORS	EXAMPLES	SPECIFIC TREATMENTS
Pharmacologic	Anticholinergics	
A. Commonly prescribed medications	Proton pump inhibitors Calcium channel blockers  Cyclosporine Exenatide Pramlintide Lithium Octreotide	
B. Controlled substances	Narcotics	Methylnaltrexone— $\mu$ antagonist
Mechanical	Superior mesentery artery syndrome Median arcuate ligament syndrome	Surgery
Metabolic	Neuromyelitis optica with autoantibodies to astrocytic aquaporin-4 water channels	Steroids
	Anorexia nervosa, bulimia nervosa	
Endocrine	Hypothyroidism Hypoadrenal states Hyperglycemia (blood sugar > 275)	
Central nervous system disorders	Multiple sclerosis Parkinson's disease	
Paraneoplastic	Antineuronal nuclear antibodies type 1 (ANNA-1), sometimes called <i>anti-Hu</i>	Immunomodulators Plasmapheresis

antiemetic relief through inhibiting D<sub>2</sub> dopamine within the chemoreceptor trigger zone of the brain as well as some antagonism of 5-HT<sub>3</sub> receptors. Thus metoclopramide's clinical efficacy is explained by a combination of prokinetic effects peripherally and antiemetic properties centrally.

## 12. What are some tips on dosing metoclopramide?

Metoclopramide is available in oral, suppository, and injectable routes of administration. Intravenous (IV) dosing can range from 10 mg every 6 hours to 20 mg every 4 hours depending on tolerance. Subcutaneous metoclopramide (2 mL=10 mg) can be used either as an adjunct to oral medications, overcoming the limitations of erratic absorption in the setting of gastroparesis and vomiting, or as a rescue if symptoms worsen because the plasma levels achieved are 80% of the IV levels, thus avoiding the need for emergency room visits. Orally disintegrating tablets (Metozolv ODT), available in 5 mg and 10 mg, facilitate patient compliance but absorption still occurs in the small bowel and not through the buccal mucosa.

## 13. What are the side effects of metoclopramide?

Approximately 40% percent of patients cannot maintain long-term use. The medication can cross the blood–brain barrier leading to inhibition of central D<sub>2</sub> receptors in the basal ganglion involved in movement pathways, manifesting in a wide array of involuntary movement disorders. An acute dystonic reaction can occur within the first few hours of beginning administration, typically when given intravenously, and resolves with discontinuation. Within the first 1 to 3 months, akathisia, anxiety, tremor, drug-induced Parkinsonism, and depression can develop and are reversible after discontinuation. The United States Food and Drug Administration (FDA) released a “black box” warning for metoclopramide in 2009 relating to the risk of tardive dyskinesia after more than 3 months of use. The incidence of tardive dyskinesia, which can be irreversible and is defined by disfiguring and involuntary movements, is actually less than 1%, not the 1% to 10% previously reported. The key to prevention is actually examining the patient in follow up, not refilling prescriptions without seeing the patient.

## 14. What is the status of domperidone?

Domperidone (Motilium), a dopamine receptor antagonist that has both central antiemetic and gastric prokinetic properties, is the best prokinetic and antiemetic. It is not FDA approved but is available through an investigational new drug application from the FDA. QT elongation (>450 milliseconds in males and >475 milliseconds in females) is the leading concern regarding ventricular arrhythmias. The infrequent side effects of gynecomastia, breast tenderness, galactorrhea, and menstrual irregularities are due to increased levels of prolactin. Both the pituitary and the chemoreceptor trigger zone emetic areas are regarded as being outside the blood–brain barrier, consistent with domperidone's lack of CNS side effects. Dosing is 20 mg four times a day up to a maximum of 120 mg per day for at least 3 months to ascertain clinical response. Chronic therapy does not appear to lead to decreased efficacy.

## 15. Where do we stand with using erythromycin as a prokinetic?

The macrolide class of agents are motilin receptor agonists (erythromycin and azithromycin) that promote motility in the stomach and small bowel. Erythromycin lactobionate IV at up to 3 mg/kg every 6 to 8 hours facilitates gastric and small bowel motility. The liquid formulation is more effective than tablets to maximize absorption in gastroparesis. However, oral efficacy is limited because of dose tolerance after a few weeks. Starting with a low oral dosing of 150 mg to 250 mg twice to three times a day is recommended to reduce “saturation” of motilin receptors and dose tolerance.

## 16. What antiemetics are effective in gastroparesis?

### A. Phenothiazines

Phenothiazines are dopamine and cholinergic receptor antagonists, and examples include prochlorperazine, promethazine, and trimethobenzamide. Promethazine is available by IV, intramuscular, oral, and rectal suppository routes. Possible side effects include sedation, slurred speech, and dystonia.

### B. Muscarinic antagonists

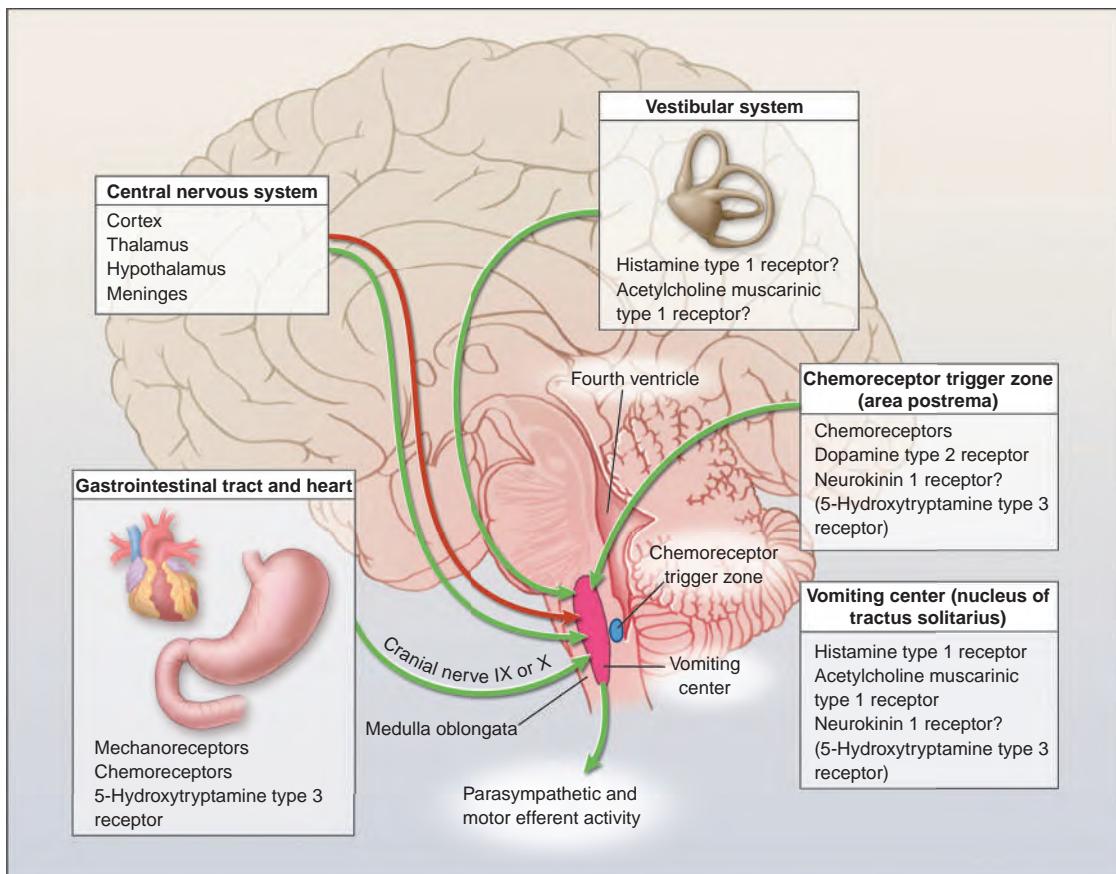
Scopolamine is a selective competitive antagonist of muscarinic cholinergic receptors, and it is available as a 1.5-mg patch for 3 days, providing sustained plasma levels that overcome vomiting and intolerance to oral intake and erratic absorption of other oral antiemetics.

### C. 5-HT<sub>3</sub> antagonists

Ondansetron, granisetron, and dolasetron are 5-HT<sub>3</sub> receptor antagonists, and they inhibit 5-HT<sub>3</sub> receptors in the area postrema. Peripheral effects are also present via efferent fibers of the vagus nerve. They can be given by oral or parenteral administration. Ondansetron orally dissolvable tablets are also available for very nauseated patients. High doses of IV ondansetron can lead to torsades de pointes related to cytochrome P450 pathways, and the 32-mg single dose vial has been removed from the market. Granisetron is also available as a patch (Sancuso) effective for up to 7 days. A newly FDA approved drug in this class, palonosetron (Aloxi), has a longer half-life, allowing a single dose of 0.25 mg IV to be effective for 5 days in chemotherapy-related vomiting.

### D. Cannabinoids

Cannabinoids are agonists of CB1 receptors in the brain and gut, and they are effective as both antiemetics and appetite stimulants. Dronabinol (Marinol) is available in the United States, and there are a subset of gastroparesis patients who respond to this medication in doses of 5 mg to 10 mg three times a day.



**Figure 12-2.** The pathophysiologic characteristics of nausea and vomiting and the targets of antiemetic therapies in gastroparesis. (From Krakauer EL. Case 6–2005. A 58-Year Old Man with Esophageal Cancer and Nausea, Vomiting, and Intractable Hiccups. NEJM. © Medical Massachusetts Society. Published with permission.)

#### E. Neurokinin-1 (NK-1) antagonists

Aprepitant (Emend) is a selective, oral nonpeptide antagonist of the NK1 receptor with the ability to penetrate the CNS. Direct administration of substance P into the area of the nucleus tractus solitarii of the hindbrain induces emesis. The action of substance P in these centers is controlled by the NK-1 receptor and antagonism of NK-1 receptor has demonstrated antiemetic activity. It is effective in preventing vomiting in chemotherapy patients and is being evaluated for gastroparesis in doses of 125 mg per day (Figure 12-2).

#### 17. What is the role of tricyclics for gastroparesis?

Low doses of tricyclic antidepressants can be used as neuromodulators for treatment of nausea, vomiting, and abdominal pain in patients with gastroparesis. Idiopathic gastroparesis patients treated with nortriptyline for 12 weeks did not differ in overall symptomatic improvement versus placebo, although abdominal pain and early satiety showed improvement with doses of 50 to 75 mg and nausea at doses of 10 to 25 mg. In diabetic patients without gastroparesis, nausea and vomiting did improve after treatment with a tricyclic. This class is considered a valuable adjunct for symptom control in gastroparesis, but further studies to address specific symptoms and dosing strategies are needed.

#### 18. What patients can benefit from botulinum injections into the pylorus?

Patients with gastroparesis may have periods of increased pyloric tone and phasic contractions, known as “pylorospasm” or have chronic pyloric sphincter-impaired relaxation. Botulinum toxin is an inhibitor of neuromuscular transmission. Botulinum injections (100 to 200 units) into the pylorus via endoscopy did not improve gastric emptying or symptoms more than placebo in two randomized, double-blind, placebo-controlled studies, although numbers were small. Several open-label reports suggest more positive outcomes. Although empiric botulinum injections cannot be justified in gastroparesis patients pending further trials, one recommended clinical algorithm is that two successive impressive responses to pyloric botulinum injections (greater than 6 weeks’ improvement) suggest that a surgical pyloroplasty may be warranted.

#### 19. When should pyloroplasty be used in gastroparesis?

Pyloroplasty is an option in gastroparesis patients refractory to prokinetic therapy. Improved gastric emptying time and decreased prokinetic therapy have been noted after pyloroplasty. Gastroparesis secondary to vagotomy

may be the best candidates because pyloroplasty can overcome the tonic motor activity of the pylorus, termed *pylorospasm*, and impaired pyloric relaxation resulting from vagotomy. The addition of pyloroplasty to gastric electrical stimulation (GES) placement was recently shown to improve and often normalize delayed gastric emptying time in postvagotomy patients as well as show symptom efficacy.

## 20. What are the clinical pearls for feeding tubes in gastroparesis patients?

- Bypass the nonfunctional stomach and place a jejunostomy (J) tube surgically, endoscopically, or radiologically beyond the ligament of Treitz. Specific guidelines are the following: (1) J tube feedings only at night (6 PM to 6 AM) while slowly trying to increase oral intake during the day, (2) combining tube feeds and oral intake simultaneously leads to nausea and vomiting, and (3) medications can be given via J tubes.
- Gastrostomy venting tubes are not recommended because they lead to potassium and fluid depletion and have no nutritional potential.
- A percutaneous endoscopic gastrostomy or jejunostomy is limited to temporary use because vomiting invariably displaces the tube back into the stomach. Essentially the need for a J tube is the signal for GES and we recommend one surgery to accomplish both.

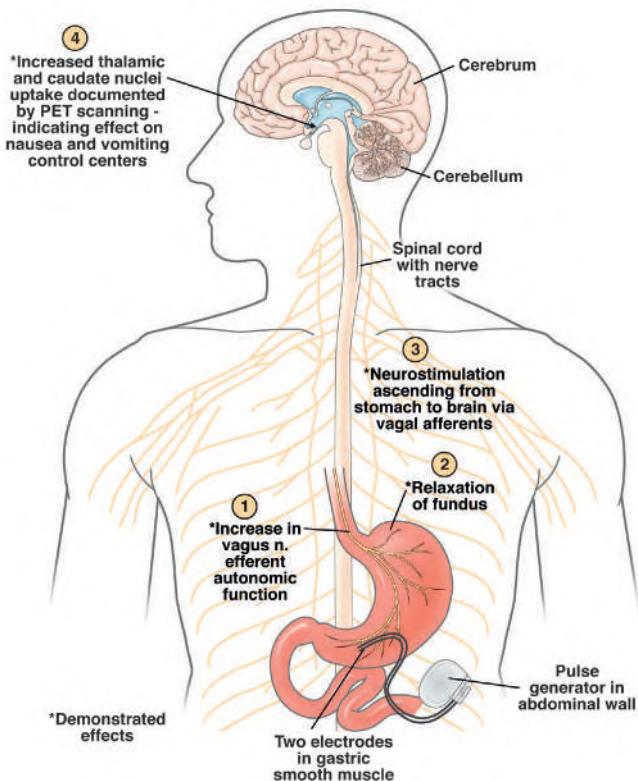
## 21. What is GES for gastroparesis?

GES using the Enterra device delivers high-frequency, low-energy electrical stimulation to the stomach, and is FDA approved through a humanitarian device exemption for the 20% to 30% of patients who fail or cannot tolerate medical therapy. The GES system consists of two electrodes sutured into the muscularis propria of the greater curvature, 9 and 10 cm from the pylorus via laparotomy or laparoscopy. The leads are connected to a pulse generator, which is subcutaneously implanted in the abdominal wall. The programming parameters are low-energy 330-microsecond pulse width, 14 cycles per minute, 0.1 seconds on, 5 seconds off, 12-Hertz trains, and a current of 5 milliamps (**Figure 12-3**).

## 22. How does GES work?

- The major effect is increased vagal activity based on the sympathetic/vagal ratio of spectral analysis of heart rate variability.

### Proposed mechanisms of action of the gastric neurostimulator



**Figure 12-3.** Gastric electrical stimulation device. ED, Emergency department; J, jejunostomy; PET, positron emission tomography. (From Reddymasu SC: Severe gastroparesis: medical therapy or gastric electrical stimulation, Clin Gastroenterol Hepatol 8:117–124, 2010.)

2. The GES results in better fundic relaxation and the ability to eat and store more food through this increased vagal activity.
3. Positron emission tomography shows increased activity in the thalamic and caudate nuclei after chronic GES therapy. The device stimulates vagal afferent pathways to the solitary tract nucleus in the dorsal medulla and to the thalamus via the reticular formation, and exerts an inhibitory influence on nausea and vomiting control mechanisms. Essentially, it is the best antiemetic we have. Electrical dysrhythmias and gastric emptying do not significantly improve. Combining GES with a surgical pyloroplasty to accelerate gastric emptying achieves better results, as recently reported.

### 23. What are the outcomes of GES?

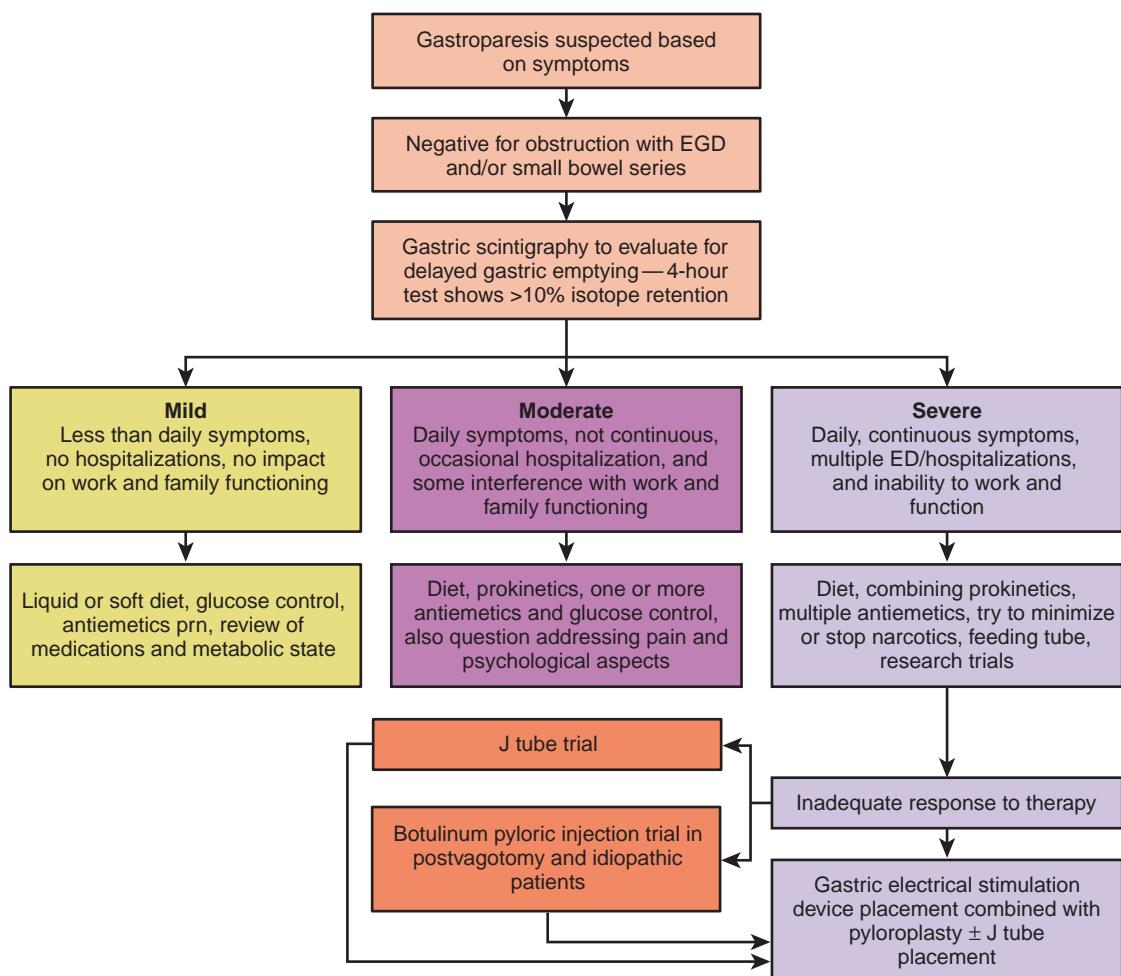
The symptom response is nausea, vomiting, fullness, and food intake. Epigastric abdominal pain is minimally changed unless it is linked to vomiting. More patients with DGP (58%) and postsurgical gastroparesis (53%) had a greater than 50% reduction in total symptom score, compared with idiopathic disease (48%). Mean hemoglobin A1c decreased on average from 8.5% to 7.8%; hospitalizations decreased by 87%, and 89% of J-tubes could be removed within 12 months.

### 24. When is a total gastrectomy indicated?

Total gastrectomy is a final approach if patients fail GES therapy or have a Billroth I–or II–related gastroparesis with a limited gastric reservoir and bezoar formation. The goal is to stop the vomiting and hence the need for hospitalizations by performing an esophagojejunostomy with an accompanying J tube for temporary use during adaptation to eating with this new anatomy. Nausea and retching may intermittently still occur, but admissions can be avoided and quality of life is improved, although sometimes back-up J tube use for hydration and nutrition continues.

### 25. Describe the strategy for escalating therapy in gastroparesis.

See Figure 12-4.



**Figure 12-4.** Algorithm for gastroparesis management. EGD, Esophagogastroduodenoscopy.

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## BIBLIOGRAPHY

1. Abell TL, Camilleri M, Donohoe K, et al. Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. *J Nucl Med Technol* 2008;36(1):44–54.
2. Abell T, McCallum R, Hocking M, et al. Gastric electrical stimulation for medically refractory gastroparesis. *Gastroenterology* 2003;125(2):421–8.
3. Bountra C, Bunce K, Dale T, et al. Anti-emetic profile of a non-peptide neurokinin NK1 receptor antagonist, CP-99,994, in ferrets. *Eur J Pharmacol* 1993;249(1):R3–R4.
4. Camilleri M, Bharucha AE, Farrugia G. Epidemiology, mechanisms, and management of diabetic gastroparesis. *Clin Gastroenterol Hepatol* 2011;9(1):5–12, quiz e17.
5. Camilleri M, Grover M, Farrugia G. What are the important subsets of gastroparesis? *Neurogastroenterol Motil* 2012;24(7):597–603.
6. Camilleri M, Parkman HP, Shafi MA, et al. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013;108(1):18–37, quiz 38.
7. Cherian D, Sachdeva P, Fisher RS, et al. Abdominal pain is a frequent symptom of gastroparesis. *Clin Gastroenterol Hepatol* 2010;8(8):676–81.
8. Choung RS, Locke GR, Schleck CD, et al. Risk of gastroparesis in subjects with type 1 and 2 diabetes in the general population. *Am J Gastroenterol* 2012;107(1):82–8.
9. FDA. FDA requires boxed warning and risk mitigation strategy for metoclopramide-containing drugs. February 26, 2009. <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm149533.htm> [Accessed September 22, 2014].
10. Fontana RJ, Barnett JL. Jejunostomy tube placement in refractory diabetic gastroparesis: a retrospective review. *Am J Gastroenterol* 1996;91(10):2174–8.
11. Hibbard ML, Dunst CM, Swanström LL. Laparoscopic and endoscopic pyloroplasty for gastroparesis results in sustained symptom improvement. *J Gastrointest Surg* 2011;15(9):1513–9.
12. Kaplan L, McCallum R, Koch K, Sederman R, Henderson B. High prevalence and underdiagnosis of gastroparesis symptoms among patients with type 1 and type 2 diabetes mellitus. *DDW* 2013, Abstract.
13. Koch KL. Diabetic gastropathy: gastric neuromuscular dysfunction in diabetes mellitus: a review of symptoms, pathophysiology, and treatment. *Dig Dis Sci* 1999;44(6):1061–75.
14. Kuo B, McCallum RW, Koch KL, et al. Comparison of gastric emptying of a nondigestible capsule to a radiolabeled meal in healthy and gastroparetic subjects. *Aliment Pharmacol Ther* 2008;27(2):186–96.
15. Lee A. Gastroparesis: what is the current state-of-the-art for evaluation and medical management? What are the results? *J Gastrointest Surg* 2013;17(9):1553–6.
16. Lin Z, Sarosiek I, Forster J, et al. Association of the status of interstitial cells of Cajal and electrogastrogram parameters, gastric emptying and symptoms in patients with gastroparesis. *Neurogastroenterol Motil* 2010;22(1):56–61, e10.
17. McCallum RW, Dusing RW, Sarosiek I, et al. Mechanisms of symptomatic improvement after gastric electrical stimulation in gastroparetic patients. *Neurogastroenterol Motil* 2010;22(2):161–7, e150–61.
18. McCallum RW, Lin Z, Forster J, et al. Gastric electrical stimulation improves outcomes of patients with gastroparesis for up to 10 years. *Clin Gastroenterol Hepatol* 2011;9(4):314–9, e311.
19. McCallum RW, Polepal S, Schirmer B. Completion gastrectomy for refractory gastroparesis following surgery for peptic ulcer disease. Long-term follow-up with subjective and objective parameters. *Dig Dis Sci* 1991;36(11):1556–61.
20. McCallum RW, Valenzuela G, Polepal S, et al. Subcutaneous metoclopramide in the treatment of symptomatic gastroparesis: clinical efficacy and pharmacokinetics. *J Pharmacol Exp Ther* 1991;258(1):136–42.
21. Naftali T, Yishai R, Zangen T, et al. Post-infectious gastroparesis: clinical and electrogastrographic aspects. *J Gastroenterol Hepatol* 2007;22(9):1423–8.
22. Nusrat S, Bielefeldt K. Gastroparesis on the rise: incidence vs awareness? *Neurogastroenterol Motil* 2013;25(1):16–22.
23. Parkman H, Van Natta M, Abell T, et al. Effect of nortriptyline on symptoms of idiopathic gastroparesis: the NORIG randomized clinical trial. *JAMA* 2013;310(24):2640–9.
24. Rao AS, Camilleri M. Review article: metoclopramide and tardive dyskinesia. *Aliment Pharmacol Ther* 2010;31(1):11–9.
25. Rao SS, Kuo B, McCallum RW, et al. Investigation of colonic and whole-gut transit with wireless motility capsule and radiopaque markers in constipation. *Clin Gastroenterol Hepatol* 2009;7(5):537–44.
26. Reddymasu SC, McCallum RW. Small intestinal bacterial overgrowth in gastroparesis: are there any predictors? *J Clin Gastroenterol* 2010;44(1):e8–e13.
27. Ricci DA, Saltzman MB, Meyer C, et al. Effect of metoclopramide in diabetic gastroparesis. *J Clin Gastroenterol* 1985;7(1):25–32.
28. Rossi M, Giorgi G. Domperidone and long QT syndrome. *Curr Drug Saf* 2010;5(3):257–62.
29. Sarosiek I, Forster J, Lin Z, et al. The addition of pyloroplasty as a new surgical approach to enhance effectiveness of gastric electrical stimulation therapy in patients with gastroparesis. *Neurogastroenterol Motil* 2013;25(2):e134–e180.
30. Sawhney MS, Prakash C, Lustman PJ, et al. Tricyclic antidepressants for chronic vomiting in diabetic patients. *Dig Dis Sci* 2007;52(2):418–24.
31. Snape WJ, Battle WM, Schwartz SS, et al. Metoclopramide to treat gastroparesis due to diabetes mellitus: a double-blind, controlled trial. *Ann Intern Med* 1982;96(4):444–6.
32. Tattersall FD, Rycroft W, Francis B, et al. Tachykinin NK1 receptor antagonists act centrally to inhibit emesis induced by the chemotherapeutic agent cisplatin in ferrets. *Neuropharmacology* 1996;35(8):1121–9.

## Websites

American Neurogastroenterology and Motility Society. Sponsored manuscripts. <http://www.motilitysociety.org/clinician/manuscripts.php> [Accessed September 22, 2014].

# EVALUATION OF ABNORMAL LIVER TESTS

Emily Carey, DO, and William D. Carey, MD, MACG

## 1. What are liver tests?

Usually the term refers to the routine chemistry panel that includes alanine aminotransferase (ALT), aspartate aminotransferase (AST),  $\gamma$ -glutamyl transpeptidase (GGT), alkaline phosphatase (AP), bilirubin, albumin, and protein. Other terms for the same tests are *liver function tests (LFTs)* and *liver-associated enzymes*, but neither is totally accurate. Only the first four are properly called *enzymes*, and only the last two provide a measure of liver function. These tests help to characterize injury patterns and provide a crude measure of the synthetic function of the liver. Individually none are diagnostic of any specific condition. Other tests help to define specific causes of liver disease.

## 2. What are the true LFTs?

True LFTs evaluate the liver's synthetic capacity or measure the ability of the liver either to uptake and clear substances from the circulation or to metabolize and alter test reagents. Of commonly used tests, the prothrombin time comes closest to a true LFT, as it is a reflection of the liver's capacity to synthesize coagulation factors, some of which have a half-life measured in hours. Vitamin K is needed to synthesize prothrombin so it is important to replete any vitamin K deficiency prior to assuming a prolonged prothrombin time is related to decreased liver function. Albumin, as a general marker of liver protein synthesis, is another commonly used indicator of synthetic function, although it is not highly sensitive and may be affected by poor nutrition, renal disease, and other factors. In the context of chronic liver disease, low albumin levels indicate poor synthetic function. Decreases in albumin do not occur acutely because of the long 21-day half-life of albumin.

## 3. What is the difference between cholestatic and hepatocellular injury?

A common and useful approach to the evaluation of liver tests is the determination of whether the primary insult is directed against the hepatocyte (hepatocellular injury) or the biliary tree (cholestatic). In some cases, elements of both types of damage are involved; this scenario is often called a *mixed injury pattern*.

## 4. What are serum transaminases?

The two serum transaminases commonly assayed in clinical practice are ALT (previously called *serum glutamic pyruvate transaminase*) and AST (formerly *serum glutamic oxaloacetic transaminase*) and are involved in the transfer of amino groups from one molecule to another.

Elevation of ALT or AST usually reflects the presence of hepatocellular injury. Acute elevations are most commonly related to hepatitis A, hepatitis B, drugs, alcohol, or ischemia. *Elevations of more than 1000* are usually related to viruses or drugs. *Levels of more than 5000* are related to acetaminophen toxicity, ischemia, or unusual viruses. *Alcoholic hepatitis has enzyme elevations usually less than 400 with the AST/ALT ratio greater than 2:1.* Chronic elevations (*6 months or more*) in ALT and AST are often due to hepatitis B, hepatitis C, nonalcoholic fatty liver disease (NAFLD), alcohol, and autoimmune hepatitis (Figure 13-1).

## 5. What is the most specific test for hepatocellular damage?

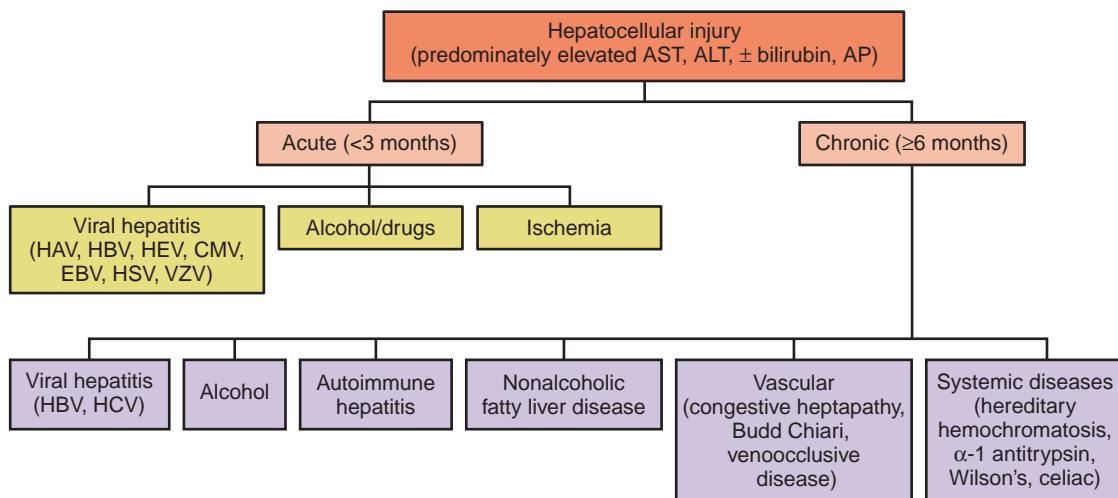
GGT is a liver-specific enzyme that is elevated in most cases of hepatocellular and cholestatic liver disease. Both AST and ALT reside in other organs, so elevated levels do not always reflect liver injury. ALT is somewhat more liver specific than AST but both may be elevated in, for example, acute muscle injury. Both enzymes are released into the circulation when liver tissue is damaged or destroyed.

## 6. What is a normal value for ALT?

Many demographic factors play a role in ALT level. Men have higher ALT levels than women; obese women have higher levels; certain racial groups have higher ALT activity than do others. Recent population studies suggest that clinicians should define abnormal as ALT greater than 30 IU/L for men and greater than 19 IU/L for women regardless of traditional "normal" values.

## 7. How is cholestatic injury best diagnosed?

In the standard panel of liver tests, cholestatic injury is suggested by an elevated AP level, an enzyme bound in the hepatic canalicular membrane. Because AP can be derived from other body tissue (e.g., bone, intestine, placenta), a concurrent elevation of GGT (an enzyme of intrahepatic biliary canaliculi) or 5'-nucleotidase helps to support a cholestatic mechanism.



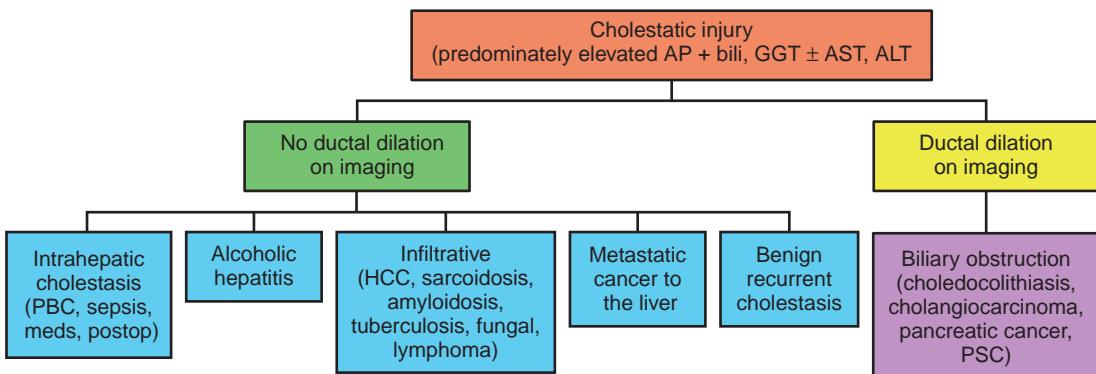
**Figure 13-1.** Diagnostic possibilities for hepatocellular pattern liver injury depend on context and duration of injury. ALT, Alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HSV, herpes simplex virus; VZV, varicella zoster virus.

## 8. What makes the AP level rise?

AP is a group of enzymes that catalyze the transfer of phosphate groups. Different isoenzymes can be identified from multiple sites in the body, including liver, bone, and intestine. Most hospital laboratories can determine the isoenzyme responsible for the elevated AP level. In one large study, elevated AP was caused by the liver in only approximately 65% of hospitalized patients. When the source is the liver, the mechanism appears to be related to stimulation of enzyme synthesis associated with local increases in bile acids. Common causes of cholestatic injury include primary biliary cirrhosis, primary sclerosing cirrhosis, large bile duct obstruction, drug-induced injury, infiltrative disease, and inflammation-associated injury (Figure 13-2). Serum AP levels may be modestly increased in hepatocellular disease; this increase is due to release of cellular enzyme without excessive stimulation of new enzyme.

## 9. What does an elevated bilirubin mean?

Bilirubin, a breakdown product of red blood cells, exists in two forms: conjugated (direct) and unconjugated (indirect). Unconjugated bilirubin is water insoluble, exists in the circulation tightly bound to albumin, is taken up by the hepatocyte and conjugated with glucuronic acid, making it water soluble and allowing it to be excreted in bile. *Jaundice occurs when the bilirubin level is greater than 2.5 mg/dL*. Unconjugated bilirubin appears in the serum when blood is broken down at a rate that overwhelms the processing ability of the liver found commonly in patients with hemolysis or reabsorption of a hematoma. Because unconjugated bilirubin is tightly albumin bound, it does not appear in urine. Accordingly, an elevated serum bilirubin with a negative urine bilirubin implies indirect hyperbilirubinemia and suggests the absence of liver injury. Conversely bilirubinuria means the elevated serum bilirubin reflects the presence of liver disease.



**Figure 13-2.** Cholestatic liver injury can be caused by large- or small-bile duct injury or by infiltrative liver disorders. Imaging studies frequently serve as the best early test to distinguish causes. ALT, Alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; bili, bilirubin; GGT, γ-glutamyl transpeptidase; HCC, hepatocellular carcinoma; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

Two genetic enzyme deficiencies result in improper or incomplete bilirubin conjugation in the liver. The most common is *Gilbert's syndrome* ( $\approx 5\%$  of general U.S. population), which is characterized by a relative deficiency of uridine diphosphate–glucuronyl transferase. Individuals often have high-normal to borderline-elevated bilirubin levels (2–7 mg/dL). When they fast, become ill, or decrease caloric intake, the bilirubin rises, exclusively because of increases in the *unconjugated* form. Other genetic disorders leading to unconjugated hyperbilirubinemia include *Crigler-Najjar I* and *II*; affected children rarely reach adulthood. Conjugated hyperbilirubinemia can result from hepatocellular dysfunction (viral-, chemical-, drug-, or alcohol-induced hepatitis; cirrhosis or metabolic disorders), cholestasis (intrahepatic or extrahepatic biliary obstruction), or genetic disorders of excretion of bilirubin (*Dubin-Johnson syndrome*, *Rotor's syndrome*). It is a common misperception that an elevated bilirubin implies cholestatic liver injury. It is just as often seen in severe acute hepatocellular damage.

#### **10. What tests should be ordered to evaluate acute viral hepatitis?**

Despite rare fatalities, hepatitis A virus (HAV) is an acute, self-limited illness in most. Both the total anti-HAV (immunoglobulin [Ig] G and IgM) and the IgM anti-HAV will be positive in acute hepatitis A. Care in selection of testing is required, as total anti-HAV will be present after immunization or even years after hepatitis A has resolved. Order IgM anti-HAV when looking for laboratory confirmation of acute hepatitis A.

In acute hepatitis B, the hepatitis B surface antigen (HBsAg) emerges within 2 weeks of exposure. If testing is delayed this level may be declining and detection of the IgM antibody directed against the hepatitis B core antigen (anti-HBc-IgM) can diagnose acute hepatitis B. The hepatitis B virus (HBV) DNA will also be positive in acute hepatitis.

#### **11. What tests detect chronic viral hepatitis?**

The diagnosis of hepatitis B requires detection of HBsAg, typically with anti-HBc (IgG) but without the development of anti-HBs. If this pattern is present for 6 months it is termed *chronic hepatitis B*. The HBe antigen may be positive. HBV DNA is usually also positive.

A confident diagnosis of hepatitis C requires demonstration of hepatitis C virus (HCV) RNA in serum. The presence of anti-HCV is suggestive but insufficient as this antibody will persist even if the infection is cleared.

#### **12. Are there tests to diagnose NAFLD?**

No specific blood test diagnoses NAFLD. The diagnosis is based on evidence of hepatic steatosis (imaging or biopsy), minimal to no alcohol history, and the absence of other etiologic factors for hepatic steatosis or other chronic liver disease. Distinguishing NAFLD (usually benign) from nonalcoholic steatohepatitis, which leads to fibrosis and cirrhosis, generally requires a liver biopsy. The NAFLD fibrosis risk score based on age, fasting glucose impairment, AST, ALT, platelet count, albumin, and body mass index has been found in a metaanalysis to be a clinically useful tool to identify individuals at risk for bridging fibrosis and cirrhosis. A score of more than 0.676 is used to predict advanced fibrosis (see <http://nafldscore.com/>).

#### **13. What tests are used to evaluate hemochromatosis?**

Hemochromatosis is a disease of iron overload in the liver and other organs. It may be hereditary or acquired. In the former, the defect is in a regulatory mechanism for iron absorption in the duodenum. Over many years, the affected individual builds up iron in the liver, heart, pancreas, and other organs. The most common screening test for hemochromatosis is serum ferritin; an elevated level suggests the possibility of iron overload. Unfortunately, ferritin is also an acute-phase reactant and may be falsely elevated in various inflammatory processes (including alcohol abuse). If ferritin is elevated (greater than 300  $\mu\text{g/L}$  in men and 200  $\mu\text{g/L}$  in women), serum iron and total iron-binding capacity (TIBC) should be assessed. If the fasting serum iron value divided by the TIBC value (serum transferrin saturation) is greater than or equal to 45%, the diagnosis of hemochromatosis should be further pursued. If the ferritin is chronically greater than 1000, there is heightened risk of cirrhosis.

The definitive diagnosis rests on a quantitative assessment of hepatic iron from a liver biopsy specimen. A modest increase in hepatic iron is normal with aging. Thus a calculation based on the patient's age and iron content in liver is used to create the *iron-age index* to determine the presence or absence of iron overload ( $>1.9$  is suggestive of hemochromatosis).

#### **14. What is the role of genetic testing in hemochromatosis?**

Many individuals with iron overload have a genetic disorder. Testing allows detection of at least one form of genetic (or hereditary) hemochromatosis. This test is called *HFE proteins*. When this test is positive in an individual with (phenotypic) iron overload, the clinician has a powerful tool for screening relatives. It must be borne in mind that genetic susceptibility does not establish the presence of iron overload. It is also apparent that the currently available genetic testing does not capture all cases. *More than 95% of cases in Australia but only 50% of Mediterranean cases will be uncovered by currently available genetic tests.*

**Table 13-1.** Likelihood of Hereditary Hemochromatosis Based on Genetic Defects

HFE Proteins	Probability of iron overload
C282Y:C282Y	High
C282Y:H63D	Moderate
H63D:H63D	Low
H63D:wild type	Low
C282Y:wildtype	Low
Wildtype:wildtype	None

Two major HFE gene defects have been described. They involve single amino acid mutations, which result in altered iron absorption. Hereditary hemochromatosis is an autosomal recessive disorder. Therefore both defective genes must be present. Table 13-1 defines the possible combinations and the association of each with iron overload. Novel gene proteins are being studied for hereditary hemochromatosis, including ferroportin, transferrin receptor 2, hemajuvelin, and hepcidin.

#### 15. Describe the role of $\alpha 1$ -antitrypsin.

The liver enzyme  $\alpha 1$ -antitrypsin helps break down trypsin and other tissue proteases. Multiple variants are described. The most common is termed MM (indicating one allele from each parent) and this is considered normal (or "wild-type"). One variant, called Z, is the product of a single amino acid gene mutation from the wild-type protein (M). The Z protein is difficult to excrete from the liver cell and causes local damage that may result in hepatitis and cirrhosis.

#### 16. What three tests are used to diagnose $\alpha 1$ -antitrypsin deficiency?

1. Serum protein electrophoresis (SPEP): The  $\alpha 1$  band on SPEP consists mostly of  $\alpha 1$ -antitrypsin. Therefore an  $\alpha 1$ -antitrypsin deficiency results in a flattening of the  $\alpha 1$  band on SPEP. This test is of marginal utility clinically.
2. Quantitative  $\alpha 1$ -antitrypsin: Subnormal levels suggest the possibility of disease.
3.  $\alpha 1$ -Antitrypsin phenotype: This test designates the allelic protein types in the serum (e.g., MM, ZZ, MZ, FZ). Patients with protein of the ZZ type are said to be homozygotic for Z-type  $\alpha 1$ -antitrypsin deficiency. This is the form most frequently associated with significant liver disease. If Z protein is trapped in hepatocytes, it can be seen in liver tissue as small globules that stain with the periodic acid-Schiff (PAS) reaction and resist subsequent digestion with an enzyme called diastase. An immunostain is also available in some institutions.

#### 17. What is the relationship of $\alpha 1$ -antitrypsin abnormal phenotypes to disease?

Deficiency of  $\alpha 1$ -antitrypsin is most often associated with chronic obstructive pulmonary disease at an early age. Hepatic manifestations include neonatal jaundice. Adults with no prior history of neonatal jaundice and no lung disease may develop otherwise unexplained cirrhosis. The ZZ phenotype is most commonly associated with liver disease, although MZ may also cause cirrhosis.

#### 18. What is Wilson disease?

Wilson disease, a rare disorder of copper storage, is associated with deficiency of an enzyme derived from liver cells. Like iron, copper may accumulate in many tissues in the body, especially liver and brain. Copper deposition may be seen in the eye (Kayser-Fleischer rings) and parts of the brain. Indeed, the first description of this disorder (by Wilson) highlighted its neurologic features. Many cholestatic diseases of the liver (e.g., primary biliary cirrhosis) also result in aberrant copper storage but not to the degree seen in true Wilson disease.

#### 19. How is Wilson disease diagnosed?

The initial screening test is the serum ceruloplasmin level, which is low in more than 95% of patients with Wilson disease. A low or low-normal ceruloplasmin level in a young individual with either liver disease or neurologic disease is Wilson disease until proven otherwise. It is particularly helpful to recognize that most non-Wilson liver diseases are associated with high-normal or elevated ceruloplasmin levels. Conditions in which the ceruloplasmin may be low include massive liver failure of any cause or terminal cirrhosis of any cause. Some individuals have idiopathic hypoceruloplasminemia.

Total serum copper levels are not useful in diagnosis because most circulates bound to ceruloplasmin. However, measurement of serum-free copper is possible in many laboratories. A value greater than 25 mcg/dL suggests copper overload. Twenty-four hour urine copper levels higher than 40 mcg/24 hours also suggest copper overload.

Kayser-Fleischer rings are virtually always present when there are neurologic features of Wilson disease.

Demonstration most often requires a slit lamp examination. Absence of Kayser-Fleischer rings does not exclude Wilson liver disease. Kayser-Fleischer rings have rarely been reported in other conditions (e.g., primary biliary cirrhosis).

A quantitative assessment of copper in liver tissue from liver biopsy provides definitive diagnosis. Copper statins (e.g., rhodanine stain) are often falsely negative in those with Wilson disease so quantitative copper levels in liver tissue are needed. As mentioned, chronic cholestatic liver disease may also result in hepatic copper accumulation, usually to a moderate degree. Hepatic copper levels of greater than 250 mcg/g dry weight is diagnostic of Wilson disease.

## 20. Summarize the tests for common metabolic disorders of the liver.

See Table 13-2 for testing for common metabolic disorders of the liver. Numerous other rare hereditary diseases of the liver, including Gaucher disease, Niemann-Pick disease, and hereditary tyrosinemia usually diagnosed in children are beyond the scope of this chapter.

**TABLE 13-2.** Tests for Common Metabolic Disorders of the Liver

DISEASE	PRIMARY TEST	SUPPORTIVE TEST	DEFINITIVE TEST
Hemochromatosis	Serum ferritin > 300 mcg/L in men and 200 mcg/L in women	Iron saturation ≥ 45% Iron age index > 2	C282Y homozygosity; compound heterozygote (C282Y:H63D), C282Y heterozygote or non-C282Y need liver biopsy
α-Antitrypsin	SPEP or α-antitrypsin level	Phenotype (Pi ZZ type)	Liver biopsy with PAS-positive diastase-resistant granules
Wilson Disease	Ceruloplasmin < 20 mg/dL	Urine copper > 40 mcg/24 hr, Kayser-Fleischer rings	Liver biopsy with quantitative copper > 250 mcg/g dry weight

PAS, Periodic acid-Schiff test; SPEP, serum protein electrophoresis.

## 21. What autoimmune tests are useful in liver disease?

Autoimmune markers determine the presence of antibodies to specific cellular components that have been epidemiologically associated with the development of specific liver diseases. Autoimmune markers include antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA; also called *antiactin antibody*), liver-kidney microsomal antibody type 1 (LKM-1), antimitochondrial antibody (AMA), soluble liver antigen (SLA), and anti-asialoglycoprotein receptor antibody. ANA, ASMA, and AMA are the most readily available tests and help to define the probability of the more common classes of autoimmune liver disease. Currently, SLA is not easily obtained in the United States.

## 22. How are the common antibody tests performed and interpreted?

The common antibody tests are performed by exposure of the patient's serum to cultured cells and labeling with a fluorescein-tagged antibody against human antibodies. The cells are examined by fluorescent microscopy and graded according to intensity of the signal and which part of the cell binds the antibody. Therefore reading of antibody levels and determination of positive or negative results are highly subjective, and most hepatologists require positive results in dilution titers greater than 1:80 or 1:160 before considering the tests as part of a diagnostic algorithm. Newer assays permit determination of an antibody level directly. ANA and ASMA are particularly common in older people, women, and patients with a wide spectrum of liver diseases. Therefore the diagnosis of autoimmune liver disease depends on a broad clinical picture that takes into account age, sex, presence of other autoimmune processes, γ-globulin levels, and liver biopsy findings. An international panel has codified the diagnostic criteria for autoimmune hepatitis and is beyond the scope of this chapter (see Czaja, 2006). In addition, the overlap in antibodies in different autoimmune liver diseases is considerable.

## 23. When should screening or diagnostic tests be ordered for patients with suspected liver disease?

The transaminases, bilirubin, and AP serve as screening tests when liver disease is suspected. The history, physical examination, and estimation of risk factors help determine which specific diagnostic tests should be ordered. In general, patients should have at least two sets of liver enzyme tests to eliminate laboratory error before a full workup for liver disease is begun. Many diseases (hepatitis B and hepatitis C) generally require proof of chronicity (abnormality greater than 6 months) before therapy is initiated or confirmatory and staging liver biopsy samples are obtained. The severity of enzyme abnormality and the likelihood of finding a treatable process may modify the typical waiting period. For example, a woman with transaminase levels 10 times normal, a history of autoimmune thyroid disease, and an elevated globulin fraction probably has a flare of previously unrecognized chronic autoimmune hepatitis. An autoimmune profile and early liver biopsy may help to support this hypothesis and lead to prompt treatment. For those suspected of certain hereditary diseases (hemochromatosis, Wilson disease, α1-antitrypsin deficiency), screening even in the absence of abnormal liver tests is warranted.

**24. What are noninvasive markers of fibrosis, and what is their utility?**

Noninvasive markers of fibrosis fall into three major categories. These include serum biomarkers, imaging techniques to evaluate degree of fibrosis, and transient elastography, which uses sound waves to evaluate liver stiffness. It has been known for some time that there is a positive correlation between markers of early portal hypertension and the presence or absence of advanced liver fibrosis. Platelet counts below normal in a patient with liver disease often indicate the presence of fibrosis, which has caused portal hypertension, splenomegaly, and platelet sequestration. Recently, more or less complex indices, including the AST/platelet ratio index, FIB-4, Fibrotest, and Fibrosure, have been described. They are moderately reliable in identifying cirrhosis and absence of fibrosis, although error rates of 20% to 30% have been reported and are relatively poor at close comparison (F2 versus F3). Imaging modalities include ultrasound, computed tomography, magnetic resonance imaging (MRI), and single-photon emission computed tomography. Of these, only MRI, using special equipment and unique algorithms, has reproducibly predicted fibrosis stage at a level that is clinically useful. The most recent development is transient elastography, which determines liver stiffness and not just fibrosis. Results are significantly affected by the presence or absence of inflammation and, to a lesser degree, steatosis and hepatic iron concentration. Widely accepted as a substitute for histologic examination in Europe, the device was recently approved by the Food and Drug Administration in the United States in April 2013. As more centers acquire this capability, it will become a standard test.

**25. What is the role of liver biopsy?**

Liver biopsy is used to confirm suspected diagnoses and to evaluate prognostic finding in a patient with a known disease process (e.g., degree of fibrosis and inflammation in a patient with chronic HCV infection). Biopsy may also be used to evaluate etiologic factors when there is etiologic uncertainty. The value of the biopsy depends on two factors—provision of an adequate specimen, defined as an intact liver slice containing more than 11 portal areas, and review by a qualified pathologist or hepatopathologist. Liver biopsy provides important prognostic information in many patients with various chronic liver diseases.

*The authors would like to acknowledge the contributions of Dr. Kenneth E. Sherman, who was the author of this chapter in the previous edition.*

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

**BIBLIOGRAPHY**

1. Ahmed A, Keeffe EB. Liver chemistry and function tests. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease. 9th ed. Philadelphia: Saunders; 2010. p. 1227–38.
2. Approach to the patient with liver disease: a guide to commonly used liver tests. <http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/hepatology/guide-to-common-liver-tests/> [Accessed September 22, 2014].
3. Bacon BR, Adams PC, Kowdley KV, et al. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011;54:328–43.
4. Carey E, Carey WD. Noninvasive tests for liver disease, fibrosis, and cirrhosis: is liver biopsy obsolete? Cleve Clin J Med 2010;77:519–27.
5. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 2012;142:1592–609.
6. Czaja AJ. Autoimmune hepatitis—approach to diagnosis. Med Gen Med 2006;8(2):55.
7. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335–74.
8. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50:661–2.
9. Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. Hepatology 2010;51:2193–213.
10. Musso G, Gambino R, Cassader M, et al. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Intern Med 2011;143:617–49.
11. Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med 2002;137:1–10.
12. Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: an update. Hepatology 2008;47:2089–111.
13. Tavill A. Masters in medicine iron overload and the liver part 1, 2, 3, 2013 online webcast. <http://www.clevelandclinicmeded.com/online/webcasts/masters-in-medicine/tavill/iron-overload-and-the-liver-part-1/> [Accessed September 22, 2014].

# GENERAL CONCEPTS ON VIRAL HEPATITIS

Christina Hanson, NP-C, Gail Pearson, FNP-C, and Marcelo Kugelmas, MD

## 1. What is viral hepatitis?

Viruses may infect hepatocytes in the liver, triggering an inflammatory process known as *viral hepatitis*. In the process of infecting hepatocytes, viral antigens get transported to the cell membrane where these antigens become recognized by immune cells. If the immune system recognizes these antigens as foreign, it creates an inflammatory response. This response may be strong enough to kill all the cells that harbor virus, and eradicate the infection causing acute hepatitis (symptomatic or not, even fatal). In other cases the immune system is not able to eradicate the infection, leading to chronic hepatitis. Persistent immune activity may lead to progressive liver damage, more so in the presence of other liver insults, including chemical agents such as alcohol and drugs, genetic disorders, and metabolic liver disease.

## 2. Which viruses cause viral hepatitis?

Two distinct groups of viruses may cause viral hepatitis. The hepatitis A, B, C, D, and E viruses are called *hepatotropic viruses* because these predominantly replicate in hepatocytes. The other group is composed of viruses that replicate outside of the liver but may trigger hepatitis nonetheless; the most common culprits in this group are the Epstein-Barr virus, cytomegalovirus, herpes simplex viruses types I and II, yellow fever, and adenovirus.

*Hepatitis A virus (HAV)* is a nonenveloped RNA virus in the picornavirus family. After exposure, there is a 2- to 6-week incubation period. Unlike Hepatitis B and C, HAV does not enter a chronic phase. There is immunologic clearance of HAV and immunoglobulin (Ig) G antibodies are formed, providing lifelong immunity.

*Hepatitis B virus (HBV)* is a small, double-stranded DNA virus of the *Hepadnaviridae* family and is classified into eight genotypes, with different geographic distribution. HBV replicates through an RNA intermediate and can integrate into the host genome. Infection with HBV can lead to a wide range of liver disease, including acute or fulminant hepatic failure, chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Acute hepatitis B infection can be asymptomatic or present with classic symptomatic acute hepatitis. The risk for acute HBV to become chronic hepatitis varies inversely by the age at which acute infection occurs:

- 90% HBV chronicity for perinatal (vertical)-acquired infection
- 20% to 50% HBV chronicity for infection during the ages of 1 to 5 years
- 5% chronicity for adult-acquired HBV infection

*Hepatitis C virus (HCV)* is an RNA virus in the *Flaviviridae* family. There are six genotypes of HCV. The incubation period is usually 2 to 12 weeks. Most patients infected with HCV never develop symptoms of acute hepatitis. HCV RNA is detectable 1 to 3 weeks after infection. However, HCV antibodies are not protective and 70% to 80% of acute HCV infections become chronic.

*Hepatitis D virus (HDV)* is a satellite virus, meaning that the virus can thrive only with simultaneous hepatitis B infection as it uses the HBV envelope protein to transport virions from cell to cell. HDV infection can present in two forms. HDV and HBV may cause simultaneous coinfection, which usually results in a more severe acute hepatitis with a higher mortality rate than is seen with acute hepatitis B alone, but rarely results in chronic infection. A second form presents with a superinfection of HDV in a carrier of HBV and can manifest as a severe, seemingly acute hepatitis in a previously asymptomatic HBV carrier or as an exacerbation of underlying chronic hepatitis B. The result of this superinfection of HDV with an HBV carrier is nearly always a chronic infection of both viruses.

*Hepatitis E virus (HEV)* is a single-stranded RNA virus with a unique genomic structure that defines the *Hepeviridae* family. There are four genotypes of HEV. HEV usually causes acute hepatitis, much like the HAV, but with a higher mortality rate, particularly in pregnant women. After an incubation period of 3 to 8 weeks, symptoms, when present, will last up to several weeks. HEV can also cause chronic hepatitis, mostly in immunocompromised hosts, like recipients of organ transplants ([Table 14-1](#)).

## 3. What are the risks of acute and chronic viral hepatitis?

Acute viral hepatitis can be symptomatic or asymptomatic. A strong immune response causes greater liver parenchymal inflammation increasing the likelihood of having a clinically symptomatic and apparent process. Fulminant cases of acute hepatitis occur most commonly with hepatitis A, B, and E, and can lead to liver failure and even death or require life-saving liver transplantation.

Acute viral hepatitis can occur to a patient with established chronic liver disease. In this second scenario, there is a greater risk of liver failure. This is the basis of the recommendation to test and vaccinate those patients with chronic liver disease not previously exposed to hepatitis A or B.

**Table 14-1.** The Hepatotropic Viruses

VIRUS	HAV	HEV	HCV	HBV	HDV
Nucleic acid	RNA	RNA	RNA	DNA	RNA
Mode of transmission	Fecal-oral	Fecal-oral	Parenteral	Parenteral	Parenteral
Acute hepatitis	+	+	±	+	±
Chronic hepatitis	-	+	+	+	+
Vaccine	Yes	No	No	Yes	Yes (HBV)
Available treatment	Supportive	Supportive	Yes	Yes	Yes

HAV, Hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus.

Lastly, some patients experience chronic viral hepatitis over a period of years or usually decades that may lead to a progressive liver injury, fibrosis, and cirrhosis. This chronic infection may increase the risk of developing chronic liver failure or hepatocellular carcinoma.

#### 4. Describe the signs and symptoms of viral hepatitis.

Patients with acute viral hepatitis may feel healthy or have only minor symptoms that don't trigger medical consultation. In cases of more severe acute hepatitis, patients will most commonly experience fatigue, right upper quadrant discomfort, and nausea with or without vomiting. Other common symptoms include low-grade temperature, choloria, acholia, headache, jaundice, and scleral icterus.

Patients with chronic viral hepatitis are most commonly asymptomatic. In those who experience symptoms, the most common is fatigue. A plethora of hepatic and extrahepatic symptoms have been associated with chronic viral hepatitis associated with the multiorgan system involvement. These symptoms are often not well understood and in many cases the association with the hepatitis is not recognized until viral eradication leads to a particular symptom resolution.

#### 5. What biochemical and hematologic abnormalities are associated with viral hepatitis?

The typical biochemical abnormalities seen with viral hepatitis are elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The ALT/AST ratio is maintained unless liver failure ensues or there is concomitant alcoholic hepatitis. In a minority of cases, the pattern of enzyme abnormalities is more mixed or frankly cholestatic, with more significant elevations of alkaline phosphatase and bilirubin. HAV is more likely than the other viruses to cause acute cholestatic hepatitis.

In cases of acute liver failure and chronic end-stage liver disease, a multitude of other abnormalities may be seen. These abnormalities include acute hypoglycemia, renal insufficiency, and coagulopathy with international normalized ratio (INR) prolongation, hypoalbuminemia, hypergammaglobulinemia, dilutional hyponatremia, hypocholesterolemia, and hematologic abnormalities including thrombocytopenia, anemia, and eventually neutropenia. Significant elevations of the ferritin level (released from destroyed hepatocytes) and acute-phase reactants, like ceruloplasmin and alpha-1 antitrypsin, can be seen in cases of more severe acute hepatitis.

#### 6. How are the hepatitis viruses transmitted?

HAV and HEV are primarily transmitted by the fecal-oral route. This may occur by either person-to-person contact or ingestion of contaminated food or water. Contaminated foods are often a source of outbreaks. Waterborne outbreaks do not often occur in developed countries with safe water supplies and adequate sewage disposal as adequate chlorination of water kills HAV. HEV genotypes 1 and 2 infect humans via the fecal-oral route and are associated with epidemics in developing countries. HEV genotypes 3 and 4 are swine viruses that infect humans through exposure to pigs and ingestion of undercooked pork or wild game, and are more commonly associated with endemic hepatitis in developed countries.

HBV, HCV, and HDV viruses are transmitted by parenteral contact with infected blood or body fluids. Risk factors include unprotected sexual activity, intravenous drug use or intranasal drug use, accidental needle stick, blood transfusion, hemodialysis, and mother-to-infant vertical transmission through childbirth.

#### 7. Which tests should the provider order for a patient with acute viral hepatitis?

As a provider, you need to determine if the process is an acute or chronic insult and if acute, if the patient is at any immediate risk for hepatic decompensation. This can be evaluated through a combination of clinical assessment and biochemical evaluation.

Patients with marked elevations in their liver tests or transaminases (approximately 15 times the upper limit of normal or higher) often have acute hepatitis, although in some cases, there may be underlying chronic liver disease such as chronic HBV with superinfection with HDV. In other cases of chronic viral hepatitis, an acute superimposed hepatitis may occur. The practitioner should consider drug-induced liver injury (acetaminophen, penicillin derivatives, others), ischemia, biliary pathologic conditions, and Budd-Chiari

syndrome. Tests to order for the patient with acute viral hepatitis are anti-HAV IgM, hepatitis B surface antigen (HBsAg; this will be positive in acute and chronic infection), anti-HBc IgM and anti-HCV antibody (Ab). In some cases of acute hepatitis C, the Ab will not be detectable if tested too early and an HCV RNA polymerase chain reaction (PCR) test may be more sensitive. Diagnosis of acute HEV is best made with the IgM against HEV, if locally available.

#### **8. Which tests should the provider order for a patient with chronic viral hepatitis?**

In all cases basic blood work applies, including a comprehensive metabolic panel, complete blood count, and INR. In cases of chronic hepatitis B and C, testing should include anti-HAV IgG (total) to vaccinate those who are not immune to HAV. In cases of chronic hepatitis C, test for exposure to HAV and HBV and vaccinate if negative. A comprehensive evaluation includes antinuclear Ab, anti-smooth muscle Ab, antimitochondrial Ab, quantitative immunoglobulins, iron studies, ceruloplasmin, alpha-1 antitrypsin level with or without phenotype, and serologic markers for celiac disease. Less commonly needed blood tests may include anti-liver-kidney-microsomal Ab and antisoluble liver antigen Ab. Imaging of the liver and assessment of fibrosis is discussed separately in this chapter and in [Chapter 13](#).

In the United States HDV infection is rare and therefore testing for HDV in patients who have acute or chronic hepatitis B is not necessary in all patients. However, testing should be performed in patients who emigrated from countries with high HDV prevalence, including Eastern and Mediterranean European countries, and countries in South America. Initial testing is often limited to a total anti-HDV, but when possible, diagnosis should be confirmed by immunohistochemical staining of liver tissue through biopsy for HDAg or by obtaining reverse transcription-PCR assay for HDV RNA in the serum. A negative test for total anti-HDV does not necessarily exclude a diagnosis of acute HBV/HDV coinfection.

#### **9. When are liver imaging and histology needed?**

Ultrasound (US) is the most common initial modality used to image the liver. It is indicated in the assessment of the patient with cirrhosis or potential cirrhosis. US is also indicated in the surveillance for hepatocellular carcinoma in the setting of cirrhosis as well as in different categories of chronic hepatitis B infections.

The role of liver biopsy in the management of patients with viral hepatitis has been controversial because of the invasive nature of the procedure, the risks and cost associated with it, and the significant risk of sampling error, as well as inaccurate interpretation. Most often liver biopsy is best used when it aids in the management of the liver condition, whether by defining the diagnosis or coexistent conditions, or by documenting advanced liver fibrosis and cirrhosis that may require a different set of management decisions altogether. A liver biopsy in the setting of fulminant liver failure may be helpful to assess the extent of liver necrosis.

This is a rapidly changing field as noninvasive techniques to assess liver fibrosis are available and gaining greater acceptance. New, more effective medical treatments of chronic viral hepatitis B and C can arrest or eliminate viral replication and reverse liver injury to include some degrees of cirrhosis. This makes serial noninvasive measurements of liver fibrosis preferable to repeated liver biopsies.

#### **10. What is the general management for acute hepatitis A–E?**

Immune globulin, when administered before exposure or during the early incubation period is effective in preventing clinically apparent HAV. The primary treatment of acute hepatitis of any type is mainly supportive. No specific antiviral therapy is available for the treatment of hepatitis A. Patients should avoid alcohol and take acetaminophen only under cautious medical advisement. Alcohol and acetaminophen are best avoided in patients with acute viral hepatitis.

*Small doses of acetaminophen, usually less than 2 g per day are well tolerated in patients with mild to moderate hepatitis while appropriately monitored.* In general, patients do not require hospitalization unless the disease is complicated by significant hepatic failure as evidenced by encephalopathy, coagulopathy with bleeding, renal failure, or inability to maintain adequate nutrition and fluid intake. Liver failure from acute hepatitis A is greater in patients with chronic hepatitis C, other chronic liver diseases, and older patients.

Antiviral therapy is generally not necessary in patients with symptomatic acute hepatitis B because more than 95% of immunocompetent adults with acute hepatitis B recover spontaneously. In fact, treatment is generally only indicated for patients with fulminant hepatitis B and those with protracted severe acute hepatitis. There are known subgroups of patients whose prognosis is relatively worse. These include patients who are immunocompromised, have concomitant infection with HCV, have preexisting liver disease, or are older.

Frequent physical assessment and close monitoring of biochemical and synthetic markers of liver function is mandatory to ensure resolution of symptoms and normalization of serum levels.

Acute HCV is often asymptomatic; hence the diagnosis of acute HCV is made infrequently. Acute HCV is most often diagnosed in the setting of postexposure surveillance. Those identified with acute HCV infection should be closely monitored for the first 12 to 24 weeks to determine if a spontaneous viral clearance will occur. There aren't well-established treatment guidelines for acute HCV and treatment for acute HCV remains controversial. However, the American Association for the Study of Liver Diseases (AASLD) 2009 guidelines state sufficient data exists to consider treatment for patients with interferon after waiting 8 to 12 weeks for spontaneous resolution.

## 11. What is the general management for chronic HBV and HCV?

The initial evaluation of an individual with chronic hepatitis B infection should entail thorough history and physical examination with emphasis on the risk factors for coinfection, family history of HBV and liver cancer or other chronic liver diseases, and alcohol use. Laboratory testing should include testing for coinfection with other viral hepatitis, including hepatitis A, C, and D, as well as for human immunodeficiency virus (HIV) in those at risk. Additional blood work should be obtained to assess for liver function and markers of HBV disease status, in particular e antigen status and HBV DNA quantitation.

The AASLD has developed guidelines for follow-up of patients with chronic hepatitis B not initially considered for treatment and for screening for hepatocellular carcinoma.

The main goal of therapy for chronic hepatitis B is to suppress viral replication, normalize liver biochemical markers and functions, prevent or delay the progression of liver disease before the development of liver cirrhosis or hepatocellular carcinoma, and if possible cure the infection.

The management of a patient with chronic HCV should include evaluation to determine the severity of liver disease and assessment for potential treatment. Patients should be counseled to decrease the risk of horizontal and vertical transmission. Those not previously exposed should be vaccinated against HAV and HBV. Patients should be counseled about the potential harm of excessive alcohol use, marijuana use, and unhealthy body mass index. Regular use of marijuana has been identified as a risk factor for steatosis and increased fibrosis. Another study found a statistically significant association between daily marijuana use and moderate to severe fibrosis.

With the availability of better tolerated and more effective treatments, the indications for treatment of chronic hepatitis C may change in the years to come. The goal of treatment is to achieve a sustained viral response (SVR) that equals viral cure. Achieving an SVR has been associated with reduced mortality.

## 12. How can we prevent hepatitis A–E?

Vaccination is the best way to prevent HAV and HBV infection. Hepatitis A vaccination is recommended for all children at 1 year of age and for any person desiring immunity. The vaccination should be recommended for patients at high risk. The Centers for Disease Control and Prevention recommends vaccination for those living in or traveling to areas with high or intermediate risk, men who have sex with men, those who inject illegal drugs, those with high occupational risk, persons with chronic liver disease, persons receiving clotting factor concentrates, and household members and other close contacts of adopted children arriving from countries with high or intermediate hepatitis A endemic rate.

In 2007 U.S. guidelines were revised to recommend hepatitis vaccinations to be used for postexposure to hepatitis A. A healthy person aged 12 months to 40 years exposed to hepatitis A who has not been previously vaccinated should be administered a single dose of hepatitis A vaccine as soon as possible within 2 weeks of exposure. For persons 40 years of age and older Ig is preferred. Ig should be used in children younger than 12 months, immune-compromised persons, persons with chronic liver disease, and those allergic to the vaccine.

HBV vaccination is administered in a series of three injections and it is recommended that the first injection should be given to infants prior to leaving the hospital. If the baby's mother is a carrier of HBV, the first injection is given shortly after birth. The second injection is given between 1 and 2 months of age and the third shot given at 6 months of age. Adolescents who had not been previously vaccinated in infancy should be given the three-injection vaccination series at the earliest possible date. Immunization should also be offered to high-risk individuals, including health care and public safety workers exposed to blood on the job, residents and staff of facilities for developmentally disabled persons, travelers to regions with intermediate or high rates of hepatitis B, persons with multiple sex partners or sex partners of infected persons, men who have sex with men, injection drug users, persons seeking evaluation or treatment for a sexually transmitted disease, household contacts of infected individuals, persons with other chronic liver disease including HCV-infected persons, persons with HIV, and persons with chronic end-stage kidney diseases requiring dialysis. Infants born to HBsAg-carrier mothers should be protected against perinatal transmission by administration of hepatitis B Ig and HBV vaccine.

No vaccine is available for HCV. Prophylaxis with Ig is not effective in preventing HCV infection after exposure. Reducing the burden of HCV relies on primary prevention activities that reduce exposure to HCV and secondary prevention activities that reduce risk of liver and other chronic diseases in persons with chronic HCV infections.

*The authors would like to acknowledge Dr. Kenneth Sherman, who was the author of this chapter in the previous edition.*

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

1. American Association for the Study of Liver Diseases. AASLD practice guidelines for chronic hepatitis B: update 2009.
2. Centers for Disease Control and Prevention (CDC). Hepatitis A FAQs for health professionals. <http://www.cdc.gov/hepatitis/HAV/HAVfaq.htm> [Accessed September 22, 2014].
3. Centers for Disease Control and Prevention (CDC). Hepatitis A information for health professionals. <http://www.cdc.gov/hepatitis/HAV/index.htm> [Accessed September 22, 2014].

4. Centers for Disease Control and Prevention (CDC). Update: prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5641a3.htm> [Accessed September 22, 2014].
5. Centers for Disease Control and Prevention (CDC). Recommendations for prevention and control of hepatitis C virus (HCV) infections and HCV-related chronic disease. <http://www.cdc.gov/mmwr/preview/mmwrhtml/00055154.htm> [Accessed September 22, 2014].
6. Centers for Disease Control and Prevention (CDC). Viral hepatitis populations. <http://www.cdc.gov/hepatitis/Populations/index.htm> [Accessed September 22, 2014].
7. Chou R, Wasson N. Blood test to diagnosis fibrosis or cirrhosis in patients with chronic hepatitis C infection: a systematic review. *Ann Intern Med* 2013;158(11):807–20.
8. Ghany MG, Strader DB, Thomas DL, Seiff LB. AASLD practice guidelines: diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009;49(4):1335–74.
9. Hezode C, Zafraani ES, Roudot-Thoraval F, et al. Daily cannabis use: a novel risk factor of steatosis severity in patients with hepatitis C. *Gastroenterol* 2008;134:432–9.
10. Hoofnagle JH, Nelson KE, Purcell RH. Hepatitis E. *N Engl J Med* 2012;367(13):1237–44.
11. Ishida JH, Peters MG, Jin C, et al. Influence of cannabis use on severity of hepatitis C disease. *Clin Gastro Hepatol* 2008;6:69–75.
12. Jindal A, Kumar M, et al. Management of acute hepatitis B and reactivation of hepatitis B. *Liver Int*. doi:10.1111/liv.12081. <http://onlinelibrary.wiley.com/doi/10.1111/liv.12081/full> [Accessed September 22, 2014].
13. Liang JT. Hepatitis B: the virus and disease. *Hepatology* 2009;49(5):S13–S21.
14. Lok AS. Clinical manifestations and natural history of hepatitis B virus infection. Up to Date. <http://www.uptodate.com/contents/clinical-manifestations-and-natural-history-of-hepatitis-b-virus-infection> [Accessed September 22, 2014].
15. Longo DL, Fauci AS. Harrison's gastroenterology and hepatology. ed 2. Columbus, Ohio: McGraw-Hill; 2013.
16. National Digestive Diseases Information Clearinghouse. Viral hepatitis: A through E and beyond. <http://digestive.niddk.nih.gov/ddiseases/pubs/viralhepatitis/> [Accessed September 22, 2014].
17. Negro F, Lok ASF. Diagnosis of hepatitis D virus infection. <http://www.uptodate.com/contents/diagnosis-of-hepatitis-d-virus-infection> [Accessed September 22, 2014].
18. Ng V, Saab S. Effects of a sustained virologic response on outcomes of patients with chronic hepatitis C. *Clin Gastroenterol Hepatol* 2011;9(11):923–30.
19. O'Donovan DJ. Hepatitis viruses and the newborn: clinical manifestations and treatment. <http://www.uptodate.com/contents/hepatitis-viruses-and-the-newborn-clinical-manifestations-and-treatment> [Accessed September 22, 2014].
20. Souza RD, Graham RF. Diagnosis and treatment of chronic hepatitis B. *JR Soc Med* 2004;97(7):318–21.
21. Vogt TM, Wise ME, Bell BP, Finelli L. Declining hepatitis A mortality in the US during the era of hepatitis A vaccination. *J Infect Dis* 2008;197(9):1282.
22. Yamada T, Hasler WL, Inadomi JM, Anderson MA, Brown RS. Handbook of gastroenterology. Philadelphia: Lippincott Williams & Wilkins; 2005.

# ANTIVIRAL THERAPY FOR HEPATITIS C

Jorge L. Herrera, MD

Therapeutic Advancements in the field of Hepatic C have rapidly revolutionized the treatment of this disease. In fact, the therapeutic options for chronic hepatitis C are evolving so rapidly, that the reader is urged to visit the online website developed by the American Association for the Study of Liver Disease (AASLD) and Infectious Diseases Society of America (IDSA) at <http://www.hcvguidelines.org>. This website is actively updated with the most current information on testing, managing and treating hepatitis C. The summary recommendations for the treatment of Hepatitis (effective - July, 2014) are summarized in **Table 15-1**.

**Table 15-1a.** Summary of Recommendations for Patients Who are Initiating Therapy for HCV Infection for the first time or Who Experienced Relapse after Prior PEG/RBV based Therapy, by HCV Genotype (G-Type).

G-TYPE	RECOMMENDED	ALTERNATIVE
1	<b>IFN eligible:</b> SOF + PEG/RBV × 12 wks	<b>IFN eligible:</b> SMV* × 12 wks + PEG/RBV × 24 wks
	<b>INF ineligible:</b> SOF + SMV* ± RBV × 12 wks	<b>INF ineligible:</b> SOF + RBV × 24 wks
2	SOF + RBV × 12 wks	None
3	SOF + RBV × 24 wks	SOF + PEG/RBV × 12 wks
4	<b>IFN eligible:</b> SOF + PEG/RBV × 12 wk	SMV × 12 wks + PEG/RBV × 24–48 wks
	<b>INF ineligible:</b> SOF + RBV × 24 wk	
5 or 6	SOF + PEG/RBV × 12 wks	PEG/RBV × 48 wks

\*For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present. IFN and/or RBV ineligible is defined as one or more of following: intolerance to IFN, autoimmune hepatitis and other autoimmune disorders, hypersensitivity to PEG or any of its components, decompensated hepatic disease, major uncontrolled depressive illness, a baseline neutrophil count below 1500/ $\mu$ L, a baseline platelet count below 90,000/ $\mu$ L or baseline hemoglobin below 10 g/dL, or a history of preexisting cardiac disease. Abbreviations: INF (interferon), SOF (sofobuvir), SMV (simeprevir), RBV (ribavirin), PEG (pegylated interferon-2 $\alpha$ ). See <http://www.hcvguidelines.org>

**Table 15-1b.** Treatment Recommendations for Patients in Whom Previous HCV Treatment Has Failed.

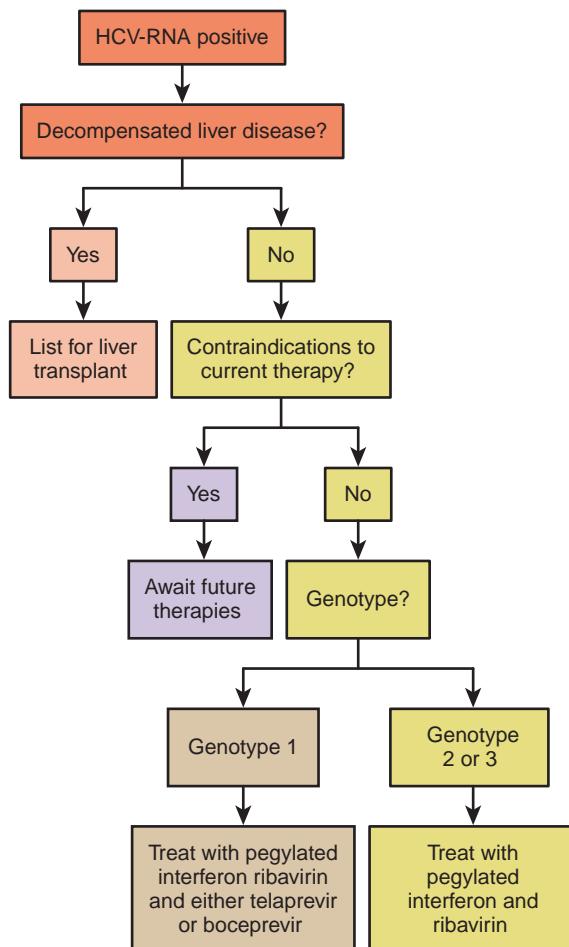
G-TYPE	RECOMMENDED	ALTERNATIVE
1	SOF + SMV* ± RBV × 12 wks	SOF × 12 wks + PEG/RBV × 12–24 wks SOF + RBV × 24 wks SMV* × 12 wks + PEG/RBV × 48 wks
2	SOF + RBV × 12 wks	SOF + PEG/RBV × 12 wks
3	SOF + RBV × 24 wks	SOF + PEG/RBV × 12 wks
4	SOF + PEG/RBV × 12 wks	SOF + RBV × 24 wks
5 or 6	SOF × 12 wks + PEG/RBV 12 wks	

\*For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present. IFN and/or RBV ineligible is defined as one or more of following: intolerance to IFN, autoimmune hepatitis and other autoimmune disorders, hypersensitivity to PEG or any of its components, decompensated hepatic disease, major uncontrolled depressive illness, a baseline neutrophil count below 1500/ $\mu$ L, a baseline platelet count below 90,000/ $\mu$ L or baseline hemoglobin below 10 g/dL, or a history of preexisting cardiac disease. Abbreviations: INF (interferon) SOF (sofobuvir), SMV (simeprevir), RBV (ribavirin), PEG (pegylated interferon-2 $\alpha$ ). See <http://www.hcvguidelines.org>

## 1. What are the indications for antiviral therapy in patients with chronic hepatitis C?

Antiviral therapy should be offered to all infected patients who have no contraindications to therapy. Hepatitis C progresses in all chronically infected patients but at different rates. The average time for development of cirrhosis is 30 years, but there is a wide range of variability. Because it is difficult to predict who will progress, everyone who is chronically infected should be evaluated for possible treatment. Many factors can accelerate progression of fibrosis, including alcohol consumption, nonalcoholic fatty liver disease, coinfection with hepatitis B or human immunodeficiency virus (HIV), iron overload, and concomitant liver disease such as  $\alpha_1$ -antitrypsin deficiency, Wilson disease, or autoimmune hepatitis, among others.

Patients with extrahepatic manifestations of hepatitis C infection should be considered for antiviral treatment regardless of the severity of the liver disease. Mixed cryoglobulinemia, leading to leukocytoclastic vasculitis, may be a systemic manifestation of hepatitis C infection and may respond to antiviral therapy. Renal disease, joint inflammation, or central nervous system complications may result from microvascular injury. The general approach to the treatment of hepatitis C infection is shown in [Figure 15-1](#).



**Figure 15-1.** Approach to the treatment of hepatitis C infection. HCV, Hepatitis C virus.

## 2. What is the recommended evaluation of patients with chronic hepatitis C before therapy is begun?

The medical history should include questions to detect the presence of depression and other psychiatric disorders that could worsen during interferon (IFN) therapy. Physical examination is important to detect evidence of decompensated cirrhosis, a contraindication to IFN-based antiviral therapy. Laboratory evaluation is designed to confirm viremia, establish the hepatitis C virus (HCV) genotype, exclude other possible causes of liver disease, detect coinfection, assess severity of liver disease, and detect contraindications to therapy such as cytopenias or renal insufficiency. Recommended laboratory tests are listed in [Table 15-2](#).

Testing for immunity against hepatitis B (hepatitis B surface antibody) and hepatitis A (anti-HAV, total) is recommended. Patients who are not immune should be vaccinated to prevent hepatitis A and B.

**Table 15-2.** Pretreatment Evaluation of Patients with Chronic Hepatitis C Infection

TEST	PURPOSE
HCV-RNA by PCR	Confirm viremia.
Serum albumin, bilirubin, PT	Assess liver function.
Iron, transferrin, ferritin	Assess for iron overload.
Antinuclear antibody	Detect autoimmune hepatitis.
$\alpha_1$ -Antitrypsin phenotype*	Detect $\alpha_1$ -antitrypsin deficiency.
Ceruloplasmin*	Detect Wilson disease.
HBsAg, HIV antibody test	Detect viral coinfection.
Hepatitis C genotype	Assess likelihood of response to therapy and determine therapeutic regimen.
Liver biopsy*	Determine severity and activity of disease.
Hepatitis B surface antibody	Determine need for hepatitis B vaccination.
Hepatitis A antibody (total)	Determine need for hepatitis A vaccination.

HBsAg, Hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; PT, prothrombin time.

\*These tests are not mandatory and are obtained depending on the clinical situation.

### 3. What is the importance of genotype testing in hepatitis C?

The type and duration of treatment for hepatitis C infection and the likelihood of response is based on the virus genotype. Based on genomic sequencing of the HCV, several genotypes (or strains) have been identified. They are classified as genotypes 1 through 6, with several subtypes denoted as 1a, 1b, 2a, and so forth. The various genotypes exhibit geographic variability. In the United States, genotype 1 accounts for approximately 70% of infections, and genotypes 2 and 3 account for the majority of the remaining 30%. In Europe, the proportion of genotype 2 and 3 infections is greater than in the United States. In the Middle East, genotype 4 predominates, and genotype 6 is more common in Asia.

Determining the genotype before therapy is important because it determines the antiviral regimen that should be used (see Figure 15-1). Current treatment regimens are different for genotype 1 compared with other genotypes. The genotype, however, has no value in predicting severity of disease or likelihood of progression to cirrhosis and should not be determined in patients who are not candidates for antiviral therapy.

### 4. Is a liver biopsy mandatory before initiation of antiviral therapy?

A liver biopsy is not required to diagnose or treat chronic hepatitis C, but it is useful to evaluate the level of hepatic inflammation and fibrosis. Liver function tests, such as prothrombin time and albumin or bilirubin level become abnormal only when extensive damage has occurred. Likewise, liver enzymes, viral load, and genotype do not correlate with severity of liver disease. A liver biopsy is not useful in patients with obvious signs and symptoms of portal hypertension and is less useful in the young patient with short duration of infection in whom progression to fibrosis is less likely. As the efficacy of treatment improves and side effects decrease, a liver biopsy prior to therapy becomes less important and its use should be individualized. Noninvasive methods have been developed to assess liver fibrosis. These include blood tests based on serum biomarkers and tests to measure liver stiffness such as transient elastography (FibroScan) and magnetic resonance elastography. These tests are moderately useful for identifying clinically significant fibrosis or cirrhosis, but less accurate in determining lesser degrees of fibrosis. They serve as complementary tests to liver biopsy; those with indeterminate noninvasive test results can be evaluated with a liver biopsy.

### 5. Can hepatitis C be cured?

Yes. The HCV is an RNA virus, does not integrate into the host's genome, and can be permanently eradicated with a finite course of antiviral therapy. Patients that test virus-negative in blood 24 weeks after completing a course of antiviral therapy have achieved a sustained viral response (SVR). Once SVR is achieved, more than 98% of patients remain virus free for more than 15 years and likely lifelong; they are considered cured. Patients should be cautioned that reinfection is possible as humans do not develop protective immunity against the HCV.

### 6. What are the treatment options for hepatitis C infection?

Several medications are approved for the treatment of chronic hepatitis C infection. Pegylated IFN $\alpha$ -2a and IFN $\alpha$ -2b, ribavirin, telaprevir, and boceprevir are currently the most often used medications.

The combination of pegylated IFN $\alpha$ -2a or IFN $\alpha$ -2b and ribavirin constitute the backbone of therapy for chronic hepatitis C infection. IFN is an immune modulator with weak antiviral activity. Ribavirin is a nucleoside analog that enhances the antiviral activity of IFN and reduces risk of relapse after completion of therapy.

Recently small molecules known as *direct-acting antivirals* have been developed that inhibit viral replication by directly targeting steps in the life cycle of the HCV. When used together with pegylated IFN and ribavirin, these drugs greatly enhance the ability to eradicate the virus. Telaprevir and boceprevir are both first-generation protease inhibitors that inhibit replication of genotype 1 HCV and are approved by the Food and Drug Administration (FDA) to treat hepatitis C in combination with pegylated IFN and ribavirin. These protease inhibitors are specific for genotype 1 and are not approved for use in the treatment of other genotypes. Genotypes 2 through 6 are currently treated only with pegylated IFN and ribavirin (see Figure 15-1).

## 7. How are the antiviral agents dosed?

Pegylated IFN $\alpha$ -2b is dosed by weight and administered as a single subcutaneous injection once a week. Pegylated IFN $\alpha$ -2a is administered as 180 mcg subcutaneously once a week regardless of the patient's weight. IFN is administered for 24 to 48 weeks depending on virologic response (Table 15-3).

Ribavirin is dosed by weight; patients who weigh less than 75 kg should receive 1000 mg of ribavirin daily, and those who weigh 75 kg or more receive 1200 mg daily given in two divided daily doses. Patients infected with genotype 2 or 3 may be treated with a fixed ribavirin dose of 800 mg daily regardless of the patient's weight; however, weight-based ribavirin may enhance results. Ribavirin is administered for the duration of IFN therapy.

Telaprevir is dosed at 750 mg every 8 hours and should be taken with a snack that contains at least 20 g of fat to enhance absorption. Telaprevir in combination with pegylated IFN and ribavirin is administered only for the first 12 weeks of the treatment period; after that the patient completes treatment using pegylated IFN and ribavirin only.

Boceprevir is dosed at 800 mg every 8 hours with a snack or meal of any fat content. Boceprevir is added to pegylated IFN and ribavirin after week 4 of therapy and is continued until treatment week 28, 36, or 48 depending on the virologic response. The initial 4 weeks of boceprevir-free therapy is known as the "lead-in period" and allows for assessment of IFN responsiveness. Patients who experience a decline in viral load of more than  $1_{\log}$  after 4 weeks of IFN and ribavirin therapy are considered IFN responsive and are more likely to achieve a cure with completion of therapy. Those who are not IFN responsive require 48 weeks of therapy with all three drugs to maximize response (see Table 15-3).

**Table 15-3.** Viral Monitoring during Antiviral Therapy

REGIMEN	VIROLOGIC TESTING POINTS	FUTILITY RULES*	DURATION OF THERAPY†
Pegylated interferon, ribavirin and telaprevir (genotype 1 only)	Weeks 4, 12, 24 (eRVR) Week 24 posttreatment (SVR)	Week 4, 12: HCV-RNA >1000 IU/mL Week 24: any detectable virus	Naïve to treatment or prior relapse: eRVR = 24 weeks no eRVR = 48 weeks Prior partial or null response = 48 weeks Cirrhosis = 48 weeks
Pegylated interferon, ribavirin and boceprevir (genotype 1 only)	Week 4 (interferon responsiveness) Weeks 8, 24 (eRVR) Week 24 posttreatment (SVR)	Week 12: HCV-RNA $\geq$ 100 IU/mL Week 24: any detectable virus	Naïve to treatment: eRVR = 28 weeks no eRVR = 48 weeks Prior nonresponders: eRVR = 36 weeks no eRVR = 48 weeks Cirrhosis = 48 weeks
Pegylated interferon and ribavirin (genotypes 2 and 3)	Week 4 (RVR) Week 12 (EVR) Week 24 posttreatment (SVR)	Any virus at week 24	24 weeks

eRVR, Extended rapid virologic response if nondetectable at all time points; RVR, rapid virologic response if nondetectable; EVR, early virologic response if nondetectable; SVR, sustained virologic response.

\*Futility rules: If met, treatment should be discontinued.

†Telaprevir is administered only for the first 12 weeks of therapy; the remainder of the treatment course is completed with pegylated interferon and ribavirin only. Boceprevir is administered starting at week 4 of therapy and stopped at week 28, 36, or 48 of therapy depending on virologic response.

## 8. What pretreatment characteristics predict a favorable response to antiviral therapy?

- Interleukin (IL) 28b CC genotype
- Infection with genotype 2 or 3
- Low viral load (less than 400,000 IU/mL)
- Liver biopsy with little or no fibrosis
- Age younger than 40 years at time of treatment
- Low body weight, no evidence of the metabolic syndrome
- Ethnicity—black patients are less likely to respond than are whites

Polymorphisms near the IL28b region of chromosome 19 have been found to be the strongest pretreatment predictor of virologic response to pegylated IFN and ribavirin therapy. Patients with the favorable polymorphism CC are much more likely to clear acute hepatitis C infection spontaneously and to respond to IFN-based therapy compared with those with the less favorable genotypes TT or CT. IL28b polymorphisms have geographic and ethnic variability. The favorable CC genotype is most common in Asians, followed by Europeans and then Caucasians. The unfavorable genotype TT predominates in blacks. The negative predictive effect of a CT or TT polymorphism in response to therapy can be partially overcome with more potent therapies. The advantages of a CC genotype is much greater in patients treated with pegylated IFN and ribavirin compared with those treated with pegylated IFN, ribavirin, and a direct-acting antiviral such as telaprevir or boceprevir. As newer, more potent therapies are developed, the importance of the IL28b genotype, as well as that of the other predictive factors listed previously, will diminish.

## 9. How is response to antiviral therapy assessed?

Because the endpoint of therapy is virologic cure, response to therapy is assessed by measuring viral load at different points (see [Table 15-3](#)). The assay used to measure viral load should be sensitive, able to quantitate viremia down to at least 25 IU/mL and detect virus even at lower levels. The exact timing of virologic testing depends on the treatment used (see [Table 15-3](#)). When treating genotype 1 infections with triple antiviral therapy, rapid and sustained clearance of virus is known as *extended rapid virologic response* (eRVR) and correlates with enhanced cure rates. Patients achieving eRVR are often able to undergo short-duration therapy (24 to 28 weeks). Patients with delayed viral clearance have lower rates of cure and require longer therapy (up to 48 weeks) to achieve a cure. Treatment regimens also have futility rules—time points at which the presence of virus indicates failure of therapy and require cessation of treatment (see [Table 15-3](#)). Patients who have failed prior attempts at treatment with pegylated IFN and ribavirin are usually treated for 48 weeks regardless of early response.

Infections with HCV genotypes 2 through 6 are currently treated with pegylated IFN and ribavirin. Rapid virologic response is defined as non-detectable virus at week 4 of therapy and early virologic response is defined as nondetectable virus at 12 weeks (see [Table 15-3](#)).

Regardless of the genotype, once treatment is completed, virologic testing is repeated 24 weeks later. If at that point the virus continues to be negative, the patient has achieved an SVR and is considered cured.

## 10. What is the efficacy of current therapy for hepatitis C infection?

Cure rates in response to virologic therapy vary depending of the treatment regimen used, the HCV genotype, and whether the patient is naïve to treatment or has failed prior attempts at therapy. In general, for genotype 1 infection naïve to treatment, cure rates range from 68% to 75% with triple antiviral therapy.

Response is less likely in those who failed prior treatment and it depends on the type of prior response experienced. For those who cleared virus during treatment and then relapsed after prior pegylated IFN and ribavirin therapy, response to retreatment with triple therapy exceeds 80%. In contrast, those who had a partial response to the initial treatment ( $>2_{\log}$  drop in viral load after 12 weeks of therapy), have an approximately 60% cure rate with retreatment. Finally, those who had little response to the initial therapy have a 30% chance of cure when retreated with triple therapy.

Among genotype 2 and 3 infections, cure rates vary between 65% and 85% when treated with pegylated IFN and ribavirin. Response to therapy is better in genotype 2 than genotype 3 infection. Regardless of genotype, the presence of cirrhosis decreases likelihood of response to therapy.

## 11. What are the side effects of IFN therapy? How should the patient be monitored?

IFN suppresses the bone marrow, potentially resulting in leukopenia or thrombocytopenia. Complete blood counts are monitored periodically, and the dose is adjusted as needed. Other side effects that can diminish quality of life include flulike symptoms, headaches, fever, depression, anxiety, sexual dysfunction, hair loss, insomnia, and fatigue. Evening administration and preinjection acetaminophen or ibuprofen can reduce the flulike symptoms.

Depression requires close monitoring. Patients with a history of severe depression or suicidal ideation or attempts should not be treated with IFN, unless under the care of a mental health professional. Patients who have required pharmacologic therapy for mild depression in the past may benefit from initiation of

antidepressants before treatment with IFN. Selective serotonin reuptake inhibitors usually are successful in reversing mild to moderate IFN-associated depression. Severe depression is an indication for immediate cessation of therapy and emergent psychiatric consultation. Close monitoring for suicidal ideation is mandatory in all patients, even those without prior history of depression.

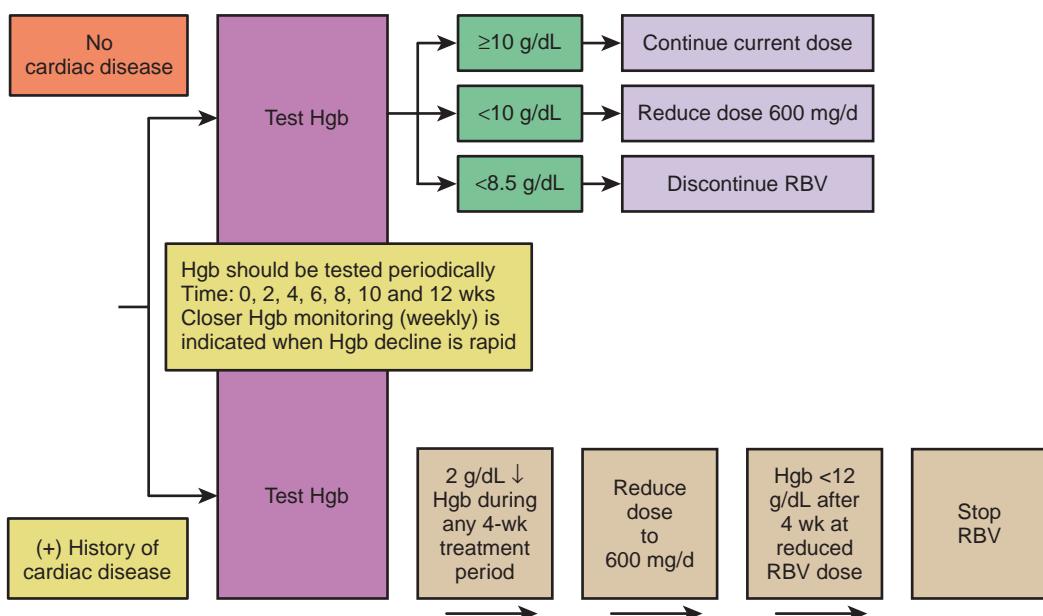
Hypothyroidism is an irreversible side effect of IFN. Levels of thyroid-stimulating hormone should be determined before initiation of therapy and at regular intervals during treatment. IFN is contraindicated during pregnancy.

## 12. What are the side effects of ribavirin therapy? How should the patient be monitored?

Ribavirin can cause hemolysis and may rapidly lead to symptomatic anemia. A reduction in hemoglobin to 10 g/dL or less, if associated with symptoms, should trigger ribavirin dose reduction. If the hemoglobin decreases to 8.5 g/dL or less, temporary discontinuation of ribavirin is advised (Figure 15-2). For patients with known ischemic cardiac disease, much closer monitoring is recommended, with reduction or discontinuation of therapy if the hemoglobin decreases by more than 2 g/dL compared with baseline.

Other side effects from ribavirin include rash, shortness of breath, nausea, sore throat, cough, and glossitis. The rash may be severe and require discontinuation of the medication. The other side effects are generally not life-threatening and can be treated symptomatically.

Because ribavirin is teratogenic, both men and women should be advised to practice effective contraception during therapy and for 6 months after completion.



**Figure 15-2.** Ribavirin dose modifications for the management of anemia. *Hgb*, Hemoglobin; *RBV*, ribavirin; *wk*, weeks.

## 13. What are the side effects of telaprevir and boceprevir?

Telaprevir worsens the anemia caused by ribavirin, likely by enhancing IFN's bone marrow suppression, leading to a diminished bone marrow response to hemolysis. As a result, a rapid and significant drop in hemoglobin is often seen early during therapy, nadir hemoglobin levels usually occur by week 12 of therapy. Hemoglobin levels should be monitored every 7 to 14 days initially and ribavirin dose reduction used to manage the anemia. A hemoglobin decrease below 10 g/dL requires reduction of ribavirin dose to 600 mg daily, and a hemoglobin level below 8.5 g/dL may require temporary discontinuation of ribavirin. When ribavirin dose is reduced in response to anemia, there is no decrease in sustained response rates. Telaprevir dose is never reduced to manage side effects.

Rash is another common side effect of telaprevir, and may be severe. Rash or pruritus develops in more than 50% of treated patients, but in the majority of patients the rash is mild and does not require drug discontinuation. In mild cases, management consists of topical steroids and systemic antihistamines; systemic corticosteroids should not be used. In less than 10% a severe rash involving more than 50% of the body surface develops and requires discontinuation of telaprevir. If systemic symptoms are absent, IFN and ribavirin should be continued and the patient carefully monitored. In less than 5% of patients, discontinuation of all three medications is

necessary for patients with severe or serious rash. Rare cases of serious rash events such as drug reaction with eosinophilia and systemic symptoms or Stevens-Johnson syndrome have been described, including reports of deaths secondary to skin reactions. The likelihood of serious skin events can be decreased by careful patient monitoring once rash develops and prompt discontinuation of telaprevir in patients with severe rash.

Other side effects from telaprevir that rarely lead to therapy discontinuation include gastrointestinal symptoms such as nausea and diarrhea, and anorectal discomfort. These can be easily managed with symptomatic therapy.

Boceprevir side effects consist mainly of anemia and dysgeusia or changes in taste. The anemia with boceprevir therapy is similar in onset and severity to that seen with telaprevir and is managed in the same way. Dysgeusia has no specific management; although it may contribute to weight loss during therapy, it rarely leads to treatment interruption. Boceprevir therapy is not associated with an increased incidence in skin problems. Like telaprevir, boceprevir dose is never reduced to manage side effects.

Both telaprevir and boceprevir are metabolized by the cytochrome P450 3A4/5. This leads to frequent interactions with other drugs. Although only a few drugs are contraindicated in combination with telaprevir or boceprevir (Table 15-4), the blood levels of many others may be affected. Consultation with a pharmacist is recommended for patients on multiple drugs.

**Table 15-4.** Drugs Contraindicated during Treatment with Telaprevir or Boceprevir

DRUG	EFFECT
Alfuzosin	Higher levels of alfuzosin
Lovastatin	Higher levels of lovastatin
Simvastatin	Higher levels of simvastatin
Rifampin	Lower levels of telaprevir or boceprevir
Ergot derivatives	Higher levels of ergot derivatives
St. John's wort	Lower levels of telaprevir or boceprevir
Pimozide	Higher levels of pimozide
Oral midazolam	Higher levels of midazolam
Sildenafil or tadalafil for the treatment of pulmonary hypertension	Higher levels of sildenafil or tadalafil
Carbamazepine*	Lower levels of boceprevir
Phenobarbital*	Lower levels of boceprevir
Phenytoin*	Lower levels of boceprevir
Drospirenone†	Risk of hyperkalemia with boceprevir

\*Contraindicated only with boceprevir but may also lower telaprevir blood levels.

†Contraindicated only with boceprevir.

#### 14. What are the contraindications to IFN therapy?

- IFN should not be used in patients who already have leukopenia or thrombocytopenia because of the potential for bone marrow suppression. It is not recommended for patients with decompensated cirrhosis because it is less effective and may worsen liver disease.
- Patients with severe depression, history of suicide attempt or ideation, psychosis, or personality disorders should not be treated or should receive treatment only under the close monitoring of a psychiatrist. Patients with manic depression do poorly with IFN therapy and should not be treated unless their psychiatric condition is well controlled and they are under the care of a psychiatrist.
- Autoimmune diseases such as rheumatoid arthritis, sarcoidosis, and systemic lupus erythematosus pose a relative contraindication to therapy. Psoriasis can worsen during therapy.
- IFN therapy should not be administered during pregnancy. If hepatitis C infection is diagnosed during pregnancy, treatment should be initiated only after delivery and breastfeeding have been completed.
- Patients with advanced comorbid conditions should not be offered antiviral therapy for hepatitis C. Hepatitis C infection progresses slowly over time. If the patient has a life expectancy of less than 5 to 10 years, treating the hepatitis C infection is less likely to be of benefit.

- Patients who have received an organ transplant other than liver should not receive IFN as the risk of rejection is increased.

#### **15. What are the contraindications to ribavirin therapy?**

Because ribavirin must be used with IFN, all contraindications to IFN apply to treatment with ribavirin. In addition, there are specific contraindications to ribavirin:

- Pregnancy is an absolute contraindication because of the teratogenic potential.
- Anemia and hemoglobinopathies should be considered relative contraindications. Extreme care should be exercised in treating such patients. As a rule, women with a hemoglobin less than 12 g/dL or men with less than 13 g/dL before therapy are at high risk of developing severe anemia during therapy.
- Patients with known ischemic heart disease should be treated with caution and monitored closely.
- Patients with renal insufficiency should not be treated with ribavirin because the development of severe, long-lasting, and life-threatening hemolysis is common.

#### **16. What are the contraindications to telaprevir and boceprevir?**

Because telaprevir or boceprevir must be used with IFN and ribavirin, all contraindications to IFN and ribavirin apply to treatment with these agents. Otherwise, there are very few specific contraindications to telaprevir or boceprevir.

- Telaprevir or boceprevir must be used together with ribavirin and IFN. If either ribavirin or IFN is permanently discontinued, telaprevir or boceprevir must be discontinued as well.
- Telaprevir or boceprevir should not be used in conjunction with medications that pose a severe drug-drug interaction potential (see Table 15-4).
- Because resistance patterns to telaprevir and boceprevir are similar, patients who failed to respond to one agent should not be treated with the other, as failure of retreatment is likely.

#### **17. Are there any specific considerations regarding contraception when using telaprevir or boceprevir?**

Yes. Both telaprevir and boceprevir lower blood levels of hormonally based contraceptives and diminish their efficacy. As a result, women patients of childbearing age must use two forms of nonhormonal contraception while taking telaprevir or boceprevir. Periodic pregnancy testing is recommended during treatment with ribavirin and for 6 months after completion of therapy.

#### **18. Should patients with cirrhosis secondary to hepatitis C infection be treated with antiviral therapy?**

Patients with compensated cirrhosis (normal albumin and bilirubin levels; normal prothrombin time; and no ascites, encephalopathy, or history of variceal bleeding) are excellent candidates for antiviral therapy. Once liver insufficiency develops or complications of portal hypertension become clinically evident, antiviral therapy is relatively contraindicated. Evaluation for liver transplantation is a better option for such patients.

For patients with compensated disease, the main concern during antiviral therapy is worsening of preexisting leukopenia or thrombocytopenia caused by hypersplenism. Leukopenia is managed with IFN dose reductions. Thrombocytopenia usually responds to eltrombopag, an oral thrombopoietin receptor agonist, or reduction of IFN dose. Reduction of IFN dose may decrease effectiveness of therapy; for that reason, the use of eltrombopag is preferred.

#### **19. Should patients with HCV-HIV coinfection receive antiviral therapy for hepatitis C infection?**

Coinfection with HIV and HCV results in marked acceleration of progression of liver disease. With the advent of newer, more effective antiretroviral agents, patients infected with HIV are living longer, and more are developing end-stage liver disease from HCV infection. For this reason, patients coinfected with HIV and HCV should be considered candidates for antiviral therapy against HCV.

Anti-HCV therapy is most likely to be effective if the patient is first placed on antiretroviral therapy, the HIV viral load is controlled, and the CD4 count is reconstituted. In general, patients with a CD4 count of less than  $250/\text{mm}^3$  are less likely to respond to antiviral therapy for HCV.

Anti-HCV therapy in patients receiving anti-HIV medications is complicated by the additive bone marrow suppression as well as other gastrointestinal side effects. Interactions between ribavirin and several antiretroviral agents may increase the risk of lactic acidosis; cotherapy with didanosine or stavudine plus ribavirin is strongly discouraged because of the increased risk of lactic acidosis. Zidovudine, although not contraindicated when used with IFN and ribavirin, will enhance bone marrow suppression and increase the need for growth factor therapy to correct anemia and leukopenia. Close monitoring of blood counts and chemistries is needed. Lower dose of ribavirin (800 mg daily) is recommended when treating patients coinfected with HIV to decrease the incidence of severe anemia. At this time, the use of boceprevir or telaprevir is not approved by the FDA for the treatment of HCV-HIV coinfection. There are significant drug-drug interactions between these agents and many antiretroviral drugs. Expert consultation is recommended.

## 20. How should patients with HCV-HBV coinfection be treated?

Because most patients with HCV-HBV coinfection have quiescent hepatitis B infection, the antiviral therapy need be directed only at the HCV. If active hepatitis B and C infection are present, as evidenced by a positive HCV-RNA and high-level viremia by HBV-DNA polymerase chain reaction assay, the patient should be treated with the recommended dose of IFN for hepatitis B in conjunction with ribavirin and direct acting agents against hepatitis C if indicated. A flare of hepatitis may occur when treating patients with hepatitis B infection.

Alternatively, the addition of a nucleoside or nucleotide analog active against hepatitis B infection could be considered (see Chapter 16).

## 21. How should patients who cleared HCV be monitored?

Patients who remain virus-negative 24 weeks after completion of antiviral therapy have achieved an SVR24 and can be considered cured. Although there is a 1% chance of relapse, repeated monitoring of HCV-RNA beyond week 24 posttreatment is not needed. Patients should be informed that they will remain HCV antibody-positive for many years, likely for life; thus only testing for HCV-RNA will determine whether there has been a relapse or re-infection. Likewise, patients should be cautioned that they are not immune against hepatitis C and re-exposure could lead to reinfection.

Patients with cirrhosis who achieve a cure after treatment should be clearly informed that the risk for hepatocellular carcinoma remains unchanged for at least the next 5 to 7 years after a cure. Continued monitoring every 6 months for hepatocellular carcinoma is mandatory. While the likelihood of progression of cirrhosis or development of new complications related to portal hypertension are unlikely after a cure, appropriate monitoring is recommended.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

1. Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. *Gastroenterology* 2012;142:1293–302.
2. Chou R, Wesson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. *Ann Intern Med* 2013;158:807–20.
3. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. *J Hepatol* 2011;55:245–64.
4. Ghany MC, Nelson DR, Strader DB, et al. An update of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011;54:1433–44.
5. Jacobson IM, Cacoub P, Dal Maso L, et al. Manifestations of chronic hepatitis C virus infection beyond the liver. *Clin Gastroenterol Hepatol* 2010;8:1017–29.
6. Jacobson IM, Pawlotsky JM, Afdhal NH. A practical guide for the use of boceprevir and telaprevir for the treatment of hepatitis C. *J Viral Hepat* 2012;19(Suppl. 2):1–26.
7. Jesudason AB, De Jong YP, Jacobson IM. Emerging therapeutic targets for hepatitis C virus infection. *Clin Gastroenterol Hepatol* 2013;11:612–9.
8. Lange CM, Zeuzem S. IL28b single nucleotide polymorphisms in the treatment of hepatitis C. *J Hepatol* 2011;55:692–701.
9. Maheshwari A, Thuluvath PJ. Management of acute hepatitis C. *Clin Liver Dis* 2011;14:169–76.
10. Mangia A. Individualizing treatment duration in hepatitis C virus genotype 2/3 infected patients. *Liver Int* 2011;31:36–41.
11. McHutchison JG, Dusheiko G, Shiffman ML, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med* 2007;357:2227–36.
12. Ng V, Saab S. Effects of a sustained virologic response on outcomes of patients with chronic hepatitis C. *Clin Gastroenterol Hepatol* 2011;9:923–30.
13. Sulkowski M, Pol S, Mallolas J, et al. Boceprevir plus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomized, double-blind, controlled phase 2 trial. *Lancet Infect Dis* 2013;13:597–605.
14. Sulkowski MS, Sherman KE, Dieterich DT, et al. Combination therapy with telaprevir for chronic hepatitis C virus genotype 1 in patients with HIV. *Ann Intern Med* 2013;159:86–96.
15. Talal AH, LaFleur J, Hoop R, et al. Absolute and relative contraindications to pegylated interferon or ribavirin in the US general patient population with chronic hepatitis C: results from a US database of over 45,000 HCV-infected evaluated patients. *Aliment Pharmacol Ther* 2013;37:473–81.

## Websites

Centers for Disease Control and Prevention. Hepatitis C information for health professionals. <http://www.cdc.gov/hepatitis/HCV/index.htm> [Accessed September 22, 2014].

U.S. Department of Veterans Affairs. Viral hepatitis. <http://www.hepatitis.va.gov/provider/hcv/index.asp> [Accessed September 22, 2014].

# ANTIVIRAL THERAPY FOR HEPATITIS B

Jorge L. Herrera, MD

## 1. Is antiviral therapy recommended for acute hepatitis B?

No. Acute hepatitis B, defined as a positive test for hepatitis B surface antigen (HBsAg) and the presence of hepatitis B core antibody-immunoglobulin M (HBcAb-IgM; [Table 16-1](#)), is a self-limited disease in more than 95% of adults and resolves without specific antiviral therapy within 3 to 6 months after the onset of clinical symptoms. For this reason, only supportive care is offered to patients with acute hepatitis B infection. Antiviral therapy is considered only for patients with chronic hepatitis B (positive HBsAg test for longer than 6 months). For patients with severe acute hepatitis B with evidence of liver dysfunction such as coagulopathy or encephalopathy, antiviral therapy may be considered; in this situation, expert consultation is advised.

## 2. Do all patients with chronic hepatitis B benefit from therapy?

No. Only patients with detectable viremia and evidence of ongoing hepatic necrosis, such as elevated liver enzyme levels or liver biopsy demonstrating active inflammation or fibrosis, are most likely to benefit from therapy ([Figure 16-1](#)). Typical candidates for antiviral therapy have high levels of hepatitis B virus (HBV) DNA by polymerase chain reaction (PCR) assays (more than 2000 to 20,000 IU/mL). In contrast, patients in the low-replicative phase of chronic hepatitis B infection, characterized by normal levels of liver enzymes, negative HBeAg, positive HBeAb, and nondetectable or low levels (<2,000 IU/mL) of HBV-DNA by PCR, do not require antiviral therapy but should be monitored for evidence of disease reactivation (see [Table 16-1](#)).

**Table 16-1.** Antiviral Therapy for Patients with Chronic Hepatitis B Infection

SEROLOGIC PATTERN	INTERPRETATION	COURSE OF ACTION
HBsAg-positive, HBcAb-IgM-positive	Acute hepatitis B	Observe; resolution likely in 90%-95% of adults
HBsAg-positive >6 mo, HBeAg-positive, HBeAb-negative, HBV-DNA >20,000 IU/mL, elevated ALT level	Chronic infection with wild virus	Initiate antiviral therapy
HBsAg-positive >6 mo, HBeAg-negative, HBeAb-positive, ALT normal, HBV-DNA-negative, or low-level viremia (<2000 IU/mL)	Low replicative stage	Observe
HBsAg-positive >6 mo, HBeAg-negative, HBeAb-positive, HBV-DNA >2000 IU/ml, elevated ALT level	Chronic infection with HBeAg mutant	Initiate antiviral therapy
HBsAg-positive >6mo, HBeAg-positive, HBeAb-negative, HBV-DNA levels >200,000 IU/mL, normal ALT levels, no inflammation or fibrosis on biopsy, age <30 years	Immune tolerant phase of chronic hepatitis B infection	Observe, do not treat until patient enters chronic infection stage

ALT, alanine aminotransferase; HBcAb-IgM, hepatitis B core antibody-immunoglobulin M; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV-DNA, hepatitis B virus DNA by polymerase chain reaction; IU, international units.

## 3. How should the HBV-DNA by PCR assay results be used to make therapy decisions?

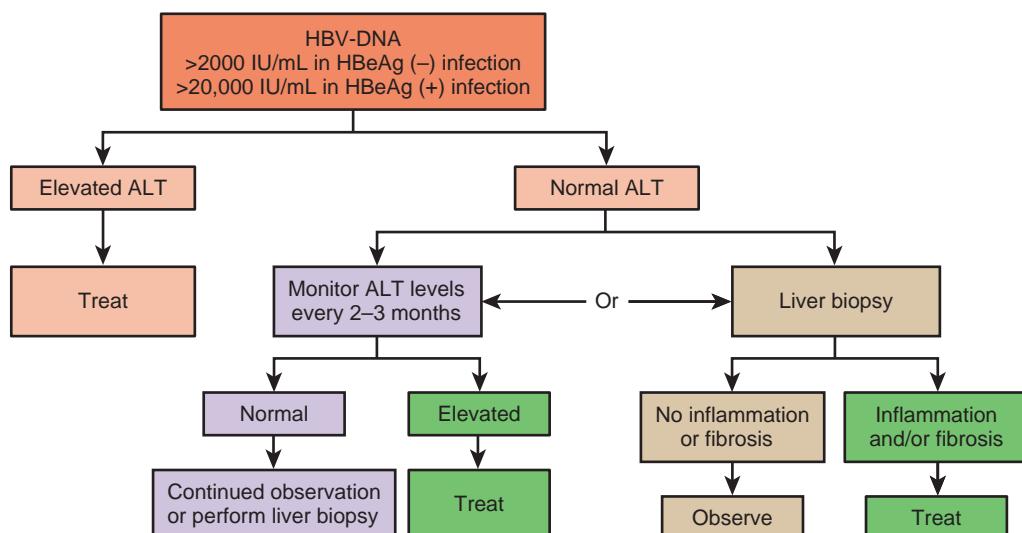
Hepatitis B infection is almost never totally eradicated. Instead, it can be controlled with medications. Treatment is indicated when the viral load is high and there is evidence of ongoing liver damage. Low levels of HBV-DNA in the absence of inflammation are not associated with progressive liver disease and do not require therapy. The upper limit of HBV-DNA levels that are consistently associated with inactive disease has not been clearly established, but it is generally agreed that treatment is not necessary when viral levels are nondetectable or consistently less than 2000 IU/mL, associated with normal alanine aminotransferase (ALT) levels or a liver biopsy showing no inflammation. It is important to note that in some cases, particularly in HBeAg-negative

disease, viral levels can fluctuate over time and multiple measurements may be necessary to confirm that levels remain at less than 2000 IU/mL. In patients with advanced liver disease, particularly decompensated cirrhosis, treatment should be considered if any detectable virus is noted, regardless of how low the reading may be.

Most importantly, a decision to initiate therapy should not only be based on viral load, but also requires evidence of ongoing hepatic damage (elevated ALT or liver biopsy showing inflammation or fibrosis). Young patients (<30 years old) in the immune-tolerant stage of hepatitis B infection, characterized by very high viral loads (>200,000 IU), e-antigen positive, normal levels of ALT, and a normal liver biopsy, are typically not treated with antiviral agents despite high levels of viremia (see [Table 16-1](#)).

#### 4. Is liver biopsy required before therapy is started?

A liver biopsy is not needed to establish the diagnosis of hepatitis B infection; however, it is an important tool to determine severity and activity of disease. Treatment decisions are different for patients with advanced fibrosis and cirrhosis compared with those with mild histologic disease. The risk of liver cancer and the intensity of surveillance for liver cancer would be greater for those patients with cirrhosis. The detection of cirrhosis on liver biopsy selects a group of patients who require closer observation as well as screening for esophageal varices. A liver biopsy is also important for patients who have high viral load (>2000 IU/mL) but normal liver enzymes. The presence of inflammation or fibrosis on biopsy is a strong indicator that therapy should be considered. The role of liver biopsy in the decision to treat HBV infection is shown in [Figure 16-1](#).



**Figure 16-1.** Algorithm for the treatment of chronic hepatitis B infection. ALT, Alanine aminotransferase; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus.

#### 5. What is the role of the hepatitis B e antigen in determining need for treatment?

The hepatitis B e antigen has traditionally been considered to be a marker of high viral replication. Although this is true for the “wild” HBV, a large number of patients are infected with mutated forms of the HBV that do not produce e-antigen despite high levels of viral replication. Thus although a positive e-antigen is a marker of high viral load, a negative e-antigen does not always indicate a low viral load. E-antigen mutant viruses do not replicate as efficiently as the e-antigen positive wild strain; for this reason viral levels in e-antigen-negative patients are typically lower and fluctuate more than in e-antigen-positive infections. Because of these differences, the level of HBV-DNA, and not the e-antigen status, is used to determine the need for therapy. However, because e-antigen-negative mutants replicate less efficiently, a lower threshold is used to determine the need for therapy in these cases. For e-antigen-positive infections, an HBV-DNA level of more than 20,000 IU/mL is considered high; in contrast, for e-antigen-negative mutant infections, a level of more than 2000 IU/mL is considered high. This distinction between e-antigen-negative and e-antigen-positive patients is controversial and not all published guidelines are in agreement. Some guidelines consider an HBV-DNA level of more than 2000 IU/mL high regardless of the e-antigen status. An algorithm for the treatment of hepatitis B infection is outlined in [Figure 16-1](#).

#### 6. What are the available options for treating chronic hepatitis B infection?

Currently, seven medications have been approved for the treatment of chronic hepatitis B infection: interferon  $\alpha$ 2b, pegylated interferon  $\alpha$ 2a, lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxil fumarate. Based on potency and barrier to resistance, current guidelines recommend that treatment-naïve patients should be treated with either entecavir, tenofovir, or pegylated interferon  $\alpha$ 2a; the other approved

medications either lack potency or have a low barrier to resistance, and are not considered optimal choices for initial treatment. The properties and dosing of the three preferred drugs to treat hepatitis B infection are shown in Table 16-2.

**Table 16-2.** Preferred Drugs for the Treatment of Hepatitis B Infection

	PEGYLATED INTERFERON α-2A	ENTECAVIR	TENOFOVIR
Potency	++	++++	++++
e-Antigen seroconversion (1 yr)	≈30%	≈15%-25%	≈15%-25%
<b>Duration of Treatment</b>			
HBeAg (+) chronic hepatitis	52 wk	≥1 year (until e-antigen seroconversion)	≥1 year (until e-antigen seroconversion)
HBeAg (-) chronic hepatitis	52 wk	Indefinite	Indefinite
Route	Subcutaneous	Oral	Oral
Dose	180 mcg weekly	0.5 mg daily* on an empty stomach	300 mg daily without regard to food
Side effects	Common and expected	Uncommon, similar to placebo	Uncommon, similar to placebo
Drug resistance	None reported	<1% by 5 years in naïve patients, up to 40% after 4 years in lamivudine-resistant patients	No resistance reported after 5 years in naïve or lamivudine-resistant patients

HBeAg, Hepatitis B e antigen;

\*1 mg daily for lamivudine-resistant infection or prior nonresponse to the 0.5-mg dose.

Interferon is an injectable immunomodulatory and antiviral medication. Although it has a relatively weak antiviral effect, it enhances clearance of the HBV by improving immune detection and clearance of infected hepatocytes. Unfortunately, its use is associated with frequent side effects.

Entecavir is an oral nucleoside analogue and tenofovir is an oral nucleotide analogue. Both are dosed once a day and inhibit viral replication without enhancing immune response. Entecavir and tenofovir are very potent and in treatment-naïve patients have a high barrier to resistance. After 5 years resistance to entecavir is observed in less than 1% of patients and so far resistance to tenofovir has not been documented. The side effect profile is excellent and similar to placebo. Because of the ease of administration and the low likelihood of side effects, most patients in the United States are treated with oral agents rather than interferon.

## 7. What are the endpoints of antiviral therapy?

The goals of antiviral therapy are to suppress viral replication and prevent liver damage. In addition to viral suppression, there are certain serologic endpoints that signal response to therapy. For patients who are e-antigen-positive at the initiation of therapy, induction of e-antigen seroconversion (defined as achieving HBeAg-negative, HBeAb-positive status) is a major milestone. After e-antigen seroconversion is achieved, antiviral therapy is continued for an additional 24 to 48 weeks and then may be discontinued. In this situation, remission is usually long-lasting, but as long as the patient continues to test positive for HBsAg, he or she is at risk of reactivation and should be monitored closely.

Patients who are viremic but e-antigen-negative at initiation of therapy will require lifelong therapy. Even after 5 or more years of nondetectable HBV-DNA levels on therapy, discontinuation of antiviral therapy results in reactivation of disease in the majority of patients. For this reason, when a decision is made to treat e-antigen-negative disease, treatment is usually lifelong or until the patient loses HBsAg, which is a rare event in chronic e-antigen-negative infection.

During treatment with entecavir or tenofovir, clearance of HBsAg in e-antigen-positive patients is uncommon. After 5 years of therapy, only 7% to 9% clear surface antigen and are considered cured. In contrast, clearance of the surface antigen during oral therapy in e-antigen-negative infection is extremely rare. Because

interferon has immunomodulatory effects, the chance of clearing surface antigen is somewhat greater in responders. Among patients who experience a substantial decrease in viral load during interferon therapy (viral load <2000 IU/mL at the end of therapy), approximately 30% will lose surface antigen when followed for up to 5 years after completing interferon therapy.

#### **8. What is the expected response to interferon therapy?**

Because interferon stimulates the immune response, increased clearance of the HBV is expected during therapy. Clearance of the virus is achieved by immune-mediated necrosis of infected hepatocytes. Thus a flare of hepatitis may be seen during treatment with interferon. The flare typically occurs soon after initiation of interferon therapy and is manifested by elevated levels of ALT and aspartate aminotransferase. The flare may be accompanied by jaundice and signs and symptoms typical of acute viral hepatitis but is associated with reduction or disappearance of HBV-DNA in blood. As the liver enzyme levels return to normal, the HBeAg assay becomes negative, followed by seroconversion to positive HBeAb. The virologic response is often long-lasting if e-antigen seroconversion is achieved. Positive predictors of response to interferon therapy include HBeAg-positive patients, low viral levels, elevated ALT levels (>150 IU/mL), infection with HBV genotype A, and absence of cirrhosis. Seroconversion to HBeAg-negative and HBeAb-positive status occurs in approximately 30% of patients treated with interferon; the majority of responders have a durable response.

#### **9. What is the expected response to oral nucleoside or nucleotide therapy?**

In contrast to interferon, nucleosides and nucleotides inhibit viral replication but do not stimulate immune clearance of the virus. For this reason, immune-mediated hepatocyte necrosis is unusual, and biochemical flare of hepatitis is rarely seen with these agents. In most patients, the HBV-DNA serum level decreases dramatically or becomes undetectable soon after initiating therapy. This decrease is associated with normalization of liver enzyme levels. Seroconversion from HBeAg-positive to HBeAg-negative status and from HBeAb-negative to HBeAb-positive status during the first year of therapy is less common than with interferon therapy. After 4 to 5 years of continuous oral antiviral therapy, rates of e-antigen seroconversion approach or exceed those seen with interferon therapy.

Response to therapy should be monitored with HBV-DNA levels and liver enzymes. When treated with entecavir or tenofovir, the majority of patients will achieve nondetectable levels of HBV-DNA within 24 to 48 months. Because these agents have a high barrier to resistance, a rise in HBV-DNA of more than  $1_{\log}$  during therapy usually indicates lack of compliance rather than emergence of resistant mutants.

#### **10. What are the advantages of interferon therapy for chronic hepatitis B infection?**

Therapy with interferon is of finite duration (52 weeks in most cases) and is successful in 15% to 30% of selected patients. Successful response is durable, and relapses are rare once interferon is discontinued. Once the HBV infects the liver cell, the HBV genome localizes to the nucleus of the hepatocyte and is converted to covalently closed circular DNA. Clearance of this HBV-DNA is needed to achieve HBsAg seroconversion and can be only achieved by immune-mediated lysis of infected hepatocytes. Cases of HBsAg seroconversion (HBsAg status becomes negative and HBsAb status becomes positive) have been documented years after inducing e-antigen seroconversion by interferon. Finally, interferon resistance has not been described.

#### **11. What are the disadvantages of interferon therapy?**

Interferon therapy is associated with significant side effects, including flulike syndrome, fever, depression, insomnia, irritability, and bone marrow suppression (see Chapter 15). The interferon-induced flare of hepatitis may be severe and is particularly dangerous in patients with advanced liver disease and cirrhosis, who may not be able to tolerate a flare of hepatitis. For this reason, interferon therapy is relatively contraindicated in patients with cirrhosis caused by chronic hepatitis B infection and is absolutely contraindicated in patients with decompensated cirrhosis secondary to hepatitis B infection.

Another disadvantage is that patients with persistently normal liver enzyme levels, those who acquired the disease at birth, and those infected with HBV genotype C or D are unlikely to respond to interferon therapy.

#### **12. Which parameters predict a good response to interferon therapy?**

Patients likely to respond to interferon therapy are characterized by elevated liver enzymes (ALT > 150 U/dL), low viral load (HBV-DNA <  $2.0 \times 10^8$  IU/mL), HBV genotype A, positive HBeAg status, female sex, and acquisition of infection during adulthood. Such patients have a 30% to 40% chance of achieving e-antigen seroconversion after a 52-week course of interferon. In contrast, patients with normal or minimal elevations of liver enzymes have a less than 5% chance of achieving sustained remission.

#### **13. What are the advantages of oral nucleoside and nucleotide therapy?**

Oral agents are taken once daily and are associated with minimal to no side effects. They have potent antiviral activity and in more than 98% of cases achieve a profound decrease in viremia with normalization of the liver enzymes. Oral agents can be safely used in patients with decompensated liver disease at times, with dramatic responses.

#### **14. What are the disadvantages of oral nucleoside and nucleotide therapy?**

The treatment course is long; most patients require treatment for multiple years; and in the case of e-antigen–negative disease, treatment is usually lifelong. The cost of these medications is significant. Oral agents have a lower rate of HBeAg seroconversion compared with interferon; however, with prolonged therapy, e-antigen seroconversion rates approach those of interferon therapy. Relapse is common once therapy is discontinued, particularly in e-antigen–negative disease. Development of resistance, although rare with entecavir and not yet documented with tenofovir, is always a concern with long-term use.

#### **15. Should patients with advanced, decompensated cirrhosis secondary to hepatitis B receive antiviral therapy or be referred for liver transplantation without a trial of therapy?**

Although patients with decompensated disease cannot be treated with interferon, treatment with nucleoside or nucleotide analogs is beneficial and often lifesaving. In many such patients, evidence of severe decompensation reverses, and patients no longer need to be listed for liver transplantation after a response to antiviral therapy. In addition, oral therapy, when continued after transplantation in conjunction with hepatitis B immune globulin, is associated with a decreased chance of recurrence of infection in the graft. In general, patients with severe liver disease caused by hepatitis B infection, in addition to listing for transplantation, should be treated with oral nucleosides or nucleotides. Once a response is achieved, lifelong therapy is recommended as flares induced by discontinuation of antiviral therapy could be fatal in these patients.

#### **16. How should response to therapy be monitored?**

After initiation of therapy, repeat viral load should be performed at 3-month intervals. After achieving viral reduction to less than 2000 IU/mL and normalization of the liver tests, testing should be repeated at least every 6 months for the duration of therapy to document sustained response. Because development of resistance is very rare, a rise in viral load of more than  $1_{\log}$  during therapy most often occurs when patients are not compliant with the medication regimen. *All oral nucleoside and nucleotide antivirals are renally excreted, and dosing should be adjusted when renal function is compromised.* For that reason, renal function should be assessed prior to therapy and monitored at least once a year and the dose of the oral antiviral agent adjusted if renal insufficiency is present.

#### **17. Can therapy reverse fibrosis or cirrhosis?**

Yes, continued viral suppression with oral nucleotide or nucleoside therapy has been shown to reverse fibrosis and improve liver histologic findings in a substantial number of patients. After 5 years of tenofovir therapy in hepatitis B e-antigen–negative and e-antigen–positive patients, histologic improvement was noted in 87%, and regression of fibrosis in 51%. Of the patients with cirrhosis at baseline, 74% no longer had cirrhosis after 5 years of therapy with tenofovir. Similar results have been shown in a smaller number of patients with prolonged entecavir therapy.

#### **18. Are treatment decisions for hepatitis B infection different if patients are immune suppressed?**

The immune system plays a pivotal role in the control of hepatitis B infection. Patients who are HBsAg-positive but have no detectable viremia or low level of virus can promptly reactivate if immunosuppressed. If immunosuppression is planned (i.e., cancer chemotherapy, anti-tumor necrosis factor therapy, high-dose corticosteroid therapy, etc.), patients should be screened for HBsAg. If positive, initiation of antiviral therapy with a nucleoside or nucleotide analog is indicated even if HBV-DNA is nondetectable and the ALT level is normal. Ideally, antiviral therapy should be started 2 to 4 weeks before or at the time of the introduction of the immunosuppressant and continued for at least 6 to 12 months after completion of immunosuppression. Patients who would have met criteria for hepatitis B therapy before immunosuppression (i.e., high viral load, elevated ALT) should continue on long-term antiviral therapy even after immunosuppression ceases until traditional endpoints of treatment are achieved.

#### **19. How should HBV infection be treated in patients coinfecte<sup>d</sup> with the human immunodeficiency virus (HIV)?**

Most of the antiviral agents currently available for the treatment of hepatitis B have activity against HIV. *Initiation of monotherapy for HBV in patients with known or undiagnosed HIV can lead to emergence of HIV-resistant mutants.* All patients infected with HBV should be tested for HIV. If coinfecte<sup>d</sup> with HIV, they should be evaluated for highly active antiretroviral therapy (HAART). Current HIV treatment guidelines consider the presence of hepatitis B infection an indication to initiate HAART. Selection of a HAART regimen that includes at least two drugs active against HBV (i.e., tenofovir and emtricitabine or lamivudine) is recommended. Patients coinfecte<sup>d</sup> with HBV and HIV should not receive lamivudine as the only HBV-active drug in the HAART regimen, as HBV resistance to lamivudine develops rapidly.

#### **20. Should hepatitis B be treated during pregnancy?**

Hepatitis B infection is vertically transmitted. The introduction of the hepatitis B vaccine and hepatitis B immune globulin injection for babies born to HBsAg-positive mothers has markedly decreased vertical transmission of HBV but has not eliminated the risk. A high maternal viral load ( $>10^{6-7}$  copies/mL or  $>200,000$  IU/mL) has been associated with an increased risk of vertical transmission. Even when appropriate passive and active immunization is used at birth, 7% to 9% of children born to mothers with high viral load will

develop chronic hepatitis B infection. Limited clinical research suggests that lowering the viral load during the last trimester of pregnancy decreases the risk of vertical transmission.

The choice of antiviral agent to use during pregnancy is difficult; none of the currently approved drugs to treat hepatitis B have been formally tested during pregnancy. Pegylated interferon is contraindicated. Lamivudine, entecavir, and adefovir are classified as Class C pregnancy drugs by the Food and Drug Administration (FDA). *Telbivudine and tenofovir are Class B pregnancy drugs.* Extensive experience exists with lamivudine therapy during pregnancy in HIV-infected patients. This experience indicates that lamivudine appears safe and is not associated with an increased incidence of birth defects. Significant experience also exists with tenofovir use. Pregnancy registries include more than 2000 patients who have received tenofovir at some point during pregnancy with good results. The experience with telbivudine is more limited but also appears to be safe if used during the last trimester of pregnancy. None of these drugs are FDA approved for use in pregnancy. Based on limited data, tenofovir, telbivudine, and lamivudine seem to be safe, but long-term follow up of exposed children is not available. The benefits and potential risks of initiating antiviral therapy during pregnancy must be carefully discussed and documented with all parties involved.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

1. Buster EH, Hansen BE, Lau GK, et al. Factors that predict response of patients with Hepatitis B e antigen-positive chronic hepatitis B to peginterferon alfa. *Gastroenterology* 2009;137:2002–9.
2. Coppola N, Tonziello G, Pisaturo M, et al. Reactivation of overt and occult hepatitis B infection in various immunosuppressive settings. *J Med Virol* 2011;83:1909–16.
3. Dusheiko G. Treatment of HBeAg positive chronic hepatitis B: interferon or nucleoside analogues. *Liv Int* 2013;33 (Suppl. 1):137–50.
4. European Association for the Study of the Liver (EASL). EASL clinical practice guidelines: management of chronic hepatitis B infection. *J Hepatol* 2012;57:167–85.
5. Gambarin-Gelwan M. Hepatitis B in pregnancy. *Clin Liver Dis* 2007;11:945–63.
6. Ko HK, Wong DK, Heathcote J. Management of hepatitis B. *Clin Gastroenterol Hepatol* 2011;9:385–91.
7. Lampertico P, Vigano M, Colombo M. Why do I treat HBeAg-negative chronic hepatitis B patients with pegylated interferon? *Liv Int* 2013;33(Suppl. 1):157–63.
8. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open label follow up study. *Lancet* 2013;381:468–75.
9. Martin-Carbonero L, Poveda E. Hepatitis B virus and HIV infection. *Semin Liver Dis* 2012;32:114–9.
10. Pan CQ, Duan ZP, Bhamidimarri KR, et al. An algorithm for risk assessment and intervention of mother to child transmission of hepatitis B virus. *Clin Gastroenterol Hepatol* 2012;10:452–9.
11. Rijckborst V, Sonneveld MJ, Janssen HL. Review article: chronic hepatitis B—anti-viral or immunomodulatory therapy? *Aliment Pharmacol Therapeut* 2011;33:501–13.
12. Scaglione SJ, Lok AS. Effectiveness of hepatitis B treatment in clinical practice. *Gastroenterology* 2012;142:1360–8.
13. Singal AK, Fontana RJ. Meta-analysis: oral anti-viral agents in adults with decompensated hepatitis B virus cirrhosis. *Aliment Pharmacol Therapeut* 2012;35:674–89.
14. Wen WH, Chang MH, Zhao LL, et al. Mother to infant transmission of hepatitis B virus infection: significance of maternal viral load and strategies for intervention. *J Hepatol* 2013;59:24–30.
15. Woo G, Tomlinson G, Nishikawa Y, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. *Gastroenterology* 2010;139:1218–29.

## Websites

Centers for Disease Control and Prevention. Hepatitis B information for health professionals. <http://www.cdc.gov/hepatitis/HBV/> [Accessed September 22, 2014].  
 Hepatitis Foundation International. <http://www.hepatitisfoundation.org> [Accessed September 22, 2014].

# AUTOIMMUNE HEPATITIS: DIAGNOSIS

Albert J. Czaja, MD

## 1. What is autoimmune hepatitis (AIH)?

AIH is an unresolving inflammation of the liver of unknown cause that is characterized by interface hepatitis on histologic examination, autoantibodies, and hypergammaglobulinemia. There are no disease-specific features, and the designation requires the exclusion of other conditions, including chronic viral hepatitis, Wilson disease, drug-induced hepatitis (most commonly, minocycline or nitrofurantoin toxicity), alcoholic and nonalcoholic fatty liver disease, and the immune-mediated cholangiopathies of primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC; Table 17-1).

## 2. What are its principal clinical and laboratory features?

AIH affects mainly women (71%) and occurs at any age (most commonly before the age of 40 years). Smooth muscle antibodies (SMAs) and antinuclear antibodies (ANAs), occurring alone (44% and 13%, respectively) or together (43%), are the principal serologic findings in North American adults. Antibodies to liver kidney microsome type 1 (anti-LKM1) occur in 14% to 38% of European children, usually exclusive of SMA and ANA, and they are present in 4% or fewer of North American adults. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) abnormalities predominate, and hypergammaglobulinemia, especially an increased serum immunoglobulin G (IgG) level, is another hallmark. Concurrent immune diseases are present in 38% (especially autoimmune thyroiditis, Graves disease, or ulcerative colitis) (Table 17-2).

## 3. What are the symptoms of AIH?

The major symptoms of AIH are fatigue and arthralgia. Jaundice is usually indicative of an acute severe disease or a chronic indolent process with advanced fibrosis, and it occurs in 69% of these patients. AIH is asymptomatic at presentation in 25% to 34%, but symptoms emerge later in 26% to 70%. Features of chronic severe cholestasis (pruritus and hyperpigmentation) must redirect the diagnostic effort.

## 4. What are the characteristic histologic findings in AIH?

Interface hepatitis is the *sine qua non* for the diagnosis of AIH. The limiting plate of the portal tract is disrupted by a lymphocytic infiltrate, which extends into the lobule (Figure 17-1). Plasma cells are present in 66% of the inflammatory infiltrates, but they are neither specific nor required for the diagnosis (Figure 17-2). Hepatocyte rosettes and emperipoleisis (penetration of one cell into and through a larger cell) are also characteristic histologic features. Centrilobular (Rappaport zone 3) necrosis probably represents an early acute stage or an acute injury on chronic disease (Figure 17-3). Most patients (78%) with centrilobular necrosis have interface hepatitis, and cirrhosis may be present. Lymphoid and pleomorphic cholangitis (not destructive cholangitis) is present in 7% to 9%.

## 5. Can AIH have an acute or acute severe (fulminant) presentation?

Yes. AIH has an acute presentation, defined as the abrupt onset symptoms coincident with the onset or discovery of the disease, in 25% to 75% of patients. An acute severe (fulminant) presentation, defined as the development of hepatic encephalopathy within 26 weeks of disease discovery, occurs in 6% of North American patients.

## 6. What are the clinical features of an acute or acute severe (fulminant) presentation?

Symptoms may resemble an acute viral or toxic hepatitis, and the classical phenotype of AIH may be unrecognizable. The serum IgG level is normal in 25% to 39%, ANAs are absent or weakly demonstrated in 29% to 39%, and serum  $\gamma$ -globulin levels are lower than in chronic presentations. Centrilobular hemorrhagic necrosis with lymphoplasmacytic infiltration, lymphoid aggregates, or plasma cell infiltration is the main histologic finding in acute severe (fulminant) AIH, and unenhanced computed tomography of the liver may disclose heterogeneous hypoattenuated areas in 65% (versus 0%-5% in virus-induced acute liver failure).

## 7. Which patients are most difficult to diagnose?

Infants, older adults, patients with acute or acute severe (fulminant) presentations, and nonwhite patients have AIH that can be unsuspected, confused with other diseases, or atypical. Patients aged 60 years and older constitute 23% of adults with AIH, but their disease may be masked by concurrent thyroid, rheumatic, or other

**Table 17-1.** Differential Diagnosis of Autoimmune Hepatitis and Discriminative Tests

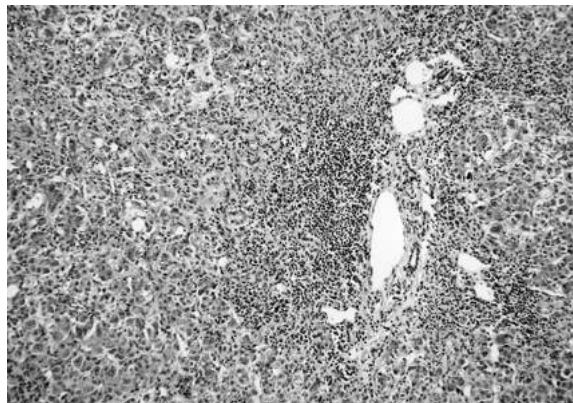
DIFFERENTIAL DIAGNOSIS	DIAGNOSTIC ASSESSMENTS	DIAGNOSTIC FINDINGS
$\alpha_1$ -Antitrypsin deficiency	Phenotyping	ZZ (strongest association) MZ, MS, SZ (probably comorbid factors)
	Liver biopsy	Diastase-resistant PAS-positive intrahepatocyte globules
Chronic viral hepatitis	Serologic tests	HBsAg, HBV-DNA Anti-HCV, HCV RNA
	Liver biopsy	Ground-glass hepatocytes Viral inclusions Portal lymphoid aggregates Steatosis
Drug-induced hepatitis	Clinical history	Recent exposure to medication, nutritional supplements, or herbal agents (especially, minocycline or nitrofurantoin)
	Clinical behavior	Acute idiosyncratic reaction Resolves after drug withdrawal No recurrence
	Liver biopsy	Little or no hepatic fibrosis Portal neutrophils Intracellular cholestasis
Hemochromatosis	Genetic testing	C282Y and H63D mutations Positive family history
	Iron studies	Transferrin saturation index, >45%
	Liver biopsy	Increased iron by stain Hepatic iron index >1.9
Nonalcoholic steatohepatitis	Clinical findings	Obesity (BMI >30 kg/m <sup>2</sup> ) Type 2 diabetes Hyperlipidemia
	Hepatic ultrasonography	Hyperechogenicity
	Liver biopsy	Macrosteatosis Mallory-Denk bodies Megamitochondria Absent apoptotic bodies Ballooned hepatocytes
Primary biliary cirrhosis	Genetic tests	PNPLAS3 gene (investigational)
	Serologic tests	AMA titer $\geq$ 1:40 Antipyrurate dehydrogenase-E2
	Liver biopsy (see Figure 17-5)	Destructive cholangitis (florid duct lesion) Increased hepatic copper concentration
Primary sclerosing cholangitis	Cholangiography (see Figure 17-6)	Focal biliary strictures and dilations
	Liver biopsy (see Figure 17-7)	Ductopenia Portal fibrosis and edema Fibrous obliterative cholangitis (rare)
Wilson disease	Copper studies	Low ceruloplasmin Low serum copper level High urinary copper excretion
	Slit lamp eye examination	Kayser-Fleischer rings
	Liver biopsy	Increased hepatic copper concentration
	Genetic tests	ATP7B gene (chromosome 13q14.3) $\geq$ 200 disease-causing mutations H1069Q mutation

AMA, Antimitochondrial antibodies; ATP7B, ATPase copper transporting beta polypeptide; BMI, body mass index; C282Y, mutation within *HFE* gene associated with substitution of tyrosine for cysteine at amino acid position 282 in  $\alpha_1$  loop; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; H63D, mutation within *HFE* gene associated with substitution of histidine for aspartate at amino acid position 63 in  $\alpha_1$  loop; H1069Q, mutation within ATP7B gene of Wilson disease in which histidine is replaced by glutamic acid at position 1069; HFE, high iron Fe gene; PAS, periodic-acid-Schiff; PNPLAS3, adiponutrin/patatin-like phospholipase domain-containing protein 3 gene associated with hepatic fat accumulation; ZZ, MZ, MS, and SZ, major protease inhibitor (PI) deficiency phenotypes associated with  $\alpha_1$ -antitrypsin deficiency.

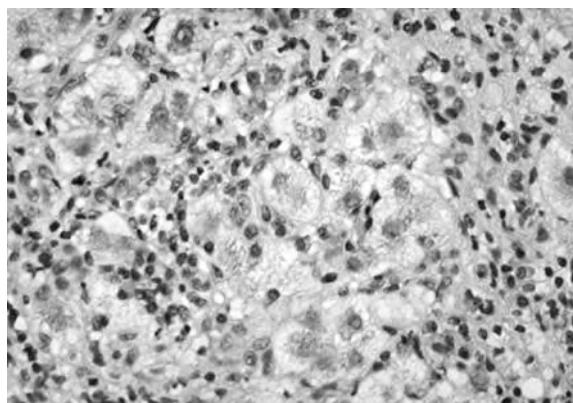
**Table 17-2.** Concurrent Immune-mediated Diseases Associated with Autoimmune Hepatitis

Autoimmune sclerosing cholangitis	Lichen planus
Autoimmune thyroiditis*	Myasthenia gravis
Celiac disease	Neutropenia
Coombs-positive hemolytic anemia	Pericarditis
Cryoglobulinemia	Peripheral neuropathy
Dermatitis herpetiformis	Pernicious anemia
Erythema nodosum	Pleuritis
Fibrosing alveolitis	Pyoderma gangrenosum
Focal myositis	Rheumatoid arthritis*
Gingivitis	Sjögren syndrome
Glomerulonephritis	Synovitis*
Graves disease*	Systemic lupus erythematosus
Idiopathic thrombocytopenic purpura	Ulcerative colitis*
Insulin-dependent diabetes	Urticaria
Intestinal villous atrophy	Vitiligo
Iritis	

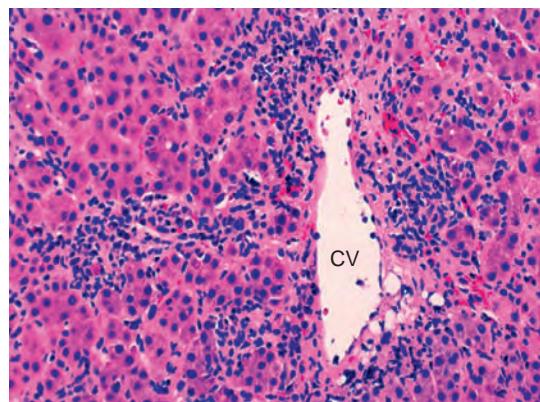
\*Most common association.



**Figure 17-1.** Interface hepatitis. The limiting plate of the portal tract is disrupted by inflammatory infiltrate (hematoxylin and eosin, original magnification  $\times 100$ ).



**Figure 17-2.** Plasma cell infiltration. Plasma cells, identified by the cytoplasmic haloes about their nucleus, infiltrate the periportal region (hematoxylin and eosin, original magnification  $\times 400$ ).



**Figure 17-3.** Centrilobular (zone 3) necrosis. Inflammatory and degenerative changes concentrate around the central vein (CV) and involve the centrilobular or Rappaport zone 3 region of the liver tissue (hematoxylin and eosin, original magnification,  $\times 200$ ).

diseases. These patients also frequently have an acute onset that can be mistakenly attributed to liver toxicity associated with polypharmacy. Nonwhite patients may be unsuspected because of prominent cholestatic features, male occurrence, different age predilections, and failure to meet the diagnostic criteria developed for white North American and European patients.

#### 8. What are the different types of AIH?

Two types predominate in the clinical jargon based on distinctive serologic markers (Table 17-3). These types do not define subgroups of different etiologic factor or prognosis, and they have not been endorsed by the international societies. They are clinical descriptors that denote a clinical phenotype and maintain homogeneity of study populations. Type 1 AIH is characterized by SMA or ANA, and it is the most common form worldwide. Antibodies to actin (antiactin) also support the diagnosis. Type 2 AIH is characterized by anti-LKM1, and it denotes mainly young (ages, 2 to 14 years), white, European patients. Antibodies to liver cytosol type 1 (anti-LC1) also support this diagnosis. Anti-LKM1 and anti-LC1 typically do not coexist with SMA and ANA.

#### 9. What are the clinical criteria for diagnosis?

The *definite diagnosis* requires predominant serum AST or ALT abnormalities, serum  $\gamma$ -globulin or IgG levels greater than 1.5-fold the upper limit of the normal (ULN) range, the presence of SMA, ANA, or anti-LKM1 in titers greater than 1:80 by indirect immunofluorescence (IIF) or strong positivity by enzyme immunoassay (EIA), and histologic features of interface hepatitis with or without plasma cell infiltration (Table 17-4). Viral, heredity, drug-induced, alcohol-related, and metabolic disorders must be excluded. The *probable diagnosis* is based on similar, but less pronounced or certain, findings.

#### 10. What are the diagnostic scoring systems for AIH?

The *comprehensive diagnostic scoring system* for AIH ensures the systematic assessment of all key clinical features of AIH. It evaluates 12 clinical components and renders 27 possible scores. Response to corticosteroid therapy is scored, and the treatment outcome influences the diagnosis (Table 17-5). A *simplified diagnostic scoring system* has been developed for easy clinical application. It evaluates only four clinical components and renders seven possible grades (Table 17-6). It is based on the presence and level of autoantibody expression, serum IgG concentration, histologic features, and viral markers. It does not grade treatment outcome.

#### 11. What are the performance parameters of the diagnostic scoring systems?

The comprehensive scoring system has greater sensitivity for the diagnosis of AIH than the simplified scoring system (100% versus 95%), but the simplified scoring system has superior specificity (90% versus 73%) and predictability (92% versus 82%). Clinical judgment has been the “gold standard” against which performance has been measured, and it always supersedes the results of the scoring systems. The comprehensive scoring system is useful in evaluating patients with absent or atypical features in which every component must be assessed. The simplified scoring system is useful in excluding AIH in patients who have concurrent immune features. The scoring systems have not been validated prospectively, and they should be used mainly to support clinical judgment.

**Table 17-3.** Types of Autoimmune Hepatitis

FEATURES	TYPE 1	TYPE 2
Autoantibodies	Smooth muscle Nucleus Actin $\alpha$ -Actinin (investigational) Soluble liver antigen	Liver/kidney microsome type 1 Liver cytosol type 1 Liver/kidney microsome type 3
	Atypical pANCA	
Organ-specific antibodies	Thyroid	Thyroid Parietal cells Islets of Langerhans
Target autoantigen	Unknown	CYP2D6 (P450 IID6)
HLA associations	B8, DRB1*03, DRB1*04	DQB1*02, DRB1*07, DRB1*03, B14
Susceptibility alleles	DRB1*0301, DRB1*0401 (North American and northern Europe) DRB1*04 alleles (Japan, China, Mexico) DRB1*1301 (South America)	DQB1*0201 (principal) DRB1*0701 DRB1*03 C4A-Q0
Predominant age	Adult	Childhood (2-14 years)
Acute onset	25%-75%	Possible
Acute severe (fulminant) onset	6% (North American patients)	Possible
Concurrent immune disease	38%	34% Autoimmune sclerosing cholangitis (children)
Progression to cirrhosis	36%	82%
Corticosteroid responsive	Yes	Yes

CYP, cytochrome mixed-function oxygenase; HLA, human leukocyte antigen; LKM1, liver/kidney microsome type 1; pANCA, perinuclear antineutrophil cytoplasmic antibodies.

## 12. What is the standard serologic battery for diagnosis?

ANA, SMA, and anti-LKM1 are the standard diagnostic markers of AIH (Table 17-7). They do not connote prognosis, and they cannot be used to monitor treatment response. ANA, SMA, and anti-LKM1 have sensitivities of 32%, 16%, and 1%, respectively, for AIH in North American adults, and their diagnostic accuracy ranges from 56% to 61%. The combination of ANA and SMA at presentation has superior sensitivity (43%), specificity (99%), positive predictability (97%), negative predictability (69%), and diagnostic accuracy (74%) to each marker alone. Serum titers of 1:320 or more have high diagnostic specificity (91%-99%) but low sensitivity (29%-43%). Weak positivity (titer, 1:40) cannot be ignored, and some patients with AIH may lack the conventional markers.

## 13. What serologic assays are best for detecting the standard autoantibodies?

Assays based on IIF are regarded as the “gold standards” of serologic diagnosis in liver disease, but EIAs based on recombinant antigens are less time- and labor-intensive and less prone to intraobserver interpretative error than assays based on IIF. The antigens recognized by the semiautomated EIA kits may not be the same antigens detected by IIF; the strength of the reactivity and the clinical implication of the result may not correlate with those obtained by IIF; and there are no mechanisms to convert results between assays. EIAs are replacing IIFs in most North American medical centers.

## 14. What other autoantibodies may have diagnostic and prognostic implications?

Multiple autoantibodies have been described in AIH, but none has been incorporated into a codified diagnostic algorithm. These serologic markers are ancillary diagnostic tools (see Table 17-7). Antibodies to soluble liver antigen (anti-SLA) have high specificity (99%) for AIH but low sensitivity (16%). They identify individuals with severe disease who are treatment dependent, and they have a strong association with DRB1\*0301 (concurrence, 83%) and antibodies to Ro/SSA (concurrence, 96%). Antibodies to actin (anti-actin) are a subset of SMA that

**Table 17-4.** Codified Diagnostic Criteria for Autoimmune Hepatitis

DIAGNOSTIC TESTS	DEFINITE DIAGNOSIS	PROBABLE DIAGNOSIS
Autoantibodies	Serum ANA, SMA, or anti-LKM1 $\geq 1:80$ titer (confident EIA level uncertain) Absent AMA	Titers $\geq 1:40$ Titers negative but anti-SLA, anti-LC1, or atypical pANCA positive
Biochemical tests	Increased serum AST and ALT levels ULN Serum AP level $\leq$ twofold ULN Normal serum ceruloplasmin level Normal $\alpha_1$ -antitrypsin phenotype	Same as for definite
Immunoglobulin levels	Serum $\gamma$ -globulin or IgG levels $\geq 1.5$ ULN	Any abnormal value
Liver tissue examination	Interface hepatitis No biliary lesions or granulomata No changes indicating alternative diagnosis	Same as for definite
Toxic exposures	No hepatotoxic drugs Alcohol consumption $<25$ g daily	Previous but not recent drugs or alcohol Alcohol consumption $<50$ g daily
Viral markers	No serologic markers for hepatitis A, B, and C	Same as definite

ALT, Alanine aminotransferase; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; AP, alkaline phosphatase; AST, aspartate aminotransferase; EIA, enzyme immunoassay; IgG, immunoglobulin G; LC1, liver cytosol type 1; LKM1, liver kidney microsome type 1; pANCA, perinuclear antineutrophil cytoplasmic antibodies; SLA, soluble liver antigen; SMA, smooth muscle antibodies; ULN, upper limit of the normal range.

\*Adapted from the report of the International Autoimmune Hepatitis Group, *J Hepatol* 31:929–938, 1999.

**Table 17-5.** Revised Original Scoring System for the Diagnosis of Autoimmune Hepatitis

CLINICAL FEATURES	SCORE	CLINICAL FEATURES	SCORE
Female	+2	Average alcohol intake $<25$ g/day	+2
		$>60$ g/day	-2
AP: AST (or ALT) ratio $<1.5$	+2	Histologic findings Interface hepatitis	+3
1.5-3.0	0	Lymphoplasmacytic infiltrate	+1
$>3.0$	-2	Rosette formation	+1
		Biliary changes	-3
		Other atypical changes	-3
		None of above	-5
Serum $\gamma$ -globulin or IgG level ULN $>2.0$	+3	Concurrent immune disease	+2
1.5-2.0	+2	Other AIH-related autoantibodies	+2
1.0-1.5	+1	HLA DRB1*03 or DRB1*04	+1
$<1.0$	0		
ANA, SMA, or anti-LKM1 $>1:80$	+3	Response to corticosteroids Complete	+2
1:80	+2	Relapse after drug withdrawal	+3
1:40	+1		
$<1:40$	0		
AMA positive	-4	Aggregate score posttreatment Definite AIH	$>15$
		Probable AIH	10-15
Hepatitis markers Positive	-3	Aggregate score pretreatment Definite AIH	$>17$
Negative	+3	Probable AIH	12-17
Hepatotoxic drug exposure Positive	-4		
Negative	+1		

AIH, Autoimmune hepatitis; ALT, alanine aminotransferase; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; AP, alkaline phosphatase; AST, aspartate aminotransferase; HLA, human leukocyte antigen; IgG, immunoglobulin G; LKM1, liver/kidney microsome type 1; SMA, smooth muscle antibodies; ULN, upper limit of the normal range.

\*Adapted from the revised original scoring system of the International Autoimmune Hepatitis Group, *J Hepatol* 31:929–938, 1999.

**Table 17-6.** Simplified Scoring System of the International Autoimmune Hepatitis Group

FEATURES	RESULT	POINTS
<b>Autoantibodies</b>		
Antinuclear antibodies or smooth muscle antibodies	≥1:40	+1
Antibodies to liver/kidney microsome type 1	≥1:80	+2
Antibodies to soluble liver antigen	≥1:40 Positive	+2 +2
<b>Immunoglobulin Level</b>		
Immunoglobulin G	>Upper limit of normal >1.1 times upper limit of normal	+1 +2
<b>Histologic Findings</b>		
Morphologic features	Compatible with AIH Typical of AIH	+1 +2
<b>Viral Infection</b>		
Absence of viral hepatitis	No viral markers	+2
Diagnostic scores	Definite AIH Probable AIH	≥7 6

AIH, autoimmune hepatitis.

\*Adapted from the simplified scoring system of the International Autoimmune Hepatitis Group, *Hepatology* 48:169–176, 2008.**Table 17-7.** Autoantibodies Associated with Autoimmune Hepatitis

AUTOANTIBODY SPECIES	FEATURES
<b>Standard Serologic Battery</b>	
Antinuclear antibodies	Type 1 AIH Reactive to multiple nuclear antigens Lacks disease or organ specificity
Smooth muscle antibodies	Type 1 AIH Reactive to actin (mainly) and nonactin components Frequently associated with ANA Lacks disease or organ specificity
Antibodies to liver/kidney microsome type 1	Type 2 AIH Target antigen, CYP2D6 Typically unassociated with ANA and SMA May occur in chronic hepatitis C
<b>Ancillary Serologic Battery</b>	
Antibodies to soluble liver antigen	Antigenic target is Sep [O-phosphoserine] tRNA:Sec [selenocysteine] tRNA synthase High specificity (99%) but low sensitivity (16%) for AIH Associated with DRB1*0301 Can indicate severe disease and relapse after treatment Frequently coexists with anti-Ro/SSA
Antibodies to actin	Diagnostic specificity better than SMA Associated with SMA Commonly young patients Immune reactive region, $\alpha$ -actinin Aggressive disease (if antibodies to $\alpha$ -actinin present) Nonstandardized assay
Antibodies to liver cytosol type 1	Type 2 AIH Young patients Possibly worse prognosis May be sole serologic marker of AIH Directed against formiminotransferase cyclodeaminase

Continued on following page

**Table 17-7.** Autoantibodies Associated with Autoimmune Hepatitis (Continued)

AUTOANTIBODY SPECIES	FEATURES
Atypical perinuclear antineutrophil cytoplasm	Common in type 1 AIH Absent in type 2 AIH Common in CUC and PSC Atypical because reactive against nuclear membrane May be useful in otherwise seronegative patients
<b>Investigational Serologic Markers</b>	
Antibodies to asialoglycoprotein receptor	Generic marker of AIH Correlates with histologic activity Disappears with resolution of AIH during treatment Associated with relapse after drug withdrawal Promising EIA based on recombinant subunit (H1) of ASGPR

AIH, Autoimmune hepatitis; ANA, antinuclear antibody; anti-Ro/SSA, antibodies to ribonucleoprotein/Sjögren's syndrome A antigen; ASGPR, asialoglycoprotein receptor; CUC, chronic ulcerative colitis; EIA, enzyme immunoassay; PSC, primary sclerosing cholangitis; SMA, smooth muscle antibody.

react against filamentous (F) actin, and they have greater specificity for AIH than SMA. An assay that detects "double reactivities" against  $\alpha$ -actinin and F-actin promises to identify individuals with severe clinical and histologic disease. Antibodies to liver cytosol type 1 (*anti-LC1*) occur mainly in young patients, and they are detected in 32% of patients with anti-LKM1. They have been associated with severe disease, and they may be the sole marker in 14% of European patients with AIH. They are rare in North American adults.

#### 15. What autoantibodies should be sought if the usual markers are absent?

Atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA) are present in 49% to 92% of patients with AIH who lack anti-LKM1 (see Table 17-7). They are also common in patients with chronic ulcerative colitis or PSC. Atypical pANCA can indicate the possibility of AIH in patients who lack other autoantibodies. IgA antibodies to tissue transglutaminase (tTG) or endomysium are valuable in excluding celiac disease. Celiac disease can coexist with AIH or be associated with a liver disease that resembles AIH. All presentations of AIH can be mimicked by celiac disease, and this diagnosis must be excluded in all seronegative patients that otherwise resemble AIH.

#### 16. What investigational autoantibodies have promise as diagnostic and prognostic markers?

Antibodies to asialoglycoprotein receptor (*anti-ASGPR*) are present in 82% of patients with SMA or ANA, 67% of patients with anti-LKM1, and 67% of patients with anti-SLA (see Table 17-7). They are associated with histologic activity and the propensity to relapse after corticosteroid withdrawal. The ASGPR receptor is composed of two subunits (H1 and H2), and an EIA based on recombinant H1 may prove useful in monitoring the treatment response.

#### 17. What is the significance of antimitochondrial antibodies (AMAs) in AIH?

AMAs can be present in 7% to 34% of patients with AIH, and antibodies to the E2 subunit of the pyruvate dehydrogenase complex can be demonstrated in 8%. Histologic findings may be similar to those of patients without AMA, and the AMA can persist or disappear in the absence of cholestatic clinical or laboratory features. The occurrence of AMA does not compel a change of diagnosis or treatment in these patients as observation intervals up to 27 years have not demonstrated a transition to PBC. The possibility of PBC or transition to PBC must always be considered, and patients with PBC can have features that resemble AIH ("overlap syndrome").

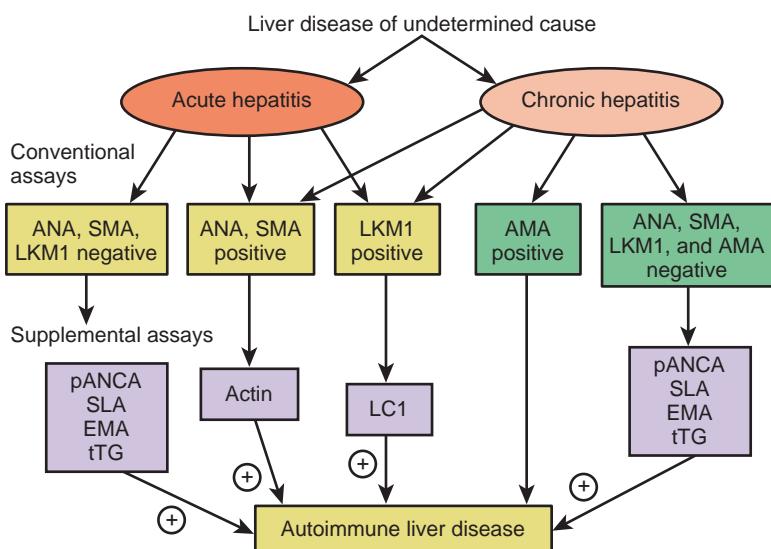
#### 18. Is there an autoantibody-negative AIH?

Yes. Thirteen percent of adults with chronic cryptogenic hepatitis satisfy the diagnostic criteria for AIH but lack the conventional autoantibodies. These patients are similar by age, gender, human leukocyte antigen (HLA) phenotype, laboratory findings, and histologic features to patients with classical AIH. They may also respond as well to corticosteroid therapy, entering remission as commonly (83% versus 78%) and failing treatment as infrequently (9% versus 11%). Some may express SMA or ANA later or have other autoantibodies (anti-SLA, anti-LC1, or pANCA). Nonalcoholic fatty liver disease and celiac disease must be excluded. The comprehensive diagnostic scoring system (see Table 17-5) can be useful in securing the diagnosis.

#### 19. What is the appropriate testing sequence for autoantibodies?

All patients with acute and chronic hepatitis of undetermined cause should be assessed for ANA, SMA, and anti-LKM1. Adults with chronic hepatitis of undetermined cause should also be assessed for AMA (Figure 17-4). Patients who lack these markers should undergo a second battery of tests that include determinations of atypical pANCA, anti-SLA, and IgA antibodies to tTG or endomysium. Patients strongly suspected of having bile duct disease who are AMA negative by IIF should be assessed for antibodies to the E2 subunits of the pyruvate

**Figure 17-4.** Serologic testing sequence for diagnosing autoimmune liver disease in patients with acute or chronic hepatitis of undetermined cause. The conventional serologic battery includes antinuclear antibodies (ANA), smooth muscle antibodies (SMA), antibodies to liver/kidney microsome type 1 (LKM1), and antimitochondrial antibodies (AMA). Supplemental serologic tests to confirm or further direct the diagnosis include atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA), antibodies to soluble liver antigen (SLA), antibodies to liver cytosol type 1 (LC1), and antibodies for celiac disease, including immunoglobulin A antibodies to endometrium (EMA) and tissue transglutaminase (tTG).



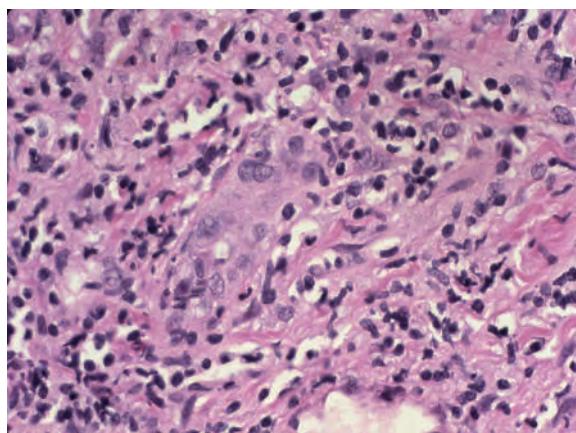
dehydrogenase complex by EIA. The conventional testing battery of ANA, SMA, and anti-LKM1 should be repeated in seronegative patients because these autoantibodies may be expressed later. Once detected, autoantibodies do not need to be reassessed.

## 20. When should AIH be considered?

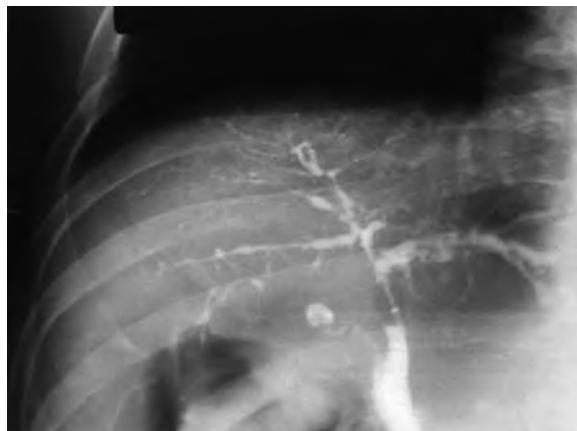
AIH should be considered whenever acute, acute severe (fulminant), or chronic hepatitis is encountered or graft dysfunction develops after liver transplantation. AIH recurs in at least 17% of patients after liver transplantation, and it develops de novo in 3% to 5% of children and adults who are transplanted for nonautoimmune liver disease. The frequency of recurrence increases with the time after transplantation, affecting 8% to 12% of patients at 1 year and 36% to 68% after 5 years. The aggressiveness of untreated AIH and the responsiveness of this disease to conventional corticosteroid treatment mandate that it be considered in all patients with acute or chronic liver disease of undetermined nature.

## 21. What are the overlap syndromes of AIH?

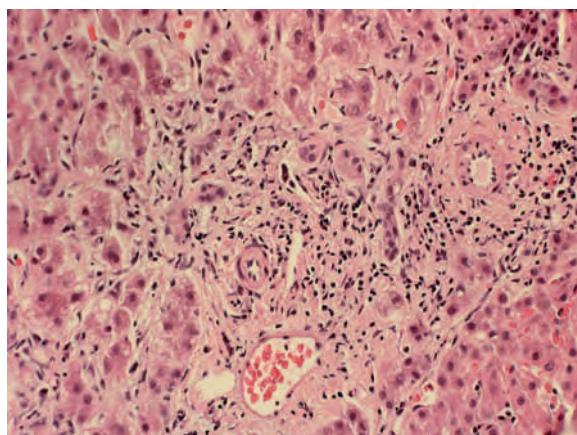
The overlap syndromes of AIH are popular designations for patients with predominant features of AIH and ancillary cholestatic features that may resemble PBC or PSC. Patients with AIH may have AMA and histologic findings of bile duct injury or loss that suggest PBC (Figure 17-5). They may have an absence of AMA and a cholangiogram that suggests PSC (Figure 17-6), or they may have a cholestatic syndrome characterized by the absence of AMA, normal cholangiogram, and histologic features of bile duct injury or loss (Figure 17-7). This latter category probably includes patients with AMA-negative PBC and small duct PSC. Their major value is to characterize patients with predominant features of AIH who have variable responses to conventional corticosteroid therapy.



**Figure 17-5.** Destructive cholangitis (florid duct lesion). Lymphocytic and histiocytic inflammatory cells destroy the bile duct. The histologic pattern suggests the possibility of primary biliary cirrhosis (hematoxylin and eosin, original magnification  $\times 400$ ).



**Figure 17-6.** Endoscopic retrograde cholangiogram disclosing features of primary sclerosing cholangitis. Focal biliary strictures and dilations are demonstrated.



**Figure 17-7.** Ductopenia. Portal tract contains a venule, fibrosis, edema, and arteriole, but there is no evidence of a bile duct. Cholangioles proliferate at the periphery of the portal tract. The histologic pattern suggests the possibility of primary sclerosing cholangitis (hematoxylin and eosin, original magnification  $\times 200$ ).

## 22. What is the frequency of the overlap syndromes of AIH?

The estimated frequency of the overlap syndromes of AIH is 14% to 20%, and composites of reported experiences indicate that the frequencies of AIH with features of PBC, features of PSC, and features of an indeterminate cholestatic nature are 2% to 13%, 2% to 11%, and 5% to 11%, respectively. These frequencies are probably overestimated because the overlap syndromes lack codified diagnostic criteria; the diagnostic scoring systems of AIH are commonly misapplied to patients with PBC or PSC to define the overlaps, and patients with PBC or PSC with features of AIH are equated with patients with AIH and features of PBC or PSC.

## 23. What are the “Paris criteria” for the overlap syndrome with PBC?

The “Paris criteria” characterize patients with PBC and overlapping features of AIH, and they were endorsed with modification by the European Association for the Study of the Liver. All patients must have interface hepatitis, and they must also have a serum ALT level fivefold or more of the ULN, serum IgG level twofold or more of the ULN, or SMAs. The PBC component must have two of three features, including serum alkaline phosphatase level twofold or more of the ULN or  $\gamma$ -glutamyl transferase level fivefold or more of the ULN, AMA, and florid duct lesions on histologic examination. Only 1% of patients with PBC satisfy these criteria, and individuals with less pronounced features are not accommodated by these criteria.

## 24. What are the caveats in diagnosing the overlap syndromes?

The major caveat is to recognize that patients with AIH and features of PBC or PSC have different phenotypes and outcomes than patients with PBC or PSC and features of AIH. Each syndrome should be designated by its predominant component. The diagnostic scoring systems for AIH should not be used to define AIH in patients with PBC or PSC as they have not been validated for this purpose. The features of AIH are not

disease-specific. The rarity of an overlap between PBC and PSC suggests that most overlap syndromes constitute a classical disease with nonspecific inflammatory features that resemble AIH. The appendage of AIH to a patient with PBC or PSC is probably presumptuous.

#### **25. Is the diagnosis of AIH more difficult in children?**

Yes. Children with AIH are commonly asymptomatic, their serologic markers may be weakly expressed, and AIH may not be suspected. ANA, SMA, or anti-LKM1 in any titer or level is pathologic in children, and children are more likely to express anti-LKM1 than adults (14%-38% versus 4%). Testing for only ANA and SMA in children may misdirect the diagnosis. Children may also have concurrent *autoimmune sclerosing cholangitis* in the absence of inflammatory bowel disease or cholestatic clinical features, and this consideration lowers the threshold for cholangiography.

#### **26. Can drugs cause an autoimmune-like hepatitis?**

Yes. Minocycline and nitrofurantoin are the principal drugs that have been implicated in current practice, accounting for 90% of all drug-induced autoimmune-like hepatitis (Table 17-8). Other drugs that have been well documented to cause a liver injury indistinguishable from classical AIH are infrequently used (dihydralazine, halothane, methyldopa) or withdrawn from the market (oxyphenisatin, tienilic acid). Numerous other drugs, nutritional supplements, herbal medicines, and environmental pollutants (trichloroethylene) have been proposed, and the possibility of drug-induced liver injury must be considered in all patients with AIH. The frequency of drug-induced autoimmune-like hepatitis among patients with classical features of AIH is 9%.

#### **27. How is drug-induced autoimmune-like hepatitis distinguished from classical disease?**

Drug-induced autoimmune-like hepatitis is typically an acute idiosyncratic reaction (66%) with low frequency of cirrhosis at presentation (0%). It fully resolves after discontinuation of the drug, and it does not recur unless rechallenged. Suppositions that the drug potentiates or unleashes latent AIH cannot be discounted, but such occurrences must be rare. In contrast, classical AIH is self-perpetuating and does not resolve after drug withdrawal. It has a low frequency of acute onset (16%-25%), high occurrence of advanced fibrosis or cirrhosis at presentation (16%-28%), and high frequency of recurrence or relapse after corticosteroid withdrawal (50%-87%). Portal neutrophils and intracellular cholestasis are histologic features that suggest drug-induced disease.

#### **28. What are the genetic predispositions for AIH?**

Susceptibility to AIH in white northern European and North American populations relates mainly to the presence of HLA DRB1\*03 and DRB1\*04. HLA DRB1\*03 is the principal risk factor, and HLA DRB1\*04 is a secondary but independent risk factor. Eighty-five percent of white North American patients with type 1 AIH have HLA DRB1\*03, DRB1\*04, or both. HLA DQB1\*02 is probably the principal susceptibility factor for type 2 AIH, and it is in close association with HLA DRB1\*07 and DRB1\*03. HLA DRB1\*13 is associated with AIH in South America, especially in children. The HLA phenotype identifies individuals with a predisposition for AIH, but it does not predict the disease or familial occurrence.

#### **29. How do the susceptibility alleles produce AIH?**

Each susceptibility allele for AIH encodes an amino acid sequence in the antigen binding groove of the HLA DR molecule, and this sequence influences recognition of the displayed antigen by the T-cell antigen receptor (TCR) of CD4<sup>+</sup> T helper cells. The sequence encoded by DRB1\*0301 and DRB1\*0401 in white northern Europeans and North Americans consists of six amino acids at positions 67 through 72 of the DR $\beta$  polypeptide chain. Different susceptibility alleles that encode the same or similar short amino acid sequence in this critical

**Table 17-8. Implicated Causes of Drug-induced Autoimmune-like Hepatitis**

DEFINITE DRUG ASSOCIATION	PROBABLE DRUG ASSOCIATION	NUTRITIONAL AND HERBAL SUPPLEMENTS
Minocycline*	Atorvastatin	Black cohosh
Nitrofurantoin*	Clometacine	Dai-saiko-to
Dihydralazine	Diclofenac	Germander
Halothane†	Infliximab	Hydroxycut
Methyldopa†	Isoniazid	Ma huang
Oxiphenisatin‡	Propylthiouracil	
Tienilic acid‡		

\*Most commonly implicated in current clinical practice.

†Largely replaced by alternative medications.

‡Removed from marketplace.

Adapted from Czaja AJ: Drug-induced autoimmune-like hepatitis, *Dig Dis Sci* 56:958-976, 2011.

location carry the same risk for AIH. AIH associated with alleles that encode dissimilar amino acid sequences is probably triggered by different antigens, which may be region- and ethnic-specific.

### **30. How do regional and ethnic factors affect the clinical phenotype of AIH?**

Certain regions may have indigenous antigens that can trigger AIH, and individuals within that region may have nonclassical clinical phenotypes. The strong association between AIH and children with *DRB1\*1301* in South America may reflect protracted exposure of these children to viral antigens, such as the hepatitis A virus. Other geographic regions may have other indigenous etiologic agents and genetic susceptibilities, and phenotypes may vary between age groups in the same region and within the same ethnicity. Nonwhite patients tend to have cholestatic features, male predominance, and cirrhosis at presentation more commonly than white patients, and diagnostic criteria must be flexible to accommodate these ethnic differences.

### **31. Why do patients with the same HLA have different clinical phenotypes?**

Multiple genetic polymorphisms that are not disease-specific may influence the clinical phenotype of AIH. These polymorphisms may influence cytokine pathways that affect the occurrence and severity of AIH, and the variable distribution of these polymorphisms in different individuals may account for the diversity of phenotypes. Polymorphisms of the *tumor necrosis factor-alpha* gene (*TNFA\*2*), *cytotoxic T lymphocyte antigen-4* (*CTLA-4*), and *Fas* gene (*TNFRSF6*) are examples of immune modifiers that may act singly, in various combinations, or in synergy (epistasis) with the principal drivers of the disease to affect the clinical phenotype. The distribution of these modifiers may vary within and between ethnic groups.

### **32. Should HLA typing be part of the standard diagnostic algorithm?**

No. HLA *DRB1\*03* and *DRB1\*04* are common in healthy white North American and northern European populations, and these HLAs would be expected to occur coincidentally in 19% and 16%, respectively, of normal individuals and patients with other liver diseases. Furthermore, their presence would not change immediate management, and HLA typing is expensive. Similarly, the HLA associated with different types of AIH (HLA *DRB1\*07*, *DQB1\*02*) and AIH in other ethnicities and age groups (HLA *DRB1\*13*) have an uncertain clinical value, and they should not be routinely assessed.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## **BIBLIOGRAPHY**

1. Boberg KM, Chapman RW, Hirschfield GM, et al. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. *J Hepatol* 2011;54:374–85.
2. Carpenter HA, Czaja AJ. The role of histologic evaluation in the diagnosis and management of autoimmune hepatitis and its variants. *Clin Liver Dis* 2002;6:685–705.
3. Czaja AJ. Acute and acute severe (fulminant) autoimmune hepatitis. *Dig Dis Sci* 2013;58:897–914.
4. Czaja AJ. Autoantibodies in autoimmune liver disease. *Adv Clin Chem* 2005;40:127–64.
5. Czaja AJ. Autoantibody-negative autoimmune hepatitis. *Dig Dis Sci* 2012;57:610–24.
6. Czaja AJ. Autoimmune hepatitis in diverse ethnic populations and geographical regions. *Expert Rev Gastroenterol Hepatol* 2013;7:365–85.
7. Czaja AJ. Autoimmune hepatitis. Part B: diagnosis. *Expert Rev Gastroenterol Hepatol* 2007;1:129–43.
8. Czaja AJ. Cryptogenic chronic hepatitis and its changing guise in adults. *Dig Dis Sci* 2011;56:3421–38.
9. Czaja AJ. Diagnosis and management of the overlap syndromes of autoimmune hepatitis. *Can J Gastroenterol* 2013;27:417–23.
10. Czaja AJ. Drug-induced autoimmune-like hepatitis. *Dig Dis Sci* 2011;56:958–76.
11. Czaja AJ. Performance parameters of the conventional serological markers for autoimmune hepatitis. *Dig Dis Sci* 2011;56:545–54.
12. Czaja AJ. Performance parameters of the diagnostic scoring systems for autoimmune hepatitis. *Hepatology* 2008;48:1540–8.
13. Czaja AJ. The overlap syndromes of autoimmune hepatitis. *Dig Dis Sci* 2013;58:326–43.
14. Czaja AJ, Manns MP. Advances in the diagnosis, pathogenesis and management of autoimmune hepatitis. *Gastroenterology* 2010;139:58–72.
15. Manns MP, Czaja AJ, Gorham JD, et al. Practice guidelines of the American Association for the Study of Liver Diseases: diagnosis and management of autoimmune hepatitis. *Hepatology* 2010;51:2193–213.

## **Websites**

- American College of Physicians. ACP smart medicine. <http://smartmedicine.acponline.org/smartmed/content.aspx?gbosId=274> [Accessed September 22, 2014].
- Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. AASLD Practice Guidelines. <http://www.aasld.org/practiceguidelines/Documents/AIH2010.pdf> [Accessed September 22, 2014].

# AUTOIMMUNE HEPATITIS: TREATMENT

*Albert J. Czaja, MD*

## 1. What is the preferred treatment of autoimmune hepatitis (AIH)?

Prednisone or prednisolone (30 mg daily tapered over a 4-week induction period to 10 mg daily) in combination with azathioprine (50 mg daily) is the preferred treatment (Table 18-1). Prednisone or prednisolone alone (60 mg daily tapered over a 4-week induction period to 20 mg daily) is preferred in patients with an acute severe (fulminant) presentation, severe cytopenia, little or no thiopurine methyltransferase (TPMT) activity, known azathioprine intolerance, or pregnancy (Table 18-2). It is also preferred in patients undergoing a short treatment trial ( $\leq 6$  months). Both regimens are equally effective, but the combination schedule has fewer drug-related side effects (10% versus 44%).

**Table 18-1.** Recommended Treatment Regimens

INTERVAL DOSE ADJUSTMENTS	SINGLE-DRUG THERAPY (mg daily)	COMBINATION THERAPY (mg daily)	
	Prednisone (or Prednisolone)	Prednisone (or Prednisolone)	Azathioprine
Week 1	60	30	50
Week 2	40	20	50
Week 3	30	15	50
Week 4	30	15	50
Daily maintenance dose until endpoint	20	10	50

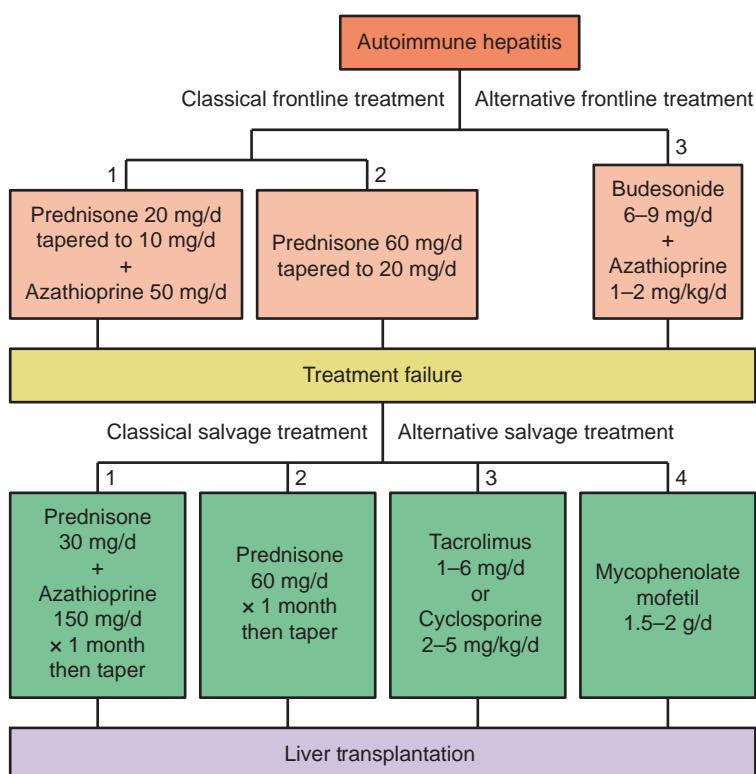
**Table 18-2.** Indications for Therapy and Criteria for Treatment Selection

INDICATIONS FOR TREATMENT	CRITERIA FOR TREATMENT SELECTION
Urgent	Prednisone or Prednisolone Regimen
Acute severe (fulminant) presentation AST or ALT $\geq 10$ -fold normal AST or ALT $\geq 5$ -fold normal and $\gamma$ -globulin $\geq 2$ -fold ULN Histologic findings of bridging or multilobular necrosis Incapacitating symptoms Disease progression	Acute severe (fulminant) presentation Severe cytopenia Little or no thiopurine methyltransferase activity Pregnancy or contemplation of pregnancy Known azathioprine intolerance Short-term ( $\leq 6$ months) treatment trial
Nonurgent	Prednisone or Prednisolone and Azathioprine Regimen
Asymptomatic mild disease Mild symptoms Mild-moderate laboratory changes	Preferred therapy (fewer side effects) Postmenopausal women Obesity Osteopenia Brittle diabetes Labile hypertension Long-term ( $>6$ months) treatment
None	
Inactive or minimally active cirrhosis	

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of the normal range.

## 2. Can budesonide be used in place of prednisone as frontline therapy?

Yes, but the appropriate target population is uncertain, the durability of the response is unclear, and the frequency of histologic resolution is unknown (Figure 18-1). Budesonide (6-9 mg daily) in combination with azathioprine (1-2 mg/kg daily) normalized serum aminotransferase levels more commonly (47% versus 18%) and with fewer side effects (28% versus 53%) than prednisone (40 mg daily tapered to 10 mg daily) and azathioprine (1-2 mg/kg daily) when administered as frontline therapy for 6 months in a large randomized European trial. The strongest rationale for its use may be in patients with osteoporosis, diabetes, hypertension, or obesity that might be worsened by treatment with prednisone.



**Figure 18-1.** Frontline and salvage therapies for autoimmune hepatitis. Prednisone in combination with azathioprine is the preferred classical frontline treatment and a higher dose of prednisone alone is appropriate for patients with severe pretreatment cytopenia, absent thiopurine methyltransferase activity, or azathioprine intolerance. Budesonide in combination with azathioprine can be considered for selected patients (mild disease, no cirrhosis, no concurrent immune diseases, or premorbid conditions for therapy with prednisone). The order of preferences is shown by numbers. The possible salvage therapies for treatment failure include high-dose corticosteroids, calcineurin inhibitors, and mycophenolate mofetil. The preferences are given in numerical order.

## 3. What are the caveats of using budesonide in place of prednisone as frontline therapy?

There are many uncertainties besides the durability of the response and frequency of histologic resolution. Budesonide has low systemic bioavailability because of its high (>90%) hepatic first-pass clearance, and concurrent immune-mediated diseases, such as vasculitis and synovitis, may not be managed effectively. Patients with cirrhosis and decreased hepatic clearance can develop side effects similar to those associated with prednisone. The effectiveness of budesonide in patients with severe, rapidly progressive, or life-threatening disease is uncertain. The appropriate target population may be patients with mild noncirrhotic, uncomplicated AIH or individuals with preexistent comorbid conditions that could be worsened by conventional corticosteroid therapy.

## 4. What are the indications for treatment?

All patients with active AIH are candidates for treatment regardless of symptoms or disease severity (see Table 18-2). Patients requiring immediate therapy have an acute severe (fulminant) presentation, incapacitating symptoms, or severe inflammatory activity as assessed by serum aspartate aminotransferase (AST) or alanine aminotransferase level, serum  $\gamma$ -globulin concentration, and histologic findings (bridging or multilobular necrosis). The mortality of these patients if untreated is as high as 40% within 6 months. Treatment is less urgent but still important in patients with few or no symptoms and less severe inflammatory activity. Treatment is not indicated in patients with inactive or minimally active cirrhosis.

## 5. Can some patients improve without therapy?

Yes. Controlled trials and retrospective studies have indicated spontaneous improvement in 10% to 15% of patients with AIH, and these remissions can be long-lasting. Furthermore, patients may have inactive AIH with or without cirrhosis at presentation. These patients have had an indolent, unsuspected AIH that has become inactive spontaneously (albeit often with cirrhosis as a consequence). Such patients do not require treatment as they may have more risk than benefit from the medication (see Table 18-2). Unfortunately, the patients who resolve spontaneously cannot be reliably identified at presentation.

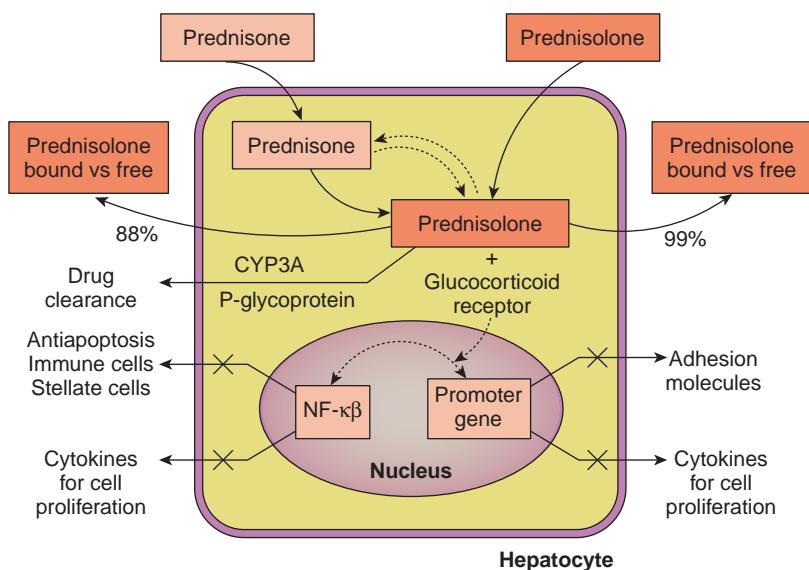
## 6. Do asymptomatic patients require treatment?

Yes. Asymptomatic patients have the same frequencies of moderate-severe lobular hepatitis (91% versus 95%), periportal fibrosis (41% versus 39%), and bridging fibrosis (41% versus 48%) on histologic examination as asymptomatic patients, and 26% to 70% become symptomatic. Furthermore, untreated asymptomatic patients improve less commonly than treated symptomatic patients (12% versus 63%), and they have a lower 10-year survival (67% versus 98%). The fluctuating and unpredictable nature of disease activity in AIH compels the institution of treatment in all patients with active disease (see Table 18-2).

## 7. How does prednisone work?

Prednisone is a prodrug that is converted within the liver to prednisolone (Figure 18-2). Prednisolone binds with the glucocorticoid receptor within the cytosol. The complex translocates to the nucleus, interacts with glucocorticoid responsive genes, reduces cytokine production, and inhibits the proliferation of activated lymphocytes. Prednisolone also inhibits nuclear factor-kappa B (NF- $\kappa$ B) and the cytokine pathways necessary for the expansion of plasma cells and the production of immunoglobulin. Antiinflammatory actions include impaired production of adhesion molecules that attract inflammatory cells, increased apoptosis of lymphocytes and hepatic stellate cells, and decreased hepatic collagen production.

**Figure 18-2.** Metabolic pathways of prednisone and prednisolone and the putative actions of prednisolone. Prednisone is a prodrug, and prednisolone is the active metabolite. Prednisolone that is not protein-bound (unbound or free) is responsible for treatment efficacy and toxicity. Prednisolone blocks (X) antiapoptotic factors and cytokines required for lymphocyte proliferation by inhibiting nuclear factor-kappa B (NF- $\kappa$ B). It also blocks (X) the production of adhesion molecules needed for the trafficking of inflammatory cells and cytokines that modulate cell proliferation by inhibiting promoter genes. (Reproduced with permission of Future Drugs, LTD, London, UK from Czaja AJ. Drug choices in autoimmune hepatitis: Part A – steroids. Expert Rev Gastroenterol Hepatol 6 (5):603-615, 2012.)



## 8. How does azathioprine work?

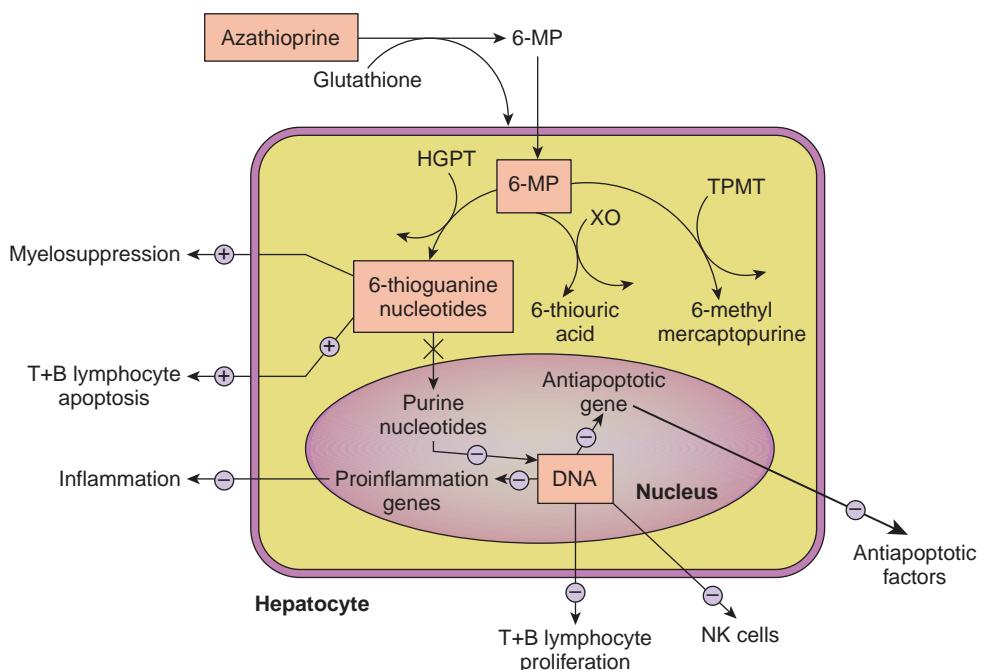
Azathioprine is a prodrug that is converted to 6-mercaptopurine (6-MP) in blood by a nonenzymatic, glutathione-based pathway (Figure 18-3). The 6-MP is converted in the liver to either 6-thioguanine nucleotides by hypoxanthine guanine phosphoribosyl transferase, 6-thiouric acid by xanthine oxidase, or 6-methyl mercaptopurine by TPMT. The 6-thioguanine nucleotides block the synthesis of purine-based nucleotides and limit the proliferation of activated lymphocytes. The 6-thioguanine nucleotides can also inhibit expression of genes affecting inflammatory reactivity, and they can promote the apoptosis of activated T and B cells and reduce the number of natural killer cells in blood and tissue.

## 9. What are important points to remember at the start of therapy?

Azathioprine is a corticosteroid-sparing agent with a slow onset of action ( $\geq 3$  months), and it is not an essential drug. Azathioprine should not be given if there is known drug-intolerance, severe cytopenia (leukocyte count less than  $2.5 \times 10^9/L$  or platelet count less than  $50 \times 10^9/L$ ), severe TPMT deficiency, or pregnancy. Prednisone and prednisolone are equally effective, but prednisolone does not require intrahepatic conversion. Its faster peak plasma concentration ( $1.3 \pm 0.7$  hours versus  $2.6 \pm 1.3$  hours) and greater systemic bioavailability ( $99 \pm 8\%$  versus  $84 \pm 13\%$ ) justify its preference to prednisone in treating acute severe (fulminant) AIH. Corticosteroids have a short half-life ( $3.3 \pm 1.3$  hours), and they must be administered daily.

## 10. What are the side effects of therapy with prednisone?

Prednisone induces cosmetic changes, including facial rounding, dorsal hump formation, striae, weight gain, acne, alopecia, and facial hirsutism, in 80% after 2 years (Table 18-3). Severe side effects, including osteopenia, vertebral compression, diabetes, cataracts, emotional instability, pancreatitis, opportunistic infection, and



**Figure 18-3.** Metabolic pathways of azathioprine and its putative actions. Azathioprine is a prodrug that is converted to 6-mercaptopurine (6-MP), which in turn is converted to the 6-thioguanine nucleotides via a pathway mediated by hypoxanthine guanine phosphoribosyl transferase (HGPT). Detoxification pathways are mediated by xanthine oxidase (XO) and thiopurine methyltransferase (TPMT). The 6-thioguanine nucleotides can cause myelosuppression (+), apoptosis of T and B lymphocytes (+) as well as inhibit (-) the creation of new DNA necessary for the proliferation of immune cells, including natural killer (NK) cells, antiapoptotic factors, and inflammatory activity. (Reproduced with permission of Future Drugs, LTD, London, UK, from Czaja AJ: Drug choices in autoimmune hepatitis: part B—nonsteroids, *Expert Rev Gastroenterol Hepatol* 6(5):617-635, 2012.)

**Table 18-3.** Side Effects Associated with Prednisone and Azathioprine Therapy

PREDNISONE-RELATED SIDE EFFECTS		AZATHIOPRINE-RELATED SIDE EFFECTS	
Type	Frequency	Type	Frequency
Cosmetic (usually mild)	80% (after 2 years)	Hematologic (mild)	46% (especially with cirrhosis)
Facial rounding		Cytopenia	
Acne			
Weight gain			
Dorsal hump			
Striae			
Hirsutism			
Alopecia			
Somatic (severe)	13% (treatment ending)	Hematologic (severe)	6% (treatment ending)
Osteopenia		Leukopenia	
Vertebral compression		Thrombocytopenia	
Cataracts		Bone marrow failure (rare)	
Diabetes			
Emotional instability			
Hypertension			
Inflammatory/neoplastic	Rare	Somatic (variable severity)	5%
Pancreatitis		Cholestatic hepatitis	
Opportunistic infection		Pancreatitis	
Malignancy		Opportunistic infection	
		Nausea	
		Emesis	
		Rash	
		Fever	
		Arthralgias	
		Villous atrophy and malabsorption	
		Neoplastic	3% (after 10 years)
		Diverse cell types	

hypertension, necessitate drug withdrawal in 13%, and they typically develop while receiving prednisone alone for more than 18 months. Serum bilirubin levels of more than 1.3 mg/dL or serum albumin levels less than 2.5 g/dL for more than 5 months increases the frequency of side effects because of decreased steroid binding sites and increased unbound free prednisolone. Patients with cirrhosis develop side effects more commonly (25% versus 8%).

#### **11. What are the side effects of therapy with azathioprine?**

Azathioprine can induce cholestatic liver injury, nausea, emesis, rash, pancreatitis, opportunistic infection, arthralgias, and cytopenia, including severe myelosuppression (see Table 18-3). Five percent develop early adverse reactions (nausea, vomiting, arthralgias, fever, skin rash, or pancreatitis) that warrant drug withdrawal. The frequency of side effects in patients treated with 50 mg daily is 10%, and side effects typically improve after dose reduction or drug withdrawal. Cytopenia occurs in 46%, and the occurrence of severe hematologic abnormalities is 6%. The probability of extrahepatic neoplasm is 3% after 10 years, and the risk of malignancy is 1.4-fold greater than normal.

#### **12. What are the factors contributing to prednisone (or prednisolone) toxicity?**

The dose and duration of treatment are most important. Age and preexistent comorbidities, especially obesity, osteoporosis, and cirrhosis, also contribute. Doses of prednisone of less than 10 mg daily (median dose, 7.5 mg daily) can be well tolerated long-term (median follow-up, 13.5 years; range, 7-43 years), whereas higher doses for longer than 18 months cannot. Postmenopausal women have a higher cumulative frequency of drug-related complications (77% versus 48%) and greater occurrence of multiple complications (44% versus 13%) than premenopausal women, probably because of age-related comorbidities. Cirrhosis can be associated with protracted hyperbilirubinemia and hypoalbuminemia and thereby increase the risk of side effects.

#### **13. What are the factors contributing to azathioprine toxicity?**

Azathioprine toxicity relates to the integrity of its detoxification pathways, which in turn influence the erythrocyte concentration of the 6-thioguanine nucleotides. Competing enzymatic pathways convert 6-MP to the inactive metabolites of 6-thiouric acid via the xanthine oxidase pathway or 6-methyl mercaptapurine by the TPMT pathway (see Figure 18-3). Drugs that inhibit xanthine oxidase activity, such as allopurinol, or deficiencies in TPMT activity can increase the production of 6-thioguanine metabolites and favor toxicity (and drug efficacy). At least 10 variant alleles are associated with low TPMT activity, and inheritance of these deficiency alleles can result in low or absent TPMT activity.

#### **14. Can drug toxicity be predicted?**

No. Old age and the presence of comorbid conditions are not predictive of corticosteroid intolerance, but they are precautionary indices that compel an individualized treatment strategy. Similarly, the occurrence of azathioprine-induced side effects cannot be reliably predicted by measuring TPMT activity or determining the TPMT genotype. Patients with azathioprine intolerance do have lower TPMT activity than patients with azathioprine tolerance, but most patients with azathioprine intolerance have normal TPMT activity. Similarly, alleles associated with low TPMT activity are present in only 50% of patients with azathioprine intolerance. Pretreatment cytopenia is the most common precautionary index affecting azathioprine tolerance.

#### **15. Should TPMT activity be measured before azathioprine therapy?**

Yes. There is insufficient evidence to promulgate a formal recommendation, but routine pretreatment TPMT testing is appropriate until studies demonstrate otherwise (Table 18-4). The assay for TPMT activity is readily available, and patients with near-zero TPMT activity are at risk for life-threatening myelosuppression. TPMT activity is absent in only 0.3% of the normal population, and not all completely deficient individuals develop bone marrow failure. Nevertheless, pretreatment TPMT testing provides the greatest level of reassurance about the unlikelihood of a serious hematologic consequence. Moderate reductions in TPMT activity are present in 6% to 16% of normal individuals, and they have not been associated with serious azathioprine-induced toxicity.

#### **16. What adjuvant measures should be undertaken before and after therapy?**

All susceptible patients should be vaccinated against the hepatitis A and B viruses prior to treatment (see Table 18-4). A bone maintenance regimen, consisting of calcium (1-1.5 g daily), vitamin D, and a regular weight-bearing exercise program should be recommended in all corticosteroid-treated patients. Bone density should be determined pretreatment in all postmenopausal women and men 60 years or older, and it should be reassessed after 1 year of corticosteroid treatment. Bisphosphonate therapy should be instituted in all osteopenic patients, and bone status monitored every 2 to 3 years in all patients during treatment. Leukocyte and platelet counts should be determined at 6-month intervals in all patients receiving azathioprine.

**Table 18-4.** Management Strategies to Reduce Treatment-Related Side Effects

CLINICAL SITUATION	MANAGEMENT STRATEGY
No protective antibodies against hepatitis A virus or hepatitis B virus infection	Vaccinate against hepatitis A and B viruses before treatment.
Never taken azathioprine previously	Assess thiopurine methyltransferase activity and avoid azathioprine if near zero enzyme activity.
Preexistent cytopenia	Assess thiopurine methyltransferase activity and avoid azathioprine if near zero enzyme activity. Avoid azathioprine treatment if leukocyte counts below $2.5 \times 10^9/L$ or platelet counts below $50 \times 10^9/L$ regardless of thiopurine methyltransferase activity. Monitor leukocyte and platelet counts at 6-month intervals while on treatment. Discontinue azathioprine if leukocyte counts decrease below $2.5 \times 10^9/L$ or platelet counts below $50 \times 10^9/L$ .
Pregnancy	Provide early counseling about potential hazards to mother and fetus. Use prednisone instead of azathioprine. Anticipate flare in disease activity after delivery and treat accordingly.
Osteopenia or its possibility	Institute bone maintenance regimen in all patients on long-term corticosteroid treatment ( $\geq 12$ months). Encourage calcium supplements, 1 to 1.5 g daily, vitamin D, and an active exercise program daily. Assess bone density pretreatment in postmenopausal women and older men ( $\geq 60$ years) and repeat after 12 months on corticosteroid treatment. Initiate therapy with bisphosphonates if pretreatment osteopenia. Perform bone density assessment every 2-3 years on corticosteroid treatment in all patients.

### 17. Can azathioprine be used during pregnancy?

Probably, but the clinical need and theoretical risks do not justify its use in AIH (see Table 18-4). Azathioprine has been administered without complication in pregnant women with AIH, inflammatory bowel disease, and liver transplantation. These limited retrospective successes must be counterbalanced against the drug's Category D rating. Congenital malformations have occurred in the offspring of treated mice, and 6-thioguanine nucleotides have been detected in human infants delivered from treated mothers. The odds ratio of congenital malformations in the neonates of treated women with Crohn's disease is 3.4. Azathioprine can be discontinued during pregnancy without consequence in AIH and control maintained by dose-adjusted prednisone.

### 18. What are the endpoints of treatment?

Standard corticosteroid treatment should be continued until resolution of all laboratory indices of active inflammation and histologic improvement to normal liver tissue or inactive cirrhosis (remission), drug toxicity, treatment failure, or incomplete response. Treatment failure connotes progressive worsening of laboratory tests, persistent or recurrent symptoms, ascites formation, or features of hepatic encephalopathy despite compliance with therapy. An incomplete response connotes clinical and laboratory improvement that is insufficient to satisfy remission criteria. An alternative treatment is warranted in these patients after 3 years of continuous therapy because the risk of serious drug toxicity exceeds the likelihood of remission.

### 19. When should a liver biopsy be performed during therapy?

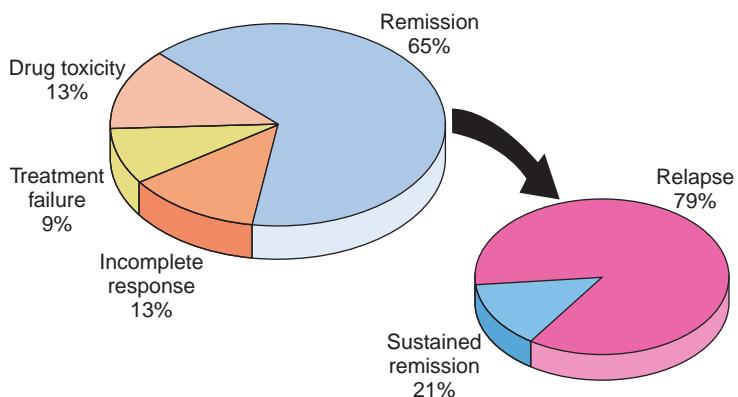
Liver tissue should be examined immediately prior to treatment withdrawal after clinical and laboratory resolution and at any time during treatment if the disease worsens. Typically, histologic improvement lags

behind clinical and laboratory resolution by 3 to 8 months. Histologic activity is present in 36% to 45% of liver specimens from patients with normal liver tests during treatment, and tissue examination is the only method to document disease resolution before drug withdrawal. Liver tissue evaluation is essential to evaluate treatment failure, especially to exclude corticosteroid-related fatty liver disease or a previously unrecognized or emerging cholestatic syndrome (biliary cirrhosis or primary sclerosing cholangitis).

## 20. What are the results of therapy?

Normal liver tests are achieved in 66% to 91% of treated patients within 2 years, and the average duration of treatment until normalization of tests is 19 months. Clinical, laboratory, and histologic remission is achieved within 2 years in 65%, and improvements are usually sufficient to attempt drug withdrawal after 22 to 27 months (Figure 18-4). Thirteen percent develop drug-related side effects that prematurely limit treatment (drug toxicity), and intolerable obesity or cosmetic change and osteoporosis with vertebral compression are the most common reasons for premature drug withdrawal. Treatment failure occurs in 9%, and improvement but not resolution (incomplete response) occurs in 13%.

**Figure 18-4.** Responses to conventional corticosteroid therapy.



## 21. Is survival improved?

Yes. Three controlled clinical trials have established this benefit. The 10-year survivals of treated patients with and without cirrhosis are 89% and 90%, respectively, in tertiary referral centers. The overall 10-year survival rate in these centers is 93%, and it is comparable to that of age- and sex-matched normal individuals from the same geographical region (94%). In nontransplant centers, the survivals from liver-related death or liver transplantation are 91% and 70% after 10 and 20 years, respectively, and the standardized mortality ratio (SMR) for all-cause death is 1.63.

## 22. Does corticosteroid treatment prevent or reverse fibrosis?

Yes. Corticosteroid therapy reduces hepatic fibrosis in 53% of patients or prevents its progression in 26% during a mean observation interval of 5 years. By suppressing inflammatory activity, corticosteroids eliminate metalloproteinase inhibitors, stimulate degradation of the fibrotic liver matrix, and enhance apoptosis of hepatic stellate cells. Corticosteroids have been reported to reverse cirrhosis in AIH, but this outcome is infrequent and uncertain. Cirrhosis still develops in 36%, usually during the early, most active, stages of AIH. The mean annual incidence of cirrhosis is 11% during the first 3 years of illness and 1% thereafter.

## 23. Are there any predictors of outcome prior to treatment?

Yes, but they have limited accuracy (Table 18-5). A score of at least 12 points at presentation that is derived from the Model of End-stage Liver Disease (MELD) has a sensitivity of 97% and specificity of 68% for treatment failure, death from liver failure, or need for liver transplantation. Patients with human leukocyte antigen (HLA) DRB1\*03 have a higher frequency of treatment failure than patients with other HLAs, and individuals with antibodies to soluble liver antigen frequently have severe disease, relapse after drug withdrawal, and have treatment dependence. These findings do not alter the initial management strategy. Histologic cirrhosis at presentation is not predictive of the treatment response.

**Table 18-5.** Clinical Indices Associated with Treatment Outcomes

CLINICAL INDEX	FINDING	IMPLICATION
Model of End-stage Liver Disease (MELD)*	Score $\geq 12$ points at presentation	Sensitivity of 97% and specificity of 68% for treatment failure
United Kingdom End-stage Liver Disease (UKELD) <sup>†</sup>	Failure to improve pretreatment score by $\geq 2$ points within 7 days of therapy in icteric patients	Sensitivity of 85% and specificity of 68% for a poor outcome
Laboratory changes	Unimproved hyperbilirubinemia after 2 weeks of therapy in patients with multilobular necrosis	Sensitivity of 60%, specificity of 96%, and positive predictability of 43% for death within 4 months
Rapidity of clinical, laboratory, and histologic resolution	Failure to achieve resolution within 12 months of treatment	Progression to cirrhosis, 54% Need for liver transplantation, 15%
HLA phenotype (white patients)	HLA DRB1*03 or DRB1*04	HLA DRB1*03: young age and frequent treatment failure HLA DRB1*04: concurrent immune diseases, female gender, and treatment responsiveness
Antibodies to soluble liver antigen	Pretreatment seropositivity	Relapse after drug withdrawal, 100% Associated with HLA DRB1*03, 83%

HLA, Human leukocyte antigen.

\*MELD =  $(3.78 \times \ln \text{ serum bilirubin [mg/dL]}) + (11.2 \times \ln \text{ INR}) + (9.57 \times \ln \text{ serum creatinine [mg/dL]}) + 6.43$

<sup>†</sup>UKELD =  $(5.395 \times \ln \text{ INR}) + (1.485 \times \ln \text{ creatinine}) + (3.13 \times \ln \text{ bilirubin}) - (81.565 \times \ln \text{ sodium}) + 435$

#### 24. Does the rapidity of the response to treatment have prognostic value?

Yes. Dynamic indices measured during therapy have greater prognostic value than indices measured at presentation (see Table 18-5). Failure to improve a pretreatment hyperbilirubinemia or the worsening of any liver test within 2 weeks of therapy in patients with multilobular necrosis predicts death within 4 months. Failure to improve the United Kingdom End-stage Liver Disease score by at least 2 points within 7 days of therapy in icteric patients has a sensitivity of 85% and specificity of 68% for a poor outcome. Failure to induce resolution of AIH within 2 years of treatment is associated with increased frequencies of progression to cirrhosis (54%) and need for liver transplantation (15%).

#### 25. What are the factors that influence the rapidity of treatment response?

Disease severity and patient age are important factors. Patients with mild disease respond more quickly to corticosteroid therapy than patients with severe disease, and older adult patients (aged  $>60$  years) respond more rapidly than young adults (aged  $<40$  years). Resolution within 6 months (18% versus 2%) and within 24 months (94% versus 64%) occur more commonly in the older than in young adults. Older adult patients also have HLA DRB1\*04 more commonly (47% versus 13%) and HLA DRB1\*03 less frequently (23% versus 58%) than young adults.

#### 26. What is the most common treatment problem?

Relapse after drug withdrawal is the most common treatment problem. Fifty percent of patients relapse within 6 months after termination of treatment, and 79% to 86% relapse within 3 years. The frequency of relapse increases after each subsequent retreatment and drug withdrawal, and it decreases with the duration of a sustained remission. The frequency of relapse after a sustained remission of 6 months or more is 8%, but the risk never disappears. Relapse has occurred 4 to 22 years after drug withdrawal, and the unpredictable propensity for relapse warrants lifelong surveillance for this possibility. Liver tissue examination is not necessary to diagnose relapse if it occurs within 6 months of drug withdrawal, and the serum AST level has increased from normal to at least threefold the upper limit of the normal range (ULN).

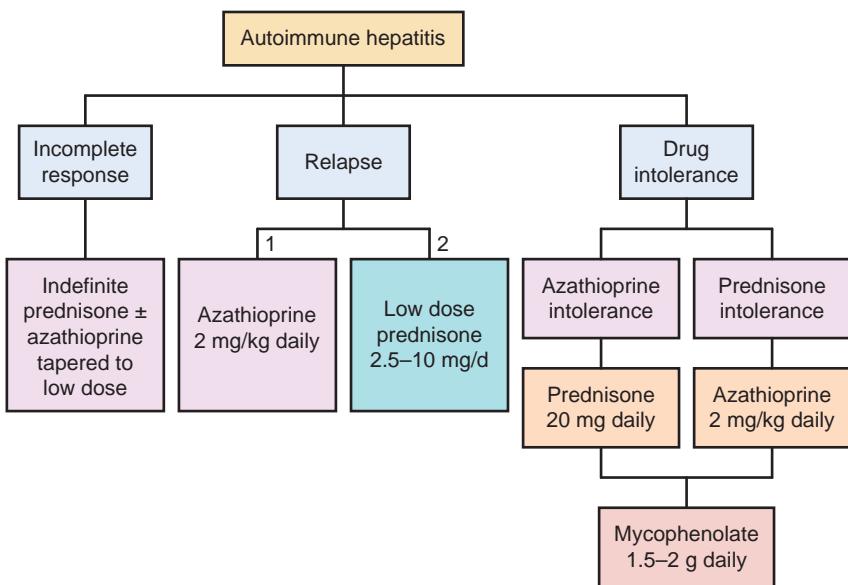
#### 27. What are the consequences of relapse and retreatment?

The consequences of relapse and retreatment are progression to cirrhosis, death from liver failure, requirement for liver transplantation, and drug-induced side effects. Repeated relapse and retreatment have a cumulative morbidity and mortality. Cirrhosis develops more commonly (38% versus 4%,  $P = 0.004$ ), death from hepatic failure or need for liver transplantation occurs more often (20% versus 0%,  $P = 0.008$ ), and drug-induced side effects are more frequent (70% versus 30%,  $P = 0.01$ ) in individuals who relapse than in those who sustain remission after drug withdrawal. The frequencies of each complication increases with each subsequent relapse and retreatment. The optimal time to interrupt this sequence is after the first treatment and relapse.

## 28. How should relapse be managed?

Relapse is managed by maximizing efforts at prevention and by instituting long-term maintenance therapy immediately after the first relapse. The frequency of relapse can be reduced from 79% or more to as low as 28% by treating patients until normal serum AST and  $\gamma$ -globulin levels and normal liver tissue are present before drug withdrawal. If relapse occurs, a long-term maintenance regimen is justified, preferably with azathioprine (Figure 18-5). Laboratory resolution is first achieved with conventional therapy, and then the dose of azathioprine is increased to 2 mg/kg daily as the dose of prednisone is withdrawn. Eighty percent of patients can sustain remission over 10 years. Low-dose prednisone (2.5–10 mg daily; median dose, 7.5 mg daily) can be used for azathioprine intolerance.

**Figure 18-5.** Management of incomplete response, relapse, and drug toxicity. The preferred treatments for relapse are shown in numerical order. Indefinite low dose prednisone (range, 2.5–10 mg daily; median dose, 7.5 mg daily) can be considered after initial relapse in patients with severe cytopenia, pregnancy, or azathioprine intolerance.



## 29. How should treatment failure be managed?

High-dose prednisone (60 mg daily) or prednisone (30 mg daily) in conjunction with azathioprine (150 mg daily) induces clinical and laboratory remission in 75% of patients within 2 years (see Figure 18-1). The doses of medication are reduced each month of clinical and laboratory improvement by 10 mg of prednisone and 50 mg of azathioprine (if patients are receiving combination therapy) until conventional doses are achieved (prednisone, 10 mg daily and azathioprine, 50 mg daily, or prednisone, 20 mg daily). Histologic resolution occurs in 20% or less, and most patients are treatment-dependent and at risk for disease progression and drug-related complications. Progression to liver failure is an indication for liver transplantation.

## 30. Can the calcineurin inhibitors be used for treatment failure?

Yes (see Figure 18-1). The compilation of experiences with cyclosporine as a salvage therapy have indicated a positive response of any degree in 93% of 133 patients included in 10 reports (Table 18-6). The compilation of experiences with tacrolimus as a salvage therapy has indicated a positive response of any degree in 98% of 44 patients included in four reports. The problems with the calcineurin inhibitors in AIH are the possibility of a paradoxical enhancement of the autoimmune response because of impaired negative selection of autoreactive lymphocytes, lack of dosing guidelines and safety profile in AIH, failure of these drugs to prevent or treat AIH that develops after liver transplantation, and the risk of serious side effects, especially neurotoxicity.

## 31. Can mycophenolate mofetil be used for treatment failure?

Yes (see Figure 18-1). The next-generation purine antagonist, mycophenolate mofetil, has been effective as a salvage agent in 45% of patients reported in 11 small single-center experiences (see Table 18-6). The drug seems to be more effective in rescuing patients from azathioprine intolerance (58%) than from corticosteroid-refractory AIH (23%). Its major limitations relate to its expense (6–7 times more expensive than azathioprine); frequency of side effects (3% to 34%); and association with severe cranial, facial, and cardiac abnormalities in human neonates born of treated mothers (Category D drug). Mycophenolate mofetil is ineffective in children and adults with cholangiographic changes of sclerosing cholangitis.

**Table 18-6.** Alternative Salvage Therapies for Autoimmune Hepatitis

AGENT	PUTATIVE ACTIONS	EXPERIENCE
Cyclosporine	Calcineurin inhibitor that impairs lymphokine release and prevents cytotoxic T-cell expansion	Ten reports involving 133 patients Positive response (any type), 93% Serious toxicities, including neurotoxicity Possible paradoxical autoimmunity Ineffective in AIH developing after liver transplantation Uncertain dosing schedule, monitoring mechanisms, safety profile, and long-term results
Tacrolimus	Calcineurin inhibitor that prevents cytotoxic T-cell expansion, inhibits interleukin-2 receptor, and impairs antibody production	Four reports involving 44 patients Positive response (any type), 98% Can stimulate experimental fibrogenesis Uncertain dosing schedule, monitoring mechanisms, safety profile, and long-term results
Mycophenolate mofetil	Purine antagonist that impairs creation of new RNA and DNA Prevents lymphocyte proliferation and activation Independent of TPMT pathway	Eleven clinical experiences, mainly as salvage Single experience as frontline drug Salvage efficacy, 45% Frontline efficacy (with prednisone), 88% Corticosteroid withdrawal, 60% Efficacy for azathioprine intolerance, 58% Efficacy for steroid-refractory disease, 23% Teratogenicity (Category D drug) Side effects, 3%-34% 6-7 times more expensive than azathioprine Uncertain dosing schedule, monitoring mechanisms, safety profile, and long-term results

AIH, Autoimmune hepatitis; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; TPMT, thiopurine methyltransferase.

### 32. Is liver transplantation effective in AIH?

Yes (see Figure 18-1). The 5-year survival after liver transplantation is 75% to 79% in adults and up to 86% in children. Patients transplanted for AIH experience acute rejection more frequently than patients transplanted for other liver diseases, and AIH recurs in 8% to 68% depending on the length of follow-up after the procedure. Graft failure occurs in 13%, and 13% to 23% of patients undergo retransplantation. The actuarial 5-year survival for recurrent AIH ranges from 89% to 100%. Ten percent of patients with AIH who fail conventional treatment require transplantation, and steroid-refractory patients with a MELD score of more than 16 points, acute decompensation, intractable symptoms, treatment intolerance, or early liver cancer are candidates for the procedure.

### 33. What strategy is best for patients with drug toxicity or incomplete response?

For drug toxicity, the dose of the implicated medication is reduced to the lowest possible level or withdrawn (see Figure 18-5). Disease activity is controlled by the medication (prednisone or azathioprine) that has been tolerated and dose adjusted to suppress inflammation. Mycophenolate mofetil has been used for azathioprine intolerance, but its side effects are similar to those of azathioprine, including cytopenia. It should be avoided in patients with marked cytopenia or pregnancy. For an incomplete response, the medication is reduced to the lowest level possible to prevent symptoms and suppress histologic activity as reflected by a serum AST level maintained threefold or more of the ULN. Inadequately controlled patients may require liver transplantation.

### 34. Does hepatocellular carcinoma occur?

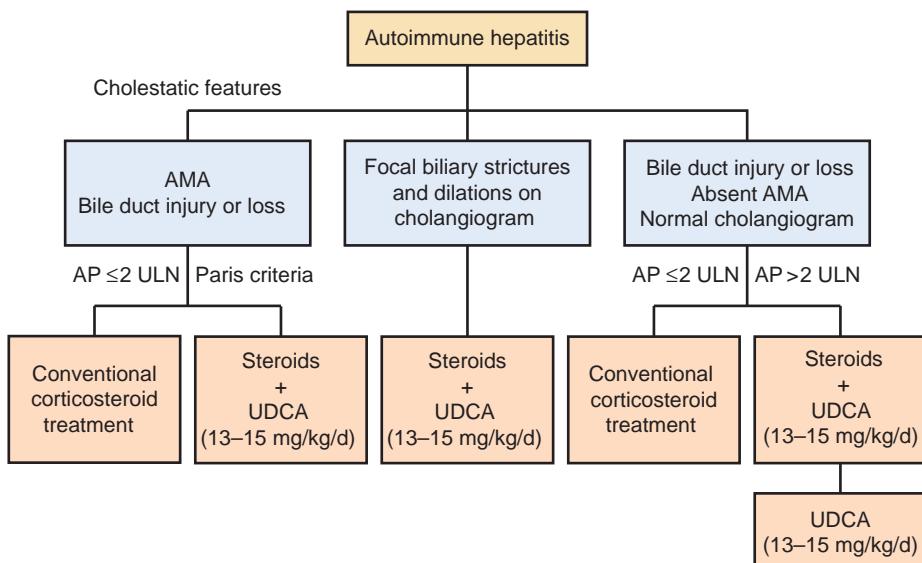
Yes. The frequency of hepatocellular carcinoma in patients with AIH and cirrhosis ranges from 1% to 9%, and the incidence is 1.1% to 1.9% per year. The standardized incidence ratio for hepatocellular carcinoma in Swedish patients with AIH is 23.3 (95% confidence interval, 7.5-54.3), and the SMR for hepatobiliary malignancy in New Zealand patients is 42.3 (95% confidence interval, 20.3-77.9). Cirrhosis is a requisite for hepatocellular carcinoma in AIH, and the median duration from cirrhosis to hepatocellular carcinoma ranges from 12-195 months (mean interval, 102 months). The hazard ratio for hepatocellular carcinoma in patients with cirrhosis of 10 years' duration or more is 8.4 (95% confidence interval, 1.69-41.9).

### 35. Should patients undergo surveillance for hepatocellular carcinoma?

Yes. Surveillance has not been formally endorsed as cost-effective, but it has been recommended in the guidelines for managing AIH in otherwise healthy individuals. Patients with cirrhosis for 10 years or more, immunosuppressive therapy for 3 years or more, and worsening laboratory tests during corticosteroid treatment have the greatest risk, but surveillance should include all patients with AIH and cirrhosis. Hepatic ultrasonography every 6 months is the cornerstone of surveillance. Determination of the serum alpha fetoprotein level increases the frequency of tumor detection by 9%, but also increases the frequency of false-positive findings by 2.4-fold and decreases the positive predictive value by 2.2-fold. Its additive value remains controversial.

### 36. How are the overlap syndromes of AIH managed?

Conventional corticosteroid therapy in combination with ursodeoxycholic acid (13–15 mg/kg daily) has been endorsed for patients satisfying the “Paris criteria” for AIH with overlapping features of primary biliary cirrhosis and for patients with AIH and cholangiographic changes of primary sclerosing cholangitis (Figure 18-6). Patients with AIH and an undetermined cholestatic syndrome can be treated with corticosteroids in combination with ursodeoxycholic acid, ursodeoxycholic acid alone (13–15 mg/kg daily), or conventional corticosteroid therapy depending on the strength of the cholestatic component. All therapies are empiric, and recommendations are not strongly evidence-based.



**Figure 18-6.** Treatment algorithm for the overlap syndromes of autoimmune hepatitis. Autoimmune hepatitis may have cholestatic features that can resemble the clinical phenotypes of primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC). Some patients may have an indeterminate cholestatic phenotype that may resemble antimitochondrial antibody (AMA)-negative PBC or small duct PSC. Patients with AMA, histologic evidence of bile duct injury or loss, and a serum alkaline phosphatase (AP) level  $\leq$  twofold the upper limit of the normal range (ULN) may respond to conventional corticosteroid therapy, whereas patients who satisfy Paris criteria with florid duct lesions and serum AP  $>$  twofold ULN are candidates for conventional corticosteroid therapy combined with ursodeoxycholic acid (UDCA) (13–15 mg/kg daily). This combination regimen has also been recommended for patients with focal biliary strictures and dilations on cholangiogram that resemble PSC. Individuals with an indeterminate cholestatic syndrome lack formal recommendations, and their empiric therapy must be directed by the strength and nature of the cholestatic features and resemblances to PBC or PSC.

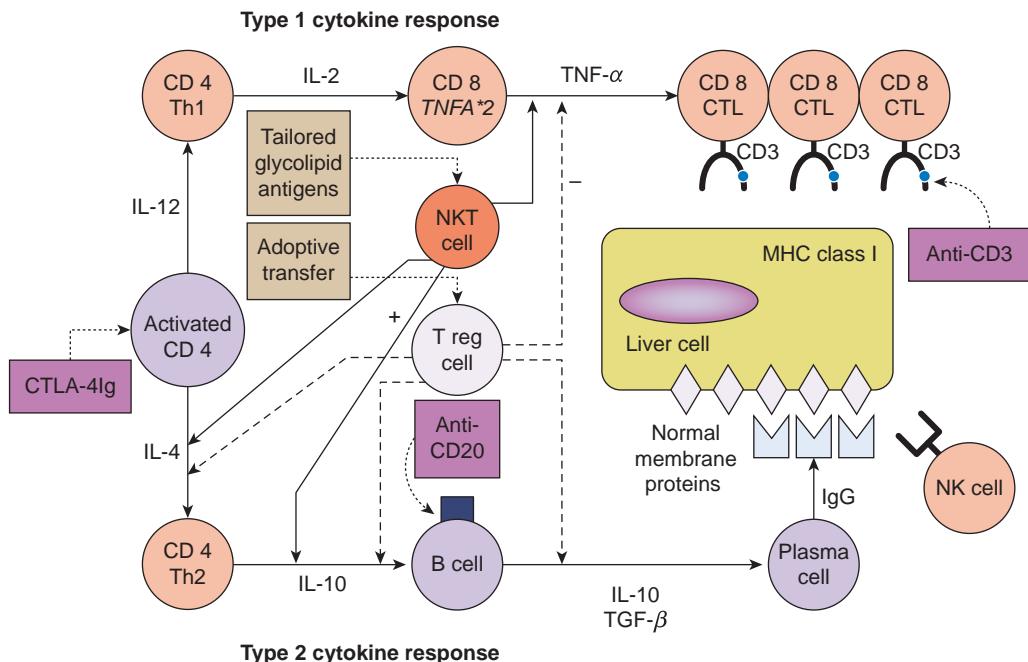
### 37. What new therapies are promising?

Molecular and cell-directed interventions have promise in AIH mainly because of successes already achieved in animal models and humans with other immune-mediated diseases (Table 18-7). They constitute investigational opportunities in AIH that have not yet emerged into clinical practice. Monoclonal antibodies against key components of the cytokine pathways, recombinant molecules that dampen immune reactivity, and manipulations of regulatory T cells and natural killer T cells in a disease-specific fashion are examples of these promising new interventions (Figure 18-7).

**Table 18-7.** Promising New Therapies Based on Site-Specific Molecular Interventions and Cellular Manipulations

THERAPY	PRINCIPAL ACTION	EXPERIENCE
Recombinant CTLA-4 fused with immunoglobulin	Blocks ligation of B7 to CD28 and prevents CD4 T helper cell activation	Approved for use in rheumatoid arthritis Successful in preventing rejection after mismatched bone marrow transplantation Effective in animal model of PBC Untried in AIH
Monoclonal antibodies to CD3	Targets T cell antigen receptor and induces apoptosis of cytotoxic T lymphocytes	Effective in animal models and humans with diabetes Untried in AIH
Monoclonal antibodies to CD20	Targets B lymphocytes and prevents clonal expansion of plasma cells and antibody production	Effective in cryoglobulinemia and small series of AIH
Adoptive transfer of T-regulatory cells	Replenishes and strengthens regulatory T cell response and promotes antiinflammatory cytokine pathways	Effective in animal model of experimental AIH
Tailored glycolipid antigen stimulation of natural killer T cells	Stimulates favorable stimulatory and inhibitory cytokine pathways in disease-specific fashion	Successful in animal models of lupus erythematosus, collagen-induced synovitis and diabetes Untried in experimental AIH

AIH, Autoimmune hepatitis; CTLA-4, cytotoxic T lymphocyte antigen 4; PBC, primary biliary cirrhosis.



**Figure 18-7.** Feasible molecular and cellular interventions for investigation in autoimmune hepatitis. Monoclonal antibodies can be directed against CD3 (anti-CD3) within the T cell antigen receptor of liver-infiltrating CD8 cytotoxic T lymphocytes (CTL) and induce their apoptosis, or against CD20 (anti-CD20) expressed on B lymphocytes and inhibit antibody production and an antibody-dependent, cell-mediated hepatocyte injury by natural killer (NK) cells. Recombinant cytotoxic T lymphocyte antigen-4 fused with immunoglobulin (CTLA-4Ig) can block the second costimulatory signal required for T lymphocyte activation and impair the autoreactive response. Manipulations of regulatory T cells (T Reg cell) by adoptive transfer or natural killer T cells (NKT cell) by tailored glycolipid antigens can inhibit (-) cytotoxic cytokine pathways mediated by tumor necrosis factor-alpha (TNF- $\alpha$ ) and stimulate (+) antiinflammatory cytokine pathways mediated by interleukin 10 (IL-10) and transforming growth factor-beta (TGF- $\beta$ ). These interventions have been successful in animal models and humans with diverse immune-mediated diseases, including autoimmune hepatitis.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

1. Czaja AJ. Advances in the current treatment of autoimmune hepatitis. *Dig Dis Sci* 2012;57:1996–2010.
2. Czaja AJ. Diagnosis and management of the overlap syndromes of autoimmune hepatitis. *Can J Gastroenterol* 2013;27:417–23.
3. Czaja AJ. Drug choices in autoimmune hepatitis: part A—steroids. *Expert Rev Gastroenterol Hepatol* 2012;6:603–15.
4. Czaja AJ. Drug choices in autoimmune hepatitis: part B—nonsteroids. *Expert Rev Gastroenterol Hepatol* 2012;6:617–35.
5. Czaja AJ. Emerging opportunities for site-specific molecular and cellular interventions in autoimmune hepatitis. *Dig Dis Sci* 2010;55:2712–26.
6. Czaja AJ. Hepatocellular cancer and other malignancies in autoimmune hepatitis. *Dig Dis Sci* 2013;58:1459–76.
7. Czaja AJ. Management of recalcitrant autoimmune hepatitis. *Curr Hepatitis Rep* 2013;12:66–77.
8. Czaja AJ. Nonstandard drugs and feasible new interventions for autoimmune hepatitis. Part I. *Inflamm Allergy Drug Targets* 2012;11:337–50.
9. Czaja AJ. Nonstandard drugs and feasible new interventions for autoimmune hepatitis. Part-II. *Inflamm Allergy Drug Targets* 2012;11:351–63.
10. Czaja AJ. Promising pharmacological, molecular and cellular treatments of autoimmune hepatitis. *Curr Pharm Des* 2011;17:3120–40.
11. Czaja AJ. Review article: the management of autoimmune hepatitis beyond consensus guidelines. *Aliment Pharmacol Ther* 2013;38:343–64.
12. Czaja AJ. Safety issues in the management of autoimmune hepatitis. *Exp Opin Drug Saf* 2008;7:319–33.
13. Gleeson D, Heneghan MA. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. *Gut* 2011;60:1611–29.
14. Heneghan MA, Allan ML, Bornstein JD, et al. Utility of thiopurine methyltransferase genotyping and phenotyping, and measurement of azathioprine metabolites in the management of patients with autoimmune hepatitis. *J Hepatol* 2006;45:584–91.
15. Manns MP, Czaja AJ, Gorham JD, et al. Practice guidelines of the American Association for the Study of Liver Diseases: diagnosis and management of autoimmune hepatitis. *Hepatology* 2010;51:2193–213.
16. Manns MP, Woynarowski M, Kreisel W, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. *Gastroenterology* 2010;139:1198–206.
17. Montano-Loza AJ, Carpenter HA, Czaja AJ. Consequences of treatment withdrawal in type 1 autoimmune hepatitis. *Liver Int* 2007;27:507–15.
18. Montano-Loza AJ, Carpenter HA, Czaja AJ. Features associated with treatment failure in type 1 autoimmune hepatitis and predictive value of the model of end stage liver disease. *Hepatology* 2007;46:1138–45.
19. Selvarajah V, Montano-Loza AJ, Czaja AJ. Systematic review: managing suboptimal treatment responses in autoimmune hepatitis with conventional and nonstandard drugs. *Aliment Pharmacol Ther* 2012;36:691–707.
20. Yeoman AD, Westbrook RH, Zen Y, et al. Early predictors of corticosteroid treatment failure in icteric presentations of autoimmune hepatitis. *Hepatology* 2011;53:926–34.

## Websites

- American College of Physicians. ACP smart medicine. <http://smartmedicine.acponline.org/smartmed/content.aspx?gbosId=274> [Accessed September 22, 2014].
- Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. AASLD Practice Guidelines. <http://www.aasld.org/practiceguidelines/Documents/AIH2010.pdf> [Accessed September 22, 2014].

# PRIMARY BILIARY CIRRHOSIS AND PRIMARY SCLEROSING CHOLANGITIS

John E. Eaton, MD, Jayant A. Talwalkar, MD, MPH, and Nicholas F. LaRusso, MD

## 1. Define primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).

PBC and PSC are chronic, idiopathic cholangiopathies. PBC mainly affects women in the sixth decade of life and is characterized by destruction of interlobular and septal bile ducts. PSC mainly affects men in the fifth decade of life. Classic (large duct) PSC is characterized by diffuse inflammation and fibrosis of the intrahepatic and/or extrahepatic bile ducts. Both PBC and PSC may eventually progress to end-stage liver disease, requiring consideration for liver transplantation.

## 2. Is PBC an autoimmune disorder?

The underlying cause of PBC is unknown. Evidence for an autoimmune etiologic factor includes the following:

- Frequent association with other autoimmune diseases such as Sjögren syndrome; rheumatoid arthritis; scleroderma and the syndrome consisting of calcinosis, Raynaud phenomenon, esophageal disease, sclerodactyly, and telangiectasia (CREST); thyroiditis; lichen planus; discoid lupus; and pemphigoid
- Presence of circulating serum autoantibodies, such as antimitochondrial antibodies (AMA), antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), extractable nuclear antigen, rheumatoid factor, thyroid-specific antibodies, and elevated serum immunoglobulin M (IgM) levels
- Histologic features, including lymphoplasmacytic cholangitis with portal tract expansion indicative of immunologic bile duct destruction
- Increased prevalence of circulating serum autoantibodies in relatives of patients with PBC
- Increased frequency of class II major histocompatibility complex antigens in PBC

## 3. Is PSC an autoimmune disorder?

The evidence supporting an immunogenic origin for PSC includes the following:

- The 70% to 80% prevalence of inflammatory bowel disease among patients with PSC in Europe and North America
- Increased incidence of PSC and chronic ulcerative colitis (CUC) in families of patients with PSC
- Evidence for immune system dysregulation, including increased serum levels of IgM, serum autoantibodies such as ANA, ASMA, and peripheral antineutrophil cytoplasmic antigen (pANCA), and circulating immune complexes
- Increased frequency of human leukocyte antigens (HLA) B8, DR3a, and DR4
- Aberrant expression of HLA class II antigen on bile duct epithelial cells

## 4. What are the clinical features of PBC and PSC?

The clinical presentations of both PBC and PSC may be similar, although some demographic and clinical characteristics differ. From 85% to 90% of patients with PBC are women presenting in the fourth to sixth decades of life, whereas up to 70% of patients with PSC are men with an approximate age of 40 years at diagnosis. Despite an increasing frequency of asymptomatic or subclinical disease, greater than 40% affected patients with either condition generally present with the gradual onset of fatigue and pruritus. Fatigue can be problematic, and it is important to evaluate for other causes of this symptom such as medication side effects, hypothyroidism, or depression. Right upper quadrant pain and anorexia also may be observed at diagnosis. Although uncommon, steatorrhea in PBC and PSC is usually due to bile salt malabsorption. However, other etiologic factors of malabsorption can include pancreatic exocrine insufficiency, coexisting celiac disease, or bacterial overgrowth. Jaundice as a primary manifestation of PBC is uncommon but strongly associated with the presence of advanced histologic disease. In PSC, the development of bacterial cholangitis characterized by recurrent fever, right upper quadrant pain, and jaundice may occur. A history of previous reconstructive biliary surgery, the presence of dominant extrahepatic biliary strictures, or the development of a superimposed cholangiocarcinoma may also be responsible. The symptoms of end-stage liver disease, such as gastrointestinal bleeding, ascites, and encephalopathy, occur late in the course of both diseases.

## 5. What are the common findings on physical examination?

Physical examination may reveal jaundice and excoriations from pruritus in both disorders. Xanthelasmata (raised lesions over the eyelids from cholesterol deposition) and xanthomas (lesions over the extensor surfaces) are occasionally seen in the late stages of both diseases, particularly PBC. Hyperpigmentation, especially in sun-exposed areas, and vitiligo may be present. The liver is often enlarged and firm to palpation. The spleen may also be palpable if portal hypertension from advanced disease has developed. Characteristics of end-stage liver disease, including muscle wasting and spider angioma, appear in the advanced stages of both diseases.

## 6. What diseases are associated with PBC?

Up to 80% of patients with PBC also have coexistent extrahepatic autoimmune diseases. *The most common extrahepatic autoimmune disease is sicca (Sjögren) syndrome.* Other conditions described in association with PBC include autoimmune thyroiditis, scleroderma/CREST, rheumatoid arthritis, dermatomyositis, mixed connective tissue disease, systemic lupus erythematosus, renal tubular acidosis, and idiopathic pulmonary fibrosis.

## 7. What diseases are associated with PSC?

CUC and, less frequently, Crohn's colitis are present in at least 70% to 80% of patients with PSC. In contrast, *only 5% of patients with inflammatory bowel disease will have concurrent PSC.* Consequently, patients with known inflammatory bowel disease should be evaluated for PSC if liver test abnormalities are detected. In addition, patients with PSC should undergo a colonoscopy at the time of diagnosis regardless of the presence of concurrent inflammatory bowel disease or symptoms of inflammatory bowel disease. CUC can develop even after a liver transplant just as PSC can develop following a colectomy.

## 8. How does CUC associated with PSC differ from CUC not associated with PSC?

Several observations have suggested that PSC-CUC is a different phenotype compared with those with CUC alone. For example, patients with PSC-CUC tend to have pancolitis with minimal endoscopic inflammation. A higher risk of colorectal cancer, pouchitis, peristomal varices following a proctocolectomy with ileostomy, rectal sparing, and backwash ileitis has also been observed in PSC-CUC.

## 9. What important biochemical abnormalities are associated with PBC and PSC?

In both disorders, serum alkaline phosphatase is frequently elevated at least three to four times the upper limit of normal with mild to moderate elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Elevations of ALT or AST greater than four to five times the upper limit of normal are unusual for PSC and PBC, but can be seen if a concurrent process is present (autoimmune hepatitis [AIH], acute biliary obstruction). In PBC, serum total bilirubin values are usually within normal limits at diagnosis. In PSC, serum bilirubin values are modestly increased in up to 50% of patients at the time of diagnosis. Tests reflective of synthetic liver function, including serum albumin and prothrombin time (PT), remain normal unless advanced liver disease is present. Serum IgM levels are elevated in 90% of patients with PBC. Based on the widespread use of automated blood chemistries, an increasing number of asymptomatic patients with PBC and PSC are being diagnosed.

## 10. What is the lipid profile in patients with PBC? Are they at increased risk for developing coronary artery disease?

Serum cholesterol levels are usually elevated in PBC. In the early stages of disease, increases in high-density lipoprotein (HDL) cholesterol exceed those of low-density lipoprotein (LDL) and very-low-density lipoprotein. With liver disease progression, the concentration of HDL decreases while LDL concentrations become markedly elevated. An increased risk for atherosclerotic disease has not been demonstrated among patients with persistent hyperlipidemia in association with PBC.

## 11. What serum autoantibodies are associated with PBC?

Serum AMA is found in up to 95% of patients with PBC. Although considered non-organ specific as well as non-species specific, serum AMA usually is detected by an enzyme-linked immunosorbent assay. However, antibodies directed against a specific group of antigens on the *inner mitochondrial membrane (M2 antigens)* are present in 98% of patients with PBC. This subtyping of serum AMA increases the sensitivity and specificity for disease detection.

Other AMA subtypes related to PBC react with antigens on the outer mitochondrial membrane.

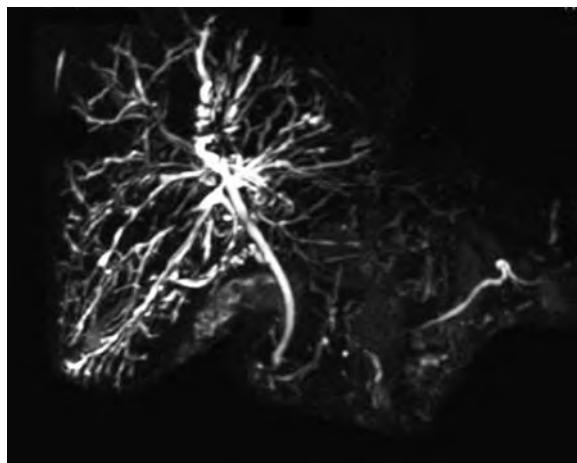
Anti-M4 occurs in association with anti-M2 in patients with overlap syndromes of AIH and PBC. Anti-M8, when present with anti-M2, may be associated with a more rapid course of disease progression in selected patients. Anti-M9 has been observed with and without anti-M2 and may be helpful in the diagnosis of early-stage PBC.

## 12. What serum autoantibodies are associated with PSC?

In PSC, serum AMA is rare and, if present, is usually seen in very low titers. However, detectable titers of serum ANA, ASMA, and antithyroxineperoxidase antibodies have been found in up to 70% of patients with PSC. *pANCA has been observed in up to 65% of patients with PSC.* The lack of specificity of autoantibodies limits their use in the diagnostic evaluation of PSC, and their use for diagnosis is not routinely recommended. A small subset of patients diagnosed with PSC based on biliary strictures seen on cholangiography may indeed have immune-associated cholangitis or autoimmune pancreatitis with concurrent biliary strictures. Therefore it is recommended that all patients with PSC have a serum IgG4 measured.

### 13. What are the cholangiographic features of the biliary tree in PSC?

Evaluation of the biliary tree in PSC by cholangiography may reveal diffuse stricturing of both intrahepatic and extrahepatic ducts with saccular dilatation of intervening areas. These abnormalities result in the characteristic *beads-on-a-string* appearance seen with PSC. Exclusive intrahepatic and hilar involvement occurs in only 20% of patients. Secondary causes of sclerosing cholangitis such as ischemic cholangitis or portal hypertensive bilopathy can mimic the cholangiographic findings of PSC. Traditionally, endoscopic retrograde cholangiography (ERC) has been used to diagnose PSC. However, magnetic resonance cholangiography (MRC) also has an excellent diagnostic performance, and it is more cost effective and avoids radiation when compared with ERC. Hence, MRC is the preferred diagnostic imaging modality ([Figure 19-1](#)).



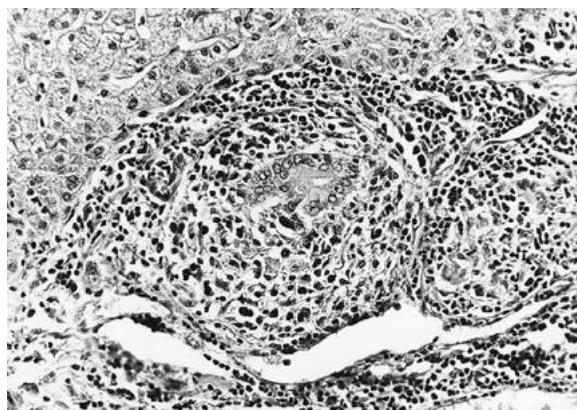
**Figure 19-1.** Magnetic resonance cholangiogram exhibiting classic features of primary sclerosing cholangitis, including diffuse intrahepatic stricturing and dilation.

### 14. Is it important to evaluate the biliary tree in PBC?

In PBC, an ultrasound examination of the biliary tree is usually adequate to exclude the presence of extrahepatic biliary obstruction. However, in patients with atypical features such as male sex, AMA seronegativity, or associated inflammatory bowel disease, a cholangiogram should be considered to distinguish PBC from PSC and other disorders causing biliary obstruction.

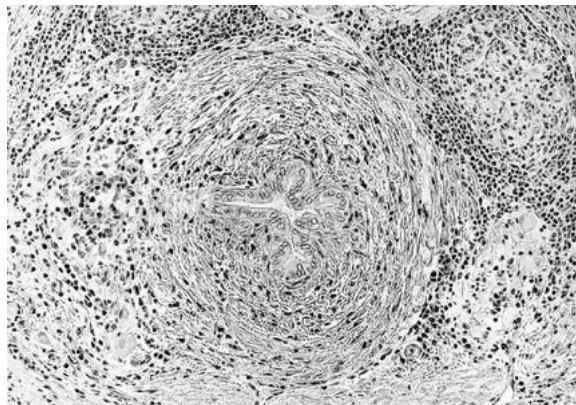
### 15. What are the hepatic histologic features of PBC and PSC?

Histologic abnormalities on liver biopsy are highly characteristic of both PBC and PSC in the early stages of disease. In PBC, the diagnostic finding is described as a *florid duct lesion*, which reveals bile duct destruction and granuloma formation. A severe lymphoplasmacytic inflammatory cell infiltrate in the portal tracts is accompanied by the segmental degeneration of interlobular bile ducts (also termed *chronic nonsuppurative destructive cholangitis*) ([Figure 19-2](#)).



**Figure 19-2.** Florid duct lesion (granulomatous bile duct destruction) in primary biliary cirrhosis. A poorly formed granuloma surrounds and destroys the bile duct in an eccentric fashion.

Early histologic changes in PSC include enlargement of portal tracts by edema, increased portal and periportal fibrosis, and proliferation of interlobular bile ducts. The diagnostic morphologic abnormality in PSC is termed *fibrous obliterative cholangitis*, which leads to the complete loss of interlobular and adjacent septal bile ducts from fibrous chord and connective tissue deposition (Figure 19-3). This histologic feature, however, occurs in only 10% of known cases. The histologic findings of end-stage liver disease for PBC and PSC are characterized by a paucity of bile ducts and biliary cirrhosis.



**Figure 19-3.** Fibrous obliterative cholangitis in PSC. The interlobular bile duct shows a typical fibrous collar, and the epithelium seems undamaged.

#### 16. Do asymptomatic patients with PBC have a normal life expectancy?

Most patients with PBC experience a progressive clinical course resulting in eventual cirrhosis. Asymptomatic patients have a longer median survival than symptomatic patients. However, a reduced median survival in asymptomatic PBC patients compared with age- and sex-matched healthy populations is observed. Estimates of overall median survival without liver transplantation range between 10 and 12 years from the time of diagnosis; advanced histologic disease imparts a median survival approaching 8 years.

#### 17. Do asymptomatic patients with PSC have a normal life expectancy?

Asymptomatic patients will have a reduced survival compared with normal controls. Indeed, nearly a quarter of patients who were asymptomatic at the time of diagnosis will develop clinical symptoms after 5 years. The median time of survival until death or liver transplant is 12 to 20 years for all PSC patients, regardless of symptoms, and approximately 9 years for those with symptoms on presentation.

#### 18. What is the role of mathematical models in estimating survival for PBC and PSC?

The development of mathematical models for both PBC and PSC has improved the ability to predict rates of disease progression and survival without liver transplantation. They are useful for developing endpoints of treatment failure and designing therapeutic trials.

A prognostic model for PBC developed at the Mayo Clinic relies on serum total bilirubin, albumin, PT, presence or absence of peripheral edema, the use of diuretics, and patient age. A revision of the Mayo Clinic PSC model includes variables such as patient age, serum total bilirubin, albumin, AST, and history of variceal bleeding. Similar results about prognosis have also been observed using the Model for End-stage Liver Disease (MELD). The MELD score is used to allocate patients for liver transplantation.

#### 19. Describe the relationship between alkaline phosphatase and the natural history of PSC.

Several studies have suggested that improvements in serum alkaline phosphatase over time are associated with improved outcomes. For example, the persistent improvement of alkaline phosphatase to less than or equal to 1.5 times the upper limit of normal (either spontaneously or with treatment) was associated with a reduction in the development of cholangiocarcinoma and liver-related endpoints, including liver-related deaths. These observations seem to occur most often in patients with intrahepatic PSC alone, but can occur with diffuse PSC. Additional studies are required to verify these initial observations.

#### 20. What vitamin deficiencies are associated with PBC and PSC?

Patients with PBC and PSC are susceptible to fat-soluble vitamin deficiencies, especially in advanced stages of disease. The occurrence of diminished visual acuity at night can be attributed to vitamin A deficiency. Vitamin D deficiency occurs commonly in association with marked steatorrhea, which is related to a decrease in small bowel bile acid concentration. Other factors that may contribute to malabsorption can include pancreatic insufficiency, bacterial overgrowth, or celiac disease. Prolongation of serum PT is associated with vitamin K deficiency (or worsening hepatic synthetic function). If the bilirubin is greater than 2 mg/dL, vitamins A, D,

and K should be checked annually. Finally, vitamin E deficiency infrequently occurs, but when present results in neurologic abnormalities affecting the posterior spinal columns, leading to areflexia, loss of proprioception, and ataxia.

## **21. What bone disease is associated with PBC and PSC?**

Metabolic bone disease (i.e., hepatic osteodystrophy), which may lead to disabling pathologic fractures, is a serious complication of both PBC and PSC. Clinical manifestations include osteopenia, osteoporosis, and fracture. Severe bone pain in an acute or chronic setting related to avascular necrosis may occur in PBC and PSC.

## **22. Describe the risk factors for osteoporosis in PBC and PSC.**

Patients with PBC are eight times more likely to develop osteoporosis compared to gender-matched controls. Risk factors for osteoporosis include advancing age, low body mass index, previous history of fractures, and advanced histologic disease. Both vitamin D deficiency and smoking have been implicated as risk factors for metabolic bone disease. Additional risk factors that have been described in the general population include glucocorticoid use, excessive alcohol intake, smoking, or having a parent who sustained a fracture. Elevations in serum bilirubin have also been correlated with the rate of bone loss in PBC patients. Osteoporosis has been reported in up to 15% of patients with PSC, which is a twenty-four-fold increase compared with a matched control population. In addition to advanced age and a lower body mass index, a duration of inflammatory bowel disease of 19 years or greater has been identified as a risk factor for osteoporosis in PSC patients. At the present time, baseline testing and regular follow-up screening with bone density scans every 2 to 3 years should be performed among PBC and PSC patients.

## **23. What are the nonmalignant hepatobiliary complications related to PSC?**

- Cholangitis may occur in 15% of individuals with PSC. This is typically after endoscopic biliary manipulation (rare in era of prophylactic antibiotics) or secondary to obstructing strictures, malignancy, or stones.
- Dominant strictures are defined as stenosis 1 mm or smaller in the hepatic duct or 1.5 mm or smaller in the common bile duct. They have been reported in up to 50% of patients with PSC and are associated with symptoms in 10% to 30% of individuals. When encountered, it should immediately raise a suspicion for the presence of cholangiocarcinoma. If a dominant stricture is detected on MRC, it should prompt an ERC to evaluate for underlying malignancy and palliate any obstructive lesions. When encountered, fluorescence *in situ* hybridization may detect chromosomal abnormalities (such as polysomy) from biliary brushings and can aid in the diagnosis of cholangiocarcinoma. Conventional biliary cytologic analysis is also routinely performed.
- Cholelithiasis, choledocholithiasis, and hepatolithiasis are common among PSC patients. For example, nearly 25% of patients with PSC have been found to have concurrent cholelithiasis, and hepatolithiasis is observed in 10% to 20% of cases
- Cirrhosis and portal hypertension may ultimately develop as the result of progressive cholestasis and fibrosis, which can lead to further complications such as ascites, hepatic encephalopathy, and varices.

## **24. What malignancies are associated with PSC and how should patients be screened?**

- Cholangiocarcinoma may occur in 5% to 10% of patients with PSC. The risk of this malignancy is nearly 400-fold higher in PSC compared with the general population. Nearly one quarter of cases are diagnosed either at the time of diagnosis or within the first 2 years after patients present. The American Association for the Study of Liver Diseases (AASLD) does not recommend routine screening for cholangiocarcinoma. Despite this, some practitioners have advocated a pragmatic approach to screening that involves an annual magnetic resonance imaging/MRCP and serum CA 19–9 measurement, followed by an ERC if a dominant stricture or CA 19–9 elevation is detected.
- Gallbladder cancer has been found in approximately 50% of PSC patients with a concurrent gallbladder mass lesion detected on imaging. Consequently, an annual ultrasound to detect gallbladder polyps is recommended. Although little is known about the natural history of gallbladder polyps, particularly small polyps, the AASLD does recommend patients undergo a cholecystectomy once a gallbladder lesion is detected. Hepatocellular carcinoma may develop in individuals with cirrhosis. The true prevalence of hepatocellular carcinoma in PSC has not been well described. However, individuals with cirrhosis should be enrolled in a 6-month, ultrasound-based screening program.
- Colorectal cancer is strongly associated with PSC and concurrent inflammatory bowel disease. Compared with patients with CUC alone, those with PSC-CUC have a tenfold increased risk of colorectal cancer. In addition, patients with colonic Crohn's disease may also have an increased risk. Importantly, colorectal neoplasia can develop soon after the two conditions are diagnosed. In addition, patients remain at risk following a liver transplant. Therefore, after a diagnosis of PSC, individuals should undergo a surveillance colonoscopy, and if inflammatory bowel disease is detected, they should continue colonoscopy with surveillance biopsies every 1 to 2 years. Surveillance should continue after liver transplantation.

## **25. How can you establish the diagnosis of cholangiocarcinoma in PSC patients?**

The presence of a mass lesion with delayed venous enhancement is indicative of cholangiocarcinoma. Establishing a diagnosis of hilar cholangiocarcinoma can be difficult as an obvious mass lesion may not always be

present. Patients without an obvious mass lesion should also be managed for cholangiocarcinoma if a malignant-appearing stricture is found particularly in the setting of a CA 19-9 level greater than 129 U/mL, or if a biopsy or cytologic examination is positive for adenocarcinoma. The presence of chromosomal polysomy detected by fluorescence in situ hybridization should also raise concern for cholangiocarcinoma.

## **26. What is the differential diagnosis of PBC and PSC?**

The differential diagnosis of PBC and PSC includes other causes of chronic cholestasis, including extrahepatic biliary obstruction caused by choledocholithiasis, iatrogenic strictures, and tumors. Although ultrasound or computed tomography may suggest the presence of biliary dilation, the performance of cholangiography is required to render a definitive diagnosis of PSC. Drug-induced cholestasis secondary to phenothiazines, estrogens, azoles, and a number of other drugs also should be considered as alternative diagnoses.

## **27. What is AMA-negative PBC?**

Patients may have the typical clinical and histologic features of PBC but have a negative AMA. This can occur in approximately 5% of patients with PBC. Patients with a negative AMA should undergo a cholangiography and select laboratory testing to rule out another cause of cholestasis. If the cholangiogram is normal, patients should have a liver biopsy to establish the diagnosis. The natural history and response to ursodeoxycholic acid (UDCA) are similar to patients with AMA-positive PBC.

## **28. What is meant by an overlap or a variant syndrome in PBC and PSC?**

The presence of features consistent with both AIH and PBC is defined as an overlap or a variant syndrome. Both serum ANA and AMA are present with increased titers by serologic testing. Lymphocytic piecemeal necrosis and coexistent portal inflammation with bile duct destruction are commonly seen. This group appears to benefit from either UDCA monotherapy, immunosuppressive treatment, or a combination of both treatments, in addition to UDCA. Using strict criteria, less than 20% of patients with PBC actually have objective evidence for an overlap syndrome with AIH. Recent data confirm that patients with typical PBC can develop AIH years later despite successful therapy with UDCA.

Similar overlap occurs in PSC and AIH in both adult and pediatric populations. Although the true prevalence of overlap is unknown, it is estimated that less than 5% of patients with PSC will have objective evidence for an overlap syndrome with AIH. In AIH-PSC, the multifocal biliary stricturing and dilation typical of PSC are often accompanied by histologic lesions seen in AIH. In patients with features of AIH and inflammatory bowel disease, or those who have been unresponsive to immunosuppression, a cholangiogram should be considered to exclude PSC. Similarly, transaminases greater than five times the upper limit in PSC patients could be suggestive of AIH-PSC. The prognosis of AIH-PSC appears to be more favorable than classic PSC but worse when compared with the prognosis of pure AIH. Patients with AIH-PSC overlap syndrome may benefit from immunosuppressive therapy.

## **29. What is meant by small-duct PSC?**

Small-duct PSC is defined by the presence of chronic cholestatic liver test abnormalities, liver histologic findings compatible with PSC, and a normal biliary tree by cholangiography. Most patients also have a concurrent diagnosis of inflammatory bowel disease. Approximately 20% of patients will progress to classic PSC in a 10-year period. Compared with classic PSC, small-duct PSC is associated with a longer survival and decreased risk of cholangiocarcinoma.

## **30. Describe the treatment of pruritus in patients with PBC and PSC.**

Cholestyramine relieves the itching associated with PBC and PSC by reducing serum bile acid levels in patients with cholestasis. In addition, it increases the intestinal excretion of bile acids by preventing their absorption. It is administered in 4-g doses (mixed with liquids) with meals or after breakfast for a total daily dose of 12 to 16 g. Cholestyramine should be given 1.5 hours before or after other medications to avoid nonspecific binding and diminished intestinal absorption. Once the itching remits, the dosage should be reduced to the minimal amount that maintains relief.

Rifampin at a dosage of 300 to 600 mg/day also has been effective in relieving pruritus caused by either p450 enzyme induction or inhibition of bile acid uptake. Anecdotal benefit with gabapentin has been reported and may be helpful when liver dysfunction precludes the safe use of rifampin.

For refractory cases, sertraline 100 mg a day or naltrexone 50 mg a day could be considered. In the setting of dominant strictures, endoscopic decompression may improve cholestasis and alleviate pruritus. Intractable pruritus is an indication for liver transplantation, which results in symptomatic relief.

## **31. How is osteoporosis treated in patients with PBC and PSC?**

Treatment of osteoporosis includes exercise, adequate supplementation of calcium and vitamin D, and a bisphosphonate. Bisphosphonates are considered a first-line agent for the treatment of osteoporosis. Alendronate has been shown to improve bone mass in PBC patients. For individuals with esophageal varices, a parenteral bisphosphonate should be used.

**32. Describe the treatment of fat-soluble vitamin deficiency in PBC and PSC.**

Problems with night vision caused by vitamin A deficiency may be alleviated by oral replacement therapy. Decreased serum levels can be corrected with the oral administration of vitamin A (25,000 to 50,000 units) two or three times per week. Because excessive vitamin A intake has been associated with hepatotoxicity, serum levels should be frequently monitored. In patients with low vitamin E levels, oral replacement therapy with 400 units/day can be instituted. If PT levels improve after a trial of water-soluble vitamin K (5 to 10 mg/day for 1 week), patients should be maintained on this regimen indefinitely. Prolongation of PT may be associated with hepatic failure in treatment-unresponsive cases. Severe vitamin D deficiency (less than 20 ng/mL) should be substituted with vitamin D 50,000 IU one to three times a week. A repeat vitamin D level should be obtained after 8 weeks of high-dose therapy and if repeated, patients should be maintained on 800 to 1000 IU each day thereafter.

**33. Describe the treatment of bacterial cholangitis in PSC.**

Bacterial cholangitis in PSC should be treated with broad-spectrum parenteral antibiotics. The administration of ciprofloxacin results in high biliary concentrations and has broad gram-negative and gram-positive coverage. Similar results can be observed with other fluoroquinolones, such as norfloxacin and levofloxacin. Prophylactic therapy with oral fluoroquinolone therapy may reduce the frequency of recurrent cholangitis, although no controlled trial has been performed to support this conclusion.

**34. What are the therapeutic options for biliary strictures in PSC?**

Balloon dilation of dominant strictures by either transhepatic or endoscopic approaches can relieve biliary obstruction in PSC. Balloon dilation is most effective in patients with acute elevations of serum total bilirubin level or recent onset of bacterial cholangitis. It appears less effective in patients with long-standing jaundice or a history of recurrent bacterial cholangitis. Although some studies have suggested an increased risk of complications following biliary stenting, this finding has not been consistently observed. Therefore temporary biliary stents should be used for strictures refractory to balloon dilation. A short course (5–7 days) of oral antibiotics following dilation or stenting can reduce the risk of postprocedural cholangitis as well. For strictures related to cholangiocarcinoma, the use of expandable metal stents can be employed for palliative treatment.

**35. What medical agents have been tried for the treatment of PBC?**

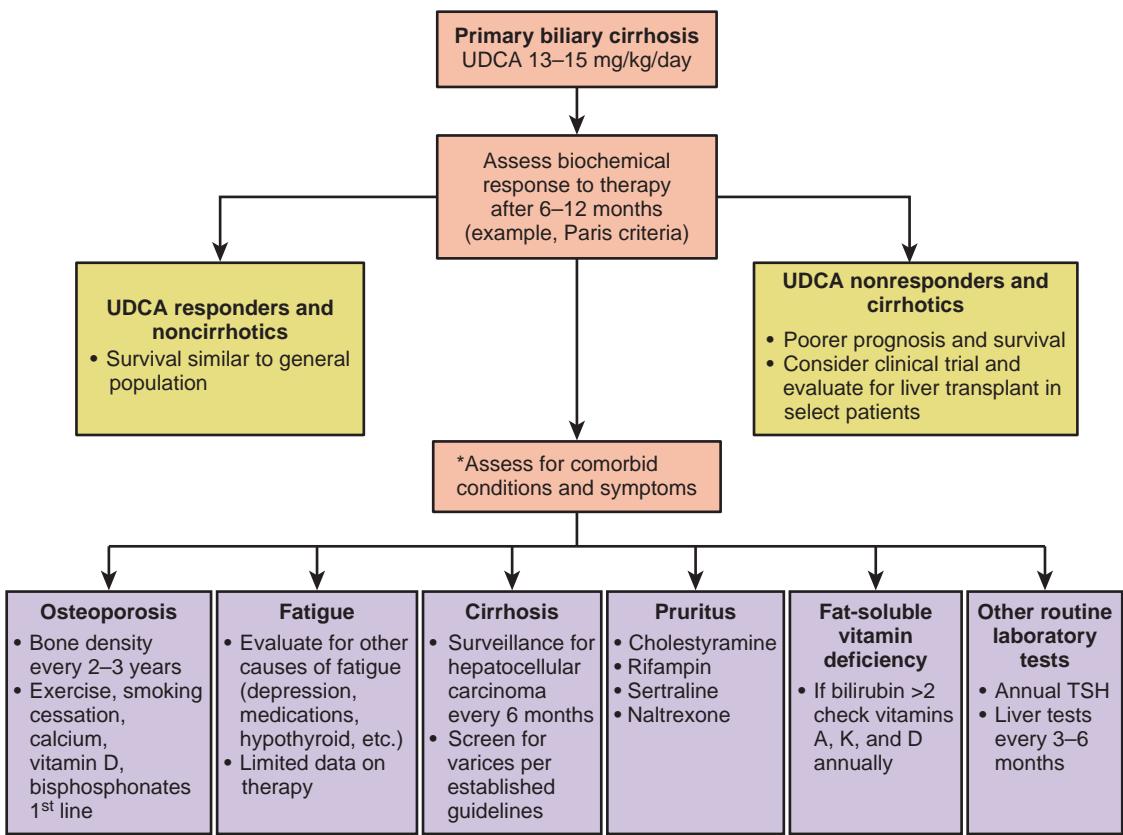
A number of potential treatments for PBC have been evaluated to date with the primary goal of stabilizing or halting disease progression. Pharmacologic agents such as colchicine, corticosteroids, cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil have demonstrated marginal clinical benefit and significant adverse effects. In five of the largest randomized, placebo-controlled clinical trials, UDCA in dosages of 13 to 15 mg/kg/day is associated with an estimated 30% risk reduction in the time to treatment failure or liver transplantation compared with placebo or inactive therapy. Furthermore, there have been several cohort studies documenting increased short- and medium-term survival for patients with early stage PBC responding to UDCA compared with the general population. In addition to initiating UDCA, the cornerstone of managing patients with PBC involves the early recognition and treatment of comorbid conditions (Figure 19-4).

**36. Which PBC patients are less likely to respond to UDCA?**

Age and gender have been associated with the response to UDCA. For example, men are less likely to respond than women (72% versus 80%, respectively). In addition, those who present at an older age (older than 70 years) have a response rate of 90% compared with a response rate of 50% among patients who were diagnosed at a younger age (younger than 30 years). Individuals who have improvements in their liver biochemistries are also more likely to be UDCA responders. Indeed, there are several criteria largely based on liver biochemistries to assess the response to UDCA. One such criterion that has been widely validated is the Paris criteria. After 1 year of treatment, individuals who met the Paris criteria (alkaline phosphatase level  $\leq 3 \times$  upper limit of normal, together with AST level  $\leq 2 \times$  upper limit of normal and a normal bilirubin level) had a 10-year transplant-free survival of 90%. In addition, patients with cirrhosis are less likely to benefit from UDCA.

**37. What medical agents have been tried for the treatment of PSC?**

Because of the variable nature of disease progression, the development of randomized clinical trials for the assessment of medical therapies in PSC has been difficult. As a potential consequence, no identified effective treatment is available. As with PBC, the use of pharmacologic agents such as *d*-penicillamine, colchicine, corticosteroids, and immunosuppressive agents such as mycophenolate mofetil has not conferred significant clinical benefit. UDCA in standard doses (13 to 15 mg/kg/day) appears to improve biochemical parameters, but no significant effect on histologic findings or survival has been observed. Although higher doses of UDCA (20 to 30 mg/kg/day) were observed to improve biochemical, cholangiographic, and Mayo risk scores in two pilot investigations, a large prospective randomized, double-blind controlled trial in Europe failed to confirm these initial results. Results from a North American trial using even higher doses of UDCA also failed to demonstrate a survival benefit and raised concerns about safety in this population.



\*Patients with refractory symptoms or end-stage liver disease should be evaluated for liver transplantation.

**Figure 19-4.** Overview of the management of PBC. TSH, Thyroid-stimulating hormone; UDCA, ursodeoxycholic acid.

### 38. Should patients with PSC receive UDCA to prevent colorectal neoplasia?

The practice of using UDCA to prevent colorectal neoplasia is not supported by high-quality evidence, and several studies have reported inconsistent results. The 2010 AASLD guidelines recommend against the use of UDCA as a chemopreventative agent. However, a recent metaanalysis suggests that lower doses of UDCA may have benefit in preventing advanced colorectal neoplasia.

### 39. What is the role of liver transplantation in PBC and PSC?

The treatment of choice for patients with end-stage PBC and PSC is liver transplantation, which confers 5- and 10-year survival rates of 85% and 70%, respectively. In addition to increased survival, improvements in health-related quality of life after liver transplantation for patients with PBC and PSC have been documented.

Factors that influence the consideration for liver transplantation are deteriorating hepatic synthetic function, the development of comorbid conditions (e.g., hepatocellular carcinoma), intractable symptoms, and diminished quality of life. A specialized protocol involving external beam and internal brachytherapy radiation, combined with chemotherapy and subsequent staging laparoscopy and liver transplantation, has produced excellent results for selected patients with early stage, perihilar cholangiocarcinoma associated with PSC.

The MELD score helps prioritize patients on the deceased donor transplant list. However, patients with intractable symptoms and diminished quality of life may have a relatively low MELD score. Therefore, patients may pursue living, related-donor transplantation. Indeed, PSC is a leading indication for living, related-donor liver transplantation for intractable symptoms such as recurrent cholangitis. However, recurrent cholangitis has not been associated with an increase in wait-list mortality.

### 40. Do PBC and PSC recur after liver transplantation?

Serum AMA levels decline and then increase to baseline levels in most patients with PBC after liver transplantation. The cumulative incidence of recurrent PBC is between 15% and 30% over 10 years based on strict clinical and histologic criteria. No significant effect on survival, however, has been associated with recurrent histologic disease. Tacrolimus-based immunosuppression is associated with a shorter time-to-recurrence than cyclosporine-based therapy. Although initial data suggest a potentially useful role for UDCA in slowing disease

progression among liver transplant recipients with early stage, recurrent PBC, further studies are required to verify this initial observation.

Recurrent PSC has been reported; yet its true prevalence depends on establishing well-defined diagnostic criteria and the rigor of excluding patients with chronic ischemic biliary strictures that can be caused by chronic ductopenic rejection, ABO incompatibility, prolonged cold ischemia time, cytomegalovirus infection, and hepatic artery thrombosis. Nevertheless, data suggest that approximately 20% to 30% of patients transplanted for PSC will develop recurrent disease over a 10-year period, with some individuals requiring consideration for hepatic retransplantation.

#### **41. What are the complications in PSC patients after liver transplantation?**

Patients with PSC appear to have an increased incidence of chronic ductopenic rejection and ischemic biliary duct strictureing. A mesenteric defect can be created during the biliary reconstruction which is typically a Roux-en-Y choledochojejunostomy. Therefore internal hernias can rarely form when bowel passes through this defect.

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#### **BIBLIOGRAPHY**

1. Al Mamari S, Djordjevic J, Halliday JS, et al. Improvement of serum alkaline phosphatase to <1.5 upper limit of normal predicts better outcome and reduced risk of cholangiocarcinoma in primary sclerosing cholangitis. *J Hepatol* 2013;58:329–34.
2. Angulo P, Grandison GA, Fong DG, et al. Bone disease in patients with primary sclerosing cholangitis. *Gastroenterology* 2011;140:180–8.
3. Baldursdottir TR, Bergmann OM, Jonasson JG, et al. The epidemiology and natural history of primary biliary cirrhosis: a nationwide population-based study. *Eur J Gastroenterol Hepatol* 2012;24:824–30.
4. Bangaralingam SY, Bjornsson E, Enders F, et al. Long-term outcomes of positive fluorescence in situ hybridization tests in primary sclerosing cholangitis. *Hepatology* 2010;51:174–80.
5. Boonstra K, Weersma RL, van Erpecum KJ, et al. Population-based epidemiology, malignancy risk and outcome of primary sclerosing cholangitis. *Hepatology* 2013; <http://dx.doi.org/10.1002/hep.26565>.
6. Brandt DJ, MacCarty RL, Charboneau JW, et al. Gallbladder disease in patients with primary sclerosing cholangitis. *Am J Roentgenol* 1988;150:571–4.
7. Carbone M, Mells GF, Pells G, et al. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. *Gastroenterology* 2013;144:560–9.
8. Corpechot C, Abenavoli L, Rabahi N, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. *Hepatology* 2008;48:871–7.
9. Darwish Murad S, Kim WR, Harnois DM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology* 2012;143:88–98.
10. Dave M, Elmunzer BJ, Dwamena BA, et al. Primary sclerosing cholangitis: meta-analysis of diagnostic performance of MR cholangiopancreatography. *Radiology* 2010;256:387–96.
11. Eaton JE, Talwalkar JA, Lazaridis KN, et al. Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management. *Gastroenterology* 2013;145:521–36.
12. Hirschfield GM, Heathcote EJ, Gershwin ME. Pathogenesis of cholestatic liver disease and therapeutic approaches. *Gastroenterology* 2010;139:1481–96.
13. Razumilava N, Gores GJ, Lindor KD. Cancer surveillance in patients with primary sclerosing cholangitis. *Hepatology* 2011;54:1842–52.
14. Selmi C, Bowlus CL, Gershwin ME, et al. Primary biliary cirrhosis. *Lancet* 2011;377:1600–9.
15. Shi J, Wu C, Lin Y, et al. Long-term effects of mid-dose ursodeoxycholic acid in primary biliary cirrhosis: a meta-analysis of randomized controlled trials. *Am J Gastroenterol* 2006;101:1529–38.
16. Singh S, Khanna S, Pardi DS, et al. Effect of ursodeoxycholic acid use on the risk of colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2013;19:1631–8.
17. Talwalkar JA, Angulo P, Johnson CD, et al. Cost-minimization analysis of MRC versus ERCP for the diagnosis of primary sclerosing cholangitis. *Hepatology* 2004;40:39–45.
18. Wariaghli G, Allali F, El Maghraoui A, et al. Osteoporosis in patients with primary biliary cirrhosis. *Eur J Gastroenterol Hepatol* 2010;22:1397–401.

#### **Website**

American Association for the Study of Liver Diseases. <http://www.aasld.org/> [Accessed September 22, 2014].

# VACCINATIONS AND IMMUNOPROPHYLAXIS IN GASTROINTESTINAL AND LIVER DISORDERS

Henry A. Horton, MD, Hayoon Kim, MD, Gil Y. Melmed, MD, MS

## 1. What is immunization?

The body's immune system is stimulated by pathogens (bacteria or viruses). This in turn causes an immunologic response through the generation of memory B cells that produce antibodies, which provide varying protection from the pathogen in the future. Immunizations allow for the controlled exposure to pathogens or proteins that induce these protective antibody responses, and have helped control the spread of infectious diseases significantly since their introduction.

## 2. What are the two main types of vaccines?

Inactivated vaccines, also known as *killed vaccines* are those in which the pathogen stimulates antibody production by triggering an immunologic response. Killed vaccines do not reproduce and thus cannot cause infection in the host.

Attenuated vaccines, also known as *live vaccines*, are made from pathogens that have been disabled from causing active disease. They are still able to stimulate antibody production resulting in protection from the disease, but in patients with compromised immunity this may theoretically result in infection with the pathogen being introduced in the vaccine.

## 3. Compare the recommended immunization schedule by vaccine and age group per Centers for Disease Control and Prevention (CDC) guidelines in adults and patients with other medical conditions.

See Figure 20-1 and Figure 20-2.

These recommendations must be read with the footnotes that follow.

VACCINE ▾	AGE GROUP ►	19-21 years	22-26 years	27-49 years	50-59 years	60-64 years	≥ 65 years
Influenza <sup>2,*</sup>					1 dose annually		
Tetanus, diphtheria, pertussis (Td/Tdap) <sup>3,*</sup>				Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs			
Varicella <sup>4,*</sup>					2 doses		
Human papillomavirus (HPV) Female <sup>5,*</sup>		3 doses					
Human papillomavirus (HPV) Male <sup>5,*</sup>		3 doses					
Zoster <sup>6</sup>						1 dose	
Measles, mumps, rubella (MMR) <sup>7,*</sup>		1 or 2 doses					
Pneumococcal polysaccharide (PPSV23) <sup>8,9</sup>				1 or 2 doses			1 dose
Pneumococcal 13-valent conjugate (PCV13) <sup>10</sup>				1 dose			
Meningococcal <sup>11,*</sup>				1 or more doses			
Hepatitis A <sup>12,*</sup>				2 doses			
Hepatitis B <sup>13,*</sup>				3 doses			

\*Covered by the Vaccine Injury Compensation Program

█ For all persons in this category who meet the age requirements and who lack documentation of vaccination or have no evidence of previous infection; zoster vaccine recommended regardless of prior episode of zoster

█ Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indication)

█ No recommendation

Report all clinically significant postvaccination reactions to the Vaccine Adverse Event Reporting System (VAERS). Reporting forms and instructions on filing a VAERS report are available at [www.vaers.hhs.gov](http://www.vaers.hhs.gov) or by telephone, 800-822-7967.

Information on how to file a Vaccine Injury Compensation Program claim is available at [www.hrsa.gov/vaccinecompensation](http://www.hrsa.gov/vaccinecompensation) or by telephone, 800-338-2382. To file a claim for vaccine injury, contact the U.S. Court of Federal Claims, 717 Madison Place, N.W., Washington, D.C. 20005; telephone, 202-357-6400.

Additional information about the vaccines in this schedule, extent of available data, and contraindications for vaccination is also available at [www.cdc.gov/vaccines](http://www.cdc.gov/vaccines) or from the CDC-INFO Contact Center at 800-CDC-INFO (800-232-4636) in English and Spanish, 8:00 a.m.–8:00 p.m. Eastern Time, Monday–Friday, excluding holidays.

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

**The recommendations in this schedule were approved by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians (AAFP), the American College of Physicians (ACP), American College of Obstetricians and Gynecologists (ACOG) and American College of Nurse-Midwives (ACNM).**

**Figure 20-1.** Recommended adult immunization schedule by vaccine and age group. (<http://www.cdc.gov/vaccines/schedules/hcp/adult.html> (Accessed September 22, 2014))

VACCINE ▼	INDICATION ►	Pregnancy	Immuno-compromising conditions (excluding Human Immunodeficiency Virus (HIV)) <sup>4,5,6,7,8,9,10</sup>	HIV Infection CD4+ T lymphocyte count <sup>4,5,6,7,8,9,10</sup>	Men who have sex with men (MSM)	Heart disease, chronic lung disease, chronic alcoholism	Asplenia (including elective splenectomy and persistent complement deficiencies) <sup>11,12</sup>	Chronic liver disease	Kidney failure, end-stage renal disease, receipt of hemodialysis	Diabetes	Healthcare personnel
Influenza <sup>2,*</sup>		1 dose IIV annually		< 200 cells/ $\mu$ L or ≥ 200 cells/ $\mu$ L				1 dose IIV annually			1 dose IIV or LAIV annually
Tetanus, diphtheria, pertussis (Td/Tdap) <sup>3,*</sup>		1 dose Td each pregnancy				Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs					
Varicella <sup>4,*</sup>		Contraindicated						2 doses			
Human papillomavirus (HPV) Female <sup>5,*</sup>			3 doses through age 26 yrs					3 doses through age 26 yrs			
Human papillomavirus (HPV) Male <sup>5,*</sup>			3 doses through age 26 yrs					3 doses through age 21 yrs			
Zoster <sup>6</sup>		Contraindicated						1 dose			
Measles, mumps, rubella (MMR) <sup>7,*</sup>		Contraindicated						1 or 2 doses			
Pneumococcal polysaccharide (PPSV23) <sup>8,*</sup>							1 or 2 doses				
Pneumococcal 13-valent conjugate (PCV13) <sup>10</sup>							1 dose				
Meningococcal <sup>11,*</sup>							1 or more doses				
Hepatitis A <sup>12,*</sup>							2 doses				
Hepatitis B <sup>13,*</sup>							3 doses				

\*Covered by the Vaccine Injury Compensation Program

Yellow box: For all persons in this category who meet the age requirements and who lack documentation of vaccination or have no evidence of previous infection; zoster vaccine recommended regardless of prior episode of zoster

Purple box: Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)

White box: No recommendation

These schedules indicate the recommended age groups and medical indications for which administration of currently licensed vaccines is commonly indicated for adults ages 19 years and older, as of January 1, 2013. For all vaccines being recommended on the Adult Immunization Schedule, a vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Licensed combination vaccines may be used whenever any components of the combination are indicated and when the other components are not contraindicated. For detailed recommendations on all vaccines, including those used primarily for travelers or that are used during the year, contact the manufacturers' package inserts and the complete statements from the Advisory Committee on Immunization Practices ([www.cdc.gov/vaccines/pubs/acip-recs.htm](http://www.cdc.gov/vaccines/pubs/acip-recs.htm)). Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

**Figure 20-2.** Recommended vaccinations based on medical indications. (<http://www.cdc.gov/vaccines/schedules/hcp/adult.html> (Accessed September 22, 2014))

#### 4. Who should receive immunization against hepatitis A?

- Travelers or individuals who live in countries where hepatitis A is endemic, including Central and South America, Africa, and large parts of Asia
- Men who have sexual contact with other men
- Users of illicit drugs whether injectable or not
- Individuals with clotting factor disorders such as hemophilia
- All children older than 12 months
- Individuals who live with someone with hepatitis A infection
- Active military personnel
- Patients with chronic liver disease from any cause

#### 5. How long after receiving the hepatitis A vaccine does it take before one is considered protected against infection?

One is considered protected 4 weeks after vaccination. There is some evidence of protection in certain individuals within 2 to 4 weeks, but currently 4 weeks is the timeframe recommended before someone can be considered to be protected from hepatitis A. This has implications if someone plans to travel to an endemic area for hepatitis A virus (HAV) within 4 weeks and is not immune. Protection after vaccination has been estimated to last 25 years in those vaccinated as adults and up to 20 years in those vaccinated as children.

#### 6. If someone naïve to HAV is traveling to an endemic area and has not previously received the vaccine, what should the person do?

He or she should receive immunoprophylaxis with anti-HAV immunoglobulin (Ig). This confers immediate protection, and lasts for up to 5 months. In addition, these individuals should also receive the HAV vaccine with the understanding that it may not "kick in" immediately.

#### 7. What are the recommendations for postexposure prophylaxis for hepatitis A?

- Children younger than 12 months of age should receive Ig. It is recommended that Ig be given within 2 weeks of exposure to hepatitis A.
- Healthy individuals ages 12 months to 40 years should receive a single dose of single-antigen hepatitis A vaccine at an age-appropriate dose. It has been found to be as effective as Ig, which was previously the only recommended way to protect individuals exposed to hepatitis A prior to 2007.
- For adults older than 40 years, Ig is preferred as there is a lack of data of vaccine performance in this age group and there are often more severe manifestations of hepatitis A in older adults, particularly those older than 75. If Ig is unavailable, the vaccine can be used.
- For those who are immunocompromised or have chronic liver disease, Ig is recommended.
- For those with vaccine allergy, Ig is recommended.

## 8. Who should receive hepatitis B vaccination?

- All children younger than 18 years
- Patients with chronic liver disease
- Travelers to or individuals who live in countries where hepatitis B is endemic (particularly Southeast Asia, sub-Saharan Africa, parts of the Middle East, and the Caribbean, where prevalence rates exceed 8%)
- Men who have sex with other men
- Users of illicit drugs
- Individuals who live or have sexual contact with someone with hepatitis B infection
- Health care workers (if you're reading this chapter, then this probably applies to you)
- Sexually active persons who are not in a mutually monogamous relationship
- Individuals with human immunodeficiency virus (HIV) infection
- Dialysis patients
- Diabetics between the ages of 19 through 59
- Anyone who wants it

## 9. Who should not receive the hepatitis A or B vaccines?

Common sense dictates that the following individuals should not be vaccinated:

- Individuals who are moderately or severely ill
- Individuals allergic to any component of the vaccine or who have previously had a serious allergic reaction to the vaccine

## 10. What are the recommended schedules for hepatitis B vaccination?

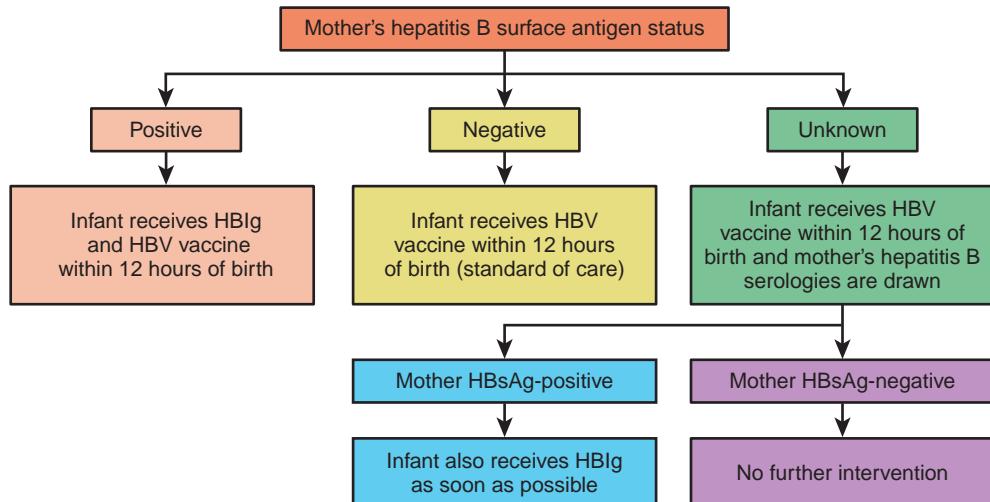
The most common recommendation is to give a three-dose series of hepatitis B vaccine. Give the first dose when indicated. Give the second dose 1 month after the first dose, and give the third dose approximately 5 months after the second. Alternate schedules have been approved for combined vaccines and special populations, such as individuals with cirrhosis who may benefit from a double dose of the HBV vaccine at the usually scheduled intervals.

## 11. What should be done postexposure to hepatitis B virus (HBV)?

After a person has been exposed to HBV, appropriate prophylaxis is to be given as soon as possible, preferably within 24 hours. It can effectively prevent infection. The mainstay of postexposure immunoprophylaxis is the hepatitis B vaccine, but in certain circumstances the addition of hepatitis B immunoglobulin (HBIG) will provide increased protection and should be given as soon as possible, within 14 days of exposure.

## 12. What is the recommended strategy for infants born to mothers with HBV?

- Infants whose mothers who are hepatitis B surface antigen–positive should receive HBIG and the first dose of hepatitis B vaccine within 12 hours of birth.
- If the mother's hepatitis B status is unknown, her hepatitis B serologies should be drawn and the infant should receive the hepatitis B vaccine *without* HBIG within 12 hours of birth. If the mother turns out to be hepatitis B surface antigen–positive, then HBIG should be administered at that time (Figure 20-3).



**Figure 20-3.** Algorithm for the management of infants born to mothers with hepatitis B. HBIG, Hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B vaccine.

**13. If there is an interruption between doses of hepatitis B vaccine, does the vaccine series need to be restarted?**

No, the series does not need to be restarted. If the vaccine series was interrupted after the first dose, the second dose should be administered as soon as possible. The second and third doses should be separated by an interval of at least 8 weeks. If only the third dose is delayed, it should be administered as soon as possible.

**14. Are booster doses of hepatitis B vaccine recommended?**

Booster doses of hepatitis B vaccine are recommended only in patients on dialysis with hepatitis B surface antibody levels less than 10 mIU/mL and other immunocompromised persons (e.g., HIV infected, transplant recipients, those receiving chemotherapy). For a person with a normal immune system who has received previous vaccination, booster doses are not recommended.

**15. Why are patients with liver cirrhosis susceptible to infection?**

The liver plays a key role within the innate immune response because it encounters ingested pathogens from the gut via circulation from the portal vein system. Cirrhotic patients have a fibrotic and poorly functioning liver with dysfunction of the reticuloendothelial system (Kupffer cells in the liver, macrophages, and monocytes) as well as granulocytes (neutrophils, eosinophils, and basophils). There have been studies demonstrating increased gut permeability of bacteria and associated toxins in patients with cirrhosis leading to spontaneous infections. There is frequently extensive shunting of venous circulation away from the liver in patients with cirrhosis, thus impairing clearing capacity following infections.

**16. What vaccine-preventable bacterial infections pose an increased risk for patients with cirrhosis?**

- Pneumococcal pneumonia in up to 15% of patients
- Bacteremia following instrumentation
- Meningitis with high rates of mortality

**17. Why is vaccination against hepatitis A and B strongly recommended in patients with cirrhosis?**

- A cirrhotic liver can't sustain any more injury (i.e., infection) without serious risk of decompensation and liver failure.
- Cirrhotic patients who develop acute hepatitis A infection are at significantly increased risk for liver failure and have a much higher risk of death compared with those patients without liver disease.
- When patients with cirrhosis develop acute hepatitis B infections, they more frequently have severe manifestations, including encephalopathy, ascites, hypoprothrombinemia, and acute liver failure.

**18. When should vaccinations against hepatitis A and B be given to cirrhotic patients?**

For both hepatitis A and B it is recommended that vaccinations be given early in the disease course. Patients have a better immune response to the vaccines when they are given shortly after developing cirrhosis when compared with those who receive it in the later stages of their disease. The patients should receive the standard two doses of the hepatitis A vaccine and three doses of the hepatitis B vaccine per normal guidelines if in the early stages of chronic liver disease, although patients with more advanced disease (i.e., cirrhosis) benefit from a double-dose of the HBV vaccine at standard intervals.

**19. Should patients with cirrhosis receive vaccination against the influenza virus?**

Yes. The influenza vaccine is recommended for patients with cirrhosis. Furthermore, studies have demonstrated increased hepatic decompensation in patients with advanced cirrhosis who develop influenza infections.

**20. When should the pneumococcus vaccine be given to patients with cirrhosis?**

Patients with cirrhosis should receive the pneumococcus vaccine as close as possible to the time of diagnosis, regardless of age. In addition to individuals older than 65 years, pneumococcal infections are more prevalent in patients with cirrhosis and others with chronic liver disease. In patients with concurrent alcoholism and liver cirrhosis, their risk of death from pneumococcal pneumonia, meningitis, or bacteremia is greatly increased.

**21. What other vaccinations should patients with cirrhosis receive?**

Patients with cirrhosis should receive the standard immunizations that are applicable to an otherwise healthy population. This includes routine diphtheria and tetanus booster immunizations every 10 years, and other age-appropriate vaccines. In general, killed or nonlive vaccines are preferred to live vaccines, when possible.

**22. Are patients with inflammatory bowel disease (IBD; Crohn's and ulcerative colitis) more susceptible to vaccine-preventable infections? If so, why?**

Yes. Several infections, including herpes zoster, human papilloma virus (HPV), pneumonia, and acute HBV infection are more common in patients with IBD and can be particularly dangerous, particularly among those who are on immunosuppressive therapies.

Patients with IBD are more susceptible to infections, including vaccine-preventable infections, for two primary reasons. First, IBD is characterized by dysregulation of the immune system, which is activated inappropriately by commensal gut bacteria, resulting in an abnormal intestinal immune response. Second, patients are frequently treated with short- and long-term immunosuppressive medications, namely glucocorticoids; immune modulators (including azathioprine, 6-mercaptopurine, and methotrexate); and tumor

necrosis factor-alpha (TNF- $\alpha$ ) inhibitors such as infliximab (Remicade), adalimumab (Humira), golimumab (Simponi), and certolizumab (Cimzia). Infections are the most common serious adverse events associated with these therapies.

### **23. When is the best time to address issues regarding vaccination status in patients with IBD?**

As soon as the diagnosis is made is the best time to address vaccinations, ideally before starting immunosuppressive medications, which may blunt immune responses to vaccines. Most vaccines can be given at any time, but should be timed ideally before the initiation of immunosuppressive therapy.

### **24. Which vaccines are recommended in IBD regardless of immunosuppression?**

In general, all *killed* or *nonlive* vaccines should be given according to routine guidelines. These include the following:

- Inactivated influenza vaccine (ideally before immunosuppression)
- Tetanus vaccine or booster (as part of tetanus-diphtheria, tetanus-diphtheria-pertussis, or diphtheria-tetanus-pertussis)
- HPV vaccine
- Meningococcus vaccine
- Hepatitis A vaccine
- Hepatitis B vaccine
- Pneumococcus (ideally before immunosuppression)
- Pertussis (ideally before immunosuppression)

### **25. Which vaccines are currently contraindicated in patients with IBD who are on immunosuppressive therapies such as corticosteroids, immunomodulators, and anti-TNF therapies?**

In general, all *live* vaccines are contraindicated. These include the following:

- Live, attenuated influenza vaccine (intranasal vaccine)
- Varicella zoster vaccine (generally)
- Herpes zoster (generally)
- Yellow fever vaccine
- Measles-mumps-rubella vaccine
- Typhoid live oral vaccine
- Tuberculosis bacillus Calmette-Guérin (BCG) vaccine (not given in the United States)
- Polio live oral vaccine (no longer used in the United States)
- Anthrax vaccine
- Smallpox vaccine

### **26. Which live vaccines might be considered in patients with IBD on immunosuppressive therapies in special circumstances?**

Although generally contraindicated, certain live vaccines (varicella and zoster) might be considered in patients with IBD who cannot discontinue immunosuppressive treatments. Special considerations are warranted when the risk of natural infection outweighs the risks of the vaccine. Clinical circumstances in which natural infection risk for varicella and zoster are increased include occupations such as preschool teachers and health care workers.

Some considerations are necessary for patients with varicella zoster (chicken pox) and herpes zoster (shingles). Adults and children with IBD who may be immunosuppressed who acquire varicella infection can develop widespread dissemination of varicella zoster virus, which can be fatal. Given that the varicella and zoster vaccines are live attenuated virus vaccines (the zoster vaccine is a concentrated form of the varicella vaccine), they are generally considered contraindicated in immunocompromised patients. However, according to the U.S. ACIP, patients with low-dose immunosuppression treatments such as steroid therapy (less than 20 mg/day) may receive the vaccine. The same holds true for those on low doses of methotrexate, azathioprine, or 6-mercaptopurine. Recent data also suggests that the zoster vaccine is safe in patients on anti-TNF therapies, and that older adult patients who receive zoster vaccination while on anti-TNF therapies are less likely to develop zoster infection than their nonvaccinated counterparts.

### **27. Can household contacts of immunosuppressed patients with IBD receive live vaccines?**

Yes. They should receive live vaccines, including MMR, rotavirus, and varicella. However, if the recipient of a varicella vaccine develops a rash, they should avoid direct contact with the immunosuppressed individual until the rash resolves. It is recommended that household contacts *not* receive the live influenza vaccine, because there is a theoretical risk of live virus transmission and a killed (injected) alternative is available.

### **28. Should the yellow fever vaccine be given to an IBD patient on immunosuppression who will be traveling to an endemic area?**

No. It is a live, attenuated vaccine and serious adverse effects have been noted such as encephalitis and multiorgan system failure. Travel to these endemic areas (including sub-Saharan Africa and parts of South America) should ideally be avoided among patients who can't receive the vaccine safely. If travel to these areas is absolutely necessary, patients should be counseled on the risks of the disease and prevention of mosquito bites, which is the transmission vector for the disease. They will also require a formal vaccination waiver from a travel medicine specialist.

**29. Do IBD patients on immune suppression have an adequate immune response to vaccinations?**

Not to all. Several studies have demonstrated that patients who are on combination therapy (azathioprine or 6-mercaptopurine together with a TNF inhibitor) have significantly decreased immunologic responses to several vaccines compared with those not on combinations of immunosuppressants. Therefore patients should be targeted for vaccination soon after diagnosis, before immunosuppression is initiated, whenever possible.

**30. Should women with IBD receive the HPV vaccine? If so, why?**

Yes. Women with IBD have higher rates of cervical dysplasia and cancer-causing HPV serotypes, particularly if on immunosuppression for longer than 6 months. The vaccine is recommended for women and men ages 9 to 26.

**31. Can babies born to mothers who received anti-TNF agents during pregnancy receive their usual childhood vaccinations?**

For the most part, yes, with the notable exception that no live vaccines should be administered during the first 6 months of life in newborns whose mothers received anti-TNF therapy during pregnancy. Many anti-TNF therapies are monoclonal antibodies, which may be actively transported across the placenta, particularly during the third trimester, such that the drug concentrations at birth may be higher in the newborn than in the mother. In the United States, the only live vaccine during this initial 6-month period is the rotavirus vaccine, although in other countries there may be additional live vaccines (such as the BCG vaccine) that should be withheld because of concerns for disseminated infection from live vaccines.

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**BIBLIOGRAPHY**

1. Bridges CB, Woods L, Coyne-Beasley T, et al. Advisory Committee on Immunization Practices (ACIP) recommended immunization schedule for adults aged 19 years and older—United States. MMWR 2013;(Suppl. 62):9–16.
2. Centers for Disease Control and Prevention. Update: prevention of hepatitis A after exposure to hepatitis A virus and in international travelers: updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2007;19:1080–4.
3. Centers for Disease Control and Prevention. Vaccines and immunizations, <http://www.cdc.gov/vaccines/> [Accessed September 22, 2014].
4. Chow J, Golan Y. Vaccination of solid-organ transplantation candidates. Clin Infect Dis 2009;49:1550–3.
5. Dezfoli S, Melmed GY. Vaccination issues in patients with inflammatory bowel disease receiving immunosuppression. Gastroenterol Hepatol 2012;8:504–12.
6. Duchini A, Goss JA, Karpen S, Pockros PJ. Vaccinations for adult solid-organ transplant recipients: current recommendations and protocols. Clin Microbiol Rev 2003;16:357–64.
7. Duchini A, Hendry RM, Nyberg LM, et al. Immune response to influenza vaccine in adult liver transplant recipients. Liver Transpl 2001;7:311.
8. Harpaz R, Ortega-Sanchez IR, Seward JF. Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008;57:1–30.
9. Leber B, Spindelboeck W, Stadlbauer V. Infectious complication of acute and chronic liver disease. Semin Respir Crit Care Med 2012;33:80–95.
10. Leise MD, Talwalkar JA. Immunizations in chronic liver disease: what should be done and what is the evidence. Curr Gastroenterol Rep 2013;15(1):300.
11. Mast EE, Weinbaum CM, Fiore AE, et al. Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention(CDC). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR Recomm Rep. 2006 Dec 8;55(RR-16):1–33.
12. Melmed GY, Agarwal N, Frenck RW, et al. Immunosuppression impairs response to pneumococcal polysaccharide vaccination in patients with inflammatory bowel disease. Am J Gastroenterol 2010;105:148–51.
13. Melmed GY, Ippoliti AF, Papadakis KA, et al. Patients with inflammatory bowel disease are at risk for vaccine-preventable illnesses. Am J Gastroenterol 2006;101:1834–40.
14. Melmed GY. Vaccination strategies in patients on immunosuppression and biologics. Inflamm Bowel Dis 2009;15(9):1410–6.
15. Sands BE, Cuffari C, Katz J, et al. Guidelines for immunizations in patients with inflammatory bowel disease. Inflamm Bowel Dis 2004;10:677–92.
16. Sjögren MH, Cheatham JG. Hepatitis vaccines and immunoprophylaxis. In: GI/Liver secrets plus. 4th ed. Mosby; 2010. p. 151–7.
17. Soesman NM, Rimmelzwaan GF, Nieuwkeep NJ, et al. Efficacy of influenza vaccination in adult liver transplant recipients. J Med Virol 2000;61:85.
18. Wasan SK, Baker SE, Skolnik PR, Farraye FA. A practical guide to vaccinating the inflammatory bowel disease patient. Am J Gastroenterol 2010;105:1231–8.
19. Zhang J, Xie F, Delzell E, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA 2012;308(1):43–9.

**Websites**

Centers for Disease Control and Prevention. Vaccines and immunizations. [www.cdc.gov/vaccines/](http://www.cdc.gov/vaccines/) [Accessed September 22, 2014].

# PREGNANCY AND LIVER DISEASE

Devina Bhasin, MD, and Roshan Shrestha, MD

## NORMAL ANATOMIC AND PHYSIOLOGIC CHANGES DURING PREGNANCY

### 1. What are the structural and functional hepatic adaptations during pregnancy?

Liver size and histologic characteristics do not change. Maternal blood volume and cardiac output increase significantly, without a corresponding increase in hepatic blood flow, with a net decrease in fractional blood flow to the liver. An enlarging uterus makes venous return via the inferior vena cava progressively more difficult toward term. Blood is shunted via the azygous system with possible development of esophageal varices.

### 2. Does liver function change during pregnancy?

Hepatic function remains normal during pregnancy, but the normal range of laboratory values changes because of hormonal changes and an increase in blood volume with subsequent hemodilution. Aspartate aminotransferase (AST), alanine aminotransferase (ALT),  $\gamma$ -glutamyl transpeptidase (GGTP), bilirubin, and prothrombin remain within normal limits. Total alkaline phosphatase (AP) is elevated. The placenta is a major source of AP; levels return to normal within 20 days after delivery. Estrogen increases the synthesis of fibrinogen, as well as other coagulation proteins (factors VII, VIII, IX, and X). Also attributed to estrogen's effects are significant increases in serum concentrations of major lipid classes (triglycerides, cholesterol, and low- and very-low-density lipoproteins). These levels may be twice the normal limit of nonpregnant women of the same age. Serum albumin decreases slightly, contributing to the approximately 20% decline in serum protein concentration. Plasma concentrations of other serum proteins (ceruloplasmin, corticosteroids, testosterone, serum binding protein for thyroxine), as well as vitamin D and folate, also increase during pregnancy.

## DISEASES DURING PREGNANCY

- Coincident occurrence of liver disease (viral hepatitis, alcoholic hepatitis, gallstone disease, autoimmune hepatitis)
- Intrahepatic cholestasis of pregnancy (IHCP)
- Acute fatty liver of pregnancy (AFLP)
- Hemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome)

### 3. Can gestational age differentiate between different liver diseases in pregnancy?

Yes. Hyperemesis gravidarum presents in the first trimester of pregnancy. Patients have severe nausea and vomiting, and approximately one-half have associated elevations of bilirubin, AST, or ALT. Cholestasis of pregnancy, viral hepatitis, and abnormal liver chemistries caused by cholelithiasis may present at any point in gestation, from the first to the third trimester. AFLP and preeclamptic liver disease (HELLP, hepatic infarct, and hepatic rupture) are specifically encountered in the third trimester of pregnancy. Both herpes simplex virus and hepatitis E virus are exacerbated in pregnancy and usually present in the third trimester. The presentation may be a mild elevation in transaminases or severe hepatic failure. Budd-Chiari syndrome presents from the second half of pregnancy to 3 months postpartum.

## COINCIDENT OCCURRENCE

### 4. Can we assume the presence of chronic liver disease in a pregnant patient with angiomas and palmar erythema on physical examination and small esophageal varices detected endoscopically?

No. Spider angiomas and palmar erythema are common and appear in approximately two thirds of pregnant women without liver disease. Small esophageal varices are present in approximately 50% of healthy pregnant women without liver disease because of the increased flow in the azygous system.

### 5. What is the most common cause of jaundice in pregnancy?

Viral hepatitis is the most common cause of jaundice during pregnancy.

## 6. How severe is the course of viral hepatitis acquired during pregnancy?

- Hepatitis A, B, and C run a similar course in pregnant and nonpregnant patients.
- Hepatitis E runs a different course in pregnancy. It is fulminant in up to 20% of patients, compared with less than 1% of nonpregnant women. The fatality rate is 1.5% during the first trimester, 8.5% during the second trimester, and up to 21% during the third trimester compared with 0.5% to 4% in nonpregnant women. Fetal complications and neonatal deaths are increased if infection is acquired in the third trimester of pregnancy.
- Herpes simplex hepatitis can be fulminant in pregnancy and associated with high mortality rates. Patients present in the third trimester with fever, systemic symptoms, and possibly vesicular cutaneous rash. Associated pneumonitis or encephalitis may be present. Liver biopsy is characteristic, showing necrosis and inclusion bodies in viable hepatocytes, along with few or no inflammatory infiltrates. Response to acyclovir therapy is prompt; there is no need for immediate delivery of the baby.

## 7. What signs and symptoms suggest the diagnosis of Budd-Chiari syndrome?

The clinical triad of sudden onset of abdominal pain, hepatomegaly, and ascites, near term or shortly after delivery. Ascitic fluid shows a high protein content in approximately one half of cases. Biopsy typically shows centrilobular hemorrhage and necrosis, along with sinusoidal dilation and erythrocyte extravasation into the space of Disse. Hepatic scintigraphy and computed tomography (CT) typically show compensatory hypertrophy of the caudate lobe resulting from its separate drainage into the inferior vena cava. Doppler analysis of portal and hepatic vessels and magnetic resonance imaging (MRI) establish hepatic vein occlusion.

## 8. Is the serum ceruloplasmin level a good diagnostic marker in pregnant women at term who are suspected of having Wilson disease?

No. Ceruloplasmin levels increase gradually during pregnancy, reaching the maximum at term. Because of this, in a patient with Wilson disease who usually has a low level of ceruloplasmin, the level may increase misleadingly into the normal range (greater than 20 mg/dL) during pregnancy.

## 9. Can we maintain a woman with Wilson disease on therapy during pregnancy?

Absolutely. Therapy must continue during pregnancy; otherwise, the mother is at risk for hemolytic episodes associated with fulminant hepatic failure. Agents approved by the U.S. Food and Drug Administration (FDA) are D-penicillamine, trientine, and zinc. Evidence indicates that penicillamine and trientine (tissue copper-chelating agents) are teratogenic in animal studies, and there are reports of penicillamine effects in humans, including cutis laxis syndrome or micrognathia, low-set ears, and other abnormalities. According to the current consensus, penicillamine and trientine are safe in doses of 0.75 to 1 g/day during the first two trimesters; the dosage should be reduced to 0.5 g/day during the last trimester and in nursing mothers. Zinc therapy is an attractive alternative with a different mechanism of action; it induces synthesis of metallothionein, which sequesters copper in enterocytes, blocking its absorption. No teratogenic effects have been reported in animals or humans. The recommended doses are 50 mg three times/day for patients with 24-hour urinary copper values greater than 0.1 mg and 25 mg three times/day for patients with lower urinary copper values. Close monitoring of urinary copper and zinc levels is suggested; the zinc dose should be adjusted accordingly.

## INTRAHEPATIC CHOLESTASIS OF PREGNANCY

### 10. What is the most common liver disorder unique to pregnancy?

IHCP is the most common disorder unique to pregnancy.

### 11. What is the major clinical manifestation of IHCP?

Severe pruritus with onset in the second or, more commonly, third trimester (more than 70% of cases).

### 12. What biochemical changes are noted in IHCP?

Serum bile acids, often measured as choleylglycine, increase by 10- to 100-fold. Serum levels of AP rise by seven- to tenfold, along with a modest rise in serum levels of 5'-nucleotidase (confirming the hepatic source of AP). AST, ALT, and direct bilirubin also rise. No evidence of hemolysis is found. GGTP is usually normal, as is prothrombin time (PT) and international normalized ratio (INR).

### 13. What is the expected clinical and biochemical course after delivery for patients with IHCP?

Pruritus should improve promptly after delivery (within 24 hours). Jaundice is rare and, if present, may persist for days. Biochemical abnormalities may persist for months.

### 14. What is a possible cause for abnormal bleeding in a postpartum woman previously diagnosed with IHCP? What is the treatment?

Malabsorption of liposoluble vitamins, including vitamin K, especially in patients treated with cholestyramine for pruritus. The INR corrects with parenteral administration of vitamin K.

### **15. What is the effect of IHCP on the fetus?**

Fetal distress requiring cesarean section develops in approximately 30% to 60% of cases. Prematurity occurs in approximately 50% of cases and fetal death in up to 9% of affected pregnancies. All of these effects are more likely if the disorder begins early in pregnancy.

### **16. What is the therapy for IHCP?**

Alleviating pruritus is the main goal. Therapeutic agents include:

- Ursodeoxycholic acid, 15 mg/kg/day; up to 24 mg/kg/day studied with good results
- Cholestyramine, 4 g four or five times/day (bile acid-binding resin)
- Hydroxyzine hydrochloride (Atarax) or pamoate (Vistaril) (antihistamines); Atarax 25 to 50 mg every 6 hours as needed, Vistaril 15 to 30 mg every 6 hours as needed
- Phenobarbital, 100 mg/day (choleretic and centrally acting sedative)
- Phototherapy with ultraviolet B light as directed by a dermatologist

Vitamin K before delivery is highly recommended to minimize the risk of postpartum hemorrhage. Mother and fetus should be observed closely. Elective induction is recommended at 36 weeks (severe cases) or 38 weeks (average cases) if the fetal lungs have matured.

### **17. Can IHCP recur?**

Yes. Approximately 40% to 70% of subsequent pregnancies show evidence of mild intrahepatic cholestasis. The same pattern can be seen with use of estrogen-containing contraceptives.

### **18. What atypical signs and symptoms make the diagnosis of IHCP doubtful?**

Fever, hepatosplenomegaly, pain, jaundice preceding or without pruritus, and pruritus after delivery or before 21 weeks of pregnancy, especially with a singleton pregnancy, should prompt the search for an alternate diagnosis.

### **19. What biochemical changes suggest an alternate diagnosis?**

- Normal AST and ALT levels
- Elevated AP and GGT (i.e., biliary disease)
- Predominantly unconjugated hyperbilirubinemia (i.e., hemolysis)

## **ACUTE FATTY LIVER OF PREGNANCY**

### **20. What are the clinical and laboratory features of AFLP?**

AFLP is a rare disorder with an incidence of 1 in 13,000 to 1 in 16,000 pregnancies. Onset occurs in the second half of pregnancy, usually during the third trimester, although occasionally postpartum onset is reported. Clinical manifestations include nausea and vomiting, jaundice, malaise, thirst, and altered mental status. Severe cases progress rapidly to hypoglycemia, disseminated intravascular coagulation (DIC), renal insufficiency, coma, and death. Signs of coexistent preeclampsia may be present, such as moderately increased arterial blood pressure, proteinuria, and hyperuricemia. Laboratory abnormalities consist of moderate AST and ALT elevations (usually less than 1000), conjugated hyperbilirubinemia, elevated PT, fibrin split products, and D-dimers, along with low platelet count, elevated levels of ammonia and serum uric acid, and leukocytosis. Hypoglycemia is a sign of extreme severity; blood glucose levels must be monitored closely.

### **21. How do we diagnose and treat AFLP?**

High clinical suspicion is crucial for early recognition and appropriate management. AFLP is suggested by hepatic failure at or near term or shortly after delivery in the absence of risk factors or serologic findings suggesting viral hepatitis. Thirst, a symptom of underlying vasopressin-resistant diabetes insipidus, is characteristic to AFLP and HELLP syndrome. Liver biopsy, if feasible, is diagnostic in the appropriate clinical context. Treatment consists of admission to hospital, close monitoring by a multidisciplinary team (hepatologist, maternal-fetal medicine specialist, intensive care specialist), and immediate delivery. Recovery is usually complete, although it may be delayed in patients with significant clinical complications before delivery (e.g., DIC, renal failure, infections).

### **22. Is biopsy pathognomonic for AFLP?**

Biopsy is confirmatory but not pathognomonic or indispensable in making the diagnosis. Histologic findings are characterized by microvesicular fatty infiltration, mostly in centrilobular zones. In general, lobular and trabecular architecture is preserved, and inflammatory infiltrates and cell necrosis are mild, if present at all. AFLP is a systemic disorder. Similar fatty changes have been noted in pancreatic acinar cells and tubular epithelial cells of the kidneys. The same prominent microvesicular steatosis is seen in other conditions such as Reye syndrome, sodium valproate toxicity, Jamaican vomiting sickness, and congenital defects of urea cycle enzymes or beta-oxidation of fatty acids.

**23. Describe the pathogenesis of AFLP.**

Pathogenesis remains somewhat unclear. In some cases the fetus has an isolated deficiency of long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), which leads to a disorder of mitochondrial fatty acid oxidation. The inheritance pattern is recessive and involves a mutation from glutamic acid to glutamine at amino acid residue 474 (Glu474Gln) on at least one allele. It is hypothesized that in the presence of this mutation in homozygous or compound heterozygote fetuses, long-chain fatty acid metabolites produced by the fetus or placenta accumulate in the mother and are highly toxic to the maternal liver. The mother is phenotypically normal; her genotype does not correlate with development of AFLP.

**24. What is the outcome of a child whose mother has AFLP?**

Previously reported fetal mortality rates of 75% to 90% have been significantly reduced by better awareness, earlier diagnosis, availability of neonatal intensive care units, and institution of close monitoring and dietary treatment through childhood. In pregnancies associated with LCHAD defects, children present at a mean age of 7.6 months (range, 0-60 months) with acute hepatic dysfunction (incidence of 79%). They may experience hypoketotic hypoglycemia, hypotonia, hepatomegaly, hepatic encephalopathy, high transaminase levels, and fatty liver. The condition may progress rapidly to coma and death. Frequent feedings of a low-fat diet in which the fats are medium-chain triglycerides prevent hypoketotic hypoglycemic liver dysfunction. According to recent studies, 67% of children treated with dietary modification are alive, and most attend school.

**25. Does AFLP recur in subsequent pregnancies?**

In the cases associated with LCHAD defects, the disorder is recessive, affecting one in four fetuses. The rate of recurrence of maternal liver disease is 15% to 25%.

**26. Is genetic testing indicated in women diagnosed with AFLP?**

All women with AFLP, as well as their partners and children, should be advised to undergo molecular diagnostic testing. Testing for Glu474Gln only in the mother is not sufficient to rule out LCHAD deficiency in the fetus or other family members.

**HEMOLYSIS, ELEVATED LIVER ENZYMES, AND LOW PLATELETS****27. What is the spectrum of liver involvement in preeclampsia?**

Liver involvement in preeclampsia ranges from subclinical, with biopsy evidence of fibrinogen deposition along hepatic sinusoids, to several, possibly severe disorders. In patients with HELLP syndrome, the chief complaint is abdominal pain, which usually presents in the second half of gestation but may occur up to 7 days after delivery (almost 30% of affected women). Hepatic infarction is another rare manifestation of liver involvement in preeclampsia. Patients present in the third trimester or early after delivery with unexplained fever, leukocytosis, abdominal or chest pain, and extremely elevated aminotransferases (greater than 3000). The diagnosis depends on visualization of hepatic infarcts on CT contrast images or MRI. Subcapsular hematomas and hepatic rupture are life-threatening complications with high morbidity and mortality rates. A high index of suspicion and early CT imaging allow diagnosis and prompt intervention.

**28. How common is HELLP syndrome?**

The incidence of HELLP syndrome is 0.2% to 0.6% in all pregnancies and 4% to 12% in preeclamptic patients. The incidence is higher in multiparous, white, and older women, but the mean age of occurrence is around 25 years.

**29. Describe the incidence and prognosis of spontaneous intrahepatic hemorrhage.**

Spontaneous intrahepatic and subcapsular hemorrhage occurs in approximately 1% to 2% of patients with preeclampsia, with an estimated incidence of 1 in 45,000 live births. Prognosis improves with awareness, early diagnosis by imaging studies, and aggressive surgical management. Recent reported maternal mortality rates range from 33% to 49%. Fetal mortality remains high (60%).

**30. What findings typically lead to the diagnosis of HELLP syndrome?**

Diagnosis relies on typical laboratory evidence of liver involvement with associated thrombocytopenia. Not all patients have clinical hypertension or proteinuria at presentation. Liver test abnormalities are hepatocellular. Liver function is normal. Thrombocytopenia is present, usually less than 100,000/mm<sup>3</sup>. Hemolysis is mild, with microangiopathic findings on peripheral smear. Biopsy is characteristic but may be extremely risky and is not needed for diagnosis. It shows periportal hemorrhage, fibrin deposition, and necrosis, possibly with steatosis or deposition of fibrinogen along sinusoids with focal parenchymal necrosis. A normal biopsy does not exclude the diagnosis, because involvement may be patchy.

**31. What is the treatment for severe preeclamptic liver disease?**

The initial priority is to stabilize the mother by administering intravenous fluids, correcting any concurrent coagulopathy, administering magnesium for seizure prophylaxis, and treating severe hypertension. Early hepatic imaging is indicated to rule out infarcts or hematomas. Fetal functional status should be determined. Fetal

outcome is related mostly to gestational age. Beyond 34 weeks of gestation with evidence of fetal lung maturity, delivery is the recommended therapy. If fetal lungs are immature, the fetus can be delivered 48 hours after administration of two doses of steroids. Delivery should be attempted immediately with evidence of fetal or maternal distress. In cases of ruptured subcapsular hematoma, massive transfusions and immediate surgical intervention are required. In cases in which surgical intervention is not possible and there are signs and symptoms of acute liver failure, liver transplantation should be considered for survival. Liver transplantation is usually being done under urgent category "status 1," thus giving top priority for organ offers and both graft and patient survival outcomes have been excellent.

### **32. Does HELLP recur in subsequent pregnancies?**

Possibly. Studies report recurrence risks as low as 3.4% and as high as 25%.

### **33. What information helps to differentiate AFLP from HELLP?**

At presentation, AFLP and HELLP may be difficult to differentiate. Hypertension is usually but not invariably associated with HELLP syndrome. Patients with HELLP have mild, predominantly unconjugated hyperbilirubinemia caused by hemolysis, along with severe thrombocytopenia, but no laboratory values suggestive of hepatic failure. Laboratory abnormalities are significantly more severe in AFLP; evidence of hepatic synthetic failure manifests as prolonged PT and significant hypoglycemia in advanced stages. Fibrinogen is low, and ammonia is elevated. Biopsy shows microvesicular steatosis, predominantly in the central zone, in patients with AFLP, whereas patients with HELLP show predominantly periportal fibrin deposition, necrosis, and hemorrhage.

### **34. Is prospective screening necessary in pregnancies complicated by AFLP or HELLP?**

From 15% to 20% of pregnancies complicated by AFLP and less than 2% of pregnancies complicated by HELLP syndrome are associated with fetal LCHAD deficiency. Newborns should be screened prospectively at birth in all pregnancies complicated by AFLP. Homozygosity and heterozygosity for the Glu474Gln would indicate the need for avoidance of prolonged fasting and replacement of dietary long-chain fatty acids with medium-chain fatty acids. Parents and physicians should be educated in the risk of metabolic crises and sudden death and instructed in the need for early intervention with intravenous glucose during episodes of vomiting, lethargy, and even minor illnesses.

Recent results do not justify routine screening of newborns in pregnancies complicated by HELLP syndrome. Molecular diagnostic testing should, however, be considered in women with recurrent HELLP syndrome in multiple pregnancies.

## **CARE OF PATIENTS WITH PREEXISTING LIVER DISEASE**

### **BEFORE AND DURING PREGNANCY**

- Contraception
- Management of underlying liver disease
- Management of portal hypertension
- Management in the setting of transplantation
- Prevention of vertical transmission

### **CONTRACEPTION**

#### **35. What methods of contraception are available for patients with liver disease?**

Patients with advanced or untreated liver disease commonly experience amenorrhea and infertility. If clinical improvement leads to restoration of fertility, multiple methods of contraception are available, including barrier methods and intrauterine devices. Tubal ligation may be used in women who have completed their families. Estrogen-based contraceptive agents are generally contraindicated, especially for patients with acute liver disease, but progestin contraceptives are safe alternatives. Combination contraceptives are absolutely contraindicated in patients with cholestatic jaundice of pregnancy or jaundice with prior use, and World Health Organization is listing them as category 4 type drugs for patients with decompensated cirrhosis of any cause. Numerous formulations and delivery systems are available.

## **MANAGEMENT OF UNDERLYING LIVER DISEASE**

#### **36. How should patients with preexisting liver disease be managed if pregnancy occurs?**

Patients are best managed by a multidisciplinary team that includes a maternal-fetal medicine specialist, perinatologist, and hepatologist. They have an increased risk for maternal complications along with a higher incidence of fetal loss and prematurity. In general, patients should be maintained on the previous therapy that was successful in controlling liver disease and restoring fertility. Women with autoimmune hepatitis should be continued on corticosteroids alone or in combination with azathioprine, which is not teratogenic at standard doses. Patients with Wilson disease should be continued on the anticopper agent. Patients with portal hypertension should have a baseline endoscopy. If they have never bled and medium or large varices are present,

they are at increased risk for variceal hemorrhage during pregnancy. Primary prophylaxis with a nonselective beta blocker or isosorbide mononitrate should be instituted. The fetus should be monitored for bradycardia or growth retardation if the mother is maintained on beta blockers. Variceal bleeding is safely managed with variceal band ligation or sclerotherapy. Octreotide in customary doses is safe in pregnancy if needed. Performing surgical portacaval shunts for patients with well-preserved liver function is possible. Placement of a transjugular intrahepatic portosystemic shunt and splenectomy (in patients with massive splenomegaly, varices, and thrombocytopenia) also have been reported.

## MANAGEMENT OF PORTAL HYPERTENSION

### 37. What are the effects of pregnancy on the mother with portal hypertension?

The morbidity rate is 30% to 50% because of possible onset of hepatic encephalopathy, spontaneous bacterial peritonitis, and progressive liver failure. The incidence of variceal hemorrhage is 19% to 45%, especially in the second trimester and during labor. Postpartum hemorrhage is seen in 7% to 10% of women, most frequently in those with cirrhotic portal hypertension; thrombocytopenia plays a major role. The mortality rate of these complications is 4% to 7% in noncirrhotic and 10% to 18% in cirrhotic patients with portal hypertension. Data regarding this topic originate mostly from case series and prospectively acquired data are few.

### 38. What is the effect of maternal portal hypertension on pregnancy?

Spontaneous abortion rates for patients with cirrhosis range from 15% to 20%. Most cases occur in the first trimester. Of interest, patients with extrahepatic portal hypertension and patients with well-compensated cirrhosis who underwent surgical shunting before conception have abortion rates similar to the general population. The incidence of premature termination of pregnancy in the second and third trimesters is similar in all previously mentioned groups. Fetal mortality rates are approximately 50% if the mother requires emergent surgical intervention for variceal hemorrhage. Perinatal mortality rates in cirrhotic mothers are as high as 11% to 18% because of premature delivery, stillbirth, and neonatal death, but they are similar to those for the general population in noncirrhotic patients with portal hypertension and patients who underwent previous portal surgical decompressive procedures.

## MANAGEMENT IN THE SETTING OF ORTHOTOPIC LIVER TRANSPLANTATION

### 39. When can a liver transplant recipient actively seek conception?

At least a 1-year waiting period is advisable. Case reports suggest that conception close to the transplant date may result in increased maternal and fetal morbidity and mortality. Contraception should be instituted before resuming sexual relations, preferably with barrier methods.

### 40. Is pregnancy possible after liver transplantation?

Pregnancy will become possible once normal menstrual cycles resume. In women with chronic liver disease, most pretransplant amenorrhea resolves in approximately 3 to 10 months following liver transplantation.

### 41. What are the possible complications of pregnancies occurring after liver transplantation?

Hypertensive complications, preterm delivery, infection, and fetal growth restriction are possible complications. Immunosuppressive agents used such as cyclosporine and tacrolimus cause hypertension and renal insufficiency, as well as impairment of placental amino acid transport systems, leading to fetal growth restriction. Cytomegalovirus (CMV) infection can cause congenital anomalies and liver disease if the mother was infected early in the pregnancy. Risk for CMV infection is greatest immediately after transplant or in case of increased immunosuppression caused by rejection episodes. Rejection is a rare complication; only approximately 10% of the reported pregnancies have been complicated by biopsy-proved rejection.

### 42. What is recommended in the management of a pregnancy occurring following liver transplantation?

Management as high-risk pregnancy by a specialist in maternal-fetal medicine is preferred. Immunosuppression should be continued with close monitoring of blood levels. Abnormal liver function tests should be evaluated aggressively. Percutaneous liver biopsy is not contraindicated but should be performed under ultrasound guidance. Monitoring for maternal and fetal CMV infection is indicated. Quantitative CMV immunoglobulins or detection of CMV viremia and viruria in the mother are adequate tests, and even amniotic fluid analysis could be used if there is suspicion of fetal infection. Deliveries should be via cesarean section if there are active herpes simplex lesions present. Prophylactic antibiotics should be used for deliveries in general.

### 43. What are pregnancy safety data regarding maintenance immunosuppressive agents used in orthotopic liver transplantation?

- Category B (no evidence of risk in humans): prednisone
- Category C (risks cannot be ruled out): cyclosporine, tacrolimus (FK506), rapamycin (Sirolimus), OKT3, antithymocyte globulin, antilymphocyte globulin

- Category D (evidence of risk): azathioprine
- Category D with black box warning (high risk: mutagenic/teratogenic): mycophenolate mofetil (CellCept, Myfortic). It is advised that anyone pregnant or wishing to become pregnant be changed to azathioprine.

#### **44. Is breastfeeding permitted after delivery in a liver transplant recipient?**

At this time, it is believed that breastfeeding should be discouraged. A woman administered immunosuppressive drugs should not breastfeed. Calcineurin inhibitors could cause immunosuppression and nephrotoxicity, and no recommendation can be made at this time regarding azathioprine-based regimens because there is extremely limited experience. Manufacturer recommends against breastfeeding in mothers administered interferon therapy, ribavirin, ganciclovir, or lamivudine. No specific recommendation can be made regarding foscarnet. No data are available regarding ursodeoxycholic acid excretion in breast milk.

#### **45. Are immunosuppressive agents safe during pregnancy?**

Corticosteroids, azathioprine, cyclosporine, tacrolimus, and OKT3 have no apparent teratogenic potential. All may contribute to low birth weights and fetal prematurity. Tacrolimus crosses the placenta and may contribute to transient perinatal hyperkalemia and mild, reversible renal impairment. There are no reports of allograft loss as a result of pregnancy in the tacrolimus-treated group of 35 patients at the University of Pittsburgh. The Philadelphia-based cyclosporine registry reports an allograft rejection rate of 17% and a graft loss rate of 5.7% in 35 patients taking cyclosporine during gestation and the postpartum period. Mycophenolate mofetil should not be used during pregnancy because of increased risks of birth defects and miscarriage. Patients should have one pregnancy test immediately before starting mycophenolate mofetil and another pregnancy test 8 to 10 days later. Pregnancy tests should be repeated during routine follow-up visits. Patients should be counseled about acceptable birth control during mycophenolate mofetil therapy, and continue birth control for 6 weeks after it is discontinued. A risk evaluation and mitigation strategy was mandated by the FDA to minimize the risks associated with mycophenolate mofetil use in the childbearing population.

### **PREVENTION OF VERTICAL TRANSMISSION**

#### **46. How may vertical transmission of viral hepatitis A be prevented?**

Maternal infection with the hepatitis A virus (HAV) is not associated with fetal loss or teratogenic effects. Vertical transmission of HAV is rare. There are no restrictions concerning breastfeeding. Passive immunization can be performed with immunoglobulin for urgent postexposure prophylaxis. HAV vaccine is safe and recommended in pregnant women at risk for acquiring the disease, such as women traveling to endemic areas.

#### **47. How may vertical transmission of viral hepatitis B be prevented?**

The hepatitis B virus (HBV) may be transmitted vertically. If the mother acquires HBV in the first trimester of pregnancy, there is a 10% risk that the infant will test positive for hepatitis B surface antigen (HBsAg) at birth. The percentage dramatically increases to 80% to 90% if the acute maternal infection develops during the third trimester. In mothers who have chronic hepatitis B and test positive for the hepatitis B e antigen (HBeAg), 90% of neonates develop chronic hepatitis B without prophylaxis. If the mother has HBeAg- and HBeAb-negative chronic hepatitis B, 40% of neonates develop chronic hepatitis B infection without prophylaxis. The rate decreases to less than 5% if the mother is HBeAg-negative and HBeAb-positive. Antepartum serum HBsAg testing is mandatory. Neonates of HBsAg-positive mothers or HBsAg status-unknown mothers are treated with HBV human hyperimmunoglobulin, 0.5 mL intramuscularly, at delivery. At the same time, they are given the first dose of HBV vaccine. The second dose is administered at 1 month of age, and the third dose at 6 months of age. If the mother is HBsAg-negative, the child should be vaccinated only with the three-dose regimen, with the first inoculation at birth. The regimen is approximately 85% effective in preventing chronic hepatitis B in neonates and is ineffective in cases of hematogenous transplacental transmission, which are seen in approximately 15% of pregnancies as a result of small placental tears. Active and passive immunization at birth also reduces the possibility of viral transmission by breastfeeding. Hepatitis B vaccination is safe in pregnant women. Lamivudine and tenofovir are pregnancy class C and B drugs, respectively. Tenofovir has a higher barrier to resistance and may be a better option for mothers who may need antiviral therapy long term postpartum. General recommendations are to offer prophylaxis against vertical transmission to women to have a high viral load starting 4 to 8 weeks prior to delivery to allow for an adequate decline in the HBV viral load.

#### **48. What is the risk of vertical transmission of viral hepatitis C?**

The risk of perinatal transmission is approximately 2% for infants of anti-hepatitis C virus (HCV) seropositive women. When a pregnant woman is HCV-RNA-positive at delivery, this risk increases to 4% to 7%. Higher HCV RNA levels appear to be associated with a greater risk. Levels of RNA of 1 million copies/mL are reportedly associated with vertical transmission rates as high as 50%. HCV transmission increases up to 20% in women coinfecting with HCV and human immunodeficiency virus (HIV). There are currently no data to determine whether antiviral therapy reduces perinatal transmission. Immunoglobulin therapy is ineffective. Rate of infection is similar among first- and second-born children.

#### **49. Is it possible to prevent vertical transmission of viral hepatitis D and G?**

Perinatal transmission of the hepatitis D virus (HDV) is rare. There are no documented cases of vertical transmission of HDV in the United States. No clinical data about hepatitis G infection during pregnancy are

available, and no studies of vertical transmission have been done. Because of the lack of data on HDV, recommendations regarding breastfeeding are unknown.

#### **50. Are HCV-infected women allowed to breastfeed?**

HCV-infected women should be told that hepatitis C transmission via breastfeeding has not been documented. Current available studies show that the average rate of infection is 4%, similar for breastfed and bottle-fed infants. According to the Centers for Disease Control and Prevention and a 1997 consensus statement from the National Institutes of Health (NIH), "Breastfeeding is not contraindicated for HCV-positive mothers," and "the maternal to baby transmission of HCV infection through breast milk has not been documented." Risk of transmission by breastfeeding was not found to be significant unless coinfection with HIV was present.

#### **51. Does the mode of delivery influence hepatitis C transmission?**

Current data are limited but indicate that infection rates are similar in infants delivered vaginally and cesarean-delivered infants. There are no prospective studies evaluating the use of elective cesarean section for the prevention of mother-to-infant transmission of HCV. However, avoiding fetal scalp monitoring and prolonged labor after rupture of membranes may reduce the risk of transmission to the infant.

#### **52. How can perinatal HCV infection be diagnosed?**

Infants passively acquire maternal antibodies that can persist for months. Anti-HCV antibodies after 15 months of age or positive HCV-RNA, which can be detected as early as 1 or 2 months, are diagnostic of perinatal transmission of HCV. A recent NIH consensus conference recommends that infants born to HCV-positive mothers be tested for HCV infection by HCV-RNA tests on two occasions between the ages of 2 and 6 months and/or have tests for anti-HCV after 15 months of age. Positive anti-HCV in infants prior to 15 months of age may be due to transplacental transfer of maternal anti-HCV antibody.

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#### **BIBLIOGRAPHY**

- Armenti VT, Herrine SK, Radomski JS, et al. Pregnancy after liver transplantation. *Liver Transpl* 2000;6:671–85.
- Barton JR, Sibai BM. HELLP and the liver diseases of preeclampsia. *Clin Liver Dis* 1999;3:31–49.
- Brewer GJ, Johnson WD, Dick RD, et al. Treatment of Wilson's disease with zinc. XVII: Treatment during pregnancy. *Hepatology* 2000;31:364–70.
- Carr DB, Larson AM, Schmucker BC, et al. Maternal hemodynamics and pregnancy outcome in women with prior orthotopic liver transplantation. *Liver Transpl* 2000;6:213–21.
- Connolly TJ, Zuckerman AL. Contraception in the patient with liver disease. *Semin Perinatol* 1998;22:78–182.
- European Pediatric Hepatitis C Virus Network. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. *Br J Obstet Gynaecol* 2001;108:371–7.
- Everson GT. Liver problems in pregnancy: distinguishing normal from abnormal hepatic changes. *Medscape Womens Health* 1998;3:3.
- Ibdah JA, Yang Z, Bennett MJ. Liver disease in pregnancy and fetal fatty acid oxidation defects. *Mol Genet Metab* 2000;71:182–9.
- Jain A, Venkataraman R, Fung JJ, et al. Pregnancy after liver transplantation under tacrolimus. *Transplantation* 1997;64:559–65.
- Misra S, Sanyal AJ. Pregnancy in a patient with portal hypertension. *Clin Liver Dis* 1999;3:147–63.
- National Institutes of Health. Consensus development conference statement: management of hepatitis C. Bethesda, MD: National Institutes of Health; 2002.
- Oral contraceptives. An update on health benefits and risks. *J Am Pharm Assoc* 2001;41:875–86.
- Polywka S, Schröter M, Feucht H-H, et al. Low risk of vertical transmission of hepatitis C virus by breast milk. *Clin Infect Dis* 1999;29:1327–9.
- Reinus JF, Leikin EL. Viral hepatitis in pregnancy. *Clin Liver Dis* 1999;3:115–31.
- Riely CA. Contraception and pregnancy after liver transplantation. *Liver Transpl* 2001;7(Suppl. 1):S74–S76.
- Riely CA, Fallon HJ. Liver diseases. In: Burrow GN, Duffy TB, editors. *Medical complications during pregnancy*. 5th ed. Philadelphia: WB Saunders; 1999. p. 269–94.
- Rinaldo P, Raymond K, Al-Odaib A, et al. Clinical and biochemical features of fatty acid oxidation disorders. *Curr Opin Pediatr* 1998;10:615–21.
- Sandhu BS, Sanyal AJ. Pregnancy and liver disease. *Gastroenterol Clin North Am* 2003;32:407–36.
- Sheikh RA, Yasmeen S, Pauly MP, et al. Spontaneous intrahepatic hemorrhage and hepatic rupture in the HELLP syndrome. *J Clin Gastroenterol* 1999;28:323–8.
- Van Nunen AB, De Man RA, Heijtink RA, et al. Lamivudine in the last 4 weeks of pregnancy to prevent perinatal transmission in highly viremic chronic hepatitis B patients. *J Hepatol* 2000;32:1040–1.
- World Health Organization. Hepatitis B and breastfeeding. *J Int Assoc Physicians AIDS Care* 1998;4:20–1.
- Yang Z, Yamada J, Zhao Y, et al. Prospective screening for pediatric mitochondrial trifunctional protein defects in pregnancies complicated by liver disease. *JAMA* 2002;288:2163–6.
- Zanetti AR, Ferroni P, Magliano EM, et al. Perinatal transmission of the hepatitis B virus and of the HBV-associated delta agent from mothers to offspring in Northern Italy. *J Med Virol* 1982;9:139–48.

#### **Websites**

American Association for the Study of Liver Diseases. <http://www.aasld.org> [Accessed September 22, 2014].  
American Liver Foundation. <http://www.liverfoundation.org> [Accessed September 22, 2014].

# RHEUMATOLOGIC MANIFESTATIONS OF HEPATOBILIARY DISEASES

Sterling G. West, MD, MACP, FACP

## VIRAL HEPATITIS

### 1. How often is viral hepatitis associated with rheumatic manifestations?

Approximately 25% of patients with hepatitis B antigenemia develop a rheumatic syndrome. Up to 50% of patients with hepatitis C develop an autoimmune manifestation. Transient arthralgias can occur in 10% of patients during acute hepatitis A viral infection.

### 2. What are the most common extrahepatic rheumatologic manifestations of hepatitis B infection?

- Acute polyarthritis-dermatitis syndrome
- Polyarteritis nodosa (PAN)
- Membranous or membranoproliferative glomerulonephritis
- Cryoglobulinemia—usually associated with hepatitis C; only 5% of all essential mixed cryoglobulinemia is due to hepatitis B alone

### 3. Describe the clinical characteristics of the polyarthritis-dermatitis syndrome associated with hepatitis B infection

In the preicteric prodromal period of acute hepatitis B infection, 10% to 25% of patients develop a polyarthritis that is acute, severe, and symmetric, involving both small (fingers) and large (knees, ankles) joints. Classically, an urticarial rash frequently (40%) accompanies the arthritis. Both the arthritis and rash can precede the onset of jaundice or elevated liver-associated enzymes by several days. The arthritis improves with nonsteroidal antiinflammatory drugs and usually subsides soon after the onset of jaundice. Patients who develop chronic hepatitis B viremia may subsequently have recurrent arthralgias or arthritis. This syndrome is caused by deposition of circulating hepatitis B surface antigen (HBsAg)—hepatitis B surface antibody immune complexes in the joints and skin.

### 4. What is the typical presentation of hepatitis B-associated PAN?

Up to 10% of all patients with PAN have positive hepatitis B serologic findings and evidence of viral replication (HBeAg, hepatitis B virus [HBV] DNA). They may present with a combination of fever, arthritis, mononeuritis multiplex, abdominal pain, renal disease, or cardiac disease. Although liver-associated enzymes may be abnormal, symptomatic hepatitis is not a prominent feature.

### 5. How is PAN associated with hepatitis B antigenemia diagnosed?

The diagnosis is made on the basis of a consistent clinical presentation coupled with an abdominal or renal angiogram showing vascular aneurysms and corkscrewing of blood vessels (Figure 22-1). The gold standard is a tissue biopsy showing medium-vessel vasculitis.

### 6. What is the treatment of hepatitis B-associated PAN?

Patients are typically very ill and will die without aggressive therapy. Antiviral agents and plasmapheresis for removal of immune complexes are used early to control the acute symptoms and antigenemia. Corticosteroids (30 mg/d) are also used early to control inflammation. Once the acute process is controlled, corticosteroids are tapered (usually over 2 to 3 weeks) because they, alone or in combination with cytotoxic drugs, can enhance viral replication. Cyclophosphamide should be avoided. Patients older than 50 years of age and those with renal insufficiency or cardiac, gastrointestinal, or central nervous system involvement have the worst prognosis. The overall 5-year survival rate is 50% to 70%.

### 7. What are the most common hepatitis C virus (HCV)-related autoimmune disorders?

- Mixed (type II and III) cryoglobulinemia (40%-60% of HCV patients have cryoglobulins but only 5% develop vasculitis).
- Systemic PAN-like vasculitis (<1% of HCV patients).
- Membranoproliferative glomerulonephritis.



**Figure 22-1.** Renal angiogram showing vascular aneurysms in a patient with hepatitis B-associated polyarteritis nodosa (arrows).

- Nonerosive polyarthritides (2%-20%)—Patients with acute hepatitis C infection can have an acute (usually transient) polyarthritides resembling rheumatoid arthritis (RA) with involvement of hands, wrists, shoulders, knees, and hips symmetrically. Although these patients are frequently rheumatoid factor (RF)-positive because of cryoglobulinemia, they do not have anti-cyclic citrullinated peptide antibodies. Other patients have an intermittent monoarthritis or oligoarthritis affecting large-and medium-sized joints.
- Autoantibody production (40%-65%)—RF, antinuclear antibodies (ANAs), anticardiolipin antibodies, anti-smooth muscle antibodies, anti-liver-kidney microsomal antibody 1, and antithyroid antibodies.
- Sjögren's-like syndrome with dry eyes and dry mouth (5%-19%)—caused by a lymphocytic sialadenitis. Anti-SS-A(Ro) and anti-SS-B(La) antibodies are negative.
- Autoimmune thrombocytopenia, myasthenia gravis, and sarcoidosis have been rarely associated with HCV infection or its therapy.

#### 8. What is the relationship between viral hepatitis and cryoglobulinemia?

Approximately 80% to 90% of patients with essential mixed cryoglobulinemia (type II and type III) are positive for hepatitis C. Hepatitis C viral RNA is concentrated up to 1000-fold in the cryoprecipitate. Hepatitis C-infected patients are prone to develop autoimmune and lymphoproliferative diseases (35 × higher risk). This is due to HCV's predilection to bind to B lymphocytes via CD81. This binding lowers the activation threshold for these cells, facilitating autoantibody production and cryoglobulinemia. Also, HCV can infect B cells, causing proto-oncogene, *bcl-2*, recombination, which inhibits apoptosis, leading to extended lymphocyte survival. This results in cryoglobulinemia and neoplastic transformation (non-Hodgkin B-cell lymphomas).

#### 9. Describe the typical clinical features of cryoglobulinemia associated with hepatitis C infection.

A cryoglobulin is an immunoglobulin that precipitates at temperatures of less than 37 °C and redissolve with rewarming. They precipitate in blood vessels in patients, causing inflammation and a variety of symptoms. Patients present with a combination of fever, arthritis (which can be confused with RA), renal disease, paresthesias from peripheral neuropathy, and a predominantly lower extremity petechial rash, positive RF, and low complement levels (especially C4). Hepatitis is not a prominent feature. Patients have been successfully treated with combined corticosteroids, Peg-interferon α-2b/ribavirin/protease inhibitor combination, and plasmapheresis. Recently, rituximab (anti-CD20) has been used successfully to deplete the B-cell population making the cryoglobulins.

## AUTOIMMUNE AND OTHER LIVER DISEASES

### 10. What is lupoid hepatitis?

Lupoid hepatitis is now called *type I (classic) autoimmune hepatitis* (AIH). Type I AIH can occur in all age groups, but most patients are young and predominantly female (70%-80%). Many patients have clinical (arthralgias [50%]) and laboratory manifestations that may resemble systemic lupus erythematosus (SLE). Patients commonly have positive ANAs (40%-60%), antibodies against smooth muscle antigen (90%) frequently with specificity against F-actin, hypergammaglobulinemia (immunoglobulin G [IgG]), and occasionally lupus erythematosus cells. They do not have antibodies against dsDNA. Type I AIH has been described in patients with SLE, Sjögren's syndrome, mixed connective tissue disease, and limited systemic sclerosis. Patients with type I AIH can have other autoantibodies such as atypical perinuclear antineutrophil cytoplasmic antibodies.

### 11. To what degree is type I AIH similar to SLE?

See Table 22-1.

**Table 22-1.** Comparison of Type I AIH and SLE

	SLE	TYPE I AIH
Young women	+	+
Polyarthritis	+	+
Fever	+	+
Rash	+	+
Nephritis	+	-
Central nervous system disease	+	-
Photosensitivity	+	-
Oral ulcers	+	-
ANA	99%	40%-60%
LE cells	70%	Uncommon
Polyclonal gammopathy	+	+
Anti-Smith antibodies	25%	0
+ Anti-dsDNA	70%	Rare
+ Anti-F-actin	Rare	60%-95%

AIH, Autoimmune hepatitis; ANA, antinuclear antibody; LE, lupus erythematosus; SLE, systemic lupus erythematosus.

### 12. What is the difference between anti-Sm and anti-SM antibodies?

Anti-Sm antibodies are antibodies against the Smith antigen, which is an epitope on small nuclear ribonuclear proteins. It is highly diagnostic of SLE. The anti-SM antibody is an antibody against the smooth muscle antigen (which is frequently F-actin). It is highly diagnostic of type I AIH (Table 22-2).

**Table 22-2.** Anti-Sm Versus Anti-SM Antibodies

	SLE	TYPE I AIH
Anti-Smith (Sm) antibodies	Yes	No
Anti-smooth muscle (SM) antibodies	No	Yes

AIH, Autoimmune hepatitis; SLE, systemic lupus erythematosus.

### 13. List the common autoimmune diseases associated with primary biliary cirrhosis (PBC).

Approximately 50% of patients with PBC have one or more additional autoimmune diseases. The following disorders are most commonly seen:

- Keratoconjunctivitis sicca (mostly secondary Sjögren's syndrome)—25% to 30%
- Autoimmune thyroiditis (Hashimoto disease)—20%
- Raynaud's —20%
- RA—8% to 10%

**Table 22-3.** PBC Arthritis versus RA

	PBC ARTHRITIS	RA
Frequency in patients	10% develop RA	1%-10% develop PBC
No. of joints*	Polyarticular	Polyarticular
Symmetry	Symmetric	Symmetric
Inflammatory	Yes	Yes
Rheumatoid factor	Sometimes	Yes (85%)
Erosions on radiograph	Rare	Common

PBC, Primary biliary cirrhosis; RA, rheumatoid arthritis.

\*PBC can involve distal interphalangeal joints of fingers, whereas RA does not involve these joints.

- Limited systemic sclerosis (calcinosis, Raynaud phenomenon, esophageal, telangiectasia [CREST]) occurs in 4% to 8% of PBC patients and antedates PBC by an average of 14 years
- Others: pernicious anemia (4%), celiac disease, SLE (1.5%), polymyositis

**14. Compare and contrast the arthritis that may occur with PBC and RA.**

See Table 22-3.

**15. What other musculoskeletal manifestations may occur in patients with PBC?**

- Osteomalacia caused by fat-soluble vitamin D malabsorption (low 25-OH vitamin D level)
- Osteoporosis caused by renal tubular acidosis
- Hypertrophic osteoarthropathy

**16. What autoantibodies commonly occur in patients with PBC?**

The most common and diagnostic antibody is the antimitochondrial antibody (AMA) seen in 80% to 90% of patients with PBC. This antibody is directed against various mitochondrial enzymes, most commonly the E2 component of the pyruvate dehydrogenase complex.

Approximately 60% of patients have one or more autoantibodies other than AMA including:

- ANAs—20% to 50%
- Antiphospholipid antibodies (usually IgM)—15% to 20%
- Anticentromere antibodies—15% to 20%.

Most patients also have manifestations of the CREST variant of limited systemic sclerosis.

**17. How commonly does arthritis occur in patients with hereditary hemochromatosis (HHC)?**

Approximately 40% to 75% of patients have a noninflammatory degenerative arthritis, most commonly involving the second and third metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, wrists, hips, knees, and ankles. Of importance, this arthropathy may be the presenting complaint (30% to 50%) of patients with hemochromatosis and is frequently misdiagnosed in young men as seronegative RA.

**18. Describe the radiographic features suggestive of hemochromatotic arthropathy (HA).**

Suggestive radiographic features include subchondral sclerosis, cyst formation, irregular joint space narrowing, chondrocalcinosis, and osteophyte formation consistent with degenerative arthritis of involved joints. The key finding is degenerative changes in the MCP joints (typically second and third) with hooklike osteophytes (Figure 22-2). This finding is important, because the MCP joints and wrists rarely develop degenerative joint disease without an underlying cause such as hemochromatosis.

**19. What is the relationship between calcium pyrophosphate disease and hemochromatosis?**

Chondrocalcinosis of the triangular fibrocartilage at the ulnar side of the wrist and the hyaline cartilage of the knees is seen in 20% to 50% of patients with hemochromatosis. Crystals of calcium pyrophosphate may shed into the joints, causing superimposed flares of inflammatory arthritis (i.e., pseudogout).

**20. Discuss the genetics of HHC.**

HHC is among the most common genetic disorders in whites of northern European descent. There are four types of HHC, and all are related to genetic mutations. Classic HHC (type 1) is the most common type (80%). It is autosomal recessive and associated with a mutation of the *HFE* gene on chromosome 6 that encodes for a protein involved in regulation of iron absorption. Between 80% and 90% of patients are homozygous for the same mutation (C282Y) of this gene. The homozygote frequency in the white population is 0.3% to 0.5% and carrier frequency is 7% to 10% (i.e., heterozygotes). However, not all patients homozygous for this *HFE* mutation develop clinical manifestations of iron overload (28% of male and 1% of female homozygotes over 12 years). Therefore other genes as well as environmental factors (alcohol, etc.) may play a role in modifying the phenotypic expression of iron overload.



**Figure 22-2.** Radiographs of hands showing degenerative arthritis with hooklike osteophytes of the second and third metacarpophalangeal joints in a patient with hemochromatosis (arrows).

**21. Compare and contrast the features of HA and RA.**

See Table 22-4.

**22. How effective is phlebotomy in halting the progression of HA?**

Phlebotomy does not halt the progression of the arthropathy.

**23. What is the correlation between the severity of arthropathy and severity of liver disease in hemochromatosis?**

There is no correlation.

**24. Why does hemochromatosis cause a degenerative arthritis?**

The arthropathy is characterized by hemosiderin deposition in synovium and chondrocytes. The presence of iron in these cells may lead to increased production of destructive enzymes (e.g., matrix metalloproteinases), free radical generation, or crystal deposition that causes cartilage damage. Other mechanisms also may be possible; the precise pathway by which chronic iron overload leads to tissue injury has not been fully established.

**Table 22-4.** Comparison of Hemochromatotic Arthropathy and Rheumatoid Arthritis

	HEMOCHROMATOTIC ARTHROPATHY	RHEUMATOID ARTHRITIS
Sex	M > F (10:1)	F > M (3:1)
Age of onset	>35 years	All ages
Joints	Polyarticular	Polyarticular
Symmetry	Symmetric	Symmetric
Inflammatory signs and symptoms	Only if pseudogout attack	Yes
Rheumatoid factor	Negative	Positive (85%)
Gene	HFE (90%)	HLA DR4 (70%)
Synovial fluid	Noninflammatory	Inflammatory
Radiographs	Degenerative changes	Inflammatory, erosive disease

F, female; HFE, hemochromatosis gene; HLA, human leukocyte antigen; M, male.

**25. What other musculoskeletal problems may occur in patients with hemochromatosis?**

- Osteoporosis caused by gonadal dysfunction from pituitary insufficiency caused by the iron overload state (low follicle-stimulating hormone [FSH], luteinizing hormone, and testosterone)
- Osteomalacia caused by vitamin D deficiency resulting from liver disease (low 25-OH vitamin D level)
- Hypertrophic osteoarthropathy—cirrhosis of any cause including hemochromatosis can be associated with periosteal reaction involving shafts of long bones

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**BIBLIOGRAPHY**

1. Alexander J, Kowdley KV. HFE-associated hereditary hemochromatosis. *Genet Med* 2009;11:307–13.
2. Allen KJ, Gurrin LC, Constantine CC, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. *N Engl J Med* 2008;358:221–30.
3. Agmon-Levin N, Shapira Y, Selmi C, et al. A comprehensive evaluation of serum autoantibodies in primary biliary cirrhosis. *J Autoimmun* 2010;34:55–8.
4. Cacoub P, Delluc A, Saadoun D, et al. Anti-CD20 monoclonal antibody (rituximab) treatment for cryoglobulinemic vasculitis: where do we stand? *Ann Rheum Dis* 2008;67:283–7.
5. Carroll GJ, Breidahl WH, Olynyk JK. Characteristics of the arthropathy described in hereditary hemochromatosis. *Arthritis Care Res* 2012;64:9–14.
6. Czaja AJ. Autoantibodies in autoimmune liver disease. *Adv Clin Chem* 2005;40:127–64.
7. Guillevin L, Mahr A, Callard P, et al. Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients. *Medicine (Baltimore)* 2005;84:313–22.
8. Iannuzziella F, Vaglio A, Garini G. Management of hepatitis C virus-related mixed cryoglobulinemia. *Am J Med* 2010;123:400–8.
9. Krawitt EL. Autoimmune hepatitis. *N Engl J Med* 2006;354:54–66.
10. Manns MP, Czaja AJ, Gorham JD, et al. 2010 Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010;51:2193–213.
11. Vaughn BP, Doherty GA, Gautam S, et al. Screening for tuberculosis and hepatitis B prior to initiation of anti tumor necrosis therapy. *Inflamm Bowel Dis* 2012;18:1057–63.
12. Watt FE, James OFW, Jones DEJ. Patterns of autoimmunity in primary biliary cirrhosis patients and their families: a population-based cohort study. *Q J Med* 2004;97:397–406.
13. Zignego AL, Ferri C, Pileri SA, et al. Extrahepatic manifestations of hepatitis C virus infection: a general overview and guidelines for a clinical approach. *Dig Liver Dis* 2007;39:2–17.

# EVALUATION OF FOCAL LIVER MASSES

Mark W. Russo, MD, MPH, FACG, and Roshan Shrestha, MD

## 1. Describe the initial work-up for a patient with a liver mass.

When evaluating a patient with a liver mass one of the key issues is determining if the mass is benign or malignant. This can frequently be determined by obtaining an accurate history and physical examination. A history of malignancy may suggest metastatic disease, particularly for breast and colon cancer, whereas a history of cirrhosis suggests hepatocellular carcinoma (HCC). Risk factors for chronic viral hepatitis B or C or a history of cirrhosis increase the possibility of a primary malignant process. Hepatomegaly or splenomegaly, abdominal pain, or stigmata of chronic liver disease, such as palmar erythema, spider angiomas, or gynecomastia, may be present. Hepatic adenoma may be associated with oral contraceptives or anabolic steroids.

Liver-associated enzymes, with the exception of  $\gamma$ -glutamyl transpeptidase, are usually normal with benign liver tumors. Serum alkaline phosphatase levels are often elevated with hepatic metastases, but not in all cases, and total bilirubin may be elevated if the mass is causing obstruction of the biliary system. An increase in serum transaminases may signify chronic hepatitis or cirrhosis. Positive hepatitis B or C serologic findings or iron studies may identify an underlying cause of liver dysfunction or cirrhosis (Table 23-1).

**Table 23-1.** Differential Diagnosis of Focal Liver Masses in Adults

BENIGN	MALIGNANT
<b>Epithelial Tumors</b>	
Hepatic adenoma	Hepatocellular carcinoma
Bile duct adenoma	Cholangiocarcinoma
Biliary cystadenoma	Biliary cystadenocarcinoma
<b>Mesenchymal Tumors</b>	
Cavernous hemangioma	Angiosarcoma Primary hepatic lymphoma
<b>Other Lesions</b>	
Focal nodular hyperplasia	Metastatic tumors
Liver abscess	
Macrogenerative nodules in cirrhosis	
Focal fatty infiltration	
Simple hepatic cyst	

Modified from Kew MC: *Tumors of the liver*. In Zakim D, Boyer TD, editors: *Hepatology: a textbook of liver disease*, ed 2, Philadelphia, 1990, WB Saunders, pp 1206–1239.

## 2. What tumor markers are useful in the evaluation of focal liver lesions?

Serum  $\alpha$ -fetoprotein (AFP) and carbohydrate-associated antigen carbohydrate antigen 19 (CA 19–9) are markers of primary hepatic malignancy and are used when radiographic studies indicate a focal neoplasm originating in the liver. Carcinoembryonic antigen is used to measure adenocarcinomas, particularly colon cancer.

Although it has its limitations, AFP is the best widely available diagnostic marker for HCC and also plays a role in screening programs of at-risk populations. *AFP levels higher than 200 ng/mL are highly suggestive of HCC, whereas lesser elevations may be due to benign chronic hepatitis and may not indicate the presence of HCC.* A universally accepted cutoff value for AFP in the diagnosis of HCC has not been established, and levels of more than 200 ng/mL have greater than 90% specificity for HCC. *Not all hepatomas secrete AFP, and approximately one third of patients have a normal AFP value, especially when the tumor is smaller than 2 cm.* AFP levels are useful to

follow after treatment for HCC and should decrease or normalize with successful treatment. Other tumor markers that have been studied for the detection of HCC including AFP-L3% and des-gamma-carboxy prothrombin (DCP). The sensitivity and specificity of AFP-L3% and DCP for HCC have been reported to be 56% and 90% and 87% and 85%, respectively.

CA 19–9 is used in the diagnosis of cholangiocarcinoma, a malignancy originating in the bile ducts. CA 19–9 levels of more than 100 U/mL are found in more than 50% of patients and values of more than 1000 suggest unresectability. This marker is more sensitive in patients with primary sclerosing cholangitis, a risk factor for cholangiocarcinoma. Significant false-positive elevations in CA 19–9 can occur with bacterial cholangitis. CA 19–9 also serves as a tumor marker for pancreatic carcinoma. Although widely used, CA 19–9 has not proven benefit for screening for cholangiocarcinoma and may create undue anxiety when elevated because it is nonspecific.

### 3. What imaging modalities are used in the detection and characterization of focal liver masses?

Recent advances in computed tomography (CT) and magnetic resonance imaging (MRI) allow detailed assessment of focal liver lesions. These imaging studies have largely supplanted previously used nuclear medicine-based protocols for the characterization of liver masses.

Triphasic CT, which is now widely available, offers substantial improvement in hepatic imaging because of its rapid scan time within a single breath-hold. This feature eliminates respiratory motion and allows contrast injection to be viewed in unenhanced, arterial (early) and portal venous phases of perfusion. Lesions that derive their vascular supply from the hepatic artery, such as HCC and hypervascular metastases, are prominent during the arterial phase. The venous or portal phase of helical CT provides maximal enhancement of normal liver parenchyma and optimizes detection of hypovascular lesions, such as colon, gastric, and pancreatic metastases. CT may be preferred in patients with cirrhosis who are claustrophobic or cannot hold their breath for MRI, or in patients with ascites, which creates motion of the liver and artifact on MRI.

MRI scanning has undergone similar refinements, with breath-hold T1-weighted images and fast (turbo) spin-echo T2-weighted sequences that eliminate motion artifacts and make use of contrast agents in a manner analogous to triphasic CT. Gadolinium-enhanced MRI should be considered in patients with contraindications to iodine-based CT, such as contrast allergies or renal insufficiency. MRI also has the benefit of obtaining images of the biliary tree (magnetic resonance cholangiopancreatography [MRCP]) in patients with suspected biliary tract tumors or biliary obstruction. MRI may be degraded in patients who cannot hold their breath or move because of claustrophobia. Nephrogenic systemic fibrosis (NSF) is a rare, serious condition associated with gadolinium-based contrast agents associated with renal failure. Thus, although MRI may be preferred to CT in patients with renal failure, caution should be taken to avoid NSF, which can be fatal.

Contrast-enhanced ultrasonography has been studied outside of the United States as a modality to distinguish benign from malignant lesions. This modality may decrease costs and exposure to radiation, but is not widely available in the United States.

Many focal liver masses are found incidentally on ultrasound examination of the abdomen. Although liver ultrasound often cannot fully characterize the lesion, it has a role in verifying simple hepatic cysts, which may have nonspecific radiographic patterns on CT or MRI. Hepatic cysts are common and present in up to 10% of the population. More than five hepatic cysts or cysts with septations warrant further investigation because the patient may have polycystic liver disease or biliary cystadenoma. See Chapter 69, Noninvasive GI Imaging, for comprehensive discussion of imaging options and examples for the evaluation of liver lesions (Table 23-2).

**Table 23-2. CT versus MRI for Evaluating a Liver Mass**

Which test should be ordered to evaluate a liver mass?

	CT	MRI
Claustrophobic patient	X	
Estimated GFR 30–40 mL/min		X
Ascites	X	
Magnetized foreign body	X	
Distinguish adenoma from FNH		X
Suspect bile leak		X (with MRCP)*

CT, Computed tomography; FNH, focal nodular hyperplasia; GFR, glomerular filtration rate; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging.

\*Hepatobiliary iminodiacetic acid scan is a nuclear imaging study that is also an excellent diagnostic test if bile leak is strongly suspected, but it does not evaluate hepatic parenchyma.

#### 4. What is the most common benign cause of a focal liver lesion?

*Cavernous hemangiomas are the most common benign hepatic tumor, occurring in up to 20% of the population.* They occur in all age groups, more commonly in women, as solitary (60%) or multiple asymptomatic masses. Most are smaller than 3 cm and usually occur in the posterior segment of the right hepatic lobe. The term *giant hemangioma* is sometimes used when the size exceeds 5 cm. Occasionally, hemangiomas are large enough to cause abdominal pain and, if compressing the spleen or other organs, may require resection. However, even for giant hemangioma, the risk of tumor growth or bleeding is minimal and does not justify surgical removal unless the patient is significantly symptomatic. Microscopically, hemangiomas consist of blood-filled vascular sinusoids separated by connective-tissue septae.

#### 5. Why is oral contraceptive use important in the differential diagnosis of focal liver masses?

*Most cases of hepatic adenomas directly relate to the use of oral contraceptive pills (OCPs).* This benign tumor was rarely seen before oral contraceptive agents came into common usage in the 1960s. Risk correlates with duration of use and age older than 30 years. Hepatic adenomas most commonly occur in young and middle-aged women, with an incidence of 3 to 4 per 100,000. Men infrequently develop adenomas, although cases have been reported with anabolic steroid use.

Hepatic adenomas are well-demarcated, fleshy tumors with prominent surface vasculature. Microscopically, they consist of monotonous sheets of normal or small hepatocytes with no bile ducts, portal tracts, or central veins.

#### 6. Why is surgical resection of hepatic adenomas recommended?

Spontaneous rupture and intraabdominal hemorrhage can occur in up to 30% of patients with hepatic adenoma, especially during menstruation or pregnancy. HCC also can develop within adenomas, especially adenomas larger than 10 cm. Approximately 50% of patients with adenomas have abdominal pain, sometimes as a result of bleeding within the adenoma. Adenomas have been known to regress with discontinuation of birth control pills, which should be recommended, but surgical resection remains the management of choice. Ablation is another modality used to treat adenoma, particularly in patients who are not good surgical candidates.

#### 7. What is focal nodular hyperplasia (FNH)?

*FNH is a round, nonencapsulated mass, usually exhibiting a vascular central scar.* Fibrous septae radiate from the scar in a spokelike fashion. Hepatocytes are arranged in nodules or cords between the septae, and the mass includes bile ductules, Kupffer cells, and chronic inflammatory cells. FNH are considered the result of a hyperplastic response to increased blood flow secondary to vascular malformations.

FNH is the second most common benign liver tumor. More than 90% occur in women and usually are diagnosed between 20 and 60 years of age. Oral contraceptives are not directly linked as a causative agent of FNH; however, OCPs may play a role in their growth, and therefore some authorities recommend discontinuing OCPs in women if FNH is diagnosed.

#### 8. List the differences between hepatic adenomas and FNH.

See Table 23-3.

**Table 23-3.** Characteristics of Hepatic Adenoma and Focal Nodular Hyperplasia

	HEPATIC ADENOMA	FOCAL NODULAR HYPERPLASIA
Size (mean)	5-10 cm	<5 cm
Kupffer cells	No	Yes
Central scar	Rare	Common
Symptoms	Common	Rare (only with large lesions)
Complications	Bleeding, malignancy	Rare lesions may grow in size
Treatment	Surgical resection Ablation Stop OCPs	Resection not necessary
Sulfur-colloid liver scan	Cold defect	Positive uptake in 60%-70%

OCP, Oral contraceptive pill.

### 9. What is the most frequent malignancy in the liver?

Metastatic disease to the liver is much more common than primary hepatic tumors in the United States and Europe. Cancers arising in the colon, stomach, pancreas, breast, lung, and melanoma are the most likely to metastasize to the liver. Esophageal, renal, and genitourinary neoplasms also should be considered when searching for the primary site. Neuroendocrine tumors may metastasize to the liver. Multiple defects in the liver suggest a metastatic process: only 2% present as solitary lesions. Involvement of both lobes is most common; 20% are confined to the right lobe alone and 3% to the left lobe.

### 10. What is the most common primary liver cancer?

HCC is by far the most common malignancy originating in the liver, accounting for approximately 80% of primary liver cancers. The incidence in the United States ranges from 2 to 3 cases per 100,000 and has doubled during the past two decades. The recent increase in HCC in the United States during the past decade is directly attributable to the rising incidence of hepatitis C. Geographic location influences both the age of peak occurrence (>55 years in the United States) and male-to-female incidence ratios. High-incidence areas in Asia and Africa, related to hepatitis B, have a much younger average age of onset and a higher male predominance. Worldwide, men are more likely than women to develop HCC by a factor of 4:1. HCC usually occurs within a cirrhotic liver; approximately 80% of patients diagnosed with HCC have cirrhosis (Box 23-1).

#### **Box 23-1. Imaging Criteria for Hepatocellular Carcinoma**

Imaging characteristics of HCC on contrast-enhanced CT or MRI that are diagnostic for HCC and biopsy of the lesion are not needed to establish the diagnosis.

<b>For Lesions &gt;1 cm and &lt;2 cm</b>	Increased contrast enhancement on late arterial phase AND Washout during portal venous phase AND Peripheral rim enhancement on delayed phases OR Increased contrast enhancement on late arterial phase and 50% growth in diameter within 6 months
<b>For Lesions ≥ 2 cm</b>	Increased contrast enhancement on late arterial phase and washout on delay/portal venous phase or late capsule enhancement OR Increased contrast enhancement on late arterial phase and 50% growth in diameter within 6 months

CT, Computed tomography; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging.

### 11. Describe the various presenting forms of HCC.

Nodular: Most common; multiple nodules of varying size scattered throughout the liver

Solitary (or massive): Occurs in younger patients; large, solitary mass, often in the right lobe

Diffuse: Rare; difficult to detect on imaging; widespread infiltration of minute tumor foci

Fibrolamellar HCC is a histologic variant that rarely occurs in young women in the absence of cirrhosis. This variant is characterized by increased stromal fibrosis, eosinophilic glass cell hepatocytes, and the absence of underlying inflammation or fibrosis. The prognosis is better than HCC associated with cirrhosis.

### 12. What types of cirrhosis most commonly are associated with HCC?

Autopsy studies indicate that 20% to 40% of patients dying with cirrhosis harbor HCC. The etiologic factors of cirrhosis most commonly related to HCC, in order of decreasing risk, are as follows:

1. Chronic hepatitis C (over 5 years, 7% of patients with HCV cirrhosis develop HCC)
2. Alcoholic cirrhosis (alcohol potentiates the carcinogenic risk in viral cirrhosis)
3. Nonalcoholic steatohepatitis 1% to 3% over 10 to 15 years
4. Chronic hepatitis B (even in the absence of cirrhosis)
5. Hemochromatosis
6. α-1-antitrypsin deficiency

### 13. What clinical and laboratory findings should raise suspicion for HCC?

Most patients with HCC are asymptomatic and lesions are detected on screening. If symptoms develop, they are related to abdominal pain from hemorrhage or paraneoplastic syndromes. Clinical findings can include:

1. New abdominal pain or weight loss
2. Hepatomegaly
3. Hepatic bruit
4. Acute hemoperitoneum

5. Blood-tinged ascitic fluid
  6. Persistent fever
  7. Sudden increase in serum alkaline phosphatase
  8. Increasing ratio of aspartate aminotransferase to alanine aminotransferase
  9. Polycythemia or persistent leukocytosis
  10. Hypoglycemia
  11. Hypercalcemia
  12. Hypercholesterolemia
- Findings 9 through 12 are paraneoplastic syndromes associated with HCC.

#### **14. What primary liver tumor occurs in young adults without underlying cirrhosis?**

The fibrolamellar variant of HCC is a distinctive, slow-growing subtype of hepatic neoplasm, occurring at a mean age of 26. Patients seldom have a history of prior liver disease. Unlike typical HCC, men and women are equally affected. Fibrolamellar tumors usually present with abdominal pain caused by a large, solitary mass, most often in the left lobe (75%). The AFP level is normal.

The term *fibrolamellar* characterizes the microscopic appearance of this lesion: thin layers of fibrosis separate the neoplastic hepatocytes. A fibrous central scar may be seen on imaging studies. Because patients do not have cirrhosis with this variant, recognition of this variant is important because nearly one-half are resectable at the time of diagnosis.

#### **15. What factors predispose to the development of cholangiocarcinoma?**

Cholangiocarcinomas, which account for approximately 10% of primary liver cancers, arise as adenocarcinomas from bile duct epithelium. Jaundice is the most frequent clinical presentation of this tumor. Risk factors for cholangiocarcinoma include:

- Primary sclerosing cholangitis
- Liver fluke infestation
- Chronic ulcerative colitis
- Congenital cystic liver diseases, choledochal cysts

Only approximately 25% of cholangiocarcinomas occur in the setting of cirrhosis. However, in more than half the cases, an underlying liver disease is not found in patients with cholangiocarcinoma. Although there are no proven screening tests for serum cholangiocarcinoma, CA 19–9 is frequently used to screen patients with PSC for cholangiocarcinoma.

#### **16. What is a Klatskin tumor?**

Cholangiocarcinomas at the hilar bifurcation of the hepatic ducts are referred to as *Klatskin tumors*. Peripheral (or intrahepatic) and extrahepatic bile duct cholangiocarcinomas are other subtypes. Delayed tumor enhancement on CT after intravenous (IV) contrast is noted in approximately 75% of intrahepatic cholangiocarcinomas. The characteristic desmoplastic reaction accompanying these tumors often makes them poorly visible on imaging studies and difficult to diagnose on biopsy. The diagnosis may require endoscopic retrograde cholangiopancreatography with brushings of a malignant-appearing stricture with cytologic examination or fluorescent in situ hybridization analysis, endoscopic ultrasound with biopsy, or both. The newly developed cholangioscopy technology is very useful in making diagnosis by direct visualization and tissue acquisition with forceps biopsy for histologic examination. Resection is the mainstay of treatment but unfortunately the majority of lesions are unresectable. In some circumstances liver transplantation may be an option for treatment. Carefully selected cases of hilar cholangiocarcinoma that undergo neoadjuvant chemoradiation and staging laparoscopy before transplantation have acceptable posttransplant survival. Unfortunately, most are unresectable when diagnosed and thus require palliative drainage of obstructive jaundice by endoscopic, percutaneous, or surgical methods.

#### **17. When should liver transplantation be considered in patients with HCC?**

Patients who meet the Milan criteria should be considered for transplant; in some regions of the country patients who meet the University of California–San Francisco criteria should be considered ([Table 23-4](#)).

**Table 23-4.** Liver Transplant Criteria for Hepatocellular Carcinoma

MILAN CRITERIA	UCSF
Solitary lesion $\leq$ 5 cm	Solitary lesion $\leq$ 6.5 cm
Or	Or
Three or fewer nodules 1-3 cm in diameter	Three or fewer lesions with largest lesion $\leq$ 4.5 cm and cumulative diameter $\leq$ 8 cm
And	And
No macroscopic vascular invasion or extrahepatic disease	No macroscopic vascular invasion or extrahepatic disease

**18. When should resection be considered in patients with HCC?**

HCC is resectable in only approximately 10% of patients in the United States because underlying cirrhosis with portal hypertension and hepatic synthetic dysfunction precludes resection. Five-year survival rates with surgical treatment range between 17% and 40%. Most patients succumb to intrahepatic recurrence of tumor. The multifocal nature of HCC carcinogenesis explains this poor prognosis. Selection criteria for resectability of HCC include:

- Child-Pugh class A cirrhosis
- Solitary lesion smaller than 5 cm
- Absence of significant portal hypertension defined as hepatic wedge pressure gradient less than 10 mm Hg
- Lack of vascular invasion or extrahepatic spread

**19. What other therapies are available for the management of HCC?**

Radiofrequency and microwave ablation is a direct application of thermal energy by percutaneous or surgical means, which destroys unresectable areas of HCC. Radiofrequency ablation is superior to percutaneous ethanol injection by decreasing local recurrence rates and enhancing directed tissue necrosis, although both modalities are now commonly used.

Transarterial chemoembolization (TACE) involves the selective administration of chemotherapy, followed by embolization, into the hepatic artery branch feeding the tumor. TACE confers a survival advantage compared with supportive therapy. It is frequently used to delay tumor progression in patients awaiting liver transplantation.

Another modality used to treat HCC is radioembolization, which introduces yttrium 90 through the hepatic artery blood supply. This modality may be used for tumors too large for TACE or in patients with portal vein thrombosis who are not candidates for TACE. However, there are no randomized clinical trials demonstrating a survival benefit with radioembolization, and it is a costly therapy.

Sorafenib, administered twice a day orally, is the only systemic chemotherapeutic that has a proven survival advantage in randomized clinical trials. The trials demonstrated a 12-week survival advantage compared with placebo in patients with unresectable HCC and cirrhosis.

**20. Who should be screened for HCC? Describe a typical screening strategy.**

Patients with cirrhosis, especially those at high risk of HCC, should be screened. Screening is done routinely in people with viral-induced cirrhosis (hepatitis B and C) and cirrhosis-related to metabolic liver disease.

Serial AFP measurements and hepatic ultrasound studies are the most commonly used screening tools. *Optimal screening intervals are not established, but AFP levels and ultrasound every 6 months are common practice.* Although surveillance may not have a definite effect on mortality rate, with only one randomized trial demonstrating a survival advantage (Zhang study), it allows more tumors to be amenable to curative resection. Other newer biomarkers such as AFP L3% (Lens culinaris agglutinin-reactive fraction of AFP), DCP offer marginal improvement in combination with AFP.

**21. What benign tissue abnormality may simulate a focal liver mass?**

Focal fatty infiltration may appear similar to the focal hepatic lesions described previously. Focal fatty liver is often seen in alcoholism, obesity, diabetes mellitus, malnutrition, corticosteroid excess or therapy, and acquired immune deficiency syndrome. MRI imaging may be necessary to fully characterize this entity. An interesting aspect of focal fat is its rapid disappearance once the inciting disease process is corrected.

**22. What new imaging techniques are under development to evaluate focal liver masses?**

$\beta$ MRI angiography, which permits the rapid acquisition of arterial and venous sequences, has shown promise in the detection of small HCCs missed by triphasic CT scanning.

Positron emission tomography (PET) scan is currently being studied to improve the difficult detection of cholangiocarcinoma. PET scans are also playing an increasing role in the detection of hepatic metastases from colorectal cancer when liver resection is contemplated.

Endoscopic ultrasound with fine-needle aspiration (FNA) has also been reported to aid in the diagnosis of suspected cholangiocarcinoma when other tissue sampling methods such as intraductal cytologic examination have failed to provide a diagnosis.

**23. Why is fine-needle biopsy of hepatic masses controversial?**

Establishing a diagnosis for a focal liver mass by FNA cytologic examination is more problematic than one would think, owing to subtle histopathologic differences between normal hepatocytes and benign lesions or even well-differentiated hepatomas. The literature reveals a wide range of sensitivity for FNA-based diagnosis of primary hepatic lesions. The most optimistic studies report sensitivities and specificities of more than 90%. Hemangiomas, FNH, and HCC appear to be more difficult to diagnose accurately by FNA; sensitivity ranges between 60% and 70% in many series. Rigorous protocols making use of two or more imaging studies to characterize a benign lesion can have an accuracy and sensitivity as high as 80% to 90%. When HCC is suspected, the use of MRI, CT, and angiography (in selected cases) can confirm the diagnosis in more than 95% of patients without the use of FNA.

Another controversy about the use of FNA in HCC is the risk of needle-tract seeding and tumor spread into the circulation, a risk that may be as high as 5%. With the increasing use of liver transplantation in the treatment of HCC, this complication can have grave consequences.

FNA plays a dominant role in the setting of suspected metastatic disease to the liver and inoperable primary cancers. When surgical resection of a lesion, based on clinical and imaging findings, is deemed necessary, preoperative biopsy is generally not advocated.

#### **24. What should be done when small incidental liver lesions are found?**

Lesions smaller than 1 cm are common incidental findings on liver imaging. In the vast majority of cases they represent benign entities such as small cysts or hemangiomas. Their small size makes further characterization by other radiographic studies or percutaneous biopsy problematic and usually impossible.

Simple, thin-walled hepatic cysts, regardless of size, need no further follow-up when definitively documented by ultrasound. Otherwise, clinical follow-up by repeating the imaging study in 6 months is recommended. This provides verification that the lesion has not grown in size. Interval growth of such lesions should prompt further work-up.

#### **25. Outline a logical approach to the evaluation of a focal hepatic mass.**

The work-up of a focal liver mass must occur in the context of a carefully considered differential diagnosis. Associated symptoms, presence of underlying liver disease or extrahepatic malignancy, drug and occupational exposures, and laboratory abnormalities must be assessed before proceeding with further radiographic studies. Symptomatic lesions and lesions noted incidentally are likely to have different etiologic factors. The patient's age and sex are important clues. Cirrhosis requires a modified approach because of the increased likelihood of HCC. See Chapter 69, Noninvasive GI Imaging, for comprehensive discussion and examples of imaging options for the evaluation of liver lesions (Box 23-2).

**Box 23-2. Evaluation of Liver Lesions**

Incidental Lesions	Cirrhosis or Risk Factors for Cholangiocarcinoma
Small lesions <1 cm → repeat study in 6 months Simple cysts → verify with ultrasound  Hemangiomas → triphasic CT with contrast → 99Tc-labeled red blood cell scan (for lesions > 2 cm) or gadolinium-enhanced MRI  FNH → triphasic CT with contrast → gadolinium-enhanced MRI → ? biopsy  Hepatic adenoma → history of OCPs → rule out hemangioma and FNH → resection (outlined previously)	HCC → AFP → triphasic CT → MRI with contrast or MRI angiography  Cholangiocarcinoma → CA 19-9 → triphasic with delayed-phase CT → MRCP, ERCP with cholangioscopy for cytologic examination, FISH and biopsy, and PET scan
Symptomatic Lesions	History of Malignancy
Hepatic adenoma → history of OCPs → rule out hemangioma/ FNH → resection  Liver abscess → sepsis → ultrasound → triphasic CT (rim enhancement)	Metastases → triphasic CT with contrast → if resection is considered → PET scan (to rule out multiple metastasis)

*AFP*, α-Fetoprotein; *CA*, Carbohydrate antigen; *CT*, computed tomography; *ERCP*, endoscopic retrograde cholangiopancreatography; *FISH*, fluorescent in situ hybridization; *FNH*, focal nodular hyperplasia; *HCC*, hepatocellular carcinoma; *MRCP*, magnetic resonance cholangiopancreatography; *MRI*, magnetic resonance imaging; *OCP*, oral contraceptive pill; *PET*, positron emission tomography.

#### **BIBLIOGRAPHY**

- Bioulac-Sage P, Balabaud C, Zucman-Rossi J. Focal nodular hyperplasia, hepatocellular adenomas: past, present, future. *Gastroenterol Clin Biol* 2010;34:355–8.
- De Groen PC, Gores GJ, LaRusso NF, et al. Biliary tract cancers. *N Engl J Med* 1999;341:1368–78.
- Durazo FA, Blatt LM, Corey WG, Lin JH, Han S, Saab S, et al. Des-gamma-carboxyprothrombin, alpha-fetoprotein and AFP-L3 in patients with chronic hepatitis, cirrhosis and hepatocellular carcinoma. *J Gastroenterol Hepatol* 2008;23:1521–8.
- Ekstedt M, Franzen LE, Mathiesen UL, et al. Long term follow up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006;44:802–5.
- El-Serag HB. Epidemiology of hepatocellular carcinoma in the USA. *Hepatol Res* 2007;37(Suppl. 2):S88–S94.
- Kerlin P, Davis GL, McGill DB, et al. Hepatic adenoma and focal nodular hyperplasia: clinical, pathologic, and radiologic features. *Gastroenterology* 1983;84:994–1002.
- Lanka B, Jang HJ, Kim TK, et al. Impact of contrast-enhanced ultrasonography in a tertiary clinical practice. *J Ultrasound Med* 2007;26:1703–14.
- Mergo PJ, Ros PR. Benign lesions of the liver. *Radiol Clin North Am* 1998;36:319–31.

9. Mor E, Kaspa RT, Sheiner P, et al. Treatment of hepatocellular carcinoma associated with cirrhosis in the era of liver transplantation. *Ann Intern Med* 1998;129:643–53.
10. Panjala C, Nguyen JH, Al-Hajjaj AN, et al. Impact of neoadjuvant chemoradiation on the tumor burden before liver transplantation for unresectable cholangiocarcinoma. *Liver Transpl* 2012;18:594–601.
11. Patel AH, Harnois DM, Klee GG, et al. The utility of CA 19–9 in the diagnosis of cholangiocarcinoma in patients without primary sclerosing cholangitis. *Am J Gastroenterol* 2000;95:204–7.
12. Peng YC, Chan CS, Chen GH. The effectiveness of serum  $\alpha$ -fetoprotein level in anti-HCV positive patients for screening hepatocellular carcinoma. *Hepatogastroenterology* 1999;46:3208–11.
13. Pomfret EA, Washburn K, Wald C, et al. Report of a national conference on liver allocation in patients with hepatocellular carcinoma in the United States. *Liver Transpl* 2010;16:262–78.
14. Rebouissou S, Bioulac-Sage P, Zucman-Rossi J. Molecular pathogenesis of focal nodular hyperplasia and hepatocellular adenoma. *J Hepatol* 2008;48:163–70.
15. Reddy KR, Schiff ER. Approach to a liver mass. *Semin Liver Dis* 1993;13:423–35.
16. Schwartz JM, Outwater EK. Approach to the patient with a focal liver lesion. In: Rose BD, editor. UpToDate. Wellesley, MA: UpToDate; 2004.
17. Takamori R, Wong LL, Dang C, Wong L. Needle-tract implantation from hepatocellular cancer: is needle biopsy of the liver always necessary? *Liver Transpl* 2000;6:67–72.
18. Torzilli G, Minagawa M, Takayama T, et al. Accurate preoperative evaluation of liver mass lesions without fine-needle biopsy. *Hepatology* 1999;30:889–93.
19. Weimann A, Ringe B, Klempnauer J, et al. Benign liver tumors: differential diagnosis and indications for surgery. *World J Surg* 1997;21:983–91.
20. Vallis C, Ruiz S, Martinez L, Leiva D. Radiological diagnosis and staging of hilar cholangiocarcinoma. *World J Gastrointest Oncol* 2013;15:115–26.

# DRUG-INDUCED LIVER DISEASE

Cemal Yazici, MD, Mark W. Russo, MD, MPH, FACG, and Herbert L. Bonkovsky, MD

## 1. How common is drug-induced liver disease?

Drug-induced liver injury (DILI) from any single medication is of highly variable incidence. However, for most drugs that can cause DILI, the incidence is between 1/10,000 and 1/1,000,000.

DILI is one of the most common reasons an approved drug is withdrawn from the market. Antibiotics are the most common class of agents that cause DILI. Of cases of acute liver failure (ALF) in the United States, 52% were found to be due to DILI. DILI accounted for 15% of liver transplants for ALF between 1990 and 2002 in the United States.

During 6 months of follow-up of DILI cases, 10% to 15% of patients had persistent laboratory abnormalities, suggestive of evolution of the disease to chronic DILI. Of these, 8% died; the cause of death was liver related in 44% of those who died within 6 months of DILI onset.

## 2. What are the main modulators of DILI?

- A. The drug (dose, duration, class)
- B. The host (age, gender, body mass index [BMI], genetic and immunologic factors)
- C. The environment (diet, other toxins, antioxidants, probiotics)

## 3. How is causality assessed?

Bayes theorem estimates the overall probability of a particular adverse event occurring in a particular individual in a particular situation, given the probability of this event occurring in a group of individuals with similar exposure.

Based on the degree of certainty of a causal interaction, different terms are used to describe the strength of the relationship such as *definite*, *very likely*, *probable*, *possible*, and *unlikely*.

Several instruments and methods for assessing the likelihood of DILI have been proposed. The most widely used is the Roussel-Uclaf causality assessment method (RUCAM), in which a numerical score is given to each of several demographic and clinical features. The higher the score, the greater the likelihood that a given drug is the cause of liver injury. However, there are numerous difficulties and uncertainties in application of RUCAM, and it is generally not used in everyday practice.

## 4. What are the patterns of DILI and how are they distinguished biochemically?

- A. Hepatocellular (HC)
- B. Cholestatic (CL)
- C. Mixed
- D. Steatotic
  - 1. Microvesicular
  - 2. Mixed micro-macromicrovesicular

See Table 24-1.

## 5. Describe the chronologic association between drug exposure, typical course, and injury types.

CL or HC liver injury typically occurs 5 to 90 days after initial exposure to the causative agent.

On withdrawal of the drug, clinical and biochemical resolution usually occurs as follows:

- HC injury resolves within 8 to 30 days in more than 50% of the cases.
- CL injury resolves within 60 to 90 days.
- Mixed injury usually follows a more protracted course than HC but less protracted than CL.
- Microvesicular steatosis has a similar course as HC injury.
- Mixed micro-macromicrovesicular injury has a more variable course than microvesicular steatosis.

Persistence of abnormal liver biochemistries beyond these intervals suggests a coexistent or independent cause of liver disease (e.g., viral or autoimmune liver disease, primary biliary cirrhosis [PBC] or primary sclerosing cholangitis [PSC]). Nevertheless, chronic DILI, defined as abnormal laboratory, imaging, or histopathologic features of the liver injury at or more than 6 months after the onset of DILI, occurs in 10% to 15% of subjects with acute DILI.

**Table 24-1.** Biochemical Features among Different DILI Patterns

	SERUM ALT, AST ( $\times$ ULN)	SERUM ALP ( $\times$ ULN)	SERUM BILIRUBIN ( $\times$ ULN)	R VALUE*
Hepatocellular	>5	<2	TB and DB, variable	>5
Cholestatic	<5	>2	TB and DB >2	<2
Mixed	>3	>2	TB and DB >2	2-5
Steatotic	5-25	1-3	TB and DB, variable	>5
Microvesicular	1-5	1-3	TB and DB, variable	2-5
Micro-macrosomicular				

\*R is defined as the ratio of serum ALT/ULN of ALT divided by serum ALP/ULN of ALP, with ALT and ALP concentrations in units per liter. By general consensus and convention, in hepatocellular DILI, R is >5. In cholestatic DILI, R is <2 and in mixed DILI, 2 < R <5.

ALP, Alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DB, direct-reacting bilirubin; DILI, drug-induced liver injury; TB, total bilirubin; ULN, upper limit of normal.

Injury patterns typically are distinguished by levels of serum ALT, AST, ALP, total bilirubin, direct-reacting bilirubin, and the so-called R value.

## 6. What is the differential diagnosis of DILI?

A high index of suspicion is needed to prevent delay in diagnosis of DILI. A detailed history, complete physical examination, and review of laboratory and imaging studies are extremely important. The diagnosis of DILI requires exclusion of other etiologic possibilities such as viral, autoimmune, and cardiovascular diseases; exposure to other toxins (alcohol, industrial toxins, etc.); inheritable disorders; gallstones; PBC; PSC; and malignant causes. Withdrawal of the offending agent and close observation often provide adequate circumstantial evidence for the diagnosis. Liver biopsy should be considered when discontinuation of the medication is not followed by prompt improvement, the cause of liver disease remains in question, there are several possible causes, or the severity requires therapeutic intervention (liver transplantation, corticosteroids). Potential viral etiologic factors that are important to exclude are hepatitis A-E, cytomegalovirus, and herpes simplex virus. Autoimmune hepatitis is one of the more common conditions and is difficult to differentiate from DILI.

## 7. Describe immunoallergic phenomena and autoimmune hepatitis-like injury.

Certain drugs or their metabolites can bind to host proteins and produce antigens, which are recognized as foreign by hosts. This can result in generation of T- or B-lymphocyte responses by hosts' immune systems. Hepatocytes, which play a key role in drug metabolism, may also display such neoantigens. This can lead to development of autoimmune hepatitis-like liver injury. Although many drugs may give rise to autoimmune-like hepatitis, several drugs have been found to trigger such reactions with greater relative frequencies. These drugs include hydralazine, methyldopa, minocycline, nitrofurantoin, and anti-tumor necrosis factor-alpha agents, such as infliximab and etanercept.

## 8. What variables influence susceptibility to DILI?

- Age: Drugs may have different effects based on the age of the host. For example, acetylsalicylic acid (ASA) and valproic acid may affect younger individuals more often, whereas acetaminophen, isoniazid, and halothane may affect older individuals more frequently.
- Gender: Women are more susceptible to DILI, probably because of lower BMI and underlying susceptibility to autoimmune hepatitis.
- Inducers of hepatic enzymes: Substances (phenobarbital, phenytoin, ethanol, cigarette smoke, and grapefruit juice) that induce the hepatic cytochrome P-450 system can alter drug metabolism and potentiate hepatotoxicity.
- Drug-drug interactions: Drug-drug interactions may play a significant role as the results and end-products of these reactions can increase liver injury. Valproic acid increases chlorpromazine-induced cholestasis. Rifampin potentiates isoniazid hepatotoxicity. Chronic alcohol ingestion enhances acetaminophen and isoniazid hepatotoxicity.
- Malnutrition: Low glutathione (GSH) levels potentiate acetaminophen hepatotoxicity and, perhaps, also toxicity caused by other chemicals for which conjugation with GSH is involved in detoxification.
- Genetic association: Amoxicillin-clavulanic acid is the most studied drug in terms of genetic association. Certain human leukocyte antigen (HLA) haplotypes such as DRB1\* 1501, \*15, and \*0602 have been identified as influencing risk of DILI caused by this combination of drugs. The most significant association was observed for haplotype HLA-A\* 201-B\* 0702-DRB\* 1501-DQB 1\* 0602 (odds ratios 13-20). Other medications with significant HLA associations include abacavir, flucloxacillin (DRB1\* 5701, OR=80.6), isoniazid (INH), lapatinib, lumiracoxib, ticlopidine, and ximelagatran.
- Route of administration: Tetracycline hepatotoxicity occurs primarily following parenteral administration, which is rarely used today.

**9. Name the two most common causes of DILI.**

- Acetaminophen
- Amoxicillin-clavulanic acid

**10. How is acetaminophen toxic to the liver?**

Acetaminophen is toxic to the liver when taken in excessive doses (more than 7.5 g per day); HC GSH stores are depleted and the protective-detoxifying pathway in the liver (formation of nontoxic mercapturate conjugates of *N*-acetyl-*p*-benzoquinone-imine [NAPQI]) is overwhelmed. Accumulation of the toxic metabolite NAPQI is responsible for liver injury and results in severe HC centrilobular necrosis. Acetaminophen is the most common cause of drug-induced ALF and the second most common cause of death from poisoning in the United States. Mitochondria are an early target, but NAPQI also forms adducts to hepatic proteins in the cytosol, microsomes, nuclei, and plasma membranes.

**11. At what dose is acetaminophen toxic?**

Acetaminophen is hepatotoxic in nonalcoholic patients at single doses greater than 7.5 g. Chronic alcoholics are at greater risk of acetaminophen injury because of alcohol induction of the cytochrome P450 2E1 system, which increases formation of NAPQI, and attendant malnutrition with low levels of GSH, an intracellular protectant normally found at high concentrations in hepatocytes.

**12. How is acetaminophen toxicity treated?**

The Rumack-Matthew nomogram helps to predict the likelihood of liver injury from acetaminophen and to direct therapy. The antidote for acetaminophen overdose is *N*-acetylcysteine (NAC). The usual oral dose of NAC is 140 mg/kg, followed by 17 maintenance doses of 70 mg/kg every 4 hours. NAC can also be administered intravenously for 48 hours with equal or better efficacy than the oral route. Although there is controversy in terms of treatment duration for NAC, experts recommend continuing NAC at least for 72 hours. If there is no clinical or biochemical improvement, treatment duration can be extended even more. Ipecac is given if the time of ingestion can be verified to be less than 4 hours. Activated charcoal is typically not administered because it can interfere with the absorption of orally administered NAC.

**13. What is the difference between intrinsic and idiosyncratic liver injury?**

- Intrinsic (predictable) liver injury: Acetaminophen is the most common cause of intrinsic liver injury, acting by mechanisms already described. It produces liver injury in virtually all animals who consume toxic doses, although there is variability in the doses required.
- Idiosyncratic (unpredictable) liver injury: Idiosyncratic reactions occur when a drug causes non-dose related (unpredictable) DILI. Idiosyncratic reactions may or may not be accompanied by immunoallergic manifestations such as fever, peripheral eosinophilia, skin rash, and arthralgias.

**14. What drugs have been reported to cause chronic hepatitis and cirrhosis?**

Rarely, drugs may be associated with a chronic liver injury. Examples of agents more frequently incriminated include methotrexate (MTX), methyldopa, nitrofurantoin, and diclofenac. MTX may be associated with developing cirrhosis, especially in the setting of chronic alcohol use.

**15. What medications are commonly associated with DILI patterns?**

See Table 24-2.

**16. Describe Mallory-Denk bodies, peliosis hepatitis, and phospholipidosis.**

Mallory-Denk bodies are cytoplasmic hyaline inclusions in hepatocytes and may develop as a result of alcoholic or nonalcoholic steatohepatitis.

Peliosis hepatitis is the presence of cystic, blood-filled cavities (vascular lesions) distributed randomly throughout the liver parenchyma.

Phospholipidosis is the excessive accumulation of phospholipids in cells, which can be seen as foamy macrophages or cytoplasmic vacuoles on light microscopy, or lamellar inclusions or myeloid bodies in electron microscopy.

See Table 24-3.

**17. What are the three most common drug-induced hepatic neoplasms?**

- HC carcinoma: Androgenic steroids, estrogenic steroids, thorium oxide (Thorotrast), vinyl chloride
- Angiosarcoma: Thorium oxide (Thorotrast), vinyl chloride, arsenic, androgenic steroids
- Hepatic adenoma\*: Estrogenic steroids, androgenic steroids

\*Before the availability of oral contraceptives, hepatic adenomas were rare. After 5 years of oral contraceptive use, the relative risk of developing a hepatic adenoma has been estimated to increase 116-fold. Hepatic adenomas often regress when exogenous estrogen is removed and can recur during pregnancy. Anabolic steroids also have been reported to cause hepatic adenomas. Hepatic adenomas are usually asymptomatic but can be associated with abdominal fullness, pain, hepatomegaly, and hemorrhage.

**Table 24-2.** Medications Commonly Associated with DILI Patterns

HEPATOCELLULAR	CHOLESTATIC	MIXED	STEATOTIC MICROVESICULAR MIXED MICRO-MACROVESICULAR
Statins	Allopurinol	Amitriptyline	Aflatoxin $\beta$ 1; FIAU
Isoniazid	Amitriptyline	Amoxicillin	Amiodarone; halothane
	Anabolic steroids	Ampicillin	L-Asparaginase methotrexate
	Androgens	Captopril	Aspirin; minocycline
	Azathioprine	Carbamazepine	Chloroform; mitomycin
	Captopril	Cimetidine	Cocaine; tamoxifen
	Carbamazepine	Flutamide	Coumadin; tetra/trichloroethylene
	Estrogens	Ibuprofen	Deferoxamine; tetracyclines
	Oral contraceptives	Imipramine	Didanosine; valproic acid
	Phenytoin	Naproxen	Ethanol
		Nitrofurantoin	
		Phenylbutazone	
		Quinidine	
		Ranitidine	
		Sulfonamides	
		Sulindac	
		Toxic oil syndrome	
		TMP-SMT	

DILI, Drug-induced liver injury; FIAU, fialuridine; SMT, sulfametrole; TMP, trimethoprim.

**Table 24-3.** Drugs and Chemicals Associated with Mallory-Denk Bodies, Peliosis Hepatis, and Phospholipidosis

MALLORY-DENK BODIES	PELIOSIS HEPATIS	PHOSPHOLIPIDOSIS
Amiodarone	Anabolic steroids; Glucocorticoids	Amphiphilic drugs; Chloroquine; Mepacrine
Diethylstilbestrol	Arsenic; Medroxyprogesterone	Amantadine; Chlorpheniramine; Promethazine
Diethylaminoethoxyhexestrol	Azathioprine; Tamoxifen	Amikacin; Chlorpromazine; Propranolol
Ethanol	OCP (steroids); Thioguanine	Amiodarone; Desipramine; TMP-SMT
Glucocorticoids	Danazol; Thorotrust	Amitriptyline; Gentamicin; Thioridazine
Griseofulvin	Diethylstilbestrol; Vinyl chloride	Chloramphenicol; Imipramine Trimipramine
Nifedipine	Estrone; Vitamin A excess	Chlortcyclizine; Iprindole; Tripeleannamine
Tamoxifen		Chloripramine; Ketoconazole

OCP, Oral contraceptive pill; SMT, sulfametrole; TMP, trimethoprim.

#### 18. What drugs are commonly cited for causing hepatic granulomas?

Allopurinol	Nitrofurantoin	Diazepam
Quinidine	Gold	Sulfonamides
Penicillin	Oral contraceptives	Phenytoin
Mineral oil	Tolbutamide	Quinine
Diltiazem	Isoniazid	Oxacillin
Phenylbutazone	Chlorpromazine	

### 19. How do nonsteroidal antiinflammatory drugs affect DILI?

- Aspirin: Risk factors include high dose, connective tissue disorders (rheumatoid arthritis [RA], systemic lupus erythematosus), and the use in children with febrile illness, Reye syndrome (probably related to congenital mitochondrial enzyme defects or deficiencies).
- Sulindac: DILI caused by sulindac typically presents with features of a hypersensitivity reaction (fever, skin rash, pruritus, and hepatomegaly). It can cause pancreatitis, massive HC necrosis, the development of Stevens-Johnson syndrome, and death.
- Diclofenac: The spectrum of injury is from HC injury to an autoimmune pattern of liver injury. Diclofenac-related liver injury is seen more often in older women with osteoarthritis. Steroids may be helpful in severe cases.
- Ibuprofen: Ibuprofen is seldom the cause of DILI and rarely causes severe DILI.
- Celecoxib (Celebrex): The pattern of liver injury ranges from HC to CL. History of sulfa allergy is common among these patients. Reexposure can cause recurrence and features suggest an immune and allergic-hypersensitivity etiologic foundation.

### 20. How should patients receiving long-term MTX be monitored for chronic hepatitis and cirrhosis?

- MTX is an antifolate and antimetabolite agent that is used widely as an antineoplastic and immunosuppressive agent.
- It is a disease-modifying antirheumatic drug used widely in psoriasis, RA, and other autoimmune diseases.
- MTX is thought to cause liver injury by direct toxicity through inhibition of RNA and DNA synthesis in the liver and by causing cellular arrest.
- If aminotransferase levels rise and stay above three times the upper limit of normal (ULN), intensive monitoring and withdrawal of therapy should be considered.

See Table 24-4 and Table 24-5.

**Table 24-4.** Risk Factors for Methotrexate-induced Liver Injury and Recommendations

RISK FACTORS	RECOMMENDATIONS
Preexisting liver disease (especially fatty liver disease)	Obtain liver biopsy prior to initiation of treatment. Monitor liver enzymes every month for 6 months, then every 3 months.
Heavy alcohol use	Avoid alcohol and take folic acid supplements.
Obesity	Encourage weight loss.
Diabetes mellitus	Obtain optimal blood glucose control.
Cumulative dose >1500 mg, >2 years of treatment, daily dosing	There is no antidote for MTX-induced hepatotoxicity; cessation of the drug leads to improvement. Closely monitor liver enzymes during long-term treatments. Prescribe once-weekly folic acid supplementation.

MTX, Methotrexate.

**Table 24-5.** Roenigk Histopathologic Classification of Methotrexate-induced Liver Injury

GRADE	FATTY INFILTRATION	NUCLEAR VARIABILITY	PORTAL INFLAMMATION	FIBROSIS
Grade I	None or minimal	None or minimal	None or minimal	None
Grade II	Moderate to severe	Moderate to severe	Moderate to severe	None
Grade IIIa	May be present or absent	May be present or absent	May be present or absent	Minimal
Grade IIIb	May be present or absent	May be present or absent	May be present or absent	Moderate to severe
Grade IV	May be present or absent	May be present or absent	May be present or absent	Cirrhosis

### 21. What are the recommendations for changing MTX therapy based on liver biopsy findings?

Grades	Recommendations
I	Can continue therapy; repeat biopsy after 1 to 1.5 g of cumulative dose.
II	Can continue therapy; repeat biopsy after 1 to 1.5 g of cumulative dose.
IIIA	Can continue therapy, repeat biopsy in 6 months.
IIIB	Discontinue MTX; exceptional cases need close histologic follow-up.
IV	Discontinue MTX; exceptional cases need close histologic follow-up.

**22. What medications used for the treatment of common endocrine disorders may cause DILI?**

See Table 24-6.

**Table 24-6. DILI and Medications Used for the Treatment of Common Endocrine Disorders**

DRUGS	MECHANISM OF INJURY: HIGHLIGHTS	COURSE RECOMMENDATIONS
<b>Diabetic Agents</b>		
TZDs Troglitazone	Peroxisome proliferator activated receptor- $\gamma$ agonists. Troglitazone is the first agent of this class. It was removed from the market in 2000 following reports of severe hepatotoxicities and fatalities.	Avoid if baseline serum ALT $> 2.5 \times$ ULN. Monitor the ALT level every 2 months for the first year. Stop if the ALT becomes $> 3 \times$ ULN or patient presents with signs of liver injury. Use with caution in patients with history of sulfonamide hypersensitivity or hepatotoxicity. Rechallenge can cause recurrence.
Rosiglitazone/Pioglitazone	Hepatotoxicity is far less common. Can cause mixed, cholestatic, or hepatocellular injury.	
<b>Sulfonylureas</b> Chlorpropamide, gliclazide, glyburide, tolazamide, tolbutamide acetohexamide	Hypersensitivity reaction is thought to be responsible.	
<b>Biguanides</b> Metformin	Rarely cause drug-induced liver injury. Metformin is safe if dose adjustments are made in renal-liver impairment, surgery, and contrast studies.	Resolves rapidly once the agent is stopped. Chronic injuries have been reported. Recovery is rapid when metformin is stopped.
<b>Steroid Derivatives</b>		
Anabolic Steroids Methyltestosterone, methandrostenolone, oxymetholone, danazol, fluoxymesterone, stanozol, norethandrolone, oxandrolone	They cause cholestasis or canalicular liver injury. Alkylation of the C-17 position of testosterone made anabolic steroids available in oral form.	Increased off-label use to improve athletic performance. Androgenic steroids must be discontinued if liver injury develops.
Oral Contraceptives Tamoxifen	They induce androgen-stimulated genes and promote cell growth and development.	Liver injury is usually reversible but fatalities have been reported.
	Estrogens and OCPs inhibit bilirubin and bile acid secretion through estrogen's effects on receptors that modulate bile metabolism. It can cause liver injury, fatty liver, steatohepatitis, and cirrhosis. Liver injury is thought to be due to an idiosyncratic reaction to tamoxifen metabolites. Presents as cholestatic, mixed, or hepatocellular injury.	
<b>Thiourea Derivatives</b>		
PTU Methimazole	PTU typically results in hepatocellular liver injury.  Methimazole liver injury is typically cholestatic.	PTU hepatotoxicity can lead to ALF and cause death or need for liver transplantation. Methimazole causes self-limited injury.

ALF, Acute liver failure; ALT, alanine aminotransferase; OCP, oral contraceptive pill; PTU, propylthiouracil; TZD, thiazolidinediones; ULN, upper limit of normal.

**23. What cardiovascular drugs are commonly associated with DILI?**

See Table 24-7.

**Table 24-7.** Common Cardiovascular Drugs and DILI

DRUGS	FEATURES OF INJURY	HIGHLIGHTS AND RECOMMENDATIONS
<b>ACE Inhibitors</b>	Acute liver injury is rare, typically cholestatic. Idiosyncratic reaction to one of the metabolites.	Ameliorates rapidly after drug is stopped.
<b>Antiarrhythmics</b>		
<b>Amiodarone</b>	Can cause a broad spectrum of liver injury. Metabolites can form intralysosomal inclusions, a hallmark of phospholipidosis. Can cause hepatic steatosis and Mallory-Denk bodies.	Monitor ALT levels regularly if dose > 400 mg/day. Decrease the dose or stop if ALT > 3 × ULN. Perform a liver biopsy if elevations persist. Results in “lupuslike reaction” more often than hepatotoxicity.
<b>Procainamide</b>	Liver injury is due to hypersensitivity reaction. It can result in granuloma formation. Causes cholestatic liver injury.	Resembles liver injury of quinidine. It can cause complex drug interactions.
<b>Quinidine</b>	Hepatotoxicity is due to a hypersensitivity reaction. Typically cholestatic or mixed.	
<b>Calcium Channel Blockers</b>		
<b>Diltiazem</b>	Likely caused by hypersensitivity. Injury pattern is hepatocellular or cholestatic.	Liver injury is rare, usually mild and reversible.
<b>Nifedipine</b>	Likely caused by formation of toxic metabolites. Usually hepatocellular or mixed.	It can result in steatosis and Mallory hyaline.
<b>Verapamil</b>	It is probably a hypersensitivity reaction. Hepatocellular, mixed, or cholestatic injury.	
<b>Diuretics</b>	There have been no case series to suggest hepatotoxicity among this class. Considered safe.	Ticrynahen, an uricosuric diuretic, was removed from U.S. market in 1979 because of acute and chronic hepatitis.
<b>Hydralazine</b>	It is metabolized to immunologic adduct, which results in autoimmune hepatitis-like syndrome. Results in hepatocellular, cholestatic, or granulomatous injury.	
<b>α-methyldopa</b>	Toxic metabolic intermediates act as antigenic haptens in susceptible hosts. It can cause acute-chronic hepatitis, cholestatic hepatitis, fulminant liver failure, and cirrhosis. Typically hepatocellular, rarely mixed or cholestatic.	An autoimmune liver injury. Rechallenge can lead to rapid recurrence of liver injury and can result in death. Women appear to be more susceptible. It can mimic autoimmune lupoid hepatitis.
<b>Antihyperlipidemics</b>		
<b>Fenofibates</b>	Typically hepatocellular injury, but mixed and cholestatic patterns are reported. Injury appears to be immunologic and it can result in autoimmune-like hepatitis.	Liver enzymes usually normalize, but chronic liver injury and fibrosis have been reported in patients who were kept on therapy despite evidence of liver injury. Toxicity is common with the sustained-release form.
<b>Niacin (Nicotinic Acid)</b>	Primarily hepatocellular; occasionally cholestatic injury occurs. Injury is dose dependent and secondary to intrinsic toxic reaction caused by high serum levels of niacin.	Liver enzymes should be monitored. It should be discontinued if enzymes are elevated.
<b>Statins (HMG-CoA Reductase Inhibitors)</b>	Serious DILI is rare. Safe to use even in patients with chronic liver disease. Act as haptens on cellular targets in susceptible hosts. Patterns of injury are approximately equally divided between hepatocellular and cholestatic/mixed injury.	It may occasionally present with an autoimmune phenotype. Experts recommend avoiding statins only in decompensated cirrhotics or patients with acute liver failure or liver injury caused by statin use.

ACE, Angiotensin-converting enzyme; ALT, alanine aminotransferase; Co-A, coenzyme A; DILI, drug-induced liver injury; HMG, 3-hydroxy-3-methyl-glutaryl; ULN, upper limit of normal.

**24. What commonly used antimicrobial agents have been shown to cause liver injury?**

See Table 24-8.

**Table 24-8. Commonly Used Antimicrobial Agents Shown to Cause Liver Injury**

ANTIBACTERIALS	HIGHLIGHTS
<b>Tetracyclines</b>	
Tetracycline	Liver injury is seen with high IV use; it is extremely rare with low-dose oral tetracyclines. Injury is due to inhibition of mitochondrial fatty acid oxidation and can cause microvesicular steatosis.
Minocycline	It can cause acute and chronic autoimmune hepatitis, with positive ANA and ASMA.
<b>Macrolides</b>	
Erythromycin	DILI is predominantly cholestatic because of an idiosyncratic immunoallergic reaction; it is rarely fatal and recovery can take a few weeks. Erythromycin and clarithromycin are potent inhibitors of CYP3A and can cause adverse drug reactions, especially with immunosuppressive agents such as tacrolimus and cyclosporine A.
Clarithromycin, Azithromycin, and Roxithromycin	Liver injury is less frequent but it does occur.
<b>Penicillins</b>	Hepatotoxicity is rare, and is due to idiosyncratic reaction with immune features. It can cause HC, cholestatic, mixed, or granulomatous injury.
<b>Amoxicillin-Clavulanic Acid</b>	These are the most common cause of antibiotic-related DILI. The disease caused is typically cholestatic, but can be mixed. Hepatotoxicity is probably immunoallergic in origin and is worse with concomitant hepatotoxic medication use, suggesting drug-drug interactions as well. It is more common in older men and patients with certain HLA types. Injury can be severe, fatalities have been reported, and rechallenge can result in recurrence. Amoxicillin alone is less likely to cause DILI, although it may.
<b>Sulfonamides</b>	
Pyrimethamine-	DILI is idiosyncratic and usually reflects hypersensitivity to sulfa-derived medications.
Sulfadoxine	Pattern of injury is usually mixed but it can be HC or cholestatic as well.
Sulfasalazine	DILI may be a part of a systemic hypersensitivity reaction such as DRESS.
TMP/SMX	Resolves rapidly with discontinuation. Rechallenge should be avoided. Used in the treatment of toxoplasmosis and some cases of resistant malaria. It is commonly used to treat inflammatory bowel disease. It causes higher incidence of allergic reactions ( $\approx 20\%$ ) in HIV-infected patients. Injury varies in severity from asymptomatic presentation to acute liver failure.
<b>Other Antimicrobials</b>	
Rifampin	Hepatotoxicity is due to idiosyncratic metabolic products. More likely to affect patients with underlying liver disease. It can induce drug metabolizing enzymes. Concurrent medications (OCP, anticoagulants, antiretrovirals, cyclosporine, benzodiazepines, and macrolides) should be monitored.
Nitrofurantoin	It can produce oxidative free radicals and result in autoimmune-type injury, reported especially in older women. (This may be because it is chiefly older women who take the drug to suppress UTIs.) It can cause acute or chronic hepatitis-like syndrome; the pattern of injury is usually HC. Severity ranges from mild elevations in liver enzymes to fulminant injury and death. Complete recovery is expected; rechallenge can cause recurrence and it should be avoided. Rare cases of cholestasis and jaundice have been reported.
Chloramphenicol	
Antifungals	
Griseofulvin	It rarely causes DILI, but the drug can precipitate attacks of acute intermittent porphyria. A potent competitive inhibitor of hepatic CYP3A that can lead to adverse drug reactions.
Ketoconazole	DILI is due to formation of an N-deacetyl metabolite that is converted to a toxic dialdehyde. Injury usually HC but can be mixed and cholestatic as well. Recovery is slow; acute liver failure and death have been reported. Rechallenge should be avoided.
Flucytosine	It rarely causes clinically apparent liver injury. Its use is very limited and DILI appears to be dose related.

ANA, Antinuclear antibody; ASMA, anti-smooth muscle antibody; DILI, drug-induced liver injury; DRESS, drug reaction with eosinophilia and systemic symptoms; HC, hepatocellular; HLA, human leukocyte antigen; IV, intravenous; OCP, oral contraceptive pill; SMX, sulfamethoxazole; TMP, trimethoprim; UTI, urinary tract infection.

## 25. Who is at risk for liver toxicity from INH therapy?

INH causes idiosyncratic hepatic reaction leading to overt clinical hepatitis. It is the second most common drug responsible for ALF requiring liver transplantation in the United States. The molecular mechanism is thought to involve formation of acetylisoniazid, which is hydrolyzed to monoacetylhydrazine and then activated to toxic metabolites. Risk factors include older age, slow acetylator status resulting from genetic variants, possibly alcohol use, cirrhosis, Asian race, malnutrition, underlying chronic hepatitis B or C, and use in combination with rifampicin and pyrazinamide. The onset is insidious and clinically it resembles acute viral hepatitis. Although it is usually self-limited, 10% of cases are severe and can lead to ALF, which results in fatality or requires liver transplantation.

## 26. How is INH toxicity prevented?

Current recommendations include screening patients for ethanol abuse and preexisting liver or renal disease. The presence of chronic liver disease is not an absolute contraindication to the use of INH, but the indications should be scrutinized and therapy monitored more closely. If the patient is taking INH alone, baseline laboratory testing for all but the healthiest, youngest (<35 years), non-human immunodeficiency virus-infected adults, and further monitoring at monthly intervals.

If the patient is also taking rifampicin or pyrazinamide, monitor liver enzymes twice weekly for 2 weeks, every 2 weeks up to 2 months, and then monthly). Stop INH if alanine aminotransferase (ALT) is more than three times the ULN with symptoms, or more than five times the ULN without symptoms.

## 27. What commonly used recreational drugs are associated with hepatotoxicity?

- Cocaine: Patients with cocaine hepatotoxicity may present with jaundice or fatigue and generalized malaise. Cocaine toxicity also may cause coagulopathy, rhabdomyolysis, and disseminated intravascular coagulation (DIC). The mechanism of hepatotoxicity is thought to be due to conversion to a toxic metabolite. The clinical phenotype is usually acute hepatic necrosis. Liver biopsy typically shows zone III necrosis and fatty change, suggesting related ischemia. It is usually self-limited, but fatalities have been reported mainly resulting from its major systemic effects. Liver injury may be multifactorial and include coexistent viral liver disease (hepatitis B, C, and delta) and acetaminophen or alcohol use. NAC usually causes injury similar to acetaminophen hepatotoxicity.
- 3,4-methylene dioxymethamphetamine (MDMA, Ecstasy): MDMA is a dangerous synthetic amphetamine commonly used for abuse. It is a potent central nervous system stimulant that causes euphoria and increases cognitive abilities. Amphetamines undergo extensive metabolism by the hepatic P450 system, and injury is thought to be secondary to generation of toxic metabolites. Liver injury is usually HC and can be severe enough to cause ALF and death. Initially thought to have little toxicity, Ecstasy can cause various systemic effects, including cardiac arrhythmias, DIC, acute renal failure, and hyperthermia.

## 28. What anesthetic agents are associated with HC injury?

Clinically significant hepatotoxicity is seen only with the halogenated volatile agents. Halothane has more propensity to cause hepatotoxicity compared with halogenated agents that were developed later, such as enflurane, isoflurane, desflurane, and sevoflurane. Liver injury usually consists of centrilobular necrosis, but CL patterns have been reported as well. Obese women between the ages of 40 and 60 years are at higher risk; a small percentage of patients may develop fulminant liver failure and may require liver transplantation.

• Halothane: Severe liver injury from halothane is rare, approximately 1 in 15,000 after initial exposure and approximately 1 in 1000 after repeated exposures. Liver injury is suspected to be immunoallergic, caused by creation of reactive intermediates. Risk factors include previous exposure to halogenated anesthetics and a history of halothane hepatitis or unexplained fever and rash after anesthesia with halogenated agents. Other risk factors are hypotension, older age, obesity, and concurrent use of CYP 2E1 inducers. Prognostic factors for poor outcome include a short latent period from exposure to jaundice, obesity, age older than 40 years, hepatic encephalopathy, and prolongation of the prothrombin time. Corticosteroids and exchange transfusions are not helpful, and the mortality rate of fulminant halothane hepatitis is nearly 80% without liver transplantation.

## 29. How does phenytoin cause DILI?

Phenytoin can cause allergic hepatitis, cholestasis, granulomatous liver disease, and fulminant hepatic failure. Formation of the reactive arene oxide metabolite followed by formation of the o-quinone leads to haptens and immune activation. Systemic symptoms include fever, malaise, lymphadenopathy, splenomegaly, and rash. Liver enzymes are elevated two to one hundred-fold ( $ALT >$  aspartate aminotransferase) and alkaline phosphatase levels two- to eightfold. It can cause leukocytosis and atypical lymphocytes suggesting mononucleosis and eosinophilia, but lupuslike syndrome and pseudolymphoma are rare. Cessation of the drug leads to resolution of toxicity in most cases. If liver failure develops, the case/fatality ratio can go up to 40%. Because of cross-reactivity, carbamazepine, oxcarbazepine, and fosphenytoin should be avoided.

### 30. Can herbal therapies cause liver injury?

The composition of herbal remedies is variable and unregulated. Some have the potential to cause liver injury. Patients with preexisting liver disease should be extremely cautious and consult their physicians.

Milk thistle (*Silybum marianum*) has not been shown to cause liver enzyme elevations or clinically apparent acute liver injury and has been used for centuries by patients with underlying liver disease. Many patients with liver disease self-medicate with milk thistle. Human studies in patients with chronic liver disease have been promising but inconclusive. A purified intravenous form of silybinin is being used in Europe for the treatment of *Amanita phalloides* mushroom poisoning.

Potentially hepatotoxic herbs include the following:

- Autoimmune hepatitis-like picture: Syo-saiko-to, Ma-huang, germander
- Acute hepatitis-like picture: Germander, greater celandine, chaparral, Jin Bu Huan, kava kava, Hydrocut, LipoKinetix
- Chronic hepatitis-like syndrome: Germander, Jin Bu Huan, He Shou Wu, valerian
- Severe hepatitis: Syo-saiko-to, chaparral, greater celandine, HerbaLife
- Fulminant hepatic failure or death: Mushrooms (usually *Amanita phalloides*), atractylis gummifera, chaparral, germander, kava kava, germander, skullcap
- Venoocclusive disease: Pyrrolizidine alkaloids (comfrey, senecio)

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

### BIBLIOGRAPHY

1. Andrade RJ, Lucena MI, Fernández MC, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology* 2005;129:512–21.
2. Bhardwaj SS, Chalasani N. Lipid lowering agents that cause drug-induced hepatotoxicity. *Clin Liver Dis* 2007;11:597–613.
3. Bonkovsky HL, Jones DP, Russo MW, Steven I, Shedlofsky SI. Drug-induced liver injury. In: Boyer TD, Manns MP, Sanyal AJ, editors. *Zakim and Boyer's hepatology: a textbook of liver disease*. 6th ed. Philadelphia: Saunders Elsevier; 2012. p. 417–61.
4. Bromer MQ, Black M. Acetaminophen hepatotoxicity. *Clin Liver Dis* 2003;7:351–67.
5. Chalasani N, Fontana RJ, Bonkovsky HL, et al. Drug-induced liver injury network (DILIN): causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* 2008;135(6):1924–34, 1934.e1–1934.e4.
6. Chang CY, Schiano TD. Review article: drug hepatotoxicity. *Aliment Pharmacol Ther* 2007;25:1135–51.
7. Cunha BA. Antibiotic therapy: antibiotic side effects. *Med Clin North Am* 2001;85:149–85.
8. Gunawan BK, Kaplowitz N. Mechanisms of drug-induced liver disease. *Clin Liver Dis* 2007;11:459–75.
9. Hussaini SH, Farrington EA. Idiosyncratic drug-induced liver injury: an overview. *Expert Opin Drug Saf* 2007;6:673–84.
10. Junaidi O, Di Bisceglie A. Aging liver and hepatitis. *Clin Geriatr Med* 2007;23:889–903.
11. Lee WM. Drug induced hepatotoxicity. *N Engl J Med* 2003;349:474–85.
12. Lewis JH. "Hy's law," "the Rezulin Rule," and other predictors of severe drug-induced hepatotoxicity. *Pharmacoepidemiol Drug Saf* 2006;15:221–9.
13. Maddrey WC. Drug-induced hepatotoxicity. *J Clin Gastroenterol* 2005;39(Suppl. 2):S83–S89.
14. Nathwani RA, Kaplowitz N. Drug hepatotoxicity. *Clin Liver Dis* 2006;10:207–17.
15. Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002;137:947–54.
16. Russo MW, Galanko JA, Shrestha R, Fried MW, et al. Liver transplantation for acute liver failure from drug induced liver injury in the United States. *Liver Transpl* 2004;10:1018–23.
17. Russo MW, Scobey M, Bonkovsky H. Drug induced liver injury associated with statins. *Semin Liver Dis* 2009;29:412–22.
18. Seeff LB. Herbal hepatotoxicity. *Clin Liver Dis* 2007;11:577–96.
19. Teoh NC, Farrell GC. Hepatotoxicity associated with non-steroidal anti-inflammatory drugs. *Clin Liver Dis* 2003;7:401–13.
20. Tolman KG, Chandramouli J. Hepatotoxicity of the thiiazolidinediones. *Clin Liver Dis* 2003;7:369–79.
21. Tostmann A, Boeree MJ, Aarnoutse RE, et al. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. *J Gastroenterol Hepatol* 2008;23:192–202.
22. Urban TJ, Shen Y, Stoltz A, et al, on behalf of the Drug-Induced Liver Injury Network, DILIGEN, EUDRAGENE, the Spanish DILI Registry, and the International Serious Adverse Events Consortium. Limited contribution of common genetic variants to risk for liver injury due to a variety of drugs. *Pharmacogenet Genomics* 2012;22(11):784–95.
23. West SG. Methotrexate hepatotoxicity. *Rheum Dis Clin North Am* 1997;23:883–915.
24. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology* 2006;11:699–707.
25. Zapater P, Moreu R, Horga JF. The diagnosis of drug-induced liver disease. *Curr Clin Pharmacol* 2006;1:207–17.
26. Zimmerman H. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1999.

### Websites

National Library of Medicine. LiverTox: clinical and research information on drug-induced liver injury. <http://www.livertox.nih.gov> [Accessed September 22, 2014].

# ALCOHOLIC LIVER DISEASE, ALCOHOLISM, AND ALCOHOL WITHDRAWAL SYNDROME

Clark Kulig, MD

## 1. What are the epidemiologic factors of alcohol use and abuse, alcoholism, and alcoholic liver disease (ALD)?

More than 50% of U.S. adults use alcohol. More than 70% of the annual U.S. consumption of alcohol is used by only 10% of the population and, of these, approximately three quarters are male. *Eleven percent of men and 4% of women, or a total of more than 6% of Americans, are alcoholics;* many more abuse alcohol. Approximately 15% to 30% of alcoholics who continue to drink daily develop cirrhosis. Alcoholic cirrhosis accounts for 28% to 50% of total deaths from cirrhosis with an age-adjusted rate of 3.8 per 100,000 population.

## 2. Is alcoholism the same as ALD?

No. ALD includes physical damage to the liver in the form of inflammation, steatosis, and scarring, whereas alcohol dependence, or alcoholism, is a behavioral diagnosis that includes physical (withdrawal or tolerance) symptoms and behavioral components (drinking despite known consequences or loss of control symptoms).

## 3. Do all alcoholics have ALD?

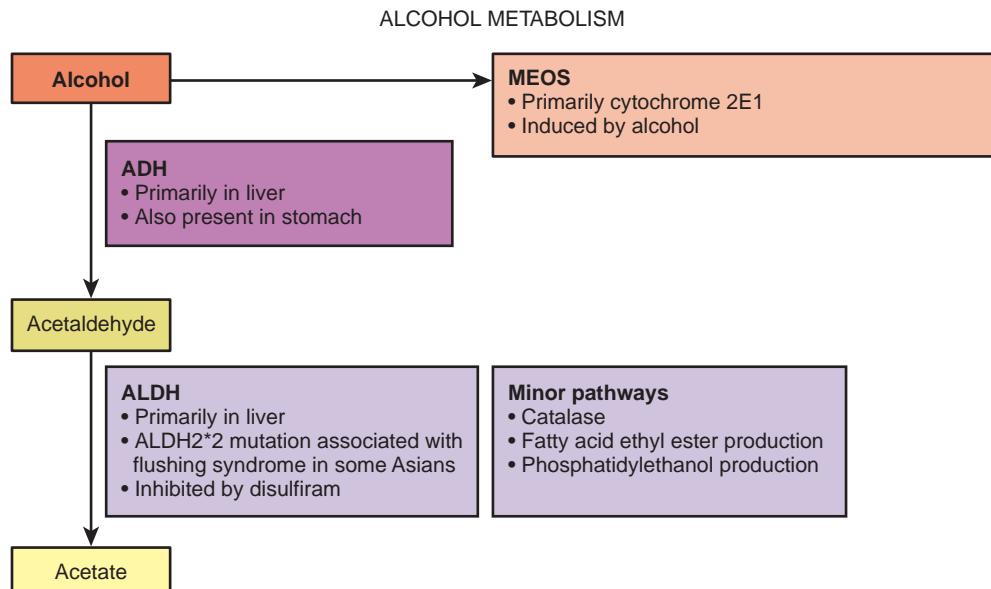
Generally, yes. The term *alcoholism* is synonymous with *alcohol dependence*, and includes physical components of withdrawal symptoms and tolerance that are generally related to an amount of alcohol intake that causes at least mild steatohepatitis, and sometimes hepatic fibrosis over time.

## 4. Are all patients with ALD alcoholic?

Often they are not. ALD may be associated with intermittent binge drinking that may be categorized more as alcohol abuse than dependence. Also, chronic daily alcohol use may occur without alcohol dependence symptoms, but still be associated with hepatic inflammation, steatosis, and even advanced scarring over time.

## 5. How does the liver metabolize ethanol?

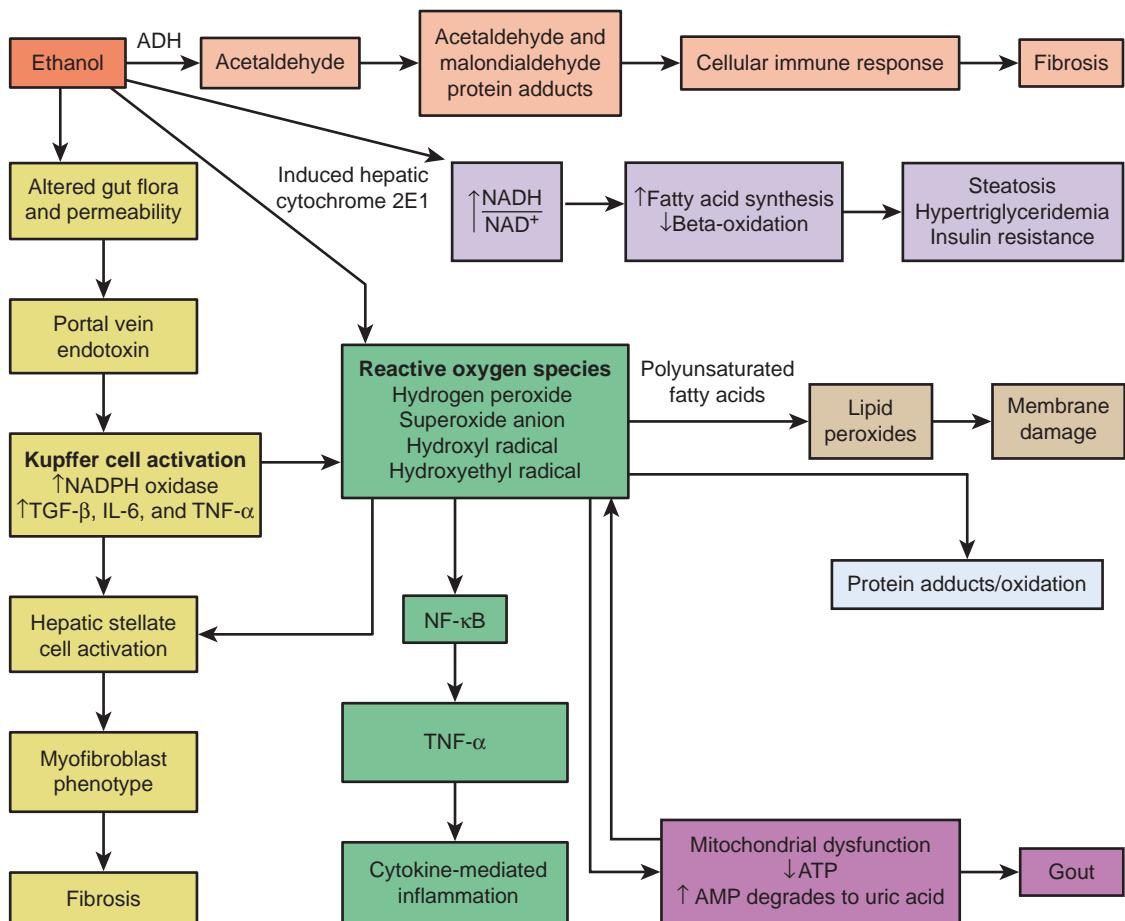
The majority of ethanol metabolism is in the liver. Following ingestion, ethanol is absorbed from the stomach and proximal small intestine, and moves via the mesenteric circulation to the liver (Figure 25-1).



**Figure 25-1.** Alcohol metabolism. ADH, Alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; MEOS, microsomal ethanol oxidation system.

## 6. What is the pathogenesis of ALD?

The pathogenesis of ALD is not well established, but there are multiple pathophysiologic pathways that likely contribute (Figure 25-2).



**Figure 25-2.** Alcohol hepatotoxicity. ADH, Alcohol dehydrogenase; AMP, adenosine monophosphate; ATP, adenosine triphosphate; IL, interleukin; NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide and hydrogen; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB; nuclear factor- $\kappa$ B; TGF, transforming growth factor; TNF, tumor necrosis factor.

## 7. What is the natural history of ALD?

As alcoholic patients are a heterogeneous population, the prevalence of liver injury from alcohol varies from person to person and a direct correlation of advanced liver disease from excessive alcohol consumption is not always observed. Genetic factors are important; monozygotic twins have a threefold increase of alcoholism in both compared with dizygotic or fraternal twins. In general, there is a direct correlation between the consumption of ethanol and subsequent liver-related mortality. Patients with fatty metamorphosis of the liver from alcohol are more likely to progress to end-stage cirrhosis with continued ethanol consumption than those lacking fatty change of hepatocytes. Fatty liver also correlates with increased all-cause mortality. *Of those who consume daily excess alcohol for 12 or more years, more than 20% will develop cirrhosis.* Risk factors for development of ALD are listed in Table 25-1.

## 8. What is the pathophysiology of alcohol withdrawal syndrome?

Chronic ethanol ingestion enhances the effect of  $\gamma$ -aminobutyric acid on brain neuroreceptors resulting in decreased brain excitability. With abrupt withdrawal of ethanol, brain hyperexcitability develops, producing the symptoms of withdrawal.

## 9. What are the different histologic types of ALD?

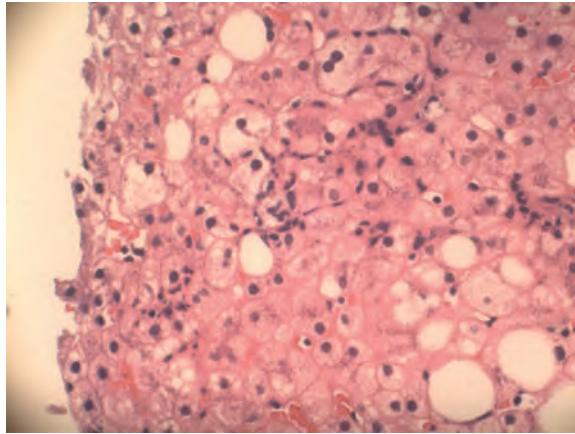
Several morphologic manifestations of alcohol consumption may be observed, although some patients with chronic alcoholism will have no histologic evidence of liver injury at liver biopsy. See Chapter 32 for the gamut of histologic findings seen with ethyl alcohol (ETOH) liver injury.

**Table 25-1.** Risk Factors for Alcoholic Liver Disease

RISK FACTOR	QUALIFIER	RELATIVE RISK
Quantity of ethyl alcohol (ETOH)		
Men	80 g/day × 10+ yr	1.1 ↑↑↑
Women	40 g/day × 10+ yr	↑↑↑
Consumption pattern	Continuous > periodic	1.2 ↑↑
Malnutrition		1.3 ↑↑
Ethnicity	Hispanic and black American > white American	1.4 ↑
Genetics	Japanese AHD gene ALDH2*2	1.5 ↑↑
Obesity	High fat content Empty calories from ETOH	1.6 ↑↑
HCV infection	PCR positive, viral replicator	1.7 ↑↑↑
Hemochromatosis	Homozygous gene	1.8 ↑↑↑
Age >65 yr	Varies with general health and nutrition	1.9 ↑

ETOH, Ethyl alcohol; HCV, hepatitis C virus; PCR, polymerase chain reaction.

- Fatty metamorphosis of the liver is the most common histologic finding and the earliest manifestation following ethanol ingestion. Fat accumulation in hepatocytes can develop within 2 days of excessive ethanol consumption and clear within 2 weeks of cessation. Fatty metamorphosis is macrovesicular with large droplet fat that displaces the nucleus of centrilobular hepatocytes. The finding of fatty liver in the alcoholic can be an indicator for future risk of developing alcoholic cirrhosis if ethanol intake continues (Figure 25-3).



**Figure 25-3.** Alcohol steatohepatitis histopathologic appearance.

- Microvesicular steatosis or alcoholic foamy degeneration is an infrequent complication of alcohol consumption. It appears to be a consequence of mitochondrial dysfunction from ethanol, largely developing within centrilobular hepatocytes, and results in hyperbilirubinemia, hepatic encephalopathy, and death.
- *Alcohol hepatitis* occurs in approximately 10% to 20% of chronic alcoholics and is the pathway for the development of cirrhosis for most patients with chronic alcohol intake. The diagnosis is established by a typical history of long-term daily ethanol consumption, appropriate laboratory findings, and liver histologic findings that includes centrilobular hepatocellular necrosis, polymorphonuclear leukocyte inflammation, and the presence of Mallory hyaline (see Figure 25-3 and Chapter 32).
- *Alcohol cirrhosis* follows alcoholic hepatitis and develops as micronodular cirrhosis. With cessation of ethanol intake, many patients will transform to macronodular (larger regenerative nodules) cirrhosis. Alcoholic hepatitis may coexist with cirrhosis in those continuing to consume ethanol. Alcoholic cirrhosis is also a predisposing lesion for hepatocellular carcinoma (HCC).

#### **10. How does ALD differ from nonalcoholic fatty liver disease (NAFLD)?**

NAFLD cannot be differentiated from ALD histologically. The prevalence of NAFLD among U.S. adults is estimated to be more than 30% in several studies. The histologic manifestations of NAFLD are not discernible from ALD, and its diagnosis depends on the exclusion of significant ethanol intake. Most use an alcohol consumption criterion of less than 20 g daily to establish the diagnosis of NAFLD, but from a practical clinical standpoint, the two exist concomitantly very often. Identification of Mallory hyaline on liver biopsy is not specific to alcoholic hepatitis and can be seen in NAFLD, as well as other liver diseases.

#### **11. What are the clinical findings in the patient with ALD?**

Aspartate aminotransferase (AST) often  $2 \times >$  than alanine aminotransferase (ALT) concentration. These findings are nonspecific and can be found in any chronic liver disease. Dupuytren's contracture and rhinophyma (gin blossom) are more closely associated with Scandinavian heritage and rosacea, respectively.

#### **12. What are the laboratory findings in patients with ALD?**

- Aspartate aminotransferase (AST) is often more than twice the alanine aminotransferase (ALT) concentration.
- Hypoalbuminemia and hypergammaglobulinemia (often with elevation of IgG and IgA).
- Ferritin levels up to 5000 ng/mL may occur as an acute phase reactant in alcohol hepatitis.
- Uric acid and triglycerides are elevated.
- International normalized ratio (INR) is elevated because of impaired hepatic production of coagulation factors and inadequate dietary vitamin K.
- Hemolysis (suggested by ↑ LDH, reticulocytosis, ↓ haptoglobin, and helmet cells and acanthocytes on peripheral smear).
- Alcoholic hepatitis is a cholestatic disease with ↑ alkaline phosphatase,  $\gamma$ -glutamyl transpeptidase, and serum bilirubin levels.
- Mean corpuscular volume may be elevated from nutritional deficiency (folic acid or vitamin B<sub>12</sub>) or alcohol effect on cell membranes.
- Leukocytosis of 12,000 to 14,000  $\mu$ L is common in alcohol hepatitis, and leukemoid reactions of 30,000 to 50,000  $\mu$ L can occur.
- Thrombocytopenia (<125,000) may be related to portal hypertension with splenomegaly, decreased bone marrow function, and decreased endogenous hepatic thrombopoietin production, and may support cirrhosis.
- All the previously discussed tests are relatively nonspecific, but add incremental support for diagnosis of ALD.
- Blood, breath, and urine tests for alcohol are similar in terms of sensitivity; the detection period is generally 8 hours or less.
- Urine ethyl glucuronide is clinically available, very specific, and supports recent alcohol ingestion with a detection period greater than standard alcohol testing.

#### **13. How does radiographic imaging help in evaluation of the patient with ALD?**

Findings on radiographic imaging of the liver in ALD are nonspecific. Changes of fatty liver are common, especially the hyperechogenicity noted via ultrasound (US), but indistinguishable etiologically from other causes of fatty liver disease. Findings of an enlarged portal vein, splenomegaly, a recanalized umbilical vein, and a nodular liver increase the suspicion for cirrhosis and portal hypertension in general, but are not specific to ALD. The reader is referred to [Chapter 69](#) for a detailed discussion of noninvasive gastrointestinal (GI) imaging.

#### **14. What are the clinical characteristics of alcohol hepatitis?**

Jaundice, palpable tender hepatomegaly, fever, hepatic encephalopathy, and sometimes hepatic systolic bruit. Chronic ALD in the form of mild steatohepatitis may have minimal or absent symptomatology and only mild aminotransferase elevations. Decreases in androgens may lead to female pattern escutcheon, testicular atrophy, and gynecomastia when cirrhosis is present. Evidence of portal hypertension such as splenomegaly and even esophageal varices may recede if severe steatohepatitis improves and there has been minimal hepatic scarring. Spider telangiectasia are common on the upper chest in those with cirrhosis.

#### **15. Which syndromes may present in a similar way to alcohol hepatitis and how can they be distinguished?**

Acute choledocholithiasis with or without infectious cholangitis may present in a very similar way to alcohol hepatitis, but is often accompanied by evidence of biliary obstruction on imaging (biliary dilatation and often stone visualization via US or magnetic resonance cholangiopancreatography [MRCP]). Acute hepatitis (and acute supra-imposed on chronic hepatitis) related to a wide variety of etiologic factors may present in a very similar way to alcohol hepatitis. Acute viral hepatitis can be diagnosed serologically (hepatitis A IgM, cytomegalovirus IgM, hepatitis B surface Ag and core IgM). Acute hepatitis B and C infection within 8 weeks of potential exposure should be assessed with quantitative DNA and RNA testing in those with a high pretest suspicion (recent new sexual partner or intravenous [IV] drug use). Toxin-associated hepatitis can be diagnosed from history (new medication recently) and laboratory testing (acetaminophen concentration, creatine kinase testing for statin hepatitis). Flares (aminotransferase elevations) of chronic NAFLD rarely manifest symptomatically, and the ALT is often higher than AST. Chronic liver diseases such as

hemochromatosis,  $\alpha_1$  antitrypsin, celiac disease–associated hepatitis, and primary biliary cirrhosis generally do not have dramatic acute biochemical or symptomatic disease flares as is seen in alcohol hepatitis. Acute Wilson disease is often associated with low ceruloplasmin and alkaline phosphatase levels, hemolytic anemia, and high 24-hour urine copper concentrations. Doppler US can diagnose acute Budd-Chiari syndrome (hepatic vein thrombosis). Hepatic abscesses and tumors are often diagnosed at presentation via US and further characterized via computed tomography (CT) or magnetic resonance imaging (MRI). Autoimmune hepatitis often has positive serologic findings (antinuclear antibody [Ab], antismooth muscle Ab, elevated IgG).

#### 16. Is liver biopsy necessary to diagnose or manage ALD?

ALD can usually be diagnosed via the combined history, physical examination, and laboratory data, often by excluding other diagnoses. When liver biopsy is needed, the internal jugular route may have a lower bleeding risk. Liver biopsy to assess fibrosis stage in the setting of known alcohol hepatitis rarely changes management (abstinence, optimizing nutrition, prednisolone) in the acute setting, but detection of cirrhosis dictates the need to screen for esophageal varices and hepatoma. Liver biopsy should be considered if liver tests continue to fluctuate despite suspected abstinence from alcohol and there is no other clear etiologic factor. Many clinicians prefer platelets of more than  $80,000 \text{ mm}^3$  and an INR of less than 1.6 for liver biopsy.

#### 17. What are the signs and symptoms of alcohol withdrawal syndrome and when do they occur?

Signs and symptoms of ETOH withdrawal can be divided into four time intervals, as described in Table 25-2.

**Table 25-2.** Signs, Symptoms, and Timing of Alcohol Withdrawal

SYMPTOMS OF ALCOHOL WITHDRAWAL	TIME FROM CESSATION TO ONSET OF SYMPTOM	PEARLS
Insomnia, tremulousness, mild anxiety, GI upset, headache, diaphoresis, palpitation, anorexia	6 to 12 h	
Alcohol hallucinations: visual, auditory, or tactile	12 to 24 h	These symptoms usually resolve in 48 h.
Withdrawal seizures: generalized tonic-clonic type Difficult to treat; avoid medications that lower seizure threshold	24 to 48 h	Do not be fooled; seizures can occur as early as 2 h after cessation of alcohol.
Delirium tremens: hallucinations (predominately visual), disorientation, tachycardia, hypertension, low-grade fever, agitation, diaphoresis	48 to 72 h	These symptoms peak at 5 days.

GI, Gastrointestinal.

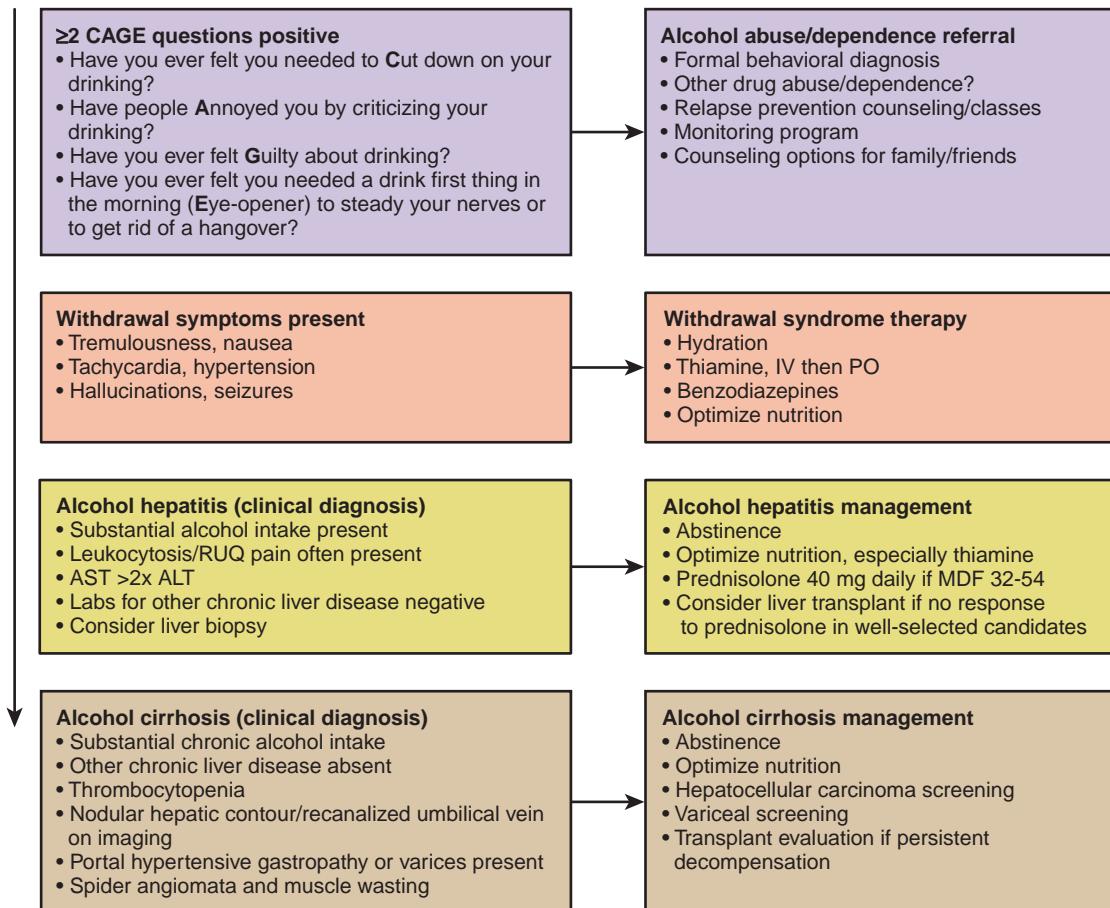
#### 18. How is a patient screened for alcoholism during an office visit?

The diagnosis of alcohol dependence can be based on *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision, criteria with positive findings in at least three of seven categories, including tolerance, withdrawal, consuming more ethanol over time, having a desire to cut down on ethanol consumption, time spent in obtaining alcohol, giving up important activities to drink ethanol, and continuing to drink despite knowledge of personal impairment. The CAGE questionnaire mnemonic is a quick and simple test that can help identify alcohol dependence. It includes four questions (Figure 25-4), and has a specificity of 76% and a sensitivity of 93% for the identification of excessive drinking and a specificity of 77% and a sensitivity of 91% for the identification of alcoholism when two or more questions are answered in the affirmative.

#### 19. What are the main components of ALD therapy?

Abstinence from alcohol is the therapy that is most obvious and generally the most difficult to achieve. Achieving abstinence for those with alcohol abuse and especially dependence often is more likely when a substance abuse specialist (psychiatry or psychology) or behavioral program (inpatient or outpatient rehabilitation and relapse prevention programs, or Alcoholics Anonymous) is used. Health care workers who provide nutritional support have more control in terms of aiding recovery. Prednisolone and pentoxifylline are pharmacologic therapies for alcohol hepatitis that improve survival in well-selected cohorts.

## CLINICAL SUSPICION OF ALCOHOL LIVER DISEASE



**Figure 25-4.** Algorithm: alcoholic liver disease diagnosis and therapy. ALT, Alanine aminotransferase; AST, aspartate aminotransferase; IV, intravenous; MDF, Maddrey discriminant function; PO, by mouth, RUQ, right upper quadrant.

## 20. What is the treatment for ALD? (See Figure 25-4.)

Step 1 is supportive care:

- ETOH abstinence
- Substance use disorder programs
- Nutrition
- Vitamin supplements: folate and thiamine

Step 2 is the identification of high-risk acute alcoholic hepatitis:

- Bilirubin and prothrombin INR levels are predictive of outcome.
- The patient with alcoholic hepatitis and a bilirubin level of less than 5 mg/dL usually does well.
- The Maddrey discriminant function (MDF) score can be used to assess the risk of death from alcoholic hepatitis and to determine when corticosteroids should be used for those with severe clinical disease.

$$\text{MDF} = \text{bilirubin (mg/dL)} + 4.6 \times (\text{prothrombin time [in seconds]} - \text{the control})$$

MDF < 32, associated mortality 15% within 2 months, prednisolone not indicated

MDF ≥ 32, associated mortality 50% within 2 months, prednisolone indicated, 40 mg daily × 28 days

MDF > 54, increased mortality with prednisolone therapy

Administration of corticosteroids can improve 30-day survival in those with MDF between 32 and 54 and those with spontaneous encephalopathy in the presence of alcoholic hepatitis.

## 21. Which patients with alcohol hepatitis are too ill for prednisolone therapy?

Patients with GI bleeding, renal failure, and active bacterial infection were generally excluded from the major trials of steroids for alcohol hepatitis. Also, patients with an MDF of more than 54 had a higher mortality with steroid therapy in one study.

## 22. Is pentoxifylline helpful for alcoholic steatohepatitis?

Yes. Survival benefit has been shown, and is associated with a lower incidence of hepatorenal syndrome. Prednisolone therapy may be more beneficial, as combination therapy yielded no benefit over prednisolone therapy alone.

## 23. How is alcohol detoxification best managed?

Detoxification management will reduce complications and improve rehabilitation of the alcoholic. Detoxification includes initiating abstinence from ethanol, treating withdrawal symptoms, and maintaining abstinence treatment to prevent recidivism. Of those going through alcohol withdrawal, approximately 10% to 20% will require in-patient treatment. You should consider hospitalization for any patient with a previous history of severe alcohol withdrawal, prior seizures during withdrawal, concomitant medical or psychiatric illness, and lack of reliable home support.

## 24. What are the usual steps taken for in-hospital treatment of alcohol withdrawal?

**Step 1** is supportive care:

- Provide a quiet room, soft lighting, and supportive care.
- Give IV fluids to treat and prevent dehydration.
- Correct electrolyte disturbance (decrease potassium, glucose, phosphorous, and magnesium).
- Give parenteral thiamine, 100 mg then daily.
- Give IV thiamine before glucose to prevent Wernicke delirium, as oral thiamine is poorly absorbed.
- Give folic acid to treat and prevent malnutrition.
- Give antiemetics for nausea.
- Give acid blockers for GI upset.

**Step 2** is treatment of withdrawal symptoms (tremulousness, hallucinations, agitation, and autonomic hyperactivity):

- Benzodiazepine drugs reduce the severity of withdrawal symptoms.
- Consider thyrotoxicosis, anticholinergic poisoning, amphetamine or cocaine excess, and other drug withdrawal.
- Drugs with a longer half-life ( $T_{1/2}$ ) are chlordiazepoxide and alazopram (use caution among older adults).
- Drugs with a shorter  $T_{1/2}$  are lorazepam and oxazepam (renal clearance, so safer in liver failure).

**Step 3** is administration of other treatments:

- For seizures, give diazepam, phenytoin, or carbamazepine.
- For agitation or hallucinations, give haloperidol.
- For tachycardia, give  $\beta$ -blockers or clonidine.

Either a fixed dose schedule of daily benzodiazepines or symptom-triggered regimens can be used. The revised Clinical Institute Withdrawal Assessment of Alcohol scale is a helpful symptom-triggered guide for the use of benzodiazepines for patients with scores of 10 or more.

The use of symptom-triggered regimens often results in less total drug dose than standard or fixed regimens of withdrawal therapy. With time, benzodiazepine doses should be reduced as withdrawal symptoms improve.

## 25. What treatments help in the long term for alcohol dependency?

Long-term abstinence should include referral to a substance use disorder clinic, as both cognitive and behavioral therapy is required to sustain ethanol abstinence. Those with repeated detoxification frequently have increased alcohol craving, which increases the severity of subsequent withdrawal episodes. Recidivism is common and pharmacologic agents to encourage abstinence can be used. Disulfiram is an acetaldehyde dehydrogenase inhibitor that prevents acetaldehyde metabolism and increases circulating acetaldehyde levels to produce symptoms of flushing, dizziness, and vomiting if ethanol is consumed. This aversion therapy may help decrease ethanol intake in the early part of the abstinence to allow time for behavioral therapy to occur. Acamprosate and naltrexone have not been very efficacious, and naltrexone has a black box warning and is NOT to be used in acute hepatitis. Baclofen, topiramate, and ondansetron are being studied. In general, despite adequate detoxification, only approximately one third of patients are abstinent or have limited ethanol consumption at 1-year follow-up.

## 26. Is disulfiram safe in the setting of ALD?

Disulfiram is safe if monitored properly with laboratory testing and brief clinic visits (approximately every 2 weeks). The idiosyncratic disulfiram hepatitis syndrome can be diagnosed early if bilirubin levels are increasing. The drug can be discontinued, and risk of liver failure can be avoided. Unfortunately use of disulfiram (often encouraged via judicial system protocols) is often not properly monitored and this author has seen three cases of disulfiram liver failure in 2 years. Whether disulfiram is safe when other types of liver disease (hepatitis C virus [HCV], NAFLD) are present in conjunction with ALD has not been studied extensively.

## 27. Can the patient with end-stage ALD undergo liver transplantation?

Patients with long-term abstinence and decompensated alcoholic cirrhosis (HCC, variceal hemorrhage, encephalopathy, or ascites) are good candidates for liver transplantation. Their outcome is similar to that of

patients with other forms of end-stage liver disease and better than those with HCV. Continued alcoholism is the most common reason for not being considered a candidate for liver transplantation. A period of 6 months of ethanol abstinence is generally recommended prior to liver transplantation coupled with careful evaluation for factors that may predict recidivism. For those who deny alcoholism, posttransplant resumption of ethanol is more likely. A relapse of alcoholism while awaiting transplantation is a contraindication to liver transplantation. Following liver transplantation, patients transplanted for alcoholic cirrhosis need continued support to prevent resumption of alcoholism. Abstinence should remain the goal of care, and continued involvement in a substance use disorder clinic is recommended. Despite best efforts, more than 20% of patients transplanted for alcoholic cirrhosis return to excessive ethanol consumption with a graft loss in 5% of those transplanted.

#### **28. Can patients with acute alcohol hepatitis be considered for liver transplantation?**

Rarely. Mathurin and colleagues reported a large survival benefit at 3 years for a select cohort that did not respond to prednisolone. However, less than 2% considered for the study were transplanted. Only patients with adequate social support, without previous alcohol hepatitis decompensations, and those who signed a contract not to use alcohol were included. Of 26 transplanted patients, one was drinking occasionally and two were using alcohol daily, and there was no graft dysfunction.

#### **29. How can patients with alcohol hepatitis be evaluated for response to steroid therapy?**

Symptomatically, recovery often correlates with patients feeling, eating, mentating, and mobilizing better. Biochemical response is seen with improvements in INR, creatinine, and bilirubin, and thus the Model of End-Stage Liver Disease (MELD) score. The Lille Model ([www.lillemodel.com](http://www.lillemodel.com)) (prothrombin time, albumin, renal function, day 0 and 7 bilirubin, and age) has been used to understand the response to prednisolone. The Lille score ranges from 0 to 1; scores greater than 0.45 after 1 week of therapy indicate a lack of response to steroids.

#### **30. What is the prognosis of patients with ALD?**

The prognosis of the patient with fatty liver who stops ethanol consumption is excellent. However, those who continue to drink are more likely to progress to cirrhosis. Alcoholic hepatitis has a broad range of mortality of 15% to 55% depending on the severity of liver disease. Alcoholic hepatitis may continue to progress for the first weeks or months after abstinence, along with the leukemoid reaction. Those with encephalopathy have a poor outcome, as do those with an MDF greater than 32. For those with alcoholic cirrhosis, the 5- and 10-year survival is 23% and 7%, respectively. For those who maintain abstinence and lack evidence of portal hypertension, a life expectancy similar to that of age-matched controls may occur. The alcohol MELD score was derived from a cohort study of 73 patients with 16 deaths, and is very easy to use (<http://www.mayoclinic.org/meld/mayomodel7.html>). Alcohol MELD scores of 27, 34, and 40 correlate approximately with 50%, 75%, and 90% mortality at 90 days.

#### **31. What percentage of heavy drinkers develop cirrhosis?**

Several studies have found that 10% to 20% of those who chronically use at least 50 g of alcohol daily for more than 5 years will develop cirrhosis.

#### **32. Of those who drink heavily, who is more likely to develop cirrhosis?**

Quantity of alcohol over time is the main risk factor for developing cirrhosis, but having another type of chronic liver disease (HCV, NAFLD, hemochromatosis) is another important risk factor. Women seem to have a higher risk of cirrhosis per amount of alcohol used, which is likely related to smaller body size and generally a higher percentage of body fat, which equates to a smaller volume of distribution. Dose, daily versus sporadic, and whether food is consumed with alcohol also seem to be risk factors. Higher rates of the *TT* and *GT* genotypes of the  $-330\ T>G$  interleukin-2 gene have been found in those with cirrhosis. Also, deletion of a nuclear factor kappa B1 polymorphism may have a higher risk for development of ALD.

#### **33. Which forms of hepatic decompensation may occur with alcohol cirrhosis?**

Those with alcohol cirrhosis, like those with cirrhosis from most other etiologic factors, are at risk for HCC, ascites, jaundice, esophageal varices, hepatic encephalopathy, and hepatorenal syndrome.

#### **34. Does alcoholic cirrhosis predispose a patient to development of HCC?**

Alcoholic cirrhosis is associated with the development of HCC with a median interval of 4 to 5 years following its diagnosis. The combination of obesity, hepatitis B virus or HCV infection, and alcoholic cirrhosis may add to the risk of HCC development. HCC is less common in those with ALD without cirrhosis.

#### **35. How should I screen patients with alcoholic cirrhosis for HCC?**

Patients with alcohol cirrhosis should be screened for HCC on a regular basis if they are abstinent and candidates for HCC therapy (sorafenib, chemoembolization, radiofrequency ablation, transplant). US screening every 6 to 12 months is reasonable.  $\alpha$ -Fetoprotein (AFP) is reasonable at these intervals as well, with the caveat that AFP has a poor negative predictive value in general, but a good positive predictive

value if the value is more than 200 ng/mL. Many liver transplant centers alternate between cross-sectional imaging (CT or MRI) and US every 6 months in patients who are good HCC therapy candidates.

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Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

- Akriviadis E, Botla R, Briggs W, et al. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000;119:1637–48.
- Dey A, Cederbaum AI. Alcohol and oxidative liver injury. *Hepatology* 2006;43(2):S63–74.
- Freiberg MS, Vasan RS, Cabral HJ, et al. Alcohol consumption and the prevalence of the metabolic syndrome in the U.S.: a cross-sectional analysis of data from the Third National Health and Nutrition Examination Survey. *Diabetes Care* 2004;27:2954–9.
- Kim WR, Brown Jr RS, Terrault NA, et al. Burden of liver disease in the United States: summary of a workshop. *Hepatology* 2002;36:227–42.
- Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. *N Engl J Med* 2003;348:1786–95.
- Lille Model. [www.lillemodel.com/score.asp](http://www.lillemodel.com/score.asp) [Accessed September 22, 2014].
- Maddrey WC, Boitnott JK, Bedine MS, et al. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology* 1978;75:193–9.
- Mathurin P, Mendenhall CL, Carithers Jr RL, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): Individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe alcoholic hepatitis. *J Hepatol* 2002;36:480–7.
- Mathurin P, Louvet A, Duhamel A, et al. Prednisolone with vs without pentoxifylline and survival of patients with severe alcoholic hepatitis: a randomized clinical trial. *JAMA* 2013;310(10):1033–41.
- Mathurin P, Moreno C, Didier S. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med* 2011;365:1790–800.
- MELD Score and 90-Day Mortality Rate for Alcoholic Hepatitis. <http://www.mayoclinic.org/meld/mayomodel7.html> [Accessed September 22, 2014].
- Mendenhall C, Roselle GA, Garstide P, et al. Relationship of protein calorie malnutrition to alcoholic liver disease: a reexamination of data from two Veterans Administration Cooperative studies. *Alcohol Clin Exp Res* 1995;19:636–41.
- McCullough A, O'Shea, Dasarathy S. Diagnosis and management of alcoholic liver disease. *J Dig Dis* 2011;12:257–62.
- Pfitzmann R, Schwenzer J, Rayes N, et al. Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease. *Liver Transpl* 2007;13:197–205.
- Raynard B, Balian A, Fallik D, et al. Risk factors of fibrosis in alcohol-induced liver disease. *Hepatology* 2002;35:635–8.
- Schwartz JM, Reinus JF. Prevalence and natural history of alcoholic liver disease. *Clin Liver Dis* 2012;16:659–66.
- Seth D, Haber PS, Syn W, et al. Pathogenesis of alcohol liver disease: Classical concepts and recent advances. *J Gastroenterol Hepatol* 2011;26:1089–105.
- 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.
- Woo GA, O'Brien C. Long-term management of alcoholic liver disease. *Clin Liver Dis* 2012;16(4):763–81.
- Zakhari S, Li T-K. Determinants of alcohol use and abuse: impact of quantity and frequency patterns on liver disease. *Hepatology* 2007;46:2032–9.

# VASCULAR LIVER DISEASE

Dawn M. Torres, MD, and Angelo H. Paredes, MD

## BACKGROUND

### 1. What vessels supply blood and are responsible for oxygen delivery to the liver?

The portal vein is responsible for approximately 70% of total liver blood flow and supplies slightly less than half the needed oxygen. Although of lower oxygen content, the portal vein delivers intestinal nutrients, drugs, and inflammatory mediators directly to the liver after intestinal absorption. The hepatic artery (branch of the celiac artery via the hepaticoduodenal artery) accounts for approximately 30% of the hepatic afferent flow but more than 50% of the oxygen. The hepatic artery supplies the majority of oxygen to the biliary tree.

### 2. Name the vessels that compose the portal vein.

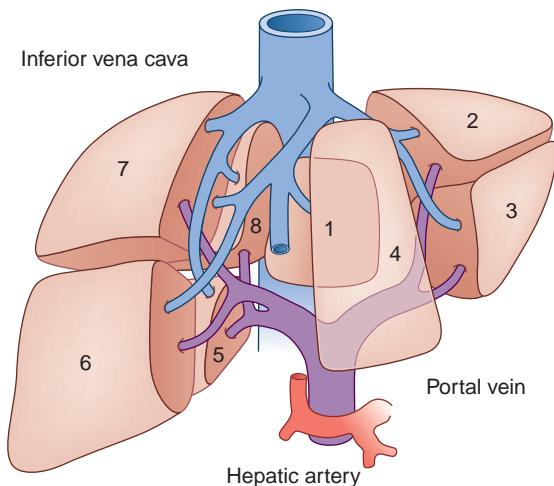
Venules drain blood from the intestinal and splenic capillaries and form the superior and inferior mesenteric veins and the splenic vein. These veins join to form the portal vein that subsequently divides into tributaries that eventually branch into fenestrated capillaries (sinusoids) of the liver.

### 3. How does blood flow occur at the microscopic level in the liver?

Blood flows down a pressure gradient from the portal venule and hepatic arteriole (derived from the portal vein and hepatic artery, respectively) through sinusoids. Fenestrated endothelial cells line these sinusoids. They supply sheets of hepatocytes before draining into the central venule.

### 4. How many anatomic segments compose the liver?

There are eight segments of the liver defined by their own afferent and efferent blood flow ([Figure 26-1](#)).



**Figure 26-1.** Vascular and surgical anatomy of the liver. According to Couinaud there are eight functional segments in the liver, which receive blood supply via the portal vein and hepatic artery. Efferent drainage is through the right, middle, and left hepatic veins. The caudate lobe (segment 1) has a separate and direct outflow into the vena cava via the dorsal hepatic veins.

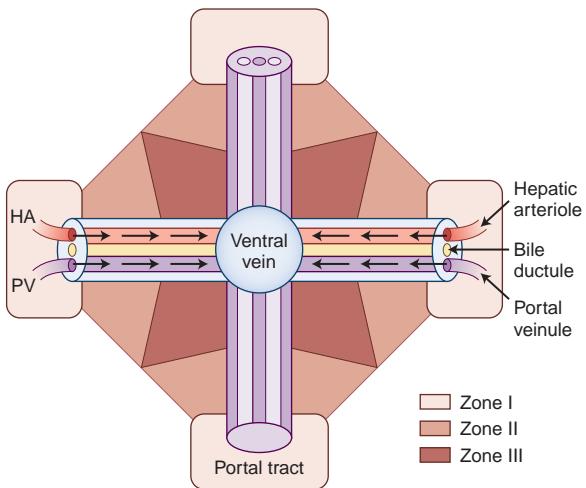
### 5. What is unique about the caudate lobe?

The caudate lobe is segment one and uniquely drains directly into the inferior vena cava (IVC) through the dorsal hepatic veins (HVs).

### 6. Describe the three “zones” of the hepatic lobule with respect to blood flow.

The hepatocytes can be defined by their proximity to either the portal triad or central venules. Zone 1 includes hepatocytes surrounding the portal tract. These hepatocytes receive the most oxygenated blood but also are the first exposed to any toxins. Zone 2 includes hepatocytes found in the intermediate area between the periportal and perivenular areas. Zone 3 is made up of perivenular hepatocytes that are the most susceptible to hypoxic mediated injury ([Figure 26-2](#)).

**Figure 26-2.** Rappaport hepatic lobule with portal (zone I), sinusoidal (zone II), and pericentral hepatocytes (zone III).



## BUDD-CHIARI SYNDROME

### 7. What is Budd-Chiari syndrome (BCS) and what blood vessels are involved?

BCS is any pathophysiologic process that results in interruption or decrease of the normal blood flow out of the liver. This commonly involves complete or partial thrombosis of one or all three major HVs (right, middle, and left) or small HVs. In Asia, pure IVC obstruction or combined IVC-HV obstruction is more commonly diagnosed.

### 8. What are secondary causes of BCS?

See Box 26-1.

#### Box 26-1. Secondary Causes of Budd Chiari Syndrome

##### Centrally Located Primary Hepatic Tumors

- Hepatocellular carcinoma
- Large nodules of focal nodular hyperplasia
- Polycystic liver disease
- Primary hepatic hemangiosarcoma
- Epithelioid hemangioendothelioma

##### Extrahepatic Tumors

- Renal adenocarcinoma
- Adrenal adenocarcinoma
- Sarcoma of the IVC
- Right atrial myxoma

##### Other causes

- Kinking of the HV after hepatic resection or transplantation
- Parasitic and nonparasitic cysts

##### Blunt Abdominal Trauma

- Intraabdominal hematoma
- IVC thrombosis related to trauma
- Herniation through a ruptured diaphragm

##### Cardiac Dysfunction

- Right heart failure with severe tricuspid insufficiency
- Constrictive pericarditis

HV, Hepatic vein; IVC, inferior vena cava.

### 9. What are the clinical features of BCS?

A diagnosis of BCS should be considered in patients with right upper quadrant (RUQ) pain, unexplained liver dysfunction, and ascites. Ascites protein content of more than 3 g/dL and serum-ascites albumin concentration gradient 1.1 g/dL or more are suggestive of BCS, cardiac disease, or pericardial disease.

### 10. What is membranous obstruction of the inferior vena cava (MOVC)?

MOVC is a congenital cause of BCS seen mostly in Asia and Africa. This is a primary IVC obstruction with a membranous web that typically occurs in the IVC just proximal to the entrance of the right HV. A concomitant hypercoagulable condition is less common, although thrombus organization usually develops at the site of the obstruction.

### 11. How does the natural history of MOVC differ from BCS?

MOVC has been associated with hepatocellular carcinoma (HCC), which is less common in classic BCS. MOVC is more amenable to angioplasty or stenting than other causes of BCS.

### 12. What is the Janus kinase 2 (JAK2)?

JAK2 is a tyrosine kinase that is found only on hemopoietic progenitor cells. JAK2 mutations are strongly implicated in the pathogenesis of myeloproliferative disorders (MPDs); they are found in approximately 90% of patients with polycythemia vera and 50% of patients with essential thrombocythemia and idiopathic myelofibrosis.

### 13. What is the role of JAK2 mutations and other hypercoagulable states in BCS?

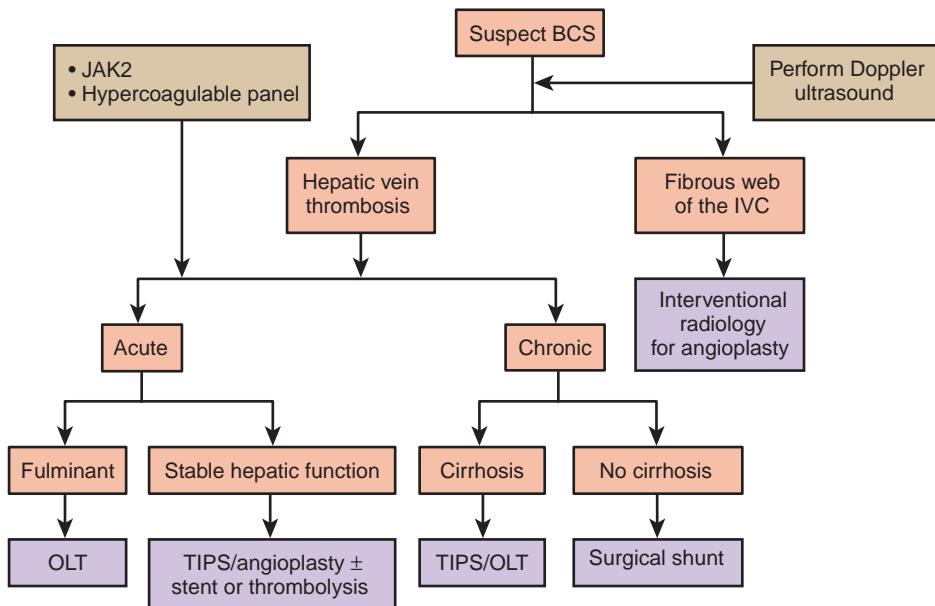
Mutations have been described in 26% to 59% of patients with BCS. A number of BCS cases labeled as *idiopathic* do not fulfill the diagnostic criteria for MPD but have mutations in JAK2. As many as 50% of all cases of BCS will have underlying MPD and upward of 75% will have a concomitant hypercoagulable condition.

### 14. What is the typical demographic of a patient with fulminant or acute BCS?

Acute BCS accounts for 20% to 30% of cases and is more commonly seen in women, particularly during pregnancy, which is considered a physiologic hypercoagulable state.

### 15. Describe the typical presentation of acute BCS.

Patients present with RUQ pain, hepatomegaly, jaundice, ascites, and high serum aminotransferase levels (>1000 U/L). The serum alkaline phosphatase is often in the range of 300 to 400 IU/L and serum bilirubin levels are usually less than 7 mg/dL. Rapid deterioration of hepatic function and resulting encephalopathy and renal failure are seen in fulminant cases. These require immediate intervention for revascularization in an effort to prevent the need for liver transplantation, although the clinical presentation depends on the location of the thrombus, stage, and rapidity of evolution (Figure 26-3).



**Figure 26-3.** Proposed algorithm for diagnostic and therapeutic management of Budd-Chiari syndrome (BCS). IVC, Inferior vena cava; JAK2, Janus kinase 2; OLT, orthotopic liver transplantation; TIPS, transjugular intrahepatic portosystemic shunt.

### 16. How does the presentation of chronic BCS differ from acute BCS?

The clinical presentation ranges from asymptomatic to fulminant liver failure with the most common presentation involving manifestations of portal hypertension. Most patients present with symptoms such as ascites or lower-extremity edema that evolve over 3 to 6 months. Liver biochemical test levels may be mildly to markedly elevated in a hepatocellular or mixed pattern.

**17. How often are patients with BCS asymptomatic?**

Asymptomatic BCS accounts for up to 20% of cases. There are often delays in diagnosis of BCS because the condition is uncommon and symptoms can be nonspecific.

**18. When should a liver biopsy be performed for BCS?**

Liver biopsy should be reserved for cases in which Doppler-sonography, magnetic resonance imaging (MRI), or computed tomography (CT) scan has not demonstrated obstructed hepatic venous outflow tract.

**19. What are the histopathologic features of BCS?**

The predominate hepatic histologic features include centrilobular congestion, hemorrhage, sinusoidal dilatation, and noninflammatory cell necrosis. In delayed diagnoses, fibrosis develops in the centrilobular areas and to a lesser extent in the periportal areas.

**20. Why does BCS result in a massive caudate lobe?**

Caudate lobe hypertrophy is found in 75% of BCS patients because of the separate venous drainage into the IVC that is not affected by obstruction of the HVs.

**21. What is the gold standard for evaluation of BCS?**

Hepatic venography has been the gold standard for the evaluation of the HVs, but other noninvasive radiographic modalities are generally adequate for diagnosis. Venography is now typically reserved for diagnosing difficult cases and for precise delineation of obstructive lesions before planning treatment.

**22. What is the radiographic modality of choice if you suspect BCS?**

Ultrasound (US) is considered the initial imaging modality of choice with a sensitivity and specificity of more than 80%. Doppler US provides information on vessel patency and blood flow direction. Absent or reversed hepatic venous flow is considered diagnostic for BCS. Both contrast-enhanced MRI and contrast CT can also diagnose BCS as well as provide indirect evidence such as enlarged caudate lobe or altered perfusion pattern as it relates to the caudate lobe and venous flow obstruction ([Figure 26-4](#)).



**Figure 26-4.** Magnetic resonance image showing features of Budd-Chiari syndrome, including hepatomegaly with caudate lobe hypertrophy, ascites, and splenomegaly. A, Ascites; C, caudate lobe.

**23. What is the role of medical management?**

The goal is to prevent further hepatic necrosis using anticoagulants and to relieve fluid retention using diuretics and a low-sodium diet. Medical therapy is considered successful if ascites is controlled and liver biochemical studies improve, although this approach is successful only in a minority of patients.

**24. What patients need anticoagulation with or without thrombolytics?**

Indefinite anticoagulation therapy is considered in patients with an underlying hypercoagulable disorder. Thrombolytic agents can be considered in patients with a strong clinical suspicion for acute or subacute BCS and no contraindications to the use of thrombolytic agents.

**25. What is the role for transjugular intrahepatic portosystemic shunt (TIPS)?**

The role for TIPS is to decompress congested liver segments by creating an alternative venous outflow tract. TIPS is useful for treating combined hepatic-vein and IVC obstruction, and can be effective in patients with fulminant BCS awaiting liver transplantation. In chronic BCS, TIPS is an effective bridge to liver transplant in those with refractory ascites or variceal bleeding. TIPS dysfunction requiring revision has been reduced by the use of polytetrafluoroethylene-covered stents.

**26. What underlying hypercoagulable states can be cured with a liver transplant?**

Liver transplantation will definitively cure an underlying hypercoagulable state caused by protein C, protein S, or antithrombin deficiency. Patients with other underlying hypercoagulable states require long-term anticoagulation.

**27. What are the long-term outcomes for patients transplanted for BCS?**

The prognosis after transplantation for BCS is good with reported 5-year survival rates of 75% to 95%, although there is an increased risk of hepatic artery and portal vein thrombosis (PVT) as well as recurrent BCS. Patients with blood dyscrasias such as polycythemia rubra vera require treatment with hydroxyurea and aspirin to reduce long-term complications after transplantation, although there is still a risk of progression and leukemic transformation.

**PORTAL VEIN THROMBOSIS****28. What is the initial work-up in a patient with a newly diagnosed PVT?**

The initial work-up includes searching for local, inflammatory, or general risk factors. Identification of a local risk factor should not preclude evaluation for a systemic prothrombotic factor because 36% of patients also have a general prothrombotic disorder (Box 26-2).

**Box 26-2. Risk Factors and Conditions Associated with PVT**

**Local Risk Factors**

- Cirrhosis
- Trauma
- Focal malignant lesions

**Inflammatory Lesions**

- Crohn's disease

**General Risk Factors**

- Myeloproliferative disorder
- Hypercoagulable state

**29. How do patients present with acute PVT?**

The main clinical features include sudden onset of abdominal or lumbar pain and a systemic inflammatory response, often with fever in the absence of an infection. Partial thrombus might be associated with fewer symptoms.

**30. What radiographic findings are associated with PVT?**

Doppler US shows the absence of flow within the portal vein or its branches. CT scan can provide additional information regarding the extent of the thrombus, the presence of related malignancy, or inflammatory lesions.

**31. How often does intestinal infarction occur with acute PVT and how does it present?**

Intestinal infarction has been reported in 2% to 28% of patients with acute PVT, with 20% to 60% mortality. Suspect the diagnosis in patients with persisting intense pain despite adequate anticoagulation, hematochezia, guarding, ascites, or multiorgan failure with metabolic acidosis.

**32. What is the duration of anticoagulation therapy?**

Recommended duration for anticoagulation therapy is 3 to 6 months for acute PVT. Long-term therapy for permanent prothrombotic conditions should be considered.

**33. What outcomes do you expect with anticoagulation therapy of acute PVT?**

Spontaneous recanalization occurs infrequently. Among patients treated with 6 months of anticoagulation, 50% had complete, 40% had partial, and 10% had no recanalization. Major complications with oral anticoagulation treatment were reported in <5%.

**34. How do patients with chronic PVT (also known as cavernous transformation of the portal vein [portal vein cavernoma]) present?**

The clinical presentation is related to portal hypertension with recurrent gastrointestinal bleeding, subclinical hepatic encephalopathy, and ascites.

**35. In cirrhosis, how often does PVT occur?**

The incidence of PVT rises with severity of liver disease: less than 1% in compensated cirrhosis and 8% to 25% in likely transplant candidates. Clinical features are nonspecific; most cases are identified at routine US during HCC surveillance. Tumor invasion of the portal vein by HCC should be considered in all patients with cirrhosis and a new PVT.

**36. How does the treatment of chronic PVT differ from acute PVT?**

Anticoagulation should be considered in patients with permanent prothrombotic conditions, although bleeding risk from esophageal varices should be established. Anticoagulation should be deferred until after adequate primary prophylaxis for variceal bleeding has been instituted.

**SINUSOIDAL OBSTRUCTION SYNDROME****37. What is the pathogenesis behind sinusoidal obstruction syndrome (SOS; also known as hepatic venoocclusive disease [VOD])?**

SOS is caused by circulatory obstruction at the level of the sinusoid secondary to injury to perivenular epithelium leading to sinusoidal congestive obstruction. Occlusion of the central vein occurs more commonly in severe cases.

**38. What are risk factors for developing SOS?**

- High-dose chemotherapy: cyclophosphamide, oxaliplatin, gemtuzumab ozogamicin
- Hematopoietic stem cell transplantation (incidence rate nearing 25%)
- Hepatic irradiation or embolization with yttrium-90-labeled microspheres
- Azathioprine, 6-thioguanine, tacrolimus
- Consumption of pyrrolizidine alkaloid-containing plants, typically in herbal teas

**39. What are the clinical features of SOS?**

Presentation can include no symptoms; nonspecific symptoms such as weight gain, ascites, RUQ pain, and hepatomegaly; or in severe cases, acute hepatic dysfunction leading to multiorgan failure and death.

**40. How is the diagnosis of SOS made?**

SOS is considered a clinical diagnosis based on exposure to a predisposing condition (medications, stem cell transplantation) as well as weight gain, RUQ pain, hepatomegaly, and jaundice in the absence of other causes such as sepsis or renal or heart failure. A transvenous liver biopsy with elevated hepatic venous pressure gradient of more than 10 mm Hg in the appropriate clinical setting is highly suggestive of SOS, although the disease may be patchy and the liver biopsy can be falsely negative.

**41. What is the treatment of SOS?**

Supportive therapy with diuretics to manage fluid retention is the mainstay of treatment. Thrombolysis not recommended. Experimental trials with defibrotide both for prophylaxis and treatment have produced mixed results, as has TIPS and liver transplantation.

**HEREDITARY HEMORRHAGIC TELANGIECTASIA****42. What is hereditary hemorrhagic telangiectasia (HHT; Rendu-Osler-Weber syndrome), and what gene is involved?**

HHT is a rare (1-2/10,000) autosomal dominant multisystemic vascular disorder that variably affects the liver, particularly with HHT type 2. Vascular malformations result from a mutation in the activin receptor-like kinase type 1 gene that encodes for transmembrane proteins involved in the transforming growth factor- $\beta$  signaling pathway.

**43. How do the vascular malformations lead to presinusoidal portal hypertension?**

Microscopic and macroscopic vascular malformations occur with direct arteriovenous and portovenous shunts that progressively enlarge. Portal hypertension develops from chronic sinusoidal hypertension secondary to increased blood flow and increased fibrous tissue deposition at the portal and periportal level.

**44. Describe the clinical presentations seen in overt HHT liver disease.**

- High-output heart failure caused by intrahepatic shunting of blood
- Portal hypertension usually with ascites
- Biliary disease caused by ischemia of the biliary tree, which can lead to severe cholestasis with or without recurrent cholangitis

**PELIOSIS HEPATIS****45. What is peliosis hepatitis?**

Peliosis hepatitis is a rare disorder characterized by focal destruction of hepatocytes and sinusoidal endothelial cells, leading to multiple cystic spaces filled with blood within the liver. Patients are usually asymptomatic, but fatal intraabdominal hemorrhage or hepatic failure may rarely occur.

**46. What factors have been linked to pathogenesis of peliosis hepatitis?**

- Infection with *Bartonella* species in acquired immune deficiency syndrome-associated peliosis
- Hematologic malignancies
- Anabolic steroid use
- Immunosuppressive drugs and oral contraceptives

**ISCHEMIC HEPATITIS****47. What are the hallmark findings of ischemic hepatitis (shock liver)?**

There is a massive increase in aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, prothrombin time (PT), and lactate dehydrogenase (LDH) levels after an episode of systemic hypotension or decreased cardiac output. Once hemodynamic instability has been corrected, values return to normal within 7 to 10 days.

**48. What are the long-term outcomes of ischemic hepatitis?**

Patients tend to be older, male, and acutely ill in the intensive care setting. Most deaths are attributed to septic shock, cardiogenic shock, or cardiac arrest. Fulminant hepatic failure is rare and seems to be restricted to patients with long-standing congestive heart failure and cardiac cirrhosis.

**CONGESTIVE HEPATOPATHY****49. What is congestive hepatopathy?**

Congestive hepatopathy is a chronic liver injury attributed to a spectrum of cardiovascular conditions, leading to increased central venous pressure.

**50. What are the histopathologic characteristics that correlate to the finding of “nutmeg liver”?**

Hepatic venous hypertension leads to central vein hemorrhage, sinusoidal engorgement, and fibrosis of the terminal hepatic venules. The nutmeg appearance reflects the alternating patterns of hemorrhage and zone 3 necrosis.

**MISCELLANEOUS****51. How does polyarteritis nodosa (PAN) vasculitis manifest as liver disease?**

PAN is a systemic necrotizing vasculitis with immune complex deposition in small and medium-sized arteries resulting in hepatic infarction, abscess, and cholecystitis in severe cases. Diagnosis is confirmed when a tissue biopsy reveals necrotizing arteritis.

**52. What is the most common vascular tumor of the liver?**

Cavernous hemangiomas are benign tumors with a 2% to 20% general prevalence found more commonly in women. Lesions smaller than 5 cm are usually asymptomatic, lesions larger than 5 cm may cause abdominal pain, and those larger than 10 cm are at risk for rupture with bleeding or can lead to disseminated intravascular coagulation (Kasabach-Merritt syndrome). MRI is the diagnostic modality of choice. Treatment with surgical resection or liver transplantation is reserved for large tumors.

*The authors would like to acknowledge the contributions of Dr. Marcello Kugelmas, who was the author of this chapter in its previous edition.*

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

**BIBLIOGRAPHY**

1. <http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/VascularDisordersLiver.pdf>. Clinical practice guidelines: vascular disorders of the liver. 2009.
2. Bornhäuser M, Storer B, Slattery JT, et al. Conditioning with fludarabine and targeted busulfan for transplantation of allogeneic hematopoietic stem cells. *Blood* 2003;102:820–6.
3. Briere JB. Budd-Chiari syndrome and portal vein thrombosis associated with myeloproliferative disorders: diagnosis and management. *Semin Thromb Hemost* 2006;32:208–18.
4. Buscarini E, Danesino C, Olivieri C, et al. Liver involvement in hereditary haemorrhagic telangiectasia or Rendu-Osler-Weber disease. *Dig Liver Dis* 2005;37:635–45.
5. Condat B, Pessione F, Hillaire S, et al. Current outcome of portal vein thrombosis in adults: risk and benefit of anticoagulant therapy. *Gastroenterology* 2001;120:490–7.
6. Condat B, Pencrae E, Maloisel F, et al. Recent portal or mesenteric venous thrombosis: increased recognition and frequent recanalization on anticoagulation therapy. *Hepatology* 2000;32:466–70.
7. Darwish Murad S, Plessier A, Hernandez-Guerra M, et al. Etiology, management, and outcome of the Budd-Chiari syndrome. *Ann Intern Med* 2009;151:167–75.
8. Garcia-Tsao G. Liver involvement in hereditary hemorrhagic telangiectasia. *J Hepatol* 2007;46:499–507.
9. Guttmacher AE, Maruchuk DA, White Jr. RI. Hereditary hemorrhagic telangiectasia. *N Engl J Med* 1995;333:918–24.
10. Joshi D, Saha S, Bernal W, et al. Haemodynamic response to abdominal decompression in acute Budd-Chiari syndrome. *Liver Int* 2011;31:1171–8.

11. Kamath PS. Budd-Chiari syndrome: radiologic findings. *Liver Transpl* 2006;12:S21–2.
12. Kew MC, Hodkinson HJ. Membranous obstruction of the inferior vena cava and its causal relation to hepatocellular carcinoma. *Liver Int* 2006;26:1–7.
13. Patel RK, Lea NC, Heneghan MA, et al. Prevalence of the activating JAK2 tyrosine kinase mutation V617F in the Budd-Chiari syndrome. *Gastroenterology* 2006;130:2031–8.
14. Perello A, Garcia-Pagan JC, Gilabert R, et al. TIPS is a useful long-term derivative therapy for patients with Budd-Chiari syndrome uncontrolled by medical therapy. *Hepatology* 2002;35:132–9.
15. Plessier A, Darwish-Murad S, Hernandez-Guerra M, et al. Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. *Hepatology* 2009;51:210–8.
16. Qi X, Yang Z, Bai M, et al. Meta-analysis: the significance of screening for JAK2V617F mutation in Budd-Chiari syndrome and portal venous system thrombosis. *Aliment Pharmacol Ther* 2011;33:1087–103.
17. Rautou PE, Moucari R, Cazals-Hatem D, et al. Levels and initial course of serum alanine aminotransferase can predict outcome of patients with Budd-Chiari syndrome. *Clin Gastroenterol Hepatol* 2009;7:1230–5.
18. Srinivasan P, Rela M, Prchalas A, et al. Liver transplantation for the Budd–Chiari syndrome. *Transplantation* 2002;73:973–7.
19. Turnes J, Garcia-Pagan JC, Gonzalez M, et al. Portal hypertension-related complications after acute portal vein thrombosis: impact of early anticoagulation. *Clin Gastroenterol Hepatol* 2008;6:1412–7.
20. Valla DC. Budd-Chiari syndrome and veno-occlusive disease/sinusoidal obstruction syndrome. *Gut* 2008;57:1469–78.

# NONALCOHOLIC FATTY LIVER DISEASE AND NONALCOHOLIC STEATOHEPATITIS

Dawn M. Torres, MD, and Stephen A. Harrison, MD

## 1. What is the difference between nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH)?

NAFLD is an umbrella classification for a group of diseases marked by excess accumulation of intrahepatic fat (steatosis), usually as the result of insulin resistance without significant alcohol use (~2-3 drinks per day in a man or ~1-2 drinks per day in a woman). NASH is a subset of NAFLD, which in addition to hepatic steatosis, has histologic evidence of hepatocyte injury to include lobular inflammation, ballooning degeneration, with or without Mallory hyaline and variable fibrosis.

## 2. How does the natural history of isolated fatty liver patients differ from those with NASH?

Whereas isolated fatty liver (the majority of patients with NAFLD) has a generally favorable prognosis with low risk for progression to cirrhosis, the clinical course of NASH patients is more variable. Natural history studies of NASH patients suggest:

- One third of NASH patients show disease (fibrosis) progression.
- One third have disease regression.
- One third have stable disease over a 5- to 10-year period.

## 3. How does the mortality of a patient with NAFLD compare with the general population?

All-cause mortality, cancer incidence (mostly hepatocellular carcinoma [HCC]), and type 2 diabetes mellitus are higher in NAFLD patients. Liver-related mortality is comparable to the general population for those with NAFLD who do not have NASH, whereas those with NASH have increased liver-related mortality.

## 4. How do patients with NAFLD present?

Patients with NAFLD are often noted to have elevated serum aminotransferases on routine blood work, which prompts a gastroenterology referral. The vast majority of these patients are asymptomatic, although a small but clinically notable fraction of patients complain of right upper quadrant discomfort. This symptom, which can range in presentation from a dull ache to sharp, severe pain, has been attributed to capsular swelling in the setting of hepatomegaly, although it is not always associated with liver enlargement and does not correlate with disease severity. Alkaline phosphatase is less frequently elevated, but can be elevated, particularly in women.

## 5. What does the serologic work-up for NAFLD patients show?

Serologic workup is typically negative with normal levels of ceruloplasmin and  $\alpha_1$ -antitrypsin and negative viral hepatitis panels. Antinuclear antibody and anti-smooth muscle antibody may be positive in up to one third of cases. As a marker of inflammation, serum ferritin may be elevated in NAFLD patients. Ferritin levels more than 1.5 times the upper limit of normal predict more advanced NAFLD histologic findings, although further study to assess for genetic markers of hereditary hemochromatosis or hepatic iron overload (via liver biopsy) should also be considered.

## 6. Describe the typical NAFLD patient.

Most patients are overweight, middle-aged adults, although the disease can present in childhood with a rising incidence secondary to the increasing numbers of obese children. There is an even distribution between males and females. The majority of patients already have met criteria for the metabolic syndrome with at least three of the following:

- Increased waist circumference (men, greater than 40 inches; women, greater than 35 inches)
- Fasting serum triglycerides of 150 mg/dL
- High-density lipoprotein of 40 mg/dL in men or 50 mg/dL in women
- Systolic blood pressure of 130 mm Hg
- Diastolic blood pressure of 85 mm Hg
- Fasting glucose of 100 mg/dL

## 7. What is the prevalence of NAFLD and NASH?

Although the exact prevalence of NAFLD is unknown, it is easily the most common chronic liver disease in the developed world. Prevalence studies suggest 30% to 40% of the U.S. population has NAFLD. Somewhat lower prevalence rates of 18% to 25% have been noted in non-American populations. Higher prevalence is seen in type 2 diabetic patients, in whom NAFLD prevalence has been documented to be as high as 70% to 75%.

Given the lack of histologic data in most prevalence studies, the rates of NASH within the larger NAFLD population are uncertain, although autopsy data suggest an overall NASH prevalence of 3% to 6%. One prevalence study of middle-aged Texans demonstrated a higher NASH prevalence of 12%, and among morbidly obese patients undergoing bariatric surgery, prevalence rates of 91% for NAFLD and 37% for NASH have been demonstrated.

## 8. Are certain ethnic populations at greater risk of NAFLD or NASH?

Preliminary evidence suggests increased prevalence in Hispanic populations and a lower prevalence in African American individuals despite similar rates of comorbid conditions. Asian populations have also been shown to have more advanced disease at a lower body mass index than white counterparts.

## 9. How can you distinguish between NAFLD and NASH?

The short answer to this is liver biopsy—it remains the gold standard and is the only test that can provide clear-cut evidence of steatohepatitis. Imaging studies, such as ultrasound (US), computed tomography, and magnetic resonance imaging (MRI), are very good at diagnosing steatosis with upward of 95% sensitivity and 80% specificity, although the accuracy of US is reduced in the morbidly obese. However, these studies are unable to distinguish NASH from isolated fatty liver.

## 10. What noninvasive markers are available for either the diagnosis of NASH or fibrosis?

See Box 27-1. Recent advances that may prove useful are US and MRI transient elastography, which show promise in noninvasively identifying advanced fibrosis (stages 3 and 4).

### Box 27-1. Non-invasive Markers to Diagnose NASH or Advanced Fibrosis

#### Laboratory Tests

- APRI (AST/platelet ratio index)  $\geq 1.5$  (significant fibrosis)
- AST/ALT ratio  $\geq 0.8$
- Cytokeratin 18  $\geq 246$  (NASH, sensitivity 75%, specificity 81%)

#### Scoring Systems

- BARD score
- FIB-4 score  $\geq 2.67$  (80% PPV for fibrosis)
- FibroMeter  $\geq 0.715$
- NAFLD fibrosis score  $>0.676$  high probability fibrosis,  $<-1.455$  low probability
- FibroTest
- SteatoTest

#### NashTest

- FibroSpect II

#### Radiologic Studies

- Conventional imaging (for steatosis, not NASH or fibrosis)
- US
- CT
- MRI
- Newer techniques:
  - ARFI
  - Transient elastography
  - MR elastography
  - Microbubbles

*ALT*, Alanine aminotransferase; *APRI*, AST to platelet ratio index; *ARFI*, acoustic radiation force impulse imaging; *AST*, aspartate aminotransferase; *BARD*, BMI, AST/ALT ratio, presence of diabetes; *CT*, computed tomography; *FIB-4*, Fibrosis 4 score uses 4 variables=age, AST, ALT, platelets; *MRI*, magnetic resonance imaging; *NAFLD*, nonalcoholic fatty liver disease; *NASH*, nonalcoholic steatohepatitis; *PPV*, positive predictive value; *US*, ultrasound.

Serum biomarkers are also intriguing but are not ready for use in clinical practice. Several research centers have developed scoring systems that use a combination of serum biomarkers, basic laboratories, or clinical indices in an effort to predict either the presence of NASH or advanced fibrosis. No one scoring system has proven universally applicable in clinical practice. General indicators suggestive of advanced disease that may sway clinicians toward liver biopsy include aspartate aminotransferase/alanine aminotransferase ratio of more than 0.8, presence of diabetes, morbid obesity, or age older than 50 years (Figure 27-1).

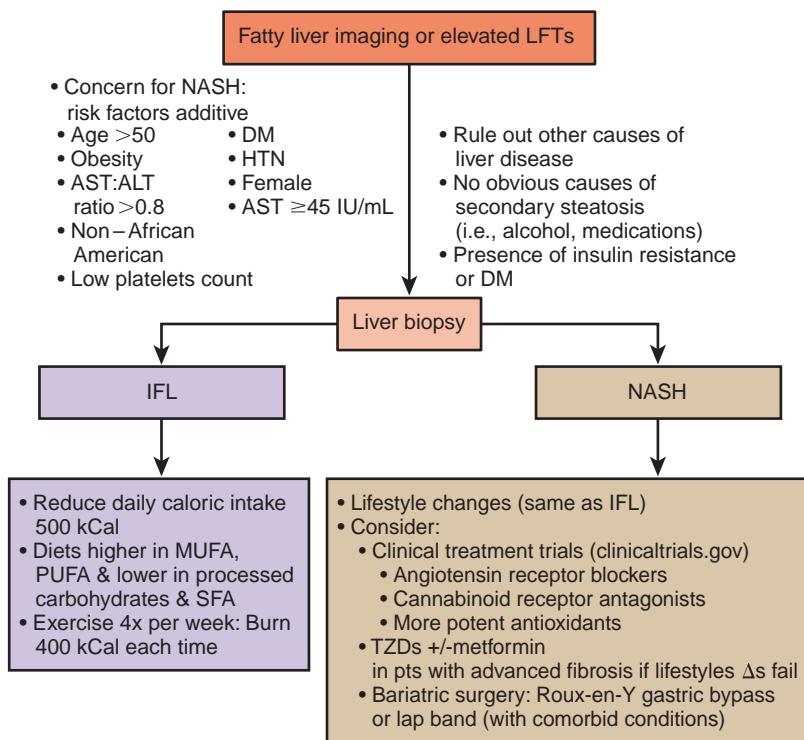
## 11. How is the severity of disease determined in patients with NASH?

Hepatic histologic characteristics are the ultimate indicator of the degree of hepatic injury. Imperfect surrogates used in research trials or clinical practice include serum aminotransferases, fasting insulin, and serum glucose.

The Brunt classification system is the predominant system used to assess hepatic histologic findings in which grade is defined by degree of steatosis and inflammation and stage is based on degree of fibrosis (Box 27-2).

## 12. Are there other causes of fatty liver besides insulin resistance, obesity, and metabolic syndrome?

Alcohol-induced steatohepatitis is indistinguishable from NASH on liver biopsy, but a lifetime adult drinking history of more than 20 g/day in men or more than 10 g/day in women supports alcohol as the primary cause of the patient's liver disease. A combination of lower alcohol intake, even as low as 40 g/week, with coexisting insulin resistance, may also lead to steatohepatitis. Other comparatively rare causes of hepatic steatosis with or without steatohepatitis are outlined in Table 27-1. Although these conditions compose less than 5% of cases of hepatic steatosis or steatohepatitis, they are important to recognize given their specific and unique treatments.



**Figure 27-1.** Nonalcoholic fatty liver disease NAFLD algorithm. ALT, Alanine aminotransferase; AST, aspartate aminotransferase; DM, diabetes mellitus; HTN, hypertension; IFL, isolated fatty liver; LFT, liver function test; MUFA, monounsaturated fatty acid; NASH, nonalcoholic steatohepatitis; pts, patients; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; TZD, thiazolidinediones.

#### Box 27-2. Brunt Classification

Grade 1	Up to 66% steatosis, minimal ballooning hepatocytes predominantly in zone 3, scattered PMNs, possibly intraacinar lymphocytes with no or mild portal inflammation
Grade 2	Steatosis of 33%–66%, more prominent PMNs, obvious ballooning hepatocytes; mild-moderate portal and intraacinar chronic inflammation also present
Grade 3	Marked steatosis, marked ballooning, intraacinar inflammation with PMNs associated with ballooned hepatocytes, mild-moderate portal chronic inflammation
Stage 1	Zone 3 perisinusoidal/pericellular fibrosis to a mild-moderate degree
Stage 2	Zone 3 perisinusoidal/pericellular fibrosis with focal or extensive periportal fibrosis
Stage 3	Zone 3 perisinusoidal/pericellular fibrosis and early bridging portal fibrosis
Stage 4	Cirrhosis

PMN, Polymorphonuclear neutrophil.

#### 13. What is the relationship between hepatic steatosis and hepatitis C virus (HCV) infection?

HCV infection is associated with hepatic steatosis, particularly in genotype 3 infection, although even genotype 1 constructs have been shown to promote triglyceride accumulation in hepatocytes. In genotype 3 infection, successful eradication of HCV infection results in a marked reduction in hepatic steatosis, suggesting direct viral involvement in this process. Preexisting NAFLD unrelated to primary HCV infection also has important implications for the severity of disease and portends the development of advanced hepatic fibrosis.

#### 14. What is the cause (pathogenesis) of NAFLD, in particular NASH?

Insulin resistance is thought to be the common denominator in an intricate multistep pathway that begins with accumulation of triglycerides in hepatocytes and ends with the activation of stellate cells that promote collagen deposition and fibrosis development. The intervening steps are thought to involve oxidative stress with increased levels of proinflammatory cytokines, decreased levels of cytoprotective cytokines, mitochondrial dysfunction, endoplasmic reticulum stress, cellular autodigestion, and molecular endotoxins leading to apoptosis, as well as genetic factors that promote hepatic steatosis, necroinflammation, and fibrinogenesis. Vitamin D deficiency and the human intestinal microbiome are newer areas under investigation for their role in the pathogenesis of NAFLD.

**Table 27-1.** Causes of Hepatic Steatosis or Steatohepatitis

CAUSE	COMMENT
<b>Drugs</b>	
<b>Associated with Steatohepatitis</b>	
Tamoxifen (and other estrogen agonists)	Steatosis (more frequently) and rarely steatohepatitis
Amiodarone	Can occur with normal serum aminotransferases
Calcium channel blockers	Three months into treatment up to 4 years after stopping
Glucocorticoids	1% to 3% of patients
Methotrexate	Usually reverses on discontinuation of drug
Irinotecan	Rare cases of cirrhosis or acute liver failure
Oxaliplatin	Controversial association Mediated by ↑ serum triglycerides and glucose Pseudoalcoholic steatohepatitis Chemotherapy-associated steatohepatitis
<b>Associated with Steatosis</b>	
Valproic acid	
Ibuprofen	
Aspirin	
Tetracycline	
Zidovudine/didanosine/stavudine	
<b>Surgery</b>	
Jejunal-ileal bypass	
Biliopancreatic diversion	
Extensive small bowel resection	
<b>Miscellaneous</b>	
Total parenteral nutrition	Jejunal diverticulosis
Bacterial overgrowth	
Abetalipoproteinemia	
Hepatitis C virus	

**15. How do you treat patients with isolated fatty liver (i.e., NAFLD patients without histologic evidence of NASH)?**

As these patients are not at a substantially increased risk of chronic liver disease (i.e., cirrhosis and liver cancer), lifestyle changes are the mainstay of therapy. Moderate reduction in caloric intake of approximately 500 calories per day along with exercise designed to expend 400 kCal four times per week are thought to be adequate to produce biochemical and histologic improvement, although large, well-designed studies are lacking. Modification of cardiovascular risk factors is essential as NAFLD patients are at an increased risk for cardiovascular events.

**16. What is the optimal treatment of patients with biopsy-proved NASH?**

No single treatment has been shown to be universally efficacious and applicable to all patients in the treatment of NASH. Treatments are typically grouped into lifestyle interventions, pharmacologic therapies, or surgical interventions.

**17. Describe the optimal lifestyle modification approach for NASH patients?**

Lifestyle interventions include caloric reduction and increased activity level similar to what is recommended for isolated fatty liver patients. There is also evidence to support diet composition modification such as low glycemic index diets with reduced fructose and saturated fatty acid intake. Increased intake of omega-3 fatty acids may also be of benefit.

The optimal physical training regimen has not been established and both resistance and cardiovascular training appear beneficial. Exercise of either aerobic or resistance training three to four times per week for 30 to 45 minutes of a moderate intensity seems a reasonable recommendation. Although these interventions are safe and efficacious, they are difficult to sustain over long periods and are difficult to apply to clinical practice.

**18. What is the role of coffee and NAFLD?**

Caffeinated coffee is composed of several bioactive compounds with favorable effects on chronic liver disease such as HCV, in which studies have linked its consumption with decreased hepatic fibrosis in patients. A recent

cross-sectional study found an inverse relationship between the amount of caffeinated coffee consumed and hepatic fibrosis in NASH patients. Moderate daily regular caffeinated coffee may be considered a reasonable adjunct to a multidisciplinary treatment plan for NAFLD patients. (Hold the cream and sugar!)

#### **19. What Food and Drug Administration (FDA)-approved medical therapies exist for NASH?**

There are no FDA-approved medical therapies. Pharmacotherapy is appealing as a treatment as many of these patients are already taking medications for coexisting hypertension or hyperlipidemia.

Numerous agents, including antioxidants, cytoprotective agents, lipid-lowering medications, weight-loss agents, and diabetic medications, have all been evaluated with mixed results. Vitamin E and the thiazolidinediones, in particular pioglitazone, have been the most studied and have shown some beneficial effects on NASH histologic findings.

#### **20. What is the role of pioglitazone in the treatment of NASH?**

Pioglitazone can be considered in NASH patients who are diabetic or have advanced histologic findings as it has generally been shown to improve hepatic steatosis, necroinflammation, and, in certain cases, fibrosis. Patients should be counseled on side effects, which include weight gain (~2-5 kg after 1 year of therapy), peripheral edema, congestive heart failure exacerbation, osteoporosis, and possibly increased rates of bladder cancer. Histologic benefits do not appear to be sustained with cessation of medication.

#### **21. What is the role of vitamin E in the treatment of NASH?**

The antioxidant vitamin E has been studied in adult NASH with generally beneficial results. A dose of 800 IU once daily demonstrated significant improvements in hepatic steatosis and lobulation inflammation but not fibrosis, although another smaller trial suggested fibrosis improvement with treatment. Although once considered a completely benign therapy, vitamin E has recently been reported to increase cardiovascular risk, all-cause mortality, and prostate cancer rates. Notwithstanding these potentially negative effects, the tri-society [AASLD (American Association for the Study of Liver Disease), AGA (American Gastroenterological Association), ACG (American College of Gastroenterology)] guidelines currently recommend vitamin E in nondiabetic patients with biopsy-proven NASH.

#### **22. What are potential future therapies for NASH?**

Weight loss medications, other diabetic medications such as incretin analogs (e.g., exenatide), angiotensin receptor blockers, the nuclear hormone agonist obeticholic acid, and pentoxifylline are a few of the medications currently being studied in NASH.

#### **23. What is the role of bariatric surgery as a treatment for NASH?**

Studies in patients undergoing bariatric surgery for morbid obesity have suggested surgical weight loss may improve NASH histologic findings. Early studies in patients undergoing biliopancreatic diversion showed some concern over worsening of hepatic fibrosis, but the vast majority of studies using either Roux-en-Y gastric bypass or laparoscopic band placement have shown significant improvement in hepatic histologic findings, with even total resolution of steatohepatitis reported. These studies offer compelling evidence that bariatric surgery in morbidly obese patients improves steatohepatitis. These invasive procedures may be considered for those with comorbid conditions that would justify the risks of an invasive surgical procedure.

#### **24. How many patients diagnosed with NASH go on to require liver transplants?**

Decompensated cirrhosis or HCC caused by NASH is currently the third most common indication for liver transplantation in the United States, but is expected to be the leading indication for liver transplantation by 2020.

20% of all NAFLD patients have NASH. Of those patients with NASH, ~11 develop cirrhosis and over a varying period of time from months to years 7-31% of those with cirrhosis decompensate or develop HCC.

#### **25. What is the role of hepatic steatosis in liver transplant donors?**

Up to 30% of all livers evaluated for transplant show some steatosis. Donor livers with 30% steatosis are considered acceptable, donor livers with 30% to 60% steatosis are considered with caution, and donor livers with more than 60% steatosis are considered unsuitable by many transplant centers. Two recent studies revealed that moderate and even severe steatosis shows comparable short- and long-term mortality to patients with absent or mild steatosis, although with longer initial intensive care unit stays.

#### **26. Do NAFLD or NASH recur after liver transplant?**

Most of the data pertaining to NASH posttransplantation are limited to case reports or series of recurrence of preexisting NASH or de novo steatohepatitis. The development of NAFLD or NASH following orthotopic liver transplantation (OLT) is likely multifactorial, with some contribution from host metabolic factors and some from of posttransplant immune suppressive medications such as prednisone and tacrolimus, which promote the development of diabetes. Retrospective data on 68 OLT patients followed for a mean of  $28 \pm 18$  months showed 18% of patients developed de novo NAFLD and 9% of patients developed de novo NASH.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

- American Association for the Study of Liver Disease. AASLD practice guidelines 2012. Available at [http://www.aasld.org/practiceguidelines/Documents/NonalcoholicFattyLiverDisease2012\\_25762\\_ftp.pdf](http://www.aasld.org/practiceguidelines/Documents/NonalcoholicFattyLiverDisease2012_25762_ftp.pdf).
- Adams LA, Sanderson S, Lindor KD. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. *J Hepatol* 2005;42:132–8.
- Belfort R, Harrison SA, Brown K, et al. A placebo controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006;355:2297–307.
- Brunt EM. Nonalcoholic steatohepatitis: definition and pathology. *Semin Liver Dis* 2001;21:3–16.
- Chalasani C, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* 2012;55:2005–23.
- Ekstedt M, Franzen LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006;44:865–73.
- Harrison SA, Day CP. Benefits of lifestyle modification in NAFLD. *Gut* 2007;56:1760–9.
- Kowdley KV, Belt P, Wilson LA, et al. Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease. *Hepatology* 2012;55:77–85.
- Kwok RM, Torres DM, Harrison SA. Vitamin D and NAFLD: is it more than just an association? *Hepatology* 2013;58(3):1166–74.
- Machado M, Marques-Vidal P, Cortez-Pinto H. 2006 Hepatic histology in obese patients undergoing bariatric surgery. *J Hepatol* 2006;45:600–6.
- Molloy JW, Calcagno CJ, Williams CD, et al. Association of coffee and caffeine consumption with fatty liver disease, nonalcoholic steatohepatitis and degree of hepatic fibrosis. *Hepatology* 2012;55:429–36.
- McCormack L, Petrowsky H, Jochum W, et al. Use of severely steatotic grafts in liver transplantation: a matched case control study. *Ann Surg* 2007;246:940–8.
- Nikeghbalian S, Nejatollahi SMR, Salahi H, et al. Does donor's fatty liver change impact on early mortality and outcome of liver transplantation? *Transplant Proc* 2007;39:1181–3.
- Soderberg C, Stal P, Askling J, et al. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up period. *Hepatology* 2010;51:595–602.
- Stravitz RT, Sanyal AJ. Drug-induced steatohepatitis. *Clin Liver Dis* 2003;7:435–51.
- Torres DM, Harrison SA. Diagnosis and therapy of nonalcoholic steatohepatitis. *Gastroenterology* 2008;134:1682–98.
- Torres DM, Williams CD, Harrison SA. Features, diagnosis, and treatment of nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2010;10:837–58.
- Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology* 1990;12:1106–10.
- Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology* 2011;140:124–31.
- Zivkovic AM, German JB, Sanyal AJ. Comparative review of diets for the metabolic syndrome: implications for non-alcoholic fatty liver disease. *Am J Clin Nutr* 2007;86:285–300.

# LIVER TRANSPLANTATION

Stevan A. Gonzalez, MD, MS, and James F. Trotter, MD

## 1. What is the current basis for prioritizing patients for cadaveric transplantation?

Priority for liver transplantation is currently determined by the Model of End-Stage Liver Disease (MELD) score, which incorporates serum creatinine (Cr), bilirubin (bili), and international normalized ratio (INR) into the following mathematical equation predictive of 90-day survival:

$$\text{MELD score} = (0.957 \times \ln[\text{Cr mg/dL}] + 0.378 \times \ln[\text{bili mg/dL}] + 1.12 \times \ln[\text{INR}] + 0.643) \times 10$$

A MELD score predicts 90-day mortality, and therefore patients with high MELD scores have a higher priority for transplantation. Patients with a MELD score lower than 9 have only a 2% 90-day mortality rate, whereas patients with a MELD score of 40 or more have a 71% mortality rate. Liver allocation based on MELD score differs in two major respects compared with the previous system:

- A. Subjective measures such as degree of ascites and encephalopathy are not included.
- B. Time on the waiting list plays a minor role, serving only to break ties between patients with the same score. Some transplant candidates have an increased mortality risk that is not reflected in the MELD score. This occurs in patients with hepatocellular carcinoma (HCC) and in a small proportion of patients who have hepatopulmonary syndrome or portopulmonary hypertension. In these individuals, exception MELD points may be awarded based on regional practices. To increase organ availability to critically ill patients, recent changes in the organ allocation policy have widened the geographic area of organ acquisition for patients with MELD scores of 35 or more. The goal of this new policy is to reduce the waiting list mortality rate for these sick patients.

## 2. For patients with chronic liver disease, when is the appropriate time to refer for liver transplantation?

The decision to list a patient for transplantation ultimately rests on the judgment and experience of the physicians at the transplant center. In general, patients should be considered for listing if they have a MELD score of 15 or more, or life-threatening complications of end-stage liver disease including ascites, encephalopathy, portal hypertensive bleeding, jaundice, significant weight loss, or HCC. Coexistent medical disorders such as coronary artery disease, chronic obstructive lung disease, cardiomyopathy, or pulmonary hypertension may jeopardize successful liver transplantation, especially in older adults. Consequently, patients with comorbid conditions need to be evaluated to determine their candidacy for transplantation. There is no advantage gained by early listing of patients for liver transplantation, because waiting time no longer determines priority for transplantation.

## 3. Which patients with HCC are considered and prioritized for transplantation?

Long-term survival for carefully selected patients with HCC is similar to patients undergoing transplantation for nonmalignant causes. The United Network for Organ Sharing (UNOS) requires careful staging of candidates with HCC to determine the extent of malignant disease. The extent of hepatic disease is assessed with abdominal computed tomography (CT), and chest CT (and bone scanning at some centers) is used to determine the presence of metastatic hepatoma. Liver transplant recipients fulfilling the **Milan criteria** have the same 3- to 4-year actuarial survival as patients without malignancy, with a 4-year survival rate of 85%:

- A. One tumor 5 cm or smaller; or three or fewer tumors, each smaller than 3 cm
- B. No macrovascular involvement
- C. No radiographic evidence of extrahepatic disease

Patients who fulfill the Milan criteria are awarded a high priority for transplant with 22 points. A 10% increase is given to patients for every 3 months on the waiting list. In most centers, such patients are transplanted within a few months before HCC progresses.

Although controversial, recent studies have proposed expanding the current selection criteria for patients with HCC. For example, the **University of California–San Francisco criteria** include:

- A. Single tumor smaller than 6.5 cm
- B. Maximum three tumors with none larger than 4.5 cm
- C. Cumulative tumor size smaller than 8 cm

Use of this set of criteria in liver allocation for HCC has been reported to have a 5-year posttransplantation survival rate of 75%. These criteria, however, are not currently used by UNOS to prioritize patients for transplantation.

#### 4. What is the risk of HCC in patients with hepatitis C and how has this influenced trends in liver transplantation?

Chronic hepatitis C is currently the most common risk factor for HCC in the United States and accounts for more than half of HCC cases. Hepatitis C infection is associated with a *twentyfold increase in risk of HCC and an annual risk as high as 5% per year in patients with hepatitis C and cirrhosis.* The incidence of HCC has tripled in the United States during the last 3 decades, with a large proportion of this trend attributed to hepatitis C. Although the overall number of liver transplants performed for hepatitis C appears to have reached a plateau, the number of transplants for HCC has sharply increased, with the majority of cases attributed to hepatitis C infection. In contrast, liver transplants are performed less frequently for chronic hepatitis B, likely as a result of more effective antiviral therapy.

#### 5. Given the high waiting list mortality, is living donor liver transplantation (LDLT) an option?

Yes. Approximately 10% of patients listed for liver transplantation in the United States die each year awaiting a suitable donor organ. LDLT was developed in response to the deceased donor (DD) organ shortage and waiting list mortality. In addition, an equal number are removed from the list as “too sick to transplant.” Currently, living donor liver transplants constitute 3% of all transplants. Most adult-to-adult LDLTs in the United States use the right hepatic lobe. The most important advantage of LDLT is a reduction in waiting time for the recipient and lower risk of dying on the list. Disadvantages of LDLT include risk to the donor (risk of death and morbidity) and the risk that LDLT recipients may have more biliary complications than recipients of cadaveric organs.

#### 6. Who are potential recipients for LDLT?

The most appropriate recipients are ideal liver transplant candidates in urgent need of transplantation who are at substantial risk of dying prior to DD transplant, that is, decompensated liver disease or HCC.

The LDLT recipient candidate undergoes the same evaluation as the DD recipient. LDLT may be associated with a significant survival advantage rather than waiting for DD liver transplant; however, candidates with HCC who have low MELD scores (<15) may not benefit from LDLT. Patients with multiple coexisting conditions, previous major abdominal surgery or extensive mesenteric-vein thrombosis have increased risk for postoperative complications and may not be suitable for LDLT.

#### 7. List the diseases for which liver transplantation is performed.

- A. Acute liver failure (ALF) (8%)—the ABCs
  - A:** Acetaminophen, Autoimmune hepatitis, *Amanita* mushroom toxin
  - B:** Hepatitis B, Budd-Chiari syndrome
  - C:** Cryptogenic
  - D:** Drugs (acetaminophen, isoniazid, disulfiram, other)
  - E:** Esotera (Wilson disease)
  - F:** Fatty infiltration (Reye syndrome, acute fatty liver of pregnancy)
- B. Chronic liver disease (82%)
  - Chronic viral hepatitis (hepatitis C, hepatitis B)
  - Alcoholic liver disease
  - Cryptogenic cirrhosis
  - Autoimmune hepatitis
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis
  - Nonalcoholic steatohepatitis (NASH)
  - Budd-Chiari syndrome
  - Drug-induced cirrhosis (methotrexate, amiodarone)
  - Sarcoidosis
  - Polycystic liver disease
- C. Congenital and metabolic liver disease (8%)
  - Hemochromatosis
  - Wilson disease
  - $\alpha_1$  Antitrypsin deficiency
  - Cystic fibrosis
  - Amyloidosis
- D. Other (2%)
  - Hepatoblastoma
  - Hemangioendothelioma
  - Metastatic carcinoid tumor
  - Retransplantation

The most common indication for liver transplantation is chronic hepatitis C followed by alcoholic liver disease, followed by NASH. With the increasing prevalence of NASH, it will soon surpass alcoholic liver disease as the second most common indication for liver transplantation.

### **8. What is the definition of acute liver failure (fulminant hepatic failure)?**

There are approximately 2500 cases of ALF in the United States each year. *Acute liver failure* is defined by an acute decline in hepatic function characterized by jaundice, coagulopathy (INR >1.5), and encephalopathy occurring within 8 weeks of disease onset in the absence of preexisting liver disease. Patients typically present with progressive lethargy and jaundice over several days. *The most common causes of acute liver failure in the United States, in descending order, are acetaminophen (46%), indeterminate (14%), drug-induced (11%), hepatitis B (6%), autoimmune hepatitis (6%), ischemia (4%), hepatitis A (3%), and other (9%).*

Because of the rapid progression of ALF, patients require prompt referral to a liver transplant center. Patients may progress from mild encephalopathy to coma within hours. Patient survival varies based on the etiologic factors of ALF, in which acetaminophen hepatotoxicity is more likely associated with spontaneous recovery (65%); however, this occurs in fewer than half of patients overall when accounting for other etiologic factors. The two most common causes of death are cerebral edema and infection. Survival after transplant for ALF ranges from 70% to 80% depending on the etiologic cause. Prognostic tools, such as the King's College criteria, are useful in identifying patients with the highest risk of death and who would benefit from urgent liver transplantation. The King's College criteria predict high mortality risk based on acetaminophen versus nonacetaminophen ALF:

The following criteria identify ACETAMINOPHEN-ASSOCIATED ALF:

- pH <7.30
- Prothrombin time (PT) >100 seconds (INR >6.5), serum creatinine >3.4 mg/dL, and grade 3 or higher encephalopathy

The following criteria identify NONACETAMINOPHEN-ASSOCIATED ALF:

- PT >100 seconds (INR >6.5) or any three of the following:
  - Age younger than 10 years or older than 40 years
  - Etiologic factors: non-A, non-B hepatitis; halothane; drug reaction
  - Duration of jaundice before onset of encephalopathy more than 7 days
  - PT more than 50 seconds (INR >3.5)
  - Serum bilirubin more than 18 mg/dL

### **9. A 21-year-old woman is admitted following an overdose of acetaminophen. How is it determined whether she should be referred for liver transplantation?**

The most common cause of ALF is acetaminophen. Acute ingestion of acetaminophen may cause severe hepatic injury via the toxic metabolite, N-acetyl-p-benzoquinone imine, a metabolite of the cytochrome P450 system. Chronic alcohol ingestion may result in induction of the cytochrome P450 system and a reduction in the amount of acetaminophen required to cause hepatotoxicity. *Without treatment, an acetaminophen level of more than 300 mcg/mL at 4 hours or more than 45 mcg/mL at 15 hours is associated with a 90% risk of hepatotoxicity.* If patients present within 4 hours of ingestion, activated charcoal can reduce acetaminophen absorption. N-acetylcysteine (NAC, Mucomyst), a glutathione precursor, should be given in all cases of suspected acetaminophen overdose regardless of the dose or timing of acetaminophen ingestion. Early administration of NAC is recommended not only in patients with acetaminophen hepatotoxicity, but should also be given in cases of nonacetaminophen ALF with grade 1 or 2 encephalopathy, in which it is associated with a significant survival benefit.

### **10. Is human immunodeficiency virus (HIV) infection a contraindication to liver transplantation?**

No. Although HIV infection was previously a contraindication to liver transplant, the advent of highly active antiretroviral therapy (HAART) has altered the selection process for infected patients. The selection criteria for HIV patients are evolving but include:

- Patient on HAART treatment
- CD4 count 100 to 200 mm<sup>3</sup> or higher
- Absence of HIV-related infections or malignancies

In HIV-infected candidates who meet these criteria, survival following liver transplantation is comparable to non-HIV patients; however, individuals coinfective with hepatitis C virus (HCV) and HIV have significantly lower posttransplant survival rates. Therefore some centers will not consider such coinfective patients for liver transplantation. Careful recipient and donor selection are important in optimizing outcomes in this population.

### **11. Is liver transplantation an effective management option for cholangiocarcinoma?**

In most cases, cholangiocarcinoma remains a relative contraindication for liver transplantation; however, some transplant centers have reported acceptable outcomes in selected individuals. Liver transplants are more commonly performed in unresectable cases of early stage perihilar cholangiocarcinoma (tumor size <3 cm, no metastases) in which protocols involving neoadjuvant chemotherapy followed by liver transplantation are associated with recurrence-free survival rates of 68%. In cases of intrahepatic cholangiocarcinoma, liver transplantation is generally not performed because of very high recurrence rates.

### **12. What conditions are considered contraindications to liver transplantation?**

The decision to perform a liver transplant in a specific patient is based on the judgment and experience of the physicians at the transplant center.

**Absolute contraindications include:**

- Extrahepatic malignancy (excluding squamous cell carcinoma of the skin)
- Active uncontrolled sepsis or infection
- Active alcohol or illicit drug use
- Psychosocial factors precluding recovery after transplantation
- Uncontrolled cardiopulmonary disease (coronary artery disease, congestive heart failure, valvular disease, pulmonary hypertension, restrictive lung disease, and severe chronic obstructive pulmonary disease)

**Relative contraindications include:**

- Advanced age ( $\geq 65$  years old)
- Obesity
- Portal vein or mesenteric vein thrombosis
- Cholangiocarcinoma (see earlier discussion)
- Psychiatric illness
- Poor social support
- HIV infection (see earlier discussion)

*There is recent data that selected liver transplant recipients with alcoholic liver disease who have not met the standard abstinence criteria ( $>6$  months) have identical outcomes as other patients. However, this practice has not been widely adopted in the United States.*

### 13. A liver transplant candidate develops worsening renal failure. At what point should a simultaneous liver and kidney (SLK) transplantation be considered?

The inclusion of creatinine in the MELD score has linked renal dysfunction with prioritization of liver transplant candidates. As a result, the proportion of liver recipients with acute and chronic renal insufficiency has increased since institution of MELD-based liver allocation. Some recipients' renal function is so poor that they require a simultaneous renal transplant at the time of liver transplantation to provide sufficient renal function for measurable long-term survival. In fact, the number of SLK transplants has increased over the last several years. Providing a kidney transplant in selected liver transplant recipients can have a major effect on posttransplant survival and quality of life. Proposed criteria for considering SLK in liver transplant candidates include:

**Persistent acute kidney injury of  $\geq 4$  plus one of the following:** threefold increase in creatinine from baseline, creatinine 4 mg/dL or higher with acute increase 0.5 mg/dL or more, requirement for renal replacement therapy (RRT), estimated glomerular filtration rate (GFR) 35 mL/min or less

**Chronic kidney disease of  $\geq 3$  months plus one of the following:** estimated GFR 40 mL/min or less, proteinuria 2 g/day or more, kidney biopsy with more than 30% glomerulosclerosis or more than 30% interstitial fibrosis, metabolic disease

### 14. Do liver transplant candidates with hepatorenal syndrome (HRS) require kidney transplants?

HRS occurs in patients with cirrhosis and ascites as a result of effective hypovolemia and renal hypoperfusion in the setting of a hyperdynamic circulation, reduction in cardiac output, and severe renal vasoconstriction. Two types of HRS are defined as follows:

**HRS type 1:** Rapid doubling of baseline creatinine to a level greater than 2.5 mg/dL within 2 weeks, typically occurring after a precipitating event

**HRS type 2:** Slow progression with creatinine 1.5 to 2.5 mg/dL, typically associated with refractory ascites  
Additional diagnostic criteria include:

- No improvement in creatinine to 1.5 mg/dL or less after 48 hours of diuretic withdrawal and volume expansion with intravenous albumin
- No shock, exposure to nephrotoxic medications, or evidence of parenchymal kidney disease (proteinuria  $>500$  mg/day, hematuria  $>50$  red blood cells per high-power field, abnormal kidney imaging)

Although HRS type 1 is associated with progressive renal failure, requirement for RRT, and a very high mortality risk (median survival 1 month), the associated renal dysfunction is potentially reversible following liver transplantation. Data suggest that the majority of individuals who undergo liver transplantation within 4 to 6 weeks of onset of type 1 HRS will recover renal function and may not require a kidney transplant.

### 15. Which features of a patient's psychosocial profile connote a good prognosis for continued abstinence from alcohol prior to liver transplantation?

For patients with a history of alcohol abuse, most centers require a period of abstinence (at least 6 to 12 months) and an evaluation by a substance abuse professional prior to transplantation. Recognition of alcoholism by the patient and family members is especially important, and patients demonstrate this through adherence to an alcohol rehabilitation program. Features associated with a low rate of recidivism include absence of comorbid substance abuse, good social function, and absence of family history of alcohol abuse.

**16. Which factors measured in the recipient prior to transplant correlate with reduced postoperative survival?**

Reports have suggested that pretransplant clinical factors such as Child-Pugh class and MELD score are not good predictors of survival after transplantation, although recipients with a high MELD score immediately prior to transplant may have decreased posttransplant survival. Pretransplant recipient characteristics associated with an increased risk of liver-related death beyond 1 year after transplant include requirement for retransplantation, renal insufficiency, and diabetes. Additional pretransplant factors associated with overall decreased posttransplant survival include increased age and hepatic malignancy (HCC or cholangiocarcinoma). HCV infection significantly impairs long-term patient and allograft survival due to recurrent HCV in the transplanted liver.

**17. Which immunosuppressants are used in liver transplantation? What are their mechanisms of action and side effects?**

See Table 28-1.

**Table 28-1.** Mechanism of Action and Side Effects of Immunosuppressants

DRUG	MECHANISM OF ACTION	TOXICITIES
Tacrolimus	Calcineurin inhibitor: suppresses IL-2-dependent T-cell proliferation	Renal insufficiency, neurologic, diabetes mellitus, diarrhea
Cyclosporine	Same as tacrolimus	Hypertension, renal insufficiency, neurologic, hyperlipidemia, hirsutism
Azathioprine	Inhibits T- and B-cell proliferation by interfering with purine synthesis	Bone marrow depression, hepatotoxicity, dyspepsia
Mycophenolate mofetil Mycophenolic acid	Selective inhibition of T- and B-cell proliferation by interfering with purine synthesis	Bone marrow depression, diarrhea, dyspepsia
Corticosteroids	Cytokine inhibitor (IL-1, IL-2, IL-6, TNF, and IFN- $\gamma$ )	Diabetes mellitus, obesity, hypertension, osteopenia, infection, emotional lability
Sirolimus Everolimus	mTOR inhibitor: inhibits signal transduction from IL-2 receptors decreasing T- and B-cell proliferation	Neutropenia, thrombocytopenia, pneumonitis, hyperlipidemia, hepatic artery thrombosis*
Daclizumab/ Basiliximab/ Thymoglobulin	Monoclonal antibody that blocks IL-2 receptor inhibiting T-cell activation	Hypersensitivity reactions with basiliximab

IFN, Interferon; IL, interleukin; mTOR, mammalian target of rapamycin; TNF, tumor necrosis factor.

\*Sirolimus is associated with a "black box warning" because of hepatic artery thrombosis.

**18. What is the typical immunosuppressive regimen?**

The specific immunosuppressive regimen varies from center to center. Current immunosuppressive therapy usually involves two or three agents to prevent allograft rejection in the immediate postoperative period. Typically, this involves combination of a calcineurin inhibitor (CNI) such as tacrolimus (TAC, FK506) or cyclosporine with one or more other agents. Currently more than 90% of liver transplant recipients receive TAC and the remainder cyclosporine. A secondary agent such as mycophenolate mofetil (MMF), mycophenolic acid (MPA), or azathioprine is used along with a CNI. These agents operate through different mechanisms to increase the immunosuppressive effect while minimizing the nephrotoxic side effect of CNIs. Cyclosporine and TAC prevent T-cell activation through inhibition of calcineurin, a calcium-dependent phosphatase involved in intracellular signal transduction. Azathioprine, MMF, and MPA prevent expansion of activated T- and B-cells. Azathioprine is a purine analogue that becomes metabolized to its active compound, 6-mercaptopurine, and then inhibits DNA and RNA synthesis, particularly in rapidly proliferating T cells. MMF and MPA are noncompetitive inhibitors of an enzyme necessary for synthesis of guanine, a purine nucleotide.

Corticosteroids are used as first-line therapy in immunosuppression at many centers. However, there is increasing evidence that long-term maintenance corticosteroids may not be necessary to prevent rejection. Therefore most liver transplant recipients are weaned completely off of corticosteroids within a few months after surgery. The most common regimen in the immediate postoperative period is TAC with MMF or MPA with a

short course (weeks to months) of corticosteroids. Recently, the Food and Drug Administration approved a drug, everolimus, which is in a new class of immunosuppression (inhibitors of the mammalian target of rapamycin [mTOR]). Sirolimus, another mTOR inhibitor, is not approved in liver transplantation, but is administered to liver recipients on a limited basis.

Liver allocation based on the MELD score has affected the administration of immunosuppression. Inclusion of creatinine as a determinant in MELD has increased the priority and number of liver transplant recipients with renal insufficiency. As a result, posttransplant immunosuppressive regimens are configured to minimize nephrotoxicity. One strategy is to reduce or avoid CNI exposure immediately after surgery. Many centers have introduced the use of rabbit antithymocyte globulin as induction therapy. Other strategies to reduce CNI exposure include using interleukin-2 receptor antibodies such as daclizumab or basiliximab, mTOR inhibitors such as sirolimus or everolimus, or increasing doses of MMF or MPA. In recipients who develop renal insufficiency later in their posttransplant course, CNIs are commonly reduced in dose or withdrawn and then replaced or supplemented with mTOR inhibitors, MMF, or MPA.

**19. A liver transplant patient has just sustained a grand mal seizure 36 hours posttransplant. The cyclosporine level is within acceptable limits. The patient is in a postictal state but has no obvious focal neurologic deficits. Which factors contribute to an increased risk of seizures posttransplant?**

Both cyclosporine and TAC are associated with neurotoxicity, including tremor, seizures, paresthesias, ataxia, and delirium. The neurologic side effects are usually reversible with a reduction in dosage or discontinuation of the drug.

**20. Does erythromycin affect immunosuppressive therapy?**

Cyclosporine and TAC are metabolized by the cytochrome P450-3A4 system. Medications that inhibit P450-3A4 raise cyclosporine and TAC levels and place the patient at risk for toxicity or over-immunosuppression. Medications that induce P450-3A4 lower levels and increase the risk of rejection or require higher doses of the immunosuppressant. If these medications are necessary, dose adjustment and monitoring of cyclosporine and TAC may be necessary (Box 28-1).

**Box 28-1. Medications That Commonly Interact with Cyclosporine and TAC**

Increase Cyclosporin/Tacrolimus Levels	Reduce Cyclosporin/Tacrolimus Levels
Erythromycin	Phenytoin
Clarithromycin	Carbamazepine
Ketoconazole	Phenobarbital
Fluconazole	Rifampin
Itraconazole	
Verapamil	
Diltiazem	
Amiodarone	
Telaprevir/boceprevir	

**21. What are the histologic findings of acute rejection versus posttransplant hepatitis C on liver biopsy?**

The differentiation between recurrent hepatitis C and acute cellular rejection is one of the most problematic areas in clinical transplantation. In many cases, the histologic findings on the liver biopsy are inconclusive in differentiating these two disorders. *The histologic features of acute cellular rejection include:*

- Mixed cellular infiltrate (including eosinophils) in the portal triad
- Inflammation of the bile ducts presenting as either apoptosis or intraepithelial lymphocytes
- Endotheliitis of the central or portal veins

Recurrent hepatitis C can be difficult to distinguish from rejection. The histologic findings may demonstrate a predominant lymphocytic infiltrate in the portal areas rather than the mixed cellular infiltrate of rejection. Other histologic findings of HCV include spotty parenchymal inflammation, presence of acidophil bodies, and vacuolization of the biliary epithelium. In contrast, bile duct inflammation and venous endothelial inflammation are more prominent features in rejection.

**22. Describe the other posttransplant complications manifested by elevated liver enzymes.**

Hepatic artery thrombosis remains a serious complication following transplant. The clinical presentation may be variable, but is usually associated with elevated aminotransferases. Other signs include decreased bile output, persistent elevation of the PT, bilirubin, or bacteremia. Cessation of hepatic artery blood flow preferentially causes ischemic damage to the biliary tree, resulting in breakdown of the biliary tree and development of bilomas, bile leaks, and eventually strictures. Treatment of early hepatic artery thrombosis may be amenable to an

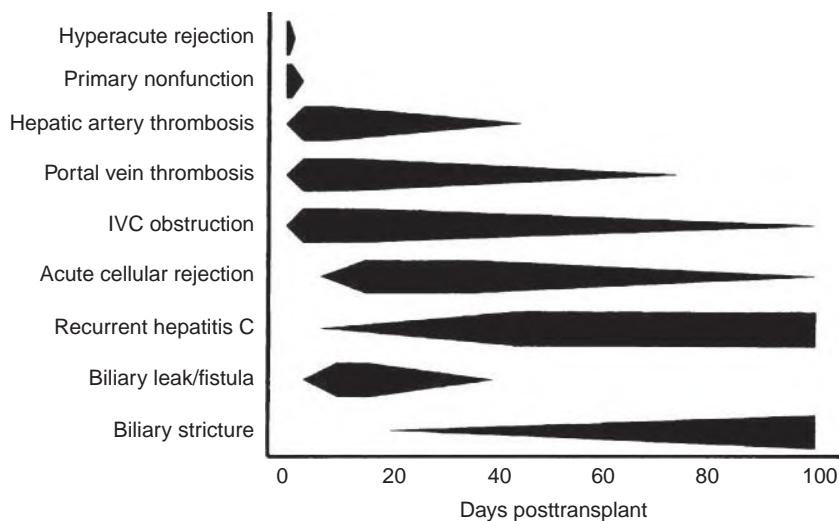
interventional radiologic approach, but usually warrants surgical intervention. In hepatic artery thrombosis, retransplantation is usually required for successful long-term outcomes.

In the early posttransplant period, portal vein thrombosis may present with signs of graft dysfunction and require immediate revascularization or retransplantation. Late thrombosis may be well tolerated or lead to graft dysfunction or portal hypertension. Balloon angioplasty, stent placement, and thrombolytic infusion have been used to reestablish the portal circulation.

Biliary leaks or strictures may be asymptomatic but can also lead to jaundice, bacteremia, or sepsis. Biliary leaks can occur at the biliary anastomosis and within the liver as a result of bile duct destruction. Ischemic damage from hepatic artery thrombosis may be a contributing factor.

Medications may also cause elevated liver enzymes. A cholestatic pattern may occur with cyclosporine, TAC, azathioprine, sulfa drugs, and various antibiotics. A hepatocellular pattern may occur with azathioprine, nonsteroidal antiinflammatory drugs, and some antibiotics.

The most common opportunistic infection of the hepatic allograft is cytomegalovirus (CMV) infection, and the infection may present as elevated liver enzymes, fever, cytopenias, or lethargy. Tissue invasive disease may cause life-threatening complications when the liver, lungs, or gastrointestinal tract are involved. The most common period for CMV disease is 4 to 12 weeks after transplantation. With generally lower levels of immunosuppression and effective prophylaxis, the occurrence of CMV disease in liver transplant recipients is decreasing to less than 5% at some centers (Figure 28-1).



**Figure 28-1.**  
Posttransplantation complications and time of occurrence. IVC, Inferior vena cava.

### 23. What are the clinical, biochemical, and histologic features of chronic rejection?

Chronic allograft rejection is generally characterized by an insidious but progressive rise in alkaline phosphatase and bilirubin. Patients are usually asymptomatic and synthetic function remains intact until the late stages. The pathogenesis of this syndrome remains unclear, but the evidence favors loss of bile ducts and the development of obliterative arteriopathy in the small hepatic arteries. Histologic findings include a normal-appearing parenchyma with few mononuclear infiltrates in the portal areas but absence of bile ducts in almost all of the portal triads. Later in the course, patients develop strictures and dilations in the larger bile ducts resembling primary sclerosing cholangitis. In these cases, the clinical course may be complicated by recurrent attacks of biliary sepsis. The differential diagnosis at this stage includes hepatic artery thrombosis, CMV cholangitis, anastomotic strictures of the biliary tree, and recurrent primary sclerosing cholangitis.

Chronic rejection is very uncommon and usually occurs in liver transplant recipients who are noncompliant with their immunosuppressive therapy. The process frequently progresses to graft failure, but recent reports indicate that 20 to 30 percent of patients may respond to additional immunosuppressive therapy. Patients with progressive liver failure caused by chronic rejection may require evaluation for retransplantation.

### 24. How often is it necessary to perform a second liver transplant, and for what reasons are retransplantations performed?

Fewer than 10% of the liver transplants performed in the United States are retransplants. Early retransplants are usually performed for primary nonfunction and hepatic artery thrombosis. Improved surgical techniques have reduced the early retransplant rate. Late retransplants may occur for recurrence of the original disease or chronic rejection. Recurrent disease may occur within 5 to 10 years in recipients with autoimmune hepatitis (36%-68%), primary sclerosing cholangitis (20%-25%), and primary biliary cirrhosis (21%-37%). Recurrent hepatitis C occurs in all transplant recipients with viremia at the time of transplantation. In contrast, the incidence of recurrent hepatitis B has declined to less than 10% with the use of posttransplant hepatitis B immunoglobulin

(HBIG) and nucleoside and nucleotide analogues. The availability of increasingly potent nucleoside and nucleotide analogues with a high barrier to resistance, such as entecavir or tenofovir, have led to negligible recurrence rates and may decrease the need for HBIG altogether.

## **25. Is retransplantation for recurrent hepatitis C recommended?**

Chronic hepatitis C remains the most common indication for liver transplantation in the United States. The prevalence of HCV infection in patients undergoing retransplantation has significantly increased since 1990. Because recurrent hepatitis C causes graft failure in an increasing number of patients, retransplantation is being considered more frequently. However, retransplantation for patients with graft failure caused by recurrent hepatitis C is controversial for *three reasons*:

1. Long-term survival rates for retransplantation of recipients with graft failure caused by HCV are only 50%.
2. The critical shortage of DD livers forces clinicians to select patients with the best chance of survival after transplantation.
3. Liver recipients who develop graft failure from recurrent HCV typically have more comorbidities than at the time of their first transplant. They are older and may have suffered the side effects of prolonged exposure to immunosuppressants, namely, diabetes, hypertension, and renal insufficiency.

Although HCV infection was initially found to be an independent predictor of mortality following retransplantation, subsequent reports have described similar rates of survival in HCV and non-HCV recipients, likely attributed to improved patient and donor selection. However, survival following retransplantation for cholestatic hepatitis C is very poor. Consequently, most transplant centers will not offer retransplantation to patients with graft loss caused by recurrent HCV or offer it on a very limited basis.

## **26. Describe the long-term metabolic complications that occur in the liver transplant recipient.**

Although patients experience a dramatic improvement in their quality of life following liver transplant, they are at risk for complications associated with the use of immunosuppressive regimens. The most common metabolic complications include diabetes, hypertension, and renal insufficiency. Diabetes caused by corticosteroids or CNIs may occur following transplantation. Hypertension is common with cyclosporine and TAC, and the associated renal insufficiency may exacerbate this problem. Hyperlipidemia caused by corticosteroids, sirolimus, and cyclosporine also occurs following transplant. Although metabolic complications may be ameliorated by a reduction in immunosuppression, persistent hyperlipidemia or diabetes requires aggressive treatment. All of these factors may place patients at greater risk for cardiovascular or cerebrovascular disease, and patients should receive counseling regarding appropriate diet, exercise, and smoking cessation. Renal insufficiency frequently occurs after liver transplantation and is more frequent in patients receiving cyclosporine than TAC. Up to 28% of patients develop end-stage renal disease (ESRD) 10 years after transplant. Other risk factors for developing ESRD include advanced age, hypertension, diabetes, hepatitis C, renal disease prior to liver transplantation, and postoperative acute renal failure.

Patients may be at risk for osteoporosis associated with corticosteroid use, particularly if they received significant steroids prior to transplantation. A low threshold for measurement of bone density prior to transplantation may be appropriate in high-risk populations such as patients with cholestatic liver disease. Patients at risk should consult with an endocrinologist for an assessment of appropriate therapy, which may include calcium, vitamin D supplementation, and other agents.

## **27. How frequently does nonalcoholic fatty liver disease (NAFLD) recur following liver transplantation?**

NAFLD is increasingly recognized as a major cause of chronic liver disease leading to cirrhosis. Most patients with cryptogenic cirrhosis who meet criteria for the metabolic syndrome (abdominal obesity, diabetes, hyperlipidemia, and hypertension) and otherwise have no identifiable cause of chronic liver disease are likely to have underlying NAFLD. As *posttransplant metabolic syndrome may occur in up to 50% of transplant recipients* overall, the development of posttransplant NAFLD is a concern, particularly in those with likely pretransplant NAFLD. The recurrence rate of NAFLD following liver transplantation has been reported to be 40% to 70%. Although a large proportion of these patients also demonstrate NASH, it is not clear whether this may lead to allograft failure or a decrease in survival. The development of de novo NAFLD may occur in up to one third of transplant recipients, although the prevalence of NASH in this group may be much lower at less than 5%.

## **28. Are liver transplant recipients at increased risk of developing cancer?**

Immunosuppression significantly increases the *risk of malignancy, which complicates approximately 15%* of liver transplants. The most common malignancy following liver transplantation is squamous cell carcinoma of the skin. Therefore patients should avoid exposure to ultraviolet light and wear protective clothing and sunscreen if they participate in activities leading to sun exposure.

Posttransplant lymphoproliferative disorder (PTLD) occurs in 1% of patients after liver transplantation. Most are large B cell–type non-Hodgkin's lymphoma caused by Epstein-Barr virus (EBV) infection in the setting of chronic immunosuppression. The two most important risk factors for PTLD are the degree of immunosuppression and EBV donor mismatch (EBV immunoglobulin G-negative recipient and EBV IgG-positive donor). The clinical presentation is variable and includes fever, lymphadenopathy, weight loss, or organ involvement. Extranodal involvement is common in the gastrointestinal tract, liver, lung, and bone

marrow. Treatment is a marked reduction in immunosuppression or use of antiviral agents, which may result in complete resolution of disease. Referral for oncology consultation is also necessary for consideration of chemotherapy or radiation, which is required for many patients.

## 29. What factors contribute to metabolic bone disease after transplantation?

Chronic liver diseases, particularly cholestatic liver diseases, are associated with osteopenia. The pathogenesis was originally thought to be related to decreased bile salt flow and vitamin D malabsorption, but plasma vitamin D levels are normal. Instead, these patients appear to have inhibition of bone formation and low or normal bone resorption. Prior to transplantation, these patients may already have significant bone loss. Following transplantation, glucocorticoids worsen the condition and place the patients at risk for fractures. One study measured the bone density of 20 women with primary biliary cirrhosis. At 3 months after transplantation, their bone density declined at a mean rate of 18.1% per year. The nadir in bone density appeared to occur within the first 6 months. As glucocorticoid use decreased, bone density improved and ultimately surpassed the pretransplant density at 2 years.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

- Angeli P, Gines P. Hepatorenal syndrome, MELD score and liver transplantation: an evolving issue with relevant implications for clinical practice. *J Hepatol* 2012;57:1135–40.
- Berg CL, Merion RM, Shearon TH, et al. Liver transplant recipient survival benefit with living donation in the model for endstage liver disease allocation era. *Hepatology* 2011;54:1313–21.
- Carbone M, Neuberger J. Liver transplantation in PBC and PSC: indications and disease recurrence. *Clin Res Hepatol Gastroenterol* 2011;35:446–54.
- Cholongitas E, Gouliis J, Akriviadis E, et al. Hepatitis B immunoglobulin and/or nucleos(t)ide analogues for prophylaxis against hepatitis B virus recurrence after liver transplantation: a systematic review. *Liver Transpl* 2011;17:1176–90.
- Czaja AJ. Diagnosis, pathogenesis, and treatment of autoimmune hepatitis after liver transplantation. *Dig Dis Sci* 2012;57:2248–66.
- Darwish Murad S, Kim WR, Harnois DM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for hilar cholangiocarcinoma at 12 US centers. *Gastroenterology* 2012;143:88–98.e83, quiz e14.
- Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 2010;138:513–21.
- Dureja P, Mellinger J, Agni R, et al. NAFLD recurrence in liver transplant recipients. *Transplantation* 2011;91:684–9.
- El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012;142:1264–73.
- El-Serag HB. Hepatocellular carcinoma. *N Engl J Med* 2011;365:1118–27.
- Gordon FD, Kwo P, Ghalib R, et al. Peginterferon-alpha-2b and ribavirin for hepatitis C recurrence postorthotopic liver transplantation. *J Clin Gastroenterol* 2012;46:700–8.
- Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology* 2009;137:856–64, 864 e851.
- Massoud O, Wiesner RH. The use of sirolimus should be restricted in liver transplantation. *J Hepatol* 2012;56:288–90.
- Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med* 2011;365:1790–800.
- Nadim MK, Sung RS, Davis CL, et al. Simultaneous liver-kidney transplantation summit: current state and future directions. *Am J Transplant* 2012;12:2901–8.
- Pagadala M, Dasarathy S, Egheesad B, et al. Posttransplant metabolic syndrome: an epidemic waiting to happen. *Liver Transpl* 2009;15:1662–70.
- Perrillo R, Buti M, Durand F, et al. Entecavir and hepatitis B immune globulin in patients undergoing liver transplantation for chronic hepatitis B. *Liver Transpl* 2013;19:887–95.
- Razumilava N, Gores GJ. Classification, diagnosis, and management of cholangiocarcinoma. *Clin Gastroenterol Hepatol* 2013;11:13–21, e11, quiz e13–14.
- Terrault NA, Roland ME, Schiano T, et al. Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. *Liver Transpl* 2012;18:716–26.
- Verna EC, Abdelmessih R, Salomao MA, et al. Cholestatic hepatitis C following liver transplantation: an outcome-based histological definition, clinical predictors, and prognosis. *Liver Transpl* 2013;19:78–88.
- Watt KD, Pedersen RA, Kremers WK, et al. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. *Am J Transplant* 2010;10:1420–7.
- Wiesner RH, Fung JJ. Present state of immunosuppressive therapy in liver transplant recipients. *Liver Transpl* 2011;17 (Suppl. 3):S1–9.

## Websites

MELD Score. <http://www.mdcalc.com/meld-score-model-for-end-stage-liver-disease-12-and-older/> [Accessed September 22, 2014].

# ASCITES

*Phillip S. Ge, MD, Carlos Guarner, MD, PhD, and Bruce A. Runyon, MD*

## 1. What are the most common causes of ascites?

Ascites is the accumulation of fluid within the peritoneal cavity. More than 80% of patients with ascites have decompensated chronic liver disease. However, it is important to know the other possible causes of ascites, because the treatment and prognosis may be quite different. In general, the most common causes of ascites are cirrhosis, heart failure, peritoneal carcinomatosis, alcoholic hepatitis, and fulminant liver failure. The differential diagnosis of ascites can be categorized according to its pathophysiology (Table 29-1).

**Table 29-1.** Differential Diagnosis of Ascites Categorized According to Pathophysiology

MECHANISM	DIFFERENTIAL DIAGNOSIS
Portal hypertension	Cirrhosis Alcoholic hepatitis Acute liver failure Hepatic vein occlusion (Budd-Chiari syndrome) Heart failure Constrictive pericarditis Dialysis ascites
Hypoalbuminemia	Nephrotic syndrome Malnutrition Protein-losing enteropathy
Peritoneal disease	Malignant ascites Tuberculous peritonitis Fungal peritonitis Peritoneal dialysis Eosinophilic gastroenteritis Starch granulomatous peritonitis
Miscellaneous	Chylous ascites Pancreatic ascites Myxedema Hemoperitoneum

## 2. Should a diagnostic tap be performed routinely on all patients with ascites at the time of admission to the hospital?

Ascites is diagnosed when large amounts of fluid are present in the peritoneal cavity. If clinical examination is not definitive in detecting or excluding ascites, ultrasonography may be helpful, and may provide information about the cause of ascites. Abdominal paracentesis is safe, rapid, and cost-effective. Analysis of ascitic fluid via abdominal paracentesis provides important data for differentiating causes of ascites, and for evaluating for spontaneous bacterial peritonitis (SBP).

Ascites in heart failure can mimic ascites in cirrhosis, and the distinction between the two entities can be challenging. Measurement of plasma brain natriuretic peptide (BNP) or N-terminal prohormone of BNP can be used to distinguish ascites caused by cirrhosis from ascites resulting from heart failure. However, this does not forego the need for paracentesis, as patients may have ascites in the setting of both heart failure and cirrhosis.

The diagnostic paracentesis is an essential and irreplaceable step in the evaluation of new-onset ascites. Delays in diagnostic abdominal paracentesis lead to serious delays in diagnosis and appropriate treatment. As a rule, diagnostic abdominal paracentesis should be performed:

- At the time of detection of new onset ascites
- At the time of admission in all patients with ascites

- When there is evidence of clinical decompensation, such as SBP, secondary bacterial peritonitis, hepatic encephalopathy, gastrointestinal hemorrhage, or deterioration of renal function

### 3. How should a diagnostic paracentesis be performed?

Although paracentesis is simple and safe, precautions should be taken to avoid complications. The abdomen should be disinfected with an iodine or similar solution, and the physician should wear sterile gloves during the entire procedure. The needle should be inserted in an area that is dull to percussion. A site in the **left lower quadrant** two finger-breadths cephalad from the anterior superior iliac spine and two finger-breadths medial to this landmark appears to be the best site for needle insertion. Because the panniculus is less thick in this area, the needle traverses less tissue. Therapeutic taps in the lower quadrants drain more fluid than midline taps. *Patients on lactulose tend to have a distended cecum*, and therefore the left lower quadrant is chosen over the right lower quadrant. Scars should be avoided, as they are often sites of collateral vessels and adherent bowel. Between 30 and 50 mL of ascitic fluid should be withdrawn for analysis.

### 4. What tests should be routinely ordered on ascitic fluid?

Analysis of ascitic fluid is useful for the differential diagnosis of ascites. However, it is not necessary to order all tests on every specimen. **The cell count with differential is the single most important test performed on ascitic fluid, because it provides immediate information about possible bacterial infection.** An absolute neutrophil count of 250 cells/mm<sup>3</sup> or more (total white cell count or nucleated cell count × % polymorphonuclear [PMN] cells) provides presumptive evidence of bacterial infection of ascitic fluid and warrants initiation of empiric antibiotics. An elevated white blood cell count with a predominance of lymphocytes suggests peritoneal carcinomatosis or tuberculous peritonitis.

Ascitic fluid should be cultured by inoculating blood culture bottles at the bedside. The sensitivity of this method is higher than that of sending a tube or syringe of fluid to the laboratory in detecting bacterial growth. Specific culture for tuberculosis should be ordered when tuberculous peritonitis is clinically suspected and the ascitic fluid white cell count is elevated with a lymphocytic predominance. Gram stain of ascitic fluid usually demonstrates no bacteria in patients with cirrhosis and early SBP, but it may be helpful in identifying patients with gut perforation, in whom multiple types of bacteria are seen.

Albumin concentration of ascitic fluid allows calculation of the serum-ascites albumin gradient (SAAG) to classify specimens into high- or low-gradient categories (see Question 6). Total protein concentration of ascitic fluid is useful for determining which patients are at high risk of developing SBP (total protein <1 g/dL) and for differentiating spontaneous from secondary bacterial peritonitis. Measurement of glucose and lactate dehydrogenase (LDH) in ascitic fluid also has been found to be helpful in making this distinction (see Question 11). Amylase activity of ascitic fluid is markedly elevated in pancreatic ascites and gut perforation into ascites and may be considered when there is clinical suspicion of such situations. Cytologic examination of ascitic fluid is useful in detecting malignant ascites when the peritoneum is involved with the malignant process. Unfortunately, ascitic fluid cytologic examination is not useful in detecting hepatocellular carcinoma, which seldom metastasizes to the peritoneum.

Patients with refractory ascites are currently submitted to repeated large-volume paracentesis in the outpatient clinic. The incidence of ascitic fluid infection or bacterascites is very low in these patients. Therefore it is reasonable to obtain a cell count and differential on all samples of ascitic fluid in the paracentesis clinic setting and culture only samples of ascitic fluid of symptomatic outpatients (i.e., abdominal pain or fever) and when the fluid is cloudy in appearance.

### 5. Should a diagnostic thoracentesis be performed in patients with cirrhosis and pleural hydrothorax?

Hepatic hydrothorax is defined as the accumulation of ascitic fluid in the pleural space in a patient with cirrhosis, in whom a cardiac, pulmonary, or pleural cause has been excluded. Approximately 5% to 10% of patients with cirrhosis and ascites develop hepatic hydrothorax, mainly in the right side (almost 70% of the cases), but it can also be in the left side or bilateral. Almost 10% of patients with cirrhosis admitted to the hospital with hepatic hydrothorax have a spontaneous bacterial empyema and 40% of these episodes are not associated with SBP. In consequence, **a diagnostic thoracentesis in patients with cirrhosis with ascites could be useful to evaluate other causes of pleural effusion in selected situations** and to diagnose spontaneous bacterial empyema in patients with cirrhosis with a suspected bacterial infection and negative studies of ascitic fluid, blood, and urine specimens. *Chest tube insertion is contraindicated in patients with hepatic hydrothorax, and can lead to rapid clinical deterioration.*

### 6. Why is it useful to measure SAAG?

SAAG is more useful than the total protein concentration of ascitic fluid in the classification of ascites. This gradient is physiologically based on oncotic-hydrostatic balance and is related directly to portal pressure. The SAAG is calculated by subtracting the albumin concentration of ascitic fluid from the albumin concentration of serum obtained on the same day:

*Patients with gradients of 1.1 g/dL or more have portal hypertension, whereas patients with gradients less than 1.1 g/dL do not have portal hypertension.*

### 7. What are the causes of high (i.e., $\geq 1.1$ g/dL) SAAG?

The most common cause of a high SAAG is cirrhosis, but any cause of portal hypertension leads to a high gradient (Table 29-2). Mixed ascites is due to multiple concurrent causes, including at least one that causes portal hypertension (e.g., cirrhosis and tuberculous peritonitis).

**Table 29-2.** Classification of Ascites Based on SAAG

SAAG	DIFFERENTIAL DIAGNOSIS
High (SAAG $\geq 1.1$ g/dL)	Cirrhosis Heart failure Alcoholic hepatitis Acute liver failure Massive hepatic metastases Hepatic vein occlusion (Budd-Chiari syndrome) Constrictive pericarditis Portal vein thrombosis Myxedema Fatty liver of pregnancy Mixed ascites
Low (SAAG $< 1.1$ g/dL)	Peritoneal carcinomatosis Tuberculous peritonitis Pancreatitis Biliary ascites Nephrotic syndrome Serositis Bowel obstruction or infarction

SAAG, Serum-ascites albumin gradient.

$$\text{SAAG} = \text{albumin}_{\text{serum}} - \text{albumin}_{\text{ascites}}$$

### 8. What are the causes of low (i.e., $< 1.1$ g/dL) SAAG?

Low-gradient ascites is found in the absence of portal hypertension and is usually due to peritoneal disease (see Table 29-2). The most common cause is peritoneal carcinomatosis.

### 9. What are the variants of ascitic fluid infection?

Ascitic fluid infection can be spontaneous or secondary to an intraabdominal, surgically treatable source of infection. More than 90% of ascitic fluid infections in patients with cirrhosis are spontaneous. According to the characteristics of ascitic fluid culture and PMN count, four different variants of ascitic fluid infection have been described in patients with cirrhosis:

- **SBP** is defined as an ascitic fluid infection with PMN count of  $250 \text{ cells/mm}^3$  or more and positive culture (usually for a single organism).
- **Culture-negative neutrocytic ascites** is defined as an ascitic fluid PMN count of  $250 \text{ cells/mm}^3$  or more with a negative culture.
- **Bacterascites** is defined as an ascitic fluid PMN count less than  $250 \text{ cells/mm}^3$  with a positive culture for a single organism.
- **Polymicrobial bacterascites** is defined as an ascitic fluid with PMN count less than  $250 \text{ cells/mm}^3$  with a positive culture for more than one organism. This condition can be caused by gut puncture by the needle during attempted paracentesis.

### 10. What is the diagnostic criterion of spontaneous bacterial empyema?

Current diagnostic criterion of spontaneous bacterial empyema is a positive pleural fluid culture with a pleural fluid PMN count of  $250 \text{ cells}/\mu\text{L}$  or more and the exclusion of parapneumonic infections. Culture-negative spontaneous bacterial empyema is defined when the patient has a negative pleural fluid culture and a PMN count of  $500 \text{ cells}/\mu\text{L}$  or more without a parapneumonic infection.

### 11. How do you differentiate spontaneous from secondary peritonitis?

It is important to differentiate spontaneous from secondary peritonitis in patients with cirrhosis, because treatment for SBP is medical, whereas treatment for secondary peritonitis is usually surgical. Although secondary peritonitis represents less than 10% of ascitic fluid infections, it should be considered in any patient with neutrocytic (PMN count  $\geq 250 \text{ cells}/\mu\text{L}$ ) ascites. Analysis of ascitic fluid is helpful in differentiating the two

entities. Secondary bacterial peritonitis should be suspected when ascitic fluid analysis shows two or three of the following criteria (Runyon criteria):

- Total protein more than 1 g/dL
- Glucose less than 50 mg/dL
- LDH more than 225 mU/mL (or more than the upper limit of normal for serum).

These criteria were recently validated and shown to have a sensitivity of 66.6% and specificity of 89.7%. When combined with the presence of a polymicrobial ascitic fluid culture, specificity improved to 95.6%. Most of the ascitic fluid cultures in patients with secondary bacterial peritonitis are polymicrobial, whereas in patients with SBP the infection is usually monomicrobial. Patients with suspected secondary peritonitis based on ascitic fluid analysis must be evaluated promptly by abdominal computed tomography imaging and early surgical consultation.

In patients with nonperforation secondary peritonitis, these criteria are not as useful; however, PMN cell count after 48 hours of treatment will increase beyond the pretreatment value and ascitic fluid culture will remain positive. Conversely, ascitic fluid PMN cell count decreases rapidly in appropriately treated patients with SBP, and ascitic fluid culture becomes negative. Determination of ascitic fluid carcinoembryonic antigen and alkaline phosphatase levels ( $>5$  ng/mL and/or  $>240$  U/L, respectively) may be helpful to diagnose secondary bacterial peritonitis caused by occult intestinal perforation (higher specificity than Runyon criteria in one study).

## 12. Who is at high risk of developing SBP?

See Box 29-1.

### Box 29-1. Risk Factors for Development of Spontaneous Bacterial Peritonitis

- Admitted to the hospital with gastrointestinal hemorrhage
- Cirrhosis and ascitic fluid total protein  $<1.5$  g/dL and advanced liver disease, especially:
  - Hyperbilirubinemia ( $>3.2$  mg/dL)
  - Thrombocytopenia ( $<98,000$  cells/mm $^3$ )
  - Child-Pugh score  $\geq 9$
- Hyponatremia ( $\leq 130$  mEq/L)
- Renal dysfunction (serum creatinine  $\geq 1.2$  mg/dL or blood urea nitrogen  $\geq 25$  mg/dL)
- Patients with cirrhosis who have survived an episode of SBP
- Fulminant hepatic failure

*SBP*, Spontaneous bacterial peritonitis.

## 13. What is the pathogenesis of SBP?

Gram-negative bacteria are the most common causative agents isolated in bacterial infections in patients with cirrhosis. Therefore it has been suggested that the gut may be the source of the bacteria. Direct passage of intestinal bacteria to portal blood or ascitic fluid has not been documented in patients with cirrhosis, if the gut mucosa has not lost its integrity. Bacterial translocation, defined as the passage of viable bacteria from gastrointestinal tract to mesenteric lymph nodes, has been demonstrated in an experimental model of rats with cirrhosis and ascites and in patients with cirrhosis who underwent laparotomy. In fact, genetic identity has been observed between bacteria isolated in the gut, mesenteric lymph nodes, and ascitic fluid in rats with cirrhosis. Intestinal bacterial overgrowth seems to be the main mechanism of bacterial translocation in cirrhotic rats. Reducing the quantity of intestinal flora has been shown to decrease the incidence of bacterial translocation and SBP. An experimental study observed that rats with cirrhosis and severe intestinal oxidative damage in the ileum and cecum have a higher incidence of bacterial translocation, suggesting a possible role of functional mucosal alterations in the pathogenesis of SBP. Immune deficiencies, especially decreased activity of the reticuloendothelial system and low serum complement levels, lead to frequent and prolonged bacteremia in patients with cirrhosis and to colonization of body fluids, such as ascitic fluid. The development of a bacterial infection depends on the capacity of ascitic fluid to kill the bacteria. *In vitro*, the capacity of ascitic fluid to kill bacteria (i.e., opsonic activity) is related directly to total protein and C3 concentration of ascitic fluid. Patients with cirrhosis and low ascitic fluid opsonic activity have low C3, low total protein, and thus a higher incidence of SBP. In contrast, patients with high ascitic fluid opsonic activity have high C3 and high total protein; thus bacterial colonization may resolve spontaneously.

## 14. What single test provides early information about possible ascitic fluid infection?

The decision to start empirical antibiotic treatment must be made as soon as possible, because the survival rate depends on early diagnosis and treatment. Gram stain is positive in only 5% to 10% of patients, and bacterial culture of ascitic fluid takes at least 12 hours to demonstrate growth. **The ascitic fluid neutrophil count is highly sensitive in detecting bacterial infection of peritoneal fluid.** An absolute neutrophil count of 250 cells/mm $^3$  or more warrants empiric antibiotic treatment.

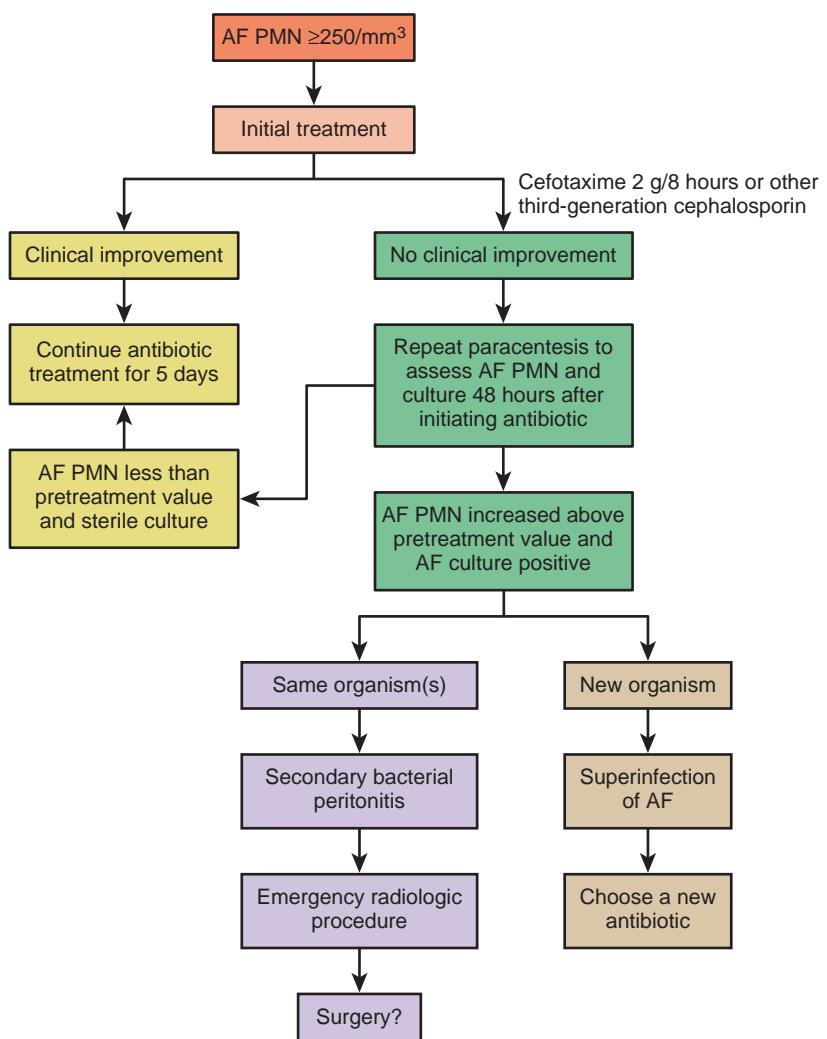
## 15. What is the treatment of choice for suspected SBP?

Third-generation cephalosporins such as cefotaxime cover most of the flora responsible for SBP, and have been demonstrated in randomized trials to be superior to the previously used combination of ampicillin and

gentamicin with less complications of nephrotoxicity or superinfection. **Cefotaxime or a similar cephalosporin should be started when SBP is suspected.** Cefotaxime should be dosed at 2 g intravenously every 8 hours. A short course of therapy (5 days) has been shown to be as effective as a long course (10 days). Cefotaxime is favored over other third-generation cephalosporins because of its superior ascites fluid penetration; ceftriaxone may be alternatively used at a dose of 2 g intravenously per day. Concurrently, intravenous albumin should be administered at a dose of 1.5 g/kg at the time of diagnosis of SBP and 1 g/kg on day 3 of treatment. Studies have shown that this regimen reduces the incidence of renal impairment and death. Albumin should be considered especially in patients with SBP and blood urea nitrogen (BUN) of more than 30 mg/dL, serum creatinine of more than 1 mg/dL, or serum total bilirubin of more than 4 mg/dL (Figure 29-1). If renal impairment has already developed, consideration should be given to treatment with a combination of midodrine and octreotide (see Questions 31 and 40).

In patients for whom a third-generation cephalosporin is not a viable option because of medication allergy, fluoroquinolones may be considered. A short course of intravenous ciprofloxacin 200 mg twice daily during 2 days followed by oral ciprofloxacin (500 mg twice daily for 5 days) was shown to be an effective treatment of SBP. Another study showed that patients with uncomplicated SBP (i.e., those without shock, ileus, gastrointestinal hemorrhage, or hepatic encephalopathy) can be safely treated with oral ofloxacin (400 mg twice daily). In general, oral or intravenous fluoroquinolones should not be used as empiric treatment of patients who are taking an oral fluoroquinolone for SBP prophylaxis; in these situations, the infecting organism may already be resistant to fluoroquinolones, although cefotaxime appears to still be effective in such patients. Nephrotoxic antibiotics such as aminoglycosides should be avoided as patients with cirrhosis and SBP already have underperfused kidneys with increased risk of injury.

**Figure 29-1.** Management of spontaneous bacterial peritonitis. AF, ascitic fluid; PMN, polymorphonuclear (cells).



When treated swiftly, patients with SBP tend to improve swiftly as well. In patients who are insufficiently responding to intravenous antibiotics, urgent susceptibility testing of ascitic fluid cultures is warranted.

#### **16. What is the treatment of choice for nosocomial or cephalosporin-resistant SBP?**

As cephalosporins become increasingly used in patients with community-acquired SBP and other bacterial infections, and for prophylaxis of bacterial infections in gastrointestinal bleeding, there is increasing incidence of SBP with bacteria resistant to third-generation cephalosporins. This was demonstrated in a recent study of the risk factors for resistance to ceftriaxone and its effect on mortality in community-acquired versus nosocomial SBP. Given these concerns, carbapenems should be recommended as first-line therapy of nosocomial SBP or when patients treated with third-generation cephalosporins fail to respond adequately in the first 24 hours of treatment.

#### **17. When should antibiotic treatment be started in a patient with cirrhosis and suspected ascitic fluid infection?**

Empirical antibiotic treatment must be started **as soon as possible** to improve survival rates. The order should state “first dose stat” to avoid the possibility that the first dose may cycle to the next shift of nurses or the next 8-hour cycle. It is important to immediately perform bacterial cultures of ascitic fluid, blood, urine, and sputum as well as an ascitic fluid cell count and differential when a hospitalized patient with ascites develops clinical signs of possible SBP (fever, abdominal pain, encephalopathy) or shows deterioration in clinical or laboratory parameters. Ascitic fluid and urine should be analyzed when patients with cirrhosis and ascites are admitted to the hospital. A high level of suspicion for bacterial infection is appropriate, because it is a reversible cause of deterioration and a frequent cause of death in patients with cirrhosis. Empiric antibiotics should be started immediately after performing cultures and ascitic fluid analysis whenever:

- Bacterial infection is suspected based on abdominal pain or fever
- Ascitic fluid neutrophils are  $250 \text{ cells/mm}^3$  or more (see [Figure 29-1](#)).

Studies in the pulmonary and critical care literature have referred to the strategy of early, goal-directed therapy for the treatment of severe sepsis and septic shock. One of its central tenets is the early initiation of antibiotics, ideally within the first hour. Guidelines from the Surviving Sepsis Campaign continue to affirm the concept of the “golden hour,” during which **intravenous antibiotics should be initiated as early as possible and always within the first hour** of recognizing severe sepsis and septic shock. These concepts apply to SBP.

#### **18. Should the PMN cell count in ascitic fluid be monitored during treatment of SBP?**

Ascitic fluid culture becomes negative after a single 2-g dose of cefotaxime in 86% of patients with SBP. The neutrophil count also decreases rapidly to normal values during therapy in 90%. Superinfection or early recurrence after treatment with third-generation cephalosporins is uncommon. Repeat paracentesis is not necessary, if the setting (advanced cirrhosis) is typical, one organism is cultured, and the patient has the usual dramatic response to treatment.

#### **19. Does bacterascites represent a real peritoneal infection? Should it be treated?**

Studies have documented the short-term natural history of monomicrobial nonneutrocytic bacterascites. A repeat paracentesis of patients with bacterascites before starting antibiotic therapy showed that in 62% to 86%, the episode of bacterascites resolved spontaneously. All patients who progressed to SBP had symptoms of bacterial infection at the time of the first tap. Such data demonstrate that bacterascites is a dynamic process; its evolution may depend on several factors, including systemic and ascitic fluid defenses as well as organism virulence. According to these studies, symptomatic patients with bacterascites should be treated with antibiotics. Asymptomatic patients need not receive antibiotic treatment but should be reevaluated with a second tap. If the PMN count is  $250/\text{mm}^3$  or more, antibiotics should be started.

#### **20. What does the presence of bacterial DNA in blood and ascitic fluid represent in patients with cirrhosis?**

Molecular biologic techniques have demonstrated the presence of bacterial DNA in blood and ascitic fluid in both patients and rats with cirrhosis and ascites. In 30% of patients with cirrhosis and ascites, bacterial DNA can be detected despite a negative culture and normal PMN count in ascitic fluid. The presence of bacterial DNA represents episodes of bacterial translocation, as has been demonstrated in rats with cirrhosis. These patients have a systemic cytokine response similar to those observed in patients with SBP and its presence has been related to poor survival. More studies are required to determine if these patients require antibiotic treatment or prophylaxis.

#### **21. Which subgroups of patients with liver disease should receive prophylaxis against bacterial infection?**

Because enteric aerobic gram-negative bacteria are the most frequent causative agents isolated in bacterial infections in cirrhosis and because bacterial translocation seems to be an important step in pathogenesis, inhibition of intestinal gram-negative bacteria should be an effective method of preventing bacterial infections. Patients with liver disease who are at high risk of developing bacterial infection or SBP should be considered for selective intestinal decontamination (SID). SID consists of the inhibition of the gram-negative flora of the gut with preservation of gram-positive cocci and anaerobic bacteria. Preservation of gut anaerobes is important in preventing intestinal colonization, overgrowth, and subsequent translocation of pathogenic bacteria. Several

trials have shown that SID with oral norfloxacin is highly effective in preventing bacterial infections and SBP in patients with cirrhosis and:

- Gastrointestinal hemorrhage (ceftriaxone 1 g/day or norfloxacin 400 mg twice daily or ceftri) or
- Prior episodes of SBP (norfloxacin 400 mg/day)
- Low ascitic fluid protein (norfloxacin 400 mg/day) and
- Fulminant hepatic failure (norfloxacin 400 mg/day)

Long-term antibiotic therapy has been used in preventing the first episode of SBP as well as recurrences. Long-term prophylactic treatment decreases the incidence of SBP in both conditions, but increases the appearance of quinolone-resistant bacteria and infections. Secondary prophylaxis is generally well accepted, especially in patients awaiting liver transplantation. Long-term primary prophylaxis has been evaluated in patients with advanced liver disease, such as those with low ascitic fluid total protein (less than 1.5 g/dL) and high serum bilirubin (greater than 3 mg/dL) or low platelet count (less than 98,000 cells/mm<sup>3</sup>), hyponatremia (less than 130 mEq/L) or impaired renal function (serum creatinine level 1.2 mg/dL or greater, BUN level 25 mg/dL or greater). Primary prophylaxis with norfloxacin had a great effect in the clinical course of these patients, because it reduced the incidence of SBP, the development of hepatorenal syndrome, and improved survival.

## **22. Are there alternative prophylactic treatments to quinolones for preventing bacterial infections in cirrhosis?**

Trimethoprim-sulfamethoxazole (1 double strength tablet daily) is a reasonable alternative to oral quinolones in the United States, as it is generic and often inexpensive. Prophylaxis with oral quinolones or trimethoprim-sulfamethoxazole promotes infections caused by resistant gram-negative bacilli; this reduces the efficacy of the preventive treatment, especially in patients submitted to long-term prophylaxis. It will be important to develop alternative drugs for preventing bacterial infections in cirrhosis.

In patients admitted to the hospital with gastrointestinal hemorrhage and severe liver disease, a randomized controlled trial has demonstrated that parenteral ceftriaxone (1 g daily for 7 days) is more effective than oral norfloxacin (400 mg twice daily) in preventing SBP in this population.

## **23. What is the treatment of spontaneous bacterial empyema?**

Microbiologic studies of pleural fluid have shown that gram-negative bacteria are present in almost 50% of patients with spontaneous bacterial empyema, the others being culture negative. Therefore patients with spontaneous bacterial empyema should be treated with broad-spectrum antibiotics as in patients with SBP. Chest tube is not necessary and should be avoided. Patients surviving a spontaneous bacterial empyema should be evaluated for liver transplantation.

## **24. Why is it important to understand sodium balance in patients with cirrhosis and ascites?**

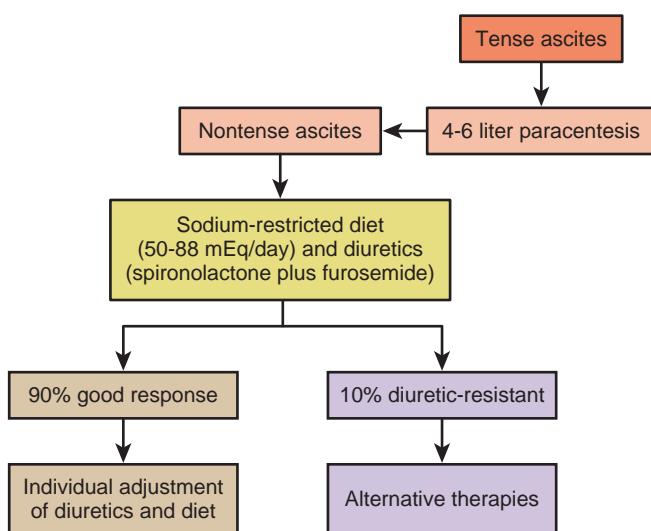
Ascites formation in cirrhosis is due to renal retention of sodium and water. The aim of medical treatment of ascites in patients with cirrhosis is to mobilize the ascitic fluid by creating a net negative balance of sodium. This goal is accomplished by reducing sodium intake in the diet and increasing urinary sodium excretion. Therefore knowledge of urinary excretion of sodium allows the clinician to plan initial treatment. In addition, urinary sodium excretion is an easily determined prognostic indicator. Patients with cirrhosis and a urinary sodium excretion less than 10 mEq/day have a 2-year survival rate of 20%, whereas those with sodium excretion more than 10 mEq/day have a 2-year survival rate of 60%.

## **25. Describe the initial treatment of patients with cirrhosis and ascites.**

Patients with cirrhosis and ascites should be treated initially by dietary sodium restriction (50-88 mEq/day) and diuretics. A more severe restriction of sodium intake may worsen anorexia and malnutrition. Water restriction is usually not necessary, if serum sodium concentration is more than 120 mEq/L. In 15% to 20% of patients, a negative sodium balance may be obtained with dietary sodium restriction in the absence of diuretics. However, because 80% to 85% of patients need diuretics, it is reasonable to start diuretics in all patients. The initial dose of diuretics should be 100 mg of spironolactone and 40 mg of furosemide—both drugs are given orally in a single morning dose. If the body weight does not decrease or the urinary sodium excretion does not increase after 2 to 3 days of treatment, the dose of both diuretics should be progressively increased, usually in simultaneous increments of 100 mg/day and 40 mg/day, respectively. Serial monitoring of urinary sodium excretion and daily weight is the best way to determine the optimal dose of diuretics. Doses should be increased until a negative sodium balance is obtained (i.e., random or spot urinary sodium concentration > potassium concentration) with corresponding weight loss. The ceiling doses of spironolactone and furosemide are 400 mg and 160 mg per day, respectively. Once ascites has been mobilized, diuretic dosage should be adjusted individually to keep the patient free of ascites or at least comfortable with the volume of fluid. Some patients become encephalopathic if their ascites is fully controlled; therefore the benefits of higher diuretic doses must be carefully weighed against the risk of encephalopathy. Patients with tense ascites should be treated initially with a therapeutic paracentesis of 4 L or more (Figure 29-2).

## **26. What is refractory ascites?**

Refractory ascites is an inadequate response to sodium-restricted diet and high-dose diuretic treatment (400 mg/day spironolactone and 160 mg/day furosemide). This inadequate response is manifested by the absence of weight



**Figure 29-2.** Initial management of ascites in patients with cirrhosis.

loss (less than 0.8 kg over 4 days) or the development of complications of diuretics, such as hepatic encephalopathy, renal impairment, hyponatremia, or hypokalemia or hyperkalemia. Excessive sodium intake, bacterial infection, occult gastrointestinal hemorrhage, and intake of prostaglandin inhibitors (e.g., aspirin or nonsteroidal antiinflammatory drugs) should be excluded before labeling patients as refractory. Early ascites recurrence (within 4 weeks after initial mobilization) is also considered refractory ascites. Less than 10% of patients with cirrhosis are refractory to standard medical therapy. This group should be evaluated for other therapeutic options, such as liver transplantation, chronic outpatient paracentesis (usually every 2 weeks), peritoneovenous shunt, or transjugular intrahepatic portosystemic stent-shunt (TIPS).

## 27. What is the relationship between blood pressure and survival in patients with cirrhosis and ascites?

The correlation between blood pressure and survival in patients with cirrhosis has been suggested in multiple studies. In a survival analysis of patients with cirrhosis and ascites, **mean arterial pressure was found to be an independent predictor of survival**. Mean arterial pressure of 82 mm Hg or lower was the single variable most strongly correlated with shortened survival; the survival probability rate of patients with mean arterial pressure of 82 mm Hg or lower was approximately 20% at 24 months and 0% at 48 months, in contrast with approximately 70% at 24 months and 50% at 48 months among patients with mean arterial pressure of more than 82 mm Hg.

Cirrhosis is a dynamic clinical process, and there are significant hemodynamic differences between early cirrhosis without ascites and late cirrhosis with refractory ascites. Most profoundly, decreases in effective arterial blood volume results in the progressive stimulation of the sympathetic nervous system and decline in cardiac compensatory reserve. Over time, cirrhosis effectively cures hypertension. Patients should ideally be followed closely with home blood pressure monitoring and frequent clinic visits to minimize the risk of any antihypertensive medications, including beta-blockers used for primary and secondary prophylaxis of variceal hemorrhage.

## 28. How should antihypertensive medications be managed in patients with cirrhosis and ascites?

Beta-blockers are used in the primary and secondary prophylaxis of variceal hemorrhage in patients with cirrhosis. However, beta-blockers may be effective only within a particular clinical window of advanced liver disease. In early cirrhosis, beta-blockers are ineffective because of a milder splanchnic and systemic hyperdynamic circulatory state. In advanced cirrhosis with refractory ascites, there is maximal up-regulation of the sympathetic nervous system and of the renin-angiotensin-aldosterone system. At the same time, cardiac compensatory reserve is compromised, and the circulatory system is unable to further increase cardiac output during situations of increased physiologic stress, resulting in decreased mean arterial pressures, decreased perfusion to vital organs, azotemia, and increased risk for hepatorenal syndrome and end-organ damage.

A small prospective observational study from the same investigators who introduced the liver world to the use of beta-blockers for prophylaxis of variceal hemorrhage showed that the use of beta-blockers in patients with refractory ascites may be associated with poor survival, suggesting that beta-blockers should be contraindicated in this subclass of patients. In general, **beta-blockers should be tapered and discontinued in those patients who develop refractory ascites, worsening hypotension, or worsening azotemia**. Endoscopic band ligation of varices can be considered as a substitute treatment to prevent variceal hemorrhage. Consideration can also be given to agents such as midodrine that increase cardiac output and blood pressure.

Studies investigating the effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with cirrhosis have likewise shown worsened outcomes in advanced

cirrhosis and ascites. The latest guidelines recommend against the use of ACE inhibitors and ARBs in patients with ascites because of concerns of hypotension and renal failure.

### **29. Which patients should be treated with large-volume paracentesis?**

Large-volume paracentesis is an old but effective procedure to mobilize ascitic fluid in patients with cirrhosis. Interest in this procedure has been renewed in the past decade. It has been shown that therapeutic paracentesis not only is safe but also may have additional beneficial effects on the hemodynamic status of patients with tense ascites. However, repeated large-volume paracentesis causes depletion of proteins and may theoretically predispose to SBP. Therefore therapeutic paracentesis should not be used as a routine treatment of all patients with cirrhosis and ascites and should be reserved for treating patients with tense or refractory ascites.

### **30. Which treatments should be considered to prevent paracentesis-induced circulatory dysfunction following large-volume paracentesis?**

Paracentesis-induced circulatory dysfunction, defined as an increase in plasma renin activity of more than 50% of the preparacentesis value to a level of more than 4 ng/mL/h, is observed with a higher incidence in patients with cirrhosis not submitted to volume expansion or treated with nonalbumin expanders after a large-volume paracentesis. Studies have observed that the development of paracentesis-induced circulatory dysfunction, which may itself be clinically silent, is associated with a worse long-term prognosis.

Volume expanders including albumin were introduced to avoid theoretical hemodynamic disturbances that may develop in patients with cirrhosis after therapeutic paracentesis of 5 L or more of ascitic fluid. Because albumin infusion is expensive, alternative treatments have been widely investigated, including artificial colloids and vasoconstrictors. A recent metaanalysis included 17 clinical trials and 1225 total patients demonstrated that **albumin was superior to these alternative treatments in the reduction of paracentesis-induced circulatory dysfunction, hyponatremia, and overall mortality.**

Beta-blockers should be discontinued when patients are treated with large-volume paracentesis, according to a recent prospective cross-over study, in which patients given propranolol experienced a significant decrease in mean arterial pressure and development of paracentesis-induced circulatory dysfunction following large-volume paracentesis. Following discontinuation of beta-blockers, the incidence of paracentesis-induced circulatory dysfunction was significantly decreased.

### **31. Describe the role for midodrine in the management of cirrhosis with refractory ascites and hepatorenal syndrome.**

Midodrine, an alpha-1 adrenergic agonist, was shown to have a preferential effect on the splanchnic circulation, and its acute administration overall improves systemic hemodynamics, renal function, and sodium excretion in nonazotemic patients with ascites. Midodrine therapy produces a significant increase in urinary volume, urinary sodium excretion, and mean arterial pressure, with decrease in plasma renin activity and in overall mortality. In other words, **midodrine appears to improve systemic hemodynamics without causing renal or hepatic dysfunction.** The combination of octreotide and midodrine has also been demonstrated to be an important treatment for type 1 hepatorenal syndrome.

### **32. Is there currently any indication for peritoneovenous shunt?**

Peritoneovenous shunt was originally introduced for the treatment of patients with cirrhosis and refractory ascites. Obstruction of the shunt, especially at the venous end despite the collocation of a titanium tip, is the main complication and requires the placement of a new shunt. In addition, peritoneovenous shunt does not reduce mortality during the initial hospitalization and does not improve long-term survival in patients with cirrhosis. Therefore peritoneovenous shunts should be considered only in patients with cirrhosis and refractory ascites who are not candidates for liver transplantation or TIPS and in whom large-volume paracentesis is difficult.

Recently, an implanted pump was devised in which ascitic fluid is removed from the peritoneal cavity and pumped into the bladder, where it is eliminated with normal urination. The study showed that the pump system removed 90% of ascites and significantly reduced the median number of large-volume paracentesis per month. Additional studies are needed to compare this emerging therapeutic option versus standard large-volume paracentesis.

### **33. Which patients with cirrhosis and ascites should be considered for TIPS?**

TIPS is an interventional radiologic technique that consists of creating a fistula between a hepatic vein and a portal vein and then placing an expandable metal stent in the balloon-dilated fistula to maintain patency. This technique was introduced to treat patients with recurrent variceal hemorrhage by decreasing portal pressure. Initial results showed that TIPS could be useful in the treatment of patients with cirrhosis with refractory ascites. However, the incidence of shunt dysfunction is still quite high. Two trials performed in patients with refractory ascites have demonstrated that TIPS plus medical therapy is superior to medical therapy (diuretics plus total paracentesis when required) alone for the control of ascites but does not improve survival, length of hospitalization, and quality of life. The incidence of hepatic encephalopathy was higher in the TIPS group, but other complications of cirrhosis such as variceal hemorrhage or acute renal failure were similar in the two groups. In one study, the cost of the TIPS group was significantly higher than in the medical therapy group. These data suggest that TIPS should be reserved as second-line therapy or a bridge to liver transplantation,

especially in those patients with relatively preserved liver function. An additional concern regarding TIPS is the high incidence of TIPS dysfunction that requires frequent ultrasound evaluations and reinterventions. The recent introduction of polytetrafluoroethylene-covered stents improves shunt patency and reduces the incidence of TIPS dysfunction and episodes of encephalopathy.

#### **34. Which patients with cirrhosis and ascites should be evaluated for liver transplantation?**

Ascites is the most frequent complication of patients with cirrhosis and usually is associated with poor liver function based on Model of End-stage Liver Disease (MELD) score. The probability of survival after the first onset of ascites has been estimated at 50% and 20% after 1 and 5 years of follow-up, respectively. The prognosis is even worse in patients with diuretic-resistant ascites; the 1-year survival rate is 25%. Because the 1-year survival rate after liver transplantation is greater than 75%, **patients with cirrhosis who develop ascites should be considered for liver transplantation.** Once the fluid becomes diuretic resistant, consideration for transplantation becomes even more urgent. However, some alcoholic patients with refractory ascites may become diuretic sensitive after months of alcohol abstinence.

#### **35. What is the treatment of hepatic hydrothorax?**

The initial treatment of hepatic hydrothorax is the same as ascites: salt restriction, diuretics, and large-volume paracentesis if the patient has ascites. Therapeutic thoracentesis has a high incidence of complications in patients with cirrhosis (10% develop pneumothorax) and should be avoided, if it is not necessary to relieve pulmonary symptoms. Patients with recurrent or refractory hepatic hydrothorax should be carefully evaluated. Pleurodesis is usually ineffective. Surgical repair of the diaphragmatic defects could be performed by using a videothoracoscope and may be useful for selected patients. Use of TIPS appears to be a good option for patients with refractory hepatic hydrothorax and Child-Pugh score less than 12 and MELD score less than 18. **Chest tube insertion is contraindicated in patients with hepatic hydrothorax, and can lead to rapid clinical deterioration, urgent TIPS or transplant, or death.**

#### **36. What is dilutional hyponatremia in patients with cirrhosis?**

Dilutional hyponatremia is a frequent complication of cirrhosis associated with a high morbidity and mortality and poor prognosis. One-year probability of survival after developing dilutional hyponatremia was 25.6% in a recent study. Dilutional hyponatremia is defined as serum sodium lower than 130 mEq/L in the presence of an expanded extracellular fluid volume, as indicated by the presence of ascites or edema. It is mainly due to a severe water renal retention secondary to an increased nonosmotic secretion of vasopressin.

#### **37. What is the treatment of dilutional hyponatremia?**

The cornerstone of treatment of dilutional hyponatremia is fluid restriction (1 to 1.5 L/day) and discontinuation of diuretics, if the patient has symptoms such as encephalopathy or hyponatremia is extremely severe (less than 120-125 mEq/L). Patients with cirrhosis usually do not have symptoms from hyponatremia until their serum sodium falls below 110 mEq/L or if the decline in serum sodium is extremely rapid. Initial investigations of vasopressin V2 receptor antagonists (vaptans) showed effectiveness in improving serum sodium in the short and long term in patients with cirrhosis and hyponatremia despite diuretic treatment. However, correction of hyponatremia did not appear to correlate with more important clinical outcomes. The Food and Drug Administration has issued a black box warning for tolvaptan as rapid correction of hyponatremia can occur resulting in potentially fatal osmotic demyelination. Satavaptan was specifically evaluated to determine its efficacy in the treatment of ascites and found to not be clinically beneficial in the long-term management of ascites, with increased mortality compared to placebo. Therefore **vaptans are not currently recommended** because of potential risks and lack of evidence in clinically meaningful outcomes.

#### **38. What is the hepatorenal syndrome?**

The hepatorenal syndrome occurs in patients with advanced liver failure and portal hypertension. It is a functional renal failure caused by intrarenal vasoconstriction resulting from arterial vasodilatation in the splanchnic circulation and severe reflex activation of the endogenous vasoconstrictive systems. According to clinical outcome, hepatorenal syndrome can be divided into two types:

- *Type I hepatorenal syndrome* is characterized by a rapid and progressive reduction of renal function defined by a doubling of the initial serum creatinine to a level greater than 2.5 mg/dL or a 50% reduction in the initial 24-hour creatinine clearance to a level less than 20 mL/min in less than 2 weeks. Clinical presentation is acute renal failure.
- In *type II hepatorenal syndrome*, renal failure does not have such a rapidly progressive course. These patients develop a clinical picture of refractory ascites.

#### **39. What are the criteria of hepatorenal syndrome?**

See Box 29-2.

#### **40. Describe the treatment of patients with hepatorenal syndrome.**

Liver transplantation is currently the treatment of choice in patients with hepatorenal syndrome. The mortality rate of untreated patients with type I hepatorenal syndrome is almost 100% in less than 2 months. Treatments such as hemodialysis, peritoneovenous shunt, albumin infusion, and dopamine infusion have been

**Box 29-2.** Diagnostic Criteria for Hepatorenal Syndrome

- Cirrhosis with ascites
- Serum creatinine greater than 133 µmol/L (1.5 mg/dL)
- No improvement in serum creatinine (decrease to a level of 133 µmol/L) after at least 2 days with diuretic withdrawal and volume expansion with albumin (recommended dosage of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day)
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria greater than 500 mg/day, microhematuria (greater than 50 red blood cells per high-power field), or abnormal renal ultrasonogram

evaluated and found to be of only transient benefit or without benefit. Recent studies have shown that hepatorenal syndrome can be reversed by the administration of vasoconstrictive drugs, such as octreotide and midodrine, ornipressin, terlipressin, or norepinephrine, with albumin infusion or other volume expanders. Several trials have demonstrated that terlipressin associated with albumin infusion is an effective treatment in patients with type I hepatorenal syndrome, improving renal function. These agents allow some patients to survive long enough to undergo liver transplantation. However, terlipressin is not available in the United States.

In the United States, (1) **octreotide and midodrine** or (2) norepinephrine (if the patient is in intensive care and not taking oral medications) are options for treatment of hepatorenal syndrome. Octreotide is best given as a continuous infusion of 50 mcg/h but can be given subcutaneously starting with a dose of 100 mcg followed in 8 hours by 200 mcg, then 200 mcg every 8 hours. Midodrine is given orally with a 7.5-mg dose followed in 8 hours by a 10-mg dose, then in 8 hours 12.5 mg, then 12.5 mg every 8 hours. The goal is to increase mean arterial blood pressure to 15 mm Hg. Although the original publication did not include the use of greater than 12.5 mg, 15 mg every 8 hours can be used as needed. If systolic blood pressure rises above 140 mm Hg, the dose can be reduced. However, hypertension on this treatment is so rare that it calls into question the diagnosis of hepatorenal syndrome, as usually the systolic blood pressure is in the 70- to 80-mm Hg range in the setting of hepatorenal syndrome. Albumin is usually given at a dose of 25 g daily during treatment with octreotide and midodrine. Norepinephrine is administered by continuous infusion at an initial dosage of 0.1 mcg/kg/min and increased every 4 hours by 0.05 mcg/kg/min if mean arterial pressure does not increase at least 10 mm Hg. TIPS insertion seems to be another option for the temporary treatment of hepatorenal syndrome, especially in patients with preserved liver function.

#### **41. Is it possible to prevent hepatorenal syndrome?**

Short-term mortality of patients with type I hepatorenal syndrome is almost 100% in the following 2 months. A high proportion of episodes of type I hepatorenal syndrome have a precipitating factor. Therefore prevention of this factor is probably the best treatment of type I hepatorenal syndrome. In one study, albumin infusion (1.5 g/kg body weight on the first day plus 1 g/kg body weight on the third day) in patients with ascites and SBP decreased the incidence of type I hepatorenal syndrome from 33% to 10% and increased survival. This beneficial effect was especially observed in those patients with serum bilirubin of more than 4 mg/dL, creatinine of more than 1 mg/dL, or BUN of more than 30 mg/dL. Long-term primary prophylaxis of SBP with norfloxacin in patients with cirrhosis with advanced liver disease decreased the 1-year probability of developing hepatorenal syndrome from 41% to 28% and increased 1-year survival from 48% to 60%.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

#### BIBLIOGRAPHY

1. Akriavidis EA, Runyon BA. Utility of an algorithm in differentiating spontaneous from secondary bacterial peritonitis. *Gastroenterology* 1990;98:127-33.
2. Angeli P, Volpin R, Gerunda G, et al. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. *Hepatology* 1999;29:1690-7.
3. Ariza X, Castellote J, Lora-Tamayo J, et al. Risk factors for resistance to ceftriaxone and its impact on mortality in community, healthcare and nosocomial spontaneous bacterial peritonitis. *J Hepatol* 2012;56:825-32.
4. Bernardi M, Caraceni P, Navickis RJ, et al. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. *Hepatology* 2012;55:1172-81.
5. Chiva M, Guarner C, Peralta C, et al. Intestinal oxidative mucosal damage and bacterial translocation in cirrhotic rats. *Eur J Gastroenterol Hepatol* 2003;15:145-59.
6. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010;53:397-417.
7. Fernandez J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology* 2007;133:818-24.
8. Fernandez J, Ruiz del Arbol L, Gomez C, et al. Norfloxacin versus ceftriaxone in the prevention of bacterial infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology* 2006;131:1049-56.
9. Guarner C, Sola R, Soriano G, et al. Risk of a first community-acquired spontaneous bacterial peritonitis in cirrhotics with low ascitic fluid protein levels. *Gastroenterology* 1999;117:414-9.

10. Krag A, Wiest R, Albillos A, et al. The window hypothesis: haemodynamic and non-haemodynamic effects of beta-blockers improve survival of patients with cirrhosis during a window in the disease. *Gut* 2012;61:967–9.
11. Planas R, Montoliu S, Balleste B, et al. Natural history of patients hospitalized for the management of cirrhotic ascites. *Clin Gastroenterol Hepatol* 2006;4:1385–94.
12. Poca M, Concepcion M, Casas M, et al. Role of albumin treatment in patients with spontaneous bacterial peritonitis. *Clin Gastroenterol Hepatol* 2012;10:209–15.
13. Ricart E, Soriano G, Novella MT, et al. Amoxicillin-clavulanic acid versus cefotaxime in the therapy of bacterial infections in cirrhotic patients. *J Hepatol* 2000;32:596–602.
14. Rossle M, Ochs A, Gulberg V, et al. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. *N Engl J Med* 2000;342:1701–7.
15. Runyon BA. Low-protein-concentration ascitic fluid is predisposed to spontaneous bacterial peritonitis. *Gastroenterology* 1986;91:1343–6.
16. Runyon BA. 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;57:1651–3.
17. Runyon BA, Montano AA, Akriviadis EA, et al. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. *Ann Intern Med* 1992;117:215–20.
18. Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut* 2007;56:1310–6.
19. Sanyal AJ, Boyer T, Garcia-Tsao G, et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. *Gastroenterology* 2008;134:1360–8.
20. Singh V, Dhungana SP, Singh B, et al. Midodrine in patients with cirrhosis and refractory or recurrent ascites: a randomized pilot study. *J Hepatol* 2012;56:348–54.

**Website**

Runyon BA. Management of adult patients with ascites due to cirrhosis: update 2012. AASLD Practice Guideline. <http://www.aasld.org/practiceguidelines/Documents/ascitesupdate2013.pdf> [Accessed September 22, 2014].

# LIVER ABSCESS

Jorge L. Herrera, MD, Christopher D. Knudsen, DO

## 1. What are the two major categories of liver abscess?

There are two types of liver abscess, pyogenic and amebic. Pyogenic abscesses are formed from infections involving either aerobic or anaerobic gram-negative or gram-positive bacteria, or from fungal infections. Amebic abscesses result from infection with *Entamoeba histolytica*. Differentiation between the two types of abscess is important because treatment management differs dramatically.

## 2. Describe the clinical features of pyogenic liver abscess.

Historically patients were younger individuals; however, in recent years there has been a shift toward older male patients. The prevalence has also been increasing as a result of more instrumentation of the biliary tract and higher numbers of diabetes and liver transplantation, both of which are risk factors. The clinical findings are nonspecific and consist of low-grade fevers, malaise, anorexia, weight loss, and right upper quadrant pain. *Low-grade fevers can be absent in up to 30% of cases.* Only 37% present with the classic findings of fever and right upper quadrant tenderness, reinforcing the nonspecific nature of signs and symptoms. Diaphragmatic irritation can result in referred pain to the right shoulder, cough, or hiccups. Because of the subacute presentation, the mean duration of symptoms before hospital admission is approximately 26 days.

## 3. What are the clinical features of amebic liver abscess?

Amebic abscess are 10 times more common in men as in women. Within the United States this predominantly affects young Hispanic male migrants from affected areas or travelers to developing countries. There is also a higher prevalence in the western and southeastern United States. Symptoms usually develop rather quickly, typically 2 to 4 weeks after infection. Fever is present 85% of the time. Abdominal pain is typically well localized to the right upper quadrant. If there is involvement of the diaphragmatic surface of the liver, this may lead to right-sided pleural pain, referred shoulder pain, cough, or hiccups. Gastrointestinal symptoms occur in 10% to 30% of patients and include nausea, vomiting, abdominal cramping, distention, diarrhea, and constipation. However, concurrent hepatic abscess and amebic dysentery are unusual.

## 4. What laboratory features are distinctive in patients with liver abscess?

Results of routine laboratory tests are not diagnostic for pyogenic or amebic liver abscess. Leukocytosis, normocytic anemia, and elevated c-reactive protein and erythrocyte sedimentation rate are common. More than 90% of patients have a more pronounced elevation in alkaline phosphatase compared with aspartate aminotransferase and alanine aminotransferase. Hyperbilirubinemia is seen with biliary involvement and less common in those with cryptogenic abscess. Hypoalbuminemia is common and a value of less than 2 g/dL carries a poor prognosis. Blood cultures are positive in less than 50% of patients with pyogenic abscess and 75% to 90% of aspirates from the abscesses are positive for bacteria.

## 5. What are the most common sources of pyogenic liver abscess?

Biliary tract disease is the most common source of pyogenic liver abscess, accounting for 35% of cases. Most abscesses related to biliary disease result from cholangitis or acute cholecystitis. This can occur through infectious spread to the liver from the bile duct or along a penetrating vessel. Abscesses have also been shown to arise as a late complication of endoscopic sphincterotomy or surgical biliary-intestinal anastomosis. Malignant tumors of the pancreas, common bile duct, and ampulla account for 10% to 20% of hepatic abscesses originating in the biliary tree. Parasitic invasion of the biliary tree by roundworms or flukes can also lead to biliary infection and hepatic abscess. Abscesses occurring from a biliary source tend to be multiple and small in size, involving both lobes of the liver.

Less commonly, pyogenic abscess can occur as a complication of bacteremia from bacterial seeding through the portal vein from underlying abdominal disease. Abdominal diseases associated with this are diverticulitis, appendicitis, gastrointestinal malignancy, and inflammatory bowel disease, which account for 30% of pyogenic liver abscesses. Up to 40% of cases of pyogenic liver abscess have no obvious source of infection and are defined as *cryptogenic*. Abdominal disease causes seeding through the portal vein, resulting in abscess involving the right lobe of the liver because most of the portal vein flow goes through the right lobe. Approximately 15% of liver abscesses arise by direct extension from a contiguous source, such as a subphrenic abscess or empyema of the gallbladder. Pyogenic infection may be carried to the liver in hepatic arterial blood flow from distant localized infections, such as endocarditis or severe dental disease.

## 6. List the organisms that commonly cause pyogenic liver abscess.

Numerous bacteria have been found to cause liver abscesses. Currently the most common are gram-negative organisms occurring 50% to 70% of the time. *Escherichia coli*, which was once the most common aerobic gram-negative bacteria cultured, has now been overtaken by *Klebsiella pneumoniae* with higher prevalence in both Asian and Western countries, most commonly in those with underlying diabetes or metastatic complications. Aerobic gram-positive organisms account for approximately 25% of infections and up to 50% of cases are caused by anaerobes. However, recent reports suggest that aerobes are becoming a more common cause of abscess than anaerobes (Table 30-1). Fungal abscesses have also been found in immunocompromised individuals and those with hematologic malignancies.

**Table 30-1.** Bacteriology of Pyogenic Liver Abscess

GRAM-NEGATIVE AEROBES (50% - 70%)	GRAM-POSITIVE AEROBES (25%)	ANAEROBES (40% - 50%)
<i>Escherichia coli</i>	<i>Streptococcus faecalis</i>	<i>Fusobacterium nucleatum</i>
<i>Klebsiella</i> sp.	β Streptococci	<i>Bacteroides</i> sp.
<i>Proteus</i> sp.	α Streptococci	<i>Bacteroides fragilis</i>
<i>Enterobacter</i> sp.	Staphylococci	<i>Peptostreptococcus</i> sp.
<i>Serratia</i> sp.	<i>Streptococcus milleri</i>	<i>Actinomyces</i> sp.
<i>Morganella</i> sp.	<i>Clostridium</i> sp.	
<i>Actinobacter</i> sp.		
<i>Pseudomonas</i> sp.		

## 7. Do negative cultures from an abscess aspirate indicate a nonpyogenic abscess?

Although aspirated cultures are usually positive 75% to 90% of the time, a negative culture can occur with improper handling or prior antibiotic therapy. Proper collection and culture techniques are important for growing anaerobic organisms. Culture material should be transported to the laboratory immediately in the same syringe used for aspiration to avoid exposure to the air. Never submit swabs for culture of liver abscess. All aspirated material should be cultured for aerobic, anaerobic, and microaerophilic organisms. It is common for anaerobic organisms to require a week or more before they can be identified by culture media. For this reason, a Gram stain of the aspirate is of paramount importance.

## 8. What is the pathogenesis of amebic abscess?

Ingestion of the *Entamoeba histolytica* cysts from fecal-contaminated food or water initiates infection. Excystation then occurs in the intestinal lumen, producing trophozoites that use galactose and N-acetyl-D-galactosamine (Gal/GalNAc)-specific lectin to adhere to the colonic mucin layer and leading to colonization. Approximately 90% of the time trophozoites aggregate in the intestinal mucin layer and form new cysts, resulting in a self-limited asymptomatic infection. However, 10% of the time Gal/GalNAc-specific lectin causes lysis of the colonic epithelium and invasion of the colon by trophozoites. Colitis is then worsened by activation of the host immune system leading to up-regulation of nuclear factor kappa B, lymphokines, and neutrophils. Intestinal epithelium invasion leads to hematogenous dissemination and eventual liver abscess less than 1% of the time.

## 9. What abnormalities can be detected on standard radiologic studies of patients with liver abscess?

A chest radiograph may be abnormal in 50% to 80% of patients with liver abscess. Right lower lobe atelectasis, right pleural effusion, and an elevated right hemidiaphragm may be clues to the presence of a liver abscess. Perforation of a pyogenic liver abscess into the thoracic cavity may result in empyema. Plain abdominal radiographs demonstrate air within the abscess cavities in 10% to 20% of cases. Gastric displacement caused by enlargement of the liver also may be seen. These features are not sensitive for the diagnosis of liver abscess.

## 10. Which imaging studies should be obtained in evaluating a suspected liver abscess?

- Ultrasound (US)
- Computed tomography (CT)
- Magnetic resonance imaging (MRI)

Imaging results are similar for pyogenic and amebic abscess, with US and CT being the most common initial imaging modalities used. US is noninvasive, readily available, and highly accurate, with a sensitivity of 80% to 90%. It is the preferred modality to distinguish cystic from solid lesions and in most patients is more accurate than CT scanning for visualizing the biliary tree. US, however, is operator dependent and

its accuracy may be affected by the patient's habitus or overlying gas. CT is also very sensitive and abscesses are usually described as hypodense. A rim of contrast enhancement can be seen in less than 20% of cases. CT is also able to detect gas in the abscess and the location of the abscess related to adjacent structures. It also provides an assessment not only of the liver but also of the entire peritoneal cavity, which may provide information about the primary lesions causing the liver abscess. MRI does not add much to the sensitivity of CT scanning. Abscesses have low signal intensity of T1-weighted images and high signal intensity on T2-weighted images with enhancement using gadolinium because pyogenic liver abscess avidly takes up gallium. Amebic abscesses, however, tend to concentrate gallium only in the periphery of the abscess cavity. In general, scintigraphy is the least helpful of the scanning modalities.

#### 11. What areas of the liver are usually affected by hepatic abscess?

Right lobe only	60% of patients
Both lobes	20%-30% of patients
Left lobe only	5%-20% of patients

#### 12. How can the location, size, and number of liver abscesses help to determine the source?

- Pyogenic liver abscesses (source determines location and distribution):
  - Biliary source tends to present with bilateral lobar involvement.
  - Septic emboli tend to be solitary, predominantly found in right lobe (portal vein flow preferentially supplies the larger right liver lobe).
  - Contiguous source tends to be solitary and localized to just one lobe.
- Amebic liver abscesses tend to be solitary, large, and preferentially found in the right lobe. With amebic colitis, the amebae breach the mesenteric venous system through the cecum and right colon. The right lobe of the liver is much larger than the left and receives the majority of the mesenteric-portal blood flow, hence the predilection for amebic abscess to localize in the right lobe. Abscesses located in the dome of the liver or complicated by a bronchopleural fistula are typically amebic in origin.

#### 13. When should a hepatic abscess be aspirated?

- Hepatic abscesses should be aspirated if they are thought to be pyogenic and not amebic. Patients with multiple abscesses, coexistent biliary disease, or an intraabdominal inflammatory process are more likely to have a pyogenic abscess. In such patients, aspiration under US guidance with Gram stain and culture helps to guide antibiotic selection.
- Aspiration of amebic abscesses should be considered under the following circumstances:
  - When pyogenic abscess or secondary infection of an amebic abscess cannot be excluded
  - When the patient does not respond after 5 to 7 days of adequate therapy for amebic liver abscess
  - When the abscess is very large, usually greater than 5 cm, or in the left lobe, which are risks for rupture and severe pain

#### 14. In what situation should an amebic liver abscess be treated by surgical drainage?

When the amebic abscess is located in the left lobe of the liver, inaccessible to needle drainage, or if there is no dramatic response to therapy within the first 24 to 48 hours, surgical drainage should be performed. Complications of left-lobe amebic abscess, such as cardiac tamponade, are associated with high mortality and require prompt intervention to prevent their occurrence. Laparoscopic drainage is the preferred approach because this has been shown to have shorter surgery time, less blood loss, faster recovery times, and shorter hospital stays when compared with open surgical drainage.

#### 15. Does aspiration of an amebic hepatic abscess yield diagnostic material in most patients?

No. Trophozoites are found in less than 20% of aspirates. Although classically the contents of amebic abscess are described as "anchovy paste" in appearance, in practice most aspirated material does not conform to this description. The contents of an amebic abscess are typically odorless. Foul-smelling aspirates or a positive Gram stain should suggest a pyogenic abscess or secondarily infected amebic abscess.

#### 16. How often is the biliary tree involved in patients with amebic liver abscess?

Bile is lethal to amebae; thus infection of the gallbladder and bile ducts does not occur. In patients with a large amebic or pyogenic abscess, compression of the biliary system may result in jaundice, but cholangitis occurs only with secondary bacterial infection.

#### 17. How can the diagnosis of an amebic abscess be confirmed?

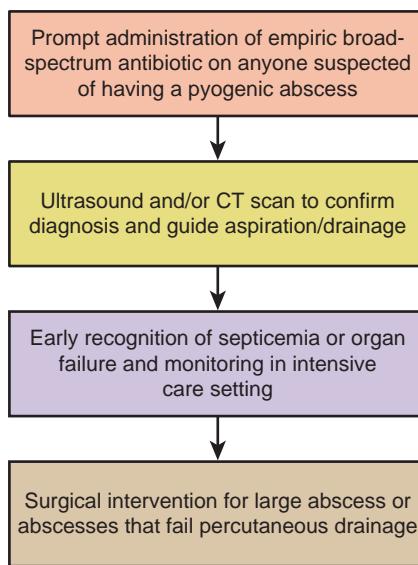
Amebic abscesses are best differentiated from pyogenic abscesses by serologic tests:

Indirect hemagglutination assay (IHA)	Gel diffusion precipitin (GDP)
Indirect immunofluorescence	Complement fixation (CF)
Counterimmunolectrophoresis	Latex agglutination
Immunoelectrophoresis	Enzyme-linked immunosorbent assay

Serologic tests are positive only in patients with invasive amebiasis, such as hepatic abscess or amebic colitis. They are negative in asymptomatic carriers. With the exception of CF, these tests are highly sensitive (95%-99%). The IHA is extremely sensitive and a negative test excludes the diagnosis; a titer greater than 1:512 is present in almost all patients with invasive disease. IHA, however, remains positive for many years, and a positive result may indicate prior infection. GDP titers usually become negative 6 months after the infection and this is the test of choice for patients from endemic areas with prior exposure to amebiasis. A high GDP titer in a patient with hepatic abscess suggests an amebic abscess, even if the patient has a prior history of invasive amebiasis. In general, the choice of serologic tests depends on availability and epidemiologic considerations.

#### 18. Describe the treatment for pyogenic liver abscess.

A combination of systemic antibiotics and percutaneous drainage has become the treatment of choice for the management of pyogenic liver abscess. Treatment is based on the size of the abscess. Abscesses smaller than 3 to 5 cm can be treated with antibiotics alone. Antibiotic coverage needs to cover against anaerobes, gram-negative aerobes, and enterococci. Aminoglycoside and ampicillin should be given when a biliary source is suspected, and a third- or fourth-generation cephalosporin plus metronidazole or clindamycin should be used to cover anaerobes if a colonic source is suspected. Vancomycin is a good choice for enterococcus coverage. Intravenous (IV) antibiotics should be continued for at least 2 weeks and then orally for up to 6 weeks. If the abscess is greater than 3 to 5 cm or the patient is not responding to antibiotics alone, percutaneous drainage should be done. Percutaneous image-guided drainage has been shown to be equally effective, with either continuous catheter drainage or intermittent needle aspiration. Surgical drainage should be considered in any patient with no clinical response after 4 to 7 days of drainage, multiple large or loculated abscesses, ruptured abscesses, or intraabdominal disease (Figure 30-1). The combination of percutaneous drainage with IV antibiotics results in a 76% cure rate, compared with 65% for antibiotics alone and 61% for surgery alone. Recurrence is more common in those with underlying biliary disease compared with those who have diabetes or cryptogenic cause.



**Figure 30-1.** Algorithm for pyogenic abscess.

#### 19. Describe the treatment for amebic liver abscess.

The only medication shown to be effective for extraintestinal amebiasis is metronidazole. The dosage is 750 mg tid for 10 days. Response to treatment occurs within 96 hours. Parasites persist in the intestine 40% to 60% of the time in those receiving metronidazole, which is why, following treatment with metronidazole, patients should be given an oral luminal amebicide such as iodoquinol 650 mg tid for 20 days, diloxanide furoate 500 mg tid for 10 days, or paromomycin 25 to 35 mg/kg tid for 7 to 10 days to prevent recurrence. Metronidazole and paromomycin should not be given together because diarrhea is a common side effect of paromomycin, making it difficult to assess the patient's response to therapy. Drainage of the abscess should be considered in patients who have no clinical response to drug therapy within 5 to 7 days or those with a high risk of rupture, defined by cavity size more than 5 cm or lesions in the left lobe. Surgical drainage is done only when the abscess is inaccessible to needle drainage or no benefit is seen following 4 to 5 days of combined medical and percutaneous drainage therapy.

## 20. List the potential complications of pyogenic liver abscess.

Untreated, patients with pyogenic liver abscess have a mortality rate of 100%. Potential complications include rupture into the peritoneal cavity, leading to subphrenic, perihepatic, or subhepatic abscess or peritonitis. Rupture can also occur into the pleural space, leading to empyema, whereas rupture into the pericardium can lead to pericarditis and tamponade. Metastatic septic emboli can occur in 10% of cases, involving the lungs, brain, and eyes.

## 21. List the potential complications of amebic liver abscess.

Complications of amebic liver abscess are similar to those of pyogenic liver abscess. Because of the close proximity to the diaphragm, rupture into the pleural space can occur, which can lead to empyema. This can then spread farther, producing lung abscess or bronchopleural fistula. Because abscesses are mostly seen in the right lobe, pericardial extension is only seen in 1% to 2% of cases and is associated with patients who have left-lobe involvement. A serous pericardial effusion may indicate impending rupture. Constrictive pericarditis occasionally follows suppurative amebic pericarditis. Brain abscess from hematogenous spread has also been reported.

## 22. What is the prognosis for patients with liver abscess?

The prognosis depends on the rapidity of diagnosis and the underlying illness. Patients with amebic liver abscess generally do well with appropriate treatment morbidity, and mortality rates are 4.5% and 2.2%, respectively, in recent series. Response to treatment is prompt and dramatic. Healing of the abscess leads to residual scar tissue associated with subcapsular retraction. Occasionally, in patients with large abscess, a residual cavity surrounded by fibroconnective tissue may persist.

The mortality rate associated with pyogenic liver abscess has been reduced to 5% to 10% with prompt recognition and adequate antibiotic therapy and is highest in patients with multiple abscesses. Mortality is highly dependent on the underlying disease process. Morbidity remains high at 50%, primarily because of the complexity of therapy and the need for prolonged drainage.

## 23. Is a vaccine against amebiasis feasible?

Vaccination would be beneficial in improving health, especially in children of developing countries. Human immunity has been shown to be linked to intestinal immunoglobulin A against Gal/GalNAc-specific lectin. The clonal population structure of *E. histolytica* and, specifically, the high degree of sequence conservation of the Gal/GalNAc-specific lectin, suggests that a vaccine could be broadly protective. However, development has been hampered because natural infection does not result in long-term immunity.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

- Akgun Y, Tacyildiz IH, Celik Y. Amebic liver abscess: changing trends over 20 years. *World J Surg* 1999;23:102–6.
- Block MA. Abscesses of the liver (other than amebic). In: Haubrich WS, Schaffner F, Berk JE, editors. *Bockus gastroenterology*. 5th ed. Philadelphia: WB Saunders; 1995. p. 2405–27.
- Chen W, Chen CH, Chiu KL, et al. Clinical outcome and prognostic factors of patients with pyogenic liver abscess requiring intensive care. *Crit Care Med* 2008;36:1184–8.
- Cheng H, Chang W, et al. Long-term outcome of pyogenic liver abscess factors related with abscess recurrence. *J Clin Gastroenterol* 2008;42:1110–5.
- Chou FF, Sheen-chen SM, Chen YS, et al. Single and multiple pyogenic liver abscesses: clinical course, etiology and results of treatment. *World J Surg* 1997;21:384–9.
- Chung RT, Friedman LS. Liver abscess and bacterial, parasitic, fungal and granulomatous liver disease. In: Slesinger MH, Fordtran JS, editors. *Gastrointestinal disease: pathophysiology, diagnosis, management*. 7th ed. Philadelphia: WB Saunders; 2002. p. 1343–73.
- Chung YFA, Tan YM, et al. Management of pyogenic liver abscesses—percutaneous or open drainage? *Singapore Med J* 2007;48:1158–65.
- Congly S, Aziz A, et al. Amoebic liver abscess in USA: a population-based study of incidence, temporal trends and mortality. *Liver Int* 2011;31:1191–8.
- Derici H, Tansug T, Reyhan E, et al. Acute intraperitoneal rupture of hydatid cysts. *World J Surg* 2006;30:1879–83.
- Felice C, Di Perri G, et al. Outcome of hepatic amebic abscesses managed with three different therapeutic strategies. *Dig Dis Sci* 1992;37:240–7.
- Ferraioli G, Garlashelli A, Zanaboni D, et al. Percutaneous and surgical treatment of pyogenic liver abscesses: observation over a 21-year period in 148 patients. *Dig Liver Dis* 2008;40:697–8.
- Foo N, Chen K, et al. Characteristics of pyogenic liver abscess patients with and without diabetes mellitus. *Am J Gastroenterol* 2010;105:328–35.
- Haque R, Houston CD, et al. Amebiasis. *N Engl J Med* 2003;348:1565–72.
- Heneghan H, Healy N, et al. Modern management of pyogenic hepatic abscess: a case series and review of the literature. *BMC Res Notes* 2011;4:80.
- Kim A, Chung R. Bacterial, parasitic, and fungal infections of the liver, including liver abscess. In: Slesinger MH, Fordtran JS, editors. *Gastrointestinal and liver disease*. 9th ed. Philadelphia: WB Saunders; 2010. p. 1351–69.
- Lederman ER, Crum NF, et al. Pyogenic liver abscess with a focus on *Klebsiella pneumonia* as a primary pathogen: an emerging disease with unique clinical characteristics. *Am J Gastroenterol* 2005;100:322–31.

17. Lodhi S, Sarwari A, et al. Features distinguishing amoebic from pyogenic liver abscess: a review of 577 adult cases. *Trop Med Int Health* 2004;9:718–23.
18. Meddings L, Myers R, et al. A population-based study of pyogenic liver abscesses in the United States: incidence, mortality, and temporal trends. *Am J Gastroenterol* 2010;105:117–24.
19. Monroe LS. Gastrointestinal parasites. In: Jaubrich WS, Schaffner F, Berk JE, editors. *Bockus gastroenterology*. 5th ed. Philadelphia: WB Saunders; 1995. p. 3123–34.
20. Ng FH, Wong WM, Wong BC, et al. Sequential intravenous/oral antibiotic vs. continuous intravenous antibiotic in the treatment of pyogenic liver abscess. *Aliment Pharmacol Ther* 2002;16:1083–90.
21. Rajak CL, Gupta S, Jain S, et al. Percutaneous treatment of liver abscesses: needle aspiration versus catheter drainage. *ARJ Am J Roentgenol* 1998;170:1035–9.
22. Setto RK, Rockey DC. Pyogenic liver abscess: changes in etiology, management and outcome. *Medicine* 1996;75:99–113.
23. Tan YM, Chung AY, Chow PK, et al. An appraisal of surgical and percutaneous drainage for pyogenic liver abscesses larger than 5 cm. *Ann Surg* 2005;241:485–90.
24. Yu S, Ho S, et al. Treatment of pyogenic liver abscess: prospective randomized comparison of catheter drainage and needle aspiration. *Hepatology* 2004;39:932–8.

**Websites**

American Association for the Study of Liver Diseases. <http://www.aasld.org/> [Accessed September 22, 2014].

# INHERITABLE FORMS OF LIVER DISEASE

Bruce R. Bacon, MD

## HEMOCHROMATOSIS

### 1. How do we classify the various iron-loading disorders in humans?

The usual way to classify iron-overload syndromes is to distinguish between hereditary hemochromatosis (HH), secondary iron overload, and parenteral iron overload.

- HH results in increased iron absorption from the gut, with preferential deposition of iron in the parenchymal cells of the liver, heart, pancreas, and other endocrine glands. Most HH (approximately 85% to 90%) is found in patients who are homozygous for the C282Y mutation found in *HFE*, the gene for hemochromatosis. Over the past several years, however, mutations in other genes have been found that can lead to iron overload. These include mutations in transferrin receptor-2 (TfR2), ferroportin, hemojuvelin, and hepcidin.
- In *secondary iron overload*, some other stimulus causes the gastrointestinal tract to absorb increased amounts of iron. Here, the increased absorption of iron is caused by an underlying disorder rather than by an inherited defect in regulation of iron absorption. Examples include various anemias caused by ineffective erythropoiesis (e.g., thalassemia, aplastic anemia, red cell aplasia, and some patients with sickle cell anemia), chronic liver disease, and, rarely, excessive intake of medicinal iron.
- In *parenteral iron overload*, patients have received excessive amounts of iron as either red blood cell transfusions or iron-dextran given parenterally. In patients with severe hypoplastic anemias, red blood cell transfusion may be necessary. Over time, patients become significantly iron loaded. Unfortunately, some physicians give iron-dextran injections to patients with anemia that is not due to iron deficiency; such patients can become iron loaded. Parenteral iron overload is always iatrogenic and should be avoided or minimized. In patients who truly need repeated red blood cell transfusions (in the absence of blood loss), a chelation program with deferoxamine should be initiated to prevent toxic accumulation of excessive iron.

### 2. What are neonatal iron overload and African iron overload?

- *Neonatal iron overload* is a rare condition that is probably related to an immune-mediated intrauterine hepatic defect. Infants are born with modest increases in hepatic iron and many patients do very poorly; liver transplantation can be lifesaving.
- *African iron overload*, previously called *Bantu hemosiderosis*, was thought to be a disorder in which excessive amounts of iron were ingested from alcoholic beverages brewed in iron drums. Recent studies have suggested that this disorder does have a genetic component and some patients have mutations in ferroportin. Thus black patients may be at risk for developing iron overload from an inherited disease.

### 3. How much iron is usually absorbed per day?

A typical Western diet contains approximately 10 to 20 mg of iron, which usually is found in heme-containing compounds. Normal daily iron absorption is approximately 1 to 2 mg, representing approximately a 10% efficiency of absorption. Patients with iron deficiency, HH, or ineffective erythropoiesis absorb increased amounts of iron (up to 3 to 6 mg/day).

### 4. Where is iron normally found in the body?

The normal adult male contains approximately 4 g of total body iron, which is roughly divided between the 2.5 g of iron in the hemoglobin of circulating red blood cells, 1 g of iron in storage sites in the reticuloendothelial system of the spleen and bone marrow and the parenchymal and reticuloendothelial system of the liver, and 200 to 400 mg in the myoglobin of skeletal muscle.

In addition, all cells contain some iron because mitochondria contain iron both in heme, which is the central portion of cytochromes involved in electron transport, and in iron sulfur clusters, which also are involved in electron transport. Iron is bound to transferrin in both the intravascular and extravascular compartments. Storage iron within cells is found in ferritin and, as this amount increases, in hemosiderin. Serum ferritin is proportional to total body iron stores in patients with iron deficiency or uncomplicated HH and is biochemically different from tissue ferritin.

## 5. Discuss the genetic defect in patients with HH.

In 1996, the gene responsible for hemochromatosis was identified and named *HFE*. *HFE* codes for a major histocompatibility complex (MHC) type 1-like protein that is membrane spanning with a short intracytoplasmic tail, a transmembrane region, and three extracellular alpha loops. A single missense mutation results in loss of a cysteine at amino acid position 282 with replacement by a tyrosine (C282Y), which leads to disruption of a disulfide bridge and thus to the lack of a critical fold in the alpha<sub>1</sub> loop. As a result, *HFE* fails to interact with β<sub>2</sub>-microglobulin (β<sub>2</sub>M), which is necessary to the function of MHC class 1 proteins.

In 1997, it was demonstrated that the *HFE*/β<sub>2</sub>M complex binds to transferrin receptor and is necessary for transferrin receptor-mediated iron uptake into cells. This observation linked *HFE* with a protein of iron metabolism. C282Y homozygosity is found in approximately 85% to 90% of patients with hemochromatosis. A second mutation, whereby a histidine at amino acid position 63 is replaced by an aspartate (H63D), is common but less important in cellular iron homeostasis. A third mutation has been characterized whereby a serine is replaced by a cysteine at amino acid position 65 (S65C). Like H63D, S65C has little effect on iron loading unless it is present as a compound heterozygote with the C282Y mutation. Additional discoveries show that hepcidin, a 25-amino acid peptide, is found to be deficient in patients with hemochromatosis and is considered the iron regulatory hormone. Thus in patients with *HFE* mutations and in those with mutations in *Tfr2*, hemojuvelin, and hepcidin, there is a deficiency of hepcidin production by the liver. Hepcidin in normal amounts interferes with the activity of ferroportin at the basolateral surface of the enterocyte, preventing iron absorption. Thus when there is hepcidin deficiency, there is an increase in iron absorption despite the fact that individuals are in fact iron loaded.

## 6. What are the usual toxic manifestations of iron overload?

In chronic iron overload, an increase in oxidant stress results in lipid peroxidation to lipid-containing components of the cell, such as organelle membranes. This process causes organelle damage. Hepatocellular injury or death ensues with phagocytosis by Kupffer cells. Iron-loaded Kupffer cells become activated, producing profibrogenic cytokines such as transforming growth factor β<sub>1</sub>, which, in turn, activates hepatic stellate cells. Hepatic stellate cells are responsible for increased collagen synthesis and hepatic fibrogenesis.

## 7. What are the most common symptoms in patients with HH?

Currently, most patients are identified by abnormal iron studies on routine screening chemistry panels or by screening family members of a known patient. When identified in this manner, patients typically have no symptoms or physical findings. Nonetheless, it is useful to be aware of the symptoms that patients with more established HH can exhibit. Typically, they are nonspecific and include fatigue, malaise, and lethargy. Other more organ-specific symptoms are arthralgias and symptoms related to complications of chronic liver disease, diabetes, and congestive heart failure.

## 8. Describe the most common physical findings in patients with HH.

The way in which patients come to medical attention determines whether they have physical findings. Currently, most patients at diagnosis have no symptoms and no findings. Thus patients identified by screening tests have no abnormal physical findings. In contrast, physical findings in patients with advanced disease may include grayish or “bronzed” skin pigmentation, typically in sun-exposed areas; hepatomegaly with or without cirrhosis; arthropathy with swelling and tenderness over the second and third metacarpophalangeal joints; and other findings related to complications of chronic liver disease.

## 9. How is the diagnosis of hemochromatosis established?

Patients with abnormal iron studies on screening blood work, any of the symptoms and physical findings of hemochromatosis, or a positive family history of hemochromatosis should have blood studies of iron metabolism either repeated or performed for the first time. These studies include serum iron, total iron-binding capacity (TIBC) or transferrin, and serum ferritin. The transferrin saturation (TS) should be calculated from the ratio of iron to TIBC or transferrin. If the TS is greater than 45% or if the serum ferritin is elevated, hemochromatosis should be strongly considered, especially in patients without evidence of other liver disease (e.g., chronic viral hepatitis, alcoholic liver disease, nonalcoholic steatohepatitis) known to have abnormal iron studies in the absence of significant iron overload.

If iron studies are abnormal, mutation analysis of *HFE* should be performed. If patients are homozygous for the C282Y mutation or compound heterozygotes (C282Y/H63D) and younger than the age of 40 years or in those with normal liver enzymes (alanine aminotransferase and aspartate aminotransferase) and a ferritin level less than 1000 ng/mL, no further evaluation is necessary. Plans for therapeutic phlebotomy can be initiated. In patients older than the age of 40 years or with abnormal liver enzymes or markedly elevated ferritin (greater than 1000 ng/mL), the next step is to perform a percutaneous liver biopsy to obtain tissue for routine histologic examination, including Perls' Prussian blue staining for storage iron and biochemical determination of hepatic iron concentration (HIC). The main purpose for performing a liver biopsy in these individuals is to determine the degree of fibrosis because increased fibrosis has been associated with markedly elevated ferritin levels and elevated liver enzymes. Also, biochemical determination of HIC can be obtained and then from the HIC, the hepatic iron index (HII) can be calculated. Calculation of the HII was more important in the past than it is now because we have genetic testing.

#### **10. Are there genetic tests available for determining non-HFE-linked causes of HH?**

Yes. Diagnostic DNA laboratories have developed assays for hemojuvelin, hepcidin, ferroportin, and transferrin-receptor-2 in addition to HFE mutation analysis.

#### **11. How commonly do abnormal iron studies occur in other types of liver diseases?**

In various studies, approximately 30% to 50% of patients with chronic viral hepatitis, alcoholic liver disease, and nonalcoholic steatohepatitis have abnormal serum iron studies. Abnormalities in serum iron studies in the absence of HH are more commonly seen in hepatocellular than cholestatic liver diseases. Usually, the serum ferritin is abnormal. In general, an elevation in TS is much more specific for HH. Thus if the serum ferritin is elevated and the TS is normal, another form of liver disease may be responsible. In contrast, if the serum ferritin is normal and the TS is elevated, the likely diagnosis is hemochromatosis, particularly in young patients. Differentiation of HH in the presence of other liver diseases is now much easier with the use of genetic testing (HFE mutation analysis for C282Y and H63D).

#### **12. Is computed tomography (CT) or magnetic resonance imaging (MRI) useful in diagnosing hemochromatosis?**

In massively iron-loaded patients, CT and MRI show the liver to be white or black, respectively, consistent with the kinds of changes associated with increased iron deposition. In more subtle and earlier cases, overlap is tremendous, and imaging studies are not useful. Thus in heavily iron-loaded patients, the diagnosis is usually apparent without imaging tests, and in mild or subtler cases, they are unhelpful. CT or MRI is useful only in the patient who is likely to have moderate to severe iron overload but for whom a liver biopsy is either unsafe or refused. Again, this problem is less common with the advent of genetic testing.

#### **13. On liver biopsy, what is the typical cellular and lobular distribution of iron in HH?**

In early HH in young people, iron is found entirely in hepatocytes in a periportal (zone 1) distribution. In heavier iron loading in older patients, iron is still predominantly hepatocellular, but some iron may be found in Kupffer cells and bile ductular cells. The periportal-to-pericentral (zone 1–zone 3) gradient is maintained but may be less distinct in more heavily loaded patients. When patients develop cirrhosis, the pattern is typically micronodular, and regenerative nodules may show less intense iron staining.

#### **14. How useful is HIC?**

Since genetic testing has become readily available, liver biopsy and determinations of HIC and HII are less important. Nonetheless, whenever a liver biopsy is performed in a patient with suspected HH, the quantitative HIC should be obtained. In symptomatic patients, HIC is typically greater than 10,000 mcg/g. The iron concentration threshold for the development of fibrosis is approximately 22,000 mcg/g. Lower iron concentrations can be found in cirrhotic HH with a coexistent toxin, such as alcohol or hepatitis C or B virus. Young people with early HH may have only moderate increases in HIC. In the past, discrepancies in HIC concentration with age were clarified by use of the HII.

#### **15. How is the HII used in diagnosing HH?**

The HII, introduced in 1986, is based on the observation that HIC increases progressively with age in patients with homozygous HH. In contrast, in patients with secondary iron overload or in heterozygotes, there is no progressive increase in iron over time. Therefore the HII was thought to distinguish patients with homozygous HH from patients with secondary iron overload and heterozygotes. The HII is calculated by dividing the HIC (in  $\mu\text{mol}/\text{g}$ ) by the patient's age (in years). A value greater than 1.9 was thought to be consistent with homozygous HH. With the advent of genetic testing, we have learned that many C282Y homozygotes do not have phenotypic expression to the degree that would cause an elevated HII and they will not have increased iron stores. Thus the HII is no longer the gold standard for the diagnosis of HH. The HII is not useful in patients with parenteral iron overload.

#### **16. How do you treat a patient with HH?**

Treatment of HH is relatively straightforward and includes weekly or twice-weekly phlebotomy of 1 unit of whole blood. Each unit of blood contains approximately 200 to 250 mg of iron, depending on the hemoglobin. Therefore a patient who presents with symptomatic HH and who has up to 20 g of excessive storage iron requires removal of more than 80 units of blood, which takes close to 2 years at a rate of 1 unit of blood per week. Patients need to be aware that this treatment can be tedious and prolonged. Some patients cannot tolerate removal of 1 unit of blood per week, and occasionally schedules are adjusted to remove only  $\frac{1}{2}$  unit every other week. In contrast, in young patients who are only mildly iron-loaded, iron stores may be depleted quickly with only 10 to 20 phlebotomies. The goal of initial phlebotomy treatment is to reduce tissue iron stores, not to create iron deficiency. Once the ferritin is less than 50 ng/mL and the TS is less than 50%, the majority of excessive iron stores has been successfully depleted, and most patients can go into a maintenance phlebotomy regimen (1 unit of blood removed every 2 to 3 months).

**17. What kind of a response to treatment can you expect?**

Many patients feel better after phlebotomy therapy has begun, even if they were asymptomatic before treatment. Energy level may improve, with less fatigue and less abdominal pain. Liver enzymes typically improve once iron stores have been depleted. Increased hepatic size diminishes. Cardiac function may improve, and approximately 50% of patients with glucose intolerance are more easily managed. Unfortunately, advanced cirrhosis, arthropathy, and hypogonadism do not improve with phlebotomy.

**18. What is the prognosis for a patient with hemochromatosis?**

Patients who are diagnosed and treated before the development of cirrhosis can expect a normal life span. The most common causes of death in hemochromatosis are complications of chronic liver disease and hepatocellular cancer. Patients who are diagnosed and treated early should not experience any of these complications.

**19. Because hemochromatosis is an inherited disorder, what is the practitioner's responsibility to family members once a patient has been identified?**

Once a patient has been fully identified, all first-degree relatives should be offered screening with genetic testing (HFE mutation analysis for C282Y and H63D) and tests for TS and ferritin. If genetic testing shows that the relative is a C282Y homozygote or a compound heterozygote (C282Y/H63D) and has abnormal iron studies, HH is confirmed. A liver biopsy may not be necessary. Human leukocyte antigen studies are no longer performed.

**20. Should general population screening be done to evaluate for hemochromatosis?**

With the advent of genetic testing, it was suggested that HH may be a good disease for population screening. This was because genetic testing was available, phenotypic expression was easy to determine, there was a long latent period between diagnosis and disease manifestations, and treatment is effective and safe. Several large-scale population studies have been performed and demonstrate that approximately half of C282Y homozygotes have evidence of phenotypic expression with increased iron stores. Thus interest in population screening has waned because many people would be identified with a genetic disorder who do not go on to develop iron overload.

 **$\alpha_1$ -ANTITRYPSIN DEFICIENCY****21. What is the function of  $\alpha_1$ -antitrypsin ( $\alpha_1$ -AT) in healthy people?**

$\alpha_1$ -AT is a protease inhibitor synthesized in the liver. It is responsible for inhibiting trypsin, collagenase, elastase, and proteases of polymorphonuclear neutrophils. In patients deficient in  $\alpha_1$ -AT, the function of these proteases is unopposed. In the lung, this can lead to a progressive decrease in elastin and development of premature emphysema. The liver fails to secrete  $\alpha_1$ -AT, and aggregates of the defective protein are found, leading by unclear means to the development of cirrhosis. More than 75 different protease inhibitor (Pi) alleles have been identified. Pi MM is normal, and Pi ZZ results in the lowest levels of  $\alpha_1$ -AT.

**22. How common is  $\alpha_1$ -AT deficiency?**

$\alpha_1$ -AT deficiency occurs in approximately 1 in 2000 people.

**23. Where is the abnormal gene located?**

The gene is located on chromosome 14 and results in a single amino acid substitution (replacement of glutamic acid by lysine at the 342 position), which causes a deficiency in sialic acid.

**24. What is the nature of the defect that causes  $\alpha_1$ -AT deficiency?**

$\alpha_1$ -AT deficiency is a protein-secretory defect. Normally this protein is translocated into the lumen of the endoplasmic reticulum, interacts with chaperone proteins, folds properly, is transported to the Golgi complex, and then is exported out of the cell. In patients with  $\alpha_1$ -AT deficiency, the protein structure is abnormal because of the deficiency of sialic acid, and the proper folding in the endoplasmic reticulum occurs for only 10% to 20% of the molecules, with resultant failure to export via the Golgi complex and accumulation within the hepatocyte. In one detailed Swedish study,  $\alpha_1$ -AT deficiency of the Pi ZZ type caused cirrhosis in only approximately 12% of patients. Chronic obstructive pulmonary disease was present in 75% of patients, and of these, 59% were classified as having primary emphysema. It is not known why some patients with low levels of  $\alpha_1$ -AT develop liver or lung disease and others do not.

**25. Describe the common symptoms and physical findings of  $\alpha_1$ -AT deficiency.**

Adults with liver involvement may have no symptoms until they develop signs and symptoms of chronic liver disease. Similarly, children may have no specific problems until they develop complications from chronic liver disease. In adults with lung disease, typical findings include premature emphysema, which can be markedly exacerbated by smoking.

**26. How is the diagnosis of  $\alpha_1$ -AT deficiency established?**

It is useful to order  $\alpha_1$ -AT levels and phenotype in all patients evaluated for chronic liver disease because no clinical presentation suggests the diagnosis (apart from premature emphysema). Certain heterozygous states can result in chronic liver disease; for example, SZ as well as ZZ patients can develop cirrhosis. MZ heterozygotes

usually do not develop disease unless they have some other liver condition, such as alcoholic liver disease or chronic viral hepatitis. There are, however, occasional patients who have significant liver disease and no other abnormalities are identified other than MZ heterozygosity. Liver disease resulting from other causes may progress more rapidly.

#### **27. What histopathologic stain is used to diagnose $\alpha_1$ -AT deficiency?**

Periodic acid-Schiff (PAS)-diastase. PAS stains both glycogen and  $\alpha_1$ -AT globules a dark, reddish-purple, and diastase digests the glycogen. Thus, when a PAS-diastase stain is used, the glycogen has been removed by the diastase, and the only positively staining globules are those resulting from  $\alpha_1$ -AT. In cirrhosis, these globules characteristically occur at the periphery of the nodules and can be seen in multiple sizes within the hepatocyte. Immunohistochemical staining also can be used to detect  $\alpha_1$ -AT globules, and electron microscopy can show characteristic globules trapped in the Golgi apparatus.

#### **28. How is $\alpha_1$ -AT deficiency treated?**

The only treatment for  $\alpha_1$ -AT-related liver disease is symptomatic management of complications and liver transplantation. With liver transplantation, the phenotype becomes that of the transplanted liver.

#### **29. What is the prognosis for patients with $\alpha_1$ -AT deficiency? Should family screening be performed?**

The prognosis depends entirely on the severity of the underlying lung or liver disease. Typically, patients who have lung disease do not have liver disease, and those who have liver disease do not have lung disease, although in some patients both organs are severely involved. In patients with decompensated cirrhosis, the prognosis relates largely to the availability of organs for liver transplantation. Patients with transplants typically do fine. Family screening should be performed with  $\alpha_1$ -AT levels and phenotype. This screening is largely for prognostic information; definitive therapy for liver disease, other than liver transplantation, is not available.

### **WILSON DISEASE**

#### **30. How common is Wilson disease?**

Wilson disease has an estimated prevalence of 1 in 30,000 people.

#### **31. Where is the Wilson disease gene located?**

The abnormal gene responsible for Wilson disease, an autosomal recessive disorder, is located on chromosome 13 and recently has been cloned. The gene has homology for the Menkes disease gene, which also results in a disorder of copper metabolism. The Wilson disease gene (called ATP7B) codes for a P-type adenosine triphosphatase, which is a membrane-spanning copper-transport protein. The exact location of this protein within hepatocytes is not definite, but it most likely causes a defect in transfer of hepatocellular lysosomal copper into bile. This defect results in the gradual accumulation of tissue copper with subsequent hepatotoxicity. Unfortunately, there are more than 60 mutations in the Wilson disease gene, and genetic testing has limited usefulness.

#### **32. What is the usual age of onset of Wilson disease?**

Wilson disease is characteristically a disease of adolescents and young adults. Clinical manifestations have not been seen before the age of 5 years. By 15 years of age, almost one-half of the patients have some clinical manifestations of the disease. Rare cases of Wilson disease have been identified in patients in their 40s or 50s and even up into the 80s.

#### **33. Which organ systems are involved in Wilson disease?**

The liver is uniformly involved. All patients with neurologic abnormalities caused by Wilson disease have liver involvement. Wilson disease also can affect the eyes, kidneys, joints, and red blood cells. Thus patients can have cirrhosis, neurologic deficits with tremor and choreic movements, ophthalmologic manifestations such as Kayser-Fleischer rings, psychiatric problems, nephrolithiasis, arthropathy, and hemolytic anemia.

#### **34. What are the different types of hepatic manifestations in Wilson disease?**

The typical patient who presents with symptoms from Wilson disease already has cirrhosis. However, patients can present with chronic hepatitis, and in all young people with chronic hepatitis a serum ceruloplasmin level should be performed as a screening test for Wilson disease. Rarely, patients present with fulminant hepatic failure, which is uniformly fatal without successful liver transplantation. Finally, patients can present early in the disease with hepatic steatosis. As with chronic hepatitis, young patients with fatty liver should be screened for Wilson disease.

#### **35. How is the diagnosis of Wilson disease established?**

Initial evaluation should include measurement of serum ceruloplasmin and, if abnormal, a 24-hour urinary copper level. Approximately 85% to 90% of patients have depressed serum ceruloplasmin levels, but a normal level does not rule out the disorder. If the ceruloplasmin is decreased or the 24-hour urinary copper level is elevated, a liver biopsy should be performed for histologic interpretation and quantitative copper determination. Histologic changes include hepatic steatosis, chronic hepatitis, or cirrhosis. Histochemical staining for copper with rhodamine is not particularly sensitive. Usually, in established Wilson disease, hepatic copper

concentrations are greater than 250 mcg/g (dry weight) and can be as high as 3000 mcg/g. Although elevated hepatic copper concentrations can occur in other cholestatic liver diseases, the clinical presentation allows an easy differentiation between Wilson disease and primary biliary cirrhosis, extrahepatic biliary obstruction, and intrahepatic cholestasis of childhood.

### **36. What forms of treatment are available for patients with Wilson disease?**

The mainstay of treatment has been the copper-chelating drug D-penicillamine. Because D-penicillamine is frequently associated with side effects, trientine also has been used. Trientine is equally efficacious and probably has fewer side effects. Maintenance therapy with dietary zinc supplementation also has been used. Neurologic disorders can improve with therapy. Patients who present with complications of chronic liver disease or with fulminant hepatic failure should be quickly considered for orthotopic liver transplantation.

### **37. Is it necessary to perform family screening in Wilson disease?**

Wilson disease is an autosomal recessive disorder, and all first-degree relatives of the patient should be screened. If the ceruloplasmin level is reduced, a 24-hour urinary copper level should be obtained, followed by a liver biopsy for histologic examination and quantitative copper determination. Genetic testing can be valuable for family screening if genotyping has been done on the proband and is available to family members.

### **38. Compare Wilson disease and HH.**

Both disorders involve abnormal metal metabolism and are inherited as autosomal recessive disorders. The mechanism of tissue damage is probably related to metal-induced oxidant stress for both disorders. In HH, the gene is on chromosome 6, whereas in Wilson disease the abnormal gene is on chromosome 13. HH occurs in approximately 1 in 250 people, but Wilson disease occurs in only approximately 1 in 30,000. The inherited defect in HH causes an increased absorption of iron by the intestine, with the liver a passive recipient of the excessive iron; in contrast, the inherited defect in Wilson disease is in the liver, resulting in decreased hepatic excretion of copper with excessive deposition and subsequent toxicity. Although the liver is affected in both Wilson disease and HH, the other affected organs are variable. In hemochromatosis, the heart, pancreas, joints, skin, and endocrine organs are affected; in Wilson disease, the brain, eyes, red blood cells, kidneys, and bone are affected. Both disorders are fully treatable if diagnosis is made promptly before the development of end-stage complications.

The reader is referred to Chapter 32, where histologic examples of most of the inheritable forms of liver disease discussed in this chapter can be reviewed.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

### **BIBLIOGRAPHY**

1. Bacon BR. Genetic, metabolic, and infiltrative diseases affecting the liver. In: Fauci AS, Braunwald E, Kasper DL, editors. *Harrison's principles of internal medicine*. 17th ed. New York: McGraw-Hill; 2008. p. 1980–3.
2. Bacon BR, Adams PC, Kowdley KV, et al. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011;54:328–43.
3. Bacon BR, Britton RS. Clinical penetrance of hereditary hemochromatosis. *N Engl J Med* 2008;358:291–2.
4. Bacon BR, Olynuk JK, Brunt EM, et al. HFE genotype in patients with hemochromatosis and other liver diseases. *Ann Intern Med* 1999;130:953–62.
5. Bacon BR, Powell LW, Adams PC, et al. Molecular medicine and hemochromatosis: at the crossroads. *Gastroenterology* 1999;116:193–207.
6. Bassett ML, Halliday JW, Powell LW. Value of hepatic iron measurements in early hemochromatosis and determination of the critical iron level associated with fibrosis. *Hepatology* 1986;6:24–9.
7. Crystal RG.  $\alpha_1$ -Antitrypsin deficiency, emphysema, and liver disease: genetics and strategies for therapy. *J Clin Invest* 1990;85:1343–52.
8. Edwards CQ, Griffen LM, Goldgar D, et al. Prevalence of hemochromatosis among 11,065 presumably healthy blood donors. *N Engl J Med* 1988;318:1355–62.
9. Eriksson S, Calson J, Veley R. Risk of cirrhosis and primary liver cancer in alpha1-antitrypsin deficiency. *N Engl J Med* 1986;314:736–9.
10. Feder JN, Gznirke A, Thomas W. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* 1996;13:399–408.
11. Fleming RE, Bacon BR. Orchestration of iron homeostasis. *N Engl J Med* 2005;352:1741–4.
12. Hill GM, Brewer GJ, Prasad AS, et al. Treatment of Wilson disease with zinc. I: oral zinc therapy regimens. *Hepatology* 1987;7:522–8.
13. Hodges JR, Millward-Sadler GH, Barbatis C, et al. Heterozygous MZ alpha1-antitrypsin deficiency in adults with chronic active hepatitis and cryptogenic cirrhosis. *N Engl J Med* 1981;304:557–60.
14. Larsson C. Natural history and life expectancy in severe alpha1-antitrypsin deficiency, Pi Z. *Acta Med Scand* 1978;204:345–51.
15. Niederau C, Fischer R, Sonnenberg A, et al. Survival and causes of death in cirrhotic and noncirrhotic patients with primary hemochromatosis. *N Engl J Med* 1985;313:1256–62.
16. Perlmuter DH. The cellular basis for liver injury in  $\alpha_1$ -antitrypsin deficiency. *Hepatology* 1991;13:172–85.
17. Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: an update (AASLD Practice Guideline). *Hepatology* 2008;47:2089–111.

18. Scheinberg IH, Jaffe ME, Sternlieb I. The use of trientine in preventing the effects of interrupting penicillamine therapy in Wilson disease. *N Engl J Med* 1987;317:209–13.
19. Schilsky ML. Identification of the Wilson disease gene: clues for disease pathogenesis and the potential for molecular diagnosis. *Hepatology* 1994;20:529–33.
20. Sternlieb I. Perspectives on Wilson disease. *Hepatology* 1990;12:1234–9.
21. Stremmel W, Meyerrose KW, Niederau C, et al. Wilson disease: clinical presentation, treatment, and survival. *Ann Intern Med* 1991;15:720–6.
22. Teckman JH. Liver disease in alpha-1 antitrypsin deficiency: current understanding and future therapy. *COPD* 2013;1:35–45.

**Website**

American Association for the Study of Liver Diseases. <http://www.aasld.org> [Accessed September 22, 2014].

# LIVER HISTOPATHOLOGY

Kiyoko Oshima, MD

## LIVER BIOPSY

### 1. Explain the role of liver biopsy.

- Diagnosis: The biopsy is particularly useful in patients with atypical clinical features and coexisting disorders such as steatosis and hepatitis C virus. Indications include abnormal liver tests of unknown cause, multiple parenchymal diseases, fever of unknown cause, and focal and diffuse abnormalities on an imaging study indicating conditions such as amyloidosis or granulomatous diseases.
- Prognosis: Assessing fibrosis to predict prognosis is of particular importance in assessing risk of complications, including hepatocellular carcinoma (HCC).
- Treatment: Develop treatment plans based on histologic analysis. For example, liver biopsy is often obtained to ascertain control of inflammation prior to steroid dose reduction or discontinuation of immunosuppression therapy for autoimmune hepatitis.

### 2. What kind of prebiopsy testing and management of medication are necessary before liver biopsy?

- Measurement of complete blood count, including platelet count, prothrombin time, and international normalized ratio.
- Antiplatelet medication should be discontinued 7 to 10 days prior to biopsy. Warfarin should be discontinued at least 5 days prior to liver biopsy.

### 3. What are contraindications for liver biopsy?

- Absolute: Uncooperative patient, severe coagulopathy, infection of hepatic bed, extrahepatic bile obstruction
- Relative: Ascites, morbid obesity, possible vascular lesion, amyloidosis, hydatid disease

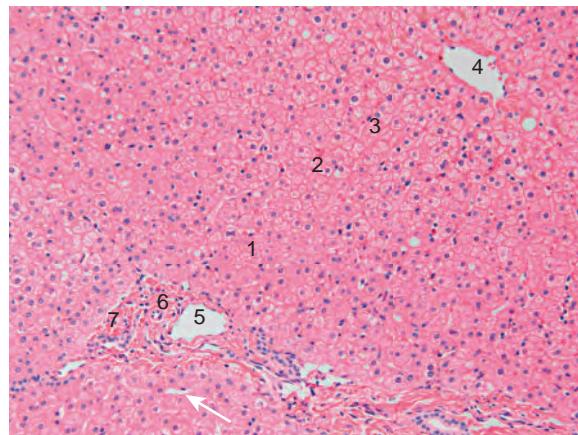
### 4. Describe adequacy of the liver biopsy.

The adequate portal tract number is more than 11, and the minimal requirement is more than 5 portal tracts. The grading and staging accuracy is reduced in biopsies less than 2.0 cm in length. Although a 1.5-cm biopsy specimen may be adequate for assessing many liver diseases, a short specimen may result in a failure to recognize cirrhosis up to 20%.

## HISTOLOGIC AND BASIC PATHOLOGIC FINDINGS

### 5. Describe the normal histology of liver.

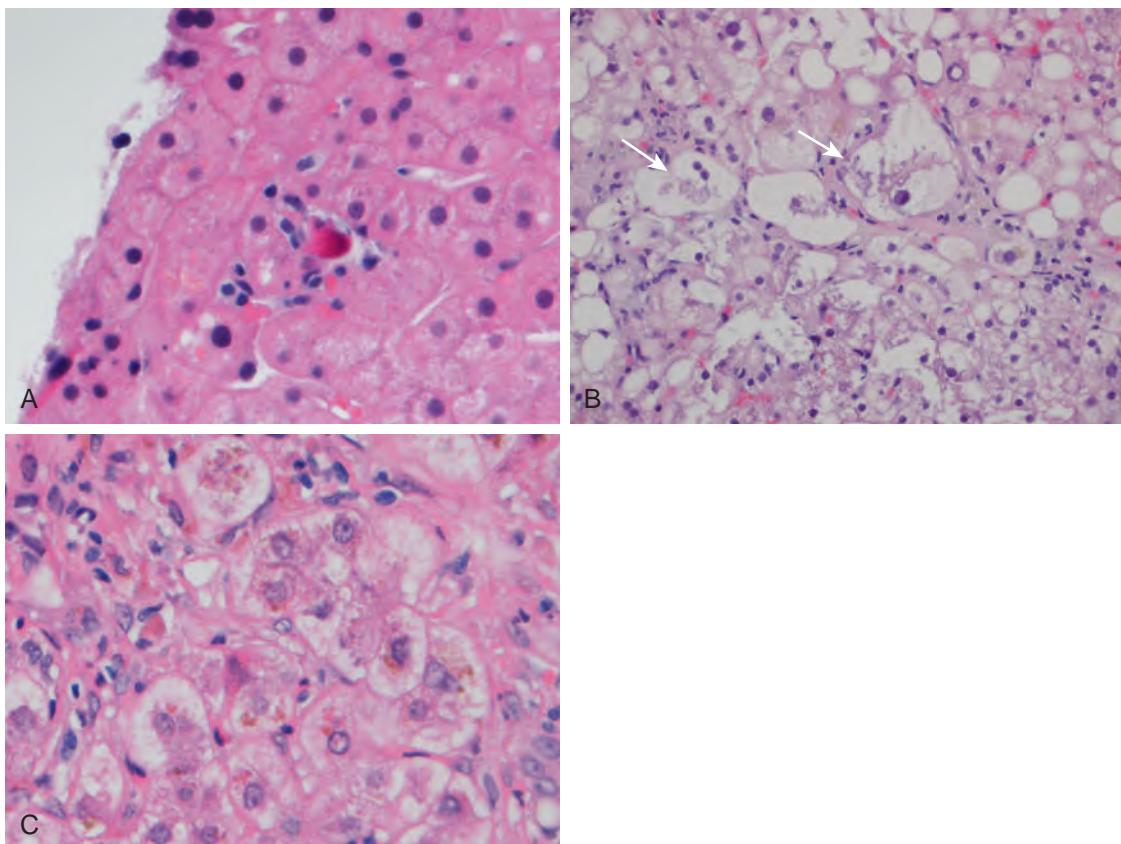
See Figure 32-1.



**Figure 32-1.** Photomicrography of normal liver. 1. Zone 1, 2. Zone 2, 3. Zone 3, 4. Central vein, 5. Portal vein, 6. Hepatic artery, 7. Bile duct, Arrow, Sinusoid. Hematoxylin and eosin stain.

## 6. What kinds of changes can you see as evidence of hepatocytes injury in the liver?

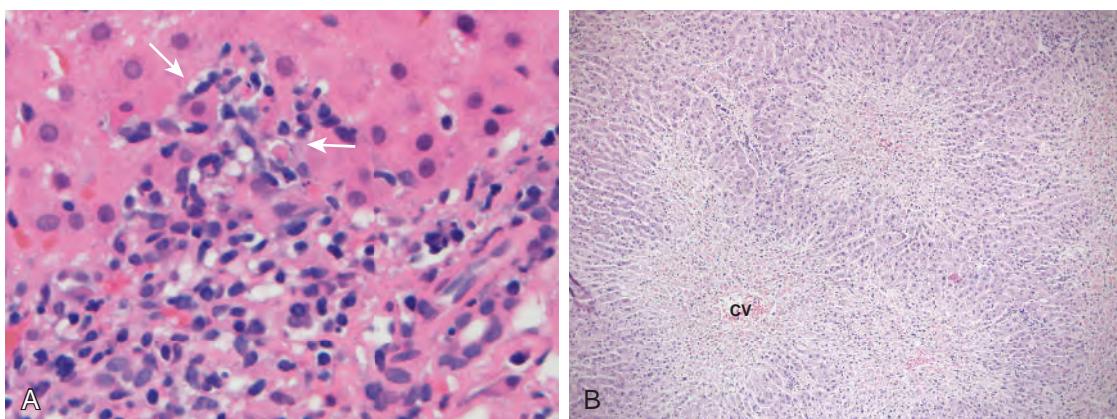
- Acidophil body (Councilman body): Dr. Councilman described acidophil bodies in a yellow fever patient for the first time. Hepatocytes show acidophilic cytoplasm and nucleus are pyknotic or apoptotic. Causes include viral hepatitis, drugs, toxins, and steatohepatitis (Figure 32-2A).
- Balloon cell degeneration: The cytokeratin forms a filamentous support network within hepatocytes. Injury of intermediate filaments in hepatocytes creates swelling and increases in volume with wisps of cytoplasmic material. Causes include steatohepatitis, acute hepatitis, and ischemia (see Figure 32-2B).
- Mallory-Denk body (Mallory hyaline): Irregular ropelike eosinophilic intracytoplasmic strings represent aggregates of cytokeratin intermediate filaments (cytokeratin 8 and 18). Causes include steatohepatitis, drugs (amiodarone, etc.), chronic cholestasis, and Wilson disease (see Figure 32-2B).
- Feathery degeneration: Hepatocyte injury is due to bile salt. Hepatocytes show reticular cytoplasm (see Figure 32-2C).



**Figure 32-2.** Photomicrography of hepatocyte injury. Hematoxylin and eosin stain. **A**, Acidophilic bodies. **B**, Balloon cell degeneration with Mallory-Denk body (arrows). **C**, Feathery degeneration. Bile pigment is noted in hepatocytes. Balloon cell degeneration and feathery degeneration resemble each other, and sometimes they are indistinguishable.

## 7. What histologic patterns of liver cell necrosis are seen?

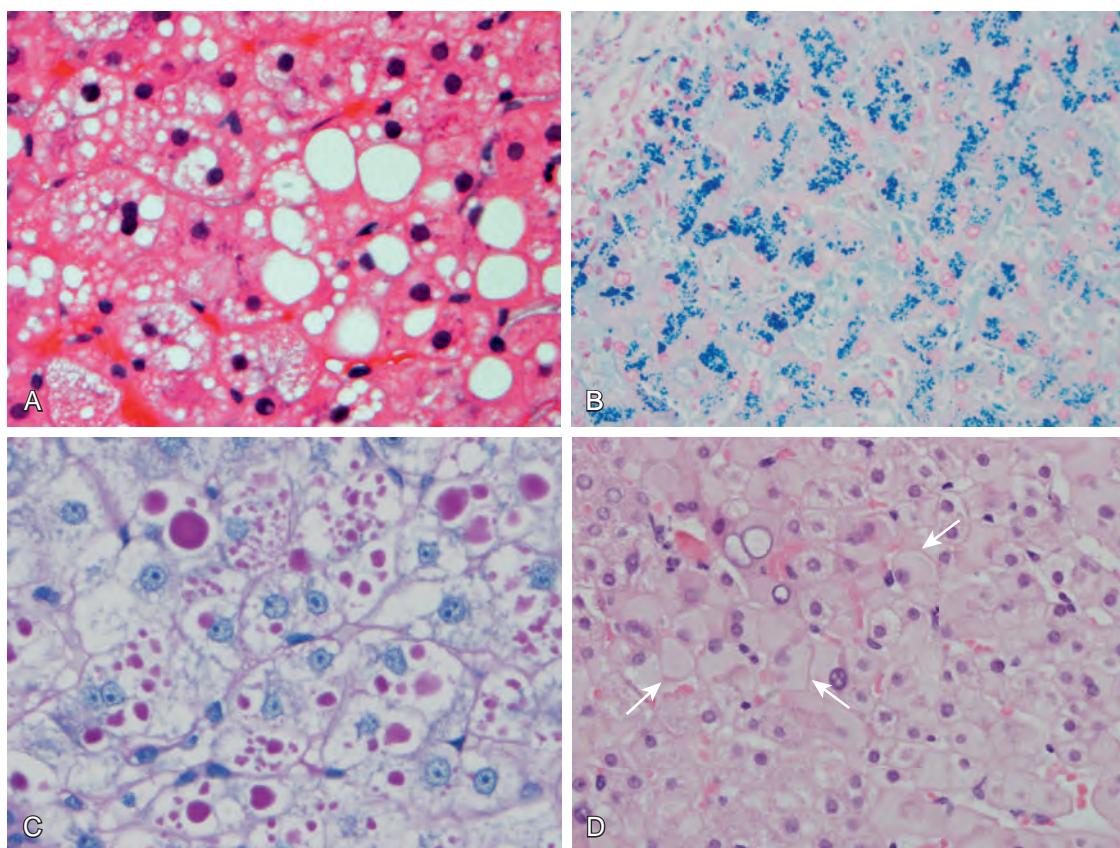
- Single cell necrosis
- Interface activity (piecemeal necrosis): Necrosis of individual hepatocytes at the limiting plate results in portal and periportal fibrosis. Causes include viral hepatitis, autoimmune hepatitis, and drugs (Figure 32-3A).
- Zonal necrosis: Zone 3 necrosis (centrilobular necrosis) is seen in ischemia and drugs (acetaminophen) (see Figure 32-3B).
- Bridging necrosis: Causes for necrosis between central-to-central and portal-to-portal include severe autoimmune hepatitis, ischemia, viruses, and drugs. It results in significant fibrosis and cirrhosis.



**Figure 32-3.** Photomicrography of hepatocyte necrosis pattern. **A**, Interface activity. Necrosis of individual hepatocytes at the limiting plate (arrow). **B**, Zone 3 necrosis (centrilobular necrosis). Zonal necrosis is seen around the central vein.

#### 8. What kind of abnormal material can accumulate in cytoplasm of hepatocytes and what is the cause?

- Steatosis: Accumulation of lipids, primarily triglycerides, in hepatocytes. Normally steatosis is seen in less than 5% of hepatocytes. Causes include ethanol, obesity, diabetes, and drugs (Figure 32-4A).
- Iron: Causes include hemochromatosis, frequent transfusions, and hemolysis (see Figure 32-4B).



**Figure 32-4.** Photomicrography of accumulation of abnormal material in cytoplasm of hepatocytes. **A**, Accumulation of lipid. Microvesicular steatosis (left side) and macrovesicular steatosis (right side). Hematoxylin and eosin stain. **B**, Accumulation of iron in hepatocytes seen in hemochromatosis. Iron stain. **C**,  $\alpha_1$ -antitrypsin globules. Accumulation of abnormal protein in hepatocytes. Periodic acid-Schiff-diastase stain. **D**, Ground-glass hepatocytes. Accumulation of viral particle of hepatitis B virus (arrow). Hematoxylin and eosin stain.

- Copper: Causes include Wilson disease, and chronic cholestasis because bile is the single excretion route for copper.
- $\alpha_1$ -Antitrypsin globules: Accumulation of abnormal protein. Periodic acid-Schiff (PAS)- and periodic acid-Schiff-diastase (PASD)-positive cytoplasmic globules are present in zone 1 hepatocytes (see [Figure 32-4C](#)).
- Ground-glass hepatocytes: The cause is a viral particle of hepatitis B virus, only seen in chronic hepatitis (see [Figure 32-4D](#)).

**9. What kinds of inflammatory cells can be seen in liver biopsy, and what kinds of etiologic factors are suspected?**

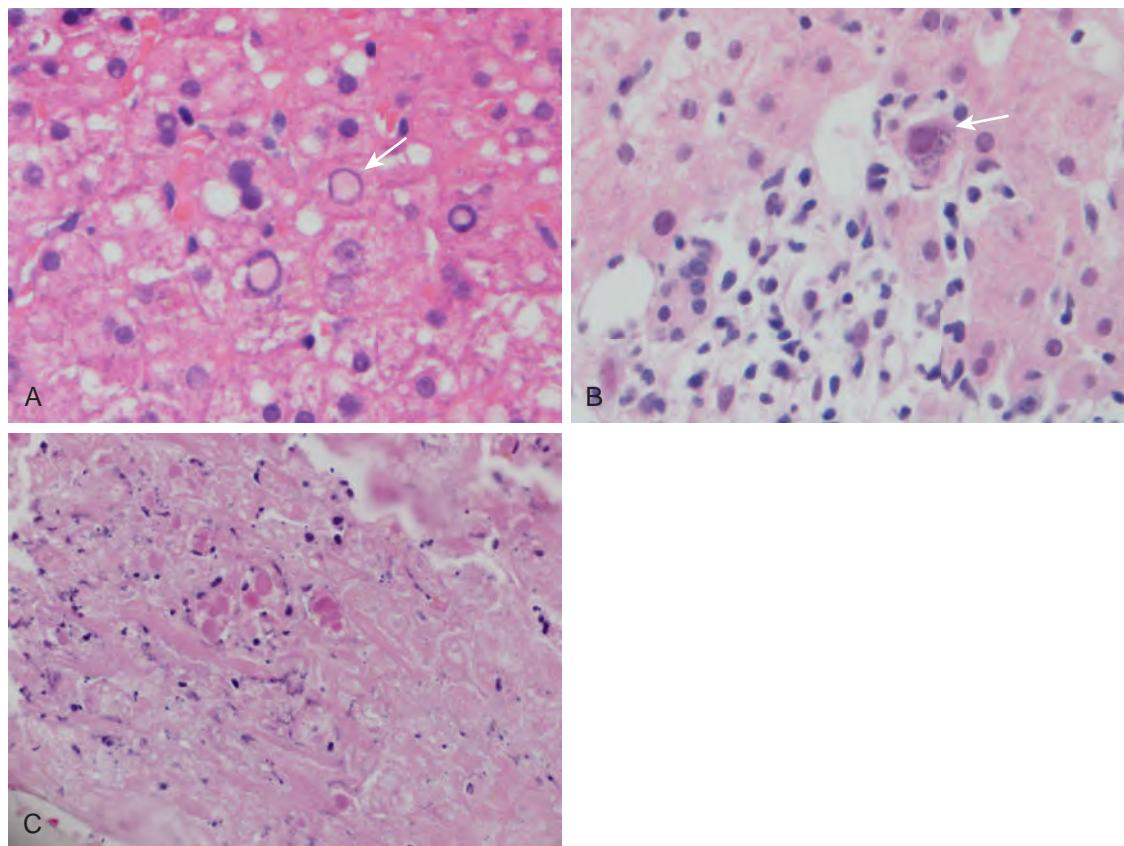
- Neutrophils: Steatohepatitis (alcoholic and nonalcoholic), surgical hepatitis (margination of neutrophil during surgery), drug toxicity
- Eosinophils: Drug toxicity, parasitic infection, autoimmune hepatitis
- Plasma cells: Autoimmune hepatitis
- Lymphocytes: Viral hepatitis, drugs

**10. What kind of pigment can be seen in the liver?**

- Hemosiderin: Golden brown pigment seen in zone 1, red cell degeneration remnants
- Lipofuscin: Brown granules seen in zone 3; “wear and tear” pigment, commonly seen in older adult patients; increased lysosomal activity
- Bile: Green-yellow pigment seen in zone 3; bile is not present in normal liver

**11. What kinds of nuclear inclusions can be seen in hepatocytes?**

- Glycogenated nuclei: Glycogen accumulation is seen. Causes include steatohepatitis, diabetes, and Wilson disease ([Figure 32-5A](#)).
- Cytomegalovirus: Owl’s eye intranuclear inclusion is seen (see [Figure 32-5B](#)).
- Herpes simplex: Multinucleated cells with intranuclear inclusions are diagnostic (see [Figure 32-5C](#)).
- Hepatitis D virus: Sanded nuclear inclusion is seen. Hepatitis D is a coinfection with hepatitis B.
- Adenovirus: Smudgy inclusions are seen.



**Figure 32-5.** Photomicrography of nuclear inclusions in hepatocytes. **A**, Glycogenated nuclei. Accumulation of glycogen in nuclei. **B**, Cytomegalovirus. Viral nuclear inclusion (arrow). **C**, Herpes simplex. The multinucleated cell with molding viral inclusions in the background of hepatocyte necrosis.

**12. What kinds of special stains are commonly used for liver biopsy?**

- Masson trichrome stain highlights fibrosis.
- Reticulin stain highlights hepatic plates and is useful to evaluate alteration in hepatic architecture such as massive hepatocyte necrosis and loss of reticulin framework in HCC.
- PAS stain highlights glycogen in hepatocytes and  $\alpha$ 1-antitrypsin globules in periportal hepatocytes. When PASD stain is used, the glycogen has been removed by diastase, and the only positive staining globules are  $\alpha$ 1-antitrypsin globules.
- Perls' iron stain shows distribution and amount of iron overload.
- Rhodamine stain detects copper accumulation.
- Congo red stain detects amyloid.
- Oil red O confirms microvesicular steatosis. Fresh tissue is required, and it is useful for the diagnosis of acute fatty liver of pregnancy.

**FATTY CHANGES AND STEATOHEPATITIS****13. What is the difference between fatty liver and steatohepatitis?**

Steatosis indicates accumulation of lipid in hepatocytes. Steatohepatitis refers to a histologic constellation of findings with evidence of additional modes of hepatocyte injury such as ballooning degeneration, Mallory-Denk bodies, or necroinflammation.

**14. What are macrovesicular steatosis and microvesicular steatosis (see Figure 32-4A)?**

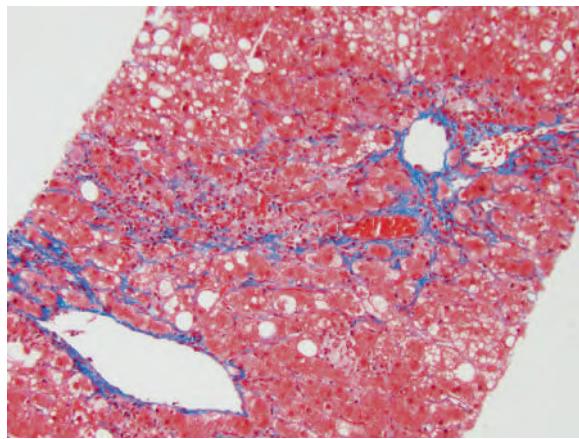
- Macrovesicular: The hepatocytes are distended with a single droplet, which displaces the nucleus.
- Microvesicular: The hepatocytes are filled with small droplets, but the nucleus is centrally located.

**15. Can histologic examination distinguish between alcoholic hepatitis and nonalcoholic hepatitis?**

Not really. Alcoholic hepatitis shows more neutrophils and Mallory hyaline, and occasionally distinction between the two is possible.

**16. How does scarring progress with steatohepatitis (Figure 32-6)?**

Fibrosis starts from pericentral vein with delicate chicken-wire-like fibrosis along the sinusoids. On the other hand, the progression of viral hepatitis starts from portal tracts.



**Figure 32-6.** Photomicrography of sinusoidal fibrosis seen in steatohepatitis.

**17. How is nonalcoholic steatohepatitis (NASH) graded?**

Because disease process including necroinflammatory response, type of hepatocyte injury and fibrosis are distinctly different between steatohepatitis and viral hepatitis, two systems, the Brunt system and the NASH Clinical Research Network (CRN) scoring system, were developed to assess activity and fibrosis particularly for NASH. Grade is based on degree of steatosis, hepatocellular ballooning, and lobular inflammation. CRN was developed to include both adult and pediatric population.

**CHRONIC HEPATITIS****18. What histologic features are typical of chronic hepatitis?**

Chronic hepatitis is a necroinflammatory process in which hepatocytes rather than bile ducts are predominantly injured. Inflammatory cells are composed of lymphocytes and plasma cells, and inflammation is predominantly

in the portal tracts with evidence of interface activity. Viral hepatitis, autoimmune hepatitis, Wilson disease, and  $\alpha 1$ -antitrypsin disease show the chronic hepatitis pattern.

#### **19. What histologic features are seen in autoimmune hepatitis?**

Histologic features of autoimmune hepatitis can be variable. Classic histologic findings include portal and lobular chronic inflammation with plasma cell–dominant interface activity associated with spotty necrosis. Hepatic rosette formation and bridging necrosis may be seen. Variants include cases without plasma cell dominance, acute hepatitis, and unexpected cirrhosis.

#### **20. What histologic features are seen in chronic hepatitis C?**

Lymphoid aggregates and mild to moderate interface activity are present. The lobular activity is mild and consists of spotty necrosis with 1 to 2 mononuclear cells and acidophil bodies. Bile ducts may show lymphocytic infiltrate.

#### **21. What histologic features are seen in chronic hepatitis B?**

Chronic hepatitis B may show ground-glass hepatocytes, which reflects accumulation of hepatitis B antigen within the endoplasmic reticulum of the hepatocytes.

#### **22. What is the goal for grading and staging systems for chronic hepatitis and what kinds of systems are there?**

The goal is to ensure the same lesions are being evaluated and given similar diagnostic weight regardless of the observers. Various systems (Kendall histologic activity index (HAI) score, Ishak modified HAI score, Scheuer system, Metavir system, and Batts and Ludwig) are available, but all assessments are based on portal chronic inflammation, interface activity, lobular necroinflammatory lesion, and fibrosis.

#### **23. How is chronic hepatitis graded and staged?**

The Batts and Ludwig system is the simplest system and is widely used.

- Grading of inflammatory activity:
  - Grade 1 (Minimal activity): Mild portal inflammation, but scant interface activity and no lobular necrosis
  - Grade 2 (Mild activity): Mild portal inflammation, interface activity, and scant lobular necrosis
  - Grade 3 (Moderate activity): Moderate portal inflammation, interface activity, and lobular spotty necrosis
  - Grade 4 (Severe activity): Marked portal inflammation, brisk interface activity, considerable spotty necrosis, and area of confluent necrosis
- Staging of fibrosis:
  - Stage 1 (Portal fibrosis): Fibrous portal expansion
  - Stage 2 (Periportal fibrosis): Periportal or rare portal-portal septa
  - Stage 3 (Septal/bridging fibrosis): Fibrous septa with architectural distortion
  - Stage 4 (Cirrhosis): Cirrhosis

### **DRUG INJURY**

#### **24. What kind of histologic pattern is seen in drug-related liver injury?**

See Table 32-1.

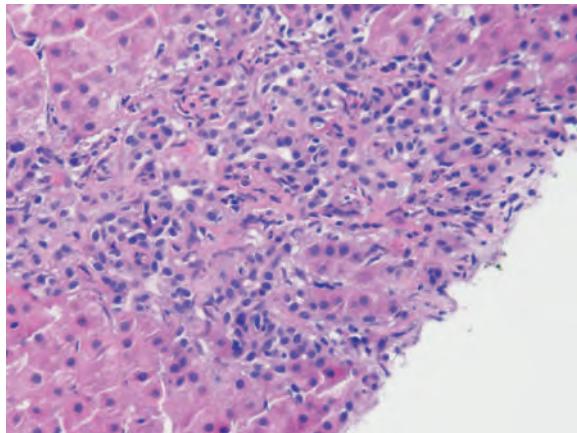
**Table 32-1. Histologic Pattern of Drug-related Liver Injury**

HISTOLOGIC FINDINGS	EXAMPLES OF ASSOCIATED AGENTS
Massive necrosis	Isoniazid, phenytoin
Zone 3 necrosis	Acetaminophen
Lobular inflammation and necrosis	Isoniazid, phenytoin
Fatty changes	Methotrexate, corticosteroids, total parenteral nutrition, ethanol
Granulomas	Allopurinol, sulfonamides, phenylbutazone
Mallory bodies	Amiodarone, ethanol
Cholestasis without inflammation	Anabolic steroid, oral contraceptive, cyclosporin A
Cholestasis with inflammation	Numerous antibiotics
Peliosis hepatis	Anabolic steroids
Sinusoidal obstruction syndrome	High-dose chemotherapy
Hepatic adenoma	Oral contraceptives, anabolic steroids

## BILE DUCT DISEASE

### 25. What are the histologic features of biliary obstruction (Figure 32-7)?

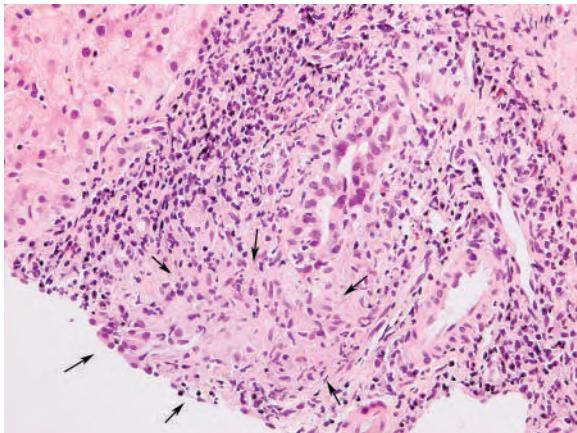
The biopsy shows centrilobular cholestasis, proliferation of bile ducts associated with neutrophil infiltrate, and portal tract edema. Neutrophils around the bile ducts are related to interleukin-8 expressed by ductular cells, not to infection.



**Figure 32-7.** Photomicrography of bile duct obstruction. Proliferation of bile duct associated with inflammatory cells.

### 26. What are the histologic features of primary biliary cirrhosis (PBC) (Figure 32-8)?

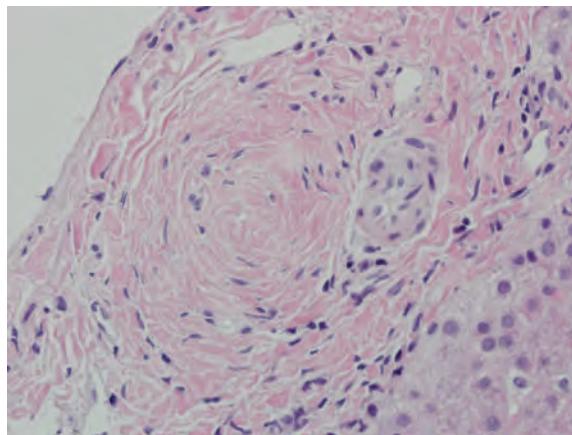
PBC affects small bile ducts. Florid bile duct lesion (nonsuppurative destructive cholangitis) is diagnostic for PBC. It is characterized by biliary epithelial damage, basement membrane destruction, and lymphoplasmacytic infiltrate. Noncaseating granulomas are seen in up to 25% of cases.



**Figure 32-8.** Photomicrography of primary biliary cirrhosis. Florid bile duct lesion with non-caseating granuloma (arrow).

### 27. What are the histologic features of primary sclerosing cholangitis (PSC) (Figure 32-9)?

PSC can affect both intra- and extrahepatic bile ducts, but more frequently affects medium to large bile ducts. Onion skin fibrosis accompanied by reduced number of bile ducts is diagnostic; however, it may be present in fewer than 40% of the liver biopsies. The most common findings on biopsy are nonspecific fibrosis with inflammation of portal tracts and paucity of normal bile ducts or the same histologic finding of extrahepatic bile duct obstruction. Imaging studies confirms the diagnosis of PSC.



**Figure 32-9.** Photomicrography of primary sclerosing cholangitis. Fibrous obliteration of bile duct.

#### 28. What is small-duct PSC?

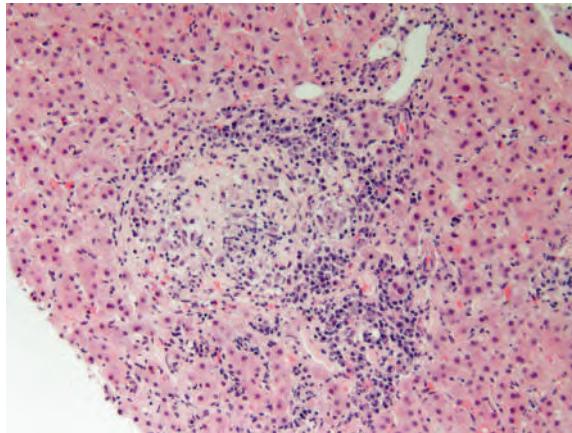
This subset of PSC affects only small bile ducts. Cholangiography is normal, and only liver biopsy can confirm the diagnosis.

#### 29. What is overlap syndrome?

The clinical and histologic features of more than one autoimmune process are seen in a patient. The most common overlap is autoimmune hepatitis with PBC or with PSC.

### GRANULOMATOUS INFLAMMATION

#### 30. What is a granuloma (Figure 32-10)?



**Figure 32-10.** Photomicrography of granuloma in the portal tract.

A granuloma is collection of epithelioid histiocytes.

#### 31. What causes granuloma in the liver?

- Infection: *Mycobacterium avium*, tuberculosis, schistosomiasis, fungal infection
- Drug related: Allopurinol, quinidine, penicillin, isoniazid, oxacillin
- Sarcoidosis
- PBC
- Extrahepatic inflammatory disease: chronic granulomatous disease, inflammatory bowel disease
- Neoplasm: Hodgkin's disease
- Foreign substance

## INHERITED LIVER DISEASE

**32. Does the pattern of accumulation of the iron help to determine the cause?**

Yes. Accumulation of iron in hepatocytes indicates genetic hemochromatosis, alcoholic liver disease, and porphyria cutanea tarda. Accumulation of iron in Kupffer cells indicates multiple transfusions or hemolytic anemia.

**33. Describe the histologic characteristics of Wilson disease.**

The biopsy shows variable portal inflammation, steatosis, periportal glycogenated nuclei, moderate to marked copper storage, and the presence of Mallory-Denk bodies in periportal liver cells. Quantitative copper testing of the liver is useful to confirm diagnosis.

**34. What are the features of  $\alpha_1$ -antitrypsin deficiency on liver biopsy?**

PAS-positive, diastase-resistant globules within periportal hepatocytes are present. It can be seen in the congestion or hypoxia. Clinical correlation with electrophoresis is required.

## VASCULAR DISEASE

**35. Does the patient with portal hypertension always have cirrhosis?**

No. The patients with nodular regenerative hyperplasia, idiopathic portal hypertension, and hepatoportal sclerosis have portal hypertension without cirrhosis.

## NEOPLASM

**36. Discuss the role of biopsy in diagnosing primary liver tumors.**

HCC can be diagnosed by imaging study alone if certain imaging criteria are met. When four-phase multidetector computed tomography or dynamic contrast-enhanced magnetic resonance imaging (MRI) shows arterial hypervascularity and venous or delayed phase washout in masses 2 cm or larger, HCC diagnosis is confirmed. When the imaging studies are inconclusive, liver biopsy is required to confirm the diagnosis.

**37. Discuss the role of liver biopsy in diagnosing metastatic neoplasm.**

Biopsies can confirm metastasis from a known primary tumor. Some biopsies show a tumor that is probably metastatic but for which no primary tumor is known. In such cases, various immunohistochemical stains can be performed on biopsy tissue to help guide further workup.

## TRANSPLANTATION

**38. What are the main histologic features of acute rejection and how are they graded by the Banff scheme?**

Portal inflammation, endotheliitis, and bile duct injury are the three main histologic features. The Banff schema uses two compartments. The first is a global assessment of the overall rejection grade (indeterminate, mild, moderate, severe). The second component involves scoring the three main features of acute allograft rejection on a scale of 0 (absent), 1 (mild), 2 (moderate), 3 (severe) to produce an overall rejection activity index. Maximum score is  $3 \times 3 = 9$ .

**39. Describe the role of liver biopsy in the first year after transplantation?**

Common causes of abnormal liver enzyme after transplantation include acute rejection, recurrent viral hepatitis, chronic rejection, steatohepatitis, and recurrent other disease (PBC, PSC, autoimmune hepatitis). Liver biopsy is helpful to differentiate the diagnosis.

**40. What is the histologic finding of chronic rejection?**

Chronic rejection often occurs as a consequence of repeated episodes of acute rejection that are unresponsive to immunosuppression. The main histologic abnormality is loss of small bile ducts or obliterative vasculopathy affecting large and medium arteries. The former can be diagnosed by biopsy, whereas the latter may require the examination of an explant. Ductopenia is characterized by bile duct loss in more than 50% of portal tracts and is diagnosed through a single biopsy or a series of biopsies.

**41. What is the histologic finding of acute and chronic graft-versus-host disease (GVHD)?**

Acute GVHD is characterized by degenerative bile duct lesions with mononuclear inflammation. Cholestasis may be seen.

## BIBLIOGRAPHY

1. Batts KP, Ludwig J. Chronic hepatitis: an update on terminology and reporting. Am J Surg Pathol 1995;19(12):1409–17.
2. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53(3):1020–2.
3. Brunt EM. Grading and staging the histopathological lesions of chronic hepatitis: the Knodell histology activity index and beyond. Hepatology 2000;31:241–6.

4. Brunt EM, Janney CG, Di Biscirglio AM, Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histologic lesions. *Am J Gastroenterol* 1999;94(9):2467–74.
5. Burt A, Portmann B, Farrell L. MacSween's pathology of the liver. 6th ed. New York: Churchill Livingstone, Elsevier; 2007.
6. Demetris AJ, et al. Banff schema for grading living allograft rejection: an international consensus document. *Hepatology* 1997;25(3):658–63.
7. Demetris AJ, et al. Update of the international Banff scheme for liver allograft rejection: working recommendations for the histopathologic staging and reporting of chronic rejection: an international panel. *Hepatology* 2000;31:792–9.
8. Kanel GC, Korula J. Atlas of liver pathology. 3rd ed. St Louis: Elsevier; 2011.
9. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005;41:1313–21.
10. Kumar V, Abbas AK, Fausto N, Aster J. Robbins and Cotran pathologic basis of disease. 8th ed. Philadelphia: Saunders, Elsevier; 2010.
11. Rockey DC, Caldwell SH, Goodman ZD, et al. Liver biopsy. *Hepatology* 2009;49:1017–35.

**Website**

Transplant Pathology Internet Services. <http://tpis.upmc.com/> [Accessed September 22, 2014].

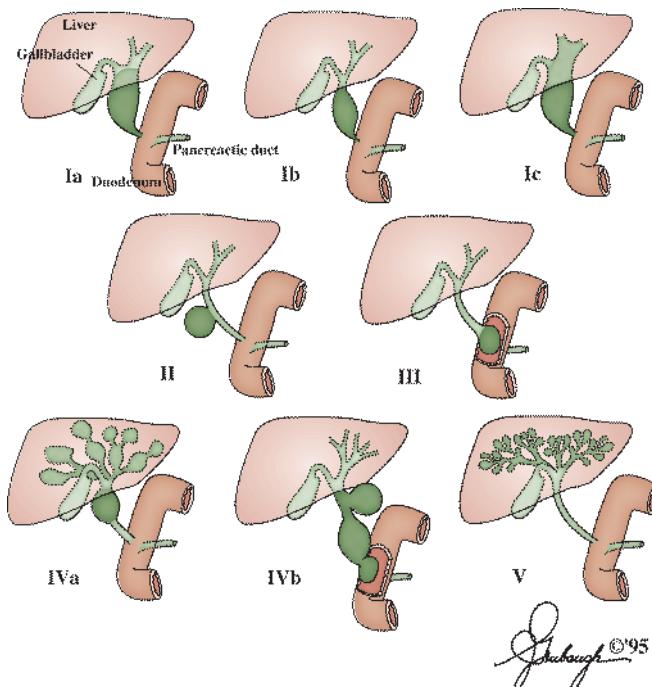
# HEPATOBILIARY CYSTIC DISEASE

*Joshua Friedman, MD, PhD, and Marianne Augustine, MD*

## LIVER CYSTIC DISEASE

### 1. Describe the five major classes and subtypes of congenital bile duct cysts.

See Figure 33-1 and Table 33-1.



**Figure 33-1.** Classification of bile duct cysts.

**Table 33-1.** Intrahepatic and Extrahepatic Involvement According to Todani Classification

TODANI CLASSIFICATION OF BILE DUCT CYSTS	TYPE	INTRAHEPATIC	EXTRAHEPATIC
Type Ia: cystic extrahepatic bile duct dilation*	1a		✓
Type Ib: segmental extrahepatic bile duct dilation*	1b		✓
Type Ic: fusiform, diffuse, or cylindrical bile duct dilation*	1c		✓
Type II: extrahepatic duct diverticula	2		✓
Type III: choledochocoele	3		✓
Type IVa: multiple intrahepatic and extrahepatic duct cysts <sup>†</sup>	4a	✓	✓
Type IVb: multiple extrahepatic duct cysts	4b		✓
Type V: intrahepatic duct cysts, also associated with Caroli disease	5	✓	

\*Type I is the most common occurring type (80%-90%).

<sup>†</sup>Usually associated with an anomalous pancreaticobiliary junction.

## 2. Describe the typical clinical presentation of a bile duct cyst.

The classic clinical presentation of a bile duct cyst is the triad of abdominal pain, jaundice, and abdominal mass. It occurs more commonly in infants and children than adults. One or two symptoms may be present. Other presenting symptoms include cholangitis or pancreatitis. Bile duct cysts may also be an incidental finding.

## 3. Compare the main features of Caroli disease and Caroli syndrome.

Both Caroli disease and syndrome are characterized by:

- Congenital cystic dilations of the intrahepatic bile duct, without extrahepatic bile duct involvement
- Diffuse or segmental dilatation
- Increased risk of cholangiocarcinoma

**Caroli disease** is a rare condition characterized by cystic dilation of the larger intrahepatic bile ducts. It may be segmental. It is associated with bile stasis, which can cause recurrent intrahepatic calculi and cholangitis. Hepatic fibrosis and its sequelae are not present.

**Caroli syndrome** is an autosomal recessive condition that is more common than Caroli disease. Cystic dilation of large and small intrahepatic ducts can occur. Hepatic fibrosis is always present, which can lead to portal hypertension. Histologic examination generally reveals ductal plate malformation. Caroli syndrome exists on a spectrum with congenital hepatic fibrosis and autosomal recessive polycystic kidney disease (ARPKD). All three are associated with mutations in the gene PKHD1 (Table 33-2). The clinical spectrum of ARPKD is widely variable. There is a mortality rate of 30% to 50% in the neonatal period, generally resulting from severe kidney disease. However, many survive into adulthood.

Treatment is patient-specific depending on disease pattern. Ursodeoxycholic acid helps to prevent choledocholithiasis, and antibiotics are used to treat cholangitis. Many patients may undergo endoscopic retrograde cholangiopancreatography (ERCP) for stone removal and duct stenting. Partial hepatic resection may be performed if disease is isolated to one lobe of the liver. Liver transplantation can be considered in select cases.

**Table 33-2.** Genes Associated with Bile Duct Cysts

LIVER DISEASE	GENE	PROTEIN	ASSOCIATED RENAL DISEASE
Congenital hepatic fibrosis Caroli syndrome	PKHD1	fibrocystin/ polyductin	ARPKD
Autosomal PLD	PKD1/2	polycystin-1 and -2	ADPKD
Isolated PLD	SEC63/ PRKCSH	sec-63/hepatocystin	None
PLD	NPHP1-8	nephrocystins	Medullary cystic kidney disease

ADPKD, Autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; PLD, polycystic liver disease.

## 4. What is the incidence of malignancy within a congenital bile duct cyst?

The reported incidence of malignancy within a congenital bile duct cyst ranges from 10% to 30%. This may be an overestimation because the true incidence of bile duct cyst disease is unknown. Malignancy has been reported in all types of bile duct cysts and the probability of malignancy increases with the age of the patient at presentation. It is thought that pancreaticobiliary reflux causes inflammation and eventually dysplasia in patients with congenital bile ducts.

Cholangiocarcinoma is the most serious complication of congenital bile duct disease. Early detection is the best preventive measure. Primary sclerosing cholangitis (PSC) accounts for 30% of cholangiocarcinoma. When PSC is the underlying diagnosis, an ultrasound and serum CA 19-9 is obtained yearly in noncirrhotics and every 6 months in cirrhotics.

## 5. Describe the preferred treatment for patients with bile duct cyst disease.

Treatment is largely supportive. For choledochal cysts the preferred treatment is complete surgical excision with hepatoenterostomy. Complete excision significantly reduces, but does not eliminate, the risks of developing bile duct malignancy, strictures, and cholangitis. Patients with symptomatic intrahepatic bile duct cyst disease may require segmental resection or liver transplantation.

## 6. What is the role of cholangiopancreatography in patients with bile duct cyst disease?

Cholangiopancreatography allows for visualization of the biliary tree. Patients with extrahepatic bile duct cysts have an increased incidence of anomalous pancreaticobiliary junction.

Direct cholangiopancreatography—percutaneously, endoscopically, or intraoperatively—allows definitive identification of the pancreatic duct insertion, which may be important in surgical planning. In addition, cholangiography can distinguish multiple intrahepatic bile duct cysts from multiple hepatic cysts, which can appear similar on computed tomography (CT).

Magnetic resonance cholangiopancreatography is helpful and less invasive in characterizing the hepatobiliary junction and has less risk associated with it.

ERCP should be performed with caution in patients with suspected Caroli disease or Caroli syndrome because of the increased risk of recurrent cholangitis and sepsis. Therapeutic ERCP remains a useful tool for the management of acute cholangitis caused by bile duct stones.

## 7. Provide a differential diagnosis for a cystic hepatic lesion.

It is important to differentiate between a simple versus complex cyst.

Simple hepatic cysts are benign fluid collections usually surrounded by a thin columnar epithelium and frequently require no treatment, whereas complex-appearing cysts are more concerning for infection or malignancy.

- Simple liver cyst
- Infectious (abscess, pyogenic, amebic, *Echinococcal* cyst)
- Polycystic liver disease (PLD)
- Neoplasm (biliary cystadenoma, hamartoma, hepatocellular carcinoma, cavernous hemangioma)
- Pseudocyst
- Hematoma
- Biloma

## 8. What is the significance of a simple hepatic cyst?

Many simple hepatic cysts are solitary and asymptomatic and are frequently found incidentally on diagnostic imaging examinations. They are not associated with cystic disease in other organs and there is no genetic transmission. No treatment is necessary for a simple hepatic cyst.

Cyst-related symptoms include abdominal pain, increasing abdominal girth, and obstructive jaundice. If symptoms develop, laparoscopic surgical unroofing of the simple cyst is the first-line definitive therapy. Percutaneous drainage is not recommended as the fluid will reaccumulate. A temporary drain is also not recommended because of the risk of infection.

## 9. Describe the ultrasonographic, CT, and magnetic resonance imaging (MRI) characteristics of a simple hepatic cyst.

On ultrasound, a simple hepatic cyst has a smooth margin with the surrounding parenchyma without an appreciable wall or internal echoes. Failure to meet any of these criteria increases the likelihood of an alternative diagnosis, such as a cyst infection, hydatid cyst, or biliary cyst disease.

On CT, a simple hepatic cyst appears as a thin-walled lesion that does not enhance with iodinated intravenous contrast agents. The density of the lesion is that of water.

On T1-weighted MRI scans, cysts appear as a homogeneous, very-low-intensity lesion. On T2-weighted scans, they can appear as a discrete high-intensity lesion.

## 10. What hepatobiliary cystic neoplasm with malignant potential can be mistaken for a simple cyst, PLD, or hydatid cyst?

Hepatobiliary cystadenoma is a rare neoplasm that has thick irregular walls and internal septations, distinguishing it from a simple cyst. Abdominal pain is the most common symptom. These cysts are lined with biliary epithelium and have a high potential for transformation to cystadenocarcinoma. The treatment of choice is surgical resection of the entire neoplasm.

## 11. What disease commonly is associated with PLD?

PLD is characterized by numerous cysts of various size scattered throughout the liver parenchyma. Half of PLD cases involve solitary cysts.

There are two forms:

- One form is associated with autosomal dominant polycystic kidney disease (ADPKD). More than 75% of all patients with ADPKD also have PLD. There are also strong associations between ADPKD and intracranial saccular aneurysms (berry aneurysms, 5%-7%), mitral valve prolapse, and colonic diverticula.
- The second form is ADPLD. Patients with ADPLD have no kidney disease but also may have an increased risk for intracranial aneurysms.

Some authors recommend that patients with PLD of either type should be screened for intracranial aneurysms by either magnetic resonance or CT angiography (see Table 33-2).

## 12. What are the risk factors for PLD in patients with ADPKD?

PLD is the most common extrarenal manifestation of ADPKD. The presence and severity of PLD in patients with ADPKD increase with age, female gender, number and frequency of pregnancies, and severity of renal disease.

**13. Describe the clinical manifestations of complicated PLD.**

The common complications of PLD are related to mass effect. Compression of adjacent structures by large cysts may cause chronic pain, anorexia, dyspnea, or obstructive jaundice. Liver cyst infection rarely occurs but is associated with significant morbidity. A definitive diagnosis of cyst infection usually requires percutaneous CT or ultrasound-guided fine-needle aspiration.

**14. How does the presence of liver cysts affect hepatic function?**

Hepatic function usually is not affected by liver cysts. In the absence of complications, the serum aminotransferase, bilirubin, and alkaline phosphatase levels typically are within normal range or only slightly elevated. In patients with ARPKD and ADPKD, serum chemistry abnormalities generally reflect the degree of renal dysfunction.

**15. What are the treatment options for patients with symptomatic PLD?**

Typically, cysts with a diameter of more than 5 cm can be treated. Symptomatic liver cysts may be treated either percutaneously or surgically. Simple ultrasound- or CT-guided percutaneous aspiration results in rapid reaccumulation of the cyst fluid. The rate of cyst recurrence is greatly reduced by instilling a sclerosing agent, such as ethanol, at the time of aspiration. Percutaneous sclerosis of a liver cyst is contraindicated when the cyst communicates with either the biliary system or peritoneal cavity. Surgical options include laparoscopic or open cyst fenestration.

Infected cysts do not resolve with systemic antibiotic therapy alone. Administration of antibiotics should be combined with either percutaneous or surgical drainage.

Patients with intractable symptoms who have failed other therapies may be candidates for either isolated orthotopic liver transplant or combined liver and kidney transplant if they are dialysis dependent.

**16. What is echinococcosis?**

Echinococcosis is a parasitic infection caused by the tapeworm *Echinococcus*. There are four known species of *Echinococcus* that cause human disease:

- *E. granulosus* (cystic echinococcosis)
- *E. oligarthrus*
- *E. vogeli* (polycystic echinococcosis)
- *E. multilocularis* (alveolar echinococcosis)

*E. oligarthrus* and *E. vogeli* are found in Central and South America. *E. multilocularis* is found throughout the planet's arctic regions, including Alaska. *E. granulosus* has a worldwide distribution. The cystic and polycystic types of echinococcosis both form large, fluid-filled cysts that do not invade adjacent tissue. In contrast, alveolar echinococcosis is characterized by exogenous budding, local tissue infiltration, and metastatic spread.

**17. Describe the usual life cycle of *E. granulosus*.**

*E. granulosus* is a small tapeworm responsible for cystic echinococcosis, measuring approximately 2 to 8 mm. The adult worm lives in the intestinal lumen of the host, such as a dog or fox. Eggs are released and leave the host in the feces. The eggs are ingested through contaminated food or water by intermediate hosts such as sheep, cattle, goats, and pigs. Ingested eggs hatch in the duodenum, and the larvae penetrate the intestinal mucosa to be carried by the circulatory system to the capillary beds of distant organs.

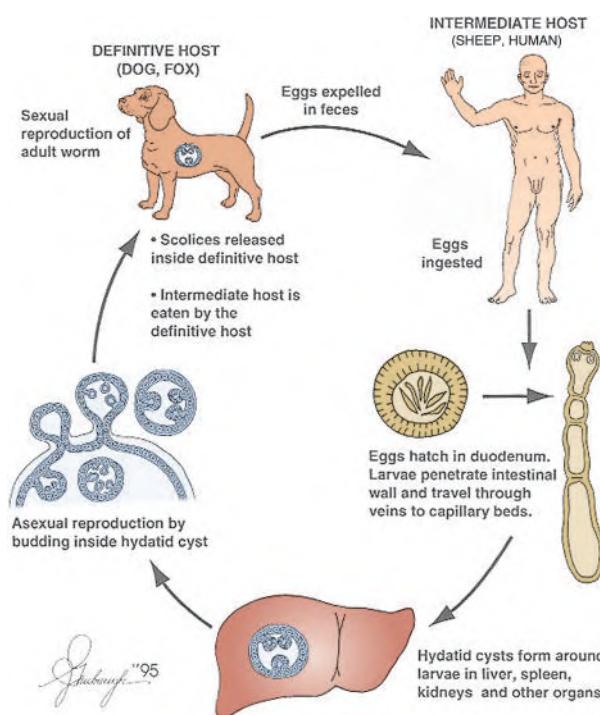
The intermediate host creates the hydatid cyst by producing surrounding fibrosis. New scolices bud from the inner wall of the cyst. Over time, daughter cysts may form within the original cyst. When infected viscera are eaten by a predator, the scolices develop into adult worms.

**18. Where and how does *E. granulosus* infect humans?**

Human infection by *E. granulosus* is the most common of the *Echinococcus* zoonoses and occurs throughout the world. It is a significant public health problem in Central and South America, China, Mediterranean and Middle East countries, eastern Europe, and the Russian Federation. Human infections occur most commonly in sheep- and cattle-raising areas where dogs assist in herding. The dogs eat infected viscera and excrete infective eggs in their feces. Humans usually are infected as intermediate hosts when they ingest feces- or egg-contaminated food or water. More than one-half of all human infections involve the liver. Other common sites for echinococcal cysts are the lungs, spleen, kidneys, heart, bones, and brain (Figure 33-2).

**19. Describe the typical clinical presentation of hepatic cystic echinococcosis.**

Patients may harbor the infection for years until they present with a palpable abdominal mass or other symptoms. The hydatid cyst diameter usually increases by 1 to 5 cm per year. The symptoms of hepatic cystic echinococcosis are related primarily to the mass effect of the enlarging cyst: abdominal pain from the stretching hepatic capsule, jaundice from compression of the bile duct, or portal hypertension from portal vein obstruction. Approximately 20% of patients have cysts that rupture into the biliary tree and may have symptoms similar to those of choledocholithiasis or cholangitis. Rupture of a cyst into the peritoneal cavity may cause an intense antigenic response, resulting in eosinophilia, bronchial spasm, or anaphylactic shock.

**Figure 33-2.** Life cycle of *Echinococcus granulosus*.

## 20. How is cystic echinococcosis diagnosed?

Confirming a diagnosis of cystic echinococcosis involves diagnostic imaging and serologic tests. CT scans may show the hydatid cyst as a sharply defined, low-density lesion with spokelike septations. The presence of a calcified rim of daughter cysts greatly enhances the specificity of the CT findings. When imaged by ultrasound, the hydatid cyst appears as a complex mass with multiple internal echoes from debris and septations. Enzyme-linked immunosorbent assay or indirect hemagglutinin serologic assays for echinococcal antibodies are positive in approximately 85% to 90% of patients. Recovery of scolices from a suspected hydatid cyst by percutaneous needle aspiration is diagnostic, but this technique must be used with caution because of the risk of spilling scolices into the peritoneal cavity.

## 21. What are the treatment options for hepatic cystic echinococcosis?

The optimal treatment of hepatic cystic echinococcosis depends on the local expertise and the characteristics of the individual patient. Surgical cyst resection generally is the preferred method of therapy for large or infected cysts. Percutaneous cyst drainage and irrigation with a scolicidal agent (puncture, aspiration, injection, reaspiration) is a safe and effective alternative therapy for those with uncomplicated cysts or for patients who are not surgical candidates. Treatment with albendazole in the peritreatment period reduces the recurrence rate of both techniques.

Pretreatment ERCP helps to rule out cyst communication with the biliary or pancreatic duct systems. Persistent postoperative biliary fistulas may be diagnosed and treated by ERCP with endoscopic sphincterotomy.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

1. Bayraktar Y. Clinical characteristics of Caroli's disease. *World J Gastroenterol* 2007;13:1930–3.
2. Bergmann C, Senderek J, Küpper F, et al. PKHD1 mutations in autosomal recessive polycystic kidney disease (ARPKD). *Hum Mutat* 2004;23:453–63.
3. Budke CM, Deplazes P, Torgerson PR. Global socioeconomic impact of cystic echinococcosis. *Emerg Infect Dis* 2006;12:296–303.
4. Everson G. Polycystic liver disease. *Gastroenterol Hepatol* 2008;4:179–81.
5. Garcea G, Patterson CJ, Stephenson J, et al. Nine-year single-center experience with nonparasitic liver cysts: diagnosis and management. *Dig Dis Sci* 2007;52:185–91.
6. Habib S, Shakil O, Couto OF, et al. Caroli's disease and orthotopic liver transplantation. *Liver Transpl* 2006;12:416–21.
7. Housset C. Cystic liver diseases. Genetics and cell biology. *Gastroenterol Clin Biol* 29:861–9.

8. Jablonska B. Biliary cysts: etiology, diagnosis and management. *World J Gastroenterol* 2012;18:4801–10.
9. Drenth J, Chrispijn M, Nagorney D, Kamath P, Torres V. Medical and surgical treatment options for polycystic liver diseases. *Hepatology* 2010;52:2223–30.
10. Kassahun WT, Kahn T, Wittekind C, et al. Caroli's disease: liver resection and liver transplantation: experience in 33 patients. *Surgery* 2005;138:888–98.
11. Mabrut JY, Partensky C, Jaeck D, et al. Congenital intrahepatic bile duct dilation is a potentially curable disease: long-term results of a multi-institutional study. *Ann Surg* 2007;246:236–45.
12. Millwala F, Segev DL, Thuluvath PJ. Caroli's disease and outcomes after liver transplantation. *Liver Transpl* 2008;14:11–7.
13. Park DH, Kim MH, Lee SK, et al. Can MRCP replace the diagnostic role of ERCP for patients with choledochal cysts? *Gastrointest Endosc* 2005;62:360–6.
14. Russell RT, Pinson CW. Surgical management of polycystic liver disease. *World J Gastroenterol* 13:5052–9.
15. Soreide K, Soreide JA. Bile duct cyst as precursor to biliary tract cancer. *Ann Surg Oncol* 2007;14:1200–11.
16. Tappe D, Stich A, Frosch M. Emergence of polycystic neotropical echinococcosis. *Emerg Infect Dis* 2008;14:292–7.
17. Thomas KT, Welch D, Trueblood A, et al. Effective treatment of biliary cystadenoma. *Ann Surg* 2005;241:769–75.
18. Todani T, Watanabe Y, Narusue M, et al. Congenital bile duct cysts: classification, operative procedures, and review of thirty-seven cases including cancer arising from choledochal cyst. *Am J Surg* 1977;134:263–9.
19. Ulrich F, Pratschke J, Pascher A, et al. Long-term outcome of liver resection and transplantation for Caroli's disease and syndrome. *Ann Surg* 2008;247:357.
20. Wen J. Congenital hepatic fibrosis in autosomal recessive polycystic kidney disease. *Clin Trans Sci* 2011;4:460–5.

# GALLBLADDER DISEASE: STONES, CRYSTALS, AND SLUDGE

Cynthia W. Ko, MD, MS, and Sum P. Lee, MD, PhD

## 1. What is the prevalence of gallstones in Western populations?

Ten to twenty percent of adults in Western countries have gallstones. Gallstones in Western populations are most commonly composed of cholesterol.

## 2. What are the different types of gallstones by chemical composition?

The common types of gallstones by chemical composition are cholesterol and calcium bilirubinate. Calcium bilirubinate stones can be characterized as brown or black pigment stones. Brown pigment stones have a soft, claylike consistency and are found in the intrahepatic and extrahepatic ducts but not the gallbladder. Black pigment stones form in the gallbladder from bilirubin precipitation. They often contain calcium salts and can be radiopaque.

## 3. Name four pathophysiologic factors associated with cholesterol gallstone formation.

- Cholesterol supersaturation of bile: The amount of cholesterol secreted by the liver into bile exceeds the solubilizing capacity of bile acids and phospholipids in bile.
- Nucleation: Cholesterol crystals precipitate from supersaturated bile, which usually occurs in the gallbladder.
- Biliary stasis: Stasis of bile in the gallbladder concentrates bile, accelerating crystal nucleation and impairing emptying of crystals into the duodenum.
- Enhanced intestinal cholesterol absorption: Increases in intestinal cholesterol absorption increase the total body pool of cholesterol.

## 4. What are the risk factors for cholesterol gallstones?

Strong risk factors for gallstones include increasing age, female sex, race and ethnicity (American Indian, Hispanic), increasing body mass index, and rapid weight loss. Low levels of physical activity also predispose to gallstones, as do diets high in carbohydrates or low in vegetable proteins or fiber. Pregnancy is a time of accelerated gallstone formation, and parity is a strong risk factor for gallstones. Medications including progesterones, oral contraceptives, and estrogen replacement therapy are also associated with gallstones.

## 5. What clinical conditions are associated with brown or black pigment stones?

- Brown pigment stones are more common in Asian populations, are associated with bile colonization by bacteria or parasites, and may present with acute pyogenic cholangitis.
- Black pigment stones are associated with chronic hemolysis, long-term total parenteral nutrition, and cirrhosis.

## 6. What is the significance of biliary sludge?

Biliary sludge is composed of microscopic precipitates of cholesterol or calcium bilirubinate, and represents the earliest stages of gallstone formation. Sludge can cause symptoms identical to those of gallstones.

## 7. Describe the characteristics of uncomplicated biliary colic.

Biliary colic is characterized by severe, episodic pain in the epigastrium or right upper quadrant. Pain can occur postprandially, but often has no inciting triggers. The pain may radiate to the right shoulder and be associated with nausea or vomiting. Pain lasting more than 6 hours should prompt consideration of gallstone complications, such as cholangitis or cholecystitis.

## 8. What is the best imaging test for detecting gallbladder stones?

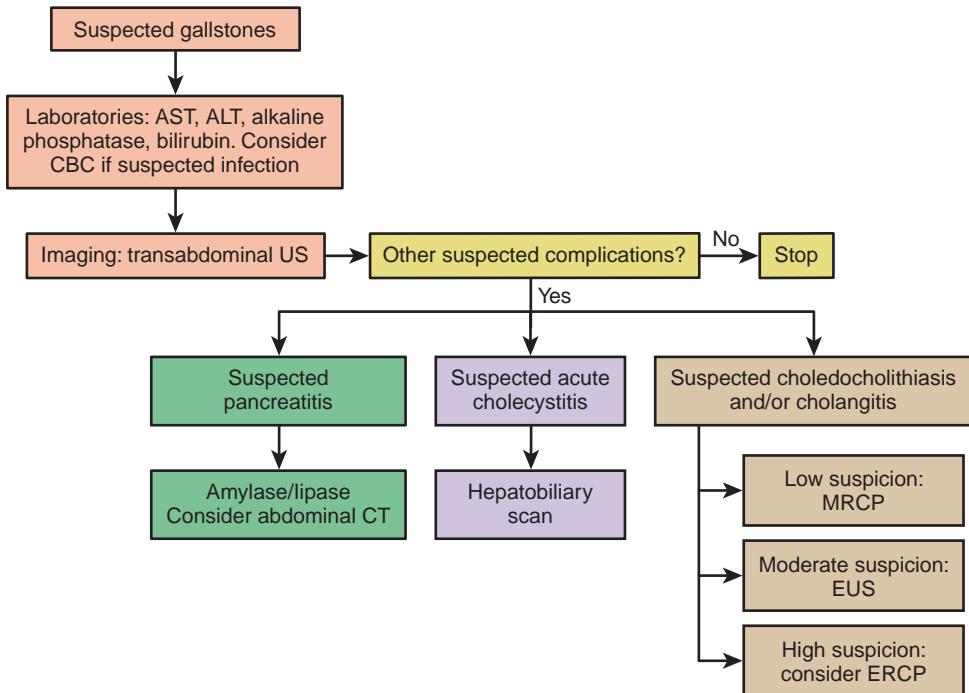
Transabdominal ultrasonography can diagnose gallstones with a sensitivity and specificity of more than 90% (Figure 34-1). On ultrasound, gallstones appear as high-amplitude echoes with postacoustic shadowing (Figure 34-2A). Ultrasonography is also the most sensitive modality for diagnosis of biliary sludge (see Figure 34-2B), which appears as movable echogenic material without postacoustic shadowing.

## 9. Should patients with asymptomatic stones undergo cholecystectomy?

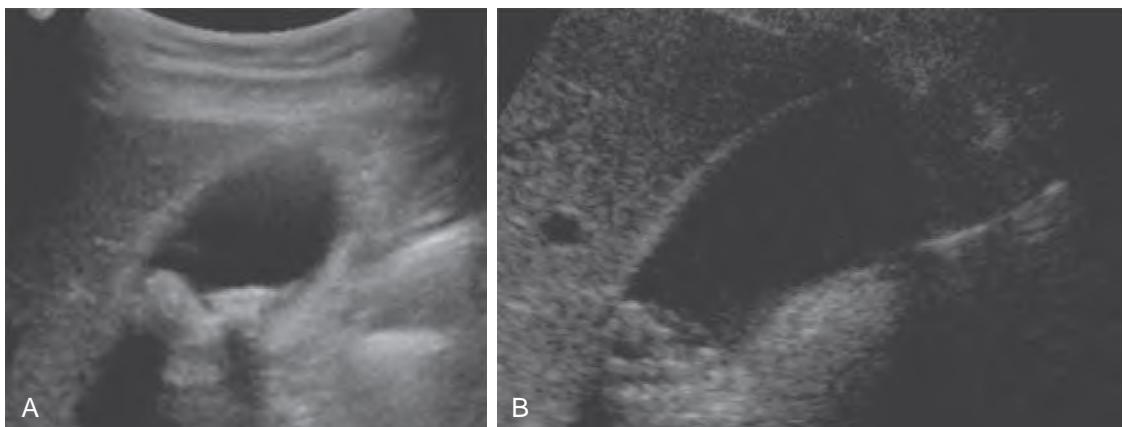
The risk of developing gallstone-related symptoms is estimated to be 2% to 4% per year. In patients with gallbladder stones, complications usually occur after development of uncomplicated biliary colic, so prophylactic cholecystectomy is not indicated (Figure 34-3).

## 10. What is the treatment of choice for patients with symptomatic stones?

Once complications develop, laparoscopic cholecystectomy is the treatment of choice (see Figure 34-3). Patients with common bile duct stones are at high risk for complications and should undergo cholecystectomy and stone



**Figure 34-1.** Algorithm for diagnosis of suspected gallstones and their complications. ALT, Alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography.

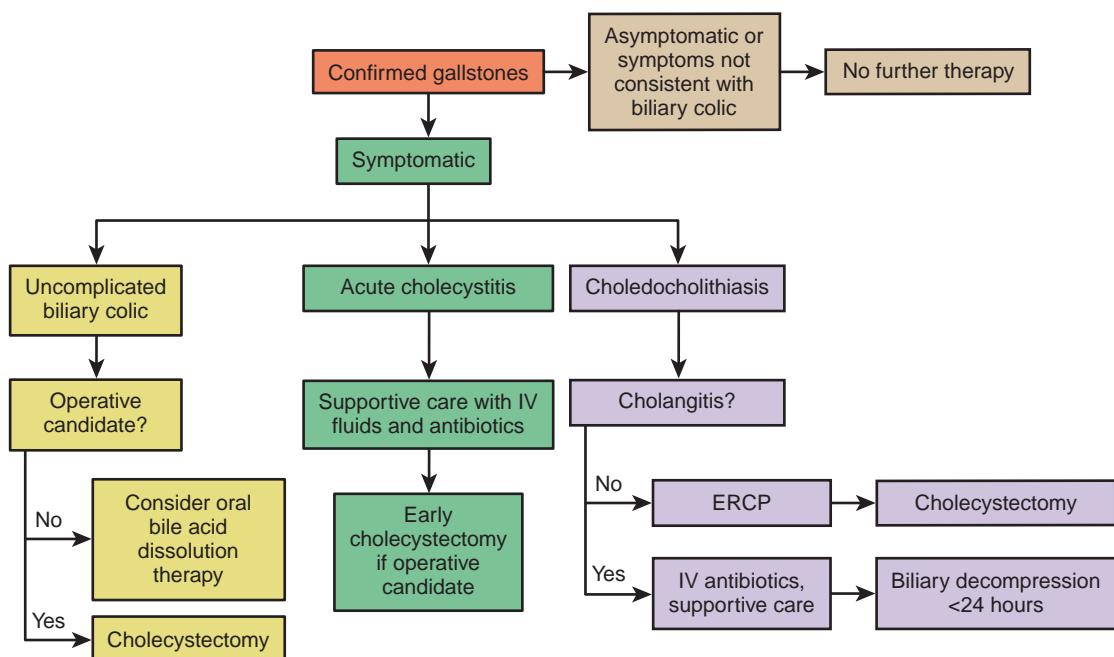


**Figure 34-2.** Ultrasound examination showing gallstones (A), which appear as high-amplitude echoes within the gallbladder with postacoustic shadowing. Biliary sludge appears as low-amplitude echoes without postacoustic shadowing (B).

extraction. Common bile duct stones may be removed at the time of surgery or with endoscopic retrograde cholangiopancreatography (ERCP). Selected patients with uncomplicated biliary colic may be treated with oral bile acid dissolution.

### 11. Can symptom characteristics predict response to cholecystectomy?

Patients most likely to respond to cholecystectomy are those with recent onset of symptoms, discrete episodes of pain, and without concomitant gastroesophageal reflux or irritable bowel syndrome. Patients with less severe pain or pain episodes lasting less than 30 minutes are less likely to respond to cholecystectomy.



**Figure 34-3.** Algorithm for management of gallstones and their complications. ERCP, Endoscopic retrograde cholangiopancreatography; IV, intravenous.

## 12. What are common complications of cholecystectomy?

Serious complications of cholecystectomy include bile leaks, which can require corrective surgery in 0.1% to 0.3%. The risk of major bowel or blood vessel injury is estimated at 0.02%. Peritonitis, postoperative bleeding, and intraabdominal abscesses all occur in fewer than 0.5% of cases. Overall perioperative mortality varies between 0% and 0.3%.

## 13. What treatment options are available for patients who do not want to undergo cholecystectomy?

Because laparoscopic cholecystectomy is generally safe and effective, it is the preferred method of treatment in patients who are adequate surgical patients. In selected patients, stones may be treated with oral bile acid dissolution therapy, such as ursodeoxycholic acid. Common bile duct stones may be removed endoscopically via ERCP.

## 14. Who is a candidate for oral bile acid dissolution therapy?

Candidates for oral bile acid dissolution therapy include patients with small (<1 cm), noncalcified stones composed primarily of cholesterol. The cystic duct must be patent and the gallbladder functional. Treatment often requires several months for complete dissolution. Recurrence rates up to 10% per year are possible.

## 15. How should pregnant women with symptomatic or complicated gallstones be managed?

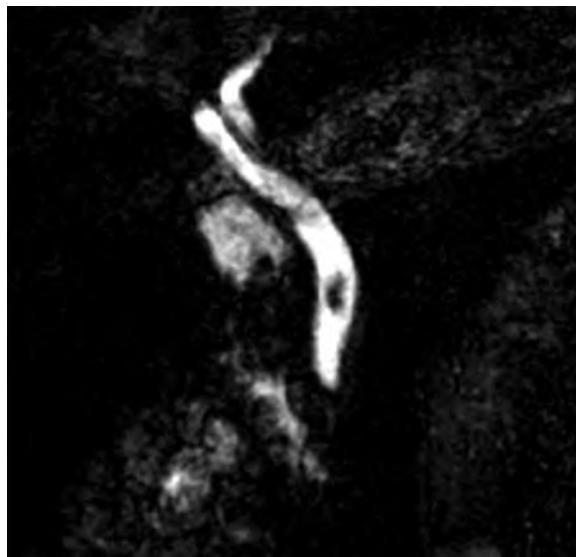
Laparoscopic cholecystectomy can be safely performed in the second trimester, but is relatively contraindicated in the first and third trimesters. Women can generally be managed with supportive care, with particular attention to adequate nutrition. If necessary, ERCP can be safely performed using techniques such as fetal shielding and anesthesia assistance for sedation.

## 16. What imaging tests are useful to diagnose common bile duct stones?

Magnetic resonance cholangiopancreatography (MRCP, Figure 34-4) and endoscopic ultrasonography (EUS) are useful, less invasive tests with more than 90% sensitivity and specificity for diagnosing common bile duct stones compared with ERCP. These modalities are commonly used to confirm the presence of common bile duct stones before proceeding to ERCP (see Figure 34-1).

## 17. What are the symptoms of acute cholecystitis?

Patients with acute cholecystitis typically have epigastric or right upper quadrant abdominal pain lasting longer than 3 hours. Low-grade fevers, nausea, and vomiting are common. Murphy's sign, an inspiratory pause during palpation of the right upper quadrant, may be present. Jaundice may be present in 15% to 20%. On ultrasound or abdominal computed tomography (CT) scan, patients will have a thickened gallbladder wall with pericholecystic fluid. Hepatobiliary scintigraphy will show absence of gallbladder filling, reflecting obstruction of the cystic duct.



**Figure 34-4.** Magnetic resonance cholangiopancreatography showing filling defect in distal common bile duct, consistent with a retained gallstone.

#### 18. How should patients with acute cholecystitis be managed?

Patients with acute cholecystitis should be hospitalized for supportive care and given antibiotics with coverage of gram-negative organisms and anaerobes. Early cholecystectomy (within 7 days of presentation) is associated with shorter hospital stays compared with delayed treatment (1 to 2 months). Early cholecystectomy can usually be completed laparoscopically but has higher rates of conversion to open procedures than in patients with uncomplicated gallstones. Delayed cholecystectomy is associated with increased risk for recurrent biliary complications.

#### 19. List key points in the management of acute cholangitis.

- Intravenous fluids
- Antibiotics aimed at gram-negative organisms and *Enterococcus* species
- Biliary decompression within 24 hours of clinical presentation. ERCP is the preferred method for biliary decompression. Percutaneous cholangiography is an alternative drainage method if endoscopic drainage is not available or not technically feasible.

#### 20. Discuss complications from the migration of gallstones.

Gallstone ileus occurs when large stones erode through the gallbladder wall into the gastrointestinal tract, where they may cause obstruction. Most frequently, the stones impact in the ileum. Pneumobilia is a common radiologic finding. Gallstones may also erode into the stomach and obstruct the pylorus (Bouveret syndrome). Cholecystocolonic fistulas may cause bile salt malabsorption diarrhea.

#### 21. What is Mirizzi syndrome?

Mirizzi syndrome occurs when a stone becomes impacted in the neck of the gallbladder or cystic duct, causing extrinsic compression of the common bile duct.

#### 22. What is the differential diagnosis for gallbladder polyps?

Cholesterol polyps are the most common type of gallbladder polyps, followed by adenomyomatosis, adenomas, or adenocarcinomas. CT and EUS may help in differentiating benign and malignant lesions. Adenocarcinomas are more likely to be sessile and larger than 1 cm. In appropriate candidates with polyps greater than 1 cm, cholecystectomy is recommended because of the potential for malignancy. Smaller polyps may be followed by periodic ultrasound.

#### 23. What is the clinical significance of a low gallbladder ejection fraction?

Gallbladder dysmotility, defined as a gallbladder ejection fraction less than 35%, is often suspected in patients with biliary-type pain but normal ultrasonography. Gallbladder dysmotility may be diagnosed by hepatobiliary scintigraphy with cholecystokinin infusion. Management of patients with gallbladder dysmotility is controversial. Symptoms of biliary-type pain will resolve in up to 80% without treatment. Conversely, symptoms often do not resolve after cholecystectomy. Thus further studies are needed to understand the clinical significance of biliary dysmotility and the role of cholecystectomy in treating this disorder.

**24. What is a porcelain gallbladder?**

Porcelain gallbladder is characterized by intramural calcification of the gallbladder wall. The diagnosis can be made by plain abdominal radiography, ultrasonography, or abdominal CT. Prophylactic cholecystectomy is recommended to prevent development of carcinoma, which may occur in more than 30% of cases.

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**BIBLIOGRAPHY**

1. ASGE Standards of Practice Committee, Andersen MA, Fisher L, Jain R, et al. Complications of ERCP. *Gastrointest Endosc* 2012;75:467–73.
2. ASGE Standards of Practice Committee, Maple JT, Ben-Menachem T, Andersen MA, et al. The role of endoscopy in the evaluation of suspected choledocholithiasis. *Gastrointest Endosc* 2010;71:1–9.
3. DiCiaula A, Wang DQ, Wang HH, Bonfrate L, Portincasa P. Targets for current pharmacological therapy in cholesterol gallstone disease. *Gastroenterol Clin North Am* 2010;39:356–64.
4. Gore RM, Thakrar KH, Newmark GM, et al. Gallbladder imaging. *Gastroenterol Clin North Am* 2010;39:265–87.
5. Gurusamy KS, Samraj K. Early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Cochrane Database Syst Rev* 2006;(4), CD005440.
6. Hansel SL, DiBiase JK. Functional gallbladder disorder: gallbladder dyskinesia. *Gastroenterol Clin North Am* 2010;39:369–79.
7. Petros MS, Savides TJ. Systematic review of endoscopic ultrasonography versus endoscopic retrograde cholangiopancreatography for suspected choledocholithiasis. *Br J Surg* 2009;96:967–75.
8. Thistle JL, Longstreth GE, Romero Y, et al. Factors that predict relief from upper abdominal pain after cholecystectomy. *Clin Gastroenterol Hepatol* 2011;9:891–6.

# ERCP PLUS SPHINCTER OF ODDI DYSFUNCTION

Raj J. Shah, MD, FASGE, AGAF

## 1. What are the established indications for endoscopic retrograde cholangiopancreatography (ERCP)?

ERCP is generally performed using a duodenoscope. This endoscope has a side-view and a working channel that is 4.2 mm in diameter, which permits the introduction of devices for sphincterotomy, balloon and catheter passage, and stent insertion. The indications can be divided into biliary and pancreatic reasons. Biliary include the removal of common bile duct stones, the diagnosis of malignant strictures by brush cytologic examination or forceps biopsy, treatment and palliation of benign and malignant biliary strictures, respectively, and the removal of neoplastic ampullary lesions. Additional indications include the treatment of bile leaks and abdominal pain consistent with sphincter of Oddi dysfunction. Pancreatic indications include the removal of pancreatic duct stones, stenting of pancreatic duct strictures, the evaluation of recurrent acute pancreatitis, and for pancreatic duct leaks and pseudocysts.

## 2. What are common complications of ERCP?

Complications are postsphincterotomy bleeding; cholangitis; perforation at the papilla from sphincterotomy or within the duodenum from duodenoscope passage; and pancreatitis that may be related to both patient-related factors (e.g., young women are at higher risk than older men) and technical such as difficult bile duct cannulation and greater than one inadvertent pancreatic duct cannulation. Suspected sphincter of Oddi dysfunction is an independent risk factor for the development of post-ERCP pancreatitis (PEP) and ranges from 15% to 30%.

## 3. Describe ERCP equipment and techniques used for bile duct cannulation.

This is often based on endoscopist preference and includes the use of cannulas, sphincterotomes, and guide wires. Guide wire sizes range from .018" to .035". Cannula and sphincterotome tips range from 4.5 F to 5.5 F. Difficult bile duct access can be encountered for reasons related to alterations in duodenoscope position or ampullary anatomy. In these cases, advanced ERCP techniques are used, which include "double-wire" technique that includes advancing the guide wire into the pancreatic duct and introducing a second guide wire side-by-side to attempt bile duct access. Additional techniques include transpancreatic stenting followed by biliary access, transpancreatic septotomy, and precut needle-knife papillotomy.

## 4. When is cholangioscopy and pancreatoscopy performed during ERCP?

This technology involves miniature endoscopes or optical catheters approximately 10 F in size ( $\approx$ 3.3 mm) that can be passed directly into the respective duct for visualization. This permits inspection of pathologic findings such as strictures for assessment and biopsy and permits intraductal lithotripsy with electrohydraulic lithotripsy or laser lithotripsy for difficult-to-remove biliary and pancreatic duct stones.

## 5. Stents used during ERCP may be made of metal or plastic. How does one decide which type to place?

For benign biliary strictures, multiple plastic stents (ranging in size 7 F to 10 F) are often used in a serial fashion over the course of several months to resolve strictures. Often, metal stents are inserted for the palliation of malignant obstructive jaundice. They have the advantage of expanding to larger diameters (8 mm or 10 mm compared with 2- to 3-mm diameters for plastic stents) and are available with a coating that permits removability. Those with a bare mesh are generally not removable. Both plastic and metal stents may occlude over time and can be replaced or a new stent inserted within the existing one, respectively.

## 6. In patients who present with gallstone pancreatitis, when is ERCP indicated?

Randomized, controlled trials have shown that the highest benefit to ERCP in the setting of acute biliary pancreatitis is when there is an obstruction of the common bile duct by a stone or if signs of obstruction are suspected based on an elevated bilirubin (total bilirubin of more than 3.5) or imaging such as ultrasound or magnetic resonance cholangiopancreatography (MRCP) that suggests a bile duct stone is present. Improved liver function tests (LFTs) or lessened abdominal pain may indicate that the stone has passed spontaneously or that a "ball-valve" effect has occurred within the duct. Thus clinical and biochemical parameters are often followed to help determine when or if ERCP is indicated. When there is not a clinical suspicion for persistent bile duct stone, cholecystectomy with or without intraoperative cholangiography should be pursued in appropriate candidates in the convalescent phase.

## 7. When should MRCP be used instead of ERCP in patients with suspected bile duct stones?

MRCP is used when there is a low index of clinical suspicion for bile duct stones. If the clinical index is high (elevated bilirubin or ultrasound with dilated bile duct but no stone), ERCP should be the procedure of choice.

MRCP limitations include the detection of smaller stones (smaller than 5 mm) and distal stones near the ampulla. For low or moderate clinical suspicion, where available, endoscopic ultrasound (EUS) should be considered, which has high accuracy for the detection of bile duct stones and sludge without the risks associated with ERCP. It could be performed immediately prior to potential ERCP and during the same endoscopic session.

#### **8. What are the signs and symptoms of ascending cholangitis?**

- Charcot's triad includes jaundice, right upper quadrant (RUQ) abdominal pain, and fever.
- Reynold's pentad includes those three plus altered mental status and hypotension, which are both indicative of sepsis.

Ascending cholangitis is the only clear indication for emergency ERCP. If the patient with ascending cholangitis is hemodynamically unstable and unable to safely undergo sedation or anesthesia for ERCP, percutaneous transhepatic biliary drainage may be required.

#### **9. In patients with surgically altered gastroduodenal anatomy, can ERCP be performed?**

With the increasing incidence of obesity, Roux-en-Y gastric bypass surgery is becoming more common. These patients pose a challenge because of long Roux limbs (ranging from 100-200 cm) prior to reaching the jejunojejunostomy, with subsequent need to intubate the afferent or pancreaticobiliary limb. Alternatives for this anatomy include laparoscopic access of the excluded stomach and transabdominal ERCP, which has a higher technical success rate but is associated with higher morbidity. Other altered surgical anatomy such as Billroth 2, Roux-Y hepaticojejunostomy, and post-Whipple's reconstruction are associated with higher rates of success. Most of the longer Roux limbs require the use of overtube-assisted enteroscopy to gain access to the papilla, biliary, or pancreatic-enteric anastomosis.

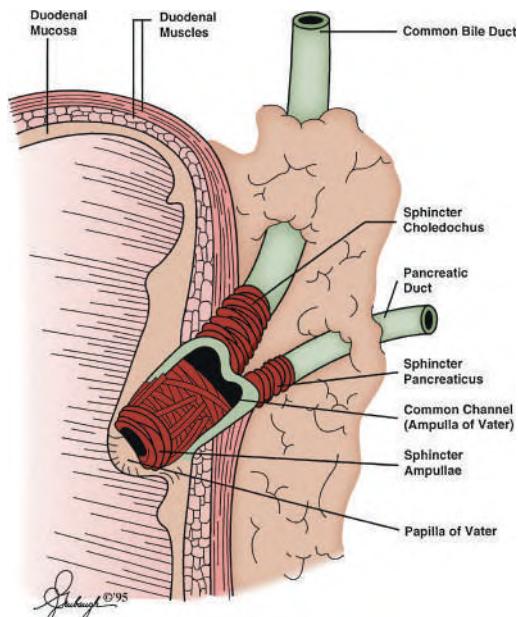
#### **10. What is the sphincter of Oddi?**

The sphincter of Oddi is a fibromuscular sheath that encircles the terminal portion of the common bile duct, main pancreatic duct (Wirsung), and common channel in the second portion of the duodenum. It is made up of smooth muscle. Three interconnected sphincters exist: choledochus, pancreaticus, and ampullae ([Figure 35-1](#)). Ruggero Oddi, as a medical student, published the early morphologic observations of the sphincter in 1887.

#### **11. How does the sphincter of Oddi function?**

- Regulates bile and pancreatic juice into the duodenum.
- Reduces duodenal reflux into the pancreatic and biliary ducts.
- Contracts tonically during the interdigestive period to promote gallbladder filling.
- Contracts phasically in the digestive period to promote flow of bile into the duodenum.

Sphincter of Oddi activity is increased by cholinergic stimulation. Endogenous substances also control the sphincter—motilin increases the intensity of sphincter contractions. Cholecystokinin (CCK) is induced by food intake and stimulates contraction of the gallbladder and relaxation of the sphincter. Both vasoactive intestinal peptide (VIP) and nitric oxide promote sphincter relaxation.



**Figure 35-1.** Sphincter of Oddi.

## 12. What is sphincter of Oddi dysfunction (SOD)?

SOD is a benign disorder characterized by a functional or structural obstruction at the level of the sphincter of Oddi. It is suspected in patients presenting with upper abdominal pain suggestive of a biliary or pancreatic origin. Objective measures such as transient elevations in liver or pancreatic enzymes and ductal dilation on noninvasive imaging, rather than the characteristics of the abdominal pain alone, are now becoming necessary to support the clinical suspicion and for consideration of ERCP.

## 13. Describe the potential pathophysiologic findings of SOD.

Two abnormalities can lead to SOD, and both may be present in a single patient. One is a primary motor abnormality of the sphincter termed *biliary dyskinesia* or *spasm* (elevated pressure). The other is fibrosis or inflammation, most likely from recurrent passage of biliary stones and microlithiasis. Symptoms may be more pronounced following cholecystectomy because of the loss of the ability to decompress elevated biliary pressure when the gallbladder distends. Further, it has been postulated that cholecystectomy may sever neuroinhibitory pathways that normally cause sphincter relaxation in response to increased biliary pressure. However, SOD is also identified in patients with an intact gallbladder.

## 14. Name typical symptoms of SOD.

Symptoms of SOD can be either biliary or pancreatic in nature. Pain is located in the epigastrium or RUQ with radiation to the back or the right infrascapular region and may be meal related. It is episodic or continuous with periodic exacerbations. Symptoms compatible with irritable bowel syndrome or nonulcer dyspepsia often coexist. Another manifestation is *idiopathic* acute pancreatitis as a result of sphincter hypertension. Other structural abnormalities such as costochondritis, ulcer, gastroesophageal reflux disease, malignancy, biliary stones, and chronic pancreatitis must be ruled out before the diagnosis of SOD is pursued.

## 15. Who is at risk for SOD?

Women in their third through fifth decades of life are at risk; the female predominance is as high as 90%. Symptoms often become apparent after cholecystectomy (hence the older term *postcholecystectomy syndrome*), but in many cases patients will have had empiric cholecystectomy for pain that was thought to originate from the gallbladder. Most importantly, the diagnosis of SOD may be diagnosed inappropriately. One controlled study suggested that somatosensory hypersensitivity of peripheral nociceptive neurons at the referred pain area (e.g., RUQ) in patients with biliary SOD may explain persistent pain.

## 16. What diagnostic evaluation should be considered in a patient presenting with symptoms suggestive of SOD?

A thorough history and physical examination will often determine which diagnostic testing is required prior to pursuing a diagnosis of SOD. The physical examination during a flare of pain often reveals a non-toxic-appearing patient with tenderness in the epigastrium or RUQ. Hepatic enzymes and pancreatic enzymes should be obtained during or soon after any flare of pain. Imaging with ultrasound or computed tomography (CT) is performed to exclude cholelithiasis, chronic pancreatitis, or other intraabdominal pathologic findings. If nausea and vomiting are predominant features, then gastric emptying studies can be considered. If dyspeptic or reflux-type symptoms are apparent, then a 24-hour esophageal pH study or upper endoscopy is reasonable.

## 17. When should you consider ERCP with sphincter of Oddi manometry (SOM)?

SOM should be considered in those patients with symptoms that are significantly disrupting the patient's quality of life, when an alternative diagnosis is not identified, and after failed therapeutic medication trials. Because there is often an overlap with dysmotility or irritable bowel syndrome-type symptoms, antispasmodics, low-dose antidepressants, or selective serotonin reuptake inhibitors (SSRIs) should initially be tried. Narcotic-requiring pain may suggest a need for manometric studies; however, these medications interfere with accurate pressure measurements. Ideally, manometry should be performed prior to patients becoming narcotic dependent.

## 18. What is the Milwaukee classification?

The standard categorization of SOD is the Milwaukee classification (also known as *Geenan-Hogan*), which is generally applied in the postcholecystectomy patient. Classification is performed before SOM and is predictive of the frequency of abnormal SOM and symptomatic response to sphincterotomy. Currently, the modified Milwaukee criteria (less stringent than the original Milwaukee criteria) are used. Abnormal laboratory values during an episode of pain should normalize in the absence of pain to be consistent with transient outflow obstruction and SOD. The schemes are similar for both biliary and pancreatic types (Table 35-1 and Table 35-2).

Table 35-3 displays the results of studies in which patients were stratified into SOD types before SOM. The right column gives the percentage of those who had biliary sphincter hypertension. In general, it is thought that patients with SOD type I or II are more likely to have a structural outflow obstruction (i.e., stenosis) versus SOD type III patients, who are more likely to have a functional problem with the sphincter.

**Table 35-1.** Modified Milwaukee Classification: Biliary

SOD TYPE	CLINICAL AND BIOCHEMICAL CHARACTERISTICS
Type I	Biliary-type pain, ALT/AST/Alk Phos $>1.1 \times$ ULN, bile duct $>10$ mm
Type II	Biliary-type pain and either ALT/AST/Alk Phos $>1.1 \times$ ULN or bile duct $>10$ mm
Type III	Biliary-type pain only

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; Alk Phos, alkaline phosphatase; SOD, sphincter of Oddi dysfunction; ULN, upper limit of normal.

**Table 35-2.** Modified Milwaukee Classification: Pancreatic

SOD TYPE	CLINICAL AND BIOCHEMICAL CHARACTERISTICS
Type I	Pancreatic-type pain, and amylase/lipase $>$ ULN and dilated pancreatic duct*
Type II	Pancreatic-type pain and either amylase/lipase $>$ ULN or dilated pancreatic duct*
Type III	Pancreatic-type pain only

SOD, Sphincter of Oddi dysfunction; ULN, upper limit of normal.

\*Pancreatic duct  $>6$  mm in the head and  $>5$  mm in the body of the pancreas.

**Table 35-3.** Percentage of Patients in SOD Patients (Types I, II, III) with Elevated Basal Sphincter Pressure

SUSPECTED BILIARY SOD TYPE	ELEVATED BASAL SPHINCTER PRESSURE
I	>90%
II	55% to 65%
III	25% to 60%

SOD, Sphincter of Oddi dysfunction.

From Sherman S: What is the role of ERCP in the setting of abdominal pain of pancreatic or biliary origin (suspected sphincter of Oddi dysfunction)? Gastrointest Endosc 56 (Suppl):S258-266, 2002.

#### 19. Which patients with suspected SOD benefit most from ERCP?

Based on the modified Milwaukee classification, patients with type I or II SOD are most likely to benefit from sphincterotomy (Table 35-4). Of note, manometry is not predictive of responsive for Type 1 patients (also termed papillary stenosis) and thus empiric sphincterotomy is recommended in these patients that clearly meet established objective criteria. The results of the Effect of Endoscopic Sphincterotomy for Suspected Sphincter of Oddi Dysfunction on Pain-Related Disability Following Cholecystectomy (EPISOD) Clinical Trial showed no reduction in disability due to pain after ERCP with manometry and sphincterotomy versus sham among type III SOD patients. The EPISOD findings do not support the use of ERCP and sphincterotomy in type III SOD patients.

**Table 35-4.** Response Rate of Endoscopic Sphincterotomy (ES)

SOD TYPE	PAIN RELIEF FROM ES IF SOM ABNORMAL	PAIN RELIEF FROM ES IF SOM NORMAL
I	>90%	>90%
II	85%	35%
III	NS	NS

SOD, Sphincter of Oddi dysfunction; SOM, sphincter of Oddi manometry; NS, non significant.

#### 20. Are there medicines to treat patients with suspected SOD?

SOD, especially milder cases, can be treated medically. A low-fat diet to decrease pancreaticobiliary stimulation may improve symptoms. The improvement, however, can also be related to concomitant upper intestinal tract dysmotility as fat increases gastric emptying time. Pharmacologic therapy has also been investigated. Medications that decrease the pressure of the sphincter (such as calcium channel blockers and nitrates) have been shown to reduce symptoms in some patients. However, treatment is often hampered by side effects. Antispasmodic agents may be useful as well.

## 21. Can pharmacologic agents cause clinical SOD?

Yes. Among the most notable substances are opiates. Increased pressure in the biliary duct has been documented following administration of fentanyl and morphine. Some patients will experience biliary-type pain following use of these agents. In addition, SOD has been documented in a series of male opium addicts. It is theorized that long-term opium use leads to sphincter hypertension and sustained dysfunction.

## 22. In SOD patients, when should the pancreatic duct be stented?

In patients undergoing biliary sphincterotomy for SOD, prophylactic pancreatic stenting in the setting of pancreatic sphincter hypertension reduces the incidence of PEP compared with those who did not receive a stent (7% versus 26%). Further, stenting reduces PEP in patients with suspected SOD and normal biductal manometry results (2.4% versus 9%). Pancreatic duct stenting should also be performed in patients undergoing pancreatic sphincterotomy and considered in those with a history of PEP. A metaanalysis of studies that compared stenting versus no stenting and included patients at a high risk of developing PEP showed a reduction in pancreatitis rates (5.8% versus 15.5%; odds ratio, 3.2; 95% confidence interval, 1.6 to 6.4) with the use of pancreatic stents. In general, however, endoscopist discretion and expertise are required in determining the appropriateness of pancreatic stenting as technical factors may prevent its placement and patients who have a failed attempt at pancreatic stenting are at a higher risk for developing PEP.

## 23. What medication can be used to reduce the risk of PEP?

A metaanalysis of four randomized controlled trials found that using rectally administered nonsteroidal antiinflammatory drugs (NSAIDs) did seem to reduce PEP risk. In a landmark *New England Journal of Medicine* paper, a prospective, randomized, double-blind, placebo-controlled multicenter study showed that the use of rectal indomethacin in high-risk patients is superior to placebo in reducing PEP. A total of 602 patients were enrolled and completed follow-up. The majority of patients (82%) had a clinical suspicion of SOD. PEP developed in 27 of 295 patients (9.2%) in the indomethacin group and in 52 of 307 patients (16.9%) in the placebo group ( $P=0.005$ ). Moderate to severe pancreatitis developed in 13 patients (4.4%) in the indomethacin group and in 27 patients (8.8%) in the placebo group ( $P=0.03$ ).

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## BIBLIOGRAPHY

- Cotton P, Durkalski V, Romagnuolo J, et al. Results of the EPISOD multi-center sham-controlled trial of sphincterotomy in patients with suspected sphincter of Oddi dysfunction Type III. Meeting of the American College of Gastroenterology, San Diego, CA. 2013.
- Dumonceau JM, Tringali A, Blero D, et al. Biliary stenting: indications, choice of stents and results: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. *Endoscopy* 2012;44(3):277–98.
- Elmunzer BJ, Scheiman JM, Lehman GA, et al. US cooperative for outcomes research in endoscopy: a randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med* 2012;366(15):1414–22.
- Elmunzer BJ, Waljee AK, Elta GH, et al. A meta-analysis of rectal NSAIDs in the prevention of post-ERCP pancreatitis. *Gut* 2008;57:1262–7.
- Freeman ML, DiSario JA, Nelson DB, et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest Endosc* 2001;54:425–34.
- Kawakami H, Maguchi H, Mukai T, et al. A multicenter, prospective, randomized study of selective bile duct cannulation performed by multiple endoscopists: the BIDMEN study. *Gastrointest Endosc* 2012;75(2):362–72.
- Kurucsai G, Joó I, Fejes R, et al. Somatosensory hypersensitivity in the referred pain area in patients with chronic biliary pain and a sphincter of Oddi dysfunction: new aspects of an almost forgotten pathogenetic mechanism. *Am J Gastroenterol* 2008; (103):2717–25.
- Moon JH, Cho YD, Cha SW, 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.
- Park S, Watkins JL, Fogel EL, et al. Long-term outcome of endoscopic dual pancreaticobiliary sphincterotomy in patients with manometry-documented sphincter of Oddi dysfunction and normal pancreatogram. *Gastrointest Endosc* 2003;57:481–91.
- Petrov MS, van Santvoort HC, Besselink MG, et al. Early endoscopic retrograde cholangiopancreatography versus conservative management in acute biliary pancreatitis without cholangitis: a meta-analysis of randomized trials. *Ann Surg* 2008;247(2):250–7.
- Piraka C, Shah RJ, Awadallah NS, Langer DA, Chen YK. Transpapillary cholangioscopy-directed lithotripsy in patients with difficult bile duct stones. *Clin Gastroenterol Hepatol* 2007;5(11):1333–8.
- Shah RJ, Adler DG, Conway JD, Diehl DL, Farraye FA, Kantsevoy SV, et al. ASGE Technology SER: cholangiopancreatscopy. *Gastrointest Endosc* 2008;68(3):411–21.
- Shah RJ, Langer DA, Antillon MR, Chen YK. Cholangioscopy and cholangioscopic forceps biopsy in patients with indeterminate pancreaticobiliary pathology. *Clin Gastroenterol Hepatol* 2006;4(2):219–25.
- Shah RJ, Smolkin M, Ross AS, et al. A multi-center, U.S. experience of single balloon, double balloon, and rotational overtube enteroscopy-assisted ERCP in long limb surgical bypass patients. *Gastrointest Endosc* 2013;77(4):593–600.
- Shah RJ, Somogyi L, Chuttani R, Croffie J, DiSario J, Liu J, et al. ASGE Technology SER: ERCP short-wire systems. *Gastrointest Endosc* 2007;66(4):650–7.
- Sharma SS. Sphincter of Oddi dysfunction in patients addicted to opium: an unrecognized entity. *Gastrointest Endosc* 2002;55:427–30.
- Singh P, Das A, Isenberg G, et al. Does prophylactic stent placement reduce the risk of post-ERCP acute pancreatitis? A meta-analysis of controlled trials. *Gastrointest Endosc* 2004;60:544–50.

18. Tarnasky PR, Palesch YY, Cunningham JT, et al. Pancreatic stenting prevents pancreatitis after biliary sphincterotomy in patients with sphincter of Oddi dysfunction. *Gastroenterology* 1998;115:1518–24.
19. Toolli J, Roberts-Thomson IC, Kellow J, et al. Manometry based randomized trial of endoscopic sphincterotomy for sphincter of Oddi dysfunction. *Gut* 2000;46:98–102.
20. Wu YV, Linehan DC. Bile duct injuries in the era of laparoscopic cholecystectomy. *Surg Clin N Am* 2010;90(4):787–802.
21. Cotton PB, Durkalski V, Romagnuolo J, Pauls Q, Fogel E, Tarnasky P, et al. Effect of endoscopic sphincterotomy for suspected sphincter of Oddi dysfunction on pain-related disability following cholecystectomy: the EPISOD randomized clinical trial. *JAMA* 2014;311(20):2101–9.

# ACUTE PANCREATITIS

Enrique Molina, MD, and Jamie S. Barkin, MD

## 1. How common is acute pancreatitis (AP)?

AP was responsible for approximately 300,000 hospital admissions in the United States in 2012 and is the most frequent gastroenterology diagnosis for hospital admission. The average duration of hospitalization is 5 days. The majority of AP cases are mild and categorized as edematous pancreatitis (80%). When AP is complicated by necrosis (20%), the clinical course is more severe with overall mortality of approximately 15%.

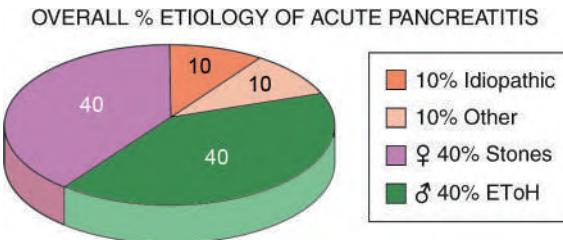
## 2. What are the most common causes of AP?

Gallstones and alcohol are the most common causes of AP in the United States and worldwide (Figure 36-1). During the past 20 years, the age-standardized rate for the incidence of pancreatitis has been 16 per 100,000 people/year in men and 10.2 per 100,000 people/year in women.

Alcohol-induced pancreatitis is the more common cause in men, accounting for approximately 50% of the cases (worldwide incidence of 7.9 per 100,000 people), followed by gallstone pancreatitis with 25% of the cases (worldwide incidence of 3.5 per 100,000 people).

In women, gallstone pancreatitis is the most common cause, accounting for 50% of the cases (worldwide incidence of 4.8 per 100,000 people/year), followed by idiopathic and alcohol-induced pancreatitis.

Idiopathic AP, a diagnosis of exclusion, ranks as the third most common cause of AP in men (worldwide incidence of 3.8 per 100,000 people/year) and second most common cause in women (worldwide incidence of 1.9 per 100,000 people/year). Approximately 10% of idiopathic cases are secondary to microlithiasis when followed with abdominal ultrasound or other type of imaging study. Previous studies showed a higher incidence of microlithiasis, ranging from 50% to 75% of the idiopathic cases. Therefore in patients with recurrent idiopathic pancreatitis, elective cholecystectomy can be considered.



**Figure 36-1.** Most common causes of acute pancreatitis.

## 3. What is a helpful mnemonic to remember the many causes of AP?

"GET SMASHED"

G Gallstones, microlithiasis, and biliary sludge

E Ethanol, endoscopic retrograde cholangiopancreatography (ERCP)

T 3 Ts: toxins (organophosphates, methanol, scorpion bites), tumors (primary pancreatic or metastatic), trauma (usually blunt from bicycle handle bar, steering wheel, or surgery)

S Steroids and ulcers

M Mumps and other infections (parasitic, viral, and bacterial)

A Autoimmune (autoimmune pancreatitis, immunoglobulin G4 [IgG4] disease, celiac disease, vasculitis)

S Stenosis: sphincter of Oddi dysfunction and papillary stenosis

H 3 Hs: hypertriglyceridemia, hypercalcemia, hypothermia

E Genetic: cystic fibrosis (CFTR), hereditary pancreatitis (PRSS1), others

D Drugs (azathioprine, 6-mercaptopurine, estrogen, human immunodeficiency virus (HIV) drugs, tetracycline, sulfa, furosemide)

## 4. Which drugs have been reported to cause AP?

Drug-induced pancreatitis is the cause of up to 2% of patients with AP and can occur immediately upon initiation of the drug or can be delayed by months; it must be considered as a potential etiologic factor of AP in all patients. The World Health Organization (WHO) database lists 525 different drugs suspected to cause AP as a side effect.

The causality for many of these drugs remains elusive and for only 37 of these 525 drugs a definite causality was established (Table 36-1). Definite proof for causality is defined by the WHO classification if symptoms reoccur upon rechallenge. Many new drugs have been released, and for several of them, cases reporting episodes of drug-induced pancreatitis exist.

Studies have classified the drugs depending on their published weight of evidence and the clinical presentation of the pancreatitis after the patient has been exposed to the agent. This classification is as follows:

- Class 1: drugs with positive rechallenge (1A: excluding other causes for pancreatitis; 1B: not excluding other causes of AP, for example, alcohol)
- Class 2: drugs with more than four cases reported in the literature
- Classes 3 and 4: no consistent data to relate the drug to AP

**Table 36-1. 37 Drugs with Definite Association to Pancreatitis**

DIDANOSINE	←MOST COMMON TO LEAST COMMON→		SIMVASTATIN	
Asparaginase	Estrogens	Sulindac	Phenformin	Bortezomib
Azathioprine	Opiates	Furosemide	Hydrochlorothiazide	Capecitabine
Valproic acid	Tetracycline	Lamivudine	Interferon 2α	Cimetidine
Pentavalent antimonials	Cytarabine	Octreotide	Cisplatin	Metronidazole
Pentamidine	Steroids	Carbamazepine	Erythromycin	Olanzapine
Mesalamine	Trimethoprim/Sulfamethoxazole	Acetaminophen	Itraconazole	Tamoxifen
Mercaptopurine	Sulfasalazine	Enalapril	Methyldopa	Oxyphenbutazone

From Nitsche C, et al: Drug-induced pancreatitis, *Curr Gastroenterol Rep* 14(2):131-138, 2012.

## 5. How is pregnancy associated with AP?

AP in pregnancy is a rare condition, with a prevalence of approximately 0.001%. Cholelithiasis or microlithiasis is present in 50% to 90% of the cases. Other causes include hyperlipidemia and medications. Most episodes occur after the second trimester and have a favorable overall prognosis. First-trimester episodes of AP are associated with a risk of fetal loss of approximately 20%, but surgery is preferably done after the first trimester. In patients with biliary AP who were managed conservatively, the recurrence rate was up to 50% versus no recurrence in those with biliary AP who underwent cholecystectomy. Therefore these patients should undergo cholecystectomy after delivery if the patient can safely wait. Endoscopists can use x-ray shielding in pregnant patients.

## 6. Which infectious agents have been implicated in causing AP?

Although an association is debated because of a lack of solid evidence, a vast number of case reports suggest a possible interrelation between infectious agents and pancreatitis. These include:

- Viruses: mumps, coxsackievirus, cytomegalovirus, and varicella-zoster, herpes simplex, Epstein-Barr, hepatitis A, and hepatitis B viruses, hepatitis E, influenza A and B
- Bacteria: *Mycoplasma*, *Legionella*, *Leptospira*, *Salmonella*, *Mycobacterium tuberculosis*, *Brucella*
- Fungi: *Aspergillus*, *Candida albicans*
- Parasites: *Toxoplasma*, *Cryptosporidium*, *Ascaris*, *Clonorchis sinensis*, *fasciola hepatica*, *taenia*

## 7. How do parasitic infections caused by *Clonorchis sinensis* and *Ascaris lumbricoides* cause AP?

These parasitic infections cause biliary-pancreatic obstruction. The parasites migrate into the pancreaticobiliary tract and can cause AP by blocking the main pancreatic duct and obstructing drainage of pancreatic secretions.

## 8. Is there an increased incidence of AP in patients with HIV and acquired immune deficiency syndrome (AIDS)?

Yes. Up to 10% of patients with HIV infection or AIDS develop AP. The cause is usually multifactorial, with drugs and infections being the most common. The likely drugs include didanosine, trimethoprim and sulfamethoxazole, and pentamidine. The most likely infections causing AP are cytomegalovirus, *Cryptosporidium*, and *Toxoplasma*.

Abnormalities of lipid metabolism have been described in HIV-infected patients receiving a protease inhibitor, including hypertriglyceridemia and hypercholesterolemia, which may lead to AP.

### 9. Does blunt trauma to the pancreas cause AP?

Penetrating trauma (e.g., gunshot or stab wounds) may cause damage to the pancreas parenchyma and may disrupt its duct system and result in AP.

However, the most common cause of trauma that results in pancreatitis is blunt trauma, caused by compression of the pancreas against the spine. This is commonly caused by motor vehicle accidents with compression of the pancreas by the steering wheel or seat belt and is usually seen in adults. Bicycle handlebar injury to the abdomen can cause pancreatic trauma in children and adults.

Trauma causing AP can range from mild to severe injury, and the latter may include transection of the gland. Nonrupture of the pancreatic duct causes AP, whereas acute rupture of the pancreatic duct may result in pancreatic ascites. Injury may cause pancreatic duct strictures with resulting chronic pancreatitis.

### 10. What is pancreas divisum? Is it associated with an increased incidence of recurrent AP?

Pancreas divisum is a common congenital anomaly of the pancreatic ducts seen in whites (7%), but rare among blacks and Asians. It occurs when the dorsal and ventral pancreatic ducts fail to fuse into one pancreatic duct. Each of the ducts then has a separate duodenal draining site, with the ventral duct draining into the major papilla and the dorsal duct draining into its own or accessory papilla (minor papilla). In patients with pancreas divisum, the majority of the exocrine pancreas drains through an accessory pancreatic duct and through an often smaller and hypoplastic accessory papilla, prompting dorsal pancreatic duct pressures to build up. Recent reports have suggested that genetic factors such as CFTR, CLADN-2, PRSS1, or SPINK1 may have a cofactor role in the development of AP, and chronic pancreatitis associated with pancreatic divisum and other anatomic abnormalities.

### 11. What is the relationship between hypertriglyceridemia and AP?

Hypertriglyceridemia can cause AP in up to 3% of patients. It is a more common cause of AP than hypercalcemia. Serum triglyceride levels greater than 800 mg/dL are usually needed to induce an episode of AP. Alcohol binge drinking and estrogen therapy can acutely drive moderate hypertriglyceridemia into the 800- to 1000-mg/dL range. These levels need to be determined when patients are on their usual medications and eating a regular diet (not when they are fasting, which results in decreased levels). Treatment options are dietary fat restriction and lipid-lowering agents to reduce recurrence after the initial AP episode has resolved. Even patients undergoing pancreas transplantation with a history of hyperlipidemia have a high incidence of AP after transplantation. Another adjuvant treatment modality is plasmapheresis.

### 12. What is the relationship between hypercalcemia and AP?

Hypercalcemia from any cause (hyperparathyroidism or paraneoplastic) can increase the risk of having an episode of AP. There is a tenfold increased risk of AP in patients with primary hyperparathyroidism compared with the normal population. Possible mechanisms are the calcium activation of trypsinogen to trypsin within the pancreas.

### 13. How is the diagnosis of AP made?

The diagnosis of AP is based on clinical assessment, biochemical analysis, and radiologic evaluation (Box 36-1). Diagnosis requires the presence of two out of three criteria to be positive.

**Abdominal Pain:** Most patients with AP experience epigastric pain that radiates to the back (40% to 70%) with nausea and vomiting. Up to 30% to 40% of patients do not present with the classic clinical presentation of pain or their pain presentation is hidden by other clinical symptoms such as altered mental status or multiorgan system failure.

**Laboratory Tests:** Diagnosis of AP requires serum amylase/lipase to be three times the upper limit of normal (ULN); levels more than five times the ULN are more specific of a pancreatic origin. Other pancreatic enzymes tested in the serum or the urine can be used for diagnosis; however, these tests are not widely available. These tests include pancreatic isoamylase, phospholipase A 2, elastase 1, trypsinogen-1, trypsinogen-2, and trypsinogen-3, procalcitonin, trypsinogen-activated protein, activation peptide of carboxypeptidase B, trypsin-2-alpha1 antitrypsin complex, and circulating DNA. These do not appear to be more sensitive than amylase or lipase.

#### Box 36-1. Acute Pancreatitis Diagnostic Criteria (Revised Atlanta Consensus 2012)

Clinical diagnosis of AP requires two of three criteria:

1. Serum amylase or lipase  $\geq 3 \times$  ULN
2. Abdominal pain strongly suggestive of AP (epigastric and radiating to back)
3. Characteristic findings of AP on imaging, with CT best and most universally available imaging modality.

AP, Acute pancreatitis; BUN, blood urea nitrogen; CT, computed tomography; ULN, upper limit of normal.

From Banks PA, Acute Pancreatitis Classification Working Group: Classification of acute pancreatitis, 2012: revision of the Atlanta classification and definitions by international consensus, Gut 63:102-111, 2012.

**Radiologic Imaging:** Contrast-enhanced computed tomography (CECT) is the single best and most readily available test to evaluate the pancreas. It is best used when the diagnosis and cause of AP are uncertain or when AP is severe or complicated by infection. CECT is safest after effective hydration and most accurate in estimating the degree of pancreatic necrosis (PNec) after 48 to 72 hours. Ultrasound is an excellent imaging test for gallstones, but often limited in the examination of the pancreas because of obesity or gas artifact from ileus often seen with AP. Magnetic resonance imaging with gadolinium is accurate in estimating severity of pancreatitis, but is often impractical in patients with severe pancreatitis. Endoscopic ultrasound (EUS) is gaining popularity to investigate for suspected microlithiasis, common bile duct (CBD), and gallstones, and therapeutically to sample or drain walled-off necrosis or other fluid collections.

#### 14. How does serum amylase compare with serum lipase in the diagnosis of AP?

Serum amylase typically increases within 6 to 12 hours of AP onset and gradually declines over the first week. Conversely, serum lipase increases within 24 hours of AP onset and remains elevated in the serum for a longer period than serum amylase, thereby making its sensitivity higher compared with serum amylase. Serum amylase levels may be falsely elevated in several nonpancreatic conditions (see Question 15). Total serum amylase is 40% from pancreatic origin and 60% from extrapancreatic sources. Therefore some studies have shown superior specificity of serum lipase compared with serum amylase in the diagnosis of AP; combination of enzymes does not improve diagnostic accuracy. Fractionation of elevated serum amylase into pancreatic-type isoamylase and salivary-type isoamylase may help in the diagnosis of AP and exclude a pancreatic source.

#### 15. What are the causes of hyperamylasemia and hyperlipasemia?

- Hyperamylasemia: AP, pancreatic pseudocyst, chronic pancreatitis, pancreatic carcinoma, biliary tract disease, increased small bowel permeability from perforation, infarction, obstruction, acute appendicitis, ectopic pregnancy
  - Other: renal failure, parotitis, macroamylasemia, malignancy with ectopic amylase production, salpingitis, HIV infection, cirrhosis, acidosis, or ketoacidosis
- Hyperlipasemia: AP, pancreatic pseudocyst, chronic pancreatitis, pancreatic carcinoma, biliary tract disease, increased small bowel permeability (perforation, infarction, obstruction), acute appendicitis
  - Other: renal failure, ketoacidosis, macrolipasemia, HIV infection

#### 16. What are macroamylasemia and macrolipasemia?

In these pathologic conditions, the lipase and the amylase are bound to serum immunoglobulins (IgA and IgG) or polysaccharides, which result in a macromolecule that is not easily excreted by the kidney. Poor renal clearance results in increased levels of these serum enzymes. Diagnosis is made by measuring the levels of amylase or lipase in the serum as well as in the urine. In macroamylasemia and macrolipasemia, the serum levels are elevated but the urine levels are low or undetectable. These conditions have been associated with celiac disease, HIV, inflammatory bowel disease, and sarcoidosis.

#### 17. What cause of AP should be suspected in patients who present with normal serum amylase levels?

- Delayed presentation (amylase has already returned to normal)
- Alcoholic pancreatitis presenting as AP superimposed on chronic pancreatitis (burned out gland)
- Severe hypertriglyceridemia (high triglycerides can interfere with measurement of amylase)

#### 18. Does the magnitude of hyperamylasemia or hyperlipasemia correlate with the severity of AP?

No. The levels of amylase and lipase do not correlate with the severity of AP or its prognosis. Serial measurements in patients with AP are not useful to predict prognosis or for altering management; therefore if elevated initially, there is no need to follow levels.

#### 19. What is the most reliable serum marker for diagnosing biliary AP?

The positive predictive value of alanine aminotransferase (ALT) value is more than 150 U/L is 95%. A combination of increased alkaline phosphatase, total bilirubin, direct bilirubin, amylase, and lipase levels may be used in prediction of biliary pancreatitis with a positive predictive value of 80%.

#### 20. How is AP classified?

The revised Atlanta classification (2012) divides AP into mild, moderate, and severe disease.

- Mild AP: No organ failure and no local or systemic complications; is associated with a self-limited course.
- Moderate AP: Organ failure resolves within 48 hours or local or systemic complications without persistent organ failure.
- Severe AP: Consists of persistent single or multiorgan failure for more than 48 hours. These patients usually have one or more local complications and are at an increased risk of death.

The level of severity and survival can be predicted by clinical scores (see Question 21), including Ranson's criteria and Acute Physiology and Chronic Health Evaluation (APACHE II) score.

The Atlanta symposium recommends assessing the following organ systems to define organ failure:

- Cardiovascular: Shock (systolic blood pressure less than 90 mm Hg)
- Respiratory: Pulmonary insufficiency ( $\text{PaO}_2/\text{FiO}_2$  less than 400)
- Renal: Renal failure (serum creatinine greater than 1.4 mg/dL)

## 21. What prognostic scoring systems are used to assess the severity of AP?

The most widely used clinical prognostic scores include Ranson's criteria, the Glasgow prognostic criteria, the APACHE II classification system, and the Balthazar computed tomography (CT) severity index; the most recent addition is the bedside index of severity in AP (BISAP). There are many free applications and online calculators that can be used for all of these scoring systems (e.g., <http://www.mdcalc.com/> and <http://medcalc3000.com/BISAPScore.htm>)

- Ranson's criteria: Consists of 11 indices measured at two time stages (admission and at 48 hours after admission). Ranson's criteria are limited by required delay of 48 hours to evaluate 6 of the 11 variables. The total score correlates with severe AP, PNec, and mortality.
- Glasgow prognostic criteria: These criteria reduce the 11 indices used in Ranson's criteria to 8. They are used to obtain the prognosis of gallstone-induced AP. The limitations of the Glasgow criteria are that it uses SI units (not used in the United States) and is solely determined after 48 hours of admission.
- APACHE II classification system: This scoring system can be used at any time after admission. This score uses age and acute physiologic parameters that are only commonly used in the intensive care unit. A score of 8 or more is associated with a high mortality. It has an accuracy of approximately 90%.

Patients with pancreatitis and poor outcome usually have systemic inflammatory response syndrome (SIRS). The SIRS criteria consist of the following and can be determined any time during the patient's admission:

- Heart rate greater than 90 beats/min
- Temperature greater than  $38^{\circ}\text{C}$  or less than  $36^{\circ}\text{C}$
- Respiratory rate greater than 20 breaths/min or  $\text{PaCO}_2$  less than 32 mm Hg
- White blood cell count greater than 12,000 cells/mL or less than 4000 cells/mL or greater than 10% band forms
- Balthazar CT severity index is a scoring system based on CECT findings of inflammation, presence of collections, and degree of necrosis. It differentiates AP into interstitial pancreatitis and necrotizing pancreatitis. In general, interstitial pancreatitis (interstitial edema and inflammation) is associated with mild disease with a mortality rate of approximately 1%. Conversely, necrotizing pancreatitis (focal or diffuse necrosis) is associated with severe disease, needing more intensive management and having a mortality rate of 10% in patients with sterile necrosis and up to 30% in patients with infected necrosis. In survivors, the presence of PNec predicted a more severe outcome (major complication, longer hospitalization, and death). A CT severity index of less than 2 is associated with a low morbidity and mortality. On the other hand, a score of greater than 5 is 17 times more likely to predict prolonged hospitalization and 10 times more likely to predict the need for surgical debridement of the necrosis, and the patient is 8 times more likely to die.
- BISAP is a new, simpler prognostic scoring system, which is as accurate as the APACHE II and Ranson's criteria for prognosis in AP. The BISAP is applicable within the first 24 hours of presentation. It uses five criteria, for which one point is given if present; these include blood urea nitrogen (BUN >25 mg/dL), altered mental status (Glasgow coma score <15), age >60 years, presence of SIRS, and presence of pleural effusions. Patients with a score of 0 had a mortality of less than 1%, whereas patients with a score of 3 or more had a mortality rate of approximately 15% (Table 36-2).

**Table 36-2. BISAP Score**

CRITERIA	POINTS
BUN >25 mg/dL	1
Impaired mental status	1
Presence of SIRS ( $\geq$ two criteria)	1
Age >60 years	1
Presence of a pleural effusion	1

BISAP, Bedside index of severity in acute pancreatitis; BUN, blood urea nitrogen; SIRS, systemic inflammatory response system.

## 22. What is the role of serum markers in assessing the severity of AP?

Several serum markers can in theory be used for prognosis and enable us to distinguish between mild and severe pancreatitis; however, data are very limited. These markers are trypsinogen activation peptide, polymorphonuclear leukocyte elastase, interleukin (IL) 6, IL-10, IL-8, tumor necrosis factor, platelet activation

factor, procalcitonin, antithrombin III, substance P, C-reactive protein, and hematocrit (hemoconcentration). Only two are clinically useful:

- A. C-reactive protein has been used in Europe with good levels of accuracy in predicting severe pancreatitis at 48 hours after admission, but not at admission.
- B. Hematocrit levels of 44 (hemoconcentration) at admission and failure to decrease in 24 hours may be predictive of necrotizing AP and organ failure. This is especially useful when combined with elevated BUN on admission. Both should decrease with adequate hydration.

#### **23. What are other prognostic indicators in AP?**

Mortality during the first week of AP results from SIRS (see Question 21). Alcohol-induced AP has been associated with increased risk of necrotizing pancreatitis and necessity for artificial ventilation. An interval between the onset of symptoms and hospital admission of less than 24 hours, as well as rebound tenderness or guarding on presentation, is associated with increased severity of AP. An additional prognostic factor is elevated body mass index. Obese individuals tend to have severe AP with increased associated morbidity and mortality compared with nonobese patients. The presence of visceral adiposity and increased waist circumference are poor prognostic factors.

#### **24. What are the major systemic complications of AP?**

- Respiratory failure: Acute respiratory distress syndrome is found in 20% of patients with acute severe pancreatitis. Exudate pleural effusion, left more frequent than right, may occur, with diagnosis made by the finding of high amylase levels in the pleural fluid more so than in the serum.
- Renal failure: Renal hypoperfusion leads to acute tubular necrosis.
- Shock: Shock is caused by third spacing of fluids, peripheral vasodilatation, and depressed left ventricular function.
- Hyperglycemia: Insulin deficiency caused by islet cell necrosis or hyperglucagonemia results in hyperglycemia.
- Disseminated intravascular coagulation: Antithrombin III value of 69% at admission was the best cutoff value to predict fatal outcome, having a sensitivity of 81% and specificity of 86%.
- Fat necrosis: Tender red nodules on the skin (subcutaneous tissue) suggests fat necrosis. This is caused by elevated circulating lipase, which can also affect peritoneum, mediastinum, bone, pericardium, pleura, and joints; the latter can mimic acute arthritis.
- Retinopathy (Purtscher's disease): Retinopathy is a very rare complication caused by occlusion of the posterior retinal artery with aggregated granulocytes.
- Encephalopathy: Encephalopathy is manifested by several stages ranging from agitation and disorientation to hallucinations and coma.

#### **25. When is infection of PNec suspected?**

Infection of PNec usually occurs 5 to 14 days after the onset of the disease (median time 8 days). The hallmark of infected PNec is failure to improve, ongoing fever, tachycardia, hypotension, leukocytosis, and worsening abdominal pain. In this case, CECT should be performed to diagnose and localize the area of necrosis and fine-needle aspiration performed (Gram stain and culture) to determine whether the necrosis is sterile or infected. If infected PNec is found and the patient is stable, antibiotics are initiated according to the organism and sensitivity. The presence of gas bubbles within the pancreas or in the retroperitoneum suggests the presence of pancreatic infection.

#### **26. What is the most common organism isolated in infected PNec?**

Infected PNec is usually caused by a single organism (80%). The infection results from bacterial translocation of intestinal flora via hematogenous, biliary, and lymphatic spread with colonization of the pancreatic necrotic tissue. The organisms most commonly isolated are *Escherichia coli* (50%), *Enterococcus* spp., *Staphylococcus* spp., *Klebsiella* spp., *Proteus* spp., *Pseudomonas* spp., *Streptococcus faecalis*, and *Bacteroides* spp. (and, rarely, *Candida* spp.).

Medical treatment depends on stability of the patient. If the patient is unstable, then debridement is the therapy of choice—this is the usual clinical situation. However, if the patient is stable, then adjusting the antibiotic coverage based on the sensitivity from the aspirate is an alternative initial management decision. If the patient does not improve, debridement is indicated.

#### **27. How is AP treated?**

The first 24 hours of AP are referred to as the “golden hours,” an opportunity to minimize morbidity and mortality by maintaining microcirculation of the pancreas and intestine. Aggressive fluid resuscitation should begin in the emergency department with 1 to 2 liters of lactated Ringer’s solution and then continued at a rate of 150 to 300 mL/h intravenously continuously for the first 24 hours (roughly 2 to 3 mL/kg/h, adjusted by physical examination and preexisting comorbid conditions), and then titrated based on urine output or change in BUN and hematocrit. Lactated Ringer’s solution is an alkalizing solution that contains calcium and has been proven to be more effective in reducing SIRS and mortality than saline solutions. In cases of AP associated with hypercalcemia, lactated Ringer’s solution should be avoided.

Mild AP is treated with general supportive care as described previously. A nasogastric tube can be placed for ileus with distention or nausea with vomiting. In AP, there is no role for prophylactic antibiotics.

Severe AP has a higher morbidity and mortality. Thus supportive care should be given in a monitored setting (intensive care unit), and special attention given to the development of systemic complications and to restoring and monitoring volume status. In patients with PNec, there is **no role for the use of prophylactic antibiotics**, as they may promote the development of resistant organisms or fungal suprainfection.

If PNec becomes infected and debridement is needed, the standard approach has been open surgical debridement. Postpone the procedure 30 days after the onset of the pancreatitis if the patient is stable. This approach was associated with less mortality but more long-term antibiotic use, fungal pancreatic infection, and antibiotic-resistant bacteria compared with immediate debridement (see Question 26).

New alternatives to open surgical debridement include a laparoscopic approach such as video-assisted retroperitoneal debridement and transperitoneal debridement. More recently, endoscopic necrosectomy has been demonstrated to be safe and effective. It is associated with a definitive resolution rate of 76%, a mortality rate of 5%, and a morbidity rate of 30% (mean of four endoscopic sessions).

#### **28. When and via what route should nutritional support be initiated in patients with AP?**

Resumption of enteral nutrition should be the goal in the treatment of AP. It should be started as soon as the patient is able to eat and does not have nausea, vomiting, or evidence of abdominal ileus. In mild AP, there is no role for parenteral feeding or nasojejunal enteral feeds, because patients tend to start oral intake within 1 week after onset of the disease. If oral feeding is predicted not to resume for a period of more than 5 to 7 days, other sources of nutrition should be considered. Total parenteral nutrition (TPN) is associated with line infections and increased bowel permeability. There is strong evidence that using enteral nutrition is more beneficial than TPN as it preserves the bowel function and integrity and reduces bacterial translocation (decreasing pancreatic infection). This can be given via nasojejunal tube feeds; however, postpyloric placement of a feeding tube is not necessarily required. In addition, enteral nutrition is less expensive than those of TPN. The delivery of elemental or semielemental formulas into the duodenum has been shown to decrease pancreatic stimuli by 50%. Also, a small randomized study showed no difference in morbidity and mortality between nasogastric delivery of nutrition (low-fat, semielemental formula) versus nasojejunal delivery. If TPN is elected, adding intravenous (IV) fat emulsions when using TPN is generally safe and well tolerated as long as baseline triglycerides are less than 400 mg/dL and there is no previous history of hyperlipidemia. Use of IV glutamine may be beneficial in reducing complications in patients with AP.

#### **29. When should ERCP be performed in biliary AP?**

ERCP with sphincterotomy should be performed emergently after admission when:

- There is evidence of acute cholangitis in the setting of acute biliary pancreatitis.
- There is evidence of a persistent CBD stone shown by radiologic or clinical features as persistent jaundice, elevated liver function tests, or dilated CBD on abdominal ultrasound. The best clinical predictor to show persistent CBD stone is an elevated serum total bilirubin level of greater than 1.35 on hospital day 2 (sensitivity, 90%; specificity, 63%). Magnetic resonance cholangiopancreatography (MRCP) can be used to determine the presence of choledocholithiasis, with the advantage that it is noninvasive. Endoscopic ultrasound before ERCP has been advocated, because it can reliably diagnose choledocholithiasis, avoiding unnecessary ERCP in patients with no stones in the biliary tract.
- Some authors believe that patients with biliary pancreatitis that is severe or predicted to be severe (controversial) should undergo ERCP.
- Pancreatic duct stenting is recommended to reduce the incidence of complications (7.7% versus 31.9%) in patients undergoing emergency ERCP for choledocholithiasis with acute biliary pancreatitis who have undergone a difficult sphincterotomy.

The routine use of prelaparoscopic ERCP for presumed biliary pancreatitis is not justified. In this case, preoperative MRCP or EUS is indicated.

Patients without evidence of choledocholithiasis or with normal liver function tests or evidence of a small stone preoperatively should have an intraoperative cholangiogram at the time of laparoscopic cholecystectomy with bile duct exploration if needed to remove a stone. If a stone cannot be removed, postoperative ERCP is indicated and is usually successful.

#### **30. Should patients undergo a cholecystectomy after an episode of biliary AP?**

Yes. There is a 20% risk of recurrent biliary complications such as AP, cholecystitis, or cholangitis that occur within 6 to 8 weeks of the initial episode of biliary AP. These recurrent complications are associated with increased readmissions and hospital stay.

#### **31. How soon should a cholecystectomy be performed in patients with biliary AP?**

In patients with mild biliary pancreatitis, laparoscopic cholecystectomy is considered safe within the first week of the index hospitalization. Studies have shown that discharging the patient home to undergo an elective laparoscopic cholecystectomy results in 20% of those patients experiencing adverse events that require readmission before the scheduled surgery, which is usually planned 6 weeks after the initial episode of AP.

In the case of severe biliary AP, laparoscopic cholecystectomy should be delayed until after 1 week of the initial episode, allowing the patient to recover from the acute episode.

In patients with comorbid diseases who are unable to undergo cholecystectomy, an endoscopic sphincterotomy may be a good choice to prevent further episodes of biliary AP.

### **32. Should patients with coexisting alcoholism and cholelithiasis undergo cholecystectomy to prevent further attacks of AP?**

No. Cholecystectomy does not prevent further attacks of AP in patients with coexisting alcoholism; in these patients, the disease follows the alcohol-related pancreatitis pattern. Alcohol abstention is mandatory does not guarantee prevention of relapsing or chronic pancreatitis. When the serum markers suggest stone passage, an elective cholecystectomy with liver biopsy and intraoperative cholangiogram should be considered.

### **33. What are acute pancreatic fluid collections?**

Acute fluid collections are accumulations of fluid resulting from pancreatic inflammation. They occur in up to 57% of patients with severe AP. They do not have communication with any pancreatic duct and lack a clear wall of confinement. Their pancreatic enzyme content level is low, and most of them improve spontaneously within 6 weeks with conservative management. A minority of these fluid collections can develop a true nonepithelialized capsule progressing to a pseudocyst formation.

### **34. What are pseudocysts?**

Pseudocysts are pancreatic fluid collections that have high pancreatic enzyme content, associated with pancreatic duct disruption and communicate initially with the pancreatic duct. They usually develop between 4 and 6 weeks from the onset of AP. Their capsule lacks an epithelial lining (hence their name). They may occur in any part of the pancreas or peripancreatic area, but most commonly are located at the body-tail of the pancreas.

### **35. When should a pseudocyst be suspected?**

A pseudocyst should be suspected in a patient after an episode of AP who exhibits:

- No improvement of AP
- Persistent elevation in amylase and lipase levels
- Development of an epigastric mass
- Persistent abdominal pain after clinical improvement of the acute episode

### **36. What are the indications for pseudocyst drainage?**

Indications for pseudocyst drainage are:

- Symptomatic (pain or abdominal bloating)
- Progressive enlargement (some experts believe that if it is greater than 6 cm or present longer than 6 weeks, drainage should be considered).
- Presence of suspected complications (infected, hemorrhagic, pancreatic ascites, extrinsic abdominal compression on organs, or obstruction)
- Suspected malignancy or if the diagnosis of a pseudocyst is in question

### **37. How are pancreatic pseudocysts drained?**

Pseudocysts that meet criteria for drainage can be treated radiologically, endoscopically, or surgically, depending on its location, size, and relationship with the pancreatic ducts as well as the experience of the physician performing the procedure.

- Asymptomatic pseudocysts or small ones (less than 6 cm) generally are treated conservatively and followed with abdominal ultrasound.
- Surgical drainage is the gold standard.
- Radiologic drainage can be done via CT-guided percutaneous catheter drainage. This procedure is mostly reserved for high-risk patients who cannot undergo surgery or who have an immature pseudocyst or infected pseudocysts.
- Endoscopic drainage can be performed with guidance of EUS when the pseudocyst is adherent to the stomach or the duodenum. It can be done by creating a cystgastrostomy or a cystduodenostomy or by insertion of a stent via the ampulla into the PD and into the pseudocyst cavity.

### **38. What are possible complications of an untreated pancreatic pseudocyst?**

- Infection: Diagnosis made by pseudocyst aspiration; may be treated with drainage.
- Pancreatic ascites: Leakage of the pseudocyst contents or pancreatic duct into the abdominal cavity may occur. Aspiration with analysis of ascitic fluid (high amylase and high protein) may be diagnostic, and placement of a stent into the pancreatic duct is a treatment choice, combined with the use of octreotide; nothing per mouth and TPN improve the outcome. If this fails, a surgical approach should be considered.
- Fistula formation: Usually occurs after external drainage of the pseudocysts.
- Rupture: Secondary to a rupture of the pseudocyst into the abdominal or thoracic cavities. Manifesting as acute abdomen or pleural effusion. Surgical approach is the treatment of choice.
- Bleeding: Bleeding is the most life-threatening complication. It occurs when the pseudocyst erodes into an adjacent vessel (pseudoaneurysm); blood becomes confined in the cyst versus spontaneous drainage into

the gut via the pancreatic duct or a fistula formation, so-called hemosuccus pancreaticus. This condition should be suspected in patients with AP and gastrointestinal bleeding or who have an acute, unexplained decrease in the hematocrit with abdominal pain. This can be diagnosed by abdomen CT and should be treated with embolization of the vessel.

- **Obstruction:** Pseudocysts can cause obstruction of (1) the biliary system (especially the CBD when located at the head of the pancreas), (2) vessels (inferior vena cava, portal vein), (3) intestinal duodenal obstruction, and (4) urinary system obstruction.
- **Jaundice:** May be due to the pseudocyst occluding the CBD.

Please access ExpertConsult to view a **Clinical Vignette** for this chapter.

## BIBLIOGRAPHY

1. Georgios I, Papachristou, Venkata Muddana et al. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. *Am J Gastroenterol* 2010;105:435–41. <http://dx.doi.org/10.1038/ajg.2009.622>.
2. Arvanitakis M, Dehay M, De Maertelaere V, et al. Computed tomography and magnetic resonance imaging in the assessment of acute pancreatitis. *Gastroenterology* 2004;126:715–23.
3. Badalow N, Baradarian R, Iswara K, et al. Drug induced pancreatitis: an evidence-based review. *Clin Gastroenterol Hepatol* 2007;5:648–61, quiz 644.
4. Balthazar EJ. CT diagnosis and staging of acute pancreatitis. *Radiol Clin North Am* 1989;27:19–37.
5. Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. *Am J Gastroenterol* 2006;101:2379–400.
6. Bertin C, et al. *Am J Gastroenterol* 2012;107:311–7.
7. Besselink MG, Verwer TJ, Schoenmaeckers EJ, et al. Timing of surgical intervention in necrotizing pancreatitis. *Arch Surg* 2007;142:1194–201.
8. Brown A, Orav J, Banks PA. Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis. *Pancreas* 2000;20:367–72.
9. Dellinger RP, Tellado JM, Soto NE, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: Randomized double blind, placebo-controlled study. *Ann Surg* 2007;245:674–83.
10. Eatock FC, Chong P, Menezes N, et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. *Am J Gastroenterol* 2005;100:432–9.
11. Felderbauer P, Karakas E, Fendrich V, et al. Pancreatitis risk in primary hyperparathyroidism: relation to mutations in the SPINK1 trypsin inhibitor (N34S) and the cystic fibrosis gene. *Am J Gastroenterol* 2008;103(2):368–74.
12. Fosmark C, Baillie J. AGA Institute technical review on acute pancreatitis. *Gastroenterology* 2007;132(5):2022–44.
13. Galasso PJ, Litin SC, O'Brien JF. The macroenzymes: a clinical review. *Mayo Clin Proc* 1993;68:349–54.
14. Garg PK, Tandon RK, Madan K. Is biliary microlithiasis a significant cause of idiopathic recurrent acute pancreatitis? A long-term follow up study. *Clin Gastroenterol Hepatol* 2007;5:75–9.
15. Grochowiecki T, Szmidt J, Galazka Z, et al. Do high levels of serum triglycerides in pancreas graft recipients before transplantation promote graft pancreatitis? *Transplant Proc* 2003;35:2339–40.
16. Hernandez A, Petrov MS, Brooks DC, et al. Acute pancreatitis and pregnancy: a 10-year single center experience. *J Gastrointest Surg* 2007;11:1623–7.
17. Isenmann R, Runzi M, Kron M, et al. German antibiotics in severe acute pancreatitis study group: prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-control double blind trial. *Gastroenterology* 2004;126:997–1004.
18. Kingsnorth A, O'Reilly D. Acute pancreatitis. *Br Med J* 2006;332:1072–6.
19. Lankisch PG, Karimi M, Bruns A, et al. Time trends in incidence of acute pancreatitis in Lueenburg: a population-based study. In: Presented at the 38th annual meeting of the American Pancreatic Association, Chicago, IL; 2007.
20. Lankisch PG, Lowenfels AB, Maisonneuve P. What is the risk of alcoholic pancreatitis in heavy drinkers? *Pancreas* 2002;25:411–2.
21. Levy P, Boruchowicz A, Hastier P, et al. Diagnostic criteria in predicting a biliary origin of acute pancreatitis in the era of endoscopic ultrasound: multicentre prospective evaluation of 213 patients. *Pancreatology* 2005;5:450–6.
22. Maeda K, Hirota M, Ichihara A, et al. Applicability of disseminated intravascular coagulation parameters in the assessment of the severity of acute pancreatitis. *Pancreas* 2006;32:87–92.
23. Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. *Br Med J* 2004;328:1407.
24. Matos C, Bali MA, Delhay M, et al. Magnetic resonance imaging in the detection of pancreatitis and pancreatic neoplasms. *Best Pract Res Clin Gastroenterol* 2006;20:157–78.
25. McCullough L, Sutherland F, Preshaw R, et al. Gallstone pancreatitis: does discharge the patient and readmission for cholecystectomy affect outcome? *J Hepatobiliary Pancreat Surg* 2003;5:96–9.
26. Mofidi R, Duff MD, Wigmore SJ, et al. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. *Br J Surg* 2006;93:738–44.
27. O'Keefe SJ, Lee RB, Anderson FP, et al. Physiological effects of enteral and parenteral feeding on pancreatobiliary secretion in humans. *Am J Physiol* 2005;289:G181–7.
28. Oriá A, Cimmino D, Ocampo C, et al. Early endoscopic intervention versus early conservative management in patients with acute gallstone pancreatitis and biliopancreatic obstruction: a randomized clinical trial. *Ann Surg* 2007;245:10–7.
29. Pamuklar E, Semelka RC. MR imaging of the pancreas. *Magn Reson Imaging Clin N Am* 2005;13:313–30.
30. Rana SS, Bhasin DK, Nanda M, et al. Parasitic infestations of the biliary tract. *Curr Gastroenterol Rep* 2007;9:156–64.
31. Rettali C, Skarda S, Garza MA, et al. The usefulness of laboratory tests in the early assessment of severity of acute pancreatitis. *Crit Rev Clin Lab Sci* 2003;40:117–49.

32. Schiphorst AH, Besselink MG, Boerma D, et al. Timing of cholecystectomy after endoscopic sphincterotomy for common bile duct stones. *Surg Endosc* 2008;22(9):2046–50.
33. Sharma VK, Howden CW. Metaanalysis of randomized controlled trials of endoscopic retrograde cholangiography and endoscopic sphincterotomy for the treatment of acute biliary pancreatitis. *Am J Gastroenterol* 1999;94:3211–4.
34. Urbach DR, Khajanchee YS, Jobe BA, et al. Cost-effective management of common bile duct stones: a decision analysis of the use of endoscopic retrograde cholangiopancreatography (ERCP) intraoperative cholangiography, and laparoscopic bile duct exploration. *Surg Endosc* 2001;15:4–13.
35. Werner J, Feuerback S, Uhl W, et al. Management of acute pancreatitis: from surgery to interventional intensive care. *Gut* 2005;54:426–36.
36. Whitcomb D. Acute pancreatitis. *N Engl J Med* 2006;354:2142–50.
37. Working Party of the British Society of Gastroenterology, Association of Surgeons of Great Britain and Ireland, Pancreatic Society of Great Britain and Ireland, Association of Upper GI Surgeons of Great Britain and Ireland. UK guidelines for the management of acute pancreatitis. *Gut* 2005;54(Suppl. 3):iii1–9.
38. Yadav D, Agarwal N, Pitchimoni CS. A critical evaluation laboratory tests in acute pancreatitis. *Am J Gastroenterol* 2002;97:1309–18.
39. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 2003;144:1252–61.
40. Yadav D, Pitchumoni CS. Issues in hyperlipidemic pancreatitis. *J Clin Gastroenterol* 2013;36:54–62.
41. Simeone DM, Pandol SJ. Special Edition The pancreas: biology, disease and therapy. *Gastroenterology* 2013;144(6):1163–326.

# CHRONIC PANCREATITIS

Enrique Molina, MD, and Jamie S. Barkin, MD

## 1. What classification system is used for chronic pancreatitis (CP)?

CP is a continuous irreversible inflammatory and fibrotic condition that leads to impairment of exocrine and endocrine function of the organ. The most used classification of CP is the Marseilles-Rome classification modified by Sarles; this classification divides CP into four groups based on epidemiologic characteristics, molecular biology, and morphologic characteristics (Table 37-1).

**Table 37-1.** Marseilles-Rome Classification

TYPE	CHARACTERISTICS	EXAMPLE
Calcifying CP (lithogenic)	Irregular fibrosis Intraductal protein plugs Intraductal stones Ductal injury	ETOH abuse is leading cause
Obstructive CP	Glandular changes Uniform fibrosis Ductal dilation Acinar atrophy Improvement with pancreatic duct obstruction removal	Common causes • Benign ductal stricture • Intraductal tumor
Inflammatory CP	Mononuclear cell infiltration Exocrine parenchymal destruction Diffuse fibrosis Atrophy	Associated autoimmune diseases: • Primary sclerosing cholangitis • Sjögren's syndrome • Autoimmune pancreatitis
Asymptomatic pancreatic fibrosis	Silent diffuse perilobular fibrosis	Idiopathic senile CP

CP, Chronic pancreatitis.

(From Sarles H, Adler G, Dani R, et al. The pancreatitis classification of Marseilles—Rome 1988. Scandinavian J Gastroenterol 1989;24:641–642.)

## 2. What is the most common cause of CP in adults?

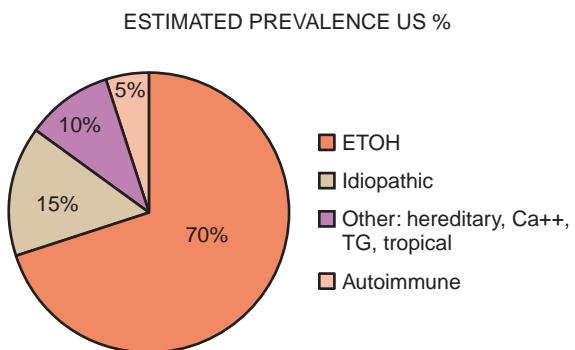
The most common cause of CP shows variation based on culture and geographical location. In Western societies, alcohol abuse comprises 70% of all cases of CP, whereas in southern India, 70% of all cases are due to tropical pancreatitis. The prevalence of other etiologic factors in US is demonstrated in Figure 37-1.

An ethyl alcohol (ETOH) consumption threshold of more than 5 drinks a day for 5 to 10 years is needed before an associated risk for pancreatitis is evident. Furthermore, only 5% of alcoholics develop CP and only 10% of alcoholic cirrhotics develop CP. The North American Pancreatitis Study 2 has identified that common genetic variants in CLDN2 and PRSS1-PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. The homozygous (or hemizygous male) x-linked CLND2 genotype confers the greatest risk for interaction with alcohol consumption and pancreatitis. The 4 or 5:1 male/ female frequency of ETOH CP may be partially explained by the CLND2 hemizygous frequency of 0.26 in men versus homozygote frequency of 0.07 in women. These new findings further support the notion that a CP is the consequence of multiple injurious “hits” and predispositions to injury. These “hits” include complex interaction between sentinel acute pancreatitis events and immune and genetic pathways (Figure 37-2).

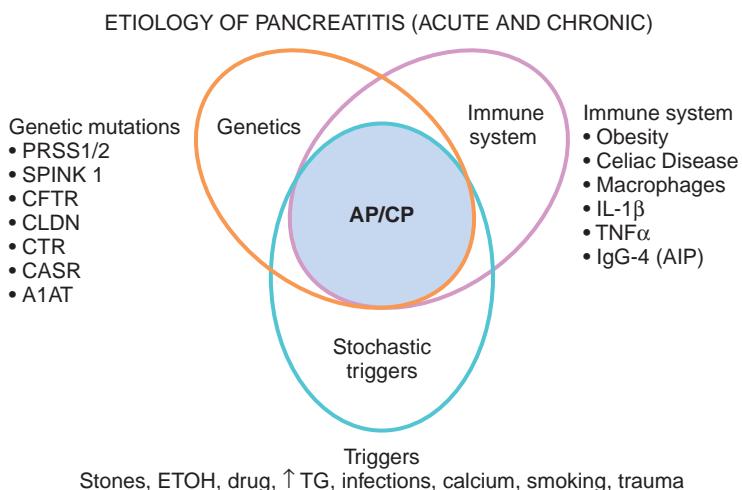
## 3. What are other causes of CP?

The TIGAR-O classification system lists possible causes of CP:

Toxic metabolic: alcoholic, tobacco smoking, hypercalcemia, hyperlipidemia, chronic renal failure  
Idiopathic: tropical and cause unknown



**Figure 37-1.** Etiologic factors of chronic pancreatitis. Ca, Calcium; ETOH, ethyl alcohol; TG, triglycerides.



**Figure 37-2.** Etiologic factors of acute and chronic pancreatitis. AP, Acute pancreatitis; CP, chronic pancreatitis; ETOH, ethyl alcohol; Ig, immunoglobulin; IL, interleukin; TNF, tumor necrosis factor.

**Genetic:** autosomal dominant, cationic trypsinogen PRSS1-PRSS2, autosomal-recessive/modifier genes, CFTR mutations, x-linked, claudin (CLND)2, SPINK1 mutations, chymotrypsin-C (CTRC), CASR, others

**Autoimmune:** type 1 and type 2

**Recurrent and severe acute pancreatitis:** postnecrotic (severe acute pancreatitis), vascular diseases or ischemia, postradiation exposure

**Obstructive:** pancreas divisum (controversial), sphincter of Oddi dysfunction (controversial), duct obstruction (tumors, posttraumatic)

#### 4. What is autoimmune pancreatitis?

Autoimmune pancreatitis is the most recently described form of CP. It is also known as *sclerosing pancreatitis*, *lymphoplasmacytic pancreatitis*, or *idiopathic tumefactive CP*. It is characterized by the presence of autoantibodies, increased serum immunoglobulin levels, elevated IgG4 levels in the serum (usually above 140 mg/dL), and a response to administration of corticosteroids (there is a recurrence rate of approximately 41% on discontinuation of steroids). The patient normally presents with an abdominal mass and jaundice with complaints of abdominal pain. Imaging shows a diffuse or focal enlargement of the pancreas with pancreatic duct stricture. Pathologic reports show lymphoplasmacytic infiltrate. This type of CP has been associated with other autoimmune disorders such as primary sclerosing cholangitis, autoimmune hepatitis, primary biliary cirrhosis, Sjögren's disease, and scleroderma (Table 37-2).

HISORt criteria proposed by the Mayo Clinic includes the presence of one or more of the following: (H) histologic examination suggestive of autoimmune pancreatitis; (I) pancreatic imaging suggestive of autoimmune pancreatitis; (S) serologic findings, with an IgG4 more than two times the upper limit of normal; (O) other organ involvement, such as parotid or lacrimal gland involvement, mediastinal lymphadenopathy, or retroperitoneal fibrosis; and (Rt) response to steroid treatment of pancreatic and extrapancreatic manifestations.

**Table 37-2.** Autoimmune Pancreatitis

	<b>TYPE 1 AIP (100% JAPAN, 80% US)</b>	<b>TYPE 2 AIP (PREDOMINANT IN EUROPE)</b>
Histologic findings	Lymphoplasmacytic sclerosing pancreatitis	Idiopathic duct-centric pancreatitis
Noninvasive diagnosis	Possible > 70% of cases	Definitive diagnosis requires histologic examination
Mean age (yr)	70s	50s
Presentation	Obstructive jaundice 75% Acute pancreatitis 15%	Obstructive jaundice 50% Acute pancreatitis ≈ 33%
Imaging	Diffuse swelling 40% Focal features 40%	Focal features ≈ 85%
IgG4 association	IgG4 ↑↑ serum and positive tissue staining IgG4	Not associated with IgG4
Other organ involvement	Multiple	None
Associated IBD	2%-6%	16%
Responds to steroids	Yes	Yes
Longterm outcome	Frequent relapses	No relapses

AIP, Autoimmune pancreatitis; IBD, inflammatory bowel disease; Ig, immunoglobulin; US, United States.

From Sah RP, Chari ST. *Autoimmune pancreatitis: an update on classification, diagnosis, natural history and management*. Curr Gastroenterol Rep. 2012;14(2):95–105.

### 5. What is tropical or nutritional pancreatitis?

Tropical pancreatitis is the most common form of CP of unknown cause that affects persons in areas of India and countries near the equator such as Indonesia, Brazil, and Africa. In some patients a mutation in the SPINK1 gene has been found. It presents in children and young adults with abdominal pain, severe malnutrition, dilated pancreatic duct with large duct calculi, and exocrine-endocrine insufficiency with development of diabetes mellitus. It may result from protein-calorie malnutrition and it is linked to nutritional antioxidant deficiencies such as zinc, copper, selenium.

### 6. What is obstructive CP?

Any type of obstruction of the pancreatic duct either malignant or benign can lead to CP. Causes include strictures from trauma, calcific stones, papillary stenosis, pseudocysts, and malignant tumors. Removing the obstruction can reverse some of the pancreatic damage and preserve organ function.

Pancreas divisum can produce a relative obstruction to flow at the minor papilla and has been associated with development of CP. There may need to be genetic mutations as a cofactor in the development of pancreatitis.

### 7. What is hereditary pancreatitis?

Hereditary pancreatitis is an autosomal dominant disorder with a high penetrance in the range of 80% that accounts for less than 1% of all cases of CP. It affects both sexes equally, and presents as episodes of recurrent acute pancreatitis in children aged 10 to 12 years who then develop CP. Patients with this condition have the predisposition of developing pancreatic cancer with an approximately incidence of 40% by age 70. In hereditary pancreatitis, genetic abnormalities include mutations in the cationic trypsinogen gene (PRSS1) and pancreatic secretory trypsin inhibitor (SPINK1); cystic fibrosis transmembrane conductance regulator (CFTR) genes have been confirmed as major risk factors for CP. Mutations in the chymotrypsin C (CTRC) and CASR genes are considered lesser risk factors for the development of CP. The PRSS1 mutation is the only autosomal dominant type of hereditary pancreatitis. These genetic studies should be offered to young patients with recurrent pancreatitis, especially those with a family history of pancreatic disease.

### 8. How is cystic fibrosis (CF) associated with CP?

CF is the most common autosomal recessive defect in white patients. Patients with CF besides the sinopulmonary disease commonly have exocrine pancreatic insufficiency in the range of 85%. CF is due to mutations in the CFTR gene (more than 1000 different genetic polymorphisms in CFTR have been identified). CFTR gene mutations cause deranged transport of chloride or other CFTR-affected ions, such as sodium and bicarbonate, which leads to thick, viscous pancreatic secretions, resulting in pancreatic duct obstruction and acinar cell destruction with posterior fibrosis and pancreatitis. Pancreatitis can occur with or without other associated manifestations of CF, and disease manifestations depend on the presence of additional genetic or environmental

disease modifiers. It should be considered in patients with pancreatitis who have pulmonary issues as well as in young men who have had a history of difficulty in conception.

#### **9. What is idiopathic CP?**

Idiopathic CP cannot be related to alcohol abuse or other conditions previously described. It accounts for 10% to 30% of cases of CP.

#### **10. What is the most common presenting symptom of CP?**

Abdominal pain is the most common symptom occurring in up to 80% of the patients. The pain is described as epigastric that radiates to the back, is dull and constant; worsens 15 to 30 minutes after meals and improves with sitting or leaning forward, and frequently is associated with nausea and vomiting. However, abdominal pain may be absent in up to 23% of patients with CP.

#### **11. What are the causes of weight loss in patients with CP?**

Causes of weight loss include:

- Pancreatic exocrine insufficiency with malabsorption of proteins, carbohydrates, and fat (needs to have more than 90% of nonfunctioning pancreas)
- Uncontrolled diabetes mellitus
- Decreased caloric intake as a result of fear of increasing abdominal pain (sitophobia)
- Early satiety caused by delayed gastric emptying or gastric outlet obstruction-duodenal obstruction.

#### **12. Is steatorrhea an early symptom of CP?**

No. Steatorrhea occurs when more than 90% of the exocrine function is impaired or insufficient. It signifies advanced disease. It occurs before protein deficiency because lipolysis decreases faster than proteolysis. It manifests as foul smelling, greasy, loose stools, and liposoluble vitamin deficiency (A, D, E, K).

Early symptoms of CP are nonspecific and include bloating, abdominal discomfort, pain, and change in bowel habits.

#### **13. Is diabetes mellitus an early manifestation of CP?**

No. Diabetes mellitus occurs late in the course of CP. Up to 70% of patients with CP will develop diabetes mellitus. Those with chronic calcifying disease are more likely to develop diabetes compared with those with noncalcifying disease patients. Diabetes is caused by the destruction of the insulin-producing beta cell by the CP, and as opposed to patients with type 1 diabetes mellitus the alpha cells that produce glucagon are also destroyed, resulting in frequent episodes of spontaneous hypoglycemia. Patients with diabetes caused by CP suffer retinopathy and neuropathy at the same levels compared with other types of diabetes. On the other hand, diabetic ketoacidosis and nephropathy are uncommon.

#### **14. Are measurements of serum pancreatic enzymes helpful in the diagnosis of CP?**

Pancreatic fibrosis results in destruction of the acinar cell with subsequent decreased production of amylase and lipase. These enzymes are not helpful in the diagnosis of CP. Levels may be elevated, normal, or decreased despite clinical symptoms of pain. There is no sensitive or specific test for the diagnosis of CP; however, low levels of trypsinogen or fecal elastase may suggest CP.

#### **15. What do elevated levels of bilirubin and alkaline phosphatase suggest in the patient with CP?**

Elevated levels of bilirubin or alkaline phosphatase in the setting of CP suggest biliary obstruction caused by compression of the intrapancreatic portion of the bile duct secondary to fibrosis, pancreatic mass or carcinoma, and edema of the organ. Also, elevated enzymes can be caused by alcohol intake or other hepatotoxic drugs.

#### **16. What specialized test directly measures pancreatic exocrine function?**

Pancreatic exocrine secretions are normally high in bicarbonate ( $\text{pH} = 7.8$  to 8). The *secretin stimulation test*, with or without the administration of cholecystokinin measures the volume of these pancreatic secretions and the concentration of bicarbonate after the injection of secretin. This is an invasive test needing placement of a duodenal catheter (Dreiling tube) to collect the secretions. Because of its complexity, this test is not widely available and it has a sensitivity of 75% to 95%. It is more sensitive for diagnosis of advanced disease (Table 37-3). Endoscopic methods have been developed and are comparable to standard secretin stimulation test; it involves aspiration of pancreatic secretions through the suction channel of the endoscope and measurements of bicarbonate levels.

**Table 37-3. Secretin Stimulation Test**

BICARBONATE LEVEL	RESULTS
<50 mEq/L	Consistent with chronic pancreatitis
50 to 75 mEq/L	Indeterminate
>75 mEq/L	Normal

**17. What conditions may be associated with a false-positive secretin stimulation test?**

Primary diabetes mellitus, celiac sprue, cirrhosis, and Billroth II gastrectomy may all result in false-positive secretin stimulation tests. Patients in the recovery phase of an episode of acute pancreatitis may also have false-positive results.

**18. What indirect tests of pancreatic exocrine function are used?**

Indirect tests measure pancreatic enzymes in the serum and stool or any metabolites of the enzymes in serum, urine, or breath after an orally administered compound. Because these studies measure the level of pancreatic maldigestion, the more advanced the disease, the more sensitive will be the measurement. Exocrine function is significantly impaired after 90% of the secretory capacity of the organ is destroyed. Therefore these studies are not sensitive in early pancreatic disease.

Some of the studies are:

- Serum trypsin: very low (20 ng/mL) in patients with advanced CP and steatorrhea
- Fecal chymotrypsin
- Fecal elastase: more stable and easier to use than the chymotrypsin stool test
- [14C]-olein absorption test
- Fecal fat determination: quantitative 72-hour fecal test collected after the patient follows a diet for 3 days that contains 100 g/day of fat
- Breath tests: labeled substrates that are digested by pancreatic enzymes have been proposed for breath tests, and are currently under study.

**19. Are plain abdominal radiographs helpful in the diagnosis of CP?**

Yes. The finding of diffuse pancreatic calcifications in plain abdominal radiographs is specific for CP. This is seen in 30% to 40% of the patients with CP. Calcifications are not seen in early stages of the disease, so abdominal radiograph usefulness is mostly in advanced disease. Calcium deposition is most common with alcohol-related patients in the United States and tropical pancreatitis patients in India.

**20. What other imaging modalities are used in the diagnosis of CP?**

- Transabdominal ultrasound (US)
- Computed tomography (CT)
- Magnetic resonance imaging (MRI)

All three studies are able to show pancreatic duct dilation, calcifications, pancreatic duct filling defects, and pseudocysts. US has a sensitivity of 60% to 70% and a specificity of 80% to 90%. CT has 10% to 20% more sensitivity than US with similar specificity. MRI shows more detail in the evaluation of the pancreatic duct.

**21. What is the role of endoscopic retrograde cholangiopancreatography (ERCP) in the diagnosis of CP?**

ERCP was previously the test of choice to visualize abnormalities in the pancreatic duct in patients with moderate-advanced CP. It is consider the gold standard in evaluating the pancreas with a sensitivity of 90% and a specificity of 100%. However, it is an invasive and risky procedure (complications of 5% and mortality of 0.1%). With the development of new technology, such as the magnetic retrograde cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS), the role of ERCP has been limited to a therapeutic role. Findings on ERCP suggestive of CP include the characteristic *chain of lakes* beading of the main pancreatic duct, ectatic side branches, and intraductal filling defects. Also, it can be useful in differentiating CP from pancreatic adenocarcinoma, with adenocarcinoma showing a dominant stricture and CP showing ductular changes with multiple areas of stenosis, dilation, irregular branching ducts, and intraductal calculi. In autoimmune pancreatitis, the main pancreatic duct is narrowed with areas of stenosis, as opposed to CP with a dilated duct with areas of stenosis.

**22. What is the Cambridge Grading system of CP based on ERCP findings?**

See Table 37-4.

**Table 37-4. Cambridge Grading System of Chronic Pancreatitis on ERCP**

GRADE	PANCREATIC DUCT	SIDE BRANCHES
Normal	Normal	Normal
Equivocal	Normal	<3 Abnormal
Mild	Normal	≥3 Abnormal
Moderate	Abnormal	≥3 Abnormal
Marked	Abnormal + one or more of the following: Large cavity (>10 mm) Ductal obstruction Severe duct dilation or irregularities Intraductal filling defects or calculi	≥3 Abnormal

ERCP, Endoscopic retrograde cholangiopancreatography.

**23. What is the role of EUS in the diagnosis of CP?**

EUS allows excellent visualization of the pancreatic duct and the parenchyma. CP can be diagnosed based on abnormal ductal findings or abnormal parenchymal findings (see Question 24). A minimum of three criteria are needed to diagnose CP. Studies comparing ERCP with EUS have shown good correlation of the findings in patients with CP. In mild CP, EUS may show abnormalities not seen in the ERCP or functional testing. Novel imaging techniques such as contrast-enhanced EUS and elastography seem promising for the evaluation of CP, pancreatic cancer, and autoimmune pancreatitis.

**24. What are the EUS criteria for the diagnosis of CP?**

See Table 37-5.

**Table 37-5. Chronic Pancreatitis (Endoscopic Ultrasound Criteria)\***

Ductal findings	Dilated main duct Dilated side branches Duct irregularities Hyperechoic duct margins Stones/calcifications
Parenchymal findings	Hyperechoic foci Hyperechoic strands Gland lobularity Cystic cavities

\*The more findings, the more likely is the accuracy of diagnosis of chronic pancreatitis

**25. What is the role of MRCP in the diagnosis of CP?**

MRCP is an excellent initial study for the evaluation of CP, because it is a noninvasive test and evaluates both pancreatic parenchyma and ducts. Studies show good correlation with the ductular findings obtained in MRCP with those obtained in ERCP. MRCP visualizes ductular anatomy, including strictures, and is able to identify cysts not connected with the ductular system. Its limitations are the inability to evaluate areas where the pancreatic duct is small (pancreatic tail or side branches). Secretin-enhanced MRCP can help characterize subtle pancreatic disease by improving imaging of the pancreatic duct anatomy, however this adds a significant cost to the study.

**26. What is the most common complication of CP?**

The most common complication of CP is the development of pseudocysts, which occurs in 20% to 40% of patients. Pseudocysts should be suspected in patients with stable CP who have:

- Persistent abdominal or back pain
- Development of an epigastric mass that may cause obstructive symptoms, such as nausea, vomiting, and jaundice

Pseudocysts can be:

- Acute (resolution within 6 weeks) or
- Chronic (no self-resolution and persisting for longer than 6 weeks)

**27. How are pseudocysts treated?**

Asymptomatic pseudocysts or ones that are not increasing in size (usually less than 6 cm) are generally treated conservatively and followed with abdominal US. Pseudocysts that meet criteria for drainage can be treated radiologically, endoscopically, or surgically, depending on location, size, experience of the physician performing the procedure, and relationship with the pancreatic ducts.

*Surgery* is the gold standard. It is done in patients who have had:

- Failure with percutaneous or endoscopic drainage (increases morbidity)
- Multiple or large pseudocysts
- Complications such as fistulas, bleeding, pseudocysts near the ampulla or pancreatic duct obstruction
- High suspicion for malignancy

*Radiology* can be done via percutaneous catheter drainage; this procedure is mostly reserved for high-risk patients who cannot undergo surgery, for immature pseudocysts, and for infected fluid collection.

*Endoscopic drainage* can be performed with the support of EUS when the pseudocyst wall has had enough time to mature and is adherent to the stomach or the duodenum. It can be done by creating a cystgastrostomy or a cystduodenostomy or with the insertion of a stent via the ampulla through the pancreatic duct into the pseudocyst cavity.

### 28. What are other complications of CP?

- *Distal common bile duct (CBD) obstruction* occurs in 5% to 10% of patients with CP. Compression of the intrapancreatic portion of the CBD at the head of the pancreas by edema, fibrosis, or pseudocyst causes jaundice, pain, dilated ducts, and potentially cholangitis. If untreated, it can lead to biliary cirrhosis.
- *Diabetes mellitus* is a late complication, and occurs in up to one third of patients with CP.
- *Duodenal obstruction* occurs in 5% of patients with CP. External compression of the duodenum by the pancreas causes nausea, vomiting, weight loss, gastric outlet obstruction, and postprandial gastric fullness.
- *External pancreatic fistulas* occur after surgical or percutaneous drainage of a pseudocyst or wall of necrosis.
- *Internal pancreatic fistulas* occur spontaneously after pancreatic duct rupture or pseudocyst leakage.
- *Pseudoaneurysms* are pseudocyst erosions into the splenic vein causing hemosuccus pancreaticus.
- *Splenic vein thrombosis* is due to pancreatic inflammation or pseudocyst obstruction in the pancreas with subsequent gastric varices formation.
- Patients with CP have a lifetime predisposition to *pancreatic adenocarcinoma* of 4%.

### 29. How is distal CBD obstruction diagnosed and treated?

Distal CBD obstruction should be suspected in the setting of CP with elevated alkaline phosphatase as an early finding. Subsequently, jaundice or ascending cholangitis may occur. They are caused by inflammation, fibrosis, or pseudocyst formation at the head of the pancreas. Imaging studies such as MRCP may demonstrate narrowing of the distal CBD in form of gradual tapering, bird beak stenosis, or hourglass stricture.

Treatment options in the case of no complications (cholangitis, secondary biliary cirrhosis), include observation of the patients for at least 2 months with serial liver function tests (LFTs). If any complication or persistent elevated LFTs are seen, surgical decompression is warranted. Endoscopic biliary stent is often chosen as the first line treatment for CBD strictures; however, it provides temporary relief and needs frequent stent exchange because of blockage or migration. Surgical biliary bypass with cholecystojejunostomy or choledochojejunostomy provides better long-term outcomes than endoscopic therapy, and therefore is preferred for younger patients. If pseudocyst is the cause of the biliary obstruction, decompression of the pseudocyst should be the initial approach, and if not amenable to endoscopic drainage then surgical biliary decompression may be combined with cystojejunostomy.

### 30. How is duodenal obstruction diagnosed and treated?

Duodenal obstruction is suspected in the setting of early satiety and postprandial abdominal bloating or diagnosis of gastric outlet obstruction. It is best diagnosed by upper gastrointestinal series. Treatment includes initial supportive therapy; however, persistent obstruction warrants surgical approach, usually gastrojejunostomy. If biliary obstruction is also present, biliary bypass is performed and may be combined with pancreateojejunostomy, if persistent pain resulting from pancreatic duct obstruction is present. If the patient is not a good surgical candidate, endoscopic placement of a duodenal stent is an option.

### 31. How are pancreatic fistulas treated?

The general approach for the treatment of pancreatic fistulas includes reducing pancreatic secretions with somatostatin analog (octreotide 50 to 250 mcg subcutaneously every 8 hours), and keeping the pancreas at rest by using total parenteral nutrition with nothing by mouth. This approach takes several weeks, and sometimes a more invasive intervention is needed.

Other approaches are ERCP placement of a pancreatic duct stent if the pancreatic disruption site is identified, or surgical decompression or resection if there is persistence of the fistula after failed medical treatment.

If pancreatic ascites or pancreatic pleural effusion develops, large-volume paracentesis with diuretics or thoracentesis with diuretics, respectively, may be an additional type of treatment.

### 32. How is pancreatic ascites or pancreatic pleural effusion diagnosed?

There needs to be a high index of clinical suspicion. The diagnosis is made by examining the fluid obtained from the paracentesis or thoracentesis, which typically has an elevated concentration of amylase (normal amylase level <150 IU/L, but it is usually >1000 IU/L), lipase and albumin more than 3 g/dL. The serum albumin ascites gradient is less than 1.1 g/dL.

### 33. Why does the presence of gastric varices in the absence of esophageal varices suggest CP?

The splenic vein travels above the body and tail of the pancreas. Chronic inflammation with CP may lead to splenic vein thrombosis in approximately 12% of patients. Splenic vein thrombosis leads to intrasplenic venous hypertension, splenomegaly, and collateral formation of gastric varices through the short gastric veins. Although massive gastrointestinal bleeding can occur from gastric varices caused by CP, it is an uncommon occurrence. Splenectomy is the treatment of choice if bleeding persists.

### 34. Are signs of fat-soluble vitamin deficiencies highly suggestive of CP?

No. Although absorption of fat-soluble vitamins (A, D, E, and K) is decreased in CP, clinical manifestations of deficiency of these vitamins are uncommon. However, long-standing CP may be associated with vitamin D deficiency and other fat-soluble vitamin deficiency.

**35. Are patients with CP predisposed to nephrolithiasis?**

Yes. Patients with steatorrhea have high concentrations of long-chain fatty acids in the colon that bind to intraluminal calcium by formation of insoluble calcium soaps. With less calcium in the lumen to bind with oxalate, more oxalate is absorbed, which increases concentration in the blood stream and subsequently in the kidney, producing oxaluria and nephrolithiasis.

**36. How should hyperoxaluria be treated in patients with CP?**

Hyperoxaluria is treated with pancreatic enzyme replacement, low-oxalate diet, diet with low concentration of long-chain triglycerides, and increased intake of calcium (3 g/day) or aluminum in the form of antacids (3.5 g/day).

**37. Can patients with CP develop vitamin B<sub>12</sub> malabsorption?**

Yes. Pancreatic proteases usually destroy cobalamin binding proteins and allow the B<sub>12</sub> to bind to the intrinsic factor. In pancreatic insufficiency, vitamin B<sub>12</sub>, instead of binding to intrinsic factor, competitively binds to the cobalamin binding protein, which decreases the absorption of the vitamin in the terminal ileum. Vitamin B<sub>12</sub> malabsorption can occur in 40% of the patients with CP because of lack of pancreatic proteases. The treatment of choice is pancreatic enzyme supplementation.

**38. How is steatorrhea from CP treated?**

Steatorrhea occurs when less than 10% of the exocrine pancreas is functional. The main therapeutic modality in the treatment of steatorrhea is pancreatic enzyme replacement.

Pancreatic enzymes replacement consists of lipase to prevent fat and other pancreatic enzymes to treat malassimilation. The initial starting dose is 30,000 IU or more with each meal. It is given during the meal to ensure adequate mixing and with meals or snacks. Pancreatic enzymes tend to be inactivated by acid. They are available in two forms: nonenteric (easily inactivated by gastric acid, appropriate for achlorhydric and Billroth II patients) and enteric-coated form, which improves effectiveness in the presence of gastric acid. However, lipase is only released from coated spheres once the pH is higher than 5, which occurs in distal segments of the gut in some patients with exocrine pancreatic insufficiency. Therefore proton pump inhibitors need to be given concomitantly.

Dietary modifications are a last resort and consist, first, of restricting fat intake usually to less than 20 g/day and giving medium-chain triglycerides (MCT), which do not need lipase, or biliary salts for its degradation and subsequent absorption. These MCTs are given after unsuccessful treatment with restricting fat intake and pancreatic enzymes.

**39. What are nonsurgical modalities for pain control in CP?**

Abdominal pain is the most common symptom of CP. It is important to initially consider lifestyle modifications such as alcohol and smoking cessation; small, low-fat meals; and the use of nonnarcotic analgesics (such as amitriptyline and pregabalin). In the case that these measures do not work, a step-up approach is usually needed.

With persistent abdominal pain, the approach can be divided between medical treatment and surgical treatment (to be discussed in Question 41).

Medical treatment for persistent pain includes:

- *Pancreatic enzyme supplement* may decrease abdominal pain by diminishing the stimulation of the pancreas and decreasing the abdominal distention and diarrhea associated with malassimilation. In the case of chronic pain, the best form of pancreatic enzymes is the one with high protease content and noncoated instead of high-lipase and enteric-coated form used for steatorrhea.
- *Somatostatin* at a dose of 200 mcg subcutaneously every 8 hours may also reduce the pain of CP. However, it has not been shown to be effective in a randomized control study.
- *Narcotic analgesics* may be needed in patients with inadequate control with previous measures; however, drug addiction is a significant risk if pain persists.
- *Celiac plexus blockage* by alcohol or steroids has limited effectiveness in decreasing pain; it lasts between 2 and 6 months and repeated sessions are required.
- *Single-dose external beam radiation* has been shown to improve pain.

**40. Does endoscopy have a role in pain control in CP?**

Endoscopy may have a role in the management of pain in CP in patients who have a ductal obstruction by a dominant stricture or an obstructing stone or stones in the pancreatic duct. No randomized study with good statistical power has been done to show effectiveness of endoscopic management of pain in CP. Some small studies have shown that endoscopic sphincterotomy with pancreatic stricture dilation and pancreatic duct stent placement relieves recurrent pain associated with CP. Other studies have shown pain improvement after removal of pancreatic stones with the combination of pancreatic duct sphincterotomy, extracorporeal lithotripsy, and stone extraction.

#### 41. What is the role of surgery in pain control in CP?

The role of surgery is reserved for those patients with persistent pain despite medical treatment. The role of surgery is to decompress the pressure inside of the pancreas. They are technically difficult procedures; however, pain relief can be achieved in 80% of patients.

Several surgical modalities are commonly used:

- Lateral pancreateojejunostomy (modified Puestow procedure) is preferred in patients with distal duct obstruction in the head of the pancreas.
- Pancreatoduodenectomy with pylorus preservation or with antrectomy “Whipple procedure” is used in patients with diffuse glandular disease.
- Partial resection of the pancreas is preferred for patients with localized small duct disease usually in the tail of the pancreas.
- Duodenum-preserving pancreatic head resection has similar indications as the Whipple procedure.
- A Thoracoscopic splanchnicectomy denervation procedure has a high response rate; however, pain relief is often incomplete.

Multiple studies have shown that organ-preserving surgeries are better in achieving pain control, likely because of less extensive (advanced) disease, but there is no change between procedures regarding preservation of endocrine and exocrine function. Despite surgery, the progression of pancreatitis continues. Several studies have shown that surgical approach is superior to endoscopic therapy for relief of pain.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

#### BIBLIOGRAPHY

1. Applebaum SE, O'Connell JA, Aston CE, et al. Motivations and concerns of patients with access to genetic testing for hereditary pancreatitis. *Am J Gastroenterol* 2001;96:1610–7.
2. Brown A, Hughes M, Tenner S, et al. Does pancreatic enzyme supplementation reduce pain in patients with chronic pancreatitis? A meta-analysis. *Am J Gastroenterol* 1997;92:2032–5.
3. Catalano MF, Lahoti S, Geenen JE, et al. Prospective evaluation of endoscopic ultrasonography, endoscopic retrograde pancreatography, and secretin test in the diagnosis of chronic pancreatitis. *Gastrointest Endosc* 1998;48:11–7.
4. Choudari CP, Lehman GA, Sherman S. Pancreatitis and cystic fibrosis gene mutations. *Gastroenterol Clin North Am* 1999;28:543–9.
5. Chowdhury RS, Forsmark CE. Review article: pancreatic function testing. *Aliment Pharmacol Ther* 2003;17:733.
6. Cohn JA, Friedman KJ, Noone PG, et al. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. *N Engl J Med* 1998;339:653–8.
7. Gress F, Schmitt C, Sherman S, et al. Endoscopic ultrasound-guided celiac plexus block for managing abdominal pain associated with chronic pancreatitis: a prospective single center experience. *Am J Gastroenterol* 2001;96:409–16.
8. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001;344:732–8.
9. Kloppel G, Luttges J, Lohr M, et al. Autoimmune pancreatitis: pathological, clinical, and immunological features. *Pancreas* 2003;27:14.
10. Kozarek RA, Ball TJ, Patterson DJ, et al. Endoscopic pancreatic duct sphincterotomy: indications, technique, and analysis of results. *Gastrointest Endosc* 1994;40:592–8.
11. Kozarek RA, Jiranek GC, Traverso LW. Endoscopic treatment of pancreatic ascites. *Am J Surg* 1994;168:223–6.
12. Lin Y, Tamakoshi A, Matsuno S, et al. Nationwide epidemiological survey of chronic pancreatitis in Japan. *J Gastroenterol* 2000;35:136.
13. Lowenfels AB, Maisonneuve P, Lankisch PG. Chronic pancreatitis and other risk factors for pancreatic cancer. *Gastroenterol Clin North Am* 1999;28:673–85.
14. Malka D, Hammel P, Sauvanet A, et al. Risk factors for diabetes mellitus in chronic pancreatitis. *Gastroenterology* 2000;119:1324.
15. Rebours V, Bourron-Rual MC, Schnee M, et al. Risk of pancreatic adenocarcinoma in patients with hereditary pancreatitis: a national exhaustive series. *Am J Gastroenterol* 2008;103:111.
16. Sarles H, Adler G, et al. The pancreatitis classification of Marseilles—Rome 1988. *Scand J Gastroenterol* 1989;24:641–2.
17. Schneider A, Suman A, Rossi L, et al. SPINK1/PSTI mutations are associated with tropical pancreatitis and type II diabetes mellitus in Bangladesh. *Gastroenterology* 2002;123(4):1026–30.
18. Scolapio JS, Malhi-Chowla N, Ukleja A. Nutritional supplementation in patients with acute and chronic pancreatitis. *Gastroenterol Clin North Am* 1999;28:695–707.
19. Shea JC, Bishop MD, Parker EM, et al. An enteral therapy containing medium-chain triglycerides and hydrolysed peptides reduces postprandial pain associated with chronic pancreatitis. *Pancreatology* 2003;3:36–40.
20. Sossenheimer MJ, Aston CE, Preston RA, et al. Clinical characteristic of hereditary pancreatitis in a large family, based on high risk haplotype. *Am J Gastroenterol* 1997;92:1113–6.
21. Strate T, Bachmann K, Busch P, et al. Resection vs drainage in treatment of chronic pancreatitis: long term results of a randomized trial. *Gastroenterology* 2008;134:1406–11.
22. Whitcomb DC. The spectrum of complications of hereditary pancreatitis: is this model for future gene therapy? *Gastroenterol Clin North Am* 1999;28:525–41.
23. Yoshida K, Toki F, Takeuchi T, et al. Chronic pancreatitis caused by an autoimmune abnormality: proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci* 1995;40:1561–8.
24. The pancreas: Biology, disease and therapy. *Gastroenterology* 2013;144:1163–326 [special issue].

# PANCREATIC CANCER

Shajan Peter, MD, Ji Young Bang, MD, MPH, Shyam Varadarajulu, MD

## 1. How common is pancreatic cancer (PC)?

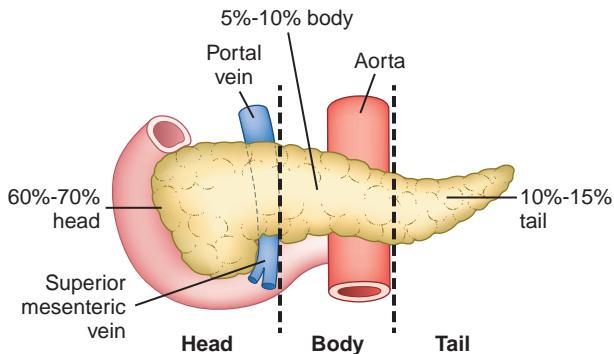
The global annual incidence rate of PC is approximately 8 per 100,000 persons per year. In the United States, of an estimated 45,220 people who are diagnosed with PC annually, approximately 38,460 people will die from disease progression. The lifetime risk of developing PC is 1.47% (1 in 68 in men and women), and it is the fourth most common cause of cancer-related deaths after lung, prostate, and colorectal cancer.

## 2. What are the most common types of pancreatic neoplasms?

Adenocarcinoma is the most common type of pancreatic neoplasm with almost 90% arising from the ductal epithelium. The remaining pancreatic neoplasms consist of neuroendocrine tumors, cystadenocarcinomas, acinar cell carcinoma, and lymphomas.

## 3. Where are the cancers located in the pancreas?

Sixty to seventy percent of cancers are localized to the head, 5% to 10% in the body, and 10% to 15% in the tail of the pancreas (Figure 38-1). The size of cancer in the head ranges from 2.5 to 3.5 cm compared with 5 to 7 cm for those located in the body and tail.



**Figure 38-1.** Distribution and location of pancreatic cancer. Tumors of the head of the pancreas are those arising to the right of the superior mesenteric-portal vein confluence. Tumors of the body of the pancreas are defined as those arising between the left edge of the superior mesenteric-portal vein confluence and the left edge of the aorta. Tumors of the tail of the pancreas are those arising to the left of the left edge of the aorta. (Adapted with permission from AJCC cancer staging handbook, ed 7, Chicago, 2010, American Joint Committee on Cancer. 2010.)

## 4. What are the clinical presentations of PC?

Jaundice caused by biliary obstruction is the most common (>50%) presentation among patients with pancreatic head cancer (Table 38-1). Jaundice may not develop or be a late presentation in cancer located in the body or tail of the pancreas. It also could indicate advanced metastatic disease to the liver. Abdominal pain localized to the upper abdomen or mid and upper back can be a major symptom and could point to invasion of the celiac or superior mesenteric arteries. Other symptoms such as nausea, weight loss, floating stools, and dyspepsia can be seen. New-onset type 2 diabetes mellitus or presentation with acute pancreatitis should call

**Table 38-1.** Clinical Presentations in Pancreatic Cancer

SYMPTOM	PERCENTAGE
Abdominal pain	78-82
Anorexia, early satiety	62-64
Jaundice	56-80
Weight loss	66-84
Diabetes	97
Back pain	48

attention to PC. Advanced tumor involvement of the duodenum can result in gastric outlet obstruction. Less common manifestations include panniculitis and depression.

#### **5. What are the named clinical signs in PC?**

*Courvoisier sign* is a palpable, distended, gallbladder in the right upper quadrant in a patient with jaundice resulting from bile duct obstruction secondary to PC. However, this finding is not specific to PC. Patients with distal cholangiocarcinoma or an ampullary mass may present similarly. *Trousseau's syndrome* is a manifestation of PC as superficial or deep vein thrombosis.

#### **6. What are the identifiable risk factors for PC?**

Smoking is firmly linked to PC, with current smokers having an odds ratio (OR) of 2.2 compared with nonsmokers for developing PC. This OR decreases to 1.2 for ex-smokers and the risk becomes equivalent to that of nonsmokers 10 to 20 years after smoking cessation. A study examining several detoxifying genes mediating the degradation of tobacco identified that variants in genes, such as CYP1B1-4390-GG and uridine 5'-diphospho-glucuronosyltransferase (UGT) reduced the risk of PC, whereas variants in glutathione S-transferases (GSTM1) increased the risk. There is some evidence that dietary factors such as consumption of red or processed meat, especially when cooked at high temperatures, and dairy products increase the risk of PC. Also, contrary to previous thought, there seems to be no protective effect from consumption of fresh fruits and vegetables, coffee, or alcohol intake. Obesity (body mass index >30) is associated with a relative risk of 1.19 for developing PC.

#### **7. What is the association between diabetes and PC?**

Patients with long-standing diabetes (4 or more years) have a 1.5-fold increased risk of developing PC. Also, gestational diabetes poses a risk for developing PC in later life. On the other hand, the risk of PC is high with new-onset diabetes (five- to eightfold), suggesting a bidirectional association. There is also growing evidence that PC can cause paraneoplastic diabetes mellitus or glucose intolerance and this can manifest a few months to 2 to 3 years prior to the clinical presentation of PC. Diabetes improves after surgical resection of PC. Interestingly, oral hypoglycemic agents such as metformin appear to have a protective relationship.

#### **8. Is there a risk for developing PC in patients with chronic pancreatitis?**

The pooled relative risk for developing PC among patients with chronic pancreatitis is 13.3 and is estimated to be approximately 2% per decade. The lifetime risk of developing PC in patients with hereditary pancreatitis (autosomal dominant mutation of trypsinogen) is 40% to 55%.

#### **9. What is the association of PC with inherited cancer syndromes?**

Germline mutations are associated with an increased risk for PC; in particular BRCA2 gene mutations account for the highest proportion of known cases among inherited cancer syndromes. Although identification of more than one first-degree relative (FDR) with PC carries a substantial risk for development of PC, the precise genetic link remains unknown. Hereditary pancreatitis and the tryptase enzymatic defect carry a potent risk for pancreatic neoplasia by age 70 years in greater than 40% of cases. Peutz-Jeghers syndrome (PJS) is an autosomal dominant polyposis syndrome, in which hamartomatous polyps are found throughout the gastrointestinal tract, but neoplasia risk is greatest outside the gastrointestinal lumen (i.e., in the thyroid, breast, gonads, and especially the pancreas). The familial atypical multiple mole melanoma syndrome is characterized by greater than 50 dysplastic nevi and malignant melanomas in two or more first- or second-degree relatives. Other conditions associated with increased risk for PC are listed in Table 38-2.

#### **10. What are the available serum markers for early detection of PC?**

There is no single marker that has been shown to be ideal for detection of PC. Carbohydrate antigen (CA 19-9) has been widely used. Using a cutoff of 37 U/mL, the sensitivity and specificity for detection of PC are 86% and 87%, respectively, and this increases to 97% and 98% at levels of more than 200 U/mL. Levels of more than 1000 U/mL can be associated with advanced disease. Importantly, high values suggestive of false-positive diagnosis are observed in patients with jaundice and higher bilirubin levels. CA 19-9 may be useful as an independent prognostic factor for survival and in monitoring the treatment response. Few other markers have been studied with varying accuracy (Table 38-3).

#### **11. What are the precursors to PC?**

There are three known precursors (Table 38-4) to PC:

- Intraductal papillary mucinous neoplasms (IPMNs)
- Mucinous cystic neoplasms (MCNs) and
- Pancreatic intraepithelial neoplasms

The latter can cause noninvasive multifocal disease and are more common in patients with a strong family history. These lesions can cause small-duct obstruction resulting in multifocal atrophy of the pancreas.

Computed tomography (CT) scan and endoscopic ultrasound (EUS) are both complementary modalities for

**Table 38-2.** Association between Pancreatic Cancer and Inherited Syndromes

ASSOCIATED DISEASE	GENETIC ABNORMALITY	RELATIVE RISK	RISK BY 70 YRS OF AGE (%)
No history	None	1	0.5
One FDR with PC	?	2.3	1.15
Three FDRs with PC	?	32	16
Familial pancreatic cancer	BRACA2, PALB2, ATM	2 FDR: 6.4 >3 FDR: 32	2 FDR: 8-12 >3 FDR: 16-38
Peutz-Jeghers syndrome	LKB1	132	36
Familial atypical multiple mole melanoma	CDKN2A/CDK4	20-34	17
Li-Fraumeni syndrome	TP53	2	<5
Hereditary breast-ovarian syndrome	BRAC1, BRAC2	2 3.5-10	1 5
Hereditary chronic pancreatitis	PRSS1, SPHINK1	50-80	25-40
Cystic fibrosis	CFTR	5.3	<5
Hereditary nonpolyposis syndrome	hMSH2, hMLH1, hPMS1	1.3	<5
Familial adenomatous polyposis	APC	4.6	<5

FDR, First-degree relative.

**Table 38-3.** Tumor Markers in Pancreatic Cancer

SERUM MARKER	SENSITIVITY (%)	SPECIFICITY (%)
CA 19-9	70-90	90
CEA	16-92	49-93
CA 50	65-90	58-73
CA 125	45-60	76-86
TIMP-1	60-99	50-90

CA, Carbohydrate antigen; CEA, carcinoembryonic antigen; TIMP-1, tissue metalloprotease 1.

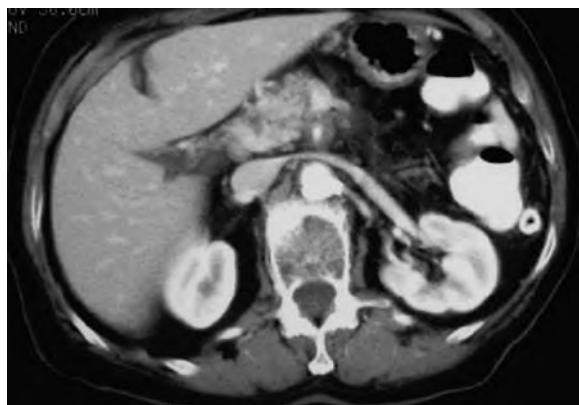
diagnosing these lesions. However, imaging, cytologic examination, and serologic examination are limited in their ability to accurately predict the malignant potential, and therefore frequent screening is important. Generally, MCNs are managed by resection and are examined for foci of invasive cancer that portend a poor prognosis. Main-duct IPMN (ductal diameter of  $\geq 10$  mm) in young patients or those with high-risk imaging features such as mural nodules, focal masses, or a large unilocular cystic component should be resected.

## 12. What are the common biochemical abnormalities in patients with PC?

Patients with biliary obstruction or metastatic disease can present with elevated serum bilirubin and alkaline phosphatase. Raised white blood cell count can be seen in patients with cholangitis. Serum amylase is elevated in only 5% of patients. Hyperglycemia is observed in patients with new-onset diabetes.

## 13. What imaging modalities are used to diagnose PC?

Transabdominal ultrasound has a sensitivity of 70% for detection of tumors and has a limited role in diagnosis. The overall sensitivity of multidetector CT (MDCT) for PC is 86% to 97% for tumors of any size, but sensitivity of only 77% for smaller ( $<2$  cm) lesions (Figure 38-2). The sensitivity of magnetic resonance imaging (MRI) (E-Figure 38-3) and integrated positron emission tomogram–CT (PET-CT) is 84% and 73.7%, respectively. While endoscopic retrograde cholangiopancreatogram (ERCP) with biliary brushings has a low diagnostic yield of 25% to 60%, the diagnostic accuracy of EUS-guided fine-needle aspiration (EUS-FNA) exceeds 85% to 90% (Figure 38-4). Newer imaging modalities such as cholangioscopy, optical coherence tomography, confocal imaging, and contrast-enhanced EUS are still being investigated and could improve the overall diagnostic accuracy.

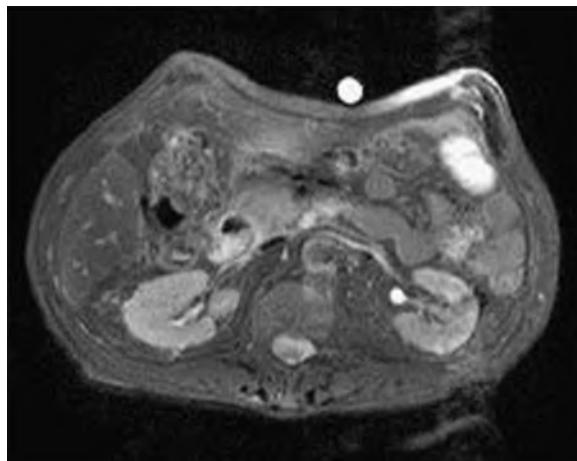


**E-Figure 38-3.** Multidetector computed tomography scan with pancreatic mass encasing the celiac artery.

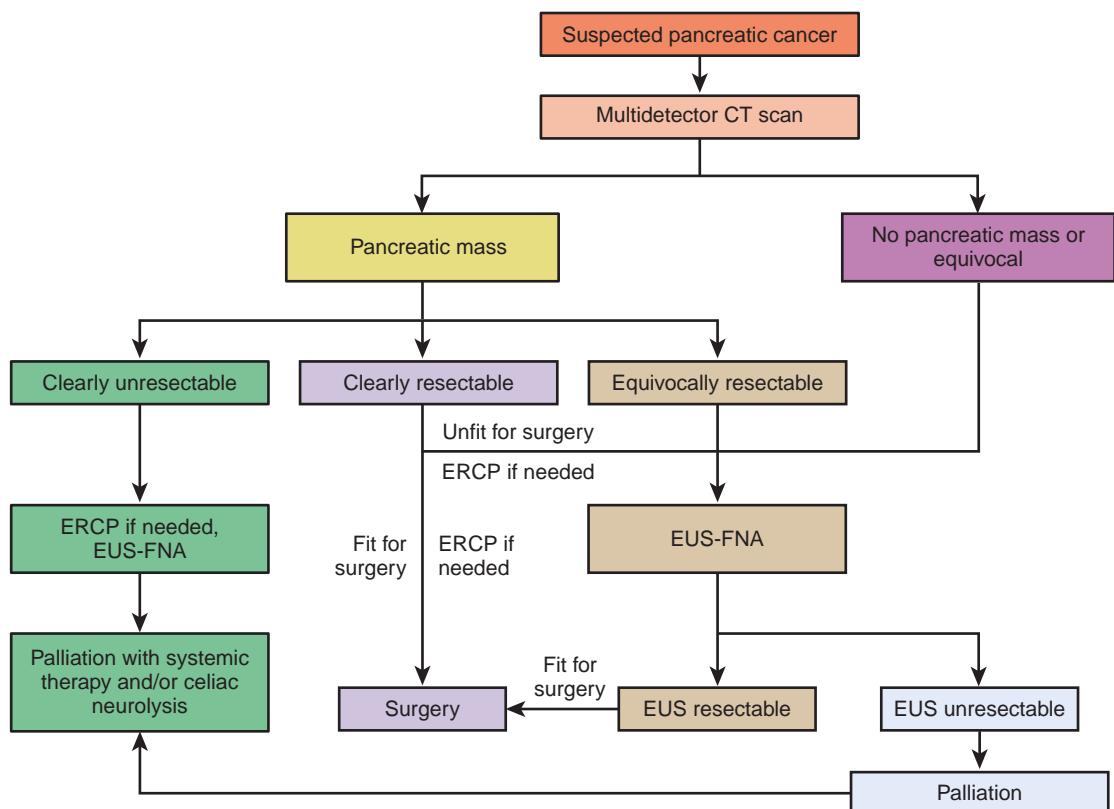
**Table 38-4.** Common Features of Pancreatic Precursor Lesions for Pancreatic Cancer

TYPE OF PRECURSOR LESION	AGE (YEARS)	GENDER	CYST-TO-DUCT COMMUNICATION	CYST SIZE (CM)	LOCATION	CEA	MUCIN FROM AMPULLA	MULTIFOCAL	RISK OF MALIGNANCY
MCN	40-50	Female > Male	Usually not connected	1-3	Body and tail of pancreas	↑ 80%	No	Rare	18%
IPMN	60s	Male = Female	Connected to MD or BD	<1	Head > tail of pancreas	↑ 80%	Yes	20%-30%	65% (MD) 40% (BD)
PanIN	↑ with age	Male = Female	N/A	Microscopic	Head > tail of pancreas	N/A	No	Often	High grade: unknown Low grade <1%

BD, branch duct; CEA, carcinoembryonic antigen; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cyst neoplasm; MD, main duct; PanIN, pancreatic intraepithelial neoplasia.



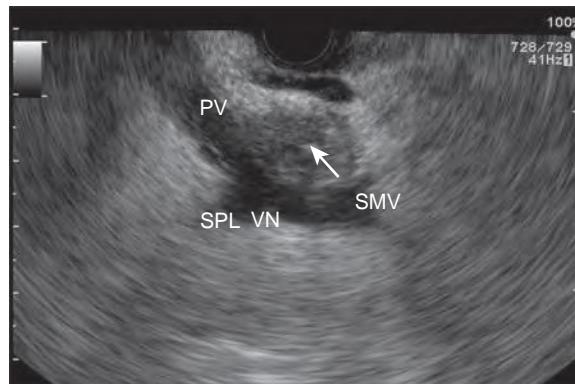
**Figure 38-2.** T2-weighted magnetic resonance image with pancreatic head mass.



**Figure 38-4.** Algorithm for treatment approach to pancreatic cancer. CT, Computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration. (Adapted with permission from Mohammad Al-Haddad, John DeWitt: EUS in pancreatic tumors. In Endosonography, ed 2, St Louis, 2011, WB Saunders, pp 148-165.)

#### 14. How has EUS influenced the management of patients with PC?

EUS is an important modality for the diagnosis and staging of PC. It is superior to CT scan for tumor staging and is more sensitive for detecting invasion of the portal venous system and its confluence as compared with CT scan (which is superior for assessing arterial involvement) (Figure 38-5). EUS-FNA of pancreatic tumors has a sensitivity of 85% and specificity of nearly 100%. Diagnostic yield appears to be maximized by the presence of on-site cytopathologic interpretation. Tumors smaller than 2 cm are better identified and targeted by EUS. EUS can also be used for placement of fiducial markers for better targeting of the tumor during radiation therapy and celiac plexus neurolysis for pain relief.



**Figure 38-5.** Hypoechoic mass in the head of the pancreas measuring 3 × 2 cm and invading the confluence of the portal vein. Endoscopic ultrasound–guided fine-needle aspiration of the mass revealed adenocarcinoma. PV, portal vein; SPL VN, splenic vein; SMV, superior mesenteric vein.

### 15. What is the double-duct sign in PC?

The double-duct sign, noted on ERCP, demonstrates the presence of stenosis of the distal common bile duct and pancreatic duct in the head of the pancreas (Figure 38-6). In patients with obstructive jaundice or a pancreatic mass, the double-duct sign has a specificity of 85% in predicting PC.



**Figure 38-6.** Endoscopic retrograde cholangiopancreatography revealing “double-duct” sign in a patient with adenocarcinoma.

### 16. What are the other differential diagnoses for PC?

In the background of chronic pancreatitis, it may be difficult to distinguish PC from chronic pancreatitis. Clinical suspicion and imaging with tissue sampling may enable this differentiation. Autoimmune pancreatitis (AIP) can mimic PC, presenting with similar clinical features such as jaundice, weight loss, and elevated CA 19-9 levels. A finding of increased serum immunoglobulin (IgG4) levels with diffuse pancreatic involvement on CT is supportive of a diagnosis of AIP.

### 17. What high-risk groups may benefit from screening?

The International Cancer of the Pancreas Screening Consortium recommends EUS and/or MRI and magnetic resonance cholangiopancreatography for screening high-risk individuals, who are defined as:

- FDRs of PC patients with at least two affected FDRs
  - Carriers of p16 or BRCA2 mutations with one affected FDR
  - Patients with PJS
  - Patients with Lynch syndrome (hereditary nonpolyposis colorectal cancer) and 1 or more affected FDRs
- However, there is no consensus on either the age to begin screening or on screening intervals.

**Table 38-5.** AJCC Classification for Pancreatic Cancer (2010)**Primary Tumor (T)**

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ*
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

**Regional Lymph Nodes (N)**

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

**Distant Metastasis (M)**

M0	No distant metastasis
M1	Distant metastasis

**Stage Grouping**

Stage 0	Tis N0 M0	Localized within pancreas
Stage IA	T1 N0 M0	Localized within pancreas
Stage IB	T2 N0 M0	Localized within pancreas
Stage IIA	T3 N0 M0	Locally invasive, resectable
Stage IIB	T1, 2, or 3 N1 M0	Locally invasive, resectable
Stage III	T4 Any N M0	Locally advanced, unresectable
Stage IV	Any T Any N M1	Distant metastases

\*This also includes the *PanInIII* classification.

**18. How is PC staged?**

Accurate staging of PC is important as only 20% of patients are resectable at the time of diagnosis. The American Joint Committee on Cancer staging is the most commonly used system and is based on tumor-node-metastasis staging (Table 38-5). Tumors are classified as *resectable*, *borderline resectable*, *locally advanced*, or *unresectable disease*.

**19. What are the staging modalities for PC?**

The most commonly used modality for the diagnosis and staging of PC is MDCT, which has a high positive predictive value for unresectability. However, MDCT has a lower sensitivity of 25% to 50% for predicting resectability. Newer three-dimensional CT imaging techniques are very accurate in detecting vascular invasion: celiac axis (CA), superior mesenteric artery (SMA), and common hepatic artery involvement. The use of MRI or fluorodeoxyglucose–PET CT scanning may help identify smaller lesions missed on CT. EUS is not only helpful in obtaining tissue but can identify smaller lesions missed on CT and therefore is a complementary technique. Because there is a 5% to 15% chance that occult metastases will be missed by CT imaging, diagnostic laparoscopy (not done routinely) can help identify these implants (e.g., peritoneal, capsular, or serosal).

**20. What are the CT features of unresectability?**

PC is deemed unresectable when features of tumor invasion are present such as absence of fat planes in the SMA territory; involvement of the inferior vena cava, aorta, or celiac artery; 180-degree or more of circumferential encasement; occlusion of the SMV-portal venous system; or if distant metastases (e.g., involvement of solid organs or lymph nodes outside the resection zone and peritoneum) are present.

**21. Is chemotherapy effective for patients with advanced PC?**

Traditional chemotherapy with 5-fluorouracil (5-FU) and folinic acid has an overall response rate of less than 10% with no effect on quality of life or survival. Gemcitabine is preferred to 5-FU because of its favorable toxicity profile, although the overall outcomes are similar. For advanced or metastatic disease, folinic acid, 5-FU, irinotecan, and oxaliplatin has shown promise with an improved median survival time of 11 months.

**22. What is the median survival after the diagnosis of advanced PC?**

PC is associated with a 5-year survival rate of less than 5% and a median survival time of 6 months from the time of diagnosis. Surgical resection is the only curative treatment for PC. However, only 15% to 20% of patients are potentially resectable at the time of diagnosis. After surgical resection, median survival is increased by 25–30 months, and when combined with adjuvant chemotherapy, 5-year survival of more than 20% may be

achieved. However, the median survival for patients with unresectable PC of head and body is less than 1 year and for those with involvement of the pancreatic tail, the survival is less than 3 months.

### **23. What are the poor prognostic factors of PC?**

Poor prognostic factors include presentation at a later stage, R1 resection (grossly negative but microscopically positive margins of resection), perineural or vascular invasion, poor performance status, low serum albumin, liver metastases, and elevated CA 19-9 levels. Poor molecular prognostic factors include mutated tumor suppressor genes such as SMAD4 and TP53.

### **24. What are the surgical procedures for resectable cancer in the pancreatic head?**

Whipple resection (pancreaticoduodenectomy) is the standard surgical procedure for resectable cancer located in the head of the pancreas ([E-Figure 38-7](#)). It involves a partial gastrectomy (resection of the antrum), cholecystectomy, and en-bloc removal of the head of the pancreas, distal common bile duct, duodenum, and regional lymph nodes. The procedure usually involves three anastomoses: pancreaticojejunostomy, hepaticojejunostomy, and gastrojejunostomy (see [Figure 38-4](#)). Pylorus-preserving pancreaticoduodenectomy may be performed to retain a functioning pylorus by preserving the stomach. Long-term studies comparing both procedures show similar surgical outcomes.

### **25. What is the surgical procedure adopted for cancer in the body and tail of the pancreas?**

Distal pancreatectomy is the procedure of choice for PC in the body and tail; the pancreas is resected from the left of the superior mesenteric vessels. A splenectomy is also conventionally performed.

### **26. Is there a role for neoadjuvant therapy?**

There is no clear role for neoadjuvant therapy in resectable PC. A recent metaanalysis showed that preoperative chemoradiation therapy might be beneficial for those patients with unresectable tumors and that downstaging enables resection in up to 30% of patients.

### **27. Is there a role for routine preoperative endoscopic drainage for malignant biliary obstruction?**

Currently, there is no evidence to suggest that routine preoperative biliary drainage improves surgical outcomes. It may, however, be reserved for resectable patients with jaundice and significant delay in surgery, those presenting with acute cholangitis, or borderline resectable patients undergoing neoadjuvant chemoradiation therapy.

### **28. What are the endoscopic therapeutic strategies in PC?**

Endoscopic biliary stent placement for obstructive jaundice remains the main method of biliary drainage in unresectable PC patients. Placements of self-expanding metal stents are preferred over plastic stents in patients with longer life expectancy. In patients with gastroduodenal obstruction by a large pancreatic mass, endoscopic placement of an expandable stent bypassing the stricture relieves the obstruction. EUS-guided celiac plexus neurolysis is done to relieve existing pain and also delay onset of pain in asymptomatic patients. This is done by injection of combination of local anesthetic (e.g., bupivacaine) and highly concentrated alcohol (50%) at the level of the CA. Pain reduction can be expected in 60% to 75% of patients within 2 weeks of the procedure.

### **29. What are other palliative considerations in PC?**

As described previously, endoscopy helps in palliation of obstructive jaundice, intractable pruritus, treatment of cholangitis, and relieving duodenal obstruction. If endoscopic treatment is not possible, percutaneous transhepatic biliary drainage catheter or stent placement can be performed by an interventional radiologist. If both modalities fail, surgical bypass, such as cholecystojejunostomy or hepaticojejunostomy for biliary drainage or gastrojejunostomy for duodenal obstruction, may be indicated. Other considerations include conventional management of pain using narcotics, treatment of malabsorption or steatorrhea with pancreatic enzyme supplements, and treatment of hyperglycemia using oral hypoglycemic medications or insulin.

Please access ExpertConsult to view the E-Figures for this chapter.

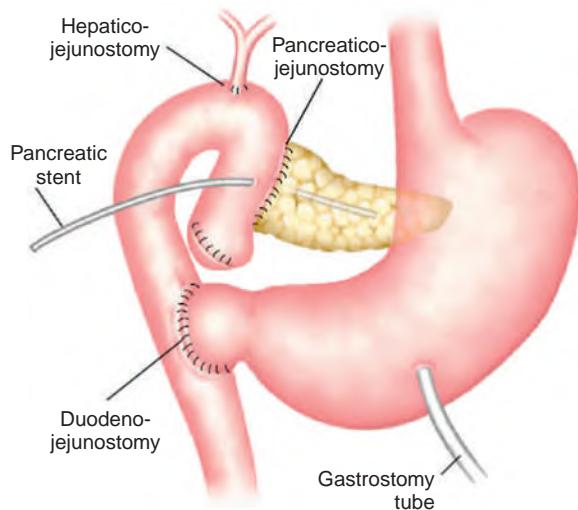
## **BIBLIOGRAPHY**

1. AJCC cancer staging handbook. Chicago: American Joint Committee on Cancer; 2010.
2. Brentnall TA. Management strategies for patients with hereditary pancreatic cancer. *Curr Treat Options Oncol* 2005;6:437–45.
3. Brugge WR, Lauwers GY, Shani D, et al. Cystic neoplasms of the pancreas. *N Engl J Med* 2004;351:1218–26.
4. Côté GA, Smith J, Sherman S, Kelly K. Technologies for imaging the normal and diseased pancreas. *Gastroenterology* 2013; 144(6):1262–71.
5. Fong ZV, Winter JM. Biomarkers in pancreatic cancer: diagnostic, prognostic, and predictive. *Cancer J* 2012;18(6):530–8.
6. Hawes RH, Fockens P. EUS in pancreatic tumors. Philadelphia: Saunders; 2011 p. 148–65.
7. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60(5):277–300.
8. Pulsom AS, Tran Cao HS, Tempero MA, Lowy AM. Therapeutic advances in pancreatic cancer. *Gastroenterology* 2013; 144(6):1316–26.
9. Puli SR, Reddy JB, Bechtold ML, et al. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. *Dig Dis Sci* 2009;54:2330–7.

10. Sharma C, Eltawil KM, Renfrew PD, et al. Advances in diagnosis, treatment and palliation of pancreatic carcinoma: 1990–2010. *World J Gastroenterol* 2011;17:867–97.
11. Shin EJ, Canto MI. Pancreatic cancer screening. *Gastroenterol Clin North Am* 2012;41(1):143–57.
12. Varadarajulu S, Eloubeidi MA. The role of endoscopic ultrasonography in the evaluation of pancreatico-biliary cancer. *Surg Clin North Am* 2010;90:251–63.
13. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. *Lancet* 2011;378(9791):607–20.
14. Werner J, Combs SE, Springfield C, Hartwig W, Hackert T, Büchler MW. Advanced-stage pancreatic cancer: therapy options. *Nat Rev Clin Oncol* 2013;10(6):323–33.
15. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 2013;144(6):1252–61.

**Website**

National Comprehensive Cancer Network. [www.nccn.org](http://www.nccn.org) [Accessed September 22, 2014].



**E-Figure 38-7.** Whipple's pancreaticoduodenectomy. (Adapted from Feldman M, Friedman LS, Brandt LJ: *Tumors of the pancreas*. In Slesinger and Fordtran's *gastrointestinal and liver disease*, Chapter 60, 2010, Philadelphia, Saunders Elsevier, p 1017–34.)

# CYSTIC LESIONS OF THE PANCREAS

Brenda Hoffman, MD, and Jason R. Roberts, MD

## 1. What are pancreatic cystic lesions (PCLs)?

A true pancreatic cyst is a liquid-filled collection lined by an epithelium. Pancreatic pseudocysts are fluid-filled collections encapsulated by an inflammatory wall resulting from pancreatitis. Solid pancreatic neoplasms may contain internal cystic components as seen in pancreatic neuroendocrine tumors and adenocarcinoma. Mucinous cysts are lined by ovarian-type stromal cells that secrete mucin.

## 2. What is the clinical importance of PCLs?

Pancreatic cysts can be malignant, premalignant, benign without risks of malignant transformation, or can be a source of symptoms. The management varies greatly from surgical resection to observation without the need for additional testing.

## 3. How common are PCLs?

PCLs are an increasingly common incidental finding on body imaging with a prevalence of 2.3% in computed tomography (CT) series and 2.4% to 13.5% in magnetic resonance imaging (MRI) series. The improved resolution of multidetector CT and MRI scanners allows for identification of smaller cysts (<1-2 cm). The malignant potential for some cysts requires that all of these lesions be further evaluated with surveillance imaging, cyst fluid analysis, or surgical resection for histopathologic diagnosis.

## 4. What is the differential diagnosis for PCLs?

The differential diagnosis for PCLs is broad and includes benign lesions without malignant potential, those with malignant potential, and those that are malignant (Table 39-1). Broadly, mucinous cysts have malignant potential, whereas nonmucinous cysts do not. Ninety percent of PCLs are benign, most of which are pseudocysts.

**Table 39-1.** Differential for Pancreatic Cystic Lesions According to Malignant Potential

BENIGN	PREMALIGNANT	MALIGNANT
Pseudocyst	Intraductal papillary mucinous neoplasm	Ductal adenocarcinoma with cystic change
Serous cystadenoma	Mucinous cystadenoma	Neuroendocrine tumor with cystic change
Cystic lymphangioma		
Lymphoepithelial cyst		Solid pseudopapillary tumor
Retention cyst		

## 5. What symptoms are associated with pancreatic cysts?

Abdominal pain is the most common indication for body imaging resulting in the finding of pancreatic cysts. It is likely that the majority of these cysts are asymptomatic and truly incidental findings, especially small cysts (<1-2 cm). Single or multiple cysts in the setting of recent acute pancreatitis or an acute exacerbation of chronic pancreatitis are most likely pseudocysts. Large pseudocysts may present as a palpable abdominal mass or cause gastric outlet obstruction related symptoms such as nausea, vomiting, and early satiety. Pseudocysts may also become infected leading to fever and leukocytosis. Cysts in the head of the pancreas may cause biliary obstruction from either extrinsic compression or invasion of the extrahepatic bile duct.

## 6. What are the treatment options for pancreatic cysts?

The management of pancreatic cysts has historically been surgical resection with the location of the lesion dictating the type of surgical intervention. Cysts in the head of the pancreas require a pancreaticoduodenectomy (Whipple procedure). Body or tail locations are removed with a distal pancreatectomy. Some cysts may be amenable to enucleation, which is an organ-preserving approach. Resection allows for treatment of cyst-related symptoms as well as histopathologic diagnosis. Pancreatic pseudocysts may be surgically resected or drained via surgical, endoscopic, or percutaneous techniques. Cyst ablation is a newer therapy aimed at destroying the epithelial lining in mucinous cysts with alcohol or chemotherapy, but is only offered at a few select centers.

## 7. What is the rate of malignancy in pancreatic cysts?

Approximately 23% of cystic lesions treated with resection based on worrisome radiographic and clinical criteria contain at least carcinoma in situ and 52% had malignant potential (intraductal papillary mucinous neoplasm [IPMN], mucinous cystic adenoma [MCA], solid pseudotumor). Twenty-five percent of IPMNs involve the main duct and more than 60% are malignant. Fifty-seven percent of IPMNs are branch duct and more than 25% are malignant. In resected MCAs, 13% had high-grade dysplasia and 4% had invasive carcinoma.

## 8. Define a pancreatic pseudocyst.

A *pancreatic pseudocyst* is a fluid collection encapsulated by a well-defined wall. An acute pancreatic fluid collection takes at least 4 weeks to mature into a pseudocyst. Most pseudocysts resolve over time; however, when there is communication with the pancreatic duct, they often enlarge or persist as chronic pseudocyst, causing symptoms such as abdominal fullness or pain, early satiety, and gastric outlet obstruction.

## 9. When do you treat pancreatic pseudocysts?

Pseudocysts that are enlarging, infected, or causing symptoms such as pain or gastric outlet obstruction require drainage. Hemorrhagic pseudocysts are a unique circumstance and may require combined surgical and angiographic treatment because of potential vascular involvement.

## 10. How are pancreatic pseudocyst treated?

Drainage of the cyst into the gastrointestinal lumen has become the preferred intervention with good technical and clinical success. A cystogastrostomy or cystoduodenostomy is created either endoscopically or surgically. Either technique is effective with local expertise dictating the procedure of choice. Delayed drainage procedures of any method (>4 weeks) are associated with improved outcomes. Magnetic resonance pancreatography or endoscopic retrograde pancreatography (ERCP) are useful studies in determining if the pancreatic duct communicates with a pseudocyst. ERCP with transpapillary pancreatic duct stenting is therapeutic in cases in which there is communication between the pseudocyst and pancreatic duct as primary or adjunctive therapy to transluminal drainage.

## 11. What are the characteristics of MCAs?

- Predominance is 95% female.
- Location is pancreas body and tail in 95%.
- Classically contain calcification in the wall.
- Internal septations appear with an outer capsule.
- Lesion is unifocal.
- Pancreatic duct is usually normal without communication.
- Presents in fourth and fifth decades.

## 12. What are the characteristics of IPMNs?

- Occurrence is equal in men and women.
- Main pancreatic duct involvement occurs if the duct size is more than 5 mm and no obstruction is present.
- Branch duct variant occurs if there are cystic side branches communicating with the pancreatic duct.
- Mixed variant occurs when both features are present.
- Branch duct involvement is often multifocal.
- Presents in sixth and seventh decades.

## 13. What is the evaluation process for PCLs that are not believed to be pseudocysts?

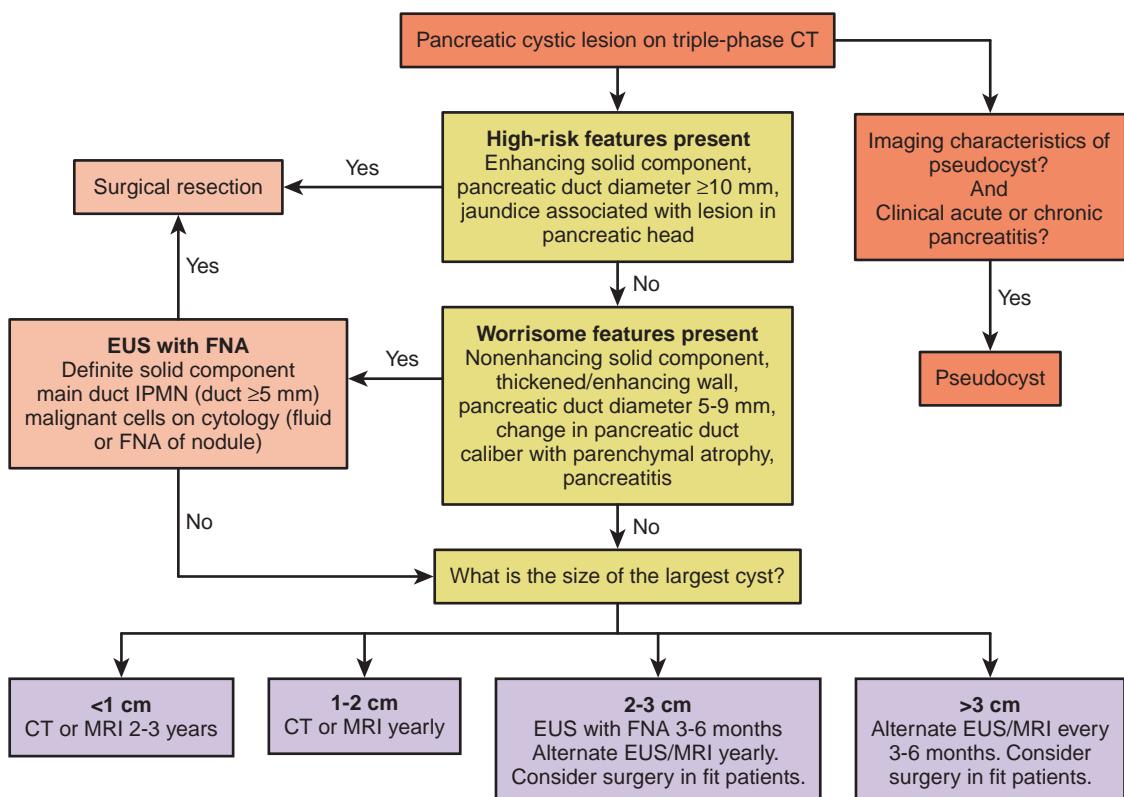
When the clinical history and imaging are not consistent with a pseudocyst, further evaluation is warranted. If high-risk features are seen on CT or MRI and the patient is a surgical candidate, then resection is recommended (Figure 39-1). A cyst without high-risk features but with worrisome features can be further characterized by endoscopic ultrasound with fine-needle aspiration. Cyst fluid analysis is 80% accurate in differentiating mucinous versus nonmucinous cysts when fluid carcinoembryonic antigen (CEA) levels are more than 192 ng/mL. Cyst fluid CEA levels are not diagnostic for high-grade dysplasia or malignancy. Although fluid cytologic examination is highly specific, it is less than 50% sensitive in detecting malignancy.

## 14. What are high risk features of pancreatic cysts?

- Obstructive jaundice with a cyst in the pancreatic head
- Enhancing solid cyst component
- Main pancreatic duct larger than 10 mm

## 15. What are worrisome features of pancreatic cysts?

- Main pancreatic duct 5 to 9 mm
- Nonenhancing solid cyst component
- Thickened or enhancing cyst wall
- Transition in duct diameter with distal gland atrophy
- Acute pancreatitis



**Figure 39-1.** Algorithmic approach to pancreatic cystic lesions identified on triple-phase computed tomography (CT). EUS, Endoscopic ultrasound; FNA, fine-needle aspiration; IPMN, intraductal papillary mucinous neoplasm; MRI, magnetic resonance imaging.

## 16. How is cyst fluid molecular analysis used in differentiating and risk stratifying pancreatic cysts?

A number of molecular targets have been identified that either aid in determining cyst histologic characteristics (mucinous vs. nonmucinous) or predict high-grade dysplasia or carcinoma. KRAS mutation, loss of heterozygosity, and DNA quantity are currently available commercial tests used to diagnose a mucinous cyst when the CEA level is indeterminate (5-192 ng/mL) or there is insufficient fluid to yield a CEA level. The presence of GNAS mutation has been demonstrated in IPMNs and not MCAs, making it a potentially useful test to distinguish branch duct IPMNs from MCAs. The role of cyst fluid molecular analysis in the evaluation of PCLs is yet to be determined, as larger multicenter studies are needed.

## BIBLIOGRAPHY

1. Al-Haddad M, DeWitt J, Sherman S, et al. Performance characteristics of molecular (DNA) analysis for the diagnosis of mucinous pancreatic cysts. *Gastrointest Endosc* 2013;1:1-9.
2. Bhutani M, Gupta V, et al. Pancreatic cyst fluid analysis—a review. *J Gastrointestin Liver Dis* 2011;20(2):175-80.
3. Brugge W, Lewandrowski K, Lee-Lewandrowski E, and the investigators of the CPC study. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology* 2004;126:1330-6.
4. Gaujoux S, Brennan M, Gonan M, et al. Cystic lesions of the pancreas: changes in the presentation and management of 1,424 patients at a single institution over a 15-year time period. *J Am Coll Surg* 2011;212:590-600.
5. Law J, Hruban R, Lennona A. Management of pancreatic cysts: a multidisciplinary approach. *Curr Opin Gastroenterol* 2013;29(5):509-16.
6. Ngamruengphong S, Bartel M, Raimondo M. Cyst carcinoembryonic antigen in differentiating pancreatic cysts: a meta-analysis. *Dig Liver Dis* 2013;45(11):920-6.
7. Parra-Herran C, Garcia M, Herrera L, Bejarano P. Cystic lesions of the pancreas: clinical and pathologic review of cases in a five year period. *J Pancreas* 2010;11(4):358-64.
8. Tanaka M, Fernandez-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 2012;12:183-97.
9. Turner B, Brugge W. Pancreatic cystic lesions: when to watch, when to operate, and when to ignore. *Curr Gastroenterol Rep* 2010;12:98-105.

# CELIAC DISEASE

Daniel A. Leffler, MD, MS, and Rohini R. Vanga, MBBS, MD

## 1. How does celiac disease (CD) manifest?

CD is a systemic immunologic disorder affecting multiple organ systems in genetically predisposed individuals triggered by ingestion of gluten-containing products such as wheat, rye, or barley.

CD has a wide clinical spectrum ranging from gastrointestinal and extraintestinal symptoms to a completely asymptomatic state. It frequently manifests as chronic diarrhea, weight loss, bloating and gas, distention, and abdominal discomfort in up to 40% to 50% of adults. However, at least half of patients have only extraintestinal or atypical manifestations of CD (Box 40-1).

### Box 40-1. Extraintestinal or Atypical Manifestations of Celiac Disease

#### Common

- Iron deficiency +/- anemia
- Chronic fatigue
- Osteopenia and osteoporosis
- Elevated liver function (enzyme) tests

- Neurologic psychiatric symptoms (migraines, depression, anxiety, peripheral neuropathy, ataxia, epilepsy with and without cerebral calcifications)
- Dermatitis herpetiformis
- Hypoproteinemia
- Infertility
- Incidental recognition during EGD for other indications

#### Less Common

- Constipation

EGD, Esophagogastroduodenoscopy.

## 2. Which populations are at risk for CD?

CD is one of the most common chronic conditions affecting humankind, with a worldwide prevalence of approximately 1%. CD is only uncommon among populations indigenous to sub-Saharan Africa and East Asia (Table 40-1).

**Table 40-1.** Risk of Celiac Disease

CONDITION OR SPECIFIC POPULATION	ESTIMATED PREVALENCE
North America and European descent	1%
First-degree relatives of person with celiac disease	10-15%
Type I diabetes	3-16%
Hashimoto's thyroiditis	5%
Down syndrome	10%*
Turner's syndrome	9%
IgA deficiency	9%
Eosinophilic esophagitis (pediatric)	5-10%†
Autoimmune liver disease, Sjögren's syndrome, IgA nephropathy	↑

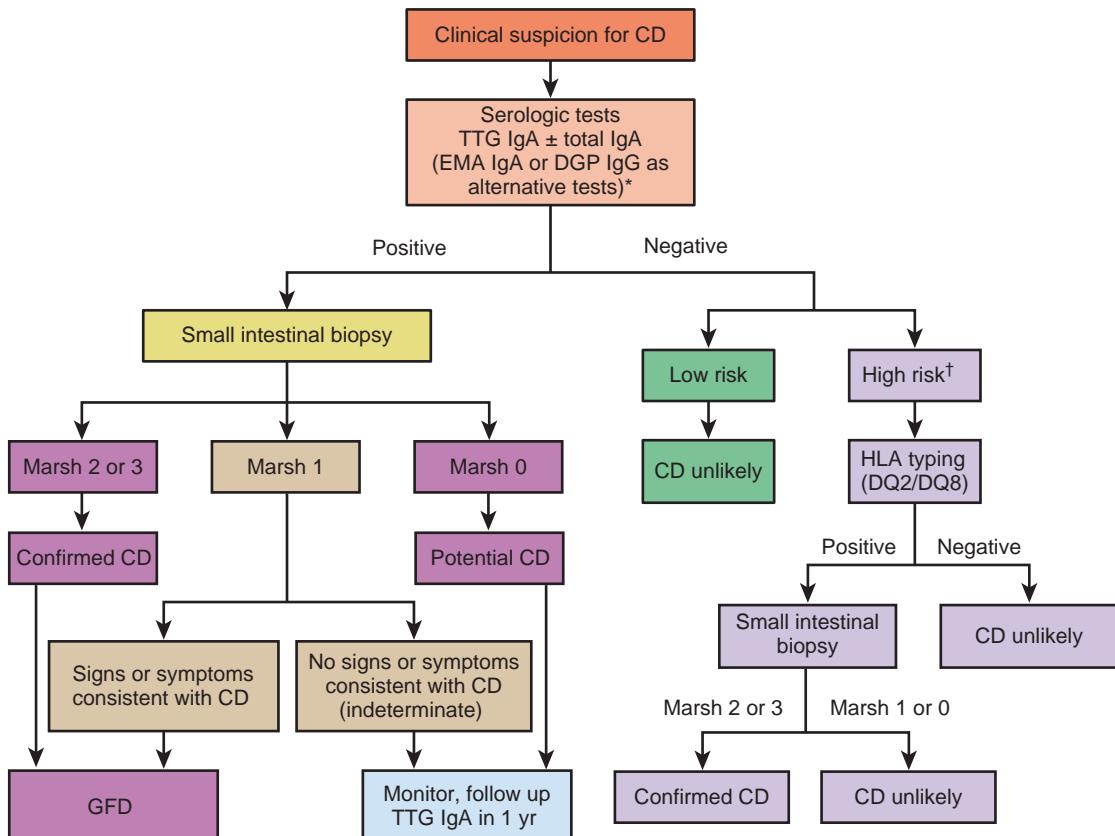
Ig, Immunoglobulin.

\*Book L, Hart A, Black J, Feolo M, Zone JJ, Neuhausen SL: Prevalence and clinical characteristics of celiac disease in Down syndrome in a US study, *Am J Med Genet* 98(1):70-74, 2001.

†Pellicano R, et al: 2013 update on celiac disease and eosinophilic esophagitis, *Nutrients* 5:3329-3339, 2013; Leslie C, Mews C, Charles A, Ravikumara M: Celiac disease and eosinophilic esophagitis: a true association, *J Pediatr Gastroenterol Nutr* 50(4):397-399, 2010.

### 3. How is CD diagnosed?

A stepwise approach aids in diagnosis of CD (Figure 40-1).



\*EMA IgA—98% specific, consider when TTG IgA is borderline positive. DGP IgG—>90% specific; useful in patients with IgA deficiency and children younger than 2 years of age.

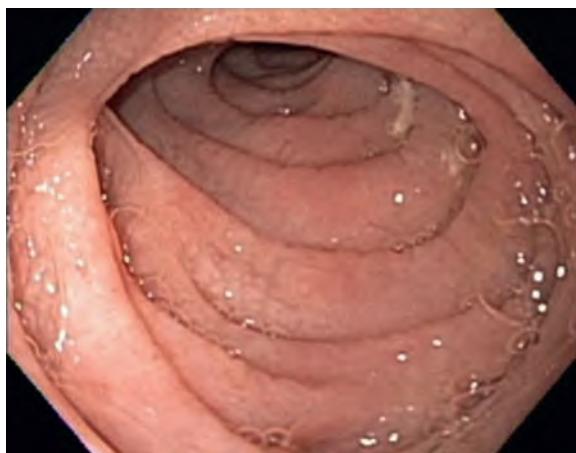
†Anemia, weight loss, chronic diarrhea or unexplained osteoporosis; family history of CD; coexisting autoimmune diseases.

**Figure 40-1.** Diagnostic algorithm for celiac disease. CD, Celiac disease; DGP, deamidated gliadin peptide; EMA, endomysial antibody; HLA, human leukocyte antigen; GFD, gluten-free diet; Ig, immunoglobulin; TTG, tissue transglutaminase.

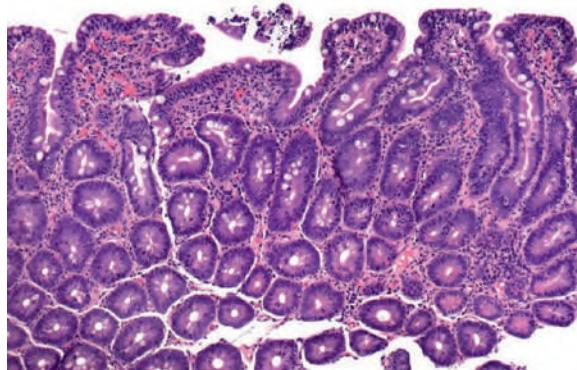
Serologic tests are the initial step to diagnose CD. Serum tissue transglutaminase (TTG) immunoglobulin A (IgA) antibody assay is greater than 95% sensitive and specific for CD screening in individuals with normal IgA levels, and should be the initial test of choice in most situations. Serum deamidated gliadin peptide IgG antibody assay has more than 90% sensitivity and specificity and is useful in the setting of IgA deficiency when TTG IgA is negative. Endomysial antibody IgA is moderately sensitive and highly specific for untreated CD and is most useful when TTG IgA is borderline positive. Gross appearance of the intestinal mucosa may suggest CD (Figure 40-2) but is not sensitive or specific. Small-bowel biopsy (typically 4–6 biopsies from the second portion of the duodenum and two from the duodenal bulb) remains the gold standard to confirm CD. Villous atrophy with increased intraepithelial lymphocytes (Marsh III) is the characteristic pathologic lesion in CD (Figure 40-3).

### 4. What are potential complications of CD?

- Untreated CD can lead to asymptomatic elevated aminotransferases in 40% to 50% of cases. Following a strict gluten-free diet (GFD) will lead to a reduction in aminotransferase levels in the majority of individuals. Progression to liver failure and cirrhosis is seen in a few cases despite a strict GFD, especially when autoimmune hepatitis, primary biliary cirrhosis, or primary sclerosing cholangitis coexist.
- Osteoporosis is another potential complication of unrecognized or untreated CD. Reduced bone density is common in patients with CD, and there is increased fracture risk.



**Figure 40-2.** Endoscopic appearance of duodenal mucosa showing characteristic scalloping in celiac disease.



**Figure 40-3.** Villous blunting with crypt hyperplasia and increased intraepithelial lymphocytes (tip heavy pattern) in celiac disease. (Adapted from McNally PR: *GI/liver secrets plus*, ed 4, Philadelphia, 2010, Mosby, online color images.)

- CD is associated with infertility in women. Screening women with unexplained infertility detects undiagnosed CD. The fertility improves with GFD.
- Patients with CD are at increased risk of mortality, adenocarcinoma of the small intestine, and enteropathy-associated T-cell lymphoma (EATCL).

##### 5. How is CD treated? Are there any management options other than a GFD?

Lifelong gluten avoidance is the only currently available treatment for CD. Although no gluten consumption is the ideal treatment for CD, a minimal degree of gluten contamination (hidden gluten) is difficult to avoid. Consultation with a registered dietitian who has expertise in GFD is important for patients' education, facilitation of adaptation to the new diet, and to minimize hidden gluten exposure. Attending a celiac support group is another source to expand knowledge about various options available for GFD. Immunosuppressive medicines such as corticosteroids (budesonide or prednisone), mesalamine, or 6-mercaptopurine are occasionally needed as adjuvant therapy in rare circumstances like celiac crisis or refractory CD (RCD); however, referral to a center with expertise in CD is recommended in these cases. Nondietary therapeutic agents such as larazotide acetate (tight junction regulator and zonulin antagonist) and glutinases are currently under investigation in phase 2 clinical trials.

##### 6. What common consequences of GFD does a primary care physician or gastroenterologist need to be aware of?

It is not only important to follow a strict GFD but also to maintain a healthy, balanced GFD. Otherwise, it can lead to undesirable weight gain, constipation, and nutritional deficiencies. Many commercial gluten-free foods are prepared mainly from white rice, corn, potato, and tapioca, which are high in carbohydrates, low in fiber, and tend to have poor nutritional value.

- On average, individuals with CD at diagnosis have lower body mass index (BMI) than the general population. However, CD can be seen in people of all weight classes. Because of a combination of different food choices and improved absorption, BMI often increases on the GFD, especially in those who adhere closely to

the GFD. Total cholesterol and low-density lipoprotein cholesterol may also rise. Weight maintenance counseling should be made an integral part of celiac dietary education.

- Constipation is another problem commonly encountered by patients on a GFD, predominantly because of the low fiber content of most gluten-free foods. Increased dietary fiber along with adequate fluid intake is the first and best treatment for constipation.
- Wheat flour products are enriched with iron and B vitamins, unlike most gluten-free baked products. A healthy GFD contains fruits and vegetables, whole grains and fiber, lean protein, low-fat dairy, calcium and vitamin D sources, and healthy fats. Nutritional supplements, including a multivitamin, calcium, and vitamin D, should also be recommended for most patients.

#### **7. How can “suspected” CD be evaluated in patients already on a GFD?**

Symptoms or symptom response to a GFD alone should not be used to diagnose CD. Celiac-specific serologic testing and intestinal biopsy are also not reliable to diagnose or exclude CD in patients already adhering to a GFD, as these tests can be expected to normalize with sufficient time on treatment. In cases with possible CD who are already on GFD, human leukocyte antigen (HLA)-DQ2/DQ8 testing should be carried out first. This test has a very high negative predictive value of more than 99% and helps to rule out CD. If the gene testing returns positive results for either DQ2, DQ8, or both, the next step is a 2- to 4-week formal gluten challenge followed by multiple duodenal biopsies and celiac serologic testing.

#### **8. What is nonresponsive CD (NRCD) and how is it managed?**

The majority of individuals with CD have substantial improvement with elimination of gluten from their diet. However, 7% to 30% of patients with CD have persistent symptoms, signs, or laboratory abnormalities typical of CD, despite being on a GFD for 6 to 12 months. This is known as NRCD and is due to a variety of etiologic factors. Inadvertent gluten exposure is the most common cause, accounting for 35% to 50% of cases of NRCD. When the symptoms fail to improve or when they recur, a systematic approach should be followed to identify and treat the specific cause (Figure 40-4). The foremost step is to reconfirm the initial diagnosis of CD by reviewing the small-intestinal histologic and serologic findings obtained at the time of diagnosis. An endoscopy should be considered if the diagnosis was solely based on celiac serologic testing. This will also help the physician assess intestinal healing and other conditions that can cause similar histologic findings.

#### **9. Describe RCD.**

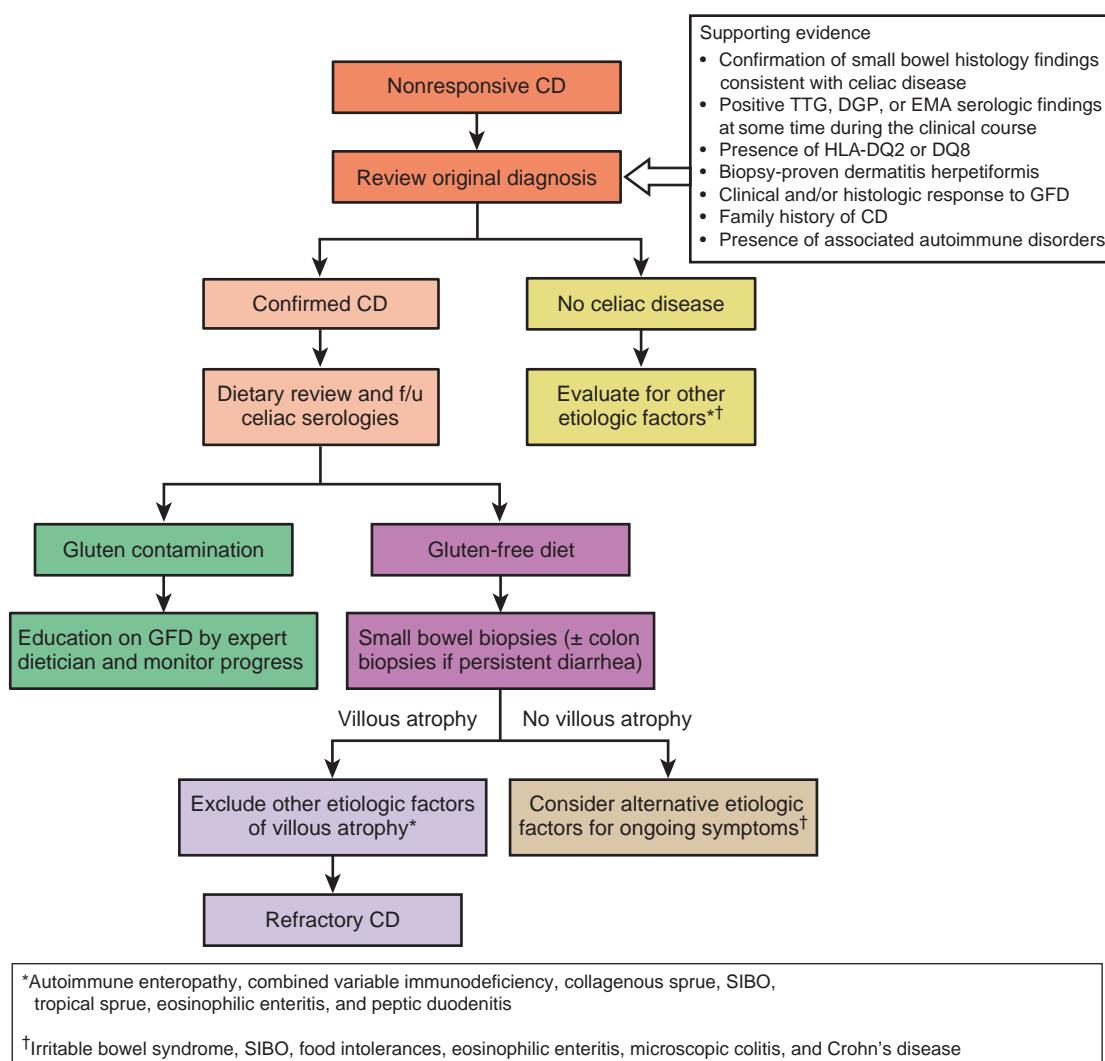
RCD is defined by persistent or recurrent malabsorptive symptoms and signs with villous atrophy despite a strict GFD for more than 12 months in the absence of other causes of nonresponsive, treated CD and overt lymphoma. RCD is uncommon, affecting 1% to 2% of patients with CD. Type I RCD is identified by polyclonal intraepithelial lymphocyte infiltration in the small intestinal mucosa, similar to that seen in untreated CD. Type II RCD is recognized by monoclonal aberrant CD3-positive T-lymphocytes that lack expression of CD8. Traditional treatment for both types I and II RCD consists of systemic corticosteroids or budesonide or immunosuppressive agents such as azathioprine. Type II RCD carries a less favorable prognosis because of the risk for malignant transformation to EATCL.

#### **10. What is the differential diagnosis of villous atrophy of the duodenum or nonceliac enteropathy (NCE)?**

Diseases other than CD may cause villous atrophy. The presence of villous atrophy with either negative CD-associated HLA-DQ2/DQ8 gene testing or negative celiac serologic findings on a gluten-containing diet as well as lack of histologic improvement on a GFD strongly suggest NCE.

Conditions associated with NCE include:

- Acquired immune deficiency syndrome (AIDS) enteropathy
- Autoimmune enteropathy
- Common variable immunodeficiency
- Collagenous sprue
- Crohn's disease
- Drug-induced enteropathy (e.g., olmesartan (Benicar), methotrexate, azathioprine)
- Eosinophilic enteritis
- Graft-versus-host disease
- Hypogammaglobulinemia sprue
- Infectious enteritis (giardiasis)
- Intestinal lymphoma
- Malnutrition
- Small intestinal bacterial overgrowth
- Tropical sprue
- Whipple's disease



\*Autoimmune enteropathy, combined variable immunodeficiency, collagenous sprue, SIBO, tropical sprue, eosinophilic enteritis, and peptic duodenitis

†Irritable bowel syndrome, SIBO, food intolerances, eosinophilic enteritis, microscopic colitis, and Crohn's disease

**Figure 40-4.** An approach to the investigation of nonresponsive celiac disease. CD, Celiac disease; DGP, deamidated gliadin peptide; EMA, endomysial antibody; f/u, follow up; GFD, gluten-free diet; HLA, human leukocyte antigen; SIBO, small intestinal bacterial overgrowth; TTG, tissue transglutaminase. (Adapted from Rubio-Tapia A, Hill ID, Kelly CP, et al: ACG clinical guidelines: diagnosis and management of celiac disease, *Am J Gastroenterol* 108(5):656-676, 2013.)

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

1. Kelly CP, Green PH, Murray JA, et al. Larazotide Acetate Celiac Disease Study Group. Larazotide acetate in patients with coeliac disease undergoing a gluten challenge: a randomised placebo-controlled study. *Aliment Pharmacol Ther* 2013;37(2):252-62.
2. Leffler DA, Kelly CP, Abdallah HZ, et al. A randomized, double-blind study of larazotide acetate to prevent the activation of celiac disease during gluten challenge. *Am J Gastroenterol* 2012;107(10):1554-62.
3. Nasr I, Leffler DA, Ciclitira PJ. Management of celiac disease. *Gastrointest Endosc Clin N Am* 2012;22(4):695-704.
4. Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc* 2012;87(8):732-8.
5. Rubio-Tapia A, Hill ID, Kelly CP, et al. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol* 2013;108(5):656-76.
6. Tio M, Cox MR, Eslick GD. Meta-analysis: coeliac disease and the risk of all-cause mortality, any malignancy and lymphoid malignancy. *Aliment Pharmacol Ther* 2012;35(5):540-51.
7. Ziegler TR, Fernandez-Estivariz C, Gu LH, et al. Severe villus atrophy and chronic malabsorption induced by azathioprine. *Gastroenterology* 2003;124:1950-7.

## Website

CeliacNow (nutrition for celiac disease). [www.celiacnow.org](http://www.celiacnow.org) [Accessed September 22, 2014].  
NIH Consensus Development Conference on Celiac Disease. <http://consensus.nih.gov/2004/2004celiacdisease118html.htm> [Accessed September 22, 2014].

# CROHN'S DISEASE

Bret A. Lashner, MD, and Aaron Brzezinski, MD

## DIAGNOSIS

### 1. What are the usual symptoms and signs suggestive of Crohn's disease?

The symptoms of Crohn's disease are determined by the site and type of involvement (i.e., inflammatory, stenotic, or fistulizing). The most common site of involvement is ileocolitis (approximately 45% of patients). These patients present with diarrhea and abdominal pain that is usually insidious, in the right lower quadrant, frequently triggered or aggravated after meals, and may be associated with a tender, inflammatory mass in the right lower quadrant and weight loss. The diarrhea is usually nonbloody, and this may be one of the clues in clinical history that helps differentiate ileocolonic Crohn's disease from ulcerative colitis, in which bloody diarrhea is almost universal. Patients frequently have fever, weight loss, perianal fistulas or fissures, and extraintestinal manifestations such as aphthous stomatitis, arthritis, and erythema nodosum. Patients with isolated colonic Crohn's disease (approximately 30% of patients) usually present with diarrhea, abdominal pain, hematochezia, and weight loss.

Perianal skin tags are very common and at times are mistaken for external hemorrhoids, and it is not until these are excised and the course is complicated by a nonhealing wound that the diagnosis of Crohn's disease is entertained. At times, the main symptoms are related to perianal fistulae or abscess, even though most of these patients have other areas of involvement by Crohn's disease. Fistulas may develop from the bowel to other organs, like the bladder or other bowel segments, or to the peritoneal cavity. Gastroduodenal Crohn's disease (approximately 5% of patients) is less common and can mimic complicated peptic ulcer disease with abdominal pain, early gastric satiety, or symptoms of duodenal obstruction.

Patients with stenotic disease will present with obstructive symptoms related to the site of the stricture. There is often cramping abdominal pain, distension, vomiting, and obstipation. With the absence of an inflammatory component to disease, surgery, rather than antiinflammatory treatment, is usually needed.

### 2. How is the diagnosis of Crohn's disease established?

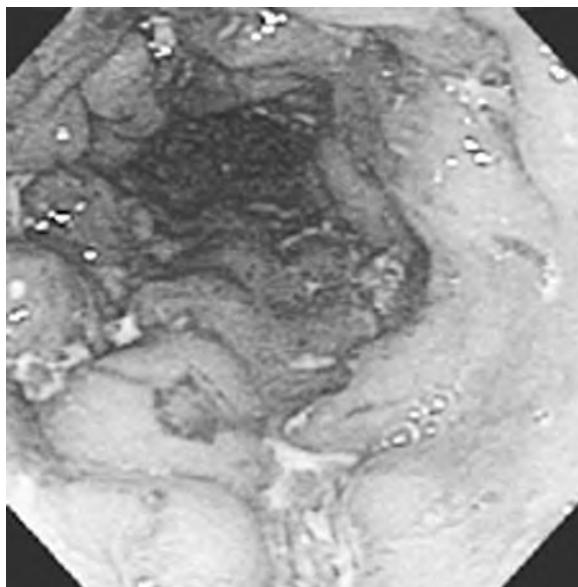
The diagnosis of Crohn's disease is established by history, physical examination, endoscopy, biopsies, radiographs, and laboratory tests. Crohn's disease presents most commonly between ages 15 and 25. The diagnosis should be suspected in patients with chronic diarrhea, finding characteristic intestinal ulcerations and excluding alternative diagnoses. The ulcerations of Crohn's disease may be aphthoid ([Figure 41-1](#); access

**Figure 41-1.** Aphthoid ulcers in a patient with Crohn's colitis.

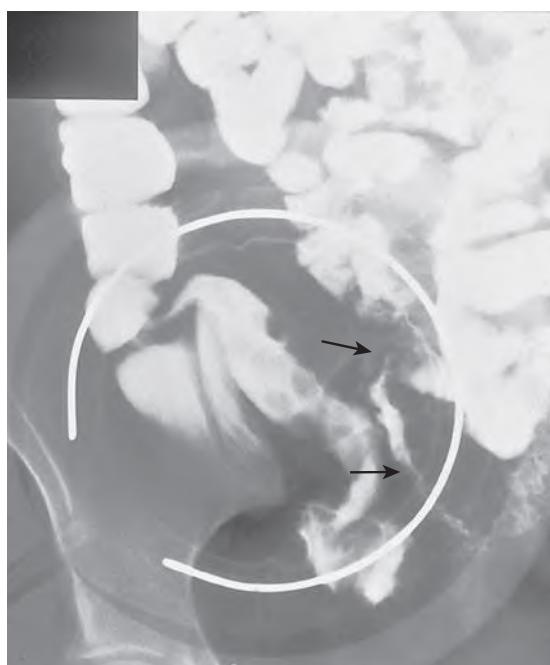




ExpertConsult to see Video 41-1) but also could be deep, serpiginous, and sharply demarcated along the longitudinal axis of the bowel (Figure 41-2). Skip areas, cobblestoning, and rectal sparing are characteristic findings. Air-contrast barium enema, small bowel series with or without a peroral pneumocolon, computed tomography enterography, or colonoscopy each may demonstrate these typical lesions. On a small bowel series, Crohn's disease often leads to separation of bowel loops, a narrowed and ulcerated terminal ileum, and in advanced cases the so-called *string sign* (Figure 41-3). The biopsies of involved areas have architectural distortion and a chronic inflammatory infiltrate, and in approximately 10% to 30% of cases of Crohn's colitis there are noncaseating granulomas that usually are diagnostic. Typical lesions of Crohn's disease also may be seen in the upper gastrointestinal tract.



**Figure 41-2.** Deep, serpiginous ulcers of Crohn's disease.



**Figure 41-3.** String sign from a small bowel series in a patient with Crohn's disease.

### 3. Which diseases can mimic the symptoms and signs of Crohn's disease?

The differential diagnosis of Crohn's disease is long. The most common mimics of Crohn's colitis are ulcerative colitis (Table 41-1), ischemic colitis, diverticulitis, or colorectal cancer. For Crohn's ileitis, infection with *Yersinia enterocolitica* or *Mycobacterium tuberculosis* may mimic Crohn's disease. In immunosuppressed patients, viral infections such as cytomegalovirus (CMV) may be mistaken for a flare of Crohn's disease. Other important diseases in the differential diagnosis of Crohn's disease include the irritable bowel syndrome, intestinal lymphoma, celiac sprue, radiation enteropathy, and nonsteroidal antiinflammatory drug-induced enteropathy.

**Table 41-1.** Some Distinguishing Features of Ulcerative Colitis and Crohn's Disease

	ULCERATIVE COLITIS	CROHN'S DISEASE
Rectal bleeding	Usual	Sometimes
Abdominal mass	Rare	Often
Abdominal pain	Sometimes	Often
Perianal disease	Extremely rare	5% to 10%
Upper gastrointestinal symptoms	Never	Occasional
Cigarette smoking	Very rare (<10%)	Common (>50%)
Malnutrition	Sometimes	Common
Low-grade fever	Sometimes	Often
Rectal disease	Usual	Sometimes
Continuous disease	Usual	Sometimes
Granulomas	Never	10%
Crypt abscesses	Common	Rare
Discrete ulcers	Rare	Common
Aphthoid ulcers	Rare	Common
Cobblestone lesions	Never	Common
Skip lesions	Rare	Common
Ileal involvement	Rare, backwash ileitis	Usual
Fistulas	Very rare	Common
Cancer	Rare	Very rare
Microscopic skip lesions	Rare	Common
Transmural inflammation	Never	Common

### 4. What serologic tests can help establish the diagnosis?

Clinical, endoscopic, and histologic findings can establish the diagnosis and differentiate between Crohn's disease and ulcerative colitis in 85% to 90% of patients. In the remaining 10% to 15% of patients with *indeterminate* colitis, serologic testing can be helpful. A positive anti-*Saccharomyces cerevisiae* antibody and a negative perinuclear antineutrophil cytoplasmic antibody are most consistent with Crohn's disease, whereas the converse is consistent with ulcerative colitis. Newer tests that look at serologic findings, as well as genetic mutations and inflammatory markers can increase the sensitivity of such testing.

## ETIOLOGIC FACTORS

### 5. Is cigarette smoking associated with Crohn's disease?

Crohn's disease is more common among cigarette smokers. Fully 50% of Crohn's disease patients smoke at least five cigarettes daily, compared with approximately 25% in the general adult population. Also, cigarette smoking is associated with adverse outcomes, such as early recurrence, more severe complications, and a higher likelihood for repeat surgery. Patients with Crohn's disease *must be strongly encouraged to quit smoking!*

## 6. What infectious agents might be responsible for Crohn's disease?

*Mycobacterium avium paratuberculosis* (MAP) causes Johne disease, a granulomatous inflammation of the terminal ileum and other parts of the intestine, in ruminants. In a small number of patients with Crohn's disease, *in situ* hybridization and polymerase chain reaction of resected specimens have found MAP and other atypical mycobacteria. However, a causal relationship has not been determined, and treatment of such infections is effective only in a few patients. Other infectious agents, such as the measles virus or the measles vaccine, have been proposed, but the evidence is inconclusive and an etiologic association has not established. It is possible that an infectious agent, like *Clostridium difficile*, CMV, or a viral agent could trigger an abnormal immune response by the innate intestinal immune system.

## 7. Is there a genetic predisposition for developing Crohn's disease?

The principal theory on the pathogenesis of Crohn's disease is that in a genetically predisposed individual, an environmental agent (i.e., infection, dietary substance that enters the bloodstream through a permeable intestine, or a component of cigarette smoke) triggers an uncontrolled inflammatory response. The incidence of Crohn's disease can be upward of 10 per 100,000 in the certain populations. Crohn's disease occurs in more than one first- or second-degree family member in approximately 20% of cases. Children whose parent has Crohn's disease have a lifetime risk of approximately 3% of developing Crohn's disease. Spouses of patients with Crohn's disease rarely develop Crohn's disease. The genetic predisposition occurs from a number of important genetic mutations in key regulatory proteins of intestinal inflammation. Studies of genetic linkages among kindreds with inflammatory bowel disease led to the discovery of the *NOD-2/CARD-15* mutation in chromosome 16 (*IBD-1*). Depending on the population studied, this mutation can be seen in as many as 30% of patients with Crohn's disease; however, it is also seen in non-Crohn's disease patients, and in Japan, this mutation is only rarely seen in patients with Crohn's disease. In the European and American white population, the presence of this mutation appears to predict stenotic disease involving the terminal ileum. There have now been more than 70 susceptibility gene mutations identified for Crohn's disease. Besides *NOD-2*, mutations in the autophagy gene *ATG16L1* is the most important susceptibility gene. Of note, mutations in the interleukin-23 receptor (*IL-23R*) gene on chromosome 1 have been shown to be protective for Crohn's disease development.

## NATURAL HISTORY

### 8. Is mortality increased in patients with Crohn's disease?

Patients with Crohn's disease, in general, do not have an increased mortality compared with age- and sex-matched controls. Some complications of Crohn's disease, such as malignancy, short bowel syndrome, hypercoagulable state, and primary sclerosing cholangitis, do have an increased mortality. Fortunately, these complications are rare.

### 9. Are there factors that predict a flare of Crohn's disease activity?

Cigarette smoking is the most important clinical risk factor for symptomatic recurrence. Smokers have a recurrence at least twice as high as nonsmokers. The effect of oral contraceptive use on recurrence rate is controversial. Although oral contraceptive use is not associated with an increased recurrence rate, there is a synergistic effect between smoking and oral contraceptive use; the combined effects are greater than the sum of the individual effects. Other important risk factors for symptomatic recurrence are intestinal infections or nonsteroidal antiinflammatory drug use.

### 10. Does behavior of disease predict its natural history?

According to its behavior, Crohn's disease has been classified as either inflammatory, stricturing, or fistulizing disease. Inflammatory-type disease is characterized by intestinal ulcerations and the main symptoms are diarrhea, abdominal pain, an inflammatory mass, and, when it is severely active, fever and weight loss. Inflammatory-type disease responds best to antiinflammatory therapy, particularly corticosteroids and infliximab, but recurrence is the rule rather than the exception. The natural history of inflammatory-type disease is aggressive with early recurrence. Stricturing-type disease, on the other hand, has a more indolent course that does not respond well to antiinflammatory therapy. Although all Crohn's disease begins as inflammation, the predominant pathologic finding in patients with stricturing disease is extensive fibrosis in the lamina propria. Surgery is the best therapeutic option in patients with stricturing disease, and the need for a second surgery is lower than with other types of Crohn's disease. Fistulizing-type disease is characterized by enterocutaneous or enteroenteric fistulas. Fistulas occur in areas of inflammation and often originate in a segment of bowel proximal to a stricture. Following successful medical or surgical therapy for fistulas, recurrence is common. Most patients with inflammatory or fistulizing disease will benefit from maintenance medical therapy to minimize the risk for recurrence.

Although surgery is necessary in many patients with Crohn's disease, it is not a cure. The endoscopic recurrence following a surgical resection of the terminal ileum and proximal colon is virtually 100%. Interestingly, postsurgical recurrence often has a similar behavior to presurgical behavior. Patients with inflammatory disease often present with postoperative inflammatory-type disease and patients with stricturing disease recur with similar behavior. To minimize the risk of a second or third surgery, long-term maintenance therapy is usually necessary.

### **11. Do patients with Crohn's disease have an excess cancer risk?**

Small bowel cancer in Crohn's disease is a rarely reported phenomenon; less than 100 cases have been reported in the literature. Epidemiologic studies, however, have suggested that the relative risk of small bowel cancer in Crohn's disease is greatly elevated. Small bowel cancer in Crohn's disease follows the same distribution as Crohn's disease (ileum > jejunum > duodenum), which is exactly opposite to the distribution of sporadic small bowel cancer. Excluded loops and chronic fistulas also are risk factors for small bowel cancer in Crohn's disease. Like in ulcerative colitis, colorectal cancer is increased in patients with extensive colonic Crohn's disease (i.e., at least one third of the colon is involved with inflammation). Colorectal cancer in Crohn's disease occurs near areas of inflammation. As in ulcerative colitis patients, patients with extensive Crohn's colitis should have routine surveillance colonoscopy with extensive biopsies to identify the benign, but premalignant lesion of dysplasia. The risk of cancer in patients with dysplasia in the colon is so high that surgery is usually recommended to minimize that risk.

### **12. What are the extraintestinal manifestations of Crohn's disease?**

The extraintestinal manifestations of Crohn's disease are similar to those seen in ulcerative colitis. A polyarticular nondeforming arthritis is the most common extraintestinal manifestation, occurring in approximately 20% of patients; the arthritis responds to treatment of bowel symptoms. Primary sclerosing cholangitis is less common in patients with Crohn's disease than in ulcerative colitis patients; it follows a course independent of disease activity, and does not respond to antiinflammatory therapy directed to the bowel, including surgery. Erythema nodosum, pyoderma gangrenosum, iritis, uveitis, pancreatitis, nephrolithiasis, cholelithiasis, amyloidosis, osteoporosis, and ankylosing spondylitis are all extraintestinal manifestations of Crohn's disease. Nephrolithiasis most often is from oxalate stones. Patients with Crohn's disease with fat malabsorption have preferential binding of luminal calcium to fatty acids rather than oxalate and the subsequent increased absorption of dietary oxalate with stone formation.

## **TREATMENT**

### **13. Which 5-aminosalicylic acid (5-ASA) preparations are effective in treating Crohn's disease patients?**

5-ASA agents have been used for many years to treat patients with inflammatory bowel disease, mostly ulcerative colitis. All are Food and Drug Administration (FDA)-approved for ulcerative colitis and none are approved for Crohn's disease. The response to 5-ASA in Crohn's disease in induction and maintenance of remission is less than in ulcerative colitis. 5-ASA is a topical agent and not a systemic medication; therefore it needs to be delivered to the site of inflammation. Sulfasalazine requires bacterial cleavage of the diazo bond between sulfapyridine and 5-ASA for the 5-ASA to have a local antiinflammatory effect. Because bacteria are present in sufficient numbers only in the large bowel, sulfasalazine is effective only in patients with Crohn's colitis. Other oral 5-ASA compounds that have colonic 5-ASA release are mesalamine (Asacol-HD, Delzicol, Lialda, Pentasa, Apriso), olsalazine sodium (Dipentum), and balsalazide (Colazal). Pentasa and Apriso are capsules with ethylcellulose-coated beads that release 5-ASA throughout the large and small bowel. Theoretically, Pentasa and Apriso should be most effective in Crohn's disease patients with extensive small bowel disease. 5-ASA is also available in the form of suppositories or enemas for patients with proctitis or involvement up to the sigmoid colon. 5-ASA agents are used only in patients with mildly to moderately active disease; their role in maintenance of remission of Crohn's disease is debatable.

### **14. Should steroids be used in Crohn's disease?**

Steroids are effective in treating inflammatory-type Crohn's disease, with approximately 85% of patients showing partial or complete resolution of symptoms. Long-term use is not recommended, however, because of the many serious adverse effects such as osteoporosis, diabetes, cataracts, and steroid-dependent disease, just to name a few. Steroids are not effective in stricturing Crohn's disease and actually may worsen patients with fistulas, especially if localized infection is not adequately drained.

Budesonide is a potent steroid with a very high rate of first-pass metabolism of 85% to 90%. Therefore the systemic side effects are greatly diminished but not entirely eliminated. The preparation available in the United States delivers the medication in the distal ileum and cecum in patients who have not had small bowel resection. Budesonide has been effective for induction of remission in patients with moderately active Crohn's disease and has been approved for maintenance of remission. It is advisable to prescribe supplemental calcium and vitamin D to patients taking steroids, regardless of the route of administration.

### **15. What is the role for immunosuppressive therapy in Crohn's disease?**

Both azathioprine and 6-mercaptopurine are commonly used in patients with Crohn's disease. Both are purine analogs that interfere with DNA synthesis of rapidly dividing cells such as lymphocytes and macrophages. Because these drugs do not have a clinical effect for 2 to 3 months, or longer, they are primarily used in maintaining remission in inflammatory-type and fistulizing-type Crohn's disease, and can be given for 4 years or longer. Important adverse effects include pancreatitis, allergy, and leukopenia. White blood cell counts and liver function tests need to be checked on a periodic basis. There are two main strategies to start these medications; traditionally, the medication was started at a low dose and the dose was increased according to the

speed at which the white blood cells decreased. The preferred option is to start the dose based on body weight and thiopurine methyltransferase (TPMT) enzyme activity: a full dose for patients with normal TPMT enzyme activity and a reduced dose for patients with intermediate TPMT enzyme activity. Alternative therapies are explored in patients with low or absent TPMT activity. Whatever regimen one chooses, it is very important to monitor liver tests and the white blood cells on a regular basis. Nonresponders can have levels of the active metabolite, 6-thioguanine (6-TG), measured to see if the lack of response is due to lack of adherence to a medical regimen (6-TG level of 0), underdosing (6-TG level of less than 230 pmol/8 × 10<sup>8</sup> red blood cells), or true lack of response (6-TG level greater than 230 pmol/8 × 10<sup>8</sup> red blood cells).

#### **16. Which biologic therapies are effective for patients with Crohn's disease?**

Infliximab (Remicade) is an immunoglobulin G<sub>1</sub> chimeric mouse-human antibody to tumor necrosis factor (TNF) that, when infused intravenously, binds to soluble TNF and to the TNF on surface membranes of inflammatory cells, causing complement fixation and cell lysis. It has been approved for use as induction and maintenance therapy in inflammatory-type Crohn's disease and fistulizing Crohn's disease. In randomized clinical trials, 48% of patients with inflammatory-type disease and 55% of patients with fistulizing disease achieved complete remission, figures significantly higher than for placebo-treated patients. Side effects during the infusion such as nausea, headache, and pharyngitis can be attenuated with slowing the infusion.

Since its approval by the FDA in 1998, there has been a great deal of experience gained with the use of infliximab. We have learned that the long-term response rate is 60% to 70% and that, with continued use every 8 weeks, patients often maintain remission. Tuberculosis, opportunistic infections, and, to a lesser extent, malignancies have been the main complications of its use, and the analysis of 500 patients at the Mayo Clinic revealed a 1% mortality rate among patients receiving infliximab. With chronic use, or intermittent use, patients may form antiinfliximab antibodies, which may decrease its effectiveness.

Adalimumab (Humira) is a fully human anti-TNF antibody that is approved for induction and maintenance therapy for Crohn's disease. It is given as a 40-mg subcutaneous injection every 2 weeks after a loading dose of 160 mg at week 0 and 80 mg at week 2. Its effectiveness and toxicities are very similar to those of infliximab. Certolizumab (Cimzia) is a pegylated Fab fragment of a humanized anti-TNF antibody. Its effectiveness and toxicity are similar to those of infliximab and adalimumab, and it is given as a monthly subcutaneous injection. Natalizumab (Tysabri), an antiintegrin antibody, is another biologic agent approved for use in Crohn's disease. Its effectiveness appears to be similar to that of other biologic agents, and rate of opportunistic infections may be lower. Natalizumab was associated with progressive multifocal leukoencephalopathy, causing its use to be restricted to patients enrolled in an international registry.

#### **17. Which medications are effective in maintaining remission?**

Patients who have a high risk of recurrence following a medically or surgically induced remission should be considered for maintenance medications. Smokers, patients who have had more than one surgery, and patients with inflammatory-type or fistulizing disease have the highest risk of recurrence. Long-term therapy with azathioprine or 6-mercaptopurine has excellent maintenance effects, as does methotrexate. 5-ASA agents have a lesser maintenance effect. Budesonide is approved for maintenance, as are infliximab, adalimumab, certolizumab, and natalizumab. All of the effective maintenance medications are associated with mucosal healing, a therapeutic endpoint associated with reduced surgery and reduced hospitalization rates. Steroids do not induce mucosal healing.

#### **18. What are the indications for surgery in Crohn's disease?**

The adage *a chance to cut is a chance to cure* does not apply to Crohn's disease because surgery is not a cure for Crohn's disease. The main goal of surgery is to treat the most important problem while preserving as much bowel as possible. Wide resection margins are not associated with decreased recurrence and should be avoided. The indications for surgery include active inflammatory-type disease refractory to medical therapy, prednisone-dependence, intestinal strictures, fistulas, abscesses, growth retardation, bleeding, perforation, severe anorectal disease, dysplasia, and cancer. Besides resection and abscess drainage, there is considerable experience with strictureplasty (opening a stricture without removing bowel) and advancement flap surgery (removing a perirectal fistula by advancing normal mucosa over the internal os). A close working relationship between the internist or gastroenterologist and colorectal surgeon is extremely important for controlling disease and decreasing morbidity. Still, recurrent disease is very common and postoperative maintenance medications should be strongly considered in high-risk patients.

#### **19. What therapeutic regimen is most often effective for stricturing-type Crohn's disease?**

Usually, stricturing-type Crohn's disease requires surgery. Antiinflammatory therapy is not likely to relieve symptoms. The goals of surgery are to relieve symptoms and preserve bowel length. The surgery offered need not be a resection, however. Strictureplasties of strictured segments of small bowel or anastomosis can provide long-term relief of obstructive symptoms. In the most common type of strictureplasty, an incision is made on the longitudinal axis of a short stricture that is sutured along a perpendicular. Prior to performing a strictureplasty, the surgeon sends a frozen section to rule out carcinoma at the site of the stricture. In some patients, endoscopic balloon dilatation at the site of an ileocolic anastomosis relieves symptoms, delaying the need for surgery. There is no evidence that steroid injection into the anastomotic site at the time of balloon dilation is effective.

## 20. What therapeutic regimen is most often effective for inflammatory-type Crohn's disease?

Inflammatory-type Crohn's disease should respond to antiinflammatory agents. 5-ASA agents usually are tried first because of the limited toxicity; however, their efficacy is limited. Antibiotics such as ciprofloxacin or metronidazole are effective, particularly in patients with colonic and perianal disease. Steroids are usually tried next because of the relatively rapid onset of action. Azathioprine/6-mercaptopurine and methotrexate are usually reserved for steroid-dependent inflammatory disease and for maintenance of remission. All of the available biologic agents—infliximab, adalimumab, certolizumab, and natalizumab—are indicated for inflammatory-type Crohn's disease. With the exception of natalizumab, which must be used as monotherapy, there is more effectiveness when biologic agents are combined with immunosuppressive therapy.

## 21. What therapeutic regimen is most often effective for fistulizing Crohn's disease?

An assessment of the degree of mucosal activity is an important determinant of therapy for fistulizing Crohn's disease. When active disease is present, antiinflammatory therapy with 5-ASA agents, azathioprine, 6-mercaptopurine, or biologic agents could be extremely helpful. In perianal fistulas, combined medical and surgical treatment is usually required. Sepsis should be adequately drained and placement of noncutting Seton sutures can facilitate continued drainage and promote healing ([E-Figure 41-4](#)). Antibiotics, azathioprine, 6-mercaptopurine, or infliximab is usually beneficial. If the mucosal disease is quiescent, then surgical therapy with an advancement flap procedure may be appropriate.

## 22. When should nutritional support be used in patients with Crohn's disease?

Nutritional support can be used as primary or adjuvant therapy for Crohn's disease. Interestingly, bowel rest and total parenteral nutrition (TPN) will greatly improve most patients with inflammatory-type or fistulizing-type disease. Enteral nutrition is almost as effective as steroids in inducing remission in inflammatory-type Crohn's disease, but has much fewer side effects. Unfortunately, when food is introduced, symptoms and signs of active disease quickly return. Nutritional support also is effective in children with Crohn's disease and growth retardation. Because of the expense and morbidity of TPN, long-term TPN should be reserved for patients with a short bowel syndrome or extensive small bowel disease.

## 23. What is the appropriate clinical action for Crohn's disease patients who initially respond to infliximab, but over time exhibit loss of response (LOR)?

The first step is to reevaluate for other cause of diarrhea, including community-acquired enteric infection, *C. difficile*, opportunistic pathogens, and progression of Crohn's disease including stricture and fistulae.

In patients who have initially responded to infliximab and then lost response, infliximab level and infliximab antibody testing may help guide therapy. If infliximab antibodies are positive, switching to another anti-TNF agent like adalimumab or certolizumab may be effective because antibodies to infliximab do not cross-react with these other agents. In patients with no infliximab antibodies and low infliximab levels, increasing the dose by shortening the infusion interval often helps. In patients with no infliximab antibodies and high levels of infliximab, and active inflammation is still present, then switching to an agent with a different mechanism of action, like natalizumab, should help.

## 24. Should patients with stricturing ileal Crohn's disease that requires surgical resection be placed on postoperative therapy to prevent relapse?

Yes. Crohn's disease is a chronic relapsing disorder. Histologic evidence of recurrent inflammation at the surgical anastomosis is evident within weeks of surgery and endoscopic findings often seen during surveillance exams within a year of surgery ([Access ExpertConsult](#) to see [E-Figure 41-5](#) and Video 41-2). Studies are in progress to determine the best agents to use to prevent postoperative Crohn's relapse, but it appears that anti-TNF agents started approximately 4 weeks postoperatively are helpful in preventing anastomotic relapse and need for surgery in the long term.



Please access [ExpertConsult](#) to see the E-Figure, Videos, and [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

1. Afif W, Loftus Jr EV, Fabion WA. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. *Am J Gastroenterol* 2010;105:1133–9.
2. Ananthakrishnan AN, Guzman-Perez R, Gainer V, et al. Predictors of severe outcomes associated with *Clostridium difficile* infection in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2012;35:789–95.
3. Brant SR, Picco MF, Achkar JP, et al. Defining complex contributions of NOD2/CARD15 gene mutations, age at onset, and tobacco use in Crohn's disease phenotypes. *Inflamm Bowel Dis* 2003;9:281–9.
4. Bousvaros A, Antonioli DA, Colletti RB, et al. Differentiating ulcerative colitis from Crohn's disease in children and young adults. *J Pediatr Gastroenterol Nutr* 2007;44:653–74.
5. Bruining DH, Loftus Jr. EV, Ehman EC, et al. Computer tomography enterography detects intestinal wall changes and effects of treatment in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2011;9:679–83.
6. Columbel JF, Loftus EV, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology* 2004;126:19–31.
7. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;132:52–65.



**E-Figure 41-4.** Seton sutures placed in the perineum.



**E-Figure 41-5.** Endoscopic demonstration of postoperative recurrent crohn's ulceration in the terminal ileum.

8. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;362:1383–95.
9. Cosnes J, Cattan S, Blain A, et al. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002;8:244–50.
10. Dubinsky MC, Lamothe S, Yang HY, et al. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. *Gastroenterology* 2000;118:705–13.
11. Dubinsky MC, Wang D, Picornell Y, et al. IL-23 receptor (IL-23R) gene protects against pediatric Crohn's disease. *Inflamm Bowel Dis* 2007;13:511–5.
12. Fazio VW, Marchetti F, Church JM, et al. Effect of resection margins on recurrence of Crohn's disease of the small bowel: a randomized controlled trial. *Ann Surg* 1996;224:563–71.
13. Feagan BG, Fedorak RN, Irvine EJ, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn Study Group Investigators. *N Engl J Med* 2000;342:1627–32.
14. Hugot JP, Chamaillard M, Zouali H, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature* 2001;411:599–603.
15. Lichtenstein GR, Targan SR, Dubinsky MC, et al. Combination of genetic and quantitative serologic immune markers are associated with complicated Crohn's disease behaviour. *Inflamm Bowel Dis* 2011;17:2488–96.
16. Munkholm P, Langholz E, Davidsen M, et al. Intestinal cancer risk and mortality in patients with Crohn's disease. *Gastroenterology* 1993;105:1716–23.
17. Ogura Y, Bonen DK, Inohara N, et al. A frameshift mutation in NOD2 is associated with susceptibility to Crohn's disease. *Nature* 2001;411:603–6.
18. Osterman MT. Mucosal healing in inflammatory bowel disease. *J Clin Gastroenterol* 2013;47:212–21.
19. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;340:1398–405.
20. Schreiber S, Khaliq-Kareemi M, Lawrence IC, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007;357:239–50.
21. Tursi A, Elisei W, Giorgette GM, et al. Factors influencing mucosal healing in Crohn's disease during infliximab treatment. *Hepatogastroenterology* 2013;60:1041–6.
22. Targan SR, Feagan BG, Fedorak RN, et al. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. *Gastroenterology* 2007;132:1672–83.
23. Targan SR, Hoenir SB, Van Deventer SCH, et al. A short-term study of chimeric monoclonal antibody cA2 to TNF-alpha for Crohn's disease. *N Engl J Med* 1997;337:1029–35.
24. Timmer A, Sutherland LR, Martin F, et al. Oral contraceptive use and smoking are risk factors for relapse in Crohn's disease. *Gastroenterology* 1998;114:1143–50.
25. Valentine JF, Sninsky CA. Prevention and treatment of osteoporosis in patients with inflammatory bowel disease. *Am J Gastroenterol* 1999;94:878–83.

# ULCERATIVE COLITIS

Ramona O. Rajapakse, MD, FRCP(UK), and Burton I. Korelitz, MD, MACG

## 1. What is ulcerative colitis (UC)?

UC is a chronic inflammatory disease of the colon. It is distinct from Crohn's disease of the colon in that the inflammation is restricted mostly to the mucosa and involves only the colon. The rectal segment is almost always involved, whereas in Crohn's disease of the colon, the rectum is usually spared.

## 2. Define *backwash ileitis*.

*Backwash ileitis* refers to some severe cases of UC that involve the terminal ileum as well as the proximal colon. The endoscopic, histologic, and radiologic appearance of backwash ileitis is the same as that of UC. When deep linear ulcers and strictures are seen in the ileum, Crohn's ileitis is the more likely diagnosis.

## 3. What is indeterminate colitis?

As more information is gathered about the pathogenesis of UC and Crohn's disease, the distinction between them at times can be unclear. In approximately 7% of patients, when the inflammatory process is limited to the colon (no ileal involvement), the endoscopic, histologic, or radiologic findings are insufficiently distinct to separate the two diseases. The colitis is then referred to as *indeterminate*. Other patients carry the diagnosis of UC for many years until a change in signs and symptoms, consistent with Crohn's disease, influences a change in diagnosis. In some patients the diagnosis of Crohn's disease of the colon is recognized only after colectomy and the development of recurrent ileitis in the ileostomy or ileoanal pouch performed for what was thought to be UC.

## 4. Why is it important to distinguish between UC and Crohn's disease?

Medical treatment of the two diseases overlaps, but UC is usually curable by total colectomy (allowing for the risk of pouchitis), whereas Crohn's disease can never be considered cured by resection. Therefore the correct diagnosis is of the utmost importance.

## 5. What causes UC?

Although the cause of UC is unknown, it appears to be caused by an abnormal intestinal immune response to an external antigen in a genetically predisposed individual. The relative risk of developing UC in a sibling is 8 to 15 and for CD 25 to 42. The probability of developing CD in a relative of a UC patient is increased by twofold, and there is a fourfold risk of UC in a relative of a CD patient. During the past decade, there have been considerable advances in the understanding of inflammatory bowel disease (IBD) genetics. Of more than 60 confirmed IBD susceptibility loci, 21 have so far been confirmed in UC alone, and a further 26 have been identified in both UC and CD. The greatest risk factor is a positive family history. Approximately 15% of patients with IBD have a first-degree relative with the disease, but the familial association is less in UC than in Crohn's disease. Similarly, the incidence of IBD in first-degree relatives of patients with IBD is 30 to 100 times higher than in the general population.

The cause technically remains unknown, although research has clarified that there are genetic, environmental, and immunologic contributions. The exact environmental link for UC has not been identified. Dietary antigens and bacteria have been proposed as possible triggers, but no evidence supports these theories. The incidence of UC is significantly higher in nonsmokers than in smokers and higher still in ex-smokers than in nonsmokers, supporting a protective effect of smoking. Whether this protective effect is secondary to nicotine or other constituents of cigarettes has not been fully established.

## 6. Who gets UC?

In most patients, UC has its onset in the second or third decade of life. However, there may be a second peak in the fifth or sixth decade, although this peak may be false because of other types of colitis that mimic UC. The disease has been described in all nationalities and ethnic group but is more common in whites than in nonwhites. It is also more common in Jews than non-Jews. The hereditary link is supported by population-based studies.

## 7. What are the signs and symptoms of UC?

The predominant symptom at onset of UC is diarrhea with or without blood in the stool. If inflammation is confined to the rectum (proctitis), blood may be seen on the surface of the stool; other symptoms include tenesmus, urgency, rectal pain, and passage of mucus without diarrhea.

Other distributions of UC are proctosigmoiditis; left-sided disease, which extends more proximal to the splenic flexure, or distal transverse colon; and extensive colitis, which involves any length proximal to the midtransverse colon and often the entire colon. The inflammation is almost always confluent in distribution and almost always involves the rectum when it is untreated with medication by enema. The terminal ileum may be involved with inflammation if there is cecal involvement and the disease is severe.

More extensive colitis may be accompanied by systemic symptoms such as weight loss and malaise in addition to bloody diarrhea. Although pain is not a dominant feature, patients may complain of crampy abdominal discomfort relieved by a bowel movement and may have abdominal tenderness, usually localized to the left lower quadrant. Occasionally patients may present with constipation secondary to rectal spasm; accompanying rectal discharge might be disclosed by careful history. Although patients may present with extraintestinal manifestations independent of bowel symptoms, more often they parallel the severity of the primary bowel disease.

#### 8. How are patients with UC classified?

Truelove and Witts divided patients into those with severe, moderate, and mild disease based on symptoms, physical findings, and laboratory values. In the Montreal extent of UC classification, UC is divided into three types: E1, proctitis; E2, left-sided colitis (distal to splenic flexure); and E3, pancolitis. The Montreal severity classification divides UC from asymptomatic to severe (S0-S3). The Mayo clinic system uses frequency of stools, presence of bleeding, endoscopic appearance, and the physician's global assessment to arrive at a number for disease activity. The score ranges from 0 to 12, with higher scores representing more severe disease. We add to this list the severity of endoscopic and radiologic appearances. A plain film of the abdomen showing any degree of dilation of the colon or ulceration and edema of the mucosa outlined by air (even if not dilated) is indicative of a severe attack. Although endoscopic appearance does not always correlate well with clinical symptoms, the presence of severe mucosal disease indicates the need for more aggressive management (Table 42-1).

**Table 42-1.** Clinical Guide for Severity of Ulcerative Colitis

Mild	Fewer than 4 stools daily, with or without blood, with no systemic disturbance and a normal ESR
Moderate	More than 4 stools daily but with minimal systemic disturbance
Severe	More than 6 stools daily with blood and systemic disturbance as shown by fever, tachycardia, anemia, or ESR >30

ESR, Erythrocyte sedimentation rate.

#### 9. How are the extraintestinal manifestations of UC classified?

Although UC involves primarily the bowel, it may be associated with manifestations in other organs. These manifestations are divided into those that coincide with the activity of bowel disease and those that occur independently of bowel disease (Table 42-2).

**Table 42-2.** Extracolonic Manifestations of Ulcerative Colitis

EXTRACOLONIC MANIFESTATION	COINCIDES WITH COLITIS ACTIVITY
Colitic arthritis	Yes
Ankylosing spondylitis	No
Pyoderma gangrenosum	Yes
Erythema nodosum	Yes
Primary sclerosing cholangitis	No
Uveitis	Often, but not always
Episcleritis	Often, not always

#### 10. What is colitic arthritis?

Colitic arthritis is a migratory arthritis affecting the knees, hips, ankles, wrists, and elbows. Usually the joint involvement is asymmetrical, not bilateral. It responds well to corticosteroids.

**11. Describe the association between UC and ankylosing spondylitis.**

Although ankylosing spondylitis is more commonly associated with Crohn's disease than UC, patients with UC have a thirtyfold increased risk of developing ankylosing spondylitis, which does not parallel the colitis activity. Many patients with early sacroiliitis alone are asymptomatic, and the diagnosis is made on radiographs.

**12. Discuss the hepatic complications of UC.**

Hepatic complications include fatty liver, pericholangitis, chronic active hepatitis, cirrhosis, and primary sclerosing cholangitis. Although most patients with sclerosing cholangitis have UC, only a few patients with UC develop sclerosing cholangitis and these cases of colitis are usually mild. It is usually suspected with the finding of an abnormally elevated alkaline phosphatase or  $\gamma$ -glutamyl transferase enzyme. Sclerosing cholangitis is sometimes improved with ursodeoxycholic acid therapy (Actigall). Patients with sclerosing cholangitis and UC have a higher risk of developing colon cancer than those without. In addition, they are also at risk of developing cholangiocarcinoma. Cholestyramine may help in alleviating the pruritus associated with the disease, but the only cure is liver transplantation.

**13. What are the ocular complications of UC?**

Ocular complications include uveitis, iritis, and episcleritis. Uveitis causes eye pain, photophobia, and blurred vision and requires prompt intervention to prevent permanent visual impairment. It usually responds to topical steroids, but sometimes systemic steroids are required.

**14. Describe the association between UC and thromboembolic events.**

Patients with IBD are at increased risk of thromboembolic events, most commonly deep venous thrombosis of the lower extremities. After a search for other causes of a hypercoagulable state, patients should receive standard therapy for the thrombosis.

**15. How should the practitioner evaluate a patient with UC?**

The management of UC depends on the severity and location of disease activity, which are best assessed by a careful clinical history, with emphasis on the duration and severity of symptoms, and physical examination, followed by endoscopic evaluation to determine the extent and severity of mucosal involvement. Although flexible sigmoidoscopy may indicate the severity of the disease, full colonoscopy is essential to determine the extent as well as the full severity. A history of recent travel and antibiotic and nonsteroidal antiinflammatory drug (NSAID) use should be sought. Laboratory evaluations should include a complete blood count, chemistries, and stool studies for culture, ova and parasites, and *Clostridium difficile*. *C. difficile* infections have been reported with increased frequency in recent years. If there is a high suspicion, multiple stool studies should be examined as false negatives are common.

These evaluations should provide an indication of severity and extent of disease (e.g., proctitis, left sided or pancolitis), which will affect choice of therapy (see Table 42-1). Some studies suggest that fecal calprotectin maybe a useful marker of degree of inflammation, but this is not routinely used. A plain radiograph of the abdomen should be performed in flat and upright positions if the disease is severe to recognize depth of ulceration and early or advanced toxic megacolon, which may be suspected by the presence of tympany in any of the segments of the abdomen. The serologic test perinuclear antineutrophil cytoplasmic antibody (pANCA) has low sensitivity and therefore cannot be used for diagnosis of UC. Anti-*Saccharomyces cerevisiae* antibody (ASCA) and a negative pANCA have no role in the primary diagnosis of UC but may be useful in differentiating between UC and Crohn's colitis. If disease severity is mild to moderate, medical therapy may be commenced on an out patient basis. However, if the disease is severe according to the previously described criteria, hospital admission should be considered.

**16. What are 5-aminosalicylic acid (5-ASA) products?**

Sulfasalazine, the first 5-ASA product, has been used successfully for many years in the treatment of mild to moderate UC. It is linked to sulfapyridine by a diazo bond that is cleaved by colonic bacteria. The active moiety is the 5-ASA. The side effects most commonly caused by sulfa include nausea, vomiting, fever, and a rash, all of which are attributable primarily to the sulfapyridine, which is only a carrier. It also may cause agranulocytosis, autoimmune hemolytic anemia, folic acid deficiency, and infertility secondary to changes in sperm count and morphologic characteristics. Newer preparations that contain only 5-ASA (mesalamine) are carried through or released in the small bowel. Mesalamine is currently available as a 4-g, 60-mL enema (Rowasa), as a suppository, and in oral formulations (Asacol, Delzicol, Pentasa, Dipentum, Colazal, Apriso, and Lialda) (Table 42-3).

**17. How do I treat proctitis and proctosigmoiditis?**

For mild to moderate ulcerative proctitis, topical therapy may suffice. If disease is limited to the anorectal region, a Canasa suppository can be used once or twice daily. Hydrocortisone foam (Cortifoam) or hydrocortisone enemas (Cortenema) also may be used either alone or in alternation with the 5-ASA product. For proctosigmoiditis, the mesalamine enema, used alone or in alternation with a hydrocortisone enema, is effective. Only the mesalamine enema, not the Cortenema, has maintenance value. The patient must lie on the left side for at least 20 minutes after introducing the enema to ensure adequate delivery to the affected area. In some instances when tenesmus is severe, the enema is better introduced in the knee-chest position, taking advantage of the downhill gravity. Occasionally oral therapy may work better than enemas or suppositories; in other cases, a combination is required.

**Table 42-3.** 5-ASA Products

5-ASA	CARRIER MOLECULE	RELEASE	SITE OF ACTIVITY
Asacol	Eudragit-S	pH>7	Terminal ileum and colon
Pentasa	Ethylcellulose beads, time release	pH>6	Small bowel and colon
Olsalazine	Azo bond	Bacteria	Colon (ileum with bacterial overgrowth)
Sulfasalazine	Sulfapyridine	Bacteria	Colon (ileum with bacterial overgrowth)
Lialda	Matrix	Colon pH>6.8	Colon
Apriso	INTELLICOR delayed and extended release	pH $\geq$ 6	Colon
Colazal	Di-Azo bond	Colon	Colon
Dipentum	Dimer	Left colon	Left colon

5-ASA, 5-Aminosalicylic acid.

#### 18. How should the practitioner treat an exacerbation of UC?

When the disease extends more proximally, oral therapies are required in addition to, or instead of, topical therapy. Topical therapies are often more effective than oral therapy for distal disease and a combination of both is more effective than each alone. Choice of oral 5-ASA products is determined by the extent of involvement. Pentasa (4 g), Asacol (3.2 g), Delzicol, Colazal (6.75 g), Lialda, or Apriso can be used for universal colitis and Dipentum (1 g) for left-sided colitis. Multimatrix formulations allow once-daily dosing with similar efficacy. The dose of Asacol may be titrated within the limits of tolerability to a maximum of 4.8 g/day. It is not yet known whether still higher doses of any of the three would have increased efficacy. Budesonide MMX (Uceris) is effective for mild to moderate UC and is orally dosed 9 mg once daily for 8 weeks. If the disease fails to resolve with 5-ASA therapy or Budesonide MMX, or is moderate to severe in severity at presentation, a short course of oral corticosteroids should be prescribed to bring the disease under control. The maximal effective oral dose of prednisone prescribed is 60 mg daily. The dose may be tapered to 40 mg/day after 2 to 7 days, if the disease is brought under control. The formula for further tapering of prednisone is individualized. The 5-ASA drugs should be given concurrently with prednisone. Prednisone and other corticosteroids are not maintenance drugs.

#### 19. What should I do if the disease is severe?

Severe disease requires admission to hospital for intravenous corticosteroids (perhaps infliximab [Remicade]) and fluids. Patients should be monitored carefully by serial physical examination, laboratory tests, and plain radiographs of the abdomen. Severe UC may progress to toxic megacolon or perforation. It is treated with intravenous corticosteroids, antibiotics, a small bowel tube attached to suction, rolling from side to side and to the supine and prone positions, and sometimes by rectal tube. If these maneuvers are not successful, subtotal colectomy should be considered, preferably before a perforation occurs. If the colon is dilated and the mucosal surface is ragged on abdominal films, a surgical colleague should be involved in management decisions.

If there is no response to intravenous corticosteroids, consideration should be given to the use of intravenous cyclosporine, infliximab, or surgery, depending on the urgency of the clinical situation and local experience in management of this most severe complication. Rapid deterioration in clinical condition warrants early surgical intervention with ileostomy and subtotal colectomy. If there is time for a trial of cyclosporine, it should be administered only by physicians with extensive experience in its use. It is administered at a dose of 4 mg/kg/day intravenously by continuous infusion, with close monitoring of blood pressure, renal function, electrolytes, and drug blood levels. Cyclosporine should not be initiated if the serum cholesterol is low because it increases the risk of seizures. Bactrim is administered concurrently to prevent *Pneumocystis carinii* pneumonia. Failure to respond within 3 days portends a poor prognosis for medical therapy. There is emerging data that infliximab is superior to cyclosporine and may be as useful in severe UC as it is in severe Crohn's disease when intravenous steroids have failed. It has the advantage of having less short-term toxicity than cyclosporine and of being useful for maintenance therapy. Early medical intervention in expert hands can significantly reduce the number of severely ill patients who go to surgery.

#### 20. Define toxic megacolon.

Toxic megacolon is defined as a severe attack of colitis with total or segmental dilation of the colon (diameter of transverse colon usually greater than 5 to 6 cm). It can be recognized by plain radiographs showing the colon to

be outlined by air (not after endoscopy) even with a diameter less than 5 cm. Megacolon is considered toxic if two or more of the following criteria are positive in addition to the colon persistently outlined by air:

- Tachycardia with a pulse rate greater than 100 beats/min
- Temperature greater than 101.5° F
- Leukocytosis greater than 10,000 cells/mm<sup>3</sup>
- Hypoalbuminemia less than 3 g/dL

#### **21. How is relapse prevented?**

Maintenance therapy should be initiated at the same time or soon after acute-phase therapy. For mild to moderate disease, a 5-ASA product either orally, topically, or both may be all that is necessary. In our experience, this will be true in only 20% to 30% of patients. For more severe or recurrent disease, an immunosuppressive medication such as 6-mercaptopurine (6-MP)/azathioprine (AZA) or infliximab (anti-tumor necrosis factor [TNF]) is more effective. 6-MP should be started at a dose of 50 mg/day, and the patient should be followed carefully with weekly blood counts for the first 3 weeks and less often thereafter. Levels of thiopurine methyltransferase (TPMT) may be checked prior to initiating therapy. Low levels of the enzyme confer greater risk of leukopenia. If the initial dose is tolerated well and the white cell count is normal, the dose may be gradually increased if clinically warranted. Early toxic reactions to these medications include leukopenia, pancreatitis (3%), hepatitis, transaminitis without hepatitis, rash, and fever. The occurrence of pancreatitis or hepatitis usually precludes further use of the same drug. Patients with allergic-type reactions may be carefully desensitized to the causative medication or its alternative (6-MP versus AZA). High levels of the 6-MP metabolites 6-methylmercaptopurine and 6-thioguanine or low levels of TPMT may predict which patients will develop toxicity.

Infliximab, an established anti-TNF for Crohn's disease, is now U.S. Food and Drug Administration approved for the treatment of UC. Hepatitis B serologic testing and a purified protein derivative should be checked prior to initiating therapy. Induction therapy consists of infusions of 5 mg/kg IV at weeks 0, 2, and 6 followed by maintenance infusions every 2 months. The maintenance dose is 5 mg/kg IV. If the patient has breakthrough symptoms before 2 months, serum infliximab levels as well as antibodies to the chimeric component (human antichimeric antibody) may be checked. The dose of infliximab maybe increased to 7.5 mg/kg or 10 mg/kg with or without premedication with diphenhydramine (Benadryl), acetaminophen (Tylenol), or steroids. There is some concern that combination therapy with 6-MP/AZA and infliximab may increase the risk of infections and lymphomas in this patient population. Until further data are available, combination versus solo therapy should be decided based on the severity and fragility of disease as well as patient and physician preference.

#### **22. Are there adjunctive therapies for UC?**

Probiotics are defined as live microbial feed that have benefit to the human host. The most widely studied probiotic is VSL#3, which is a combination of *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*. VSL#3 has been shown to reduce the incidence of the first episode of pouchitis if used immediately after total proctocolectomy and ileal-pouch anal anastomosis. It may also be useful in maintenance therapy for pouchitis after remission has been achieved with antibiotics. The evidence for benefit in active or chronic UC is less convincing, but it may be useful as an adjunctive therapy.

Omega-3 capsules in high doses may also be useful in chronic UC by providing the short-chain fatty acids that are trophic to colonocytes. Multivitamins are not necessary if the patient is eating a well-balanced diet. Oral iron supplements may cause constipation and distention. Oral potassium supplements may be irritating to the gastrointestinal tract, and magnesium supplements cause diarrhea, which is undesirable.

#### **23. How often should patients have surveillance colonoscopy?**

The current recommendations are as follows: for patients with left-sided colitis, surveillance should begin after 10 years from the onset of colitis. For patients with universal colitis, surveillance should begin after 8 years of colitis. Three biopsy specimens should be obtained every 10 cm throughout the colon. The likelihood of detecting dysplasia in flat mucosa increases with the number of random biopsies taken. To achieve a greater than 90% detection rate, more than 33 biopsies should be taken. In addition, any strictured, raised, polypoid areas or those with unusual shapes or textures should be biopsied. Surveillance colonoscopy should be repeated annually for universal disease, perhaps less often for left-sided disease. The variables that influence the risk of dysplasia and colon cancer are duration of disease, extent of disease, and severity (chronicity) of disease. It is likely that persistence of histologic inflammation should be included as a risk factor.

Newer techniques such as chromoendoscopy and narrow band imaging (NBI) allow better visualization of abnormal mucosa. In chromoendoscopy the colon is sprayed with indigo carmine or methylene blue, which allows targeted biopsies of abnormal areas. NBI is more useful in differentiating pseudopolyps from adenomatous polyps. Magnification endoscopy is a newer technique that may also facilitate targeted biopsies. Although these techniques allow targeted biopsies, their role in routine surveillance of UC has yet to be determined.

#### **24. What should be done if a polyp or dysplasia is found?**

Obvious polyps should be removed and the area surrounding the polyp biopsied. If the area is free of premalignant changes (indicating an adenomatous polyp), nothing further need be done except for the usual surveillance.

However, if dysplasia is found, colectomy is the treatment of choice. Dysplasia is a premalignant lesion classified as *high grade*, *low grade*, or *indefinite*. Although everyone agrees that high-grade dysplasia anywhere in the colon warrants proctocolectomy, there is less consensus about the management of low-grade dysplasia. The diagnosis of low-grade dysplasia can be challenged when the biopsy samples are taken from areas of marked inflammation. Intensive treatment of the disease may lead to the recognition that the diagnosis of dysplasia was not accurate. Biopsy samples should be taken preferably from flat mucosa without inflammation. If a recommendation of colectomy depends on the diagnosis of dysplasia, a second expert gastrointestinal pathologist should review the biopsy slides before the final decision is made.

It has been our experience that when dysplasia or cancer involves the rectal segment, an ileostomy with colectomy should be favored over an ileal pouch-anal anastomosis.

## **25. Is surveillance effective?**

Studies have shown that as many as 42% of patients with UC who are found to have high-grade dysplasia either already have cancer or develop it within a short time. The presence of low-grade dysplasia is also predictive of cancer: 19% of patients develop cancer of the colon or may even have cancer at the time of diagnosis. The finding of no dysplasia is predictive of a good short-term outcome. Outcome and case-controlled studies have shown that cancer in patients in a surveillance program is detected at an earlier and therefore more favorable stage. Patients who undergo screening have improved survival rates and lower cancer-related mortality rates.

## **26. Is there a role for chemoprevention in UC?**

There is some evidence that long-term mesalamine use may reduce the risk of colon cancer in these patients. There is also evidence that treatment with the immunosuppressive drugs 6-MP is more likely to reduce the risk of colon cancer than increase it. Ursodeoxycholic acid may also be useful in reducing colon cancer risk in the subpopulation of patients with primary sclerosing cholangitis.

Further studies are required to clarify these issues. It is likely that maintenance therapy is effective mainly by suppressing inflammation and that surveillance biopsies are as important for recognizing microscopic inflammation as they are for recognizing dysplasia.

## **27. Is diet important in the management of UC?**

No evidence suggests that any one diet is beneficial in patients with UC. Apart from the advice that patients with lactose intolerance should avoid lactose-containing food, no specific dietary restrictions are necessary.

## **28. Does stress exacerbate UC?**

There may be an association between stress and exacerbation of UC, but no causative role has been established. No studies to date support any role for psychological stresses, personality types, or overt psychiatric illness in the causation or exacerbation of UC. However, an anxiolytic agent or an antidepressant may be helpful if chronic illness leads to depression.

Sometimes the addition of an anxiolytic agent or an antidepressant may be the final step required to bring UC under control.

As with any chronic illness, the approach to management should be multifaceted and include expert medical and surgical teams, a psychopharmacologist, and knowledgeable ancillary staff.

## **29. How does menstruation affect UC?**

Scattered information supplements our experience that the symptoms of both UC and Crohn's disease are aggravated or provoked premenstrually and in some cases throughout menstruation. Occasionally a 2- to 3-day course of steroids is warranted.

## **30. Do patients with UC have problems with fertility and pregnancy?**

In considering the effects of UC on pregnancy and vice versa, two aspects are important: the effect of the disease itself and the effect of the medications used to treat the disease. Well-controlled disease appears to have no deleterious effects on fertility or pregnancy. However, if the disease is active at any time during pregnancy, the incidence of fetal loss may be increased. It is therefore important to maintain control of the disease before and during pregnancy.

Mesalamine (5-ASA) has a long record of safety in pregnancy. Corticosteroids have also proven to be safe during pregnancy. With regard to the immunosuppressives 6-MP and AZA, data from the transplant literature suggest safety during pregnancy. One study concerning UC and Crohn's disease treated with immunosuppressives concluded that they are safe and need not be discontinued for pregnancy. In our experience, however, these medications may cause fetal loss when used by women before pregnancy and an increased incidence of congenital abnormalities and spontaneous abortions when used by men within 3 months of conception. We therefore suggest that patients should discontinue these drugs, if clinically feasible, at least 3 months before planned conception. If a woman is in remission, immunosuppressives may be stopped without expectation of early recurrence. If the disease is active, pregnancy should be postponed. Sulfasalazine causes defects in sperm morphologic characteristics and motility. This effect is reversible in 3 months if the drug is discontinued. It should be replaced with one of the newer 5-ASA products in male patients who are contemplating starting a family.

### 31. What medications are contraindicated in patients with UC?

Evidence suggests that NSAIDs may precipitate exacerbations of the disease and in some cases may even be implicated in the onset of disease. The NSAIDs in common use include aspirin, ibuprofen, and naproxen. These drugs should be avoided in patients with UC.

Anticoagulant therapy with warfarin may lead to increased bleeding in patients with active disease and bloody diarrhea. Ironically, heparin therapy has been reported to improve disease activity in some patients. Although heparin therapy is not the standard of care, it may be useful when anticoagulation is required for patients with active UC. Opioid derivatives should be avoided if possible in patients with any type of colitis because of their propensity to cause toxic dilatation of the colon.

### 32. What are the surgical options for management of UC?

When medical management fails or complications such as perforation or dysplasia occur, subtotal colectomy with ileostomy or ileoanal pouch is the procedure of choice. Many patients are frightened by the prospect of having an ileostomy, but education can do much to alleviate their fears. Fortunately, a large number of patients with ileostomies become accustomed to them and continue to lead normal lives.

The ileoanal pouch is a possible alternative. It consists of a double loop of ileum that is fashioned into a pouch and stapled to the rectal stump and stripped of its mucosa, thereby preserving the anal sphincter. Disadvantages of the pouch include recurrent inflammation or pouchitis, frequent bowel movements, nocturnal incontinence, and the continued need for surveillance endoscopy. Pouchitis responds well to metronidazole, ciprofloxacin, or bismuth, alone or in combination. These drugs can be used to treat the acute illness and also as maintenance therapy to prevent recurrence. Probiotics may also be used (see earlier). In some cases, 5-ASA products, steroids, immunosuppressives, or biologics may be required. Refractory pouchitis may require excision of the pouch and substitution of an ileostomy at a later date.

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### BIBLIOGRAPHY

1. Adler DJ, Korelitz BI. The therapeutic efficacy of 6-mercaptopurine in refractory ulcerative colitis. *Am J Gastroenterol* 1990;85:717–22.
2. Francella, Dyan A, Bodian C, et al. The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: a retrospective cohort study. *Gastroenterology* 2003;124:9–17.
3. Korelitz BI. Expert opinion: experience with 6-mercaptopurine in the treatment of inflammatory bowel disease. *World J Gastroenterol* 2013 May 28;19(20):2979–84.
4. Korelitz BI, Present DH. 6-Mercaptopurine/Azathioprine remains an important contributor in managing Crohn's disease. *Journal of Crohn's and Colitis* - 24 January 2014 (<http://dx.doi.org/10.1016/j.crohns.2013.12.024>)
5. Korelitz BI, Sultan K, Kothari M, et al. Histological healing favors lower risk of colon carcinoma in extensive ulcerative colitis. *World J Gastroenterol* 2014 May 7;20(17):4980–6.
6. Lichtenstein S, Present DH, Kornblith A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994;330:1841–5.
7. Marshall JK, Irvine EJ. Rectal aminosalicylate therapy for distal ulcerative colitis: a meta-analysis. *Aliment Pharmacol Ther* 1995;9:293–300.
8. Orholm M, Munkholm P, Langholz E, et al. Familial occurrence of inflammatory bowel disease. *N Engl J Med* 1991;324:84–8.
9. Pemberton JH, Kelly KA, Beart RW, et al. Ileal pouch-anal anastomosis for chronic ulcerative colitis: long-term results. *Ann Surg* 1987;206:504–13.
10. Rajapakse RO, Korelitz BI, Zlatanic J, et al. Outcome of pregnancies when fathers are treated with 6-mercaptopurine for inflammatory bowel disease. *Am J Gastroenterol* 2000;95:684–8.
11. Sandborn WJ. Pouchitis following ileal pouch-anal anastomosis: definition, pathogenesis and treatment. *Gastroenterology* 1994;107:1856–60.
12. Sutherland LR, May GR, Shaffer EA. Sulphasalazine revisited: a meta-analysis of 5-aminosalicylic acid in the treatment of ulcerative colitis. *Ann Intern Med* 1993;118:340–9.
13. Truelove SC, Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. *Br Med J* 1955;2:1041–8.
14. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology* 1997;112:594–642.
15. Woolrich AJ, DaSilva MD, Korelitz BI. Surveillance in the routine management of ulcerative colitis: predictive value of low-grade dysplasia. *Gastroenterology* 1992;103:431–8.
16. Zlatanic J, Korelitz BI, Rajapakse R, et al. Complications of pregnancy and child development after cessation of treatment with 6-mercaptopurine for inflammatory bowel disease. *J Clin Gastroenterol* 2003;36:303–9.

### Websites

Crohn's and Colitis Foundation of American. <http://www.ccfa.org> [Accessed September 22, 2014].

National Institute of Diabetes and Digestive and Kidney Disease. <http://www.niddk.nih.gov> [Accessed September 22, 2014].

# EOSINOPHILIC GASTROINTESTINAL DISEASE AND EOSINOPHILIC ESOPHAGITIS

Shahan Fernando, MD, and Glenn T. Furuta, MD

## 1. How is *eosinophilic gastrointestinal disease (EGID)* defined?

EGID is a global term that describes an increasingly recognized heterogeneous group of gastrointestinal (GI) diseases found in both children and adults. It is characterized by chronic, nonspecific GI symptoms and a dense eosinophilic inflammatory response that is found in various tissues throughout the GI tract. It can manifest as eosinophilic gastroenteritis, colitis, or the well-studied eosinophilic esophagitis (EoE). Other causes of eosinophilia need to be ruled out prior to making the diagnosis of EGID.

## 2. What is EoE?

EoE is the most common form of EGID. It is a clinicopathologic disorder now recognized as a major cause of abdominal pain, vomiting, and feeding problems in young children and food impactions and dysphagia in adults. EoE is a chronic, allergen-driven inflammatory disease process that is defined by symptoms of esophageal dysfunction and mucosal eosinophilia.

## 3. What is the incidence of EGID and EoE?

EGID is a rare disorder with an estimated incidence that is likely less than 1 in 100,000. Few retrospective epidemiologic studies have been published with numbers of patients ranging from 8 to 59 that were discovered over a span of up to 37 years. The incidence of EoE, on the other hand, continues to increase with estimates of up to 40 in 100,000. The vast majority of patients with EoE are white males, but both of these disease entities have a widespread geographic and ethnic distribution.

## 4. What is the role of the eosinophil in the pathogenesis of EGID and EoE?

EGID and EoE are believed to be allergen-mediated, Th-2 cytokine inflammatory responses that develop in genetically susceptible individuals and are associated with GI eosinophilia. With the exception of the esophagus, eosinophils are prominent resident leukocytes within the intestinal mucosa whose precise role in health remains unclear. Although the exact pathogenesis is uncertain and its study is typically limited to superficial mucosal pinch biopsies, EGIDs are thought to be stimulated by exposure to an environmental or food allergen that leads to chemoattraction and recruitment of additional eosinophils to the GI tract. The exact function of eosinophils in the GI tract are unknown, but a number of basic studies support a role in antigen presentation and as effector cells that can release a host of cytotoxic granules, cytokines, chemokines, transforming growth factors, lipid mediators, and neuromediators.

Gene arrays and genome-wide association studies have identified several key molecules strongly associated with EoE, including thymic stromal lymphopoietin, eotaxin-3, interleukin (IL)-13, and IL-5. Familial susceptibility has also been reported in approximately 10% of patients with EGID.

## 5. What are some clinical features of EGID and EoE?

Early descriptions of EGIDs involving the GI tract distal to the esophagus classified the disease based on the identified depth of eosinophilia within the intestinal wall. The mucosal subtype can manifest as bleeding, diarrhea, and pain; muscular subtype as partial or complete intestinal obstruction; and serosal sub-type as abdominal distention (Table 43-1). Recent studies suggest a shift toward the mucosal form of disease. Up to 75% of patients will report a personal history of atopy, including eczema, food allergies, seasonal allergies, or asthma. Additionally, peripheral eosinophilia can occur in up to 80% of patients with EGID, but is variable and can also occur secondary to other comorbid allergic diseases, making this an unreliable biomarker of disease activity.

Patients with EoE can present with a variety of signs and symptoms of esophageal dysfunction, depending on the age of the individual (see Table 43-1). Young children, because of developmental level, are unable to articulate symptoms of dysphagia and instead present with symptoms of feeding difficulties. Many of these symptoms are similar to that of gastroesophageal reflux disease, but do not respond to standard medical or surgical antireflux therapies. Often, symptoms may require additional questions during history taking.

## 6. What is the natural history of EGID and EoE?

Because of their relatively low incidence and confounding GI symptoms, there is often a delay in diagnosis of both EGID and EoE that can sometimes reach 3 to 4 years. Based on current studies and clinical experiences, the natural history of EGID may include one of three patterns, as patients may suffer from a

**Table 43-1.** Clinical Features of EGID and EoE

	<b>EGID</b>		<b>EoE</b>
Mucosal	Abdominal pain Anemia Diarrhea GI bleeding Nausea Protein-losing enteropathy Vomiting Weight loss	Children	Abdominal pain Chest pain Choking, gagging Coughing Decreased appetite Dysphagia (e.g., food sticking) Feeding difficulties Regurgitation Sleeping difficulty Throat pain Weight loss
Muscular	Abdominal pain Gastric outlet obstruction Intestinal dysmotility Pancreatitis Small intestinal obstruction	Adults	Dysphagia Food impaction Retrosternal pain
Serosal	Eosinophilic ascites Eosinophilic peritonitis Severe bloating		

EGID, Eosinophilic gastrointestinal disease; EoE, eosinophilic esophagitis; GI, gastrointestinal.

single occurrence, a recurrent course, or a chronic disease path. Additionally, there are several potential phenotypes based on the depth of intestinal involvement.

Three issues regarding the natural history of EoE have become apparent because of broader clinical experiences. First, EoE is a chronic disease in which most patients will respond to standard medical therapies. Second, complications associated with EoE include food impactions, esophageal narrowing and feeding dysfunction. Who, how and in whom, these develop is uncertain. Third, there does not appear to be any premalignant potential to date, but long-term natural history studies are still required to assess for this concern. Finally, there may be other EoE phenotypes based on whether or not patients respond to diet elimination and topical steroids.

## 7. How are EGID and EoE diagnosed?

As mentioned previously, EGID is characterized by nonspecific GI symptoms associated with a dense intestinal eosinophilia. What is considered an “abnormal” number of intestinal eosinophils remains unclear and is a matter that should be discussed between clinicians and pathologists at local institutions. Making the diagnosis of EoE is easier as diagnostic guidelines have been established (Box 43-1).

### Box 43-1. Diagnostic Criteria for Eosinophilic Esophagitis

Symptoms are related to esophageal dysfunction.  
Esophageal biopsy demonstrates eosinophil-predominant inflammation with a peak value of  $\geq 15$  eosinophils per high-power field.

Isolated esophageal mucosal eosinophilia persists after a proton pump inhibitor trial.  
Secondary causes of esophageal eosinophilia are excluded.  
A response to treatment supports, but is not required for, the diagnosis.

Any patient with a concern for EGID should undergo a thorough evaluation to exclude any other causes of intestinal eosinophilia. No pathognomonic signs, symptoms, or blood tests exist for defining EGID or EoE. Depending on the specific intestinal organ involved and its accompanying symptoms, there are several approaches.

### History and Physical Examination

- Obtain a comprehensive history, including social and family history, that accurately outlines all GI and extraintestinal symptoms. This includes timing of onset, duration, progression, aggravating and alleviating factors, associated symptoms (e.g., weight loss), responses to previous medical therapy, travel history, and family history of EGIDs, food impactions, and esophageal dilations. Assess for normal growth and development.
- Inquire about atopic signs or symptoms pertaining to GI, skin, or respiratory reactions to food or environmental antigens.

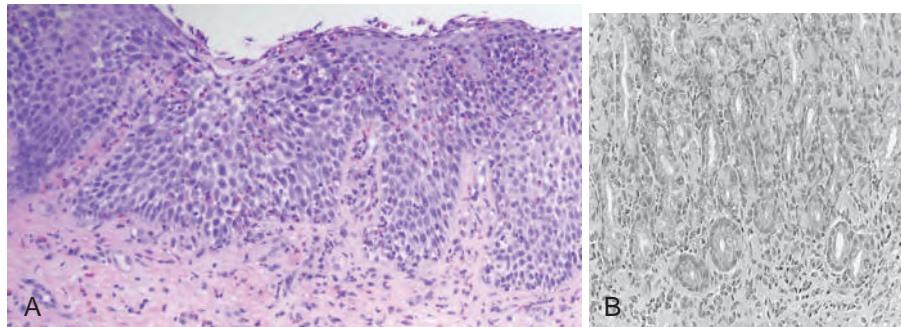
- Perform a thorough physical examination with particular attention to weight and height, stigmata of atopic disease, and signs of secondary EGIDs (e.g., skin rash, arthritis, oral lesions, perianal disease).

#### Laboratory Tests

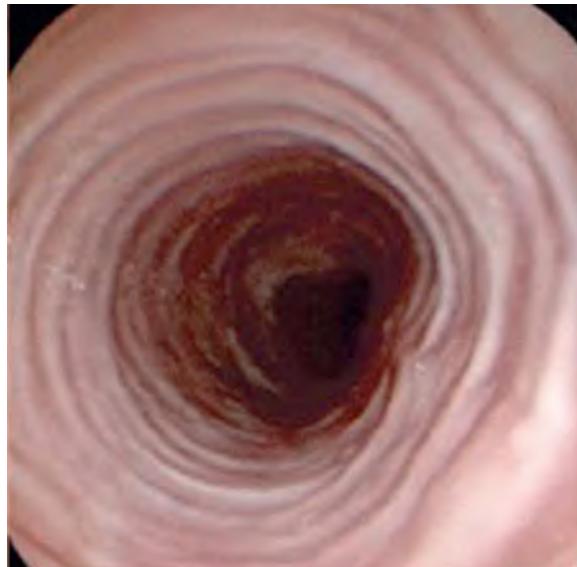
- General evaluation: Obtain complete blood count with differential, total immunoglobulin E, erythrocyte sedimentation rate, and stool for infectious evaluation (e.g., ova and parasites, *Helicobacter pylori*).
- Advanced evaluation: If ascites is present, perform paracentesis with cell count and differential. If hypereosinophilia is present, perform bone marrow analysis, echocardiogram, serum vitamin B<sub>12</sub> and tryptase, genetic analysis for *FIPL1-PDGFRα* mutation, and biopsy and evaluation of other involved tissues.
- Allergy evaluation: Referral to an allergist experienced in the assessment of non-IgE-mediated food allergy is suggested, as unwarranted limitation of foods may lead to malnutrition.

#### Endoscopy and Histopathologic Examination

- Depending on the location of GI symptoms, an upper intestinal endoscopy or colonoscopy with biopsies is essential to the diagnosis of EGID ([Figure 43-1](#)).
- EoE can be associated with several endoscopic findings such as mucosal edema, furrows, fixed rings, exudates, crepe paper appearance, reduced luminal diameter, and strictures ([Figure 43-2](#)). However, a normal mucosal appearance does not rule out EGID or EoE.
- Multiple mucosal pinch biopsies should be obtained because of the limited capture achieved by this technique and because EGIDs and EoE can have a “patchy” distribution. In cases in which deeper involvement is suspected, a surgical full-thickness biopsy may be indicated.



**Figure 43-1.** A, Esophageal biopsy demonstrating EoE, B, Gastric antrum biopsy demonstrating eosinophilic gastroenteritis.



**Figure 43-2.** Endoscopic view of concentric rings or “trachealization” of the esophagus in eosinophilic esophagitis.

### Radiologic Evaluation

- Barium esophagography is useful in evaluating patients with dysphagia and may demonstrate mucosal irregularities, narrowing of the lumen, or strictures that may not be evident during endoscopy (Figure 43-3).
- Upper GI contrast studies and computed tomography with enteral contrast may demonstrate mucosal irregularities or evidence of obstruction in areas affected by EGID. They can also be used to rule out other etiologic factors such as malrotation and inflammatory bowel diseases.
- Abdominal ultrasound can help identify ascites.

**Figure 43-3.** Upper gastrointestinal contrast study demonstrating multiple rings in the proximal esophagus in eosinophilic esophagitis.



### 8. What is hypereosinophilic syndrome (HES)?

HES is a heterogeneous group of disorders initially defined by persistent peripheral eosinophilia of greater than 1500 cells/ $\mu$ L for a minimum of 6 months, evidence of eosinophil-induced organ damage or dysfunction, and exclusion of other secondary causes of eosinophilia. Recent descriptions have modified this definition to eliminate the prolonged waiting period that may delay treatment, and have demonstrated that HES encompasses several subtypes, as outlined in a 2006 consensus report. Its prevalence is unknown, but it tends to affect young to middle-aged individuals with a predilection for males. A diagnosis of HES should always be considered in patients with EGID, high peripheral eosinophil counts, and extraintestinal signs or symptoms that may be related to eosinophilia.

### 9. What is the differential diagnosis of intestinal eosinophilia?

The differential diagnosis of EGID and EoE includes a host of diseases that also present with GI symptoms and eosinophil-predominant inflammation, and are collectively known as *secondary eosinophil-associated GI disorders*. Table 43-2 illustrates the breadth of these secondary diseases and the importance of evaluating patients with eosinophils on intestinal biopsy or any form of intestinal inflammation associated with peripheral eosinophilia.

### 10. What are current treatment and management strategies for EGID and EoE?

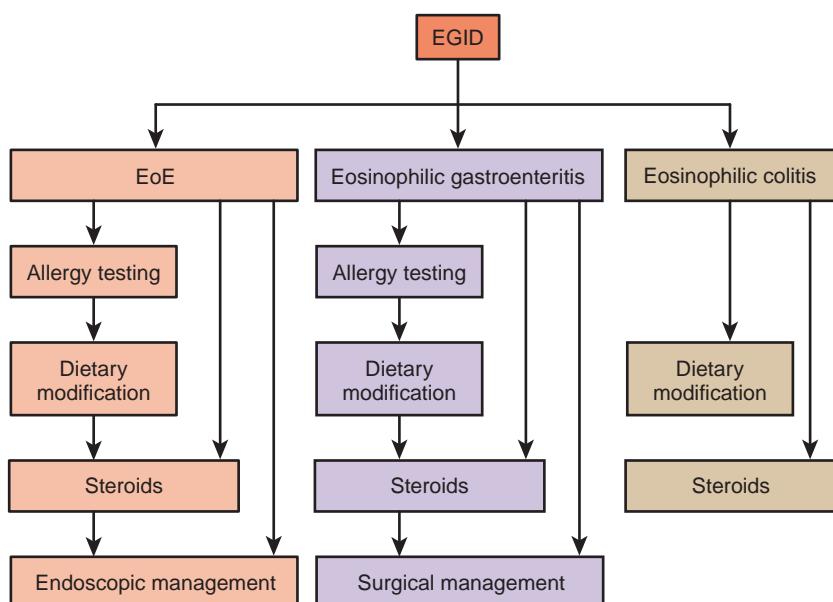
Because of its low prevalence, prospective, multicenter studies on EGID treatment are lacking. Current potential management strategies, based on retrospective studies and case reports, include a formal allergy evaluation, dietary modification, topical and systemic steroids, and endoscopic dilation or surgical resection (i.e., endoscopic and surgical therapies) (Figure 43-4). There is limited data to support the routine use of leukotriene inhibitors and mast cell stabilizers, and biologic therapies such as anti-IL5 and anti-IgE antibodies remain investigational at this time.

Therapeutic endpoints include normalizing growth and development for children, minimizing symptoms, balancing risks and benefits of treatment with quality of life, and normalization of mucosal findings when

**Table 43-2.** Differential Diagnosis of Intestinal Eosinophilia

PRIMARY EGID	OTHER CAUSES OF INTESTINAL EOSINOPHILIA
Eosinophilic esophagitis	Achalasia Celiac disease Connective tissue diseases (e.g., scleroderma) Crohn's disease Drug hypersensitivity Eosinophilic gastroenteritis GERD Graft-versus-host disease Hypereosinophilic syndrome Iatrogenic (e.g., medications) Infection Leiomyomatosis Pemphigus PPI-responsive esophageal eosinophilia
Eosinophilic gastroenteritis	Celiac disease Connective tissue diseases (e.g., scleroderma) Hypereosinophilic syndrome Iatrogenic (e.g., medications) Infection Inflammatory bowel disease Inflammatory fibroid polyps, polyposis Vasculitis (e.g., Churg-Strauss syndrome)
Eosinophilic colitis	Celiac disease Connective tissue diseases (e.g., scleroderma) Eosinophilic gastroenteritis Hypereosinophilic syndrome Iatrogenic (e.g., medications) Infection Inflammatory bowel disease Juvenile polyps, polyposis, adenomas Vasculitis (e.g., Churg-Strauss syndrome)

EGID, Eosinophilic gastrointestinal disease; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.



**Figure 43-4.** Treatment algorithm of eosinophilic gastrointestinal disease (EGID). EoE, Eosinophilic esophagitis.

possible. Specific treatment strategies should be tailored to the individual, taking into consideration factors such as extent of disease, severity of symptoms, cost, and compliance.

### Dietary Modification

- Elemental diet (i.e., amino acid-based formula)
- Targeted food elimination based on allergy testing
- Empiric six food elimination including milk, soy, eggs, wheat, nuts, and shellfish

### Steroids

- Topical (e.g., fluticasone, budesonide)
- Systemic (e.g., prednisone, methylprednisolone)

### Therapeutic Interventions

- Endoscopic dilation (preferably following pretreatment with steroids) for esophageal strictures in EoE
- Surgical resection of affected bowel in eosinophilic gastroenteritis

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### BIBLIOGRAPHY

1. Aceves S, Hirano I, Furuta GT, et al. Eosinophilic gastrointestinal diseases—clinically diverse and histopathologically confounding. *Semin Immunopathol* 2012;34(5):715–31.
2. Chang JY, Choung RS, Lee RM, et al. A shift in the clinical spectrum of eosinophilic gastroenteritis toward the mucosal disease type. *YCGH* 2010;8(8):669–75, quiz e88.
3. Chusid MJ, Dale DC, West BC, et al. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. *Medicine* 1975;54(1):1–27.
4. DeBrosse CW, Case JW, Putnam PE, et al. Quantity and distribution of eosinophils in the gastrointestinal tract of children. *Pediatr Dev Pathol* 2006;9(3):210–8.
5. Fleischer DM, Atkins D. Evaluation of the patient with suspected eosinophilic gastrointestinal disease. *Immunol Allergy Clin North Am* 2009;29(1):53–63.
6. Gotlib J. World Health Organization-defined eosinophilic disorders: 2012 update on diagnosis, risk stratification, and management. *Am J Hematol* 2012;87(9):903–14.
7. Khan S, Orenstein SR, et al. Eosinophilic disorders of the gastrointestinal tract. In: Feldman M, editor. *Sleisenger and Fordtran's gastrointestinal and liver disease*. Philadelphia: WB Saunders; 2010. p. 425–36.
8. Klein NC, Hargrove RL, Sleisenger MH, et al. Eosinophilic gastroenteritis. *Medicine* 1970;49(4):299–319.
9. Liacouras C, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128(1):3–20.e6.
10. Lowichik A, Weinberg AG. A quantitative evaluation of mucosal eosinophils in the pediatric gastrointestinal tract. *Mod Pathol* 1996;9(2):110–4.
11. Lucendo AJ. Eosinophilic diseases of the gastrointestinal tract. *Scand J Gastroenterol* 2010;45(9):1013–21.
12. Lucendo AJ, Arias A. Eosinophilic gastroenteritis: an update. *Expert Rev Gastroenterol Hepatol* 2012;6(5):591–601.
13. Masterson JC, Furuta GT, Lee JJ. Update on clinical and immunological features of eosinophilic gastrointestinal diseases. *Curr Opin Gastroenterol* 2011;27(6):515–22.
14. Mulkada VA, Haas A, Maune NC, et al. Feeding dysfunction in children with eosinophilic gastrointestinal diseases. *Pediatrics* 2010;126(3):e672–7.
15. Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). *J Allergy Clin Immunol* 2004;113(1):11–28.
16. Rothenberg ME, Hogan SP. The eosinophil. *Annu Rev Immunol* 2006;24(1):147–74.
17. Soon IS, Butzner JD, Kaplan GG, et al. Incidence and prevalence of eosinophilic esophagitis in children. *J Pediatr Gastroenterol Nutr* 2013;57(1):72–80.
18. Straumann A, Simon H-U. Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol* 2005;115(2):418–9.
19. Talley NJ, Shorter RG, Phillips SF, et al. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal disease. *Gut* 1990;31:54–8.
20. Valent P, Klion AD, Horny H-P, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol* 2012;130(3):607–9.

### Websites

The American Partnership for Eosinophilic Disorders. <http://apfed.org/drupal/drupal/index.php> [Accessed September 22, 2014].

# SMALL INTESTINAL BACTERIAL OVERGROWTH

Catherine S. Manolakis, MD, Travis J. Rutland, MD, and Jack A. Di Palma, MD

## 1. Define *small intestinal bacterial overgrowth (SIBO)*.

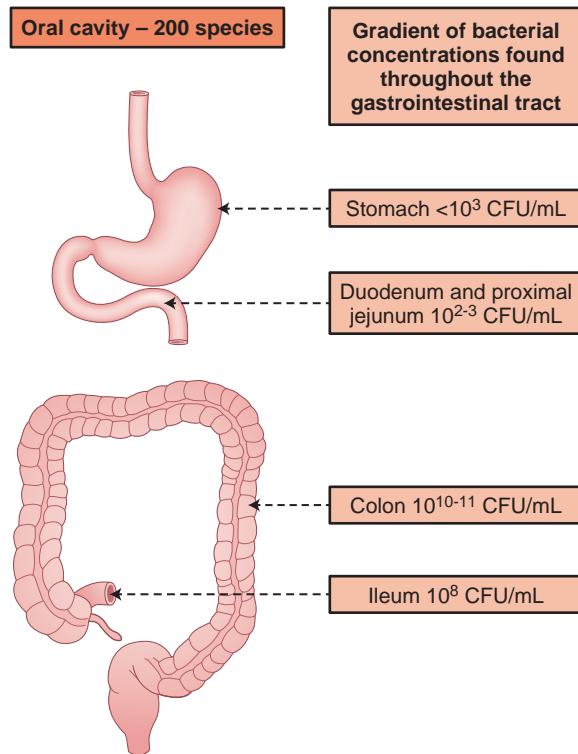
Bacterial culture derived from small bowel luminal samples containing:

- Total bacterial count more than  $10^5$  colony forming units (CFU)/mL
- Specific bacterial count more than  $10^3$  CFU/mL (coliform bacteria usually only found in the colon)

## 2. What is the usual bacterial presence in the gastrointestinal tract?

- Oral cavity 200 species
- Stomach less than  $10^3$
- Duodenum and proximal jejunum  $10^{2-3}$ /mL
- Ileum  $10^8$ /mL
- Colon  $10^{10-11}$ /mL

The type of species that colonize the small intestine is changed in bacterial overgrowth. In health, small bowel bacteria resemble oropharyngeal flora with gram-positive, facultative bacteria, which can survive under aerobic or anaerobic conditions. In overgrowth, bacteria are mostly gram-negative, such as *Escherichia coli*; anaerobic bacteria, including *Clostridia* and *Bacteroides* spp., also predominate (Figure 44-1).



**Figure 44-1.** Gradient of bacterial concentrations found throughout the gastrointestinal tract. CFU, Colony-forming units.

## 3. What are the natural protective mechanisms against SIBO?

- Peristalsis
- Gastric acid
- Bile acid
- Pancreatic enzyme activity

- Small intestinal motility (migrating motor complex)
- Ileocecal valve

#### 4. What factors influence small intestinal bacterial proliferation?

- Structural lesions
- Surgically altered anatomy
- Motility
- Excessive bacterial load
- Deficiency in host defenses

#### 5. What kinds of abnormalities predispose to bacterial overgrowth?

Obstruction to outflow of luminal contents can occur at the site of surgical anastomosis or with webs, adhesions, or strictures. Surgical diversions and blind loops or neoreservoirs, such as the continent ileostomy, predispose to SIBO. The jejunoleal bypass, once a popular surgical procedure for morbid obesity, created a long segment of diverted bowel and was often complicated by overgrowth. Diverticula and duplications are frequently colonized with colonic-type bacteria, leading to overgrowth. There is an increased prevalence of SIBO in disorders that may result in intestinal failure. There is a frequent association of SIBO and Crohn's disease, especially among those who have undergone surgery (Table 44-1).

**Table 44-1.** Physiologic Abnormalities and Overgrowth

Anatomic abnormalities	Surgical anastomosis, webs, adhesions, stricture, small intestinal diverticulosis, blind loop, neoreservoirs, acute enteric infection
Abnormal communications	Gastrocolic fistula, enterocolic fistula, ileocecal valve resection
Motility disorder	Scleroderma, diabetes mellitus, pseudoobstruction, opioid use, medications that alter motility, achlorhydria, radiation enteritis, irritable bowel syndrome
Reduced acid secretion	Medications, atrophic gastritis, vagotomy
Various mechanisms	Crohn's disease, celiac disease, rheumatoid arthritis, morbid obesity, cirrhosis, chronic pancreatitis, chronic kidney disease, cystic fibrosis, acromegaly, focal segmental ischemia

#### 6. How do motility disorders cause bacterial overgrowth?

Delayed transit of intestinal contents results in stasis. Overgrowth complicates intestinal pseudoobstruction syndromes. The *intestinal housekeeper* migratory motor complex, when disrupted, is associated with bacterial overgrowth. Paralytic ileus results in bacterial proliferation. SIBO has been identified in 62.5% of patients with scleroderma in previous studies. Any condition that can cause disordered motility, such as diabetes and irritable bowel syndrome or medications, predisposes to overgrowth.

#### 7. How can an excessive bacterial load be delivered to the small bowel?

Absence or incompetence of the ileocecal valve and enteric fistula can deliver colonic bacteria to the small bowel in amounts that exceed clearing capacity.

#### 8. Which impairments of host defenses are important for development of SIBO?

- Acid suppression by surgery or medications (After initial suggestions that proton pump inhibitor use was a risk factor for SIBO, recent work has not found an association.)
- Hypochlorhydric disorders such as pernicious anemia
- Immune deficiencies, particularly absence of secretory immunoglobulin A
- Undernutrition, which can decrease gastric acidity and immune function
- Cirrhosis, which can lead to abnormal motility and overgrowth with increased incidence of spontaneous bacterial peritonitis

#### 9. What are the symptoms of bacterial overgrowth?

Clinical manifestations vary. Diarrhea, anorexia, nausea, weight loss, and anemia are cardinal symptoms, but the nature of the small bowel abnormality influences the presentation. Patients obstructed by stricture may have bloating and pain. Overgrowth in small intestinal diverticula may present insidiously with metabolic derangements. Bacterial overgrowth leads to small bowel mucosal derangements with brush border defects and bile acid deconjugation commonly resulting in low B<sub>12</sub>, iron and vitamin deficiencies, and fat malabsorption.

#### 10. What is the differential diagnosis of bacterial overgrowth?

Differential diagnosis includes irritable bowel syndrome, celiac sprue, Whipple's disease, microscopic colitis, community acquired *Clostridium difficile* infection, hyper- and hypothyroidism, and medication adverse effects.

### 11. Why do patients with bacterial overgrowth develop anemia?

Anemia may be megaloblastic and macrocytic as a result of cobalamin deficiency. Microcytic anemia resulting from iron deficiency results mainly from blood loss or small bowel damage that are not caused by bacterial overgrowth. Anaerobic bacteria compete with the host for uptake of cobalamin–intrinsic factor complex, predisposing to B<sub>12</sub> deficiency. Whereas luminal bacteria consume cobalamin, folic acid is a product of bacterial substrate fermentation. Thus an important clinical observation in SIBO is the finding of low B<sub>12</sub> and high folate levels.

### 12. What other micronutrient deficiencies are clinically important?

In addition to iron calcium and cobalamin deficiencies, other micronutrient deficiencies include deficiencies of water-soluble vitamins (e.g., thiamine and nicotinamide) and decreased absorption of fat-soluble vitamins (vitamins A, D, E, and K). Trace element malabsorption has not been carefully studied in overgrowth syndromes.

### 13. How is SIBO diagnosed?

The gold standard for diagnosis is aspiration of small intestinal fluid and culture. More than 10<sup>5</sup> CFU/mL of duodenal aspirate (or >10<sup>3</sup> CFU/mL of normal colonic flora in a small bowel aspirate) is diagnostic. See Table 44-2 for a diagnostic approach.

**Table 44-2.** Diagnosis of Small Intestinal Bacterial Overgrowth

History	Prior surgery, older age, medical conditions or medicines associated with altered motility, evidence of malabsorption or malnutrition such as metabolic bone disease, night blindness, easy bruising, tetany
Examination	Evidence of systemic disease: weight loss, malnutrition, and malabsorption
Laboratory values	Hemoglobin (decreased), mean corpuscular volume (increased), vitamin B <sub>12</sub> (decreased), folic acid (increased), fecal fat (increased)
Tests	<sup>14</sup> C-glycocholic acid (increased), <sup>14</sup> C-D-xylose (decreased), hydrogen testing with glucose or lactulose, jejunal aspirate for bacterial colony counts and strain identification

### 14. What testing methods can be used?

- Jejunal intubation for aspiration with bacterial colony counts and stain identification can provide a definitive diagnosis by showing jejunal counts greater than 10<sup>5</sup> CFU/mL. There is a risk of potential contamination by oropharyngeal bacteria contaminating the biopsy channel of endoscopes used to obtain small bowel culture samples. Additionally, bacterial overgrowth can be patchy and thus missed by a single aspiration. Because the test is cumbersome, some clinicians rely on indirect testing. Jejunal intubation can be performed endoscopically, and protected catheters can be used to obtain more reliable aspirates.
- Radiolabeled breath tests using glycocholic acid or xylose have been used for diagnosis of overgrowth. Glycocholic acid is released by bacterial deconjugation of radiolabeled bile acids. Xylose is catabolized by gram-negative aerobes and is absorbed in the proximal small bowel. These methods are not universally available.
- Fasting breath hydrogen is elevated in overgrowth patients, and early rises after glucose or lactulose challenge reflect small bowel fermentation of the substrate by abnormal concentrations of bacteria. The diagnosis is suggested when the exhaled breath H<sub>2</sub> level increases by more than 10 parts per million greater than fasting baseline on two consecutive samplings or if the breath hydrogen level exceeds 20 parts per million, particularly if this occurs in the first 20 minutes after challenge. A second peak associated with colonic fermentations helps support the diagnosis. Approximately 15% to 27% of the population does not generate hydrogen after glucose or lactulose challenge but instead produces methane. The measurement of hydrogen alone will significantly underestimate the prevalence of SIBO in this population. Combining measurements of hydrogen and methane gas (H<sub>2</sub> + 2 × CH<sub>4</sub>) will permit the detection of those who harbor *Methanobrevibacter smithii* (Figure 44-2).

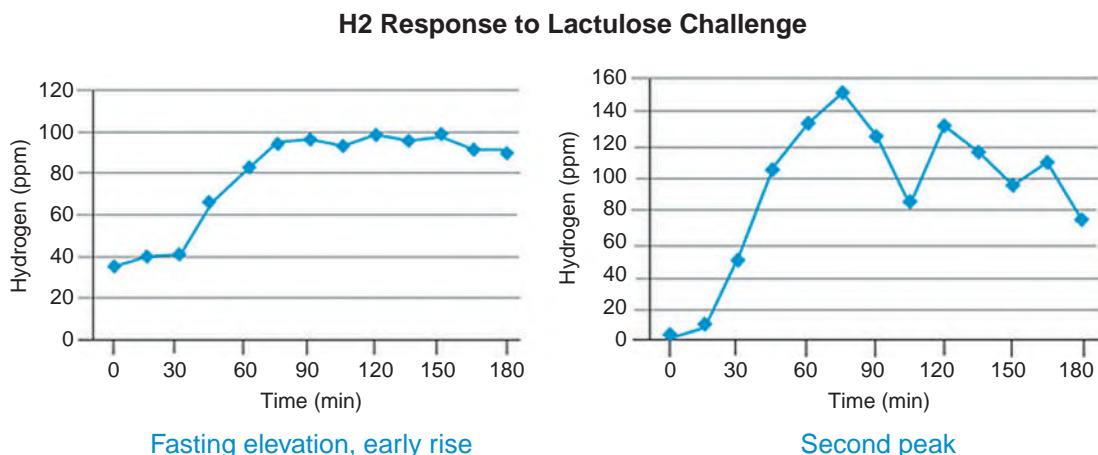
In general, hydrogen breath tests are attractive alternatives to intubation tests for bacterial overgrowth. Hydrogen testing, although simple, inexpensive, available, and nonradioactive, has limited sensitivity and specificity.

### 15. What about other testing methods?

Quantification of urinary excretion of indican, drug metabolites, and conjugated para-aminobenzoic acid does not distinguish overgrowth from other types of malabsorption. An alternative approach to consider is a therapeutic trial of antibiotics. Most patients with SIBO show a symptomatic response within 1 week of initiation of therapy.

### 16. What is the treatment for SIBO?

- Correction of the underlying condition
  - Surgery
  - Prokinetic agents (erythromycin and tegaserod)



**Figure 44-2.** Hydrogen in parts per million (ppm) represents the measured hydrogen gas plus 2 times the measured methane. Fasting elevation is defined as more than 10 ppm. An early rise is greater than 10 ppm on 2 consecutive samples or a rise greater than 20 ppm, particularly in the first 20 minutes after challenge. A second peak reflects colon fermentation.

- Nutrition
  - Lactose-free, low-residue diet
  - Increase calories
  - Micronutrient supplementation ( $B_{12}$ , fat-soluble vitamins, trace elements)
- Antibiotics
- Probiotics
- Prokinetic agents

#### 17. What are the antibiotic agents used in the treatment of SIBO?

- Amoxicillin-clavulanic acid (500 mg 3 times daily)
- Ciprofloxacin (250 mg twice daily)
- Chloramphenicol (250 mg 4 times daily)
- Doxycycline (100 mg twice daily)
- Metronidazole (250 mg 3 times daily)
- Neomycin (500 mg 4 times daily)
- Norfloxacin (800 mg daily)
- Trimethoprim-sulfamethoxazole (1 DS tablet twice daily)
- Rifaximin (400-550 mg 3 times daily)

Rifaximin seems to have superior efficacy. Patient history of penicillin allergy should be considered when choosing antibiotics.

#### 18. Do prokinetic agents help?

Surgery is often impractical or unacceptable, and prokinetic agents can help to relieve stasis and improve outflow of small intestinal contents. However, standard stimulatory agents are not very effective. In high dosages the long-acting somatostatin analog octreotide, can cause steatorrhea, but in low doses it has been shown to promote motility in normal subjects and patients with slow intestinal motility (i.e., scleroderma).

#### 19. How long should SIBO be treated with antibiotics?

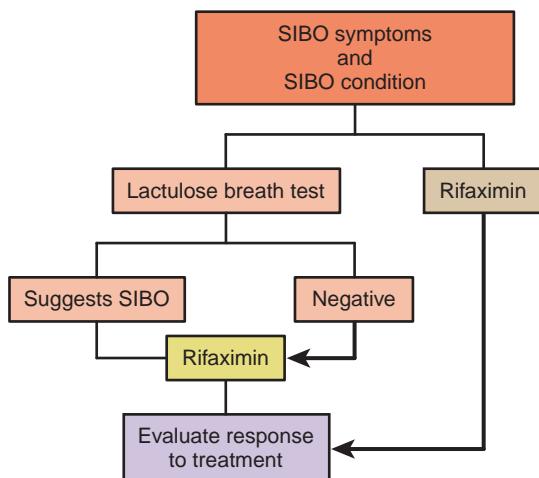
The objective of antibiotic therapy is not to eradicate the bacterial flora but rather to modify the bacterial milieu in a manner that results in symptomatic improvement. In general, a 7- to 14-day course of antibiotics may improve symptoms for several months in 46% to 90% of patients and results in negative breath tests in 20% to 75%. After completion of therapy, symptoms should be reassessed. Some patients may require extended therapy, continuous courses, or rotating antibiotic regimens. Prolonged antibiotic therapy poses significant risk, including resistance and enterocolitis (Figure 44-3).

#### 20. Can prebiotics be used to treat SIBO?

Prebiotics are nondigestable, fermentable feeds that stimulate the growth and activity of endogenous colonic bacteria, preferentially *lactobacillus* and *bifidobacteria*. There are minimal data regarding their clinical use.

#### 21. Can probiotics be used to treat SIBO?

Few studies have examined probiotic therapy in SIBO. *Saccharomyces boulardii* is a probiotic that has stated efficacy for bacterial overgrowth in children; however, it failed to show efficacy in adults. *Lactobacillus fermentum* failed to show an advantage over placebo in a double-blind crossover study.



**Figure 44-3.** Algorithm to evaluate response to antibiotic treatment. SIBO, Small intestinal bacterial overgrowth.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

- Knudsen CD, Di Palma JA. Carbohydrate challenge tests: do you need to measure methane? *South Med J* 2012;105:251–3.
- Lauritano EC, Gabrielli M, Lupascu A, et al. Rifaximin dose-finding study for the treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther* 2005;22:31–5.
- Melcher EA, Levitt MD, Slavin JL. Methane production and bowel function parameters in healthy subjects on low and high fiber diets. *Nutr Cancer* 1991;16:85–92.
- New York Times Health Guide. Small bowel bacterial overgrowth. <http://health.nytimes.com/health/guides/disease/small-bowel-bacterial-overgrowth/overview.html> [Accessed September 22, 2014].
- O'Mahony S, Shanahan F. Enteric microbiota and small intestinal bacterial overgrowth. In: Feldman M, editor. *Sleisenger and Fordtran's gastrointestinal and liver disease*. 9th ed. Philadelphia: WB Saunders; 2010. p. 1769–78.
- Pimentel Lin HC. Eradication of small bowel bacterial overgrowth reduces symptoms of irritable bowel syndrome. *Am J Gastroenterol* 2000;95:3503–6.
- Quigley EM, Quera R. Small intestinal bacterial overgrowth: roles of antibiotics, prebiotics, and probiotics. *Gastroenterology* 2006;130:S78–S90.
- Riordan SM, McIver CJ, Wakefield D, et al. Small intestinal bacterial overgrowth in the symptomatic elderly. *Am J Gastroenterol* 1997;92:47–51.
- Rose S, Young MA, Reynolds JC. Gastrointestinal manifestations of scleroderma. *Gastroenterol Clin North Am* 1998;27:63–594.
- Ratuapli SK, Ellington TG, O'Neill MT, et al. Proton pump inhibitor use does not predispose to small intestinal bacterial overgrowth. *Am J Gastroenterol* 2012;107:730–5.
- Scarpellini E, Gabrielli EM, Lauritano CE, et al. High dosage rifaximin for the treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther* 2007;25:781–6.
- Shanahan F. The host-microbe interface within the gut. *Best Pract Res Clin Gastroenterol* 2002;16:915–31.
- Soudah HC, Hasler WL, Owyang C. Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma. *N Engl J Med* 1991;325:1461–7.

# COLON DISORDERS AND COLON CANCER

Carole Macaron, MD, and Carol Ann Burke, MD

## 1. What are the incidence and mortality rates of colorectal cancer (CRC)?

In the United States, CRC is the second most commonly diagnosed cancer in men and women. According to data from the Surveillance, Epidemiology, and End Results (SEER) population-based cancer registries, the age-adjusted incidence rate during the period 2006 to 2010 was 52.2 per 100,000 men and 39.3 per 100,000 women per year. The projected number of new cases in 2013 is 142,820 with 50,830 anticipated deaths occurring, accounting for 9% of estimated new cancer cases and deaths in men and women.

The age-adjusted mortality rate of CRC in the years 2006 to 2010 was 19.6 per 100,000 men and 13.9 per 100,000 women per year.

## 2. What is the trend in CRC incidence and mortality rates in the United States in the most recent years?

CRC incidence rates established from the most recent data (2005-2009) decreased in men by 2.6% per year and by 2.1% per year in women; decreases have been largely attributed to increases in the use of CRC screening and removal of colorectal polyps.

Mortality from CRC has also been steadily declining in the United States by 2.5% to 3% per year.

## 3. What is the effect of ethnicity on CRC incidence and mortality?

Despite improvements in screening and treatment, studies show that racial disparities persist in CRC incidence and mortality. Black men have the highest incidence (65.1 versus 52.8 per 100,000) and stage-adjusted mortality (29.8 versus 19.8 per 100,000) compared to white men.

## 4. Describe the molecular pathways leading to CRC.

Three distinct forms of genomic instability have been recognized and constitute three different molecular pathways to colon carcinogenesis:

- Chromosomal instability is the most common pathway to colon cancer, accounting for 80% of cases. The resulting genomic instability is characterized by loss of heterozygosity by loss of a wild-type copy of a tumor suppressor gene such as APC. The colon cancer precursor lesion in this pathway is the adenoma.
- The microsatellite instability (MSI) pathway is due to inactivation of a mismatch repair (MMR) gene (MLH1, MSH2, PMS2, and MSH6). The loss of MMR gene function causes inability to repair DNA within the repetitive DNA sequences known as *microsatellites*. The sessile serrated polyp (SSP) is the precursor to MSI-high colon cancer.
- The CpG island methylator phenotype (CIMP) pathway is a cause of approximately 20% of CRC. The serrated neoplasm is the precursor to these cancers.

## 5. List the environmental factors implicated in the development of sporadic CRC.

Evidence from published studies suggests an association between CRC and smoking, drinking excessive alcohol, obesity, and consumption of processed and red meat. Conversely, physical activity and vegetable and fruit consumption are associated with a decreased risk of CRC. In a recent metaanalysis, Johnson and colleagues quantified the role of different environmental risk factors on the development of CRC (Table 45-1).

**Table 45-1.** Environmental Factors Implicated in the Development of CRC and Respective Relative Risks

RISK FACTOR	LEVEL OF EXPOSURE	RELATIVE RISK (95% CONFIDENCE INTERVAL)
Smoking	30 vs. 0 pack year	1.26 (1.17-1.36)
Alcohol	20 vs. 0 drinks/week	1.26 (0.68-2.32)
Body mass index	30 vs. 22 kg/m <sup>2</sup>	1.10 (1.08-1.12)
Red meat	5 vs. 0 servings/week	1.13 (1.09-1.16)
Fruits	3 vs. 0 servings/day	0.84 (0.75-0.96)
Vegetables	5 vs. 0 servings/day	0.86 (0.78-0.94)
Family history of colorectal cancer	Yes vs. no	1.8 (1.61-2.02)

**6. What is the risk of CRC in patients with inflammatory bowel disease and in patients with primary sclerosing cholangitis (PSC)?**

CRC risk is significantly increased. Once PSC is diagnosed, colon screening should begin immediately (see [Chapter 19](#) and [Chapter 62](#)).

**7. What is the difference between synchronous and metachronous CRC?**

Synchronous CRC is defined by the presence of more than one tumor at presentation. Metachronous CRC is defined by the subsequent development of another primary colorectal tumor on follow-up.

**8. What are the clinical manifestations of CRC?**

The most common presentation of CRC is abdominal pain (seen in 44% of patients). However, CRC can present with a variety of symptoms: change in bowel habits, hematochezia or melena, weakness, iron-deficiency anemia, and weight loss. *Streptococcus bovis* bacteremia, entero-enteric fistula, and diverticulitis are other unusual presentations of CRC. In addition, 6% of metastatic adenocarcinomas of unknown origin are due to CRC.

Left-sided colonic tumors are more likely to present with obstructive symptoms than right-sided colonic tumors. Right-sided colon cancers are more likely to present at an advanced stage because of the large capacity of the cecum and ascending colon.

**9. How is CRC pathologically staged?**

Dukes classification is the first system of CRC staging proposed by a Scottish pathologist, Cuthbert Esquire Dukes. Dukes classification divided staging into three stages. The fourth stage was added later to represent metastatic disease ([Table 45-2](#)).

**Table 45-2.** Dukes Classification

DUKES STAGE	DEPTH OF INVASION	CANCER-FREE 5-YEAR SURVIVAL (%)
A	Tumor penetrates the mucosa and submucosa but does not penetrate the muscularis propria.	95%-100%
B	Tumor penetrates muscularis propria and may invade serosa and pericolic fat.	80%-85%
C	Any degree of invasion occurs plus metastasis to a regional lymph node.	50%-70%
D	Distant metastasis occurs.	5%-15%

Nowadays, CRC is classified using the tumor-node-metastasis (TNM) staging system based on the extent of the primary tumor (T), the presence of locoregional lymph node involvement (N), and the presence of metastatic disease (M). The TNM staging is summarized in [Table 45-3](#) and [Table 45-4](#).

**Table 45-3.** TNM Classification

T STAGE	N STAGE	M STAGE
T0: No tumor	Nx: Lymph node cannot be assessed	Mx: Distant metastasis cannot be assessed
Tis: Adenocarcinoma in situ (tumor limited to the mucosa)	N0: No lymph node involvement	M0: No distant metastasis
T1: Tumor invades the submucosa but not the muscularis propria	N1: Metastasis in 1 to 3 regional lymph nodes	M1: Presence of distant metastasis
T2: Tumor invades into the muscularis propria	N2: Metastasis in 4 or more regional lymph nodes	Of note, involvement of nonregional lymph nodes (i.e., common iliac, external iliac, paraaortic, and supraclavicular) is considered distant metastasis.
T3: Tumor invades through the muscularis propria into the subserosa or nonperitonealized extramural tissues		
T4: Tumor invades other organs (T4a) or perforates visceral peritoneum (T4b)		

TNM, Tumor-node-metastasis.

**Table 45-4.** TNM Stages and 5-year Survival Rates

TNM STAGES		5-YEAR SURVIVAL
Stage I	T1-2, N0, M0	93.2%
Stage IIA	T3, N0, M0	84.7%
Stage IIB	T4, N0, M0	72.2%
Stage IIIA	T1-2, N1, M0	83.4%
Stage IIIB	T3-4, N1, M0	64.1%
Stage IIIC	T1-4, N2, M0	44.3%
Stage IV	any T, any N, M1	8.1%

TNM, Tumor-node-metastasis.

#### 10. Differentiate microsatellite stability (MSS) from microsatellite instability: low (MSI-L) and high (MSI-H)

Defects in the MMR genes, usually by promoter methylation but also caused by mutations as in Lynch syndrome, result in MMR deficiency or dysfunction leading to changes in the length of repetitive DNA elements in the tumor tissue, called MSI. Tumors with MSI can be classified as either MSI-H or MSI-L depending on the number of DNA markers that show instability. Using a five-marker panel, MSI-H tumors are those that have two or more of the five markers showing instability, and MSI-L, if only one of the five markers shows instability. Tumors without DNA marker instability are called MSS.

#### 11. What are the prognostic implications of MSI-H tumors?

In most studies, MSI-H tumors have been associated with significant advantages compared with MSS tumors. MSI-H tumors are associated with a survival benefit independent of tumor stage, are less likely to metastasize to regional lymph nodes or distant organs, and have lower rates of colon cancer mortality.

#### 12. What is the role of carcinoembryonic antigen (CEA) in the screening, diagnosis, prognosis, and surveillance of CRC?

CEA-related cell adhesion molecule 5, or CEACAM5 (also called CEA), is a high-molecular-weight glycoprotein that belongs to the immunoglobulin superfamily. The National Institutes of Health Consensus Conference and the American Society of Clinical Oncology Expert Panel do not recommend using CEA to screen or diagnose CRC cancer because of its low sensitivity and specificity. A CEA level is recommended preoperatively. If it is high before surgery, it is expected to normalize following successful surgery to remove all of the cancer. A rising CEA level indicates progression or recurrence of the cancer.

#### 13. How is CRC clinically staged?

Patients with invasive colon cancer require a complete staging workup, including:

- Complete blood count, chemistry profile, CEA
- Computed tomography (CT) scan of chest, abdomen, and pelvis
- Colonoscopy with tumor biopsy

According to the National Comprehensive Cancer Network (NCCN), a positron emission tomography (PET) scan is not routinely indicated at baseline in the absence of synchronous metastatic disease. If suspicious lesions are seen on CT or magnetic resonance imaging, then a PET scan may be appropriate for further delineation.

#### 14. What are the treatment options for localized colon cancer?

Surgery is the treatment of choice and offers the best chance of long-term cure. Because pericolic mesenteric lymph nodes are the initial site of metastatic spread, an en bloc resection of the primary tumor with adequate margins and removal of the regional lymph nodes is recommended. The resection should include the tumor and 5 cm of normal tissue margins on each side of the tumor. According to the NCCN guidelines in oncology, a minimum of 12 lymph nodes must be examined to clearly establish a stage II (T3-4, N0) colon cancer.

#### 15. When can a laparoscopic-assisted colectomy be considered?

According to the NCCN guidelines, a laparoscopic approach can be used based on the following criteria:

- Surgeon's expertise in laparoscopic colorectal operations
- Absence of disease in the rectum
- No prohibitive abdominal adhesions
- Absence of advanced local or metastatic disease
- Absence of acute bowel obstruction or perforation from cancer

**16. At what interval of time should a follow-up colonoscopy be done after curative surgical resection of the colon cancer?**

According to the American Cancer Society and the Multi-Society Task Force (MSTF) on Colorectal Cancer, patients with colon cancer should undergo high-quality perioperative colonoscopy to rule out synchronous neoplasia. In the case of an obstructive cancer, the colonoscopy should be performed 3 to 6 months after surgery if no unresectable metastasis was found during surgery. Subsequent surveillance colonoscopy should be performed 1 year after surgical resection or after the initial colonoscopy done to clear the colon of synchronous lesions. If normal colonoscopy is repeated at 3 years and if that colonoscopy is normal, then repeat in 5 years thereafter.

**17. What are the most frequent sites of relapse after surgical resection of colon cancer?**

After surgical resection, the most frequent sites of relapse are:

- Liver (33%)
- Lungs (22%)
- Local (colon, anastomosis) or regional (21%)
- Intraabdominal sites (18%)

Rectal cancers have more local recurrences and less retroperitoneal node involvement when compared to colon cancer.

**18. At what age should CRC screening begin in average-risk individuals?**

The American College of Gastroenterology (ACG) recommends screening to begin at age 50 years in average-risk men and women (grade 1B), except for black patients, in whom screening is recommended to begin at age 45 (grade 2C).

**19. When should CRC screening and surveillance stop?**

The United States Preventative Services Task Force recommends screening not be continued after age 85 as risk exceeds the benefit (grade D). In patients age 75 to 85 years, screening is not recommended (grade C), but should be individualized based on benefits, risks, comorbidities, and life expectancy.

**20. What are the recommended options for CRC screening?**

CRC screening tests can be divided into cancer prevention and cancer detection tests (Table 45-5). Cancer prevention tests have the potential to identify both cancer and polyps. Cancer detection tests have low sensitivity for polyp detection but are primarily effective in diagnosing CRC.

**Table 45-5. Cancer Prevention and Detection Tests**

CANCER PREVENTION TESTS	CANCER DETECTION TESTS
Colonoscopy every 10 years	Annual high-sensitivity FOBT with FIT or guaiac-based FOBT
Flexible sigmoidoscopy every 5-10 years	
CT colonography every 5 years (not recommended by USPSTF)	Fecal DNA every 3 years (not recommended by USPSTF)

CT, Computed tomography; FIT, fecal immunochemical test; FOBT, fecal occult blood test; USPSTF, U.S. Preventative Services Task Force.

The ACG recommends colonoscopy every 10 years as the preferred cancer prevention test and annual fecal immunochemical test (FIT) to detect occult bleeding as the preferred cancer detection test.

**21. What are the ACG recommendations for CRC screening and surveillance in individuals with family history of CRC?**

See Table 45-6.

**Table 45-6. ACG Recommendations for CRC Screening and Surveillance in Individuals with Family History of CRC**

FAMILY HISTORY SCREENING	RECOMMENDATION
Single first-degree relative with CRC or advanced adenoma (adenoma $\geq 1$ cm, or high-grade dysplasia or villous component) at age $\geq 60$ years	Colonoscopy every 10 years beginning at age 50 years
Single first-degree relative with CRC or advanced adenoma diagnosed at age $< 60$ or two first-degree relatives with CRC or advanced adenomas at any age	Colonoscopy every 5 years beginning at age 40, or 10 years younger than age at diagnosis of the youngest affected relative

ACG, American College of Gastroenterology; CRC, colorectal cancer.

## 22. How does a stool blood test identify blood in the stool?

Fecal occult blood tests (FOBTs) are stool-based CRC screening tests that are designed to detect occult blood loss from colorectal neoplasms. Two major types of FOBTs exist: the guaiac-based FOBT (gFOBT) and FIT. The gFOBT detects blood through the pseudoperoxidase activity of heme or hemoglobin, which converts the colorless guaiac to a blue color. The FIT is an antibody that reacts with human globin.

## 23. Compare the diagnostic accuracy of gFOBT with FIT.

Multiple studies have compared different types of FITs with Hemoccult SENSA (a high-sensitivity gFOBT). There is no clear superiority in overall test performance between highly sensitive gFOBT and FIT.

Of note, three large randomized controlled trials (RCTs) with gFOBT have demonstrated significant reduction in CRC mortality of 15% to 33%. No FIT has been studied in an RCT. The sensitivity of FIT and gFOBT was 81.8% and 64.3%, respectively, in a recent study by Allison and colleagues. In terms of specificity, FIT tend to be superior to gFOBT with a specificity of 97% for distal cancer.

## 24. Compare the performance of CT colonography (CTC) with colonoscopy.

Nonrandomized controlled studies showed that the yield for advanced neoplasia was similar between screening patients undergoing CTC (3.2%) or colonoscopy (3.4%), with a 7.9% referral rate for follow-up colonoscopy after CTC. Only limited randomized data are available to date in screening patients with inconsistent findings. A very recent large randomized study (SIGGAR study) on symptomatic patients showed that the yield for CRC or large polyps was identical with CTC and colonoscopy with a very low miss rate (1 of 29 in the CTC group). However, the referral rate for colonoscopy after CTC was unexpectedly high (30%), a fact that has major cost implications.

## 25. What is the benefit of colonoscopy?

No randomized clinical trial proving that screening colonoscopy reduces cancer mortality has been published. In the National Polyp Study, colonoscopic polypectomy was found to reduce the incidence of CRC to 66% lower than expected according to the SEER, Mayo Clinic, and St. Mark's data. It is not until 10 years later that the mortality benefit of colonoscopy polypectomy was proven. When compared with the expected deaths from CRC in the general population, colonoscopy polypectomy reduced mortality from CRC by 53%.

## 26. Is there a difference in the benefit of colonoscopy in the left and right colon?

Recent studies showed that the reduction in CRC mortality after colonoscopy varies by the site of the cancer, with less protection in reducing mortality from proximal CRC. It is suggested that the biologic differences between proximal and distal CRC (higher proportion of CIMP, DNA MSI, and BRAF mutations in the **proximal colon**) and the higher proportion of flat polyps in the proximal colon may affect the ability of endoscopy to detect and resect potential cancer precursors.

## 27. What is the interval CRC?

Interval cancers are CRCs that develop after the baseline and before the next recommended colonoscopy. A recent study using a pooled dataset from eight large prospective North American studies found 0.6% of individuals developed interval cancer within an average of 4 years following complete colonoscopy and removal of adenomas at baseline colonoscopy. Missed lesions (52%) and incompletely resected lesions (19%) seem to account for 70% of interval cancers in this series. Other cohort studies have found the proportion of patients diagnosed with CRC who underwent colonoscopy 6 to 36 months before diagnosis is up to 9%.

## 28. What are the different serrated lesions?

Serrated lesions of the colorectum include hyperplastic polyps (HPs), SSPs, and traditional serrated adenomas (TSAs). HPs are the most common serrated lesion with a prevalence of 20% to 40%. A normal continuous and symmetric proliferation at the base of the crypts defines the HP. SSPs are less common than HPs and are found on approximately 2% of screening colonoscopies. SSPs express abnormal cellular proliferation characterized by a displaced proliferative zone away from the crypt base toward their surface and L- or boot-shaped dilation of the crypt base. TSAs are rare and often left sided. The presence of nuclear atypia is the hallmark of the TSA.

## 29. Are there any chemopreventive agents that have been reported to decrease the risk of adenoma recurrence?

See Table 45-7.

**Table 45-7.** Chemoprevention Agents

AGENT	EVIDENCE	SIDE-EFFECT PROFILE	RECOMMENDATION (EXPERT OPINION)
Aspirin	RCT 35% reduction in recurrence of advanced adenoma	Major bleed (3/1000 middle-aged men on low-dose aspirin) Hemorrhagic stroke (1/10,000 users)	NOT recommended
COX2 inhibitors (celecoxib)	RCT 50% reduction in recurrence of advanced adenoma	60% increase in cardiovascular complications 40% increase in all-cause mortality	NOT recommended
Folic acid	RCT No reduction in recurrence of adenoma or advanced adenoma	Increased risk of noncolorectal cancer, mainly prostate cancer May increase number of adenomas	NOT recommended
Calcium	RCT 15% reduction in recurrence of adenoma	Renal calculi Increased cardiovascular mortality (RR 1.24 [1.07, 1.45])	May be considered in high-risk adenoma-bearing patients, family history of CRC

COX, Cyclooxygenase; CRC, colorectal cancer; RCT, randomized controlled trial; RR, relative risk.

30. According to the U.S. MSTF consensus update on CRC, what are the recommendations for surveillance colonoscopy in patients with history of adenomatous polyps and baseline average risk?  
See Table 45-8.

**Table 45-8.** U.S. MSTF Recommendations for Surveillance Colonoscopy in Patients with History of Adenomatous Polyps and Baseline Average Risk

MOST ADVANCED FINDINGS ON BASELINE COLONOSCOPY	RECOMMENDED SURVEILLANCE INTERVAL (Y)
1-2 small ( $\leq 10$ mm) tubular adenoma	5-10
3-10 tubular adenomas, presence of villous features or HGD, size $\geq 10$ mm	3
>10 adenomas	<3 (consider genetic syndrome)

MSTF, Multi-Society Task Force.

31. According to the U.S. MSTF consensus update on CRC, what are the recommendations for surveillance colonoscopy in patients with history of serrated polyps?  
See Table 45-9.

**Table 45-9.** U.S. MSTF Recommendations for Surveillance Colonoscopy in Patients with History of Serrated Polyps

MOST ADVANCED SERRATED LESIONS ON BASELINE COLONOSCOPY	RECOMMENDED SURVEILLANCE INTERVAL (Y)
Small ( $\leq 10$ mm) hyperplastic polyps in rectum or sigmoid	10
Sessile serrated polyp(s) $<10$ mm with no dysplasia	5
Sessile serrated polyp(s) $\geq 10$ mm	3
Sessile serrated polyp(s) with dysplasia	3
Traditional serrated adenoma	3
Serrated polyposis syndrome	1

MSTF, Multi-Society Task Force.

- 32. List the inherited polyposis syndromes with their respective gene mutation and mode of inheritance.**  
See Table 45-10.

**Table 45-10. Inherited Polyposis Syndrome**

SYNDROME	POLYPS	GENE MUTATION	MODE OF INHERITANCE
<b>Adenomatous Polyposis Syndrome</b>			
Classic FAP	Colonic adenomas (usually thousands) Duodenal adenoma Gastric fundic gland polyps Small bowel adenomas	APC	Autosomal dominant
Attenuated FAP	Colonic adenoma (<500, proximal location) Duodenal/periampullary adenomas Gastric fundic gland polyps	APC	Autosomal dominant
MYH-associated polyposis	Colonic adenomas (5-100, late age of onset, typically late 40s); other extracolonic features of FAP	MYH	Autosomal recessive
<b>Hamartomatous Polyposis Syndromes</b>			
Juvenile polyposis syndrome	Multiple juvenile polyps in: Colon/rectum (98%) Stomach (14%)—most commonly with SMAD4 mutations Duodenum/jejunum/ileum (7%)	SmaD 4 BMPRIA	Autosomal dominant
Peutz-Jeghers syndrome	Multiple gastrointestinal polyps: Stomach (24%) Small bowel (96%) Colon (27%) Rectum (24%)	STK11 (also called LKB1)	Autosomal dominant
Cowden syndrome	Hamartomas throughout the gastrointestinal tract: Esophagus (66%) Stomach (75%) Duodenum (37%) Colon (66%)	PTEN	Autosomal dominant
Hereditary mixed polyposis syndrome	Mixed juvenile-adenomatous polyps, adenomatous polyps, hyperplastic polyps, serrated adenomas, mixed hyperplastic-adenomatous polyps	SCG5	Autosomal dominant

FAP, familial adenomatous polyposis.

### **33. What is serrated polyposis syndrome?**

Serrated polyposis syndrome used to be called *hyperplastic polyposis syndrome*. It is characterized by the presence of serrated polyps admixed with adenomas throughout the colon, with larger polyps in the proximal colon. The risk of CRC has been reported to be as high as 50%. The World Health Organization criteria have been suggested to assist with the diagnosis:

- At least 5 serrated polyps proximal to sigmoid with two or more being 10 mm or larger
- Any number of serrated polyps proximal to sigmoid colon in patients with a first-degree relative with HPs
- More than 20 serrated polyps of any size, distributed throughout the colon

### **34. What is Lynch syndrome?**

Lynch syndrome is an autosomal-dominant inherited disease caused by a germline mutation in the MMR genes or the Epcam gene. Lynch syndrome results in CRC and extra colonic cancers.

### **35. What is hereditary nonpolyposis colorectal cancer (HNPCC)?**

The term *HNPCC* is used to describe individuals who meet the Amsterdam I criteria. It should not be used interchangeably with Lynch syndrome, which is defined as evidence of MMR gene dysfunction.

**36. What is familial CRC type X?**

The term *familial* CRC type X has been suggested for the group of patients who fulfill the Amsterdam I clinical criteria for HNPCC but in whom no evidence of MMR deficiency by gene mutation or tumor MSI exists. These individuals have a lower cumulative lifetime risk of CRC compared with patients with Lynch syndrome and no increased risk of extraintestinal cancer.

**37. What is the molecular signature of Lynch-associated cancers?**

Lynch syndrome is caused by a germline mutation in one of several DNA MMR genes: MSH2 (39%), MLH1 (32%), MSH6 (15%), and PMS2 (14%). In multiple patients in which Lynch syndrome is suspected, with no germline mutation found in the MMR genes, a heterozygous germline deletion was identified in the last two exons of the EPCAM gene. Such deletions disrupt the 3' end of the EPCAM gene, leading to silencing of its neighboring gene MSH2, and cause Lynch syndrome.

**38. List the Lynch-associated cancers.**

Patients with Lynch syndrome are at increased risk of colon cancer but also endometrial, ovarian, gastric, urothelial, small bowel, biliary and pancreatic, sebaceous gland neoplasm, and brain cancers (usually glioblastoma). The risk of cancer in patients with Lynch syndrome varies by gene mutation.

MSH6 mutation carriers have been found to be at lowest risk of cancer. Ovarian and endometrial cancer risks are highest for those with MLH1 and MSH2 gene mutations.

**39. What are the screening recommendations for patients with Lynch syndrome?**

There is strong evidence that frequent colonoscopy and polypectomy decreases CRC incidence and mortality in individuals with Lynch syndrome. Recent analysis on the causes of deaths in Lynch syndrome show that a large proportion (61%) of the cancer deaths are now associated with noncolorectal, nonendometrial cancer. Unfortunately, there is no data to support a benefit for screening extracolonic cancers. A number of guidelines recommended screening for Lynch syndrome by site of cancer. Recommendations by the NCCN are summarized in [Table 45-11](#).

**Table 45-11.** NCCN Screening Recommendations for Patients with Lynch Syndrome

SITE OF CANCER	AGE TO BEGIN SCREENING	EXAMINATION	INTERVAL
Colorectum	20-25	Colonoscopy	1-2 years
Uterus, ovaries Prophylactic TAH and BSO should be considered	30-35 After childbearing	Transvaginal ultrasound, endometrial biopsy	1 year
Stomach	30-35	EGD Screening for all carriers after age 25 for <i>H. pylori</i>	3-5 years
Urinary tract	25-30	Urinalysis	1 year

BSO, Bilateral salpingo-oophorectomy; EGD, esophagogastroduodenoscopy; TAH, total abdominal hysterectomy.

**40. What are the extracolonic manifestations of familial adenomatous polyposis (FAP) or MUTYH-associated polyposis (MAP)?**

In addition to colorectal polyposis, patients with FAP or MAP can develop a variety of benign or malignant extracolonic manifestations.

Benign extracolonic manifestations are the following:

- Skin lesions: sebaceous or epidermoid cysts, lipomas, fibromas
- Osteomas
- Dental abnormalities: unerupted teeth or supernumerary teeth
- Congenital hypertrophy of the retinal pigment epithelium
- Nasopharyngeal angiofibroma

Extracolonic malignancies are the following:

- Desmoid tumors (15%)
- Duodenum (3%-5%)
- Thyroid cancer (2%)
- Brain tumor (usually medulloblastoma) (2%)
- Pancreas (1.7%)
- Hepatoblastoma (1.6%)
- Gastric cancer (0.6%)

#### 41. What are the screening recommendations for patients with FAP?

See Table 45-12.

**Table 45-12.** Screening Recommendations for Patients with FAP

CANCER	AGE TO BEGIN SCREENING	SCREENING METHOD	SCREENING INTERVAL
Colon	10-12	Colonoscopy	1 year
Duodenal or periamppullary	20-25	EGD with side-viewing examination of the duodenal papilla	1-3 years
Thyroid	10-12	Ultrasound	1 year
Gastric	20-25	EGD	1-3 year
Brain	First decade	Annual physical examination, possible MRI of the brain in affected families	1 year

EGD, Esophagogastroduodenoscopy; FAP, familial adenomatous polyposis; MRI, magnetic resonance imaging.

#### 42. What is the surgical treatment for FAP?

Colectomy remains the keystone of cancer prevention in FAP. Surgical options are:

- Subtotal colectomy with ileorectal anastomosis
- Total colectomy with ileal pouch–anal anastomosis (IPAA)

The subtotal colectomy is a single-stage procedure, with less comorbidity than the total colectomy with IPAA. Once surgery is performed, a rectal or pouch cancer risk remains. Surveillance with flexible sigmoidoscopy every year is recommended.

#### 43. Is there adjunct to colonoscopy to decrease the polyp burden in patients with FAP?

Multiple chemopreventive agents have been studied in patients with FAP.

High-dose aspirin (600 mg a day) was not shown in an RCT (CAPP1 trial) to decrease polyp size and count when compared with placebo.

The nonsteroidal antiinflammatory drug sulindac has been shown to reduce colorectal adenoma size (65% reduction) and number (56% reduction) in numerous studies in patients with FAP patients.

The cyclooxygenase-2 inhibitor celecoxib was shown to reduce adenoma burden by 31% in FAP patients with intact colon or after surgery. It was also associated with a 14% to 31% reduction in duodenal polyps burden.

Eicosapentaenoic acid or fish oil was studied in FAP patients. In an RCT, after 6 months of treatment, there was 22.4% reduction in polyp number and 29.8% decrease in polyp size in the fish oil group compared with the placebo group.

#### 44. Does aspirin prevent CRC in patients with Lynch syndrome?

The CAPP2 trial randomly assigned 1009 Lynch syndrome patients to 600 mg enteric-coated aspirin versus placebo for 2 to 4 years. The overall burden of adenoma at the end of the treatment phase was unchanged between the two arms. However, secondary analysis when the first recruits reached 10 years of follow-up revealed a significant reduction in CRC among the patients treated with aspirin (44% risk reduction). Data on treatment side effects was not provided. Currently, patients with Lynch syndrome should be advised of the current data

#### BIBLIOGRAPHY

1. Allison JE, Sakoda LC, Levin TR, et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. *J Natl Cancer Inst* 2007;99(19):1462–70.
2. Arber N, Eagle CJ, Spicak J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 2006;355(9):885–95.
3. Atkin W, Dadswell E, Wooldrage K, et al. Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. *Lancet* 2013;381(9873):1194–202.
4. Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. calcium polyp prevention study group. *N Engl J Med* 1999;340(2):101–7.
5. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 2003;348(10):891–9.
6. Baxter NN, Goldwasser MA, Paszat LF, et al. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009;150(1):1–8.

7. Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA* 2011;305(22):2304–10.
8. Burn J, Bishop DT, Mecklin JP, et al. Effect of aspirin or resistant starch on colorectal neoplasia in the lynch syndrome. *N Engl J Med* 2008;359(24):2567–78.
9. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet* 2011;378(9809):2081–7.
10. Cole BF, Baron JA, Sandler RS, et al. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA* 2007;297(21):2351–9.
11. Desch CE, Benson III AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology Practice Guideline. *J Clin Oncol* 2005;23(33):8512–9.
12. Engstrom PF, Arnoletti JP, Benson AB, et al. NCCN clinical practice guidelines in oncology: colon cancer. *J Natl Compr Canc Netw* 2009;7(8):778–831.
13. Galanduk S, Wieand HS, Moertel CG, et al. Patterns of recurrence after curative resection of carcinoma of the colon and rectum. *Surg Gynecol Obstet* 1992;174(1):27–32.
14. Giardiello FM, Hamilton SR, Krush AJ, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 1993;328(18):1313–6.
15. Gryfe R, Kim H, Hsieh ET, et al. Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer. *N Engl J Med* 2000;342(2):69–77.
16. Hawkins NJ, Ward RL. Sporadic colorectal cancers with microsatellite instability and their possible origin in hyperplastic polyps and serrated adenomas. *J Natl Cancer Inst* 2001;93(17):1307–13.
17. Johnson CM, Wei C, Ensor JE, et al. Meta-analyses of colorectal cancer risk factors. *Cancer Causes Control* 2013;24(6):1207–22.
18. Kim DH, Pickhardt PJ, Taylor AJ, et al. CT colonography versus colonoscopy for the detection of advanced neoplasia. *N Engl J Med* 2007;357(14):1403–12.
19. Lash RH, Genta RM, Schuler CM. Sessile serrated adenomas: prevalence of dysplasia and carcinoma in 2139 patients. *J Clin Pathol* 2010;63(8):681–6.
20. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US multi-society task force on colorectal cancer, and the American College of Radiology. *CA Cancer J Clin* 2008;58(3):130–60.
21. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US multi-society task force on colorectal cancer. *Gastroenterology* 2012;143(3):844–57.
22. Lindor NM, Rabe K, Petersen GM, et al. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. *JAMA* 2005;293(16):1979–85.
23. Markowitz SD, Bertagnolli MM. Molecular origins of cancer: molecular basis of colorectal cancer. *N Engl J Med* 2009;361(25):2449–60.
24. Ogino S, Noshio K, Kirkner GJ, et al. CpG island methylator phenotype, microsatellite instability, BRAF mutation and clinical outcome in colon cancer. *Gut* 2009;58(1):90–6.
25. Phillips RK, Wallace MH, Lynch PM, et al. A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. *Gut* 2002;50(6):857–60.
26. Power DG, Glogowski E, Lipkin SM. Clinical genetics of hereditary colorectal cancer. *Hematol Oncol Clin North Am* 2010;24(5):837–59.
27. Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. *Am J Gastroenterol* 2009;104(3):739–50.
28. Robertson DJ, Lieberman DA, Winawer SJ, et al. Colorectal cancers soon after colonoscopy: a pooled multicohort analysis. *Gut* 2014 Jun;63(6):949–56.
29. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013;63(1):11–30.
30. Singh H, Nugent Z, Demers AA, et al. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. *Gastroenterology* 2010;139(4):1128–37.
31. Speights VO, Johnson MW, Stoltenberg PH, et al. Colorectal cancer: current trends in initial clinical manifestations. *South Med J* 1991;84(5):575–8.
32. Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000;342(26):1946–52.
33. Torlakovic E, Skovlund E, Snover DC, et al. Morphologic reappraisal of serrated colorectal polyps. *Am J Surg Pathol* 2003;27(1):65–81.
34. West NJ, Clark SK, Phillips RK, et al. Eicosapentaenoic acid reduces rectal polyp number and size in familial adenomatous polyposis. *Gut* 2010;59(7):918–25.
35. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. the national polyp study workgroup. *N Engl J Med* 1993;329(27):1977–81.
36. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012;366(8):687–96.

# CONSTIPATION AND FECAL INCONTINENCE

Reena V. Chokshi, MD, and Suzanne Rose, MD, MSEd

## 1. How is constipation defined?

Constipation is a symptomatically defined disorder that includes a variety of patient complaints, such as infrequent passage of stool, passage of hard stools, straining, and feelings of incomplete evacuation. Constipation can be classified as acute or chronic, and etiologic factors can be primary or secondary. Because of the heterogeneity of this symptom, the Rome consensus group developed specific criteria for chronic constipation (Table 46-1A). Note the distinction between these criteria and those of constipation-predominant irritable bowel syndrome (IBS-C, Table 46-1B), the latter requiring the symptom of pain as a major complaint.

**Table 46-1.** Rome III Criteria for Functional Constipation and Constipation-Predominant Irritable Bowel Syndrome

A. FUNCTIONAL CONSTIPATION	B. CONSTIPATION-PREDOMINANT IRRITABLE BOWEL SYNDROME
<p>Two or more of the following criteria must be present for <math>\geq 3</math> months with symptom onset at least 6 months prior to diagnosis:</p> <ol style="list-style-type: none"> <li>1. Must include two or more of the following: <ul style="list-style-type: none"> <li>• Less than three bowel movements per week</li> <li>• Straining occurring with <math>\geq 25\%</math> of defecations</li> <li>• Lumpy or hard stools occurring with <math>\geq 25\%</math> of defecations</li> <li>• Sensation of anorectal obstruction or blockage occurring with <math>\geq 25\%</math> of defecations</li> <li>• Sensation of incomplete evacuation occurring with <math>\geq 25\%</math> of defecations</li> <li>• Manual manipulation to allow for stool passage with <math>\geq 25\%</math> of defecations</li> </ul> </li> <li>2. Absence of loose stools without laxatives.</li> <li>3. Inadequate criteria to diagnose constipation-predominant irritable bowel syndrome.</li> </ol>	<p>Symptoms must be present for <math>\geq 3</math> months with symptom onset at least 6 months prior to diagnosis: Recurrent abdominal pain or discomfort occurring at least 3 days per month with two or more of the following:</p> <ol style="list-style-type: none"> <li>1. Improvement with defecation</li> <li>2. Onset associated with change in stool frequency</li> <li>3. Onset associated with change in stool form or appearance</li> </ol> <p>At least 25% of stools should be considered hard or lumpy to diagnose constipation predominance.</p>

Adapted from Longstreth GL, et al. Functional bowel disorders. *Gastroenterol* 2006;130:1480–1491, with permission, Rome Foundation.

## 2. What is the difference between primary and secondary constipation?

Secondary constipation is caused by other conditions, including metabolic, endocrine, and neurologic disorders (Table 46-2). Secondary causes should be considered before diagnosing a patient with primary constipation.

**Table 46-2.** Causes of Secondary Constipation

CATEGORY	EXAMPLES
Medications	Analgesics (especially opioids), anticholinergics, antidiarrheals, loop and thiazide diuretics, antihistamines, antidepressants, antipsychotics, anticonvulsants, antacids (containing calcium or aluminum), calcium-channel blockers, iron supplements
Structural	Colorectal neoplasm, stricture, external compression, rectal prolapse, rectocele
Metabolic	Hypercalcemia, hypokalemia, hypomagnesemia, chronic kidney disease, dehydration

Continued on following page

**Table 46-2.** Causes of Secondary Constipation (*Continued*)

CATEGORY	EXAMPLES
Endocrine	Diabetes mellitus, hypothyroidism, hyperparathyroidism, panhypopituitarism, pregnancy, pheochromocytoma
Neurogenic	Stroke, spinal cord injury, Parkinson's disease, multiple sclerosis, dementia, autonomic neuropathy, Hirschsprung's disease, colonic pseudoobstruction
Myopathic	Scleroderma, myotonic dystrophy, amyloidosis
Other	Depression, anorexia, physical inactivity

**3. Identify the prevalence and impact of constipation.**

North American studies estimate that 2% to 27% of the population experience constipation. This wide range is likely a result of the heterogeneity of the definition, and most accounts report a 12% to 19% prevalence. Constipation poses a significant economic burden, through both direct health care and indirect (e.g., work loss) costs. Additionally, patients with the symptom report decreased quality of life and increased psychiatric disorders, such as depression and anxiety.

**4. Which populations are at increased risk for experiencing constipation?**

Risk factors for constipation are listed in Table 46-3.

**Table 46-3.** Risk Factors for Constipation

Demographic	Advanced age Female gender Low socioeconomic status Low income or education Nonwhite ethnicity
Lifestyle	Dehydration Immobility Travel Low fiber diet (controversial)
Medical	Recent abdominal or pelvic surgery Critical illness Malnutrition Polypharmacy

**5. What are potential causes of acute constipation?**

Patients who present with acute constipation should be evaluated for such causes as mechanical bowel obstruction, small bowel ileus, and colonic pseudoobstruction.

**6. What are the subtypes of primary constipation?**

Primary constipation can be subdivided into normal-transit constipation, slow-transit constipation, defecatory disorders, and IBS-C. It is important to note, however, that significant overlap of subtypes exists.

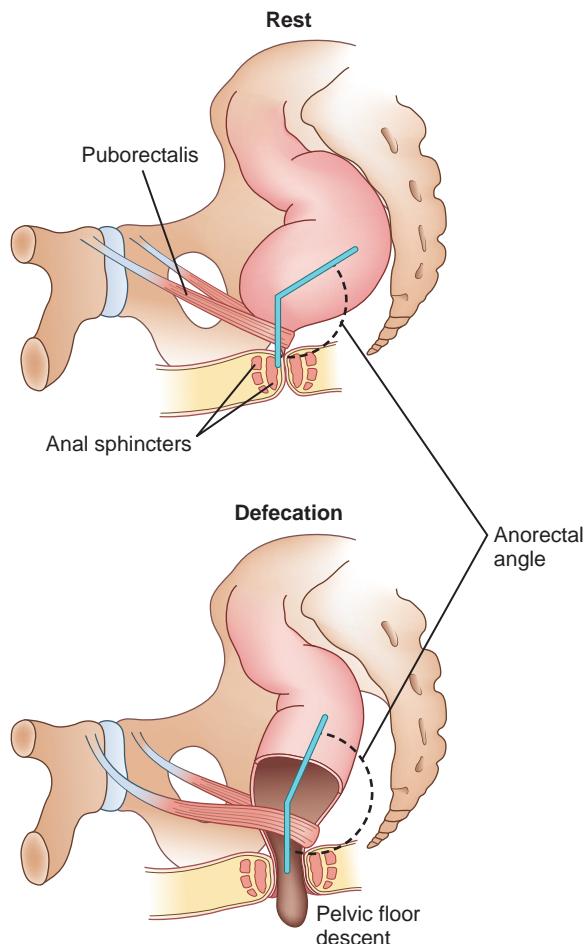
**7. Describe normal colonic motility.**

Neural control of the colon is mediated by the autonomic and enteric nervous systems as well as the interstitial cells of Cajal, which function as pacemaker cells. Motor disturbances can be caused by dysfunction of the nerves, the smooth muscle, or any of the chemical signals between them. Contractions in the colon can be nonpropagated, segmental bursts, or can be propagated throughout the colon. Propagated contractions of high amplitude are responsible for mass movements that generally occur upon awakening and after meals. The term *gastrocolic reflex* refers to the postprandial increase in colonic motor activity. Average colonic transit time is approximately 36 hours.

**8. Describe the normal mechanisms of defecation.**

The major muscles involved in defecation are the puborectalis muscle and the internal and external anal sphincters (Figure 46-1). Resting tone is provided primarily by the internal anal sphincter (approximately 80%). The puborectalis maintains tonic contraction at rest. When stool is present in the rectal vault, the internal anal sphincter relaxes via a reflex known as the rectoanal inhibitory reflex (RAIR), and the external anal sphincter

contracts under voluntary mechanisms mediated by the pudendal nerve. During the process of defecation the puborectalis relaxes, facilitating a straightening of the rectoanal angle and subsequent pelvic floor descent. With voluntary relaxation of the external anal sphincter, often in addition to increased abdominal pressure, stool is allowed to pass.



**Figure 46-1.** At rest the puborectalis muscle acts as a sling that provides tonic anterior traction on the rectum. This creates the anorectal angle (between 80 and 110 degrees) that inhibits spontaneous, involuntary passage of stool. During the act of defecation the puborectalis, the pelvic floor and the external anal sphincter muscles relax. In a synchronous fashion, the anorectal angle straightens about 15 degrees, the perineum descend 1.0 to 3.5 cm and the external sphincter relaxes resulting in passage of stool.

### 9. What is pelvic floor dyssynergia?

*Pelvic floor dyssynergia* refers to a defecatory disorder in which there is inadequate relaxation or paradoxical contraction of the anorectal muscles while attempting to pass a bowel movement. In two thirds of cases it appears to be an acquired disorder that can arise from a number of causes, including excessive straining, pregnancy, and psychological stress. Patients with dyssynergic defecation may also have delayed transit. It is important to investigate any form of defecatory dysfunction prior to assessing colonic transit.

### 10. What is a rectocele?

A rectocele is an anterior bulge of the rectum caused by a weakening of the fascial wall that separates the rectum and the vagina. Presence of a rectocele, enterocele, or excessive perineal descent may lead to symptoms of obstructive defecation.

### 11. What questions are important to ask a patient with constipation?

A thorough history should reveal the onset and duration of symptoms, stool frequency and consistency, presence of the urge to defecate, feelings of incomplete evacuation, and the need for straining or manual maneuvers for disimpaction. Ask about other gastrointestinal (GI) complaints, such as nausea and vomiting, abdominal or rectal pain, dysphagia, blood in the stool, and weight loss. A thorough review of systems is

needed to evaluate for potential secondary causes of constipation. The patient's medications, including over-the-counter medications and dietary supplements, should be reviewed. In an appropriate setting and with a plan to support the patient, soliciting a history of abuse may also be important.

## 12. What is the Bristol Stool Form Scale?

The Bristol Stool Form Scale is a validated method of assessing stool consistency in patients with constipation (Figure 46-2). Patients are asked to rate the quality of their stool according to the chart's depictions. The Bristol Stool Form Scale has been shown to correlate with stool transit time in constipated patients and is a key component of the defecation history.

Type 1		Separate, hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces, entirely liquid

**Figure 46-2.** Bristol stool form scale. (From Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol* 1997;32:920–924.)

## 13. What important physical examination characteristics should be assessed in patients with constipation?

A thorough systemic examination, including abdominal and neurologic examinations, should be performed to help rule out secondary causes of constipation. The perineal and digital rectal examinations should be detailed, as described in Table 46-4.

**Table 46-4.** Components of a Detailed Perineal and Digital Rectal Examination

Perineal	<p>Inspection</p> <ul style="list-style-type: none"> <li>• Scars, fistulae, ulcerations, trauma, abscesses, skin tags, external hemorrhoids</li> </ul> <p>Dynamic observation (view at rest and with bearing down)</p> <ul style="list-style-type: none"> <li>• Perineal descent</li> </ul> <p>Sensation</p> <ul style="list-style-type: none"> <li>• Anocutaneous reflex</li> </ul>
Digital rectal examination	<p>Pain assessment</p> <ul style="list-style-type: none"> <li>• Presence of ulcerations, fissures, pelvic floor muscle spasm</li> </ul> <p>Sphincter tone (at rest and with squeeze and bearing down)</p> <ul style="list-style-type: none"> <li>• Weakness, paradoxical contraction, rectal prolapse</li> </ul> <p>Palpation of rectal vault (at rest and with squeeze and bearing down)</p> <ul style="list-style-type: none"> <li>• Fecal impaction, hemorrhoids, rectocele, mass, anal stricture, perineal descent</li> </ul>

**14. Which laboratory studies should be checked in a patient with constipation?**

Constipation alone does not require specific laboratory testing. In fact in the absence of alarm signs and symptoms, it is recommended to proceed with treatment. Alarm features include new onset or sudden change in bowel habits, GI bleeding, weight loss, anemia, obstructive symptoms, or family history of colorectal cancer. When high suspicion exists for a secondary cause of constipation, laboratory studies should be targeted toward the suspected disorders.

**15. Which patients with constipation should get a colonoscopy?**

Colonoscopy should be reserved for patients with alarm features present. Colonoscopic cancer screening should always be considered as a separate issue.

**16. What is anorectal manometry (ARM), and how is it used?**

ARM is a test that measures the pressures and coordination of the pelvic floor muscles that control defecation. During the procedure, a probe with a balloon attached is inserted into the patient's rectum. The patient is then asked to squeeze, as if trying to hold in a bowel movement, and then bear down, as if attempting to defecate. Graded inflation of the attached balloon helps assess rectal sensation as well as the RAIR. ARM helps to assess pelvic floor dyssynergia and is now considered a first-line test for patients with constipation refractory to medications.

**17. What is balloon expulsion testing?**

Balloon expulsion testing is commonly performed alongside ARM and involves inflating a balloon in the rectum with 50 mL of water or using a special device and then asking the patient to mimic defecation into a commode. Delay in expelling the balloon has been shown to be highly specific for dyssynergia.

**18. What important finding might be seen on ARM in a patient with Hirschsprung's disease?**

Patients with Hirschprung's disease lack the RAIR. This important reflex allows relaxation of the internal anal sphincter with the presence of stool in the rectal vault. Although an uncommon finding, Hirschprung's is an important diagnosis as treatment is primarily surgical.

**19. What other tests might be performed in a patient with constipation?**

Testing used for constipation is detailed in Table 46-5.

**Table 46-5. Testing Used in the Evaluation of Constipation**

STUDY	PURPOSE AND USES
Anorectal manometry	Assesses internal and external anal sphincter pressures at rest and with squeeze. Evaluates for patterns of dyssynergic defecation. Evaluates for presence of rectoanal inhibitory reflex. Assesses rectal sensation and compliance. Is first-line testing for refractory constipation.
Balloon expulsion testing	Assesses time required to expel a 50-mL balloon from the rectum. Highly specific for identifying dyssynergic defecation, but normal values do not exclude it. Often used in conjunction with anorectal manometry.
Abdominal radiograph	Most useful in the acute setting to evaluate for ileus or obstruction.
Colonic transit (Sitzmarks) study	Assesses colonic transit delay through the use of ingested radioopaque markers. Is the most common study used to assess colonic transit.
Wireless motility capsule	Assesses colonic transit through use of an ingested pill capsule that measures temperature, pH, and pressures of its surroundings. Also provides transit assessment of stomach and small bowel to help evaluate for global motility disorders.
Colonic scintigraphy	Assesses colonic transit delay through the use of ingested radiolabeled material.
Standard or MR defecography	Provides dynamic evaluation of the pelvic floor during defecation using either barium and fluoroscopy or MRI. Evaluates for structural abnormalities, including rectocele and rectal prolapse, as well as pelvic floor dysfunction. In assessment of pelvic floor dysfunction, often used when previous testing is conflicting or inconclusive.
Colonic manometry and barostat testing	Assesses colonic motor activity. Assesses colonic sensation and tone. Evaluates for colonic neuropathy and myopathy. Only performed at highly specialized centers.

**20. Describe some dietary and lifestyle modifications that patients with constipation can adopt to improve their symptoms.**

Patients with mild constipation may benefit from increasing dietary fiber and fluid intake. Additionally, they should be encouraged to allow sufficient time for a bowel movement. Though increased activity is encouraged, there is little evidence to support its recommendation in the treatment of constipation.

**21. What is the appropriate use of fiber supplementation?**

Patients should be taught to increase their fiber intake to 25 to 35 g daily. This increase should be gradual, however, to avoid bloating and flatulence. Additionally, patients should maintain adequate hydration throughout the day. The exceptions to a high-fiber diet recommendation are patients who have true colonic inertia and those who have terminal reservoir syndrome or problems with megarectum and impaction. These patients may benefit from a low-residue diet.

**22. Describe potential pharmacologic treatments for constipation.**

Multiple pharmacologic therapies are available and are detailed in Table 46-6.

**Table 46-6.** Medications Currently Used for the Management of Constipation

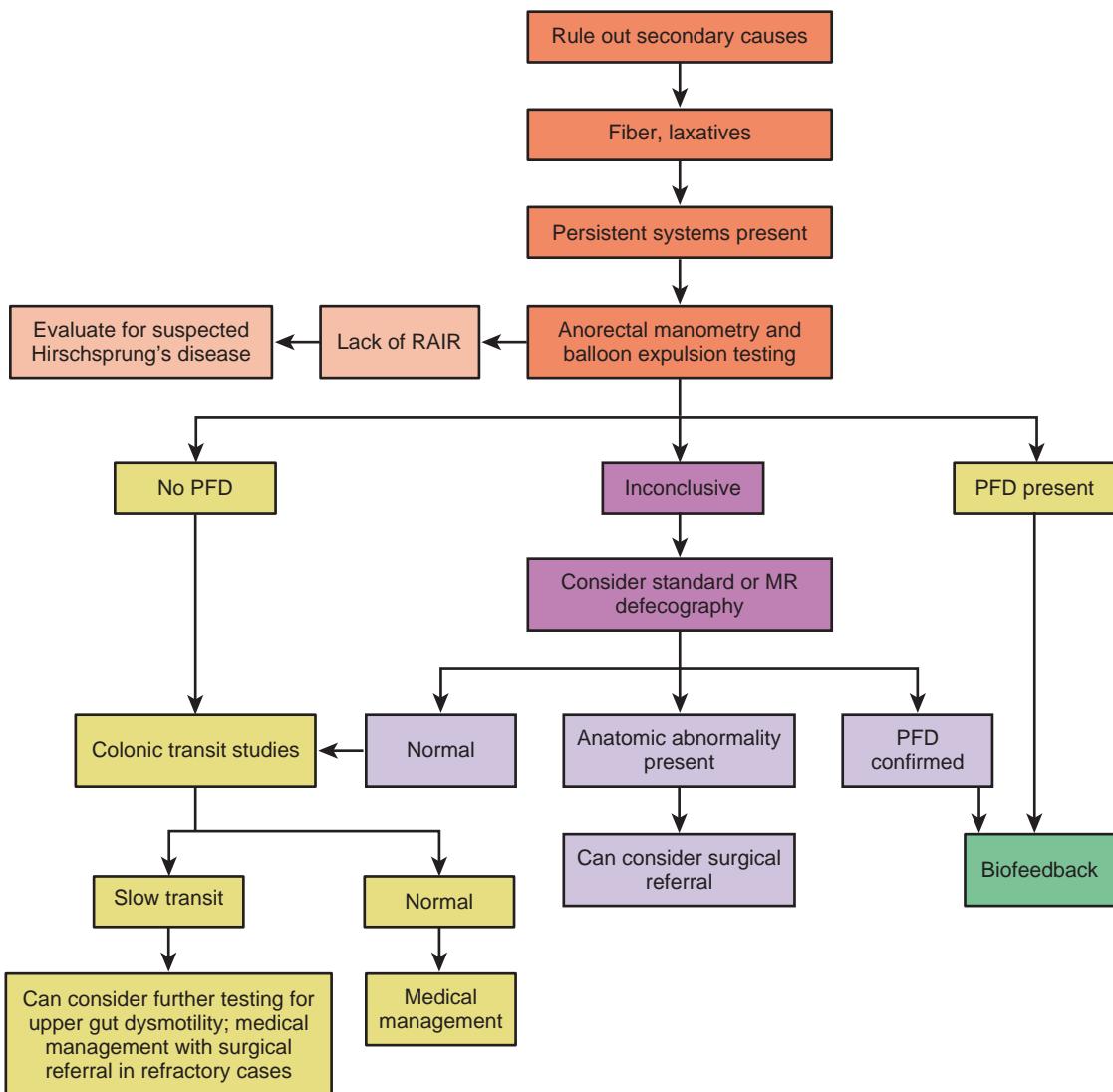
CATEGORY	EXAMPLES	MECHANISMS OF ACTION
Bulk-forming laxatives, dietary fiber	Psyllium, methylcellulose, wheat bran, calcium polycarbophil	Increase stool weight; accelerate transit.
Osmotic laxatives	PEG 3350, lactulose, sorbitol, magnesium hydroxide	Increase fluid into the bowel lumen; magnesium also decreases colonic transit time.
Stool softeners	Docusate sodium	Affects surface qualities, allowing water to interact with the stool more.
Stimulant laxatives	Bisacodyl, glycerin, senna, cascara	Stimulate nerve endings to promote intestinal contractions; may have an inhibitory effect on water absorption; glycerin provides local stimulation of the rectum to promote defecation.
Emollients	Mineral oil	Lubricate stool.
Enemas	Tap water, phosphate, soap suds, mineral oil	Lavage and distend the colon; induce evacuation.
Probiotics	<i>Bifidobacterium</i> , <i>Lactobacillus</i>	May help alter intestinal flora; some studies suggest enhanced colonic transit.
Secretagogues	Lubiprostone, linaclotide	Stimulate intestinal chloride channels to promote fluid secretion and enhanced motility.
Serotonin receptor agonists	Prucalopride	Increase colonic motility by selective stimulation of 5-HT4 receptors (not approved in the United States).
Opioid receptor antagonists	Methylnaltrexone, alvimopan	Block effects of peripheral opioid receptors without decreasing analgesic properties; only indicated for specific uses.
Ileal bile acid transporter inhibitors	Elobixibat	Block enterohepatic bile acid circulation, thus accelerating transit and softening stool (still investigational).

**23. What nonpharmacologic therapies can be used to treat constipation?**

Biofeedback is a form of behavioral training based on the theory of operant conditioning in which patients are taught how to retrain their anorectal muscles. This treatment is used most often for those with pelvic floor disorders and has shown benefit in up to 70% of patients. Nerve stimulation therapies involving the sacral and posterior tibial nerves have also shown promise in initial studies.

**24. When should referral to a gastroenterologist be considered in a patient with constipation?**

Figure 46-3 depicts an algorithmic approach to the evaluation of constipation in adults. Initial evaluation often occurs at the primary care physician's office. Referral may be warranted in more refractory cases or when specialized studies, such as colonoscopy or ARM, are indicated.



**Figure 46-3.** Diagnostic algorithm for the evaluation of constipation. MR, Magnetic resonance; PFD, pelvic floor disorder; RAIR, rectoanal inhibitory reflex. (Adapted from Bharucha AE, et al. American Gastroenterological Association Medical Position Statement on Constipation. *Gastroenterol* 2013;144(1):211–217.)

## 25. When should surgical referral be considered in a patient with constipation?

Surgical referral is rarely required and should be reserved for patients with refractory symptoms who have already seen a gastroenterologist or those with colonic inertia, Hirschsprung's disease, or anatomic abnormalities.

## 26. What are potential complications of constipation?

Complications can include hemorrhoids, anal fissures, fecal impaction, rectal prolapse, and stercoral ulcers, among others.

## 27. How is fecal incontinence defined?

Fecal incontinence is the recurrent, involuntary leakage or passage of stool or gas from the anorectum.

## 28. What causes fecal incontinence?

Normal functioning requires an intact neuromuscular system and the ability to sense and respond appropriately to impending defecation. Primary central nervous system disorders, such as stroke and multiple sclerosis, can lead to incontinence despite an intact sphincter. Impaired sensation of the anorectum can decrease the ability to feel a full rectum, as can be found in patients with diabetic or pudendal neuropathy. Decreased rectal compliance, sometimes seen in patients with inflammatory bowel disease or radiation proctitis, can lead to incontinence associated with urgency and frequency. Conversely, incontinence can also result from increased rectal compliance with diminished sensation, as in fecal impaction and megarectum. Muscle damage from direct injury to the anal sphincters, such as obstetric

trauma, or in smooth muscle disorders, such as scleroderma, can diminish the high-pressure zone necessary to maintain continence. Cognitive impairment and decreased mobility are often causes in older adult patients. Finally, massive diarrhea can overwhelm the normal continence mechanism.

#### **29. What are the prevalence and effect of fecal incontinence?**

The overall prevalence for adults in the community is approximately 8%, with a range of 2% to 15% across age groups. Epidemiologic studies often describe an increased prevalence in certain subgroup, such as nursing home residents. Early studies described an increased risk in females; however, more recent data suggest that this increase is only found in specific age groups. The often embarrassing nature of this symptom can have a detrimental effect on patients' personal and professional lives.

#### **30. Which populations are at increased risk for suffering from fecal incontinence?**

Increased rates are seen in older adult and institutionalized populations. In addition, fecal incontinence can frequently be seen in patients with neurologic disorders, diabetes mellitus, or decreased mobility. Although not a risk factor as much as an association, patients with urinary incontinence are often also found to have fecal incontinence. Obesity is thought to increase the risk, but this has not been found in all studies. Finally, traumatic deliveries (e.g., episiotomy, forceps) increase risk in women.

#### **31. What questions are important to ask a patient with fecal incontinence?**

Patients with incontinence will not always feel comfortable bringing up their problem, so you must ask them directly if they have ever had involuntary loss of stool. Once this is established, patients should be asked about sensations of urge to defecate, passage of solid or liquid stool, awareness of the episodes, duration and frequency, and presence of tenesmus and nocturnal symptoms. Additional history regarding diarrhea should be obtained. Finally, patients should be asked about urinary or sexual complaints as many of the causes of fecal incontinence can affect the entire pelvic floor. A thorough medical history, including history of diabetes, neurologic disease, prior anorectal trauma or surgery, and a complete obstetric history, should be obtained. Ask specific questions about prior deliveries, including type, use of forceps, length of labor, size of baby, and need for episiotomy. Finally, medications should be reviewed, including over-the-counter medications and dietary supplements, such as sorbitol (an osmotic laxative).

#### **32. What are important physical examination characteristics to look for in patients with fecal incontinence?**

Overall examination should include an assessment of cognitive and other neurologic deficits as well as signs of endocrinopathies and systemic inflammatory conditions. As with constipated patients, a detailed perineal and digital rectal examination should be performed (Table 46-4). Careful attention should be paid to identifying anatomic abnormalities, such as rectal prolapse.

#### **33. Which laboratory studies should be checked in a patient with fecal incontinence?**

There are no laboratory tests that need to be performed routinely in these patients. Causes of diarrhea should be pursued when appropriate.

#### **34. What other tests might be performed in a patient with fecal incontinence?**

Similar to constipation, ARM and standard or magnetic resonance defecography can be used in the evaluation of fecal incontinence (see Table 46-5). In addition, endoscopy can be useful in detecting inflammation or evaluating causes of diarrhea. Endoanal ultrasound is used to identify anatomic defects of the anal sphincters. Needle electromyography can detect denervation or other neurogenic damage. The pudendal nerve terminal motor latency (PNTML) test can assess nerve injury by measuring the time between stimulation of the terminal portion of the nerve and anal sphincter contraction. PNTML should be considered prior to surgery given less favorable surgical outcomes in the setting of neuropathy.

#### **35. Name some pharmacologic treatments for fecal incontinence.**

Fiber supplementation can help bulk stools. The antidiarrheals, loperamide, and atropine and diphenoxylate, slow intestinal transit. Tricyclic antidepressants can lead to the side effect of constipation, so they can be used in incontinence for this effect.

#### **36. What nonpharmacologic therapies can be used to treat fecal incontinence?**

Timed voiding and other behavioral techniques can be helpful. Biofeedback has been shown to be beneficial in approximately 70% of patients with pelvic floor disorders. Injection of bulking agents, such as dextranomer in stabilized hyaluronic acid, is still in its early phases but has shown promising results. Therapy using sacral nerve stimulation (SNS) or percutaneous tibial nerve stimulation may be offered, similar to patients with constipation. In SNS, patients begin with a temporary stimulator, and given positive results, a permanent stimulator can be placed. Studies regarding radiofrequency ablation are based on the premise that thermal lesions created in muscles below the mucosa aid in remodeling and tightening during healing. Outcomes appear conflicting with some promising short- and long-term results, with larger studies and a sham randomized controlled trial needed. Finally, plug devices have been tried, but they are poorly tolerated and study sizes are too small to indicate efficacy.

#### **37. When should surgical referral be used in a patient with fecal incontinence?**

Referral to surgery should be used in refractory patients or in those with anatomic defects, such as an external anal sphincter disruption. Unfortunately, there are few randomized controlled trials comparing the various

surgical techniques to their nonsurgical alternatives, and long-term results can vary. Surgical options available to patients are described in **Table 46-7**.

**Table 46-7.** Surgical Options for the Management of Fecal Incontinence

PROCEDURE	DESCRIPTION AND USES
Sphincteroplasty	Reconstructs the anal sphincter. Used specifically in those with distinct sphincter defects.
Dynamic graciloplasty	Transposes the gracilis muscle around the anal canal along with electrical stimulation of the muscle. Used to enhance sphincter tone.
Artificial anal sphincter	Similar purposes as dynamic graciloplasty, with use of an artificial device.
Anterior levatorplasty	Ligates the two sides of the levator muscle to improve pelvic floor function. Often performed in conjunction with other procedures.
Total and postanal pelvic floor repair	Postanal repair involves plication of several pelvic floor muscles, to improve overall function; rarely performed. Total repair combines postanal repair and anterior levatorplasty.
Rectal augmentation	Creates a side-to-side ileorectal pouch. Increases rectal capacity and compliance.
Fecal diversion	Creates a stoma for severe, debilitating symptoms or recurrent infections in areas of skin breakdown.
Antegrade continence enema	Irrigates the colon with large volume enemas via an ostomy site. Primarily used in children, but can be used in adults with overflow incontinence caused by constipation.

### 38. Describe some particular concerns regarding fecal incontinence in older adults.

Fecal incontinence is common in older adults and can stem from diarrhea or constipation. Fecal impaction with overflow should be ruled out. Cognition plays a role in continence; thus dementia in older patients can be a contributing factor to incontinence. In those with cognitive impairment, therapies that require active participation, such as biofeedback, may be more difficult. In addition limited mobility in some older patients may make incontinence particularly difficult to treat. Finally, management of decubitus ulcers and perineal skin in bedbound patients is essential to avoiding infection.

*The authors would like to acknowledge the contributions of Dr. Christina Tennyson, who was the author of this chapter in the previous edition.*

Please access ExpertConsult to view a **Clinical Vignette** for this chapter.

### BIBLIOGRAPHY

1. Bassotti G, Iantorno G, Fiorella S, et al. Colonic motility in man: features in normal subjects and in patients with chronic idiopathic constipation. *Am J Gastroenterol* 1999;94:1760–70.
2. Bharucha AE. Management of fecal incontinence. *Gastroenterol Hepatol* 2008;4(11):807–17.
3. Bharucha AE, Dorn SD, Lembo A, et al. American Gastroenterological Association medical position statement on constipation. *Gastroenterology* 2013;144(1):211–7.
4. Bharucha AE, Pemberton JH, Locke III GR. American Gastroenterological Association technical review on constipation. *Gastroenterology* 2013;144:218–38.
5. Brown SR, Wadhwani H, Nelson RL. Surgery for faecal incontinence in adults. *Cochrane Database Syst Rev* 2010 Sep 8;(9):CD001757. <http://dx.doi.org/10.1002/14651858.CD001757.pub3>.
6. Chokshi RV. Constipation. In: Gyawali CP, editor. *The Washington manual gastroenterology subspecialty consult*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2012. p. 33–40.
7. Costilla VC, Foxx-Orenstein AE, Mayer AP, et al. Office-based management of fecal incontinence. *Gastroenterol Hepatol* 2013;9(7):423–33.
8. Ditah I, Devaki P, Luma HN, et al. Prevalence, trends, and risk factors for fecal incontinence in US adults, 2005–2010. *Clin Gastroenterol Hepatol* 2013; <http://dx.doi.org/10.1016/j.cgh.2013.07.020>.
9. Higgins PDR, Johanson JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol* 2004;99:750–9.
10. Gras B, Magge S, Bloom A, et al. Motility disorders of the colon and rectum. *Curr Opin Gastroenterol* 2013;29(1):66–71.
11. Lembo A, Camilleri M. Chronic constipation. *N Engl J Med* 2003;349(14):1360–8.
12. National Digestive Diseases Information Clearinghouse (NDDIC). Available at: <http://digestive.niddk.nih.gov> [Accessed September 22, 2014].
13. Rao SS. Advances in diagnostic assessment of fecal incontinence and dyssynergic defecation. *Clin Gastroenterol Hepatol* 2010;8(11):910–9.
14. Rose S. *Constipation: a practical approach to diagnosis and treatment*. New York: Springer; 2014.
15. Whitehead WE, Borrud L, Goode PS, et al. Fecal incontinence in US adults: epidemiology and risk factors. *Gastroenterology* 2009;137(2):512–7.

# DIVERTICULITIS

*Luca Stocchi, MD*

## 1. What is the clinical presentation of colonic diverticulitis?

The typical clinical presentation of acute sigmoid diverticulitis consists of left lower quadrant abdominal pain associated with fever and leukocytosis. Physical examination should reveal tenderness in the left lower quadrant, which can be associated with guarding. The clinical presentation of diverticulitis can also be atypical and sometimes limited to vague abdominal pain.

## 2. What is the range of severity in the clinical presentations of sigmoid diverticulitis?

Sigmoid diverticulitis has a very variable presentation. It can range from mild, uncomplicated disease amenable to outpatient treatment to life-threatening, acute perforation of the sigmoid colon associated with feculent peritonitis requiring urgent surgical treatment.

## 3. What is the differential diagnosis?

The differential diagnosis includes irritable bowel syndrome, inflammatory bowel disease, urologic disease, appendicitis, ischemic colitis, and colonic neoplasm (Table 47-1). A diagnosis of diverticulitis exclusively

**Table 47-1** Diagnostic Approach for Acute Diverticulitis

<b>HISTORY AND PHYSICAL EXAMINATION</b>		
<ul style="list-style-type: none"> <li>Left lower quadrant tenderness and unremitting abdominal pain</li> <li>Fever</li> <li>Leukocytosis</li> </ul>		
<b>Differential diagnosis</b>		
ELDERLY PATIENTS	MIDDLE-AGED AND YOUNG PATIENTS	OTHER
Ischemia Carcinoma Volvulus Obstruction Proctosigmoiditis Penetrating ulcer Nephrolithiasis/urosepsis	Appendicitis Salpingitis Inflammatory Bowel Disease Penetrating ulcer Urosepsis	Amebiasis Collagen vascular disease Infectious colitis Post irradiation Prostatitis IBS
<b>QUALIFIERS</b>		
Extremes of age (more virulent) Asian ancestry (right-sided symptoms) Immunosuppression drugs and chronic renal failure (abdominal exam insensitive)		
<b>EVALUATIONS</b>		
Plain x-rays	Good initial first step. May show ileus, obstruction, mass effect, ischemia, perforation	
CT scan	Very helpful in staging the degree of complications and evaluating for other diseases. Should be considered in all cases of suspected diverticulitis.	
Ultrasound	Can be a safe and helpful noninvasive test to evaluate acute diverticulitis. Over 20% of exams are suboptimal because of intestinal gas; highly operator-dependent.	
Contrast Enema	Generally no longer used as routine diagnostic test. However, it can be useful in selected cases of stricture, fistula and perforating disease when other investigations are unclear.	
Endoscopy	A full colonoscopy during an attack of acute diverticulitis is generally contraindicated. However, a cautious flexible sigmoidoscopy with minimal air insufflation may be useful when the diagnosis is in doubt (rectal bleeding, anemia) to exclude ischemic bowel, Crohn's disease, carcinoma, and other possibilities.	

Adapted from Freeman SR, McNally PR:Diverticulitis. Med Clin North Am 77:1152, 1993

based on signs and symptoms is often inaccurate and requires confirmation by computed tomography (CT) scan of the abdomen and pelvis. A full colonoscopy should be performed 6 to 8 weeks after resolution of the episode.

#### 4. What are the imaging modalities used to diagnose diverticulitis?

The cornerstone of imaging for sigmoid diverticulitis is CT scan. Other tests can be useful in individual cases to corroborate the diagnosis (see [Table 47-1](#)).

#### 5. How is sigmoid diverticulitis classified?

The most widely known surgical classification of sigmoid diverticulitis remains perhaps the Hinchey classification ([Table 47-2](#)). Hinchey III and Hinchey IV indicate diffuse peritonitis, which is associated with significant morbidity and approximately 20% mortality. It is important to point out that the Hinchey classification was originally established on the basis of intraoperative findings and is therefore not completely applicable to cases of sigmoid diverticulitis not requiring, which are the majority.

**Table 47-2** Hinchey classification of sigmoid diverticulitis

	HINCHHEY CLASSIFICATION
Stage I	Pericolic abscess confined by the mesentery of the colon
Stage II	Pelvic abscess resulting from a local perforation of a pericolic abscess
Stage III	Generalized peritonitis resulting from rupture of pericolic/pelvic abscess into the general peritoneal cavity
Stage IV	Fecal peritonitis results from the free perforation of a diverticulum

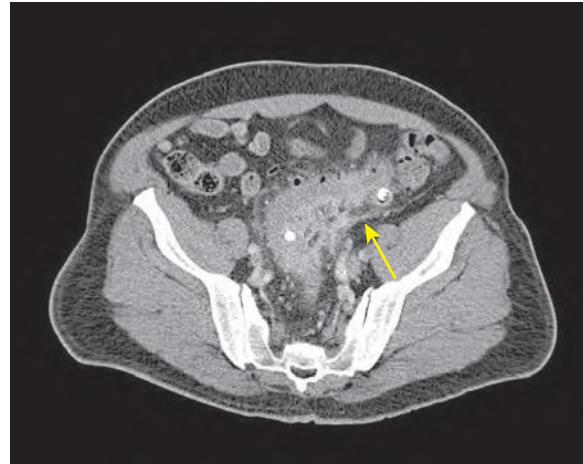
#### 6. What is the Ambrosetti classification and why is it important?

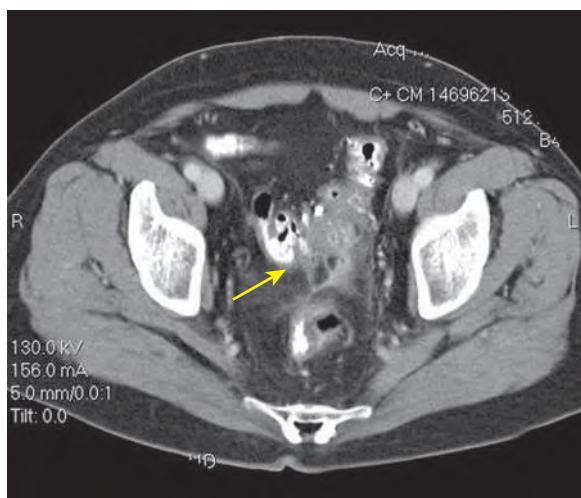
The Ambrosetti classification is based on CT criteria that can predict diverticulitis severity. Severe diverticulitis by Ambrosetti criteria is associated with a risk of subsequent surgery exceeding 50%. ([Table 47-3](#), [Figure 47-1](#), and [Figure 47-2](#)).

**Table 47-3** Ambrosetti Classification of sigmoid diverticulitis

MODERATE DIVERTICULITIS	SEVERE DIVERTICULITIS
Localized sigmoid wall thickening (>5mm) Inflammation of pericolic fat	Moderate diverticulitis associated with one of the following: Abscess Extraluminal air Extraluminal contrast

**Figure 47-1.** Computed tomography scan demonstrating Ambrosetti mild sigmoid diverticulitis. Large arrow demonstrates sigmoid diverticulitis with colonic thickening and straining. (From Stocchi L. Current indications and role of surgery in the management of sigmoid diverticulitis. *World J Gastroenterol* 2010;16:804–817.)





**Figure 47-2.** Computed tomography scan demonstrating Ambrosetti severe sigmoid diverticulitis. Arrow points to a focus of contrast extravasation and a small amount of extraluminal air. (Reproduced with permission from Stocchi L. Current indications and role of surgery in the management of sigmoid diverticulitis. World J Gastroenterol 2010 Feb 21;16 (7):804–817.)

## 7. How should uncomplicated diverticulitis be managed?

The mainstay of treatment is broad-spectrum antibiotics. In patients without severe symptoms or significant comorbidities, an outpatient treatment is reasonable. On the other hand, patients with more severe symptoms, older age, comorbidities, concerns about compliance, or concurrent immunosuppression should be preferentially admitted to the hospital.

## 8. What are the antibiotic treatment options for outpatient management of sigmoid diverticulitis?

Possible treatment options include broad-spectrum penicillin, a combination of either fluoroquinolone, cephalosporin or trimethoprim-sulfamethoxazole with metronidazole, and clindamycin (Table 47-4). The duration of treatment is generally 10 to 14 days.

**Table 47-4** Antibiotic options in the treatment of sigmoid diverticulitis

OUTPATIENT ANTIBIOTIC TREATMENT OPTIONS	INPATIENT ANTIBIOTIC TREATMENT OPTIONS
Fluoroquinolone + Anti-Anaerobic agent Ciprofloxacin 500 mg PO q 12 hrs <b>plus</b> Metronidazole 500 mg PO q 6-8 hrs	Fluoroquinolone + Anti-Anaerobic agent Ciprofloxacin 400 mg IV q 12 hrs or levofloxacin 500 mg IV + metronidazole 500 mg IV q 6 or q 8 hrs
Penicillins Amoxicilline-clavulanate 875/125mg PO q 12 hrs	Penicillins Ampicillin-sulbacam 3 g IV q 6 hrs Piperillin-tazobactam 3.375 g IV q 6 hrs
Cephalosporins Cephalexin 500 mg PO q 12 hrs <b>plus</b> metronidazole 500 mg PO q 6-8 hrs	Cephalosporins Ceftriaxone 1 gm IV q 12 hrs
Others Trimetoprim-sulfamethoxazole 800/160 mg PO q 6 hrs + metronidazole 500 mg PO q 6-8 hrs Clindamycin 450 mg PO q 6 hrs	Carbapenems Imipenem-cilastatin 500 mg IV q 6 hrs Meropenem 1 g IV q 8 hrs Ertapenem 1 g IV q 12 hours

## 9. How should an inpatient be managed?

Orders for patients admitted for acute sigmoid diverticulitis should include nothing by mouth and rehydration with intravenous fluids, while also receiving intravenous antibiotics. In this respect, possible agents include broad-spectrum penicillins or cephalosporins. A combination of a fluoroquinolone and metronidazole is a widely used alternative, particularly in patients allergic to penicillin. Rarely used but acceptable alternatives, especially in the critically ill patient, include carbapenems (see Table 47-4).

**10. What is the natural history of diverticulitis following the first attack of uncomplicated disease?**

The vast majority of hospitalized patients experience improvement of their condition during the first 48 hours following admission. However, approximately 10% to 15% exhibit clinical deterioration requiring surgery during the same hospital stay. Serial clinical examinations and monitoring of the laboratory values are critical to promptly identify patients unresponsive to medical management. Once the patient recovers from the first uncomplicated disease attack managed conservatively, up to one third of patients may experience recurrent diverticulitis after 10 years.

**11. Are there particular dietary recommendations in patients who experience an attack of sigmoid diverticulitis?**

Although there is not good objective evidence to support dietary changes, most recommend institution of a high-fiber diet. Neither seeds nor nuts have been shown to be harmful in patients with prior diverticulitis.

**12. Can diverticulitis be treated with antiinflammatory agents?**

It has been suggested that at least some cases of diverticulitis are actually the manifestation of a particular subtype of inflammatory bowel disorder and could benefit from treatment with antiinflammatory agents (mesalamine).

**13. What are the current indications for surgery in uncomplicated sigmoid diverticulitis, and have they evolved over time?**

Each case should be individualized. Recurrent severe attacks of diverticulitis occurring in short intervals should be considered for surgery. Mild attacks of recurrent diverticulitis occurring in long intervals may be managed expectantly and not require surgical intervention after the second episode.

**14. Are there unusual locations of colonic diverticulitis?**

Diverticulitis can occur in the descending colon instead of the sigmoid. In this case it is important to plan for a formal left colectomy rather than sigmoidectomy. Diverticulitis of the transverse colon is rare. On the other hand, diverticulitis of the cecum or right colon is more common and has a clinical presentation similar to acute appendicitis. CT scan is usually helpful in clarifying the diagnosis. The prevalence of right-sided diverticulitis is increased in Asian countries. Regardless of its specific location, uncomplicated colonic diverticulitis should be initially treated with antibiotics. The indications for surgery are similar to those of sigmoid diverticulitis.

**15. What are the risk factors implicated in disease recurrence after a diverticulitis attack?**

- Greater than 5 cm of colon involvement
- Retroperitoneal abscess
- Severe Ambrosetti classification
- Family history of diverticulitis
- Young age at onset

**16. What are the most important complications of sigmoid diverticulitis?**

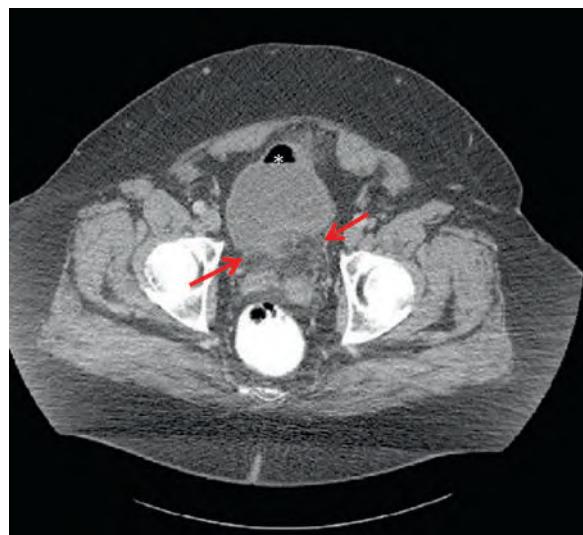
Stricture, fistula, abscess, and peritonitis are the most important complications of sigmoid diverticulitis. It is generally accepted that bleeding is not associated with an acute colonic inflammation. Phlegmon has been mentioned as an example of complicated diverticulitis but remains a somewhat arbitrary definition. Although a stricture can require surgery because of acute large bowel obstruction, surgery can also be indicated in the absence of obstructive symptoms when malignancy cannot be safely ruled out as the cause of a sigmoid stricture (Figure 47-3). More rarely, the sigmoid inflammation can extend into the retroperitoneum and cause ureteral obstruction, most commonly on the left side.



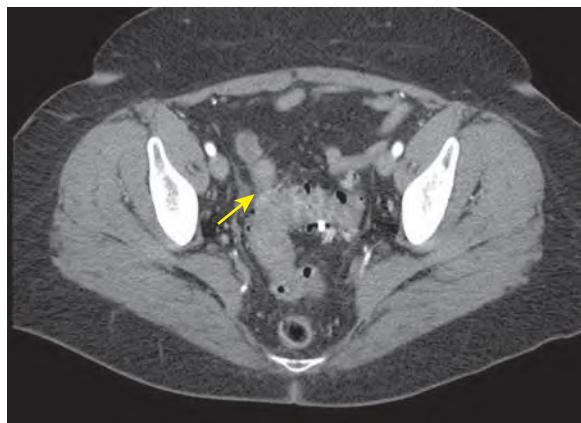
**Figure 47-3.** Sigmoid stricture. Computed tomography scan demonstrating a sigmoid stricture (arrow).

**17. Which are the target organs of complicated fistulizing sigmoid diverticulitis?**

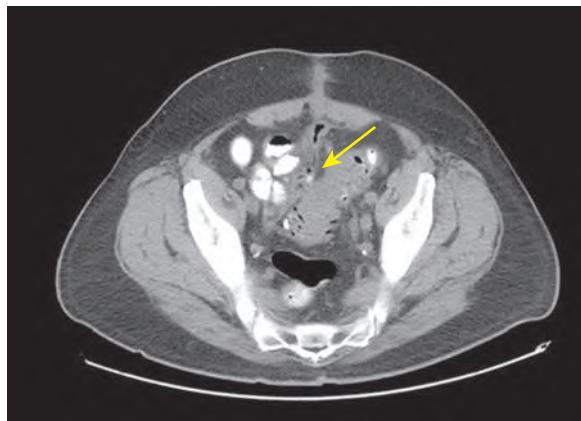
All the organs surrounding the sigmoid colon can become a fistulizing target: bladder (Figure 47-4), vagina, small bowel (Figure 47-5), uterus, and skin (Figure 47-6). Prior hysterectomy increases the risk for diverticulitis-related colovaginal fistula.



**Figure 47-4.** Computed tomography scan demonstrating colovesical fistula. Note the air in the bladder (\*) and colovesicular inflammation (arrows).



**Figure 47-5.** Computed tomography scan demonstrating a coloenteric fistula (arrow).



**Figure 47-6.** Colo-cutaneous fistula (Courtesy Ravi Pokala Kiran, MD.)

## 18. What are the general management principles of complicated diverticulitis?

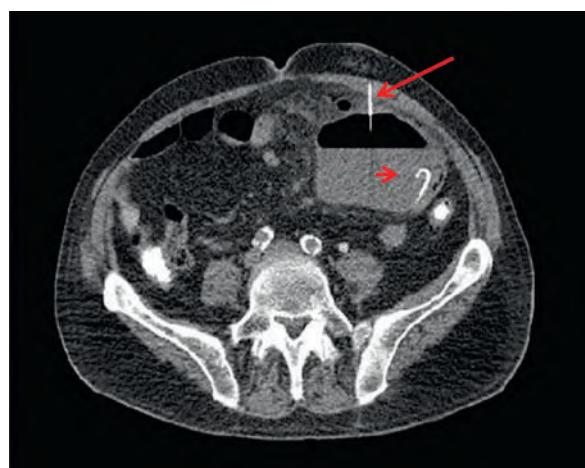
The cornerstone in the management of complicated diverticulitis remains surgery, unless the patient has prohibitive comorbidities. In most cases, patients with complicated disease should be initially treated conservatively and discharged, after which elective surgery should be planned.

However, complicated diverticulitis causing acute large bowel obstruction or diffuse peritonitis should be treated with immediate surgery.

## 19. What is the management of diverticular abscess?

A diverticular abscess should be initially approached with percutaneous drainage when technically possible (Figure 47-7), generally via CT guidance, followed by elective sigmoid resection. Abscesses with a diameter smaller than 3 cm are difficult to percutaneously drain and are typically treated with antibiotics alone. Evolving areas of study are assessing the role of both antibiotics and percutaneous drainage alone in the treatment of select cases of diverticular abscess, without further elective surgery. At this time such approaches cannot be considered standards of care.

**Figure 47-7.** Computed tomography scan demonstrating percutaneous catheter (arrows) drainage of diverticular abscess.



## 20. What are the management options in the patients with peritonitis caused by perforated diverticulitis?

Patients with diffuse fecal peritonitis (Hinchey IV) are frequently managed with resection of the sigmoid and creation of an end-descending colostomy associated with rectal stump, an operation referred to as a *Hartmann procedure*. When the level of peritoneal contamination is less severe, such as in the case of purulent diffuse peritonitis, it is generally preferable to perform a restorative sigmoid resection associated with colorectal anastomosis and proximal stoma diversion, usually by means of a diverting loop ileostomy. The creation of a diverting ileostomy is associated with a much greater probability of having the stoma eventually taken down. On the other hand, a colostomy created during a Hartmann procedure becomes permanent in approximately one third of patients, usually because of patient comorbidities.

## 21. Are there alternative surgical options in the management of purulent peritonitis?

A more recent addition to the armamentarium of treatment options in diffuse purulent peritonitis and some cases of ruptured abdominopelvic abscesses is laparoscopic intraperitoneal lavage, with or without laparoscopic suture closure of the perforation site and abdominal drainage. Further study is needed to fully appreciate the potential of this approach.

## 22. What is the elective surgical management of sigmoid diverticulitis?

Surgical treatment of sigmoid diverticulitis consists of resection of the entire sigmoid colon with colorectal anastomosis. Laparoscopic surgery is associated with faster postoperative recovery and according to some studies reduced postoperative morbidity and hospital costs.

## 23. Should patients younger than 40 years have an operation after their first episode of uncomplicated sigmoid diverticulitis?

There is a body of literature suggesting that younger patients have more severe disease at the time of their initial presentation, both clinically and at CT imaging, which is also associated with an increased risk of recurrence. However, there is no definitive indication that the traditional nonoperative approach is associated with adverse events in this patient population. At this time there is therefore insufficient evidence to recommend surgery after the first diverticulitis episode in younger individuals.

#### **24. Should immunocompromised patients be treated differently?**

There is evidence indicating that immunocompromised patients tend to suffer disease recurrence characterized by increased virulence, including the risk of perforating disease causing peritonitis. It is therefore recommended that patients receiving immunosuppressive medications, including steroids, undergo elective surgery after one attack of uncomplicated disease. Other patient subgroups who can benefit from elective surgery after the first attack of uncomplicated disease include individuals with chronic renal failure and with collagen-vascular disease.

#### **25. What is the recurrence rate after surgery?**

The reported recurrence rate after surgery ranges between 3% and 13% and should be less than 5% if surgery is performed appropriately. In this regard, the most critical factor associated with recurrent diverticulitis after surgery is an incomplete removal of the sigmoid.

#### **BIBLIOGRAPHY**

1. Ambrosetti P, Gervaz P, Fossung-Wiblishauser A. Sigmoid diverticulitis in 2011: Many questions; few answers. *Colorectal Dis* 2012;14(8):e439–46.
2. Afshar S, Kurer MA. Laparoscopic peritoneal lavage for perforated sigmoid diverticulitis. *Colorectal Dis* 2012;14(2):135–42.
3. Chapman J, Davies M, Wolff B, et al. Complicated diverticulitis: is it time to rethink the rules? *Ann Surg* 2005;242(4):576–81.
4. Constantinides VA, Heriot A, Remzi F, et al. Operative strategies for diverticular peritonitis: a decision analysis between primary resection and anastomosis versus Hartmann's procedures. *Ann Surg* 2007;245(1):94–103.
5. Freeman HJ. Segmental colitis associated with diverticulosis syndrome. *World J Gastroenterol* 2008;14(42):6442–3.
6. Hall JF, Roberts PL, Ricciardi R, et al. Long-term follow-up after an initial episode of diverticulitis: what are the predictors of recurrence? *Dis Colon Rectum* 2011;54(3):283–8.
7. Klarenbeek BR, Samuels M, van der Wal MA, et al. Indications for elective sigmoid resection in diverticular disease. *Ann Surg* 2010;251(4):670–4.
8. Reshef A, Stocchi L, Kiran RP, et al. Case-matched comparison of perioperative outcomes after surgical treatment of sigmoid diverticulitis in solid organ transplant recipients versus immunocompetent patients. *Colorectal Dis* 2012;14(12):1546–52.
9. Salem L, Flum DR. Primary anastomosis or Hartmann's procedure for patients with diverticular peritonitis? A systematic review. *Dis Colon Rectum* 2004;47(11):1953–64.
10. Stocchi L. Current indications and role of surgery in the management of sigmoid diverticulitis. *World J Gastroenterol* 2010;16(7):804–17.
11. Boynton W, Floch M. New strategies for the management of diverticular disease: insights for the clinician. *Therap Adv Gastroenterol* 2013;6(3):205–13.

#### **Websites**

- Rafferty J, Shellito P, Hyman NH, Buie WD. Practice parameters for sigmoid diverticulitis. *Dis Col Rectum* 2006;49:939–944. Accessed September 22, 2014, from [http://www.facsrs.org/files/pp\\_sigmoid.pdf](http://www.facsrs.org/files/pp_sigmoid.pdf).
- Society of Surgery of the Alimentary Tract. SSAT patient care guidelines: Surgical treatment of diverticulitis. Accessed September 22, 2014, from <http://www.ssat.com/cgi-bin/divert.cgi>.
- The Association of Coloproctology of Great Britain and Ireland (ACPGBI). Accessed September 22, 2014, from <http://www.acpgbi.org.uk>.

# DISEASES OF THE APPENDIX

Kevin Rothchild, MD, and Jonathan A. Schoen, MD

## 1. Describe the anatomy of the appendix. Does it have a function in humans?

The vermiform appendix (from Latin, *vermiform* or wormlike, and *appendere*, to hang upon) is usually 6 to 9 cm in length, arising from the convergence of the three taenia coli at the base of the cecum. It is now considered an immunologic organ that participates actively in the secretion of immunoglobulins (Ig), particularly IgA. Some theorize that the appendix may also act as a “safe house” for normal intestinal flora following periods of acute infection.

## 2. What is the presumed cause of appendicitis in adults or children?

Intestinal concretions around fecal matter, or fecoliths (in adults) or hypertrophied lymphoid tissue causing obstruction of the lumen (in children), are the dominant etiologic factors. Fecaliths are found in approximately 90% of cases of gangrenous, ruptured appendicitis. The luminal obstruction causes distention of the appendix from both continued mucosal secretion and local bacterial overgrowth. Ultimately, venous pressure is exceeded and areas of wall infarction with bacterial invasion occur.

## 3. What are the signs and symptoms of appendicitis?

Acute appendiceal distention initially stimulates visceral afferent pain fibers, producing vague, dull, diffuse pain in the midabdomen (periumbilical) or lower epigastrium. Low-grade fever, anorexia, nausea, and vomiting may occur after the onset of pain. The inflammatory process soon involves the serosa of the appendix and, in turn, the parietal peritoneum, producing the characteristic shift in pain to the right lower quadrant.

## 4. What are the laboratory findings?

Mild leukocytosis (10,000 to 18,000/mm<sup>3</sup>) is usually present with early, uncomplicated appendicitis. C-reactive protein is elevated as well, with a sensitivity of 93% and a specificity of 80%.

## 5. Where and what is McBurney's point?

Charles McBurney was an American surgeon born in 1845. He presented his treatise on the area of greatest abdominal pain during appendicitis in 1899. His point of maximal tenderness is located over an area at the distal two-thirds along an axis drawn from the umbilicus to the anterior superior iliac spine.

## 6. What are the psoas and obturator signs?

The *psoas* sign is irritation of the retroperitoneal psoas muscle (pain on right hip extension). The *obturator* sign refers to internal obturator muscle (pain on internal rotation of the flexed right hip) by an inflamed retrocecal appendix.

## 7. What is the Rovsing sign?

Palpation of the left lower quadrant leads commonly to right lower quadrant pain in acute appendicitis.

## 8. The peak incidence of acute appendicitis occurs in what age group?

The peak incidence occurs in ages 15 to 19 years.

## 9. The risk of perforation of the appendix is highest in what age groups?

Although the overall incidence is not as common as in the teen years, appendiceal perforation is higher in children (younger than 5 years) and older adults (i.e., those who have difficulty seeking out immediate medical attention). In some series, perforation rates approach 75%. Those with diabetes and immunosuppressed patients are also at overall higher risk for complications.

## 10. What is the surgical mortality rate for nonperforated appendicitis and for perforated appendicitis?

The mortality rate is less than 0.1% for nonperforated and as high as 3% for perforated appendicitis. In older adults, the mortality rate for perforated appendicitis can be as high as 15%.

**11. List the differential diagnosis for right lower quadrant pain both in women and in children.**

The list is considerably longer for women than for men. It includes ectopic pregnancy, tubo-ovarian abscess, pelvic inflammatory disease (PID), Mittelschmerz, ovarian torsion, incarcerated hernia, Crohn's stricture or abscess, diverticulitis, Meckel's diverticulitis, carcinoid tumor, infectious colitis, cholecystitis, and peptic ulcer disease. Valentino's sign is pain secondary to gastric or biliary fluid collecting in the right lower quadrant from perforated duodenal ulcer. In children, gastroenteritis, mesenteric adenitis, and terminal ileitis can be difficult to differentiate from appendicitis.

**12. What is a Meckel's diverticulum?**

A Meckel's diverticulum is a congenital omphalomesenteric mucosal remnant. Derived from pluripotent tissues, it may contain ectopic gastric or, less commonly, pancreatic mucosa. Located on the antimesenteric side of the ileum, it generally adheres to the rule of 2s: it is found in 2% of the population, within 2 feet of the ileocecal valve, and 2% will develop symptoms. Initially described in 1699, it was later named by Johann Freidrich Meckel in 1809.

**13. What is an acceptable incidence rate for negative appendectomy? Has this rate changed with the increasing use of ultrasound and computed tomography (CT) scanning?**

A negative exploration rate of 10% to 15% had been a long-standing standard of surgical care. In contrast to some earlier large-scale epidemiologic studies showing no difference in negative appendectomy rates (NAR) with the widespread use of preoperative CT, most recent single-institution studies have found improvements, with NARs approaching less than 2%.

**14. What other conditions may mimic acute appendicitis?**

Although numerous abdominal processes may have similar presentations, acute diverticulitis of either a redundant (i.e., right sided) sigmoid colon or the cecum itself may present with right lower quadrant pain, fever, and leukocytosis. Typhlitis, or neutropenic enterocolitis, is a condition most commonly seen in immunocompromised patients undergoing chemotherapy and involves a breakdown of the mucosal barrier and necrosis of the intestinal wall, most commonly at the cecum. Mesenteric lymphadenitis is a self-limiting inflammatory process involving the lymph nodes of the ileocecal region and is often exhibited in a population younger than 15 years.

**15. What features of PID can help distinguish it from appendicitis?**

High fever, cervical motion tenderness (chandelier sign), cervical discharge, pain related to menses, and tendency for bilateral pain can often differentiate PID from appendicitis.

**16. What is the most common tumor of the appendix? Describe its management.**

Carcinoid is the most common tumor of the appendix, and the appendix is the most common site of carcinoid tumors. Most large series report an incidence of 0.2 to 0.3 in appendectomy specimens. Simple appendectomy is appropriate for distal tumors that are less than 1 cm in size. If the tumor is greater than 2 cm or has extension into the mesoappendix or base of the cecum, formal right hemicolectomy is indicated. For tumors between 1 and 2 cm that do not involve the base of the appendix, factors such as lymphovascular invasion and mitotic activity influence management decisions and should be referred to a tertiary care center.

It is important to note that not all carcinoid tumors are malignant. The most common malignant tumor is mucinous adenocarcinoma, composing more than 60% of all appendiceal malignancies.

A mucocele is the second most commonly encountered tumor of the appendix, in which a distended appendix is secondary to obstruction of the appendiceal orifice by mucoid material. Cysts smaller than 2 cm are almost always benign, whereas larger tumors may harbor malignancy. Rupture of these cysts may spread epithelial cells in mucoid fluid throughout the peritoneum, or pseudomyxoma peritonei of appendiceal origin.

**17. What is the proper treatment for late or perforated appendicitis that presents as a phlegmon or abscess?**

Radiology-guided drainage (usually CT guided) is indicated in the presence of an established abscess, provided that the patient has no evidence of diffuse peritonitis or uncontrolled sepsis. Although delayed (after 6 to 8 weeks) appendectomy is not always required, rates of recurrent appendicitis can approach 20%, so many surgeons prefer to operate in an elective setting.

**18. What is the most common complication after appendectomy?**

Wound infection is the most common surgical complication after appendectomy. In the setting of perforation or abscess, the wound edges can be left open as a delayed primary closure to prevent this complication. The laparoscopic approach has reduced this complication significantly, although intraabdominal abscess rates remain unchanged.

**19. In what patient population is ultrasound particularly helpful in making the diagnosis of acute appendicitis?**

Ultrasound can be particularly helpful in the pediatric as well as pregnant patients, in whom CT scan is usually avoided. In addition, it is helpful to delineate any gynecologic abnormalities. A noncompressible, distended

(larger than 8 mm), painful tubular structure on ultrasound predicts appendicitis, with reported sensitivity of 84% to 94% and specificity of 92%.

#### **20. What is the Alvarado score and is it useful in diagnosis?**

Developed more than 20 years ago, the Alvarado score has found more widespread usage in the past decade. It is a 10-point risk stratification system with points based on findings such as anorexia and right lower quadrant pain, as well as laboratory studies like leukocytosis and left shift of white blood cells (WBCs) (see online calculator at <http://www.mdcalc.com/alvarado-score-for-acute-appendicitis>). Accessed September 22, 2014.) Although scores of 7 to 10 predict a 93% appendicitis rate, it tends to over-predict the rates of appendicitis in women and has shown some inconsistencies in children. Its best use may be in ruling out appendicitis in those with low scores (less than 4).

#### **21. When is laparoscopic appendectomy appropriate?**

Laparoscopic appendectomy was first reported in 1983, and its use has increased steadily since. Although a bias may exist toward the use of laparoscopy with less advanced appendicitis, mortality and length of stay are similar or improved. Cosmesis, postoperative pain, and wound infection rates are also improved. Although initial studies in the 1990s expressed concern about increased intraabdominal abscess formation, more recent data has shown no differences. In the ever-rising obese population, laparoscopy has shown decreased rates of morbidity overall compared with the open technique.

#### **22. During an abdominal exploration for right lower quadrant pain, is removal of a normal appendix appropriate in patients with Crohn's disease?**

Yes. If the base of the appendix and the surrounding area of the cecum are free of disease, an appendectomy should still be performed in the setting of Crohn's disease. If an enterocutaneous fistula develops postoperatively, it almost always results from diseased terminal ileum rather than the appendiceal stump.

#### **23. Is an appendectomy during pregnancy a safe procedure? Is laparoscopic appendectomy safe?**

Acute appendicitis is the most frequently encountered extrauterine disease requiring surgery during pregnancy. The appendix shifts superiorly above the right iliac crest by the fourth month of pregnancy. Abdominal tenderness is less localized because the inflamed appendix is no longer near the parietal peritoneum. These factors, along with the leukocytosis of pregnancy as well as the limited use of CT, can make the clinical diagnosis more difficult. Fetal loss increases from 5% in simple appendicitis to 28% if there is perforation; therefore early intervention is the rule if appendicitis is suspected.

Laparoscopic appendectomy has been extensively used during pregnancy. Although prospective trials are lacking, it is generally accepted as safe during all trimesters; however, there is some controversy regarding possible increased risk of fetal loss or preterm labor (up to 9% with both open and laparoscopic techniques).

Lowering the pressure of pneumoperitoneum to 10 to 12 mm Hg, using a left-side tilt to decrease pressure from the gravid uterus on the vena cava and an open Hassan entry technique are widely accepted options to decrease operative risk.

#### **24. If an ovarian tumor is discovered during laparoscopic or open exploration, what steps should be taken?**

The normal appendix should be removed after obtaining peritoneal washings, which are studied for tumor cytologic findings. The ovarian mass itself should not be touched or biopsied. Ovarian cancer is staged with a strictly performed technique and should be done at a later procedure.

#### **25. Does nonoperative therapy have any role in treating acute appendicitis?**

Treating appendicitis with antibiotics alone is not common practice in North America. European studies have shown some success, but they have documented high recurrence rates (up to 40%) and high costs of delivery. "Interval" appendectomy is more often seen after resolution of contained abscess or inflammation by antibiotics (with or without catheter drainage) in patients after perforation.

#### **26. What is "stump appendicitis"?**

Stump appendicitis is a rare but increasingly recognized entity in which patients who have had their appendix removed develop delayed (days to years following surgery) right lower quadrant pain and leukocytosis similar to their initial presentation. The entity relates to a small portion of appendiceal lumen left in place during surgery. A recent metaanalysis did not show differences in occurrence rates between laparoscopic and open procedures. A high index of suspicion is often needed to make the diagnosis, and treatment ranges from antibiotic therapy to surgical excision.

#### **27. What is a Mitrofanoff procedure?**

A Mitrofanoff appendicovesicostomy is a procedure performed to obviate the need for urethral catheterization in those with neurogenic bladder (such as patients with spina bifida). The appendix is removed from its attachments to the cecum while maintaining its blood supply; then one end is sutured to the urinary bladder and the other end is sutured to the skin to form a stoma, usually near the umbilicus.

**BIBLIOGRAPHY**

1. Affleck DG, Handrahan DL, Egger MJ, et al. The laparoscopic management of appendicitis and cholelithiasis in pregnancy. *Am J Surg* 1999;178:523–9.
2. Bollinger RR, Barbas AS, Bush EL, et al. Biofilms in the large bowel suggest an apparent function of the human vermiform appendix. *J Theor Biol* 2007;8:32.
3. Carr NJ. The pathology of acute appendicitis. *Ann Diagn Pathol* 2007;4:46–58.
4. Collins DC. 71,000 human appendix specimens: a final report summarizing 40 years of study. *Am J Proctol* 1963;14:365–81.
5. Flum D, Morris A. Misdiagnosis of appendicitis and the use of diagnostic imaging. *J Am Coll Surg* 2005;6:933–9.
6. Leff DR. Inflammation of the residual appendix stump: a systematic review. *Colorectal Dis* 2010;14:282–93.
7. Martin JP, Connor PD, Charles K. Meckel's diverticulum. *Am Fam Physician* 2000;61:1037–42.
8. McBurney C. Experience with early operative interference in cases of disease of the vermiform appendix. *N Y Med J* 1889;50:676–84.
9. McCusker M, Cote TR, et al. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973–1998. *Cancer* 2002;94:3307.
10. Mingin, Baskin LS. Surgical management of the neurogenic bladder and bowel. *Int Braz J Urol* 2003;29:53–61.
11. Ohle R, et al. The Alvarado Score for predicting acute appendicitis: a systematic review. *BMC Med* 2011;5:139.
12. Raja AS, Wright C. Negative appendectomy rate in the era of CT: an 18-year perspective. *Radiology* 2010;256:460–5.
13. Shankar S, Sardi A. Neoplasms of the appendix, current treatment guidelines. *Hematol Oncol Clin North Am* 2012;26:1261–90.
14. Temple LK, Litwin DE, McLeod RS. A meta-analysis of laparoscopic versus open appendectomy in patients suspected of having acute appendicitis. *Can J Surg* 1999;42:377–83.
15. Wilarsrusmee C, Sukrat B, et al. Systematic review and meta-analysis of safety of laparoscopic vs open appendicectomy for suspected appendicitis in pregnancy. *Br J Surg* 2012;99:1470–9.

# COLITIS: PSEUDOMEMBRANOUS, MICROSCOPIC, AND RADIATION

Stephen M. Vindigni, MD, MPH, Jill M. Watanabe, MD, MPH, and Christina M. Surawicz, MD

## PSEUDOMEMBRANOUS COLITIS

### 1. What is *Clostridium difficile*?

First isolated in 1935 and named for its difficult isolation from the feces of infants, *Bacillus difficile* is an anaerobic, gram-positive, spore-forming, toxin-producing bacteria spread by the fecal-oral route. By the 1970s, this bacillus was renamed *Clostridium difficile* and its toxins were implicated as a major cause of diarrhea and as the cause of pseudomembranous colitis (PMC). *C. difficile* infection (CDI) has historically been precipitated by the use of broad-spectrum antibiotics that disrupt the normal intestinal microbiome that allows for the overgrowth of *C. difficile*. There is an increasing prevalence of sporadic and community-acquired cases occurring in healthy hosts without prior antibiotic exposure. Although some healthy adults are asymptomatic carriers, patients with CDI can experience a spectrum of symptoms, ranging from a self-limited course of diarrhea to PMC. Severe cases of CDI can cause ileus and toxic megacolon, necessitating surgery, intensive care unit (ICU) admission, and can result in death.

### 2. How is CDI defined?

Although 20% to 30% of persons who take antibiotics develop diarrhea, only 10% to 20% of these cases are caused by *C. difficile*. CDI has been defined as three or more unformed or watery stools for 1 to 2 days with associated *C. difficile* toxin detection in stool or by culturing the toxicigenic *C. difficile*.

### 3. What causes PMC?

PMC is due to overgrowth of *C. difficile*, which causes disease by production of two toxins, A and B. *C. difficile* strains that do not produce toxins are not pathogenic. Toxins A and B cause mucosal damage and inflammation of the colon by disrupting the actin cytoskeleton of the intestinal epithelial cells while triggering an inflammatory cascade. The inflammatory exudate seen in the colon is called a *pseudomembrane*, like that seen in diphtheria infection. Although it is a sign of severe CDI, pseudomembranes can also sometimes be seen with ischemic colitis.

### 4. What are the risk factors for CDI?

The common risk factors for CDI include antibiotic exposure (usually within the prior 2 months), recent hospitalization (especially surgical patients, ICU patients, and posttransplant patients), age older than 65, comorbidities, and immunosuppression. Other risk factors include invasive procedures (with higher risk for gastrointestinal [GI] procedures), renal failure, chemotherapy, and residence in long-term care facilities. There are also reports of severe CDI in previously low-risk populations such as pregnant women. Newer risk factors include the presence of inflammatory bowel disease and taking a daily proton pump inhibitor (PPI). Hospital settings remain an important reservoir, in part, because the spores of the anaerobic bacillus, *C. difficile*, can survive for up to 5 months. As many as 20% to 30% of hospitalized patients are colonized with *C. difficile* and two thirds of these infected hospitalized patients have historically been asymptomatic carriers.

### 5. Which antibiotics are most commonly implicated?

Clindamycin and cephalosporins (especially third generation) have been most commonly associated with CDI in the past, followed by expanded-spectrum penicillins. More recently, fluoroquinolones have been implicated as a significant risk factor. Of note, CDI can occur with any antibiotic, even single-dose preoperative antibiotics.

### 6. Why do some people develop *C. difficile* diarrhea and others are simply colonized?

Up to 15% of healthy adults are carriers of *C. difficile* without symptoms; in newborns and healthy infants, the carriage rate is as high as 84%. Studies of patients with *C. difficile* colonization have shown that serum levels of immunoglobulin (Ig) G antibody against toxin A have been associated with protection from disease expression and prevention of recurrences.

### 7. How have the epidemiologic characteristics of CDI changed?

Since the early 2000s, the morbidity and mortality of CDI has been increasing with epidemics reported in the United States, Canada, Europe, and Japan. The U.S. Centers for Disease Control and Prevention has reported an increase in hospital billing attributed to CDI; there were 82,000 reported cases of CDI in 1996, 178,000 reported cases in 2003, and 250,000 reported case in 2005. A 2008 study showed a CDI prevalence rate of 13.1 per 1000 inpatients. There is also evidence to suggest the severity of CDI is increasing with more frequent hospitalizations, colectomies, and mortality. *C. difficile*-related mortality by listing on death certificates in the

United States rose from 5.7 deaths per million in 1999 to 23.7 deaths per million in 2004. On review of U.S. data through 2007, CDI was the most common cause of gastroenteritis-associated death (18.7 per million). In addition to this CDI epidemic, cases are now being reported among lower-risk patients in the community.

#### **8. What accounts for the changing epidemiologic characteristics of CDI?**

The changing epidemiologic findings of CDI has been attributed, in part, to the evolution of a hypervirulent strain, designated *BI/NAP1/027* (restriction-endonuclease analysis group BI, North American Pulsed Field type 1, polymerase chain reaction ribotype 027). This strain has a gene deletion, which accounts for increased toxin production. With the emergence of this strain, cases have been more severe. Coupled with this increased toxin production, the strain has resistance to fluoroquinolones and clindamycin. Other hypervirulent strains have been identified.

#### **9. What possible factors mediate the severity of CDI?**

The fluoroquinolone-resistant *BI/NAP1/027* strains have been associated with higher concentrations of both toxin A and B *in vitro*. The *BI/NAP1/027* strain also carries two genes of interest. The first gene, *tcdC*, has an 18-base pair deletion; this mutation renders the *tcdC* gene ineffective in inhibiting the production of toxins A and B, which may explain its pathogenicity. The second gene encodes a *C. difficile* binary toxin (CDT) similar to the iota toxin found in *Clostridium perfringens*, but it is not known if it contributes to pathogenicity. Additionally, immunocompromised patients often have more severe disease. Another consideration is the effect of CDI in the disruption of gut microbiota. The intestinal microbiome makes up a complex, interdependent ecosystem responsible for food digestion, immune system activation, vitamin production, and protection from invasive nonindigenous bacteria, which is known as *colonization resistance*. Alteration of this microbiome likely contributes to patients' symptoms.

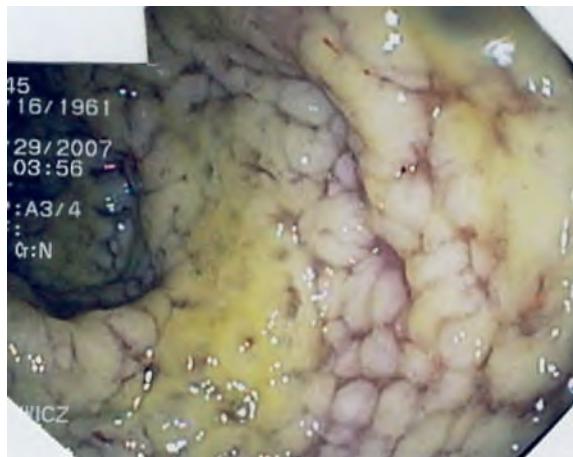
#### **10. How is the diagnosis of CDI made?**

The diagnosis of CDI has become increasingly more rapid as newer testing modalities have become available ([Table 49-1](#)). Nucleic acid amplification tests, such as polymerase chain reaction (PCR) for *C. difficile* toxin genes are now superior to previously used enzyme immunoassay (EIA) tests. While EIA tests are overall specific, they should not be stand-alone tests. Glutamate dehydrogenase (GDH) testing checks for GDH, a

**Table 49-1.** Available Tests for the Diagnosis of CDI

TEST	SENSITIVITY	SPECIFICITY	COMMENTS
PCR	High	High	Very specific and sensitive. Quick, but more expensive. Repeat PCR within 7 days is low yield.
GDH	High	Low	Good screening test. If negative, no further testing required. If positive, requires confirmatory test for toxin, often with PCR.
Tissue cytotoxin B assay	High	High	Gold standard for laboratory reference testing (detects up to 10 pg toxin), but expensive and rarely used clinically. Requires technical expertise. Results not ready for 24-48 hours.
Toxin A enzyme immunoassay	Moderate	Moderate	Prior to PCR, this was the most widely used test. Quick and inexpensive. Will miss toxin A-/B+ strains.
Toxin A and B enzyme immunoassay	Moderate	High	Detects toxin A-/B+ strains. Toxin B is more potent than toxin A and can cause disease in the absence of toxin A.
Stool culture	Moderate	Moderate	Carriers test positive. Results unavailable for 72 hours. Does not distinguish nonpathogenic vs. pathogenic strains, so not useful diagnostically. Toxigenic stool culture useful in evaluation of epidemics and as a laboratory reference test.
Endoscopy	Low	Moderate	Low sensitivity, but the presence of pseudomembranes strongly suggest <i>C. difficile</i> , can also be seen with ischemia.

GDH, Glutamate dehydrogenase; PCR, polymerase chain reaction.



**Figure 49-1.** Endoscopic findings of confluent pseudomembranes in the colon of a patient with pseudomembranous colitis. (Reprinted from Knight CL, Surawicz CM. *Clostridium difficile infection*. Med Clin N Am 2013;97:523–536, with permission from Elsevier.)

*Clostridium* antigen, but it is not specific to *C. difficile*; therefore this test can be used as a screen, but a positive test requires further confirmation of *C. difficile* toxin presence, usually with PCR. Because *C. difficile* carriage is increased in patients on antibiotics, only stools from patients with diarrhea should be tested for *C. difficile*. Repeat testing should be discouraged as a negative test is positive less than 5% of the time on testing of a second stool. Additionally, because diagnostic tests may stay positive for up to a month, a test of cure is generally not advised. Of note, regardless of testing modality, if the patient presents with severe illness and concern for CDI is high, empiric antibiotic therapy should be initiated.

#### 11. What are the typical findings on colonoscopy?

Colonoscopy may be normal or show nonspecific colitis. With severe disease, the colon mucosa has creamy white-yellow plaques (pseudomembranes) (Figure 49-1). Histologic studies show that the pseudomembrane usually arises from a point of superficial ulceration, accompanied by acute and chronic inflammation of the lamina propria. The pseudomembrane is composed of fibrin, mucin, debris of sloughed mucosal epithelial cells, and polymorphonuclear cells.

#### 12. What are the hallmarks of severe CDI?

Severe CDI is defined as hypoalbuminemia (<3 g/dL), abdominal distention or tenderness and/or leukocytosis (>15,000). There are several scoring systems aimed at assessing the clinical severity of CDI cases, although none have been very useful in daily practice beyond recognizing the previously discussed factors, which often correlate with severity.

#### 13. What are the hallmarks of severe and complicated CDI?

Patients with severe and complicated CDI are critically ill. Clinical features can include fever, severe leukocytosis or leukopenia (often with white blood cells >35,000 or <2000), hypoalbuminemia, and abdominal distension. Patients may be in shock with hypotension and an elevated serum lactate of more than 2.2 mmol/L. Inflammatory markers, such as C-reactive protein may be elevated. Ileus may also be present. Severe colitis can result in toxic megacolon and progress to colonic perforation and death with multiorgan failure. These patients should be treated with high-dose oral vancomycin and intravenous (IV) metronidazole. Urgent surgical consultation is indicated.

#### 14. When is treatment indicated? What antibiotics are used?

Implicated antibiotics should be discontinued, if possible. Clinical suspicion should prompt empiric treatment in patients with severe illness while awaiting test results. Three drugs are used for therapy: metronidazole, vancomycin, and fidaxomicin. Metronidazole has been first line in the past because of its low cost and the concern that oral vancomycin use might promote emergence of vancomycin-resistant enterococci in hospitalized patients. Historically, the efficacy of metronidazole has been equal to that of vancomycin; however, reports of metronidazole treatment failures rates have been increasing to as high as 22% to 38% during the past several years. In severe cases of CDI, the use of oral vancomycin is recommended because of its faster efficacy and higher cure rates (97% vs. 76%). Typical treatment courses are 10 to 14 days. The Food and Drug Administration (FDA) has also approved fidaxomicin, a poorly absorbed antibiotic, for treatment of mild to moderate CDI. Although similar in efficacy to vancomycin, it is more expensive. More severe cases often require additional treatment with IV metronidazole, as well as vancomycin enemas. Patients with severe and complicated disease who do not respond to maximal medical therapy may require surgical consultation with

surgical options that include total colectomy or loop ileostomy with colon lavage of vancomycin postoperatively. For a summary of CDI treatments, see [Table 49-2](#).

**Table 49-2.** Treatment Options for *Clostridium difficile* Infection

CDI	DRUG AND DOSE	COMMENT
Mild-moderate	Metronidazole 500 mg PO tid × 10 days	Inexpensive; avoid in pregnancy and with breast feeding. Switch to vancomycin if no response to metronidazole in 72 hours.
Severe	Vancomycin 125 mg PO qid × 10 days	Can increase to 250 mg qid if poor response.
Complicated	Metronidazole 500 mg IV tid and Vancomycin 500 mg PO qid +/– Vancomycin enemas, 500 mg qid	Patients with ileus, recent abdominal surgery, unable to take PO. Patients who can tolerate PO should receive +/– vancomycin enemas, 500 mg qid enteral feeding, if possible.
Recurrent	Repeat metronidazole or vancomycin pulse regimen	Consider FMT after 3 recurrences

FMT, Fecal microbiota transplantation; IV, intravenous; PO, by mouth; *qid*, four times daily; *tid*, three times daily.

#### 15. When should you expect a response to treatment?

Response to treatment usually occurs within 3 to 5 days. Do not use antidiarrheals because the number of stools must be monitored to determine response to treatment. There is no evidence to support laboratory testing for cure; therefore this should not be done. Both toxin A and B EIA may remain positive for as long as 30 days, including in patients with resolution of symptoms; false positives may further complicate patient care.

#### 16. What other treatment options are under development and investigation?

Other antibiotics and treatments have been tried, but not proven to be successful by randomized controlled trials and are not FDA approved for treatment of CDI. These include tigecycline, nitazoxanide, and IV Ig. Some case reports show benefit of rifaximin as an adjuvant to vancomycin, but this is not an FDA-approved treatment. Fecal microbiota transplant, or the infusion of stool from a healthy donor to a recipient with CDI, is not an established treatment in initial cases of CDI, but has shown benefit in recurrent CDI.

#### 17. What is recurrent CDI and how is it treated?

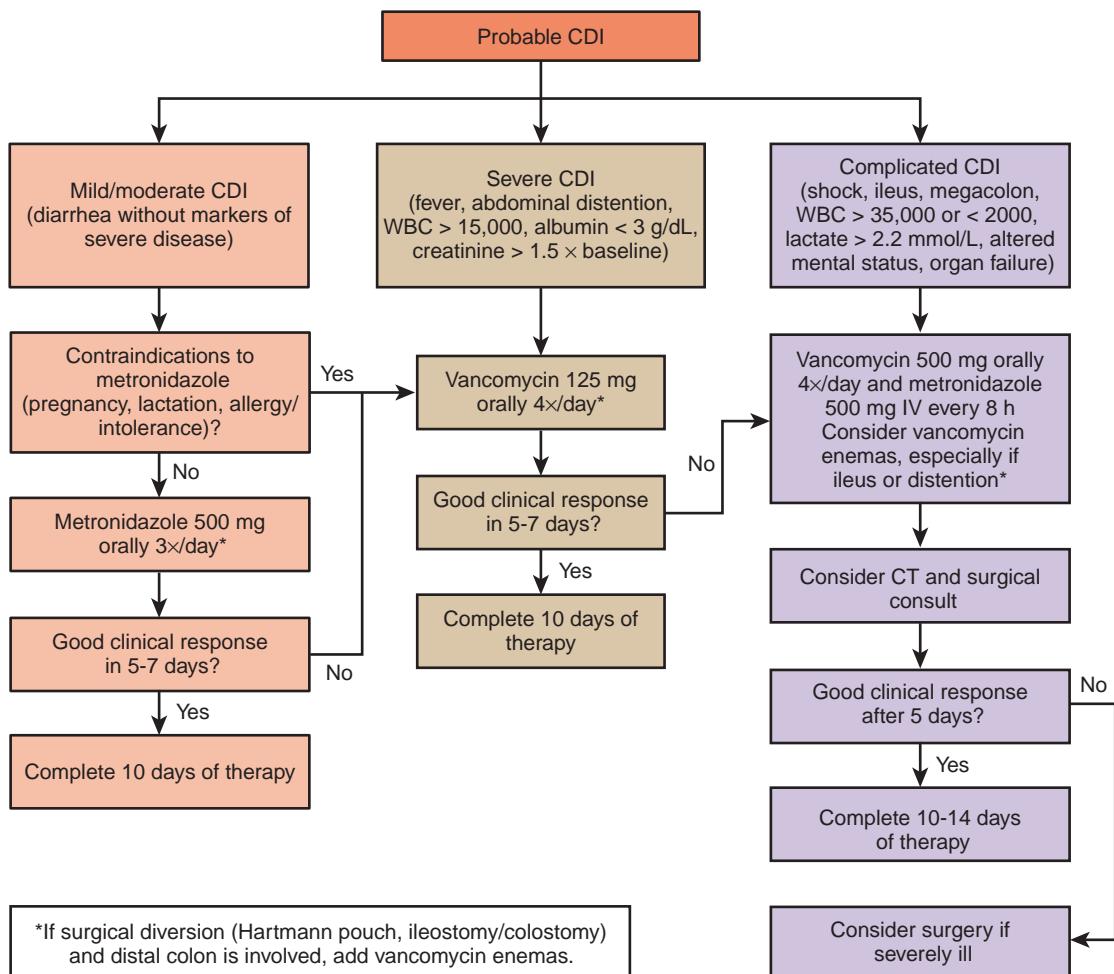
Despite therapy, approximately 10% to 20% of patients have CDI recurrence, possibly because of persistent spores despite initial elimination of the *C. difficile* bacteria. Initially, the same treatments should be tried with metronidazole or vancomycin at standard doses. Some patients benefit from a pulsed regimen of vancomycin, such as 125 mg by mouth four times a day for 10 days, then 125 mg every day every 3 days for 10 doses. Additionally, research on monoclonal antibodies directed against toxins A and B has shown promising results.

#### 18. What is the role of fecal microbiota transplantation (FMT) for recurrent CDI?

Although the goal of CDI has been focused on eradication of the pathogen with antibiotic treatment, the goal of FMT is to reestablish the diverse normal microbiome within the large intestine. Studies have shown CDI patients have decreased microbiome diversity with less Bacteroidetes and Firmicutes bacteria compared to normal hosts. Instead, recurrent CDI patients have high levels of Proteobacteria and Verrucomicrobia. These findings support the hypothesis that CDI results from altered intestinal microbiota, which FMT aims to restore. FMT repopulates bacteria relatively quickly, and the effect persists. FMT is viewed as a success if the patient does not have a CDI recurrence within 8 weeks. Multiple studies and systematic reviews have described high levels of success with FMT, with response rates of up to 98%.

#### 19. How can we control *C. difficile* epidemics in hospitals?

CDI is a leading cause of hospital-associated GI illness with significant cost to the health care system estimated at \$3.2 billion annually. Prevention of CDI involves the judicious use of antibiotics as well as vigilant environmental control. Once diagnosed, patients with CDI should be isolated in rooms with personal bathrooms until their diarrhea resolves. Contact enteric precautions should be initiated; *C. difficile* spores have been cultured from patient bathrooms, bedpans, stethoscopes, and blood pressure cuffs. Once patients depart from their isolation rooms, these rooms should be cleansed with a 10% bleach solution. *Clostridia* spores are not vulnerable to alcohol; therefore handwashing with soap and water and use of disposable equipment helps to prevent the transmission of *C. difficile* in health care settings. Additionally, there is ongoing research to determine potential *C. difficile* vaccines ([E-Figure 49-2](#)).



**E-Figure 49-2.** Treatment algorithm for *Clostridium difficile* infection based on disease severity. CDI, *Clostridium difficile* infection; CT, computed tomography; IV, intravenous; WBC, white blood cells. (Adapted from Knight CL, Surawicz CM. *Clostridium difficile* infection. *Med Clin N Am* 2013;97:523–536.)

## MICROSCOPIC COLITIS

### 20. What is microscopic colitis (MC)?

MC is a clinical syndrome characterized by chronic, nonbloody, watery diarrhea with grossly normal-appearing colonic mucosa, but abnormal histologic features. The first case was reported in 1976 when a woman with chronic diarrhea and a normal endoscopic GI evaluation was found to have an abnormal colorectal biopsy with a thickened subepithelial collagen band and a slight increase in lymphocytes in the lamina propria. This entity was thus named collagenous colitis (CC). Subsequent reports identified similar findings in other patients with chronic diarrhea but without the thickened collagen band. This clinical entity was named lymphocytic colitis (LC). Since the first case reports, MC has become more widely recognized and may account for 10% to 20% of patients with chronic, watery diarrhea. To date, CC and LC are considered distinct but related clinical entities.

### 21. What are the features of the two types of MC (CC and LC)?

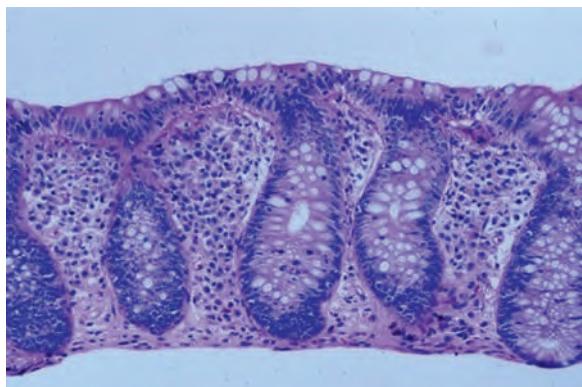
See Table 49-3, E-Figure 49-3, and Figure 49-4.

**Table 49-3.** Contrasting Features for Collagenous and Lymphocytic Colitis

FEATURE	COLLAGENOUS COLITIS	LYMPHOCYTIC COLITIS
Gender incidence (women:men)	7.5-15:1	2-3:1
Mean age onset	51 years	43 years
<b>Histologic Findings</b>		
IELs	Yes	Yes (>20 IELs per 100 epithelial cells)
Surface epithelial flattening or detachment	Yes	Yes
Subepithelial collagen band >10 microns	Yes	No

IEL, Increased intraepithelial lymphocyte.

**Figure 49-4.** Histologic demonstration of lymphocytic colitis; note the increase in intraepithelial lymphocytes in the surface epithelium and crypts.



### 22. What are the clinical features of MC?

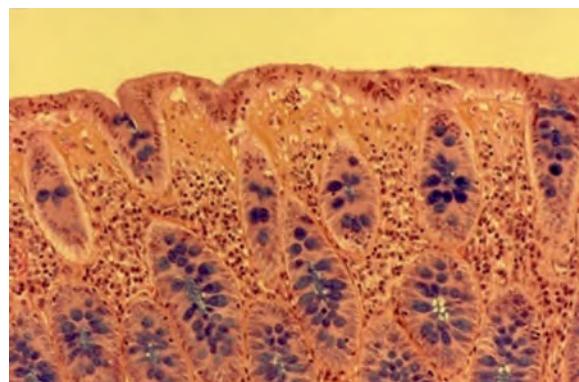
The most common clinical symptoms are chronic, nonbloody diarrhea (95%), weight loss (91%), abdominal pain (40%), urgency (29%), and nocturnal diarrhea (22%). These symptoms can be severe in some patients. Clinically, LC and CC are indistinguishable, although symptoms do tend to be worse in CC patients.

### 23. How are patients with MC distinguished from patients with irritable bowel syndrome (IBS)?

The gold standard is colorectal biopsy, which is normal in patients with IBS. There is considerable overlap of symptoms between MC and IBS. Celiac disease and lactose intolerance can also present with similar symptoms and should be ruled out. Studies have shown that as many as 33% of patients with biopsy-proven CC or LC will have a prior diagnosis of IBS and that as many as half of the patients diagnosed with MC will also meet the diagnostic criteria for IBS.

### 24. Are there any laboratory tests or imaging studies that can help establish the diagnosis of MC?

Laboratory tests and radiographic imaging are generally nondiagnostic; therefore there is no role for imaging studies in the diagnosis of MC. Fecal leukocytes may be present, but stool cultures are typically negative.



**E-Figure 49-3.** Histologic demonstration of collagenous colitis; note the thickened subepithelial collagen band (> 10 microns; note that the diameter of a normal red blood cell is 7-8 microns).

C-reactive protein levels and erythrocyte sedimentation rates may be elevated; anemia may be present. Barium enemas and colonoscopy typically are normal, but can show subtle mucosal changes.

#### **25. How common is MC?**

The incidence of MC has been rising during the past two decades. Studies show CC incidence rates of 2.6 to 10.8 per 100,000 people and LC incidence rates of 2.2 to 14 per 100,000 people. Cases have been identified in the United States, Europe, Canada, Africa, Asia, Australia, and Latin America, suggesting worldwide distribution. The highest incidence has been in northern countries (the United States, Denmark, Canada) suggesting a north-south gradient, although this is not uniformly consistent. Additionally, MC tends to be more common in older adults, with an average age of diagnosis at 65. Overall, MC is more common in females. At least some of this increased incidence is attributed to enhanced clinical awareness.

#### **26. Which parts of the colon are most commonly affected?**

MC involves the colon discontinuously and the patchy involvement of the normal-appearing colon necessitates a minimum of four biopsies to establish the diagnosis of MC. In one prior study, the highest yield was from biopsies of transverse colon. Most cases can be diagnosed by biopsies taken within the range of flexible sigmoidoscopy; colonoscopy with biopsy of the right colon may be necessary to detect 10% of patients with isolated right-sided histopathologic findings.

#### **27. What agents are associated with the pathogenesis of MC?**

Nonsteroidal antiinflammatory drugs (NSAIDs) are thought to be an important pathogenic factor, although their role in this association is unclear. A case-controlled study showed that patients with CC were three times more likely to take NSAIDs. LC has been associated with the use of sertraline. Other potential medications associated with the development of MC include aspirin, acarbose, clozapine, entacapone, flavonoid, PPIs (especially lansoprazole), ranitidine, and ticlopidine. Of note, many of these drugs have an adverse effect of chronic diarrhea; therefore attributing a drug as the cause of MC is more challenging. Although the contribution of environmental factors is not clear, smoking has been associated with MC, including with development of disease 10 years earlier than nonsmokers. In one study, previous or current smoking had an odds ratio of 2.4 for CC and 1.6 for LC.

#### **28. Are there associated conditions in MC patients?**

A wide variety of associated conditions are described in case reports, including thyroid disease, celiac disease, diabetes, rheumatoid arthritis, and asthma and allergies in up to 40% to 50% of patients with MC. If a patient with celiac disease treated with a gluten-free diet continues to have diarrheal symptoms, colonoscopy should be considered to evaluate for concurrent MC.

#### **29. What is the natural history of MC?**

The natural history is not known. Often the disease is insidious, but may have acute onset in up to 40% of patients. In one study, 505 patients with MC experienced resolution of their symptoms after 3 years. However, as many as 30% of patients treated for MC will experience persistent diarrhea 10 years after diagnosis. The clinical course may be complicated by the patient's response to medication. There is no increased risk of malignancy associated with MC; however, there are reports of colonic perforation thought to be related to mucosal tears seen during colonoscopy.

#### **30. What are the treatment options?**

Initially, patients with MC can make dietary changes (avoid caffeine, alcohol, and dairy products) and stop any medications that have been associated with MC. Some patients do well on antidiarrheal agents (loperamide) or on cholestyramine alone. A metaanalysis has shown that oral budesonide (9 mg daily) for 6 to 8 weeks has been effective in decreasing symptoms in 81% of patients with CC; however, symptoms recurred in 60% to 80% of patients with the cessation of budesonide. These patients responded to retreatment with budesonide and often required slow subsequent tapers. Budesonide has also been shown to be effective in treating LC. There are no evidence-based alternatives to budesonide. Bismuth subsalicylate and sulfasalazine-mesalamine have shown efficacy in some studies. Probiotics offered no benefit over placebo in studies. Some patients require stronger immunosuppressants such as methotrexate, 6-mercaptopurine, or azathioprine; there is ongoing research to determine the utility of anti-tumor necrosis factor therapy with infliximab and adalimumab. In rare cases, patients may require surgery, such as diverting ileostomy or colectomy, for severe and refractory disease.

## **RADIATION COLITIS**

#### **31. What is radiation colitis?**

Radiation colitis refers to radiation-induced changes in the mucosa of the colon and rectum. Generally, radiation colitis is a chronic, ischemic process caused by obliterative endarteritis, in contrast to acute inflammation seen in other types of colitis.

### **32. Which part of the GI tract is most commonly injured by radiation?**

Radiation injury to the colon occurs following treatment of rectal, cervical, uterine, prostate, urinary bladder, and testicular cancer. Because prostate cancer is the most common of these cancers, most data has been obtained in this group of patients. The peristaltic movement of the small intestine in and out of the field of radiation decreases the degree of injury to the small bowel. The colon, especially the rectosigmoid, is highly susceptible to radiation injury because it is immobile. Brachytherapy, or internal radiotherapy, can deliver high-energy radiation to more focused tissues and therefore causes less damage to the colon than external-beam radiation. Tumors in the pelvic area often require higher dosages of radiation and result in greater risk of damage to the colon.

### **33. What can be done to prevent radiation damage?**

The extent of radiation colitis depends on the cumulative radiation dose, fraction size, technique of radiation delivery, amount of tissue exposed, and presence of other treatments such as surgery or chemotherapy. Of those listed, radiation dose appears to be the most significant factor. Radiation damage can be reduced by limiting the dosage and area of exposure while shielding adjacent tissues. Additionally, amifostine has been shown to reduce the incidence of radiation colitis by scavenging free radicals produced during treatment.

### **34. What symptoms are associated with irradiation?**

The initial symptoms of radiation exposure are nausea and vomiting. Diarrhea typically develops 5 days later. Loss of mucosal defenses increases the patient's risk of developing sepsis. Acute radiation injury to the colon typically occurs within 6 weeks and is manifested by diarrhea, mucus discharge, tenesmus, and rarely, bleeding. These symptoms are self-limited and typically resolve in 2 to 6 months without therapy. Chronic symptoms of radiation colitis and proctitis (or chronic radiation proctopathy) can occur 9 to 12 months following radiation therapy, but can be delayed by decades after the initial radiation exposure. The primary symptoms associated with chronic injury to the colon and rectum include diarrhea, obstructed defecation, rectal pain, and rectal bleeding. Severe radiation colitis may manifest with bowel necrosis, perforation, fistula development, and uncontrolled rectal bleeding.

### **35. What are the effects of localized radiation to the colon?**

Colonoscopy may be normal or may show telangiectasias, pallor, and friable mucosa. Early or acute changes include microscopic damage to mucosal and vascular epithelial cells, which may be asymptomatic to the patient. One common histologic feature is the presence of atypical fibroblasts. Late changes commonly involve fibrosis with obliterative endarteritis resulting in chronic ischemia, stricture formation, and bleeding.

### **36. How can radiation colitis and proctitis be managed?**

There is limited data on the appropriate treatment for radiation colitis and proctitis. Medications used to treat radiation colitis and proctitis include oral and rectal sucralfate, steroids, 5-acetylsalicylic acid compounds, hyperbaric oxygen, and antibiotics, such as metronidazole. Stool softeners are also recommended, as straining can cause telangiectasias to bleed.

### **37. What are the endoscopic therapies for chronic bleeding?**

The primary goal of endoscopic therapy is to treat telangiectasias, which are the most common source of rectal bleeding. Argon plasma coagulator, heater probe, and bipolar cautery have all been used. Colorectal surgeons may apply formaldehyde, also known as chemical cautery, to control bleeding. Patients should be transfused with blood as needed and take oral iron.

### **38. How are chronic, radiation-induced bowel strictures managed?**

Patients with obstructive symptoms often benefit from the use of stool softeners. Balloon dilation of the strictures may be necessary. Patients with long or angulated strictures may benefit from surgery as these lesions are more likely to perforate with dilating procedures. Recurrent strictures may be treated with steroid injections. Colonic stents have also been used, but increase the risk of bowel perforation.

Please access ExpertConsult to view the E-figures for this chapter.

## **BIBLIOGRAPHY**

1. Babb RR. Radiation proctitis: a review. Am J Gastroenterol 1996;91:1309–11.
2. Bartlett JG. Historical perspectives on studies of *Clostridium difficile* and *C. difficile* infection. Clin Infect Dis 2008;46(Suppl 1):S4–S11.
3. Borody TJ, Khoruts A. Fecal microbiota transplantation and emerging applications, Nat Rev Gastroenterol Hepatol 2011 Dec 20;9(2):88–96. <<http://www.ncbi.nlm.nih.gov/pubmed/22183182>>.
4. Brandt LJ, Aroniadis OC, Mellow M, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection. Am J Gastroenterol 2012;107(7):1079–87.
5. Chande N, McDonald JW, Macdonald JK. Interventions for treating collagenous colitis, Cochrane Database Syst Rev 2008 Apr 16;(2):CD003575. <<http://www.ncbi.nlm.nih.gov.offcampus.lib.washington.edu/pubmed/18425892>>.
6. Chande N, McDonald JW, Macdonald JK. Interventions for treating lymphocytic colitis, Cochrane Database Syst Rev 2008 Apr 16;(2):CD006096. <<http://www.ncbi.nlm.nih.gov.offcampus.lib.washington.edu/pubmed/18425936>>.

7. Chang JY, Antonopoulos DA, Kalra A, et al. Decreased diversity of the fecal Microbiome in recurrent *Clostridium difficile*-associated diarrhea. *J Infect Dis* 2008;197(3):435–8.
8. Freeman HJ. Collagenous mucosal inflammatory diseases of the gastrointestinal tract. *Gastroenterology* 2005;129:338–50.
9. Hall AJ, Curns AT, McDonald LC, et al. The roles of *Clostridium difficile* and norovirus among gastroenteritis-associated deaths in the United States, 1999–2007. *Clin Infect Dis* 2012;55(2):216–23.
10. Kuipers EJ, Surawicz CM. Clostridium difficile infection. *Lancet* 2008;371:1486–8.
11. Madisch A, Miehlke S, Lindner M, Bethke B, Stolte M. Clinical course of collagenous colitis over a period of 10 years. *Z Gastroenterol* 2006;44:971–4.
12. McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med* 2005;353:2433–41.
13. McFarland LV. Update on the changing epidemiology of *Clostridium difficile*-associated disease. *Nat Clin Pract Gastroenterol Hepatol* 2008;5:40–8.
14. Münch A, Aust D, Bohr J, et al. Microscopic colitis: current status, present and future challenges. *J Crohns Colitis* 2012;6:932–45.
15. Nielsen OH, Vainer B, Rask-Madsen J. Non-IBD and noninfectious colitis. *Nat Clin Pract Gastroenterol Hepatol* 2008;5:28–39.
16. Nyhlin N, Bohr J, Eriksson S, Tysk C. Microscopic colitis: A common and an easily overlooked cause of chronic diarrhoea. *Eur J Intern Med* 2008;19:181–6.
17. Qadeer M, Vargo J. Approaches to the prevention and management of radiation colitis. *Curr Gastroenterol Rep* 2008;10:507–13.
18. Razavi B, Apisarnthanarak A, Mundy LM. *Clostridium difficile*: emergence of hypervirulence and fluoroquinolone resistance. *Infection* 2007;35:300–7.
19. Shen EP, Surawicz CM. The changing face of *Clostridium difficile*: what treatment options remain? *Am J Gastroenterol* 2007;102:2789–92.
20. Shiraishi M, Hiroyasu S, Ishimine T, et al. Radiation enterocolitis: overview of the past 15 years. *World J Surg* 1998;22:491–3.
21. Sunenshine RH, McDonald LC. *Clostridium difficile*-associated disease: new challenges from an established pathogen. *Cleve Clin J Med* 2006;73:187–97.
22. Surawicz CM. Probiotics, antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in humans. *Best Pract Res Clin Gastroenterol* 2003;17:775–83.
23. Surawicz CM, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol* 2013;108(4):478–98.
24. Van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2012;366(5):407–15.
25. Vindigni SM, Broussard EK, Surawicz CM. Alteration of the intestinal microbiome: fecal microbiota transplant and probiotics for *Clostridium difficile* and beyond, *Expert Rev Gastroenterol Hepatol* 2013 Sep;7(7):615–28. <<http://www.ncbi.nlm.nih.gov/pubmed/24070153>>.

# UPPER GASTROINTESTINAL HEMORRHAGE

Davinder Sandhu, MBBCh, FRCP, and Lisa Strate, MD, MPH

## 1. What are the major sources of upper gastrointestinal (UGI) bleeding?

The most common source of UGI bleeding is peptic ulcer disease, which accounts for 30% to 60% of cases, followed by esophageal varices, which account for 10% to 15% of cases. Other less common sources include esophagitis, angiodysplasia, Mallory-Weiss tears, cancer, gastric varices, portal hypertensive gastropathy, Dieulafoy lesions, and aortoenteric fistulas.

## 2. What are the signs, symptoms, and risk factors of UGI bleeding?

Patients with UGI bleeding typically present with melena (black, tarry stool), although melena is occasionally seen in patients with right-sided colonic bleeding. Hematemesis or coffee-ground emesis is also a common presentation of UGI bleeding. Patients with massive UGI bleeding present with hematochezia together with hemodynamic instability that can be mistaken for lower GI bleeding. Table 50-1 summarizes important presenting features in patients with UGI bleeding.

**Table 50-1.** Risk Factors, Symptoms, and Signs of UGI Bleeding

RISK FACTORS	HISTORY	EXAMINATION
Medications (aspirin, NSAIDs, corticosteroids)	Melena	Orthostasis
Stress (trauma, burns, CNS injury)	Hematemesis	Tachycardia
Alcohol abuse	Hematochezia	Hypotension
Chronic liver disease	Dizziness	Melena or hematochezia on rectal examination
<i>Helicobacter pylori</i> infection	Syncope	Nasogastric tube aspirate positive for blood or “coffee grounds”
	Acid reflux (esophagitis)	Abdominal tenderness
	Dyspepsia	Stigmata of chronic liver disease
	Vomiting prior to bleeding episode (Mallory-Weiss tear)	
	Aortic aneurysm repair (aortoenteric fistula)	
	Prior UGI bleeding	

CNS, Central nervous system; NSAID, nonsteroidal antiinflammatory drug; UGI, upper gastrointestinal.

## 3. What is the role of aspirin and nonsteroidal antiinflammatory drugs (NSAIDs) in UGI bleeding?

Regular aspirin and NSAID use increases the risk of major gastrointestinal (GI) bleeding (relative risk for aspirin is 1.4). Bleeding risk is highly related to dose, but even low-dose aspirin can result in GI bleeding. Risk factors for NSAID-related UGI bleeding include age older than 65 years; a history of peptic ulcers; and use of concomitant platelet P2Y12 inhibitors, anticoagulants, or corticosteroids.

## 4. How might one distinguish a UGI bleed from a lower GI bleed in a patient who presents with blood per rectum?

The feature most suggestive of UGI bleed rather than lower GI bleed is melenic stool on rectal examination (likelihood ratio [LR] 25). Other features suggestive of a UGI bleed rather than lower GI bleed include a blood urea nitrogen/creatinine ratio of more than 30 (LR 7.5), and a report of melena (5.1-5.9). Hematochezia (red or maroon stool) generally indicates a lower GI bleed, and the presence of blood clots in the stool decreases the likelihood of an UGI bleed (LR 0.05). Patients with hematochezia from a UGI source present with hemodynamic compromise.

## 5. When should one suspect a variceal bleed?

Risk factors for chronic liver disease (e.g., excessive alcohol use, viral hepatitis), stigmata of chronic liver disease on physical examination (e.g., spider angiomas, palmar erythema, jaundice), and hematemesis, with hematochezia and hemodynamic compromise, make a variceal bleed more likely. It is important to remember that patients with cirrhosis are at risk of bleeding from nonvariceal sources, which collectively account for approximately 50% of UGI bleeds in patients with cirrhosis.

**6. How can the amount of acute blood loss be estimated clinically?**

As little as 50 mL of blood can produce melena. The acute loss of 500 mL of blood will not result in detectable physiologic changes. Mild to moderate blood loss (500-1000 mL) results in resting tachycardia, whereas loss of 1000 mL will produce orthostatic changes. Loss of 2000 mL or more of blood will produce shock. The hematocrit at the time of presentation may not reflect blood loss. A fall in hematocrit is seen over time with fluid resuscitation or replacement of volume with extravascular fluid.

**7. What are the first steps in managing a patient with UGI bleeding?**

Patient evaluation and resuscitation are the first steps in managing UGI bleeding. Patients should have two large-bore peripheral intravenous (IV) catheters or a central venous line if indicated. Patients with active bleeding or hemodynamic instability should receive volume replacement, initially with crystalloid, to stabilize blood pressure and heart rate. Laboratories including a complete blood count, creatinine and blood urea nitrogen, prothrombin time, and partial thromboplastin time should be obtained. Patients with active bleeding should be typed and cross-matched for packed red blood cell transfusion. Clotting abnormalities and anemia need correcting in certain patients (see [Question 8](#)).

**8. What is the goal hemoglobin in patients with UGI bleeding?**

The hemoglobin goal in UGI bleed is uncertain. However, a restrictive transfusion strategy (when hemoglobin <7 g/dL) compared with a liberal transfusion strategy (when hemoglobin <9 g/dL) has been recently found to improve rebleeding and mortality rates in patients with peptic ulcer bleeding or variceal bleeding with Child-Pugh A or B cirrhosis who underwent emergent upper endoscopy with endoscopic treatment. However, patients with brisk bleeding resulting in shock and patients with significant comorbid illness, particularly cardiovascular, cerebrovascular, or peripheral vascular disease, should be transfused more aggressively (goal hemoglobin 9 g/dL).

**9. What is the goal INR and platelet count in patients with UGI bleeding?**

Conventionally, a goal INR of less than 1.5 to 2 and a platelet count of more than 50,000 are recommended prior to endoscopy. However, guidelines recommend that endoscopy should not be delayed for correction of coagulopathy.

**10. Should a nasogastric (NG) tube be placed in patients with suspected UGI bleeding?**

A bloody NG lavage increases the likelihood of severe bleeding or finding active bleeding or a nonbleeding visible vessel at the time of endoscopy. However, NG lavage is generally not necessary for diagnosis, prognosis, or visualization, and is very uncomfortable for patients. Therefore it is not routinely recommended in patients with suspected UGI bleeding.

**11. What features on presentation can be used to predict the severity of UGI bleeding?**

A number of scoring systems have been developed to predict the likelihood of adverse outcomes and need for intervention. The most commonly used are the Blatchford score ([Table 50-2](#)), the Rockall score ([Table 50-3](#)), and the AIMS65 score ([Table 50-4](#)). These scores can be used to triage patients to appropriate levels of care, including urgent endoscopy and early discharge. In general, the higher the number of risk factors, the higher the risk of adverse outcome.

**Table 50-2. The Blatchford Score**

CLINICAL PARAMETERS AT PRESENTATION	SCORE
<b>Systolic blood pressure (mm Hg)</b>	
≥110	0
100 to 109	1
90 to 99	2
<90	3
<b>Blood urea nitrogen (mg/dL)</b>	
<18	0
18 to 22	2
22 to 28	3
28 to 69	4
>70	6

**Table 50-2.** The Blatchford Score (Continued)

CLINICAL PARAMETERS AT PRESENTATION	SCORE
<b>Hemoglobin for men (g/dL)</b>	
≥13	0
12 to 12.9	1
10 to 11.9	3
<10	6
<b>Hemoglobin for women (g/dL)</b>	
≥12	0
10 to 11.9	1
<10	6
<b>Other variables at presentation</b>	
Pulse >100	1
Melena	1
Syncope	2
Hepatic disease	2
Cardiac failure	2
<b>Maximum score</b>	<b>23</b>

The risk of requiring endoscopic intervention increases with a higher score. A Blatchford score of zero was associated with a low likelihood of the need for urgent endoscopic intervention.

Adapted from Blatchford O, et al. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. *Lancet* 2000;356:1318–1321.

**Table 50-3.** The Rockall Score

VARIABLE	SCORE
<b>Age (yr)</b>	
<60	0
60 to 79	1
>80	2
<b>Shock</b>	
Normal heart rate and blood pressure	0
Heart rate >100 bpm	1
Systolic blood pressure <100 mm Hg	2
<b>Coexisting illness</b>	
No major illness	0
Ischemic heart disease, congestive heart failure	2
Renal failure, hepatic failure, metastatic cancer, other major illness	3
<b>Endoscopic diagnosis</b>	
No lesion observed, Mallory-Weiss tear (without stigmata)	0
Nonmalignant lesion	1
Cancer of upper GI tract	2
<b>Endoscopic stigmata of recent hemorrhage</b>	
Clean base ulcer, flat pigmented spot	0
Blood in upper GI tract, active bleeding, visible vessel, clot	2
<b>Maximum score</b>	<b>11</b>

bpm, Beats per minute; GI, gastrointestinal.

The clinical Rockall score includes age, shock, and coexisting illness. The complete Rockall score includes the clinical Rockall score plus endoscopic score. Patients with a clinical Rockall score of 0 or a complete Rockall score of less than or equal to 2 are considered low risk for rebleeding or death.

Adapted from Rockall TA, et al. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996;38:316–321.

**Table 50-4.** AIMS65 Score

RISK FACTOR	SCORE
Albumin <3 mg/dL	1
INR >1.5	1
Altered mental status	1
SBP <90 mm Hg	1
Age >65	1
Maximum score	5

INR, International normalized ratio; SBP, systolic blood pressure.

As the number of risk factors accumulate, length of hospital stay, cost, and mortality increases (e.g., no risk factors: 0.3% mortality; one risk factor: 1%; two risk factors: 3%; three risk factors: 9%; four risk factors: 15%; and five risk factors: 25%).

Adapted from Saltzman JR, et al. A simple risk score accurately predicts in-hospital mortality, length of stay, and cost in acute upper GI bleeding. *Gastrointest Endosc* 2011;74(6):1215–1224.

## 12. How should patients be prepared for an esophagogastroduodenoscopy (EGD)?

After initial stabilization and resuscitation is performed (see Questions 7 and 8), intubation and deep sedation should be considered in patients with altered mental status, copious hematemesis, suspicion for variceal bleeding, or alcohol dependence. The patient should take nothing by mouth. Informed consent is obtained by the endoscopist prior to the procedure. In the setting of substantial bleeding, erythromycin can be infused 30 minutes prior to the EGD to improve visualization.

## 13. How quickly should EGD be performed?

Endoscopy should be performed within 24 hours of admission, after hemodynamic stabilization and resuscitation. More urgent endoscopy (within 12 hours) may be needed in patients with significant ongoing blood loss such as those with a bloody NG aspirate, systolic blood pressure (SBP) lower than 100 mm Hg, pulse faster than 100 bpm, or a Blatchford score greater than or equal to 12.

## 14. How do findings at endoscopy guide risk stratification and treatment?

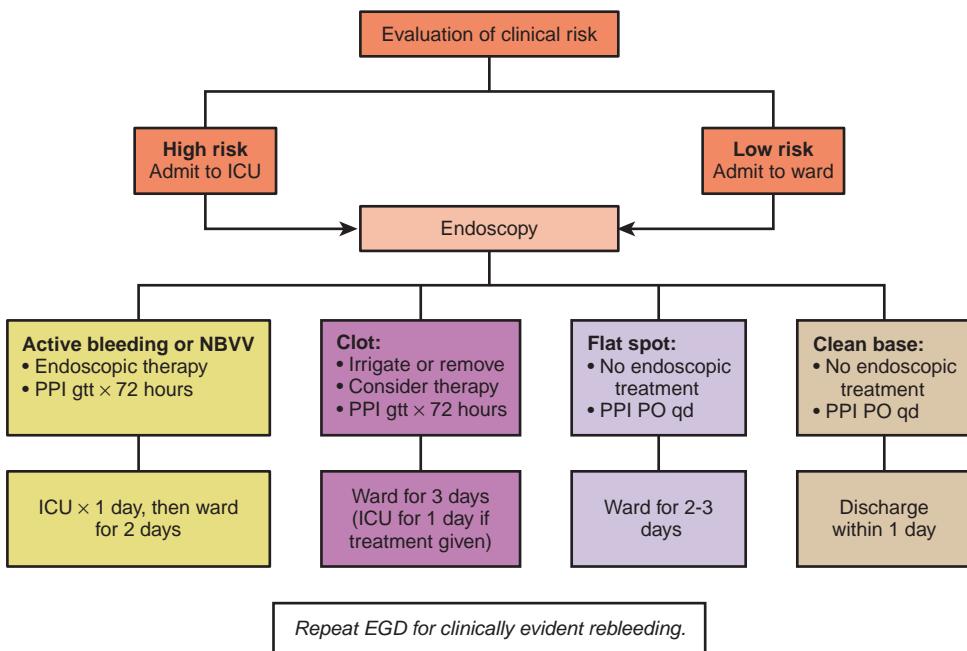
Endoscopic findings play an important role in patient assessment and management. Stigmata of recent hemorrhage describe the appearance of an ulcer at the time of endoscopy. The most commonly used classification system for peptic ulcers is the Forrest classification, which classifies endoscopic stigmata according to the risk of rebleeding and mortality (Table 50-5).

**Table 50-5.** Forrest Classification of Peptic Ulcers

FORREST CLASSIFICATION	DESCRIPTION OF ENDOSCOPIC STIGMATA	TREATMENT	REBLEEDING RATE WITHOUT ENDOSCOPIC THERAPY	MORTALITY WITHOUT ENDOSCOPIC THERAPY
1A	Spurting blood	IV PPI bolus + infusion, endoscopic treatment	70%	11%
1B	Oozing blood	IV PPI bolus + infusion, endoscopic treatment	30%	
IIA	Nonbleeding visible vessel	IV PPI bolus + infusion, endoscopic treatment	43%	11%
IIB	Adherent clot	IV PPI bolus + infusion, consider endoscopic treatment	22%	7%
IIC	Pigmented flat spot	Oral PPI	10%	3%
III	Clean based ulcer		5%	2%

IV, Intravenous; PPI, proton pump inhibitor.

Adapted from Laine L, et al. Management of patients with ulcer bleeding. *Am J Gastroenterol* 2012;107(3):345–360.



**Figure 50-1.** Algorithm for treatment of peptic ulcers. EGD, Esophagogastrroduodenoscopy; gtt, drops; ICU, intensive care unit; NBVV, nonbleeding visible vessels; PPI, proton pump inhibitor; PO, by mouth, qd, every day.

Figure 50-1 outlines an algorithm for the management of peptic ulcer disease according to risk stratification and endoscopic findings.

### 15. What is the nonendoscopic management of peptic ulcer bleeding?

IV proton pump inhibitor (PPI) bolus and infusion preendoscopy decreases the number of patients with high-risk stigmata at endoscopy and the need for endoscopic treatment, although it has not been shown to decrease related outcomes, including rebleeding, need for surgery, and mortality. Preendoscopy IV PPI is likely to be most beneficial in patients with significant, active bleeding or multiple high-risk features.

### 16. What are the endoscopic techniques for managing nonvariceal UGI bleeding?

There are a number of endoscopic modalities available for the treatment of nonvariceal UGI bleeding (Table 50-6). Epinephrine therapy is not effective as monotherapy but can be a helpful adjuvant in combination with other modalities. In general, the choice of therapy depends on the type and location of the lesion and the expertise of the endoscopist.

**Table 50-6.** Endoscopic Techniques for the Management of Nonvariceal Bleeding

TECHNIQUE	USAGE
Epinephrine (1:10,000) injected in four quadrants around the lesion	Not effective as monotherapy for hemostasis; effective in combination with another endoscopic technique
Thermal contact therapy (bipolar probes, heater probes)	Decrease further bleeding, need for surgery, and mortality
Endoclip	Decrease bleeding and need for surgery
Sclerosant (e.g., absolute alcohol, 5% ethanolamine)	Risk of tissue necrosis; decrease further bleeding, need for surgery, and mortality
Other: APC, Nd:YAG laser, monopolar thermal probe, thrombin/ fibrin glue	Not first-line (limited data, less availability, cost issues)
Hemospray	Newer modality, limited data suggest utility in massive bleeding to achieve initial control, as an adjunct to standard therapy in high-risk lesions and in tumor bleeding

APC, Argon plasma coagulation; Nd:YAG: neodymium-doped yttrium aluminum garnet.

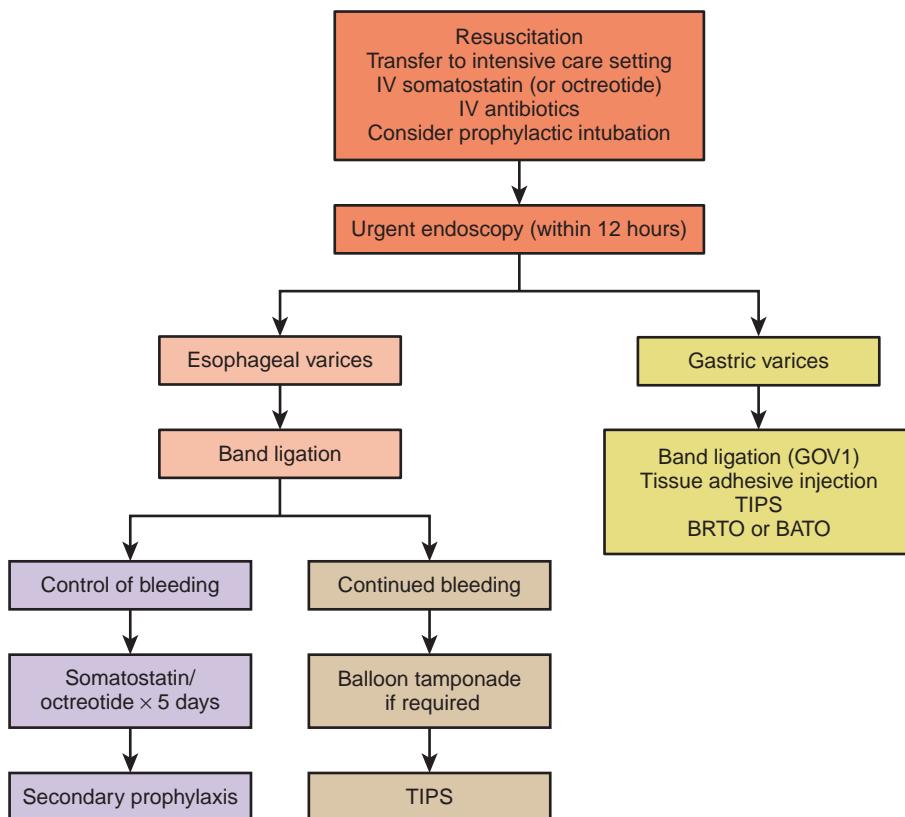
Adapted from Laine L, et al. Clin Gastroenterol Hepatol 2009;7:33–47.

### 17. What is the nonendoscopic management of variceal bleeding?

If a variceal etiologic factor is suspected, octreotide bolus (50 mcg) with subsequent infusion (50 mcg/h) should be initiated to decrease portal pressures and ongoing bleeding. Antibiotics (typically a fluoroquinolone or ceftriaxone if there is a high local prevalence of quinolone-resistant organisms) should be given for 7 days in all patients with cirrhosis who present with UGI bleeding (variceal or nonvariceal) to decrease the risk of rebleeding, infection, and mortality. Patients with cirrhosis are more likely to require correction of coagulopathy and thrombocytopenia, and may develop hepatic encephalopathy, which can be treated with lactulose or rifaximin.

### 18. What endoscopic therapy is available to control variceal bleeding?

Variceal endoscopic band ligation (EBL) and sclerotherapy are the main methods for endoscopic control of variceal bleeding, and control bleeding in approximately 90% of cases. EBL is the preferred method based on lower rebleeding (26% vs. 44%), mortality (24% vs. 31%) and complication rates (11% vs. 25%) when compared with sclerotherapy. In general, gastric varices are not amenable to band ligation (see Question 19). Figure 50-2 presents an algorithm for the treatment of variceal bleeding.



**Figure 50-2.** Algorithm for management of variceal bleeding. BATO, Balloon-occluded anterograde transvenous obliteration; BRTO, balloon-occluded retrograde transvenous obliteration; GOV1, gastoesophageal varices type 1; TIPS, transjugular intrahepatic portosystemic shunt.

### 19. What are the techniques available for rescue therapy in variceal bleeding?

Balloon tamponade is typically employed if EBL cannot be attempted because of patient instability, or if rebleeding occurs immediately after EBL. Transjugular intrahepatic portosystemic shunts (TIPSSs) are indicated in the setting of rebleeding after EBL or for initial management of gastric variceal bleeding. In experienced centers, early TIPSSs for esophageal variceal bleeding has been associated with a decrease in rebleeding and mortality in patients with Child-Pugh class C cirrhosis or class B with active bleeding.

### 20. How is gastric variceal bleeding treated?

Gastric varices are generally not amenable to EBL or sclerotherapy (except those that extend from the esophagus to the lesser curvature; GOV1 varices). Cyanoacrylate glue injection is an alternative endoscopic technique for gastric varices. Balloon-occluded retrograde transvenous obliteration or balloon-occluded anterograde

transvenous obliteration are alternative radiologic procedures increasingly used for the management of gastric variceal bleeding in patients with hepatic encephalopathy, or contraindications to TIPS, in the presence of a gastrorenal shunt.

## **21. What is the management of nonvariceal UGI bleeding that is refractory to initial endoscopic management?**

Initial endoscopic therapy is successful in obtaining permanent control of bleeding in 80% to 90% of patients with nonvariceal UGI bleeding. In patients with recurrent bleeding after endoscopic therapy, approximately 70% will be controlled after a second attempt at endoscopic therapy. Angiography or surgery is recommended in patients who continue to bleed despite two attempts at endoscopic hemostasis. Surgical or radiographic consultation should be obtained in patients who present with massive bleeding.

## **22. How are aspirin and NSAIDs managed following an episode of peptic ulcer bleeding?**

Patients with bleeding peptic ulcer disease should be tested and treated for *Helicobacter pylori* infection. Eradication of infection should be documented. NSAIDs should be stopped. If this is not possible, a coxib plus a PPI should be used. In general, low-dose aspirin for secondary prevention of cardiovascular disease should be resumed shortly after bleeding is controlled along with a PPI. Aspirin for secondary prevention should be stopped in most cases. Patients in whom the cause of ulcer disease is unknown should be continued on a PPI indefinitely.

## **23. When should patients receive follow up after their episode of UGI bleeding?**

A visit with a primary care physician within 1 to 2 weeks of discharge can be considered to screen for recurrent bleeding and reinforce medical management. Gastric ulcers, if not initially biopsied on the index endoscopy, require a follow-up EGD in 6 to 8 weeks to ensure complete endoscopic healing and to exclude gastric cancer. Patients with esophageal varices are seen for repeat EBL every 1 to 3 weeks until the varices are eradicated.

*The authors would like to acknowledge the contributions of Dr. John S. Goff, who was the author of this chapter in the previous edition.*

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## **BIBLIOGRAPHY**

1. Alharbi A, Almadi M, Barkun A, et al. Predictors of a variceal source among patients presenting with upper gastrointestinal bleeding. *Can J Gastroenterol* 2012;26(4):187–92.
2. Barkun AN, Bardou M, Kuipers EJ, et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med* 2010;152(2):101–13.
3. Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper gastrointestinal hemorrhage. *Lancet* 2000;356:1318–21.
4. Frossard JL, Spahr L, Queneau PE, et al. Erythromycin intravenous bolus infusion in acute upper gastrointestinal bleeding: a randomized, controlled, double-blind trial. *Gastroenterology* 2002;123(1):17–23.
5. Garcia-Pagan JC, Caca K, Bureau C, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. *N Engl J Med* 2010;362(25):2370–9.
6. Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Practice Guidelines Committee of the American Association for the Study of Liver Diseases. 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.
7. Huang ES, Strate LL, Ho WW, et al. Long-term use of aspirin and the risk of gastrointestinal bleeding. *Am J Med* 2011;124(5):426–33.
8. Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol* 2012;107(3):345–60. quiz 61, <http://gi.org/guideline/management-of-patients-with-ulcer-bleeding/> [Accessed September 22, 2014].
9. Laine L, MQuaid KR. Endoscopic therapy for bleeding ulcers: an evidence-based approach based on meta-analyses of randomized controlled trials. *Clin Gastroenterol Hepatol* 2009;7:33–47.
10. Rockall TA, Devlin HB, et al. Risk assessment after acute upper gastrointestinal hemorrhage. *Gut* 1996;38:316–21.
11. Saltzman JR, Tabak YP, Hyett BH, et al. A simple risk score accurately predicts in-hospital mortality, length of stay, and cost in acute upper GI bleeding. *Gastrointest Endosc* 2011;74(6):1215–24.
12. Sreedharan A, Martin J, Leontiadis GI, et al. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2010;7, CD005415.
13. Strygley FD, Gerardo CJ, Tran T, et al. Does this patient have a severe upper gastrointestinal bleed? *JAMA* 2012;307(10):1072–9.
14. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013;368(1):11–21.
15. Wolf AT, Wasan SK, Saltzman JR. Impact of anticoagulation on rebleeding following endoscopic therapy for nonvariceal upper gastrointestinal hemorrhage. *Am J Gastroenterol* 2007;102(2):290–6.

# LOWER GASTROINTESTINAL TRACT BLEEDING

*Joseph G. Cheatham, MD, and John D. Horwhat, MD*

## 1. Define lower gastrointestinal bleeding (LGIB)

Bleeding that originates distal to the ligament of Treitz is considered LGIB. There is wide variability in clinical presentation based on the volume of blood loss and whether the bleeding is acute or chronic, overt or occult.

## 2. How common is LGIB?

The annual incidence of LGIB has steadily risen from 20 to 30 per 100,000 population during the past 2 decades, whereas hospitalization for upper gastrointestinal bleeding (UGIB) has declined by 50%.

## 3. What populations are at increased risk?

Age is the strongest risk factor with a 200-fold increased incidence between the third to ninth decades of life. This relationship is explained by the large proportion of LGIB arising from age-related gastrointestinal (GI) pathophysiologic conditions such as diverticulosis, angiodysplasia, and ischemic colitis from atherosclerosis. High nonsteroidal antiinflammatory drug (NSAID) consumption in this population, including cyclooxygenase-2 (COX-2) inhibitors, compounds the risk of bleeding from diverticulosis and angiodysplasia.

## 4. What is the mortality associated with LGIB?

Most cases of LGIB (65%-85%) are self-limited and uncomplicated; however, mortality can vary from 4% to as high as 23% if the bleeding occurred after hospitalization. Patients with massive LGIB requiring 4 to 6 units of red blood cells (RBCs) in 24 hours, who rebleed after a cessation period of 24 hours, or bleed for greater than 72 hours are at the highest risk of death. Traditionally, patients who meet one of these benchmarks are considered for surgery. This recommendation may not be as strong as it was in the past as recent studies reveal that large numbers of patients who met the aforementioned criteria have been successfully managed with nonoperative care.

## 5. How is history important in assessing a patient with LGIB?

See Table 51-1.

**Table 51-1.** Clinical Characteristics and Historical Features in Suspected LGIB cases

BLEEDING SOURCE	APPEARANCE OF BLOOD			VOLUME	BLEEDING ONSET	SIGNS/SYMPOTMS ASSOCIATIONS
	BRB	Maroon	Melena			
Diverticular	4+	2+	1+	4+	Acute	Painless, NSAIDs?
Colitis (UC, Crohn's)	4+	2+	1+	2+	Chronic	Diarrhea, ABD pain, tenesmus
Malignancy	3+	2+	2+	1+	Chronic	Painless, weight loss, stool changes <sup>147,6131</sup>
Angiodysplasia	4+	3+	1+	3+	Acute/I	Painless, Heyde syndrome, prostate/cervical radiation
Hemorrhoidal	4+	1+		1+	Acute/I	Blood around stool on tissue, dripping in toilet
Ischemic	4+	1+		1+	Acute	Hypotension, bleeding preceded by ABD pain
Postpolypectomy	4+	2+		3+	Acute	History of polypectomy in past 14 days

**Table 51-1.** Clinical Characteristics and Historical Features in Suspected LGIB cases (Continued)

BLEEDING SOURCE	APPEARANCE OF BLOOD			VOLUME	BLEEDING ONSET	SIGNS/SYMPOTMS ASSOCIATIONS
	BRB	Maroon	Melena			
Infectious	3+	1+		1+	Acute/SA	Diarrhea, fevers, acutely ill
Aortoenteric fistula	4+	1+		4+	Acute	History of AAA repair
UGIB	1+	3+	4+	4+	Acute	Abdominal pain, NSAIDs, + NG lavage

AAA, Abdominal aortic aneurysm; ABD, abdominal; BRB, bright red blood; I, intermittent; LGIB, lower gastrointestinal bleeding; NG, nasogastric; NSAID, nonsteroidal antiinflammatory drug; SA, subacute; UC, ulcerative colitis; UGIB, upper gastrointestinal bleeding.

## 6. What can help differentiate between an upper and a lower source of bleeding?

Characteristics of a UGI source include the following:

- History includes prior ulcer, chronic liver disease, or use of aspirin or NSAIDs.
- Symptoms include nausea, vomiting, or hematemesis.
- Nasogastric (NG) aspirate contains blood or “coffee grounds” material (NG aspirate positive for bile but negative for blood does NOT rule out a UGI source).
- Serum blood urea nitrogen/creatinine ratio greater than 33 is highly suggestive.
- Melena indicates a UGI source (can also be seen in LGIB, specifically with colon cancer).

Characteristics of an LGI source include the following:

- Absence of UGI symptoms or risk factors indicates an LGI source (not always the case; one recent randomized controlled trial showed that the 15% of UGIB presenting as LGIB did not have UGI symptoms).
- Bright red or maroon blood per rectum indicates an LGI source (although can be seen in brisk UGIB).

## 7. What are the first steps taken in the management of a patient with significant LGIB?

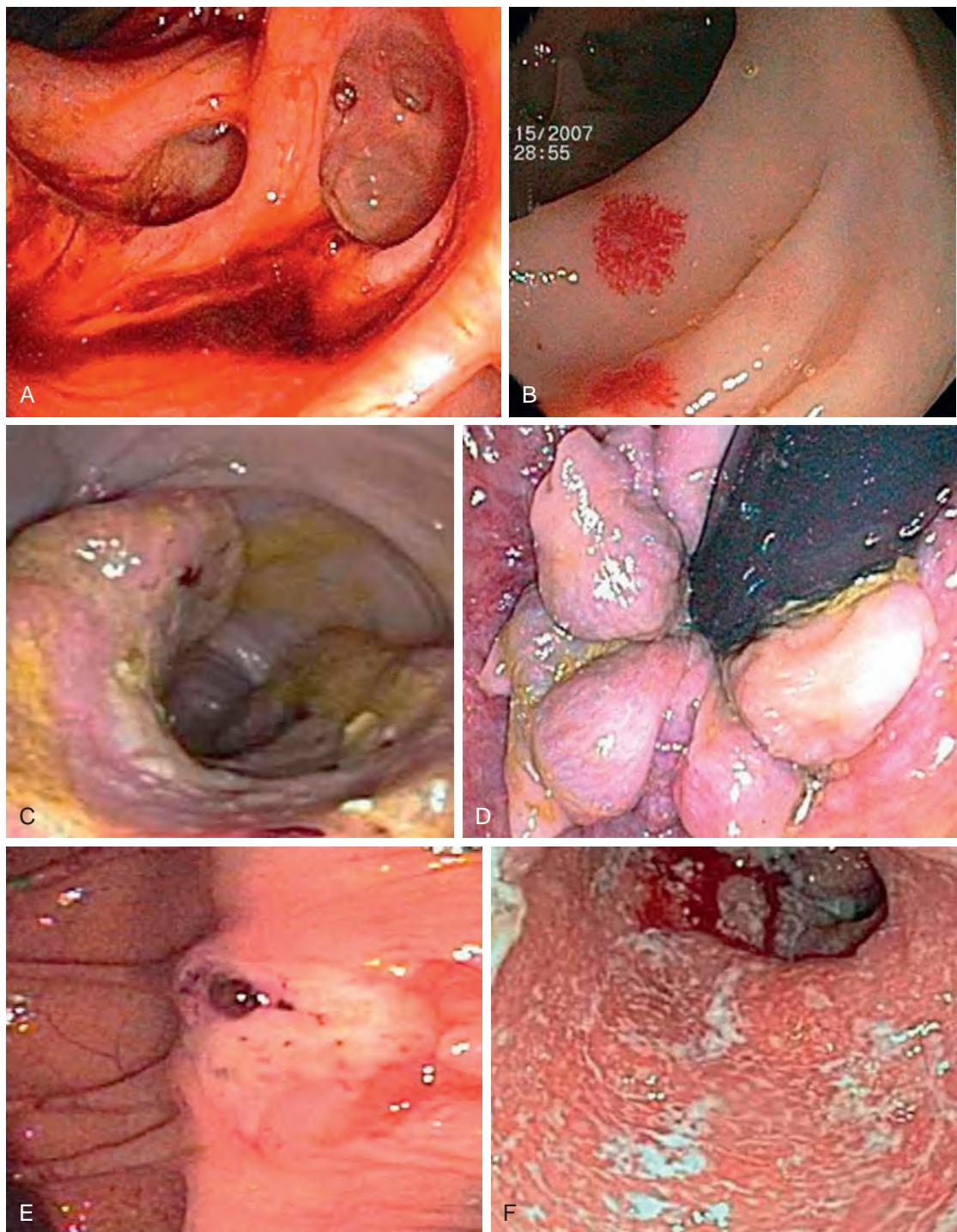
- Stabilize and resuscitate.
- Place at least one large-bore peripheral intravenous line (lactated Ringer or normal saline)
- Evaluate hemodynamic status: blood pressure, pulse, orthostatic vital signs if stable.
- Supplement oxygen by nasal cannula.
- Order laboratory tests: complete blood count, electrolytes, international normalized ratio in patients suspected of having a coagulopathy (liver disease or on warfarin), and type and screen for packed RBCs.
- Consider platelet transfusion if the patient is on aspirin.
- Get electrocardiogram for those with known arteriosclerotic heart disease or older than 50 years.
- Perform a physical examination:
  - Ear, nose, and throat examination for telangiectasias or pigmented macules may indicate Osler-Weber-Rendu disease, Peutz-Jeghers syndrome, or vascular ectasia in the gut.
  - Cardiac auscultation for aortic stenosis (Heyde syndrome) is perhaps associated with angiodyplasia of the GI tract and acquired type IIA von Willebrand syndrome.
  - Abdominal examination should assess for bowel sounds, abdominal bruit, tenderness, masses, and surgical scars. Hepatosplenomegaly, ascites, or caput medusae may indicate chronic liver disease with portal hypertension, suggesting an esophageal, gastric, or colonic variceal bleed.
  - Cutaneous purpura or petechiae suggest a coagulopathy, whereas spider angiomas or jaundice may be another indicator of chronic liver disease.
  - Joint hypermobility, swelling, or deformity may indicate a connective-tissue disorder and possible use of aspirin or NSAIDs.
  - Digital rectal examination is mandatory for all patients with LGIB to evaluate for prolapsed internal hemorrhoids or masses and to characterize the color and consistency of blood and stool in the rectal vault.

## 8. How can continued or recurrent LGIB be determined?

This determination can be challenging. Frequent monitoring of the patient's hematocrit should be performed. However, early in presentation, the hematocrit is likely to underestimate the degree of blood loss because of volume contraction. On the other hand, through dilutional effects from crystalloid hydration, the hematocrit may decrease—even in the absence of ongoing active bleeding. This decrease may not represent continued hemorrhage. Hemodynamic parameters should be monitored for signs of worsening volume depletion, especially in the setting of adequate volume resuscitation.

## 9. What are the most common causes of LGIB?

See Figure 51-1 and Table 51-2.



**Figure 51-1.** A, Diverticulosis. B, Angiodysplasia. C, Colonic adenocarcinoma. D, Internal hemorrhoids. E, Polypectomy site with stigmata of recent bleeding. F, Ulcerative colitis.

#### 10. Do NSAIDs increase the risk of LGIB?

Several case-control studies show a two- to threefold increase in LGIB with a variety of different NSAIDs. One large study in patients with rheumatoid arthritis comparing naproxen with rofecoxib demonstrated that the use of COX-2-selective inhibitors may decrease this rate by 54%. However more recent analysis of unpublished data directly challenges this optimistic result. In fact any risk reduction seen with various

**Table 51-2.** Common Causes of Lower Gastrointestinal Bleeding

ETIOLOGY	ESTIMATED PERCENTAGE
Diverticulosis	30
Colitis	15
Cancer/polyp	13
Angiodysplasia	10
Anorectal	11
Small bowel	6
No site	8
Upper gastrointestinal source	8

NSAIDs may be entirely dose related. In contrast to UGIB, there does not seem to be any risk reduction in LGIB with concomitant proton pump inhibitor use.

#### 11. Do all angiodysplasias cause LGIB?

No. Asymptomatic angiodysplasias are occasionally found during routine endoscopy. They are more common among older adults (>50 years). Most (75%) bleeding colonic angiodysplasias are found in the right colon. Small bowel angiodysplasia may occur anywhere, limiting the ability for complete endoscopic treatment by injection, laser, clips, or thermal techniques. Endoscopic treatment has been shown to be effective, however, and should be attempted if they are within reach, are actively bleeding, or are thought to be the source of bleeding or anemia. One should be cautious with any endoscopic treatment of these lesions, especially in the thin-walled right colon. Long-term octreotide may have a role in reducing transfusion requirements in patients with multiple or difficult-to-reach small bowel angiodysplasias.

#### 12. How is postpolypectomy LGIB best managed?

Postpolypectomy bleeding is the cause of 2% to 5% of all acute LGIB. Most bleeding occurs at a mean of 5 days after polypectomy. The majority of patients have been receiving NSAIDs or aspirin, antiplatelet agents, thrombin inhibitors, or anticoagulants. As such, fresh frozen plasma or platelet transfusions may be required along with endoscopic treatment. Endoscopic treatment has been shown to be successful in 95% of cases.

#### 13. What role does urgent colonoscopy have in the diagnosis of LGIB?

Ileocolonoscopy, following a rapid polyethylene glycol bowel purge, is the diagnostic method of choice for LGIB. This can establish a diagnosis in 74% to 90% of cases. Small studies have shown that alternative preparations that capitalize on the natural cathartic properties of severe colonic bleeding, augmented with tap water enemas, hydroflush waterjet irrigation pumps, and mechanical suction, offer a rapid purge-free evaluation with high diagnostic and intervention yields. To date, no study has shown that urgent colonoscopy improves clinical outcomes or lowers costs when compared with routine elective colonoscopy.

#### 14. What is the role of nuclear medicine scintigraphy, computed tomography (CT) and magnetic resonance enteroclysis, CT angiography, interventional angiography, and barium small bowel follow through in the diagnosis and treatment of LGIB?

All represent second-line tests following a nondiagnostic upper and lower endoscopy in a hemodynamically stable patient—especially in the setting of ongoing bleeding.

See Table 51-3, Figure 51-2, and Figure 51-3.

#### 15. What is the natural history of LGIB from diverticulosis?

- Bleeding is a complication in 17% of patients with colonic diverticular disease.
- Approximately 80% of patients stop bleeding spontaneously.
  - Approximately 70% will not rebleed and will not require further treatment.
  - Approximately 30% will rebleed and require treatment.

#### 16. What endoscopic methods are available for hemostasis?

Diverticular bleeding can be treated with submucosal injections of dilute epinephrine, or with contact electrocautery devices, or with hemostatic metallic clip placement. Using suction to evert a diverticulum followed by band ligation or hemostatic metallic clip placement has also been safely used. Angiodysplasias can be treated with contact electrocautery, argon plasma coagulation, or metallic clips. Visible vessels and postpolypectomy bleeding can be managed with electrocautery or endoscopically deployed metallic clips.

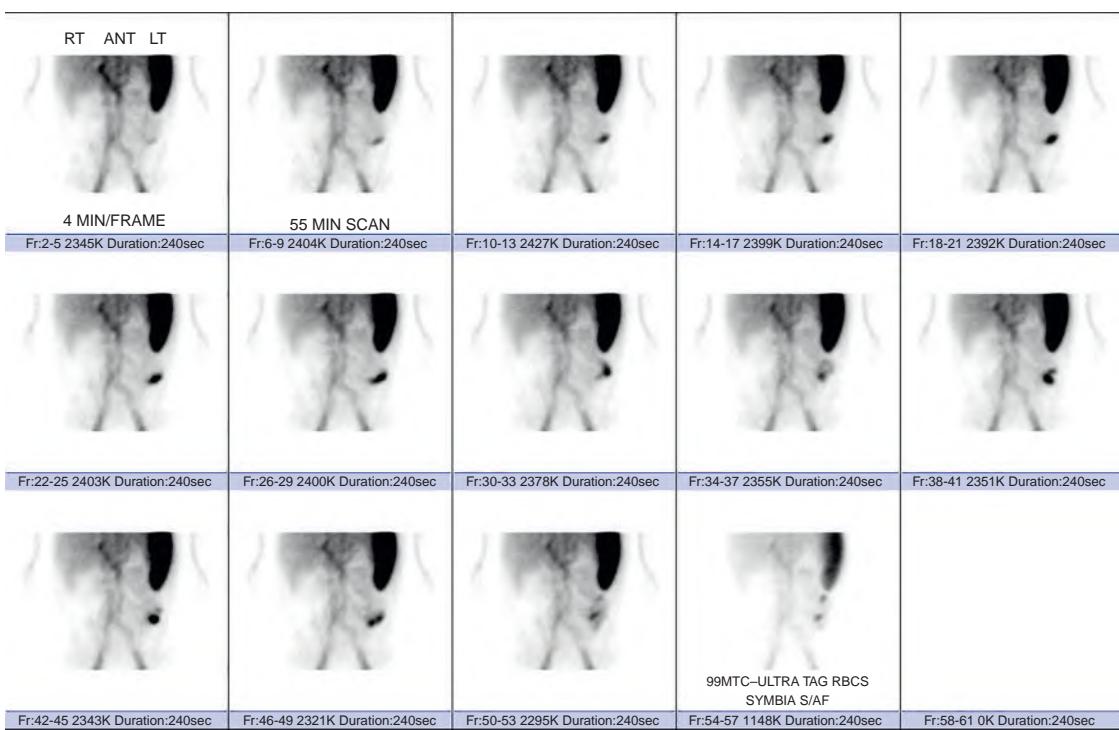
#### 17. What are the more common causes of small intestinal bleeding?

Small intestinal bleeding is commonly caused by ulceration (Crohn's, NSAIDs), angiodysplasias, and malignancy.

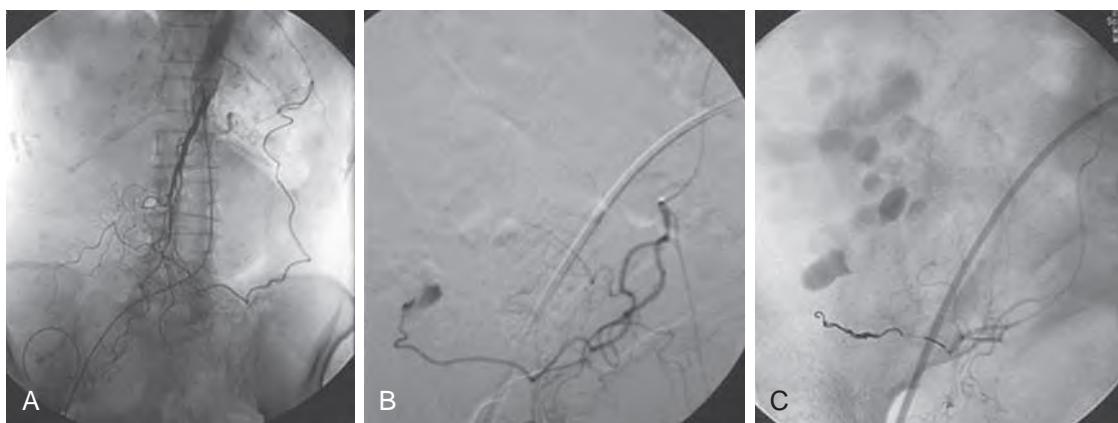
**Table 51-3.** Diagnostic Modalities for Lower Gastrointestinal Bleeding

IMAGING MODALITY	SITE DETECTED		ACTIVE BLEEDING		THERAPEUTIC ABILITY Y/N	ADVANTAGES AND DISADVANTAGES
	SB	Colon	Y/N	Rate		
Direct						
VCE	Y	N	Y	Any	N	Can also visualize nonbleeding lesions and detect recent bleeding.
DBE/SBE	Y	Y	Y	Any	Y	
Cross-sectional						
CT enteroclysis	Y	Y	+/-	N/A	N	Can visualize nonbleeding lesions and detect recent bleeding.
MR enteroclysis	Y	Y	+/-	N/A	N	
Localizing						
Scintigraphy	Y	Y	Y	0.05-0.1 mL/min	N	Can detect slow bleeding or delayed bleeding.
CT-A	Y	Y	Y	0.3-1 mL/min	N	Variable accuracy.
Angiography	Y	Y	Y	0.5-1 mL/min	Y	Rapid, accurate; can also detect recent bleeding.
Radiography						
Barium	Y	N	N	N/A	N	

CT, Computed tomography; CT-A, computed tomography angiography; DBE, double balloon endoscopy; MR, magnetic resonance; SB, small bowel; SBE, single balloon endoscopy; VCE, video capsule endoscopy.



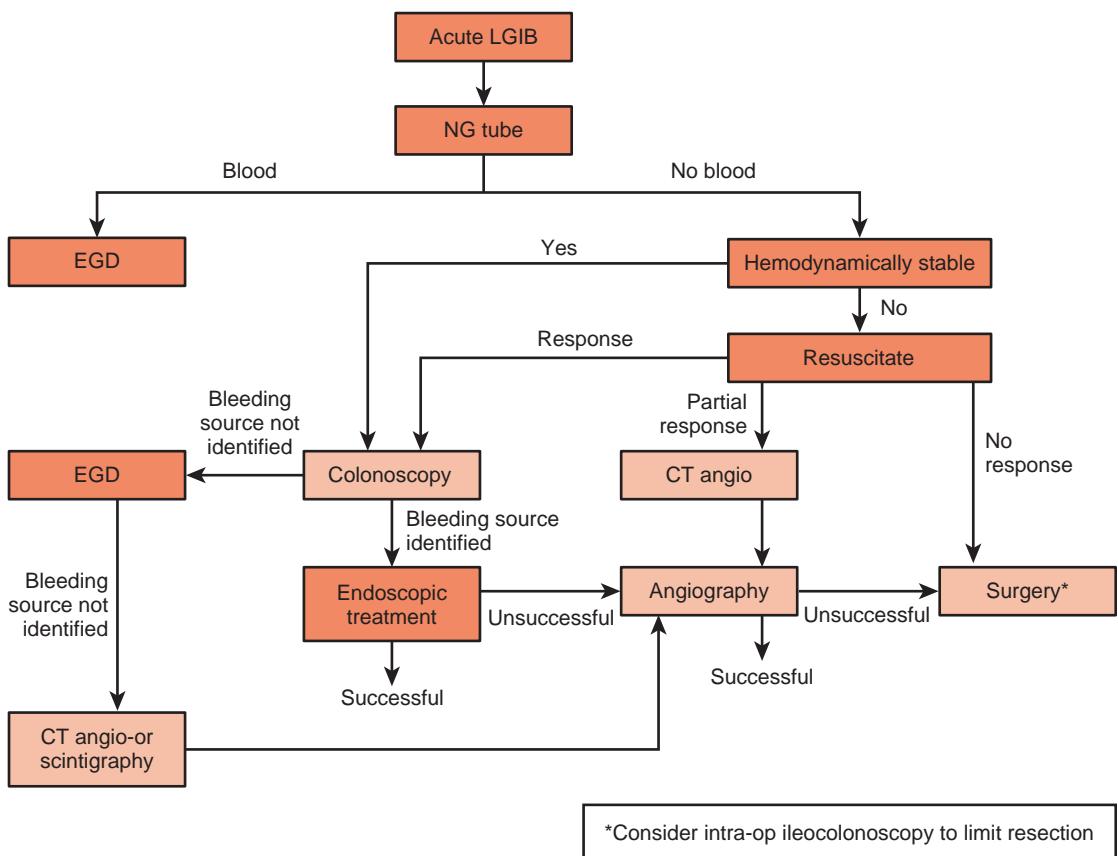
**Figure 51-2. A,** Technetium-99 m-labeled red cell scintigraphy with presumed splenic flexure hemorrhage over time. (Courtesy CDR Grant Bonavia, MD, PhD.)



**Figure 51-3.** **A**, Angiography of superior mesenteric artery with evidence of bleeding (circle, bottom left). **B**, Subselective angiography of ileocolic artery with (C) deployed coils for embolization. (Courtesy COL Kenneth H. Cho, MD.)

### 18. What is the role of surgery in LGIB?

It is good practice to obtain surgical consultation in cases of GI hemorrhage. When there is massive hemorrhage with hemodynamic instability or recurrent bleeding despite other attempted therapies, surgery for definitive therapy may become necessary. If surgery is necessary, an accurate diagnosis is vital because extent of resection and consequent postoperative morbidity and mortality depend on localization of bleeding (small bowel, cecum/ascending, transverse, right colon) *before* surgery (Figure 51-4).



**Figure 51-4.** Lower gastrointestinal bleed treatment algorithm. CT, Computed tomography; EGD, esophagogastrroduodenoscopy; LGIB, lower gastrointestinal bleeding; NG, nasogastric.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

**BIBLIOGRAPHY**

1. Bauditz J, Lochs H. Angiogenesis and vascular malformations: Antiangiogenic drugs for treatment of gastrointestinal bleeding. *World J Gastroenterol* 2007;13:5979–84.
2. Chan FK, Lanas A, Scheiman J, et al. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): A randomised trial. *Lancet* 2010;376:173–9.
3. Darcy MD, Ray CE, Vatakencherry G, et al. ACR appropriateness criteria: Radiologic management of lower GI tract bleeding. online publication, Am Coll Radiol 2011;1–5. Available at, <http://www.acr.org/Quality-Safety/Appropriateness-Criteria/%7E/media/5F9CB95C164E4DA19DCBCFBBA790BB3C.pdf>.
4. Davila R, Rajan E, Faigel D, et al. ASGE guideline: The role of endoscopy in the patient with lower-GI bleeding. *Gastrointest Endosc* 2005;62:656–60.
5. Etzel J, Williams J, Faigel D, et al. Diagnostic yield of colonoscopy to evaluate melena after a non-diagnostic EGD. *Gastrointest Endosc* 2012;75:819–26.
6. Graham D, Jewell N, Chan F. Rofecoxib and clinically significant upper and lower gastrointestinal events revisited based on documents from recent litigation. *Am J Med Sci* 2011;342:356–64.
7. Green B, Rockey D. Lower gastrointestinal bleeding—Management. *Gastroenterol Clin North Am* 2005;34:665–78.
8. Junquera F, Saperas E, Videla S, et al. Long-term efficacy of octreotide in prevention of recurrent bleeding from gastrointestinal angiodysplasia. *Am J Gastroenterol* 2007;102:254–60.
9. Kaltenbach T, Watson R, Soetikno R, et al. 2012 Colonoscopy with clipping is useful in the diagnosis and treatment of diverticular bleeding. *Clin Gastroenterol Hepatol* 2012;10:131–7.
10. Laine L, Connors LG, Reicin A, et al. Serious lower gastrointestinal clinical events with nonselective NSAID or Coxib use. *Gastroenterology* 2003;124:288–92.
11. Laine L, Shah A. Randomized trial of urgent vs. elective colonoscopy in patients hospitalized with lower GI bleeding. *Am J Gastroenterol* 2010;105:2636–41.
12. Longstreth G. Epidemiology and outcome of patients hospitalized with acute lower gastrointestinal hemorrhage: a population-based study. *Am J Gastroenterol* 1997;92:419–24.
13. Martí M, Artigas J, Soto J, et al. Acute lower intestinal bleeding: Feasibility and diagnostic performance of CT angiography. *Radiology* 2012;262:109–16.
14. Repaka A, Atkinson M, Wong R, et al. Immediate unprepared hydroflush colonoscopy for severe GI bleeding: A feasibility study. *Gastrointest Endosc* 2012;76:367–73.
15. Strate L. Lower GI bleeding: Epidemiology and diagnosis. *Gastroenterol Clin North Am* 2005;34:643–64.
16. Yi W, Vegeler R, Sava J, et al. Watch and wait: Conservative management of lower gastrointestinal bleeding. *J Surg Res* 2012;177:315–9.

# OCCULT AND OBSCURE GASTROINTESTINAL BLEEDING

Mitchell S. Cappell, MD, PhD

## 1. What is occult gastrointestinal (GI) bleeding and how does it differ from overt GI bleeding?

Occult GI bleeding is microscopic blood loss from the GI tract that is not overtly or grossly apparent. It is typically detected by a guaiac test or fecal immunologic test (FIT, see Question 5).

Overtly apparent GI bleeding includes the following (see [Chapters 50 and 51](#)):

- Hematemesis: bright red or “coffee grounds”
- Melena
- Bright red blood per rectum
- Burgundy stools
- Bloody diarrhea

## 2. How is occult GI bleeding usually detected?

Occult GI bleeding is typically detected by obtaining a stool sample, smearing the stool sample on a guaiac-impregnated card, and applying a reagent solution to the card. A positive test is indicated by change in the color of the impregnated card from colorless to bright blue because of the presence of peroxidase (or pseudoperoxidase) in the stool. As little as 2 to 5 mL of blood per rectum per day can produce a positive guaiac test.

## 3. What are the difficulties with guaiac testing for fecal occult blood?

The sensitivity of three guaiac tests obtained on three consecutive days is moderately high (up to 80%) for detecting colon cancer because colon cancers typically bleed intermittently.

Additional weaknesses of guaiac testing for colon cancer include the following:

- The benign precursor of colon cancer, adenomatous polyps usually do not bleed and are not detected by guaiac test.
- A positive stool guaiac test cannot distinguish bleeding from colonic cancer versus an upper gastrointestinal (UGI) source (e.g., gastritis, ulcer, esophagitis).
- Microscopic bleeding from the UGI tract—ulcer, gastritis, esophagitis, and so on—can cause the guaiac test to be positive.
- Approximately 5% to 10% of all guaiac tests are falsely positive.

False positivity may be due to recent ingestion of fresh fruits and uncooked vegetables, especially cruciferous vegetables (cabbage, cauliflower, and broccoli) that can catalyze the colorimetric reaction because of the presence of pseudoperoxidase in this produce; or recent ingestion of red meat, especially steak, that contains residual blood from cows or other mammals that can catalyze the reaction just like human blood. Recent ingestion of iron- or bismuth-containing medications (Pepto-Bismol) can cause stools to appear dark-blue to black and result in a false-positive stool guaiac test. Recent aspirin or nonsteroidal anti-inflammatory drug use can cause microscopic GI bleeding. A dried stool specimen can lead to a falsely negative test, whereas rehydration of a dried specimen can lead to a falsely positive test.

## 4. How should guaiac tests be ideally performed to detect fecal occult blood?

- Stool specimens should be collected over 3 consecutive days.
- Guaiac testing should be performed on a fresh specimen (<7 days).
- Dry specimens should be rehydrated.
- Patients should refrain from eating red meat and cabbage, cauliflower, or broccoli.
- Avoid taking aspirin or NSAIDs for several days before the test.

## 5. What test for fecal occult blood is superior to guaiac testing but is not commonly used clinically?

In FIT, antibodies to human hemoglobin are collected from venipuncture of rabbits previously exposed to human blood and are coupled to fluorescent proteins for easy detection. These antibodies attach to human blood (hemoglobin) in stool and are detected by their fluorescence. The FIT test is superior to guaiac tests for detection of colon cancer and colon adenomatous polyps. In Japan, patients with a positive FIT screening test undergo colonoscopy as the diagnostic test.

**Advantages of FIT Test**

- Specific for human hemoglobin, does not recognize cow or other mammalian hemoglobin.
- There are no false positive results with cabbage, cauliflower, or broccoli (pseudoperoxidase).
- Hemoglobin released from UGI tract bleeding is digested, and is not immune reactive to FIT.

**6. Is testing a nasogastric (NG) aspirate for fecal occult blood clinically useful?**

No. This test is frequently falsely positive because of incidental microscopic bleeding from nasopharyngeal or esophageal trauma during NG tube insertion.

**7. What is fecal genetic testing and can this test be used to replace the standard guaiac test for occult blood to screen for colon cancer?**

Passage of stool through the colon leads to shedding of microscopic amounts of colonic cellular DNA that remain viable in stool for many days. Genetic mutations present in microscopic amounts in this tissue can be detected by polymerase chain reaction of stool samples. An array of genetic tests is performed to detect genetic mutations associated with colon cancer, such as APC mutation (a molecular marker for adenomatous polyps), and BAT mutation (a marker for mismatch repair gene mutations). This test is currently investigational as a screening test for colon cancer and is not commercially available. The sensitivity of a single fecal DNA test is reportedly approximately 80% for colon cancer but is much lower for advanced adenomas, a characteristic that currently limits its clinical applicability. Even so, it has a higher sensitivity than guaiac testing for detecting advanced adenomas. It is hoped that future identification of novel genetic mutations in colonic carcinogenesis will yield additional genetic tests to place in the genetic array to increase test sensitivity, especially for detecting adenomas.

**8. What is the sensitivity and specificity of guaiac testing for fecal blood?**

The sensitivity of guaiac testing depends on the specific brand used. Several guaiac reagents are marketed. The most sensitive brand is the Hemoccult II-SENSA test. The sensitivity also depends on the lesion to be detected. It is not a good test for detecting colonic adenomas because adenomas infrequently bleed. It is moderately (up to 80%) sensitive at detecting colon cancer when performed on 3 consecutive days to account for intermittent bleeding from colon cancer.

The specificity of guaiac testing is only approximately 20% to 30% for detecting significant colonic lesions. The yield of colonoscopy performed for a guaiac-positive test is colon cancer in 3% to 4% of patients and colonic adenomas in 15% to 20% of patients (or higher in older adult patients).

**9. How is a patient with a positive fecal occult blood test (FOBT) evaluated?**

The evaluation of a positive FOBT depends somewhat on the clinical situation.

Asymptomatic persons with positive FOBT and iron-deficient anemia require colonoscopy. If colonoscopy is negative for a source of FOBT or anemia, then esophagogastroduodenoscopy (EGD) should be performed.

**10. How do patients with iron-deficiency anemia present clinically in terms of symptoms, signs, and laboratory abnormalities?**

- Pica
- Pallor
- Weakness
- Palpitations
- Koilonychia
- High-output congestive heart failure
- Dyspnea on exertion
- Orthostatic symptoms
- Microcytic, hypochromic indices for erythrocytes
- Percent iron saturation <16%

**11. How should young menstruating women with iron-deficiency anemia be evaluated?**

The evaluation of iron-deficiency anemia in pregnant or relatively young menstruating females is individualized according to clinical presentation and menstrual and obstetric history. Iron deficiency during pregnancy is common. In a series of 186 menstruating women, 12% had a clinically important lesion detected by endoscopy. The most common cause of bleeding was peptic ulcer disease in 3%, and gastric cancer in 3%. On multivariate analysis, independent predictors of a significant lesion at endoscopy included a positive FOBT, hemoglobin less than 10 g/dL, and abdominal symptoms. Menstruating females presenting with iron-deficiency anemia who have a positive FOBT, anemia out of proportion to menstrual blood loss, abdominal symptoms, are 40 years old or older, or have a family history of GI malignancy should be strongly considered for GI endoscopy.

**12. How often is iron-deficiency anemia caused by underlying chronic GI blood loss?**

Approximately 60% of persons with iron deficiency will have an identifiable cause detected by EGD and colonoscopy:

- EGD demonstrates 36% (11% duodenal ulcer, 5% gastric ulcer, 3% anastomotic ulcer).
- Colonoscopy demonstrates 25% (cancer was most common cause).
- Diagnostic investigations should always be directed by symptoms and signs.

Non-GI causes should be considered as a potential cause of iron deficiency:

- Pregnancy
- Hematuria
- Celiac disease
- Menstrual bleeding
- Nutritional deficiencies

### 13. What do the terms *upper GI bleeding (UGIB)*, *lower GI bleeding (LGIB)*, and *middle GI bleeding (MGIB)* mean?

See Table 52-1. Although this categorization is appealingly simplistic, sometimes clinically suspected MGIB, based on one negative EGD and one negative colonoscopy, turns out to be UGIB that was missed on an initial EGD or LGIB that was missed on an initial colonoscopy. This initial misdiagnosis can occur in up to 20% of cases of suspected MGIB.

**Table 52-1.** Categorization of Gastrointestinal Bleeding Terms

LOCATION	DEFINITION	METHOD OF EVALUATION
UGIB	Esophagus, stomach, duodenum to the ligament of Treitz	EGD
LGIB	Colon from the ileocecal valve to the anus	Colonoscopy (usually) Nuclear medicine studies or arteriography (special situations)
MGIB	Small bowel from ligament of Treitz to the ileocecal valve	Capsule endoscopy, enteroscopy (push-type, single balloon, or double balloon) Radiologic (contrast enterography)

EGD, Esophagogastroduodenoscopy; LGIB, lower gastrointestinal bleeding; MGIB, middle gastrointestinal bleeding; UGIB, upper gastrointestinal bleeding.

### 14. What is meant by *obscure GI bleeding*?

Obscure GI bleeding, sometimes referred to as *GI bleeding of obscure origin (GIBOO)*, is defined as recurrent or persistent GI bleeding without identifiable source despite EGD, colonoscopy, and a radiologic examination of the small bowel. The obscure bleeding may be acute and gross or occult and microscopic. Obscure GI bleeding constitutes approximately 5% of all GI bleeding.

This definition of GIBOO is becoming outdated because of improved detection by capsule endoscopy and a variety of small bowel endoscopic techniques.

### 15. What radiologic tests are available for patients with GIBOO and what is their yield?

- **Small bowel series:** Yield is only approximately 10%. Disadvantages: misses angiodysplasia, and contrast in the gut obscures and precludes angiography.
- **Enteroclysis:** Yield is approximately 15%. Disadvantages: misses angiodysplasia, and contrast in the gut obscures and precludes angiography.
- **Computed tomography enterography:** Method is good for Crohn's disease and small bowel tumors. Disadvantages: misses angiodysplasia, and contrast in the gut obscures and precludes angiography.
- **Nuclear medicine bleeding scan:** 99 m technetium is attached to autologous erythrocytes ex-vivo and then reintroduced intravenously. Extravasated blood in the bowel lumen confirms active bleeding. GI bleeding low as 0.1 to 0.5 mL per minute can be detected, but localization is generalized to abdominal regions.
- **Mesenteric angiography:** Yield is approximately 20%. A bleeding scan is often performed first to confirm that bleeding is active, followed via mesenteric angiography. Angiography may be therapeutic. Actively bleeding lesions can be arrested by embolization with gelfoam or metal coils delivered by the angiographic catheter. The major risk of therapeutic embolization is mesenteric ischemia, which has decreased to 1% or less with super-selective cannulation.

### 16. When a patient is referred to a tertiary center for GIBOO, is it worthwhile for the specialized gastroenterologist at this center to repeat another EGD or colonoscopy before performing specialized small bowel examinations?

Patients referred to a tertiary center for GIBOO usually undergo repeat EGD and colonoscopy. The yield on repeat EGD is approximately 10%. Commonly identified lesions include Cameron ulcers or erosions within a hiatal hernia, peptic ulcers, vascular angiodysplasia, gastric antral vascular ectasia, and Dieulafoy lesions. Esophageal varices that were thought to be incidental findings on the first EGD may be recognized as the bleeding source on repeat EGD by finding stigmata of recent hemorrhage on the varices, such as wale bites or red streaks. When a cause of iron-deficiency anemia is not identified, normal-appearing duodenal mucosa should be biopsied to exclude possible celiac disease.

Repeat colonoscopy is especially important when the initial procedure was hampered by incomplete or poor bowel preparation. Commonly identified lesions at repeat colonoscopy include colon cancer, angiodysplasia, diverticular bleeding, and Crohn's colitis.

#### **17. How is small bowel capsule used for endoscopy of the small bowel in patients with GIBOO?**

The most widely available and most commonly performed endoscopic test to evaluate the small bowel for GIBOO is small bowel capsule endoscopy. This capsule primarily supplies images of the small bowel, but can also supply limited images of the esophagus, stomach, and cecum. The capsule contains a light source to illuminate the gut, one or more cameras for color photography, a wireless transmitter to transmit the images electronically, and a battery to power these electronic operations. A recorder is usually worn by the patient to receive the transmitted images. The capsule battery generally permits transmission of endoscopic images for approximately 8 hours. The capsule is swallowed with water and passively traverses the alimentary tract by peristalsis. Patients fast overnight before the procedure and should receive a liquid polyethylene glycol–3350 bowel preparation shortly before the procedure to evacuate luminal debris and provide a clear fluid interface.

Three small bowel capsule brands are commercially available. The PillCam is the latest model produced by Given Imaging (Yoqneam, Israel), which developed the first device. It has a variable frame rate, ranging from two frames per second when stationary up to six frames per second when moving quickly. Other brands include the EndoCapsule by Olympus Corporation (Allentown, PA), and the MiRoCam capsule marketed by Medivators, Inc. (Minneapolis, MN), which was recently approved for use in America.

#### **18. What other endoscopic tests are available to evaluate the small bowel in patients with obscure GI bleeding?**

Various “long endoscope” endoscopy tests permit diagnosis and potential treatment.

- **Push enteroscopy** uses an enteroscope that is similar, but substantially longer than a standard UGI endoscope. The longer enteroscope allows intubation more distally, typically into the proximal jejunum, approximately 50 cm beyond the ligament of Treitz.
- **Spiral enteroscopy** uses a 118-cm long overtube with a soft, raised, spiral helix at its distal end (Spirus Medical Inc., Stoughton, MA) that is placed over a long enteroscope. The overtube is affixed to the enteroscope via a coupling device that permits rotation of the overtube. The spiral ridge of the overtube engages the small bowel plicae circulares (folds) during clockwise rotation like a screw into wood. The enteroscope is advanced by rotating the overtube clockwise, which pleats the small bowel onto the overtube. The most common complication is self-limited mucosal trauma from spiraling over mucosal folds. There is a low rate of major complications of 0.4%, including a 0.3% rate of GI perforations. Spiral enteroscopy is not widely available.
- **Double-balloon enteroscopy** consists of a 200-cm long enteroscope with a latex balloon at its tip, and a 145-cm long soft overtube with another latex balloon at its tip, and pumps to inflate both balloons. The enteroscope is advanced during repetitive cycles of inflation and deflation of the individual balloons coupled with alternating advancement of the enteroscope or overtube. The diagnostic yield for the indication of obscure bleeding ranges from 40% to 80%. The rate of major complications is approximately 0.7%, with a 0.4% rate of GI perforation.
- **Single-balloon enteroscopy** uses a 140-cm long overtube and a 200-cm long enteroscope. The overtube is equipped with an inflatable balloon at its tip to aid in endoscope advancement through the small bowel by pleating of small bowel on the overtube. The average depth of small bowel insertion ranges from 150 to 250 cm. Single-balloon enteroscopy has a yield somewhat lower than double-balloon enteroscopy, with a diagnostic yield of 40% to 65%. Complications include abdominal pain, pyrexia, mucosal tears, aspiration pneumonia, cardiovascular events, and perforation. The rate of GI perforation is approximately 0.4%.

#### **19. What are the common causes of GIBOO as determined by capsule endoscopy?**

Capsule endoscopy identifies a source for GIBOO in 56% of cases:

- Small bowel angiodysplasia in 22%
- Small bowel ulcers in 10%
- Small bowel tumors in 7%
- Small bowel varices in 3%
- Luminal blood without identifiable lesion approximately 8%
- Esophageal or gastric source approximately 8%
- Colonic angiodysplasia 2%

#### **20. What are the advantages, disadvantages, and contraindications of capsule enteroscopy?**

##### **Advantages**

- Approximately 60% yield of diagnosis for GIBOO
- Much better diagnostic yield than push enteroscopy and radiography

### **Disadvantages**

- Capsule retention seen in 1% (usually at site of pathologic obstruction)
  - Tumors
  - Strictures
  - Ulcers
  - Crohn's disease is the most common cause for capsule retention

### **Contraindications**

- Esophageal stricture
- Zenker diverticulum
- Known intermittent or partial small bowel obstruction
- Not approved for use during pregnancy

In a patient with high likelihood of small bowel stricture or partial obstruction, a patency capsule (Given Imaging) should be performed before capsule endoscopy. The patency capsule is identical in size and shape to the PillCam capsule, but contains barium within a lactose shell that will dissolve within 2 days of ingestion.

A plain radiograph is obtained at 24 to 30 hours after patency capsule ingestion. Small bowel luminal patency is suggested by passage of the capsule into the colon or toilet. Capsule endoscopy is contraindicated if the patency capsule is retained in the small bowel at 24 to 30 hours after ingestion.

### **21. What are angiodyplasias?**

Normally arteries are connected to veins via intervening capillaries. Arteries are exposed to high pressure because they receive blood pumped from the heart and have a relatively thick, muscular wall to contain blood under high pressure without bursting or leaking. The very narrow capillaries normally dissipate the high pressure in the arterial system through friction to produce a low pressure in the venous system.

Veins typically have thin walls because they are exposed to low pressures. Angiodysplasia is a vascular tuft or tangle of vessels with a central feeding artery directly connected directly to veins without intervening capillaries. Angiodysplasia is sometimes called *arteriovenous malformation* to describe this vascular anomaly. In angiodysplasia the veins distal to the feeding artery are exposed to abnormally high pressures because of the absence of capillaries and can become leaky, manifesting clinically as occult or gross bleeding.

### **22. How does angiodysplasia appear at endoscopy?**

At endoscopy angiodysplasia appears as a dense macular, reticular network of vessels (vascular tuft) which is typically 2 to 8 mm wide and is composed of intensely bright, red lesions resulting from the presence of oxygenated, "arterialized" blood within vessels directly supplied by an artery without an intervening capillary. Without capillaries the oxygen attached to hemoglobin is not released and the veins are not deoxygenated. A prominent feeding artery or draining vein is occasionally noted. Angiodysplasias are differentiated from mucosal erosions or hemorrhages from endoscopic trauma because angiodysplasias, unlike traumatic lesions, have a fine internal vascular structure often resembling a starburst, stellate, or arachnoid network.

### **23. How does angiodysplasia appear at angiography?**

Angiodysplasia appears as a vascular tuft or tangle of vessels resulting from a local mass of irregular vessels, best visualized in the arterial phase. It demonstrates early and intensely filling veins because of direct communication of the artery to the veins without intervening capillaries. It typically shows persistent opacification beyond the normal venous phase (slowly emptying vein) likely from venous tortuosity (ectasia). At angiography, bleeding angiodysplasia shows extravasation of blood in which the blood is seen to actively pool near the vascular tuft. Angiodysplasias bleed only intermittently, however, and demonstrate extravasation of contrast in only approximately 10% of cases at angiography.

### **24. What are common risk factors for angiodysplasia?**

Sporadic angiodysplasias most commonly occur as (acquired) lesions in older adults. They are believed to arise as degenerative lesions of aging caused by chronic, intermittent, low-grade obstruction of veins and capillaries. They most commonly occur in the cecum or proximal right colon. This predilection is explained by the greater cecal mural tension owing to its larger luminal diameter, according to Laplace's law. Exposure to greater mural tension tends to stretch the vessel wall and promote angiodysplasia.

Angiodysplasias are sometimes associated with the following syndromes or diseases:

- **Hereditary hemorrhagic telangiectasia (HHT):** HHT is a genetic vascular disorder caused by mutations of the endoglin (ENG) gene (type 1 HHT), or the ACVRL1 gene (type II HHT). These mutations impair blood vessel endothelial growth and repair, which result in tortuous blood spaces lined by a single layer of endothelial cells. These mutations lead to widening of small vessels that eventually create angiodysplasia. Because these patients have a diathesis for angiodysplasia, they can develop extensive angiodysplasia in several organs, most commonly the nasal mucosa, GI mucosa, or oropharynx and lips. Nasal angiodysplasia may present as recurrent epistaxis (nosebleeds) that are difficult to treat because of the extensiveness of these lesions. Oropharyngeal angiodysplasia may be identified on physical examination. GI angiodysplasias tend to bleed significantly and repeatedly because of their thin and fragile vascular wall that lacks a muscular layer. Patients often present with the clinical triad of telangiectasia, recurrent epistaxis, and a compatible

family history. Patients with HHT are differentiated from sporadic angiodyplasias by clinical presentation at a much younger age, multiplicity of GI lesions, positive family history, and chronic epistaxis.

- **Chronic renal failure:** Patients with chronic renal failure have a much higher frequency of bleeding from GI angiodyplasia than the general population.
- **Collagen vascular disease:** A number of case reports have associated GI angiodyplasia with scleroderma or related disorders such as calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia (CREST) syndrome.
- **Aortic stenosis:** Although somewhat controversial, numerous studies have associated aortic stenosis with chronic GI bleeding from angiodyplasia. The bleeding may not reflect an increased risk of developing angiodyplasia in patients with aortic stenosis, but an increased risk of bleeding from preexisting angiodyplasia caused by destruction of multimers of von Willebrand factor from high shear forces across a stenotic aortic valve.

## **25. How can GI angiodyplasia be treated at angiography or endoscopy to avoid surgical resection?**

Angiodyplasias that are actively bleeding, oozing, or a likely cause of recent or chronic GI bleeding may be treated at angiography or endoscopy. At angiography, bleeding angiodyplasias are identified by extravasation of dye. The catheter is snaked close to the angiodyplasia by superselective catheterization and metal coils or gelfoam are released to embolize the vessel feeding the angiodyplasia.

Angiodyplasia can be ablated at endoscopy using high energy delivered via argon plasma coagulation (APC), electrocoagulation (e.g., Bicap or Gold Probe), thermocoagulation (e.g., Heater Probe), or injection sclerotherapy (e.g., sodium tetradecyl sulfate). APC has a high rate of success at preventing rebleeding from angiodyplasia.

When encountering numerous angiodyplasias at endoscopy performed for recent GI bleeding, the practitioner should treat *only* those angiodyplasias that are actively bleeding or oozing, that have stigmata of recent hemorrhage (an adherent clot), or are unusually large. Angiodyplasias that are small, not actively bleeding, and do not have any stigmata of recent hemorrhage generally do not require endoscopic therapy.

## **26. How can lesions identified by capsule endoscopy be further defined before performing surgery?**

Capsule endoscopy often does not permit an ideal view of lesions because the capsule tumbles through the small bowel naturally by peristalsis without any opportunity to adjust position to obtain a better view. Thus lesions may be seen peripherally on only one videophotograph. Capsule endoscopy also does not permit cleaning the photographic lens or clearing the endoscopic field to improve visualization. Capsule endoscopy also does not permit biopsy or brushing of lesions for cytologic or pathologic analysis. It is solely diagnostic and not therapeutic. Single-balloon or double-balloon enteroscopy can better view small intestinal lesions identified by capsule endoscopy. Lesions can be biopsied or ablated at double-balloon enteroscopy.

## **27. What is a Meckel's diverticulum, how does it clinically present, and what test is standardly used to diagnose it?**

A Meckel's diverticulum is a congenital diverticulum or outpocketing of small intestinal mucosa that typically occurs in the middle-to-distal ileum, approximately 150 cm proximal to the ileocecal valve. It occurs in approximately 2% of the population. This congenital anomaly is clinically important because of its propensity to cause obscure GI bleeding, especially in children. The bleeding is secondary to intestinal ulceration from acid secreted by ectopic gastric mucosa lining the diverticulum. The bleeding typically occurs in children who present with painless LGIB. However, Meckel's diverticulum is also in the differential diagnosis of obscure, painless, LGIB in adults. Patients usually present with dark red or maroon stools.

Meckel's diverticular bleeding is diagnosed by a Meckel's scan, in which 99 m technetium pertechnetate is administered intravenously. Nuclear scintigraphy is then performed to identify the ectopic gastric mucosa within the diverticulum by the selective attachment of the technetium pertechnetate to it. A Meckel's scan is approximately 90% sensitive and 90% specific for bleeding from a Meckel's diverticulum in children, but is less accurate in adults.

## **BIBLIOGRAPHY**

1. Cappell MS. Gastrointestinal vascular malformations or neoplasms: Arterial, venous, arteriovenous and capillary. In: Yamada T, Alpers D, Kalloo AN, et al., editors. Textbook of Gastroenterology. 5th ed. Chichester (West Sussex), United Kingdom: Wiley-Blackwell; 2009. p. 2785–810.
2. Cappell MS, Lebwohl O. Hereditary hemorrhagic telangiectasia. In: Lebwohl MG, Heymann WR, Berth-Jones J, Coulson I, editors. Treatment of skin disease: Comprehensive therapeutic strategies. 4th ed. London: Saunders (Elsevier); 2014. p. 301–3.
3. Kato J, Morikawa T, Kuriyama M, Yamaji Y, Wada R, Mitsushima T, et al. Combination of sigmoidoscopy and a fecal immunochemical test to detect proximal colon neoplasia. Clin Gastroenterol Hepatol 2009;7(12):1341–6.
4. Kim JJ, Han A, Yan AW, Cao D, Laine L. Gastroenterologists' practice patterns for positive fecal occult blood test. J Clin Gastroenterol 2014;48(2):119–26.
5. Lepileur L, Dray X, Antonietti M, et al. Factors associated with diagnosis of obscure gastrointestinal bleeding by video capsule endoscopy. Clin Gastroenterol Hepatol 2012;10(12):1376–80.

6. Lin S, Suhocki PV, Ludwig KA, Shetzline MA. Gastrointestinal bleeding in adult patients with Meckel's diverticulum: The role of technetium 99 m pertechnetate scan. *South Med J* 2002;95(11):1338.
7. Liu K, Kaffes AJ. Review article: The diagnosis and investigation of obscure gastrointestinal bleeding. *Aliment Pharmacol Ther* 2011;34(4):416–23.
8. Rockey DC, Cello JP. Evaluation of the gastrointestinal tract in patients with iron-deficiency anemia. *N Engl J Med* 1993;329(23):1691–5.
9. Winawer SJ, Fleisher M, Baldwin M, Sherlock P. Current status of fecal occult blood testing in screening for colorectal cancer. *CA Cancer J Clin* 1982;32(2):100–12.

# EVALUATION OF ACUTE ABDOMINAL PAIN

John S. Goff, MD

## 1. Provide a useful clinical definition of an acute abdomen.

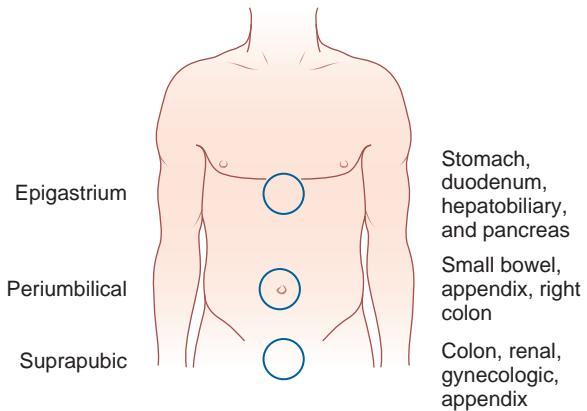
This clinical scenario is characterized by abrupt onset of severe pain caused by infarction, perforation, inflammation, obstruction, or organ rupture. Surgical intervention is usually required.

## 2. What are the four types of stimuli for abdominal pain?

1. Stretching or tension—visceral nociception
2. Inflammation—mediated by kinins, histamine, prostaglandins, and so on
3. Ischemia—similar to inflammation
4. Neoplasm—nerve invasion

## 3. What are the three categories of abdominal pain (Figure 53-1)?

1. *Visceral pain* occurs when noxious stimuli affect an abdominal viscous. The pain is usually dull (cramping, gnawing, or burning) and poorly localized to the ventral midline because the innervation to most viscera is multisegmental. Secondary autonomic effects such as diaphoresis, restlessness, nausea, vomiting, and pallor are common.
2. *Parietal pain* occurs when noxious stimuli irritate the parietal peritoneum. The pain is more intense and more precisely localized to the site of the lesion. Parietal pain is likely to be aggravated by coughing or movement.
3. *Referred pain* is experienced in areas remote from the site of injury. The remote site of pain referral is supplied by the same neurosegment as the involved organ; for example, gallbladder pain may be referred to the right scapula and pancreatic pain may radiate to the midback.



**Figure 53-1.** Location of visceral pain.

## 4. How does the character of the abdominal pain help in the evaluation?

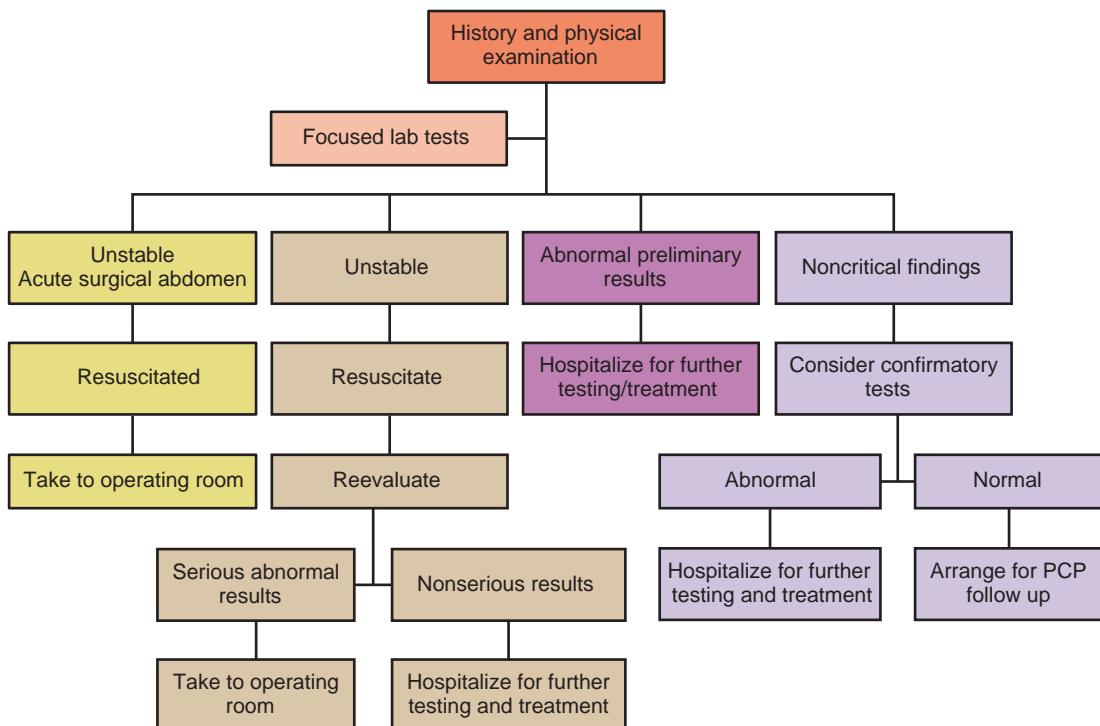
Most pain tends to be midline because of bilateral innervations, with the exception of pain from the kidneys, ureters, abdominal wall, gallbladder, and the ascending or descending colon, which tend to lateralize (Table 53-1).

## 5. What are the important historical questions to ask? (See Figure 53-2 for an algorithm of the assessment of acute abdominal pain.)

- What is the location of the pain and does it radiate?
- What are the exacerbating factors? What are the effects of eating or drinking, activity, position, passage of gas or stool from the rectum, or urination?
- What associated symptoms are there? Assess for nausea, vomiting, no passage of gas or stool, diarrhea, constipation, bloody stools or emesis, dysuria, dysmenorrhea, dyspareunia, fever, or chills.
- Especially important past medical history questions are conditions that might mute the early symptoms of an acute abdominal process such as immunosuppression, diabetes, chronic renal failure, or steroid use.

**Table 53-1.** Classification of Pain by the Rate of Development

Explosive and excruciating (instantaneous)	Myocardial infarction Perforated ulcer Ruptured aneurysm Biliary or renal colic (passage of a stone)
Rapid, severe, and constant (over minutes)	Acute pancreatitis Complete bowel obstruction Mesenteric thrombus
Gradual and steady pain (over hours)	Acute cholecystitis Diverticulitis Acute appendicitis
Intermittent and colicky pain (over hours)	Early subacute pancreatitis Mechanical small bowel obstruction

**Figure 53-2.** Algorithm for the assessment of acute abdominal pain. PCP, Primary care physician.

- Obtain a family history of medical conditions.
- Obtain a social history of drug use, alcohol abuse, smoking, and sexual behavior.
- Obtain a history of medication use, including prescribed, over the counter, and birth control pills.
- Obtain a menstrual history.

## 6. What are the important components of the physical examination for patients with acute abdominal pain?

- **General status:** Is the patient hemodynamically unstable? Does he or she need immediate hemodynamic resuscitation and emergent laparotomy (e.g., ruptured spleen, ruptured hepatic tumor, aneurysm, ectopic pregnancy, or mesenteric apoplexy)?
- **Inspection:** Visually evaluate for distention, hernias, scars, and hyperperistalsis.
- **Auscultation:** Hyperperistalsis suggests obstruction; absence of peristalsis (no bowel sounds heard over 3 minutes) suggests peritonitis (silent abdomen); bruits suggest presence of an aneurysm.

- **Percussion:** Tympany suggests either intraluminal or free abdominal air.
- **Palpation:** Start the examination away from the area of tenderness and be gentle. Abdominal pain with voluntary coughing suggests peritoneal signs. Deeply palpating the abdomen only diminishes patient trust and cooperation. The enlarged gallbladder will be missed on aggressive, deep palpation. Inspiratory arrest during light palpation of the right hypochondrium suggests gallbladder pain (Murphy's sign). Localized pain suggests localized peritonitis (e.g., appendicitis, cholecystitis, diverticulitis).
- **Pelvic and rectal examination:** These examinations should be done in *all* patients with abdominal pain. A painful examination may be the only sign of pelvic appendicitis, diverticulitis, or tubo-ovarian pathologic conditions. Bimanual examination is critical to exclude an obstetric or a gynecologic cause.
- **Iliopsoas test:** With the legs fully extended in a supine position, the patient is requested to raise the legs unilaterally. Pain occurs when the right psoas muscle is inflamed (e.g., appendicitis).
- **Obturator test:** This test is performed by flexing the patient's thigh at right angle to the trunk and then rotating the leg externally. Inflammation of the obturator internus muscle causes pain (e.g., tubo-ovarian abscess or pelvic appendicitis).

## 7. Which laboratory tests should be obtained in patients with acute abdominal pain?

Although laboratory tests are helpful in confirming the evolution of a disease process, they are frequently not helpful in localizing the cause of abdominal pain.

- Obtain a *complete blood count*. Elevation of the white blood cell count suggests inflammation; however, absence of leukocytosis may be misleading early in the course of disease. A low hematocrit with a normal mean corpuscular volume (MCV) suggests acute blood loss, whereas a low hematocrit with a low MCV suggests iron deficiency from chronic gastrointestinal (GI) blood loss or malabsorption.
- *Amylase and lipase elevations* may suggest pancreatitis, but amylase can come from various other sources, including salivary glands, lung, intestine, and ovary.
- *Liver enzyme elevations* may be suggestive of hepatobiliary causes of pain. Elevations of aspartate or alanine aminotransferase suggest hepatocyte injury. Alkaline phosphatase or  $\gamma$ -glutamine transferase elevations suggest canalicular or biliary injury. Total bilirubin elevations greater than 3 mg/dL suggest common bile duct obstruction or associated intrahepatic cholestasis, but if bilirubin elevation is predominantly unconjugated and not associated with liver enzyme elevations, it may be due to Gilbert's disease.
- *Evidence of pyuria* on urinalysis suggests urinary tract infection but also may be seen in nephrolithiasis, prostatitis or even pelvic appendicitis.
- *Chemistry analysis* can be helpful in the global assessment of patient health, hyperglycemia, acidosis, and electrolyte disturbances.
- *Pregnancy tests* (beta human chorionic gonadotropin) should be ordered for all premenopausal women.
- *Stool examination* for occult blood may be useful.
- *Electrocardiography* is performed for all patients with possible myocardial infarction or older than 50 years.

## 8. Which radiologic tests should be ordered to evaluate the patient with acute abdominal pain?

The selection of tests depends on the likelihood of the pretest clinical diagnosis and the ability of the radiologic test to confirm clinical suspicion.

- *Plain radiographs* of the abdomen are quick and readily available, and can be done at the bedside. They can detect bowel obstruction (dilated loops of bowel with air/fluid levels), volvulus, and viscus perforation (free air). Occasionally, they may suggest stone disease ( $\approx 20\%$  of gallbladder stones and  $\approx 80\%$  of renal stones are calcified) or ruptured aortic aneurysm (separation of aortic wall calcium and mass effect). Calcium in the area of the pancreas might suggest pancreatitis as the cause of pain. A gasless abdomen, air in the bowel wall, or air in the portal venous system suggests bowel infarction or severe infection. Free intraabdominal air is best detected with the patient in the left lateral decubitus position for 10 minutes, but a computed tomography (CT) scan is more sensitive for small amounts of air (see Chapter 69).
- *Ultrasound (US)* of the abdomen is quick, noninvasive, and can be performed at the bedside. The disadvantages of US include variable operator expertise and suboptimal examination in the obese or gaseous abdomen. US is excellent for evaluating the gallbladder, bile ducts, liver, kidneys, appendix, and pelvic organs (see Chapter 69).
- *CT* of the abdomen provides a detailed view of the anatomy. Oral and intravenous contrast agents are usually required. CT has become an extension of the physical examination and the single most helpful radiologic examination of the patient with acute abdominal pain. CT is better than US for evaluation of the pancreas, but often lacks the spatial resolution to identify biliary stone disease (see Chapter 69).
- *Hepatobiliaryimodiabetic (HIDA) scan* is the most accurate test for acute cholecystitis (see Chapter 70).

## 9. Pain referred to the abdomen can be confusing. What are the common extraabdominal causes of referred abdominal pain?

- *Thoracic:* pneumonia, pulmonary embolism, pneumothorax, myocardial infarction or ischemia, esophageal spasm, or perforation
- *Neurogenic:* radicular pain (spinal cord compression from tumor, abscess, compression, or varicella zoster infection), tabes dorsalis

- Metabolic: uremia, porphyria, acute adrenal insufficiency
- Hematologic: sickle cell anemia, hemolytic anemia, Henoch-Schönlein purpura
- Toxins: insect bites (scorpion bite-induced pancreatitis), lead poisoning

**10. What are some common causes of nonserious abdominal pain?**

- Mesenteric adenitis
- Irritable bowel syndrome
- Viral and bacterial enteritis
- Pre-eruptive shingles
- Abdominal migraine
- Costochondritis
- Gastroesophageal reflux disease

**11. List the common causes of acute abdominal pain in gravid women.**

- Appendicitis
- Ovarian cysts complicated by torsion, rupture, and hemorrhage
- Ectopic pregnancy
- Gallbladder problems (acalculous cholecystitis, cholecystitis, or choledocholithiasis)

**12. When the appendix is found to be entirely normal during a laparotomy performed for presumed appendicitis in a gravid woman, should the appendix be removed?**

No. Removal of the normal appendix triples the risk of fetal loss.

**13. What is the most common cause of acute abdominal pain in older adult patients?**

Biliary tract disease is responsible for 25% of all cases of acute abdominal pain in older adult patients requiring hospitalization. Bowel obstruction and incarcerated hernia are the next most common, followed by appendicitis.

**14. What symptoms are helpful in evaluating for appendicitis?**

It is decidedly uncommon for acute appendicitis to present with nausea, vomiting, or diarrhea before abdominal pain. Usually acute appendicitis is heralded by pain and often followed by anorexia, nausea, and sometimes single-episode vomiting. Acute appendicitis should be first on the differential diagnosis list in any patient with acute abdominal pain without a prior history of appendectomy. A simple scoring system of clinical parameters and laboratory tests, the Alvarado score, has been validated to be very predictive of acute appendicitis (Table 53-2).

**Table 53-2. Alvarado Score**

SYMPTOMS	SCORE
Migration of pain to right iliac fossa	1
Anorexia	1
Nausea and vomiting	1
SIGNS	
Raised temperature, >37.3° C	1
Rebound pain	1
Tenderness in the right iliac fossa	2
LABORATORY FINDINGS	
Elevated leukocyte counts	2
Neutrophil left shift (>75%)	1
<b>Total</b>	<b>10</b>

Score = 5-6 possible appendicitis

Score = 7-8 probable appendicitis

Score = 9-10 very probable appendicitis

**15. Discuss atypical forms of appendicitis.**

When the appendix is retrocecal or retroileal in location, the inflamed appendix is often shielded from the anterior abdomen. The pain is often less pronounced, and localizing signs on physical examination are uncommon. Symptoms and signs of appendicitis in older patients are subtle. Pain is often minimal, fever is only mild, and leukocytosis is unreliable. A high index of suspicion is essential.

**16. Describe the US findings of acute appendicitis.**

The appendix appears as a round target with an anechoic lumen, surrounded by a hypoechoic and thickened (greater than 2 mm) appendiceal wall. This finding with reproduction of pain under the transducer has a diagnostic accuracy of 95% and a negative predictive value of 97%. Although US evaluation for appendicitis has the advantage of bedside portability and lack of radiation, CT has been shown to have superior sensitivity, accuracy, and negative predictive value (96% versus 76%, 94% versus 83%, and 94% versus 76%, respectively).

**17. When laparotomy is performed for presumed appendicitis, what is the acceptable false-negative rate? How often is another cause identified in this setting?**

A *false-negative laparotomy rate of 10% to 20% is reported*. In roughly 30% of these cases, some other cause of abdominal pain is identified, such as mesenteric lymphadenitis, Meckel's diverticulum, cecal diverticulitis, pelvic inflammatory disease, ectopic pregnancy, or ileitis.

**18. What is the single best test to evaluate patients infected with human immunodeficiency virus (HIV) infection who complain of acute abdominal pain?**

Because of the variety of causes of abdominal pain in such patients, it has been argued that CT scan is the single best test.

**19. What are the cardinal features of a ruptured tubal pregnancy?**

- Amenorrhea (missed period or scant menses)
- Abdominal and pelvic pain
- Unilateral, tender adnexal mass
- Signs of blood loss without blood in the GI tract

**20. What are the characteristics of acute intestinal obstruction?**

- Nausea and vomiting
- Failure to expel flatus
- Prior abdominal surgery or presence of hernia
- Peristaltic pain (colicky pain—every 10 minutes for jejunal obstruction and every 30 minutes for ileal obstruction)

**21. List the clinical characteristics and causes of large bowel obstruction.**

- Most patients are older than 50 years of age.
- Lower abdominal cramping pain is gradual in onset.
- Abdominal distention is a prominent feature.
- Dilated loops of bowel with haustra distinguish the colon from the small bowel on abdominal x-rays or CT scans (see [Chapters 66 and 69](#)).
- Causes include obstructing neoplasm, diverticulitis, hematoma (trauma or bleeding disorder), and cecal or sigmoid volvulus.

**22. List the clinical characteristics of diverticulitis.**

- Age older than 50 years
  - Localized left lower abdominal pain (often for several days' duration)
  - Palpable mass in left lower quadrant
  - Low-grade fever and leukocytosis (note 45% may have normal white blood cell count)
- Right-sided diverticulitis occurs in only 1.5% of patients in Western countries but is more common among Asians. Up to 75% of these patients present with right lower quadrant pain, often misdiagnosed as acute appendicitis.

**23. What are the characteristic CT findings of diverticulitis?**

See [Chapter 69](#).

- Increased soft tissue density within pericolic fat, secondary to inflammation (98%)
  - Colonic diverticula (84%)
  - Bowel wall thickening (70%)
  - Soft tissue masses representing phlegmon and pericolic fluid collections, representing abscesses (35%)
  - Sensitivity, specificity, and positive and negative predictive values of 97%, 100%, 100%, and 98%
- Note: In 10% of patients, diverticulitis cannot be distinguished from carcinoma and a *gentle and cautious* endoscopic examination may need to be performed.

**24. List the clinical hallmarks of acute cholecystitis.**

- Patients often give a history of prior episodes of milder abdominal pain.
- Abdominal pain usually arises after a meal, especially in the evening after a large or fat-containing meal.
- Pain typically crescendos over 20 to 30 minutes and then plateaus.
- Pain lasting longer than 1 to 2 hours is usually accompanied by gallbladder wall inflammation.
- Associated nausea occurs in 90% of patients; vomiting may follow onset of pain in 50% to 80%.
- Radiation of pain to the back is common; pain radiates to the right scapula in 10% of cases.
- Low-grade fever is common.

- Right hypochondrium tenderness is generally present. Inspiratory arrest during gentle palpation of the right upper quadrant (Murphy's sign) suggests acute cholecystitis.
- Diagnostic tests include HIDA scan or US.

**25. What is the differential diagnosis of right upper quadrant pain besides acute cholecystitis?**

- Liver: severe hepatitis with swelling and stretching of the liver capsule, liver metastasis, Fitz-Hugh-Curtis syndrome, congestive hepatopathy (hepatic vein thrombosis—Budd-Chiari syndrome), hepatoma or liver adenoma with infarction or internal bleeding
- Pancreas: pancreatitis, pseudocyst
- GI tract: peptic ulcer disease with or without perforation, acute appendicitis (retrocecal)
- Kidney: pyelonephritis, nephrolithiasis
- Lung: pneumonia, pulmonary embolism, pleurisy
- Heart: myocardial infarction, pericarditis
- Preeruptive varicella zoster

**26. When should a patient undergo surgery for an acute abdomen?**

Surgery should be performed when, in the judgment of the surgeon, a problem will be identifiable or treatable by surgical intervention. There is no substitute for good surgical judgment and intuition.

**27. What conditions can result in an acute abdomen in HIV-infected patients?**

Patients with HIV can have any of the usual causes of an acute abdomen; all non-HIV-specific diagnoses must be considered. Perforation is most often due to cytomegalovirus (CMV) infection in the distal small bowel or colon; this is the most common cause of the acute abdomen in late-stage HIV infection. CMV infection of the vascular endothelial cells leads to mucosal ischemic ulceration and perforation. HIV-associated lymphoma and Kaposi sarcoma also can lead to perforation, but this finding is rare. Acquired immune deficiency syndrome cholangiopathy, papillitis, and drug-induced pancreatitis (e.g., pentamidine, sulfamethoxazole-trimethoprim [Bactrim], didanosine, ritonavir) are unique causes of abdominal pain in HIV-infected patients.

**28. Are patients with systemic lupus erythematosus (SLE) at increased risk for intraabdominal catastrophe?**

Approximately 2% of patients with SLE develop lupus vasculitis, one of the most devastating complications of SLE. The fatality rate is greater than 50%. Small vessels of the bowel wall are affected, leading to ulceration, hemorrhage, perforation, and infarction.

**29. How common are severe GI manifestations of polyarteritis nodosa (PAN)?**

PAN is a vasculitis that may have visceral involvement. GI bleeding from intestinal ischemia is seen in 6% of cases, bowel perforation in 5%, and bowel infarction in 1.4%. Acalculous cholecystitis occurs in up to 17% because of direct vasculitic involvement of the cystic artery and gallbladder.

**30. What causes of acute abdominal pain should be considered in illicit drug users?**

Intravenous and smoked cocaine has been reported to cause acute mesenteric ischemia or "crack belly." Endocarditis in parenteral drug abusers may be associated with mesenteric emboli and bowel infarction.

**31. What are some rare causes of acute abdominal pain?**

- Eosinophilic gastroenteritis
- Epiploic appendagitis
- Familial Mediterranean fever
- Hereditary angioedema
- Addison's disease (acute adrenal insufficiency)
- Diabetic ketoacidosis
- Porphyria
- Sickle cell crisis

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Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

1. Alvarado A. A practical score for the early diagnosis of acute appendicitis. Ann Emerg Med 1986;15:557–64.
2. Baker JB, Mandavia D, Swadron SP. Diagnosis of diverticulitis by bedside ultrasound in the emergency department. J Emerg Med 2006;30:327.
3. Bonkovsky HL, Siao P, Roig Z, et al. Case 20–2008: A 57-year-old women with abdominal pain and weakness after gastric bypass surgery. N Engl J Med 2008;358:2813–25.
4. Bundy DG, Byerley JS, Liles AE, et al. Does this child have appendicitis? JAMA 2007;298:438–51.
5. Denizbasi A, Unluer EE. The role of the emergency medical resident using the Alvarado Score in the diagnosis of acute appendicitis compared with the general surgery resident. Eur J Emerg Med 2003;10:296–301.

6. Dobbins C, Defontgalland D, Duthie G, et al. The relationship of obesity to the complications of diverticular disease. *Colorectal Dis* 2006;8:37.
7. Ghosheh B, Salameh JR. Laparoscopic approach to acute small bowel obstruction: Review of 1061 cases. *Surg Endosc* 2007;21:1945–9.
8. Goh V, Halligan S, Taylor SA, et al. Differentiation between diverticulitis and colorectal cancer: Quantitative CT perfusion measurements versus morphologic criteria—Initial experience. *Radiology* 2007;242:456.
9. Humes DJ, Simpson J. Acute appendicitis: Clinical review. *Br J Med* 2006;333:530–4.
10. Lyon C, Clark DC. Diagnosis of acute abdominal pain in older patients. *Am Fam Physician* 2006;74:1537.
11. McKay R, Shepherd J. The use of the clinical scoring system by Alvarado in the decision to perform computed tomography for acute appendicitis in the ED. *Am J Emerg Med* 2007;25:489–93.
12. Paulson EK, Kalady MF, Pappas TN. Suspected appendicitis. *N Engl J Med* 2003;348:236–42.
13. Pearigen P. Unusual causes of abdominal pain. *Emerg Med Clin North Am* 1996;14:593.
14. Pickuth D, Heywang-Kobrunner SH, Spielmann RP. Suspected acute appendicitis: Is ultrasonography or computed tomography the preferred technique? *Eur J Surg* 2000;166:315–9.
15. Silen W. Cope's early diagnosis of the acute abdomen. Oxford: Oxford University Press; 1990.
16. Strasberg SM. Acute calculous cholecystitis. *N Engl J Med* 2008;358:2804–11.
17. Terasawa T, Blackmore C, Bent, et al. Systematic review: Computed tomography and ultrasonography to detect acute appendicitis in adults and adolescents. *Ann Intern Med* 2004;141:537–46.
18. Wang LT, Prentiss KA, Simon JZ, et al. The use of the white blood cell count and left shift in the diagnosis of appendicitis in children. *Pediatr Emerg Care* 2007;23:69–76.
19. Westrom L, Mardh PA. Epidemiology and etiology and prognosis of acute salpingitis: A study of 1457 laparoscopically verified cases. In: Hobson D, Holmes KK, editors. Nongonococcal urethritis and related diseases. Washington, DC: American Society of Microbiology; 1997.
20. Zaidi E, Daly B. CT and clinical features of acute diverticulitis in an urban U.S. population: Rising frequency in young, obese adults. *AJR Am J Roentgenol* 2006;187:689.

**Websites**

[www.merckmanuals.com/professional/gastrointestinal\\_disorder/acute\\_abdomen\\_and\\_surgical\\_gastroenterology/acute\\_abdominal\\_pain.html](http://www.merckmanuals.com/professional/gastrointestinal_disorder/acute_abdomen_and_surgical_gastroenterology/acute_abdominal_pain.html)

Cartwright SL, Knudson MP: Evaluation of acute abdominal pain in adults. *Am Fam Physician* 2008;77(7):971–978. Accessed September 22, 2014, from [www.aafp.org/afp/2008/0401/p971.html](http://www.aafp.org/afp/2008/0401/p971.html).

[www.slideshare.net/draftis/diagnosis-and-management-of-acute-abdominal-pain](http://www.slideshare.net/draftis/diagnosis-and-management-of-acute-abdominal-pain)

# EVALUATION OF ACUTE INFECTIOUS DIARRHEA

Ramiro L. Gutiérrez, MD, MPH, CDR, MC (UMO), USN, Wesley R. Campbell, MD, Scott E. Cunningham, MD, CPT(P), MC, Mark S. Riddle, MD, MPH&TM, DrPH, and Patrick E. Young, MD

## EPIDEMIOLOGY

### 1. What is acute diarrhea?

The most important defining aspect of diarrhea is a change in frequency or consistency of bowel movements from baseline. For research purposes, *acute diarrhea* is defined as production of abnormally loose stools, with more than *three episodes daily for less than 14 days*. Generally a daily output increase from the normal of 100 to 200 mg per day is associated with the excessive frequency of defecation. Acute diarrhea commonly results as part of a response to enteric infection (although severe systemic infections may be associated with diarrhea as well) or preformed toxins, or as part of medication effects, malabsorptive and osmotic processes, inflammatory bowel disease (IBD), or vascular diseases.

### 2. How frequently does acute diarrhea caused by infection occur in the United States?

Based on recent Centers for Disease Control and Prevention estimates, approximately 9.4 million cases of foodborne illness, with approximately 56,000 hospitalizations and more than 1300 deaths, occur annually in the United States and are attributable to known pathogens. A *majority of illnesses are caused by Norovirus, Salmonella, preformed toxins, and Campylobacter*. An additional 38.4 million illnesses with 72,000 hospitalizations occur annually as a result of unidentified pathogen.

### 3. Which bacterial organisms produce preformed toxins that cause acute diarrhea?

*Symptoms that occur rapidly (<12 hours) after ingestion* and include nausea, vomiting, or diarrhea are consistent with the ingestion of a preformed toxin. Some of these toxins are heat stable thus persist despite cooking of foods. The most common syndromes are caused by the (1) heat stable *Staphylococcus aureus* enterotoxin, (2) *Bacillus cereus* enterotoxins (often associated with rice), and (3) *Clostridium perfringens* (rewarmed meats such as ham). Symptoms are generally self-limited. Point source outbreaks with multiple cases associated with one recent meal is typical. Additionally, ciguatera and scombroid seafood poisoning, caused by heat-stable toxins from bioaccumulation and spoilage, respectively, are common and can present with diarrhea as part of their syndromes.

### 4. What is persistent diarrhea?

*Diarrhea symptoms that last 14 days or longer are generally classified as persistent.* The differential diagnosis of persistent diarrhea differs somewhat from acute or chronic diarrhea. In terms of infection, bacterial enteric pathogens, parasites, and protozoa are more likely to result in persistent disease and viral pathogens are less common. The following organisms should be considered in the differential diagnosis of persistent diarrhea:

- Bacteria: *Campylobacter*, *Vibrio*, *Escherichia coli*, *Shigella*, *Salmonella*, *Clostridium difficile*, syphilis, chlamydia (lymphogranuloma venereum [LGV])
- Parasites (helminths): *Strongyloides* infection may lead to colitis
- Protozoa: *Giardia*, *Isospora*, *Cyclospora*, *Cryptosporidium*
- Malabsorptive: Tropical sprue, celiac sprue, lactose intolerance

### 5. What are the characteristics of noninflammatory and inflammatory diarrhea syndromes?

Noninflammatory diarrhea consists of a syndrome of watery, nonbloody, nonpurulent diarrhea, and often lacks prominent systemic signs and symptoms such as fever or myalgias. Specific etiologic factors often go undiagnosed and course is often self-limited. Inflammatory diarrhea consists of frequent, smaller volume, mucoid or bloody stools, often associated with tenesmus, fever, and more prominent or severe abdominal pain. On laboratory evaluation, *inflammatory diarrhea exhibits positive fecal leukocytes and positive stool lactoferrin*, and will almost always involve the colon (colitis) when there are large sheets of leukocytes present.

### 6. What disorders and infections are associated with inflammatory diarrhea?

Inflammatory diarrhea is generally associated with disorders that cause mucosal disruption. Mucosal compromise may be due to a primary (IBD) or secondary (invasive infectious organism) process. Invasive infectious agents associated with diarrhea include *Salmonella*, *Shigella*, *Campylobacter*, enterohemorrhagic *E. coli* (EHEC; O157:H7), enteroinvasive *E. coli*, and other Shiga toxin-producing *E. coli* (STEC), *C. difficile*, *E. histolytica*, and *Yersinia enterocolitica*. Noninfectious causes of inflammatory diarrhea include ulcerative colitis, Crohn's disease, radiation enteritis, ischemic and vascular diseases, and diverticulitis.

**7. What disorders and infections are associated with noninflammatory diarrhea?**

Noninflammatory diarrhea is generally caused by infection with noninvasive pathogens that generate toxins or use other means to promote a secretory process. Causative agents include *Vibrio cholerae*, enterotoxigenic *E. coli*, staphylococcal and clostridial toxins, viruses, protozoa, *Cryptosporidium*, and *Giardia*.

**8. Who is most at risk (morbidity and mortality) from acute diarrheal illness?**

The very young, older adults, and the immune compromised are most at risk for morbidity and mortality from acute diarrheal illness. Other risk factors include travel to developing countries, those who work in or attend a daycare, and those who are receiving or have recently received antibiotics, although among the young and healthy mortality is extremely rare.

Children younger than the age of 5 in developing countries, mainly sub-Saharan Africa and Asia, suffer disproportionately from diarrheal disease. Acute and persistent diarrheal infections are a major source of pediatric mortality and morbidity. Annually, 800,000 pediatric deaths are attributable to diarrheal diseases.

Meanwhile, travelers' diarrhea affects upward of 20 million people per year and is the most common illness to affect travelers.

**9. What vaccine-preventable viral pathogen is a major cause of pediatric diarrhea in developing and developed countries?**

Rotavirus infection is a major cause of outbreak and sporadic diarrhea worldwide. Among children and older adults, outbreaks of rotavirus diarrhea result in significant morbidity and mortality and on recent surveys are the most common cause of moderate to severe diarrhea among infants and toddlers in the developing world.

**10. What is the most common cause of outbreak and sporadic cases of acute infectious gastroenteritis and diarrhea in Western countries?**

*Norovirus* infection remains the most common cause of acute sporadic and outbreak-associated diarrhea and gastroenteritis in western countries. In the United States, 21 million cases of *Norovirus* gastroenteritis are estimated to occur annually. Noroviruses are members of the *Calicivirus* family and fall into five genogroups (G.I through G.V). Although some genogroups can infect and are present in both humans and animals, most outbreaks result from human-to-human transmission. The majority of pandemic strains have been G.II.4 subtypes.

**11. What organisms are most likely to present with bloody diarrhea or acute dysentery?**

Invasive bacterial pathogens, and to a lesser extent amoebae, are more likely to present with a diarrhea accompanied by fever or dysentery. Among bacterial pathogens *Shigella* spp., nontyphoid *Salmonella*, *Campylobacter* spp., STEC, and EHEC variants are the most common. *Entamoeba histolytica*, the agent of amebic dysentery, may also cause bouts of watery or bloody diarrhea with colitis.

**12. What are the diarrheagenic subtypes of *E. coli*?**

There are six subtypes of diarrheagenic *E. coli*:

- Enterotoxigenic *E. coli* (ETEC)—notable for toxin production, either heat labile, heat stable, or both, and is the most common cause of travelers' diarrhea in many developing countries.
- **Diffusely adherent** *E. coli* and enteropathogenic *E. coli*—common in children of younger than 2 years. Tight adherence to small bowel.
- Enteroinvasive *E. coli* (EIEC)—able to invade mucosal lining (type 3 secretory apparatus); causes a presentation similar to *Shigella* enterocolitis.
- Enteroadherent/aggregative *E. coli* (EAEC)—associated cause of persistent chronic diarrhea in children and travelers. A common cause of traveler's diarrhea in addition to ETEC.
- **EHEC**—associated colitis and bloody diarrhea, and the hemolytic uremic syndrome (HUS). Pathologic findings are secondary to Shigalike toxin production. Serotype O157:H7 is the most common EHEC representative. It is most commonly transmitted through food supply, in particular contaminated beef products. It is isolated on Sorbitol-MacConkey agar and toxin production with enzyme-linked immunosorbent assay (does not ferment sorbitol). HUS occurs in approximately 5% to 15% of pediatric cases in which antibiotic therapy has been associated with the onset of HUS.
- STEC—Shiga toxin-producing strains other than EHEC. A recent outbreak of O104:H4 in 2011 resulted in illness in primarily adults and was associated with HUS in some cases.

**13. What are the epidemiologic features and species most commonly associated with shigellosis?**

*Shigella* infections in developed countries such as the United States are more commonly associated with *Shigella sonnei* strains. *Shigella flexneri* infections are more common in developing countries and are the second most common *Shigella* species isolated from patients in the United States. *Shigella dysenteriae* is less common but can cause of a more severe infection and epidemic dysentery. In the United States, shigellosis is most commonly associated with children in daycare settings, institutionalized individuals, and among men who have sex with men. Shigellosis is also an important cause of watery diarrhea and dysentery among travelers.

**14. Which antibiotic class should be avoided in acute diarrhea acquired by a traveler to southeast Asia?**

Quinolone resistance is prevalent among *Campylobacter* strains found in southeast Asia and increasingly elsewhere, with rising incidence in Russia, India, and some eastern European countries. The high rate of resistance to this antibiotic class makes them a poor choice for the empiric treatment of traveler's diarrhea in these locations. *Azithromycin* is currently the agent of choice for empiric treatment of traveler's diarrhea in areas where *Campylobacter* infection is likely to be resistant. *Campylobacter* is also among the more common causes of dysentery, and avoidance of quinolones to treat such clinical presentations is reasonable regardless of geographic location.

**15. What agents of acute diarrhea are most likely to be acquired from ingestion of raw oysters?**

Oysters and other filter-feeding organisms, whether farmed or harvested from natural environments, are able to harbor and concentrate enteric pathogens. Both viral and bacterial enteric infections may be acquired by the ingestion of raw oysters. Common pathogens of concern include *Vibrio* species, in particular *Vibrio parahaemolyticus*, which causes a diarrheal illness. *Norovirus* outbreaks have also been attributed to raw oyster consumption. *Vibrio vulnificus* infection has been associated with these ingestions but is more associated with causing septicemia and bullous necrotizing fasciitis in immunocompromised patients and those with end-stage liver disease or cirrhosis.

**16. What specific unique etiologic factors exist for acute diarrheal illness in immunocompromised hosts?**

See Chapter 56 for further discussion. Immunoglobulin A deficiency, human immunodeficiency virus (HIV) and acquired immune deficiency syndrome, organ transplantation, rheumatologic disease on immune-suppressing agents, and chemotherapy all may predispose individuals to enteric infection. These hosts are susceptible to common causes of acute diarrhea but also to agents not commonly problematic for normal hosts: *Mycobacteria*, *Cyclospora*, *Isospora*, *Cryptosporidium*, cytomegalovirus (CMV), and herpes.

**17. What infectious agents are associated with acute and persistent diarrheal illness in HIV patients?**

The degree of immune deficiency influences the differential diagnosis. Generally, the same pathogens as seen among immunocompetent community dwellers is seen among patients with HIV infection, but persistent and chronic presentations may be more common for these same organisms. In addition, symptoms suggestive of invasive disease may occur with infections caused by normally noninvasive pathogens. Highly active antiretroviral therapy and direct viral involvement by HIV may also be common contributors to diarrhea.

Among bacterial contributors, *Salmonella* (nontyphoidal bacteraemia) is of particular concern and can be recurrent. Other contributors are *Campylobacter* and *Shigella*. *Mycobacterium avium* complex may be present even without significant diarrhea, and is often part of an overall wasting syndrome.

Parasite contributors are *Cryptosporidium parvum*, *Microsporidium* (a common cause of chronic diarrhea in HIV), *Giardia lamblia*, *Entamoeba histolytica*, *Strongyloides stercoralis*, *Isospora belli*, and *Cyclospora cayetanensis*.

**18. What are the common causes of acute diarrheal illness among solid organ transplant patients?**

Valganciclovir use has resulted in less CMV-related disease. Community viral pathogens, in particular *Norovirus*, are more common. In the setting of colitis, CMV remains the most common etiologic factor. CMV presence on biopsy polymerase chain reaction (PCR) does not always correlate to causative agent when on suppressive antiviral therapy and tissue evidence of CMV disease (histopathologic) is desirable.

Parasitic infection rates in organ transplant recipients are not entirely known and are more common in developing countries. Clues of infection may be bronchopneumonia, prolonged fever, and meningitis. Pathways to infection include de novo, reactivation of latent infection, or transmission from the graft.

**19. Which bacterial agent of acute diarrhea has humans as its most important reservoir and is more likely to spread and cause disease outbreaks from person-to-person contact?**

*Shigella* species (*sonnei*, *dysenteriae*, *flexneri*, and *boydii*) are highly adapted to human hosts and humans are the most significant reservoir that may contribute to outbreaks within close contacts in family, daycare settings, and through contamination of food. *S. dysenteriae* causes severe disease resulting from high Shiga toxin production and is associated with epidemic outbreaks in the developing world.

**20. What presentation and historical features are useful in defining the etiologic factors of acute diarrhea syndromes?**

Host factors (age, immune status, medications, comorbid conditions), geography, and socioeconomic status heavily influence the infectious differential diagnosis of diarrheal illness. Diarrhea type, and location of presentation are useful determinants. Table 54-1 groups the common diarrheal syndromes with epidemiologic features.

**21. What is the most common cause of traveler's diarrhea?**

ETEC infection is the most common identified cause of traveler's diarrhea in most of the world. ETEC strains cause a watery diarrhea syndrome of varying severity resulting from the production of one or two enterotoxins: heat-stable toxin and heat-labile toxin (LT). The LT variant is closely related to cholera toxin

**Table 54-1.** Prevalence and Infectious Causes of Common Infectious Diarrhea by Syndrome Type

PRESENTATION	ESTIMATED PREVALENCE (%)	DEVELOPED COUNTRIES	DEVELOPING COUNTRIES
Acute watery diarrhea	90	Viral, preformed toxins	Enterotoxigenic <i>E. coli</i> , other diarrheogenic <i>E. coli</i> , <i>C. jejuni</i> , <i>Salmonella</i> , <i>Shigella</i>
Acute dysentery	5-10	<i>Shigella</i> , enteroinvasive <i>E. coli</i> , <i>Campylobacter</i>	<i>Shigella</i> , enteroinvasive <i>E. coli</i> , <i>C. jejuni</i> , <i>E. histolytica</i>
Persistent diarrhea (>2 wk)	3-4	Enteropathogenic <i>E. coli</i> , <i>Giardia</i> , <i>Yersinia</i> , <i>Campylobacter</i>	Enteropathogenic <i>E. coli</i> , <i>Giardia</i>
Large voluminous/rice-water stool	1	<i>Salmonella</i> , enterotoxigenic <i>E. coli</i>	<i>Vibrio cholerae</i> , enterotoxigenic <i>E. coli</i>
Hemorrhagic colitis	<1	Enterohemorrhagic <i>E. coli</i> , STEC	Enterohemorrhagic <i>E. coli</i>

STEC, Shiga toxin-producing *E. coli*.

and results in profuse, watery diarrhea. Other diarrheagenic *E. coli* (EAEC), *Campylobacter*, *Shigella*, and *Salmonella* infections are common as well. Viral and parasitic infection cause a minority of episodes.

## DIAGNOSIS AND TREATMENT

### 22. What tests are used to diagnose infectious diarrhea?

Although routine stool cultures for common bacterial agents (*E. coli*, *Salmonella*, *Shigella*, and *Campylobacter*) and microscopy (for ova and parasites) can be useful in clinical practice, newer tests have emerged that are faster, more sensitive, and less labor intensive. Enzyme immunoassays (EIAs) for pathogenic antigens have become the tests of choice for many protozoa, viruses, and some bacterial products. Testing for viral pathogens is usually not clinically indicated because of the self-limited nature of the infection. PCR techniques have become widespread for a number of pathogens, and commercially available kits that perform PCR assays for multiple pathogens from a single specimen (multiplexed PCR) have recently been approved by the Food and Drug Administration and may become the test of choice for undifferentiated diarrhea (Table 54-2).

### 23. When should routine stool cultures be obtained?

Stool cultures are overused in clinical practice and are often a source of misspent time and money. Bacteria that are commonly tested include *Salmonella* spp., *Campylobacter* spp., *Shigella* spp., and STEC. They are positive in only approximately 1.5% to 5% of samples submitted. Stool cultures are clinically useful in nonhospitalized patients who have had diarrheal illnesses lasting for more than 5 days, cases suspicious for dysentery or severe diarrhea, or in cases of outbreaks. Stool cultures should not be submitted in patients who have been hospitalized for more than 3 days.

### 24. How does one differentiate IBD from acute infectious diarrhea?

The initial presentation of IBD can sometimes be difficult to distinguish from some forms of acute infectious diarrhea. IBD can be considered in patients with persistent bloody diarrhea (>7 days) with a negative infectious workup and lack of response to empiric therapy. Suspicion for IBD is increased in patients with a history of recurrent or chronic gastrointestinal (GI) complaints, in patients 20 to 30 years of age, and in those with extraintestinal manifestations of IBD (aphthous ulcers, uveitis, arthralgias, erythema nodosum, pyoderma gangrenosum). Lower endoscopy is indicated to help distinguish between these diagnoses, although the endoscopic features between IBD and acute infectious diarrhea are quite similar in the early phases of each disease. Inflammatory markers such as erythrocyte sedimentation rate (ESR) are nonspecific for IBD, but are often markedly elevated.

### 25. When should one be concerned about a systemic infection from a nonenteric pathogen in a patient presenting with diarrhea?

Most enteric pathogens present with a diarrhea-predominant clinical syndrome, although other symptoms (headache, myalgias, fever, and malaise) may also be present. Most of these infections are self-limited and resolve within a few days. Those that can cause more severe illness (*Shigella*, STEC, *C. difficile*) are usually readily identified by stool studies. Many other nonenteric infectious agents and systemic illnesses can present with diarrhea. Consideration of these potential etiologic factors is indicated when a patient has persistent diarrhea

**Table 54-2.** Sensitivity and Specificity for Common Microbiological Tests Used in the Evaluation of Infectious Diarrhea

STOOL TEST	SENSITIVITY (%)	SPECIFICITY (%)
Fecal Leukocytes	55-70*	63-87*
Lactoferrin	71-92*	79-100*
C. difficile cytotoxic assay	70-90	100
C. difficile PCR assay	100	96
C. difficile EIA (toxin A or B)	61-94	96-99
C. difficile EIA (GDH)	100	61-73
C. difficile LAMP assay	98	98
Campylobacter EIA	75-100	97-98
Shiga toxin EIA	92-100	98-100
Giardia EIA	94-99	100
E. histolytica EIA	82	99
Multiplexed PCR assays	87-100	93-100

EIA, Enzyme immunoassay; GDH, glutamate dehydrogenase; LAMP, loop-mediated isothermal amplification; PCR, polymerase chain reaction.

\*Refers to sensitivity and specificity for inflammatory diarrhea.

with negative stool studies, or develops symptoms that are not typically seen with infectious diarrhea syndromes (high fever [ $>103^{\circ}\text{F}$ ], jaundice, cough, altered mental status).

## 26. Should endoscopy be considered to evaluate acute infectious diarrhea?

Endoscopy should not be part of the routine evaluation of acute diarrhea, but can be considered in a select number of situations. Endoscopy may be useful to evaluate for IBD in patients with persistent bloody diarrhea and a negative infectious workup who do not respond to empiric therapy. When there is a strong suspicion for C. difficile and stool tests are negative or not available, flexible sigmoidoscopy may reveal characteristic pseudomembranes. Finally, endoscopy may also be useful for immunocompromised patients to evaluate for CMV colitis, which frequently requires a histologic diagnosis.

## 27. What is the best test to evaluate for *Clostridium difficile* infection?

Traditionally, the diagnosis of C. difficile infection was based on EIA tests and confirmatory toxigenic cultures or cytotoxic assays. The limited sensitivity of EIA tests, along with the time and labor requirements of the confirmatory tests, prompted the development of more rapid and reliable tests. PCR tests have become the test of choice in many institutions, as they are rapid (within hours) and highly sensitive and specific. Loop-mediated isothermal amplification assays are even faster (1 hour) and simpler than PCR and may play a larger role in diagnosing C. difficile in the future. Infection Diseases Society of American guidelines from 2010 still recommend a two-step procedure with an initial EIA test for glutamate dehydrogenase (GDH) followed by a confirmatory toxigenic culture assay or cell culture cytotoxin B assay. Endoscopy is an insensitive, invasive, and expensive means of diagnosis and should not be routinely employed for this purpose.

## 28. When is a “test of cure” necessary for acute infectious diarrhea?

In most cases of acute infectious diarrhea, resolution of symptoms is enough. There are no indications for tests of cure with C. difficile in patients whose symptoms have resolved. Many health departments require that restaurant workers with *Salmonella* infections have a stool test to demonstrate that they are no longer carrying the bacterium before they return to work, but there are no official guidelines from academic societies or the federal government to rely on. Providers should consult their local health department agencies regarding this matter.

## 29. Describe the treatments for C. difficile infection.

The first treatment for C. difficile infection is to stop any offending antibiotics, if possible. If symptoms persist, treatment depends on the clinical context. For mild to moderate infections, oral metronidazole (500 mg tid for 10-14 days) remains the agent of choice. In severe infection (two or more points based on the following: one point each for temperature  $>38.3^{\circ}\text{C}$ , age  $>60$  years, albumin  $<0.025\text{ g/L}$ , white blood cell count  $>15 \times 10^9\text{ cells/L}$ ; two points for pseudomembranous colitis or intensive care unit) oral vancomycin (125 mg qid  $\times 10-14$  days) is warranted as it is approximately 20% more effective in this setting. For complicated severe infection, intravenous (IV) metronidazole (500 mg q8h) may be added. Higher-dose vancomycin, alternative antibiotics (rifaximin), and fecal microbiota transplantation may be considered for relapsing or recurrent disease.

**30. What is the role of oral rehydration solution (ORS) for acute infectious diarrhea?**

ORS has revolutionized the treatment of acute infectious diarrhea worldwide. ORS takes advantage of the fact that sodium and glucose are cotransported in the jejunum, a mechanism unaffected by pathologic increases in intestinal secretion that leads to enhanced water absorption. The use of World Health Organization ORS has been shown in numerous trials to decrease morbidity in adults and both morbidity and mortality in children. Head-to-head trials show ORS to be equivalent to IV hydration for acute gastroenteritis therapy in children. Because it decreases diarrheal volume, the low hypoosmolar ORS is preferred.

**31. How should ORS be dosed?**

The dose depends on the degree of dehydration. For mild dehydration (3%-5% decrease in body weight), 50 mL/kg taken in 2 to 4 hours is appropriate. For moderate dehydration (6%-9% decrease in body weight), the dosage should be increased to 100 mL/kg taken over the same period. If the dehydration is more severe than this, initial treatment with IV rehydration followed by ORS at 100 mL/kg in 4 hours is recommended.

**32. What is the role of antimotility agents (AMAs) in the treatment of acute infectious diarrhea?**

Most episodes of acute diarrhea are self-limited, lasting less than 24 hours, and do not require AMAs. For longer lasting diarrheal illnesses, these agents may decrease total diarrhea duration, thus improving quality of life. In general, AMAs are safe for use in adults with the following caveats: they should be avoided if the patient is critically ill, has a known or suspected *C. difficile* or *E. coli* O157:H7 infection, fever, or dysentery. AMAs should also be avoided in children younger than 3 years because of an increased number of adverse events in this population. When combined with antimicrobials for travelers' diarrhea AMAs can shorten illness duration from a 3- to 5-day illness to less than 24 hours, particularly for those with more frequent episodes of pretreatment diarrhea.

**33. Do antiparasitic agents (APAs) play a role in the treatment of acute diarrhea?**

For immunocompetent patients in the developed world, empiric APAs play no role in the management of acute diarrhea. In patients in the developing world or those who are immunosuppressed, treatment should be guided based on the results of testing as there is not a "one size fits all" APA (Figure 54-1).

**34. What are the indications for antibiotics in acute infectious diarrhea?**

Antibiotic use for acute diarrhea depends largely on the infectious agent. In the developed world, most acute diarrhea is self-limited and viral, rendering antibiotics moot. In cases in which a particular pathogen is confirmed or highly suspected (*C. difficile*, *Giardia*, EHEC, ETEC, EIEC, *Shigella* spp., *Isospora*, *Microsporidia*, *Cyclospora*, *E. histolytica*) antibiotics are reasonable. For infections such as nontyphoidal *Salmonella*, antibiotics lend no benefit and prolong clearance of the pathogen. Unfortunately, most clinicians must make treatment decisions prior to pathogen identification. As such, the clinical presentation and suspected pathogen drive the decision. An empiric fluoroquinolone is reasonable in adults with inflammatory diarrhea not thought to be from STEC. Shiga toxin production may also be readily ruled out in most clinical microbiology laboratories.

**35. How is the risk of HUS affected by antibiotic use?**

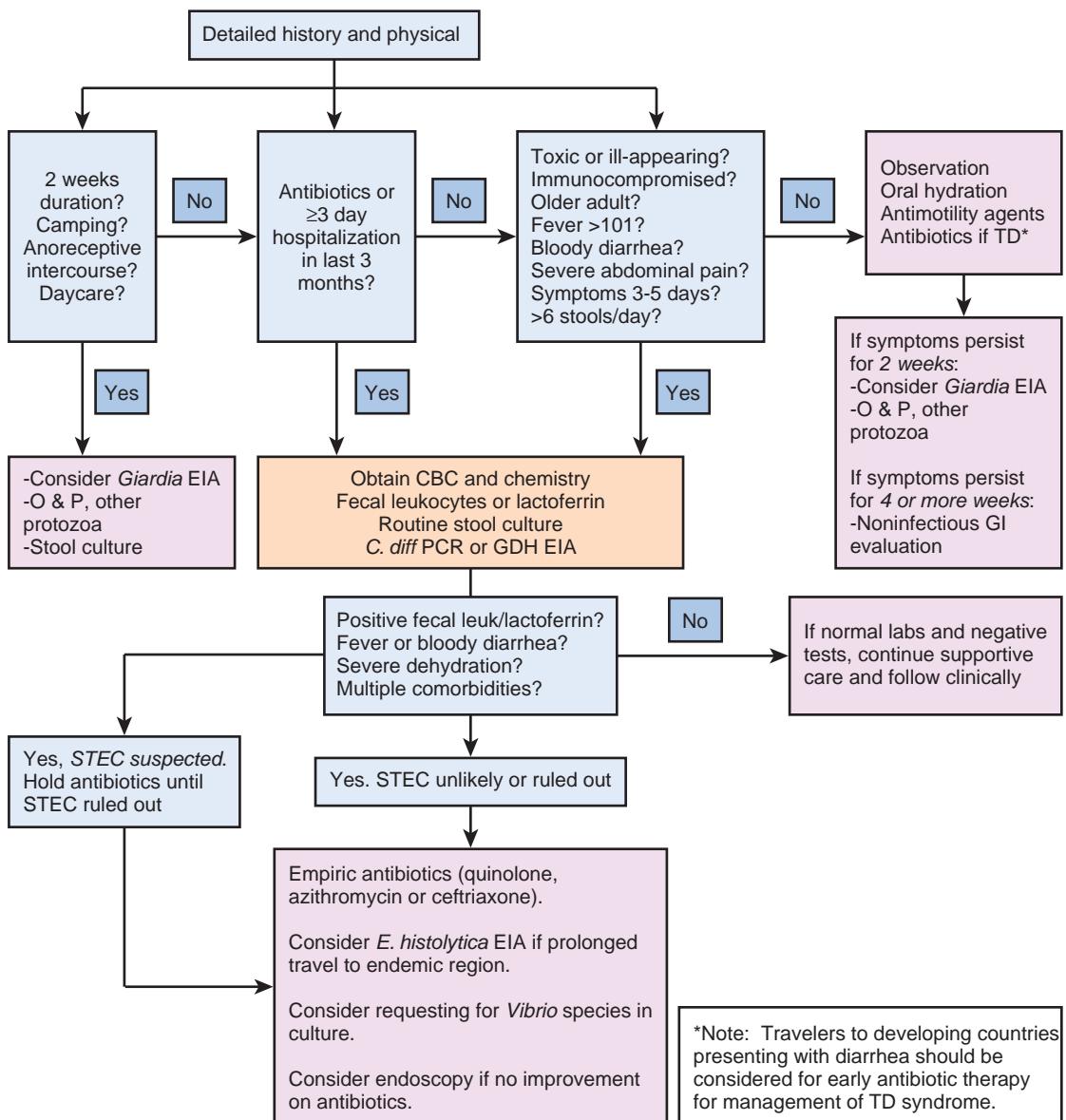
In the United States, the majority of diarrhea-associated HUS is related to infection with STEC O157:H7, generally from contaminated ground beef. In several series, the use of antibiotics appears to increase the risk of HUS in children younger than 10 years old. Although the data regarding adults are less clear, there is no evidence that the use of antibiotics shortens the duration of illness or decreases symptoms, and thus they should not be used in these cases.

**LONG-TERM CONSEQUENCES AND SEQUELAE OF DIARRHEAL ILLNESS****36. What sequelae have been associated with acute enteric infections?**

A growing list of long-term and other sequelae have been associated with enteric infections. A strong link has been established mechanistically, epidemiologically, and from animal models between enteric infection and autoimmune phenomena like the Guillain-Barré syndrome (GBS) and reactive arthritis. During the last decade, epidemiologic evidence from outbreaks and large cohort studies has established a heightened risk of development of irritable bowel syndrome and other functional GI disorders after enteric infection. Most recently, emerging evidence suggests a potential link between some enteric infections and development or unmasking of celiac disease and IBDs.

**37. Which bacterial agent of acute diarrhea is most likely to result in bacteremia and distant ectopic foci of infection?**

Nontyphoidal strains of *Salmonella* are invasive and may lead to bacteremia after enteric infection. Among older patients, endocarditis or other septic foci of infection have been reported after salmonellosis. *Salmonella* infections, both typhoidal and nontyphoidal, are situations in which bacteremia is common but highest culture yield is from bone marrow aspirate.



**Figure 54-1.** Diagnostic algorithm for diarrhea management. CBC, Complete blood count; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; GI, gastrointestinal; O & P, ova and parasites; PCR, polymerase chain reaction; STEC, Shiga toxin-producing *E. coli*; TD, travelers' diarrhea.

### 38. What enteric infection has been associated with GBS?

Respiratory and intestinal infections, vaccinations, and other immunologic influences have been associated with GBS, an autoimmune demyelinating or axonal peripheral neuropathy usually manifesting as progressive ascending weakness and paralysis. *Campylobacter jejuni* infection is the most common infection associated with GBS and is usually of an axonal subtype. Molecular mimicry of the bacterial lipopolysaccharide and ganglioside moieties on peripheral nerves appears to be a dominant mechanism. In the developing world, it is estimated that one third of all cases of acute flaccid paralysis are GBS caused by *Campylobacter*.

### 39. What enteric pathogens are associated with reactive arthritis?

Several enteric bacterial pathogens may be associated with postinfectious autoimmune arthritis syndromes. *Salmonella*, *Yersinia*, *Campylobacter*, and *Shigella* are most commonly associated. More recently, *E. coli* and *C. difficile* infection have been associated with arthralgia or arthritis syndromes as well. In addition to asymmetric oligoarthritis, some patients may develop conjunctivitis or skin eruptions (keratoderma blennorrhagica or

erythema nodosum). Management includes the treatment of the inciting infection and then judicious use of antiinflammatory therapies (nonsteroidal antiinflammatory drugs, disease-modifying antirheumatic drugs, steroids).

#### **40. What role do prebiotics and probiotics play in treatment of acute diarrhea?**

The use of probiotics for the treatment of acute diarrhea remains controversial. The rationale is based on the idea that probiotic organisms compete for binding sites and also may produce metabolites and acids harmful to enteric pathogens. Evidence for and against the approach is difficult to evaluate because of the variety of probiotics and formulation types in existence (*Saccharomyces*, *Lactobacillus acidophilus*, *Bifidobacterium*, etc.) as well as methodological factors. A Cochrane review published in 2010 included 63 studies and did demonstrate a shortening of diarrheal episodes with the use of probiotics and a low likelihood of adverse events.

#### **41. What is Brainerd's diarrhea and how is it diagnosed and treated?**

Brainerd's diarrhea is an idiopathic syndrome of chronic diarrhea that has been epidemiologically associated with point-source outbreaks. First described in 1986 after an outbreak associated with raw milk consumption, most cases in the literature have resulted as part of outbreaks. Clinically, patients report a common onset of chronic diarrhea that is unresponsive to antibiotic therapies and negative microbiologic evaluations. One endoscopic study reported colonic epithelial lymphocytosis similar to collagenous and lymphocytic colitis was more prevalent among cases. A possible infectious etiologic factor is suspected but has not been corroborated. Opioid AMAs may be used to manage symptoms in a subset of patients.

#### **42. What are the primary risk factors for foodborne illness in the United States?**

A limited number of pathogen-food combinations are estimated to be responsible for most of the foodborne illness in the United States. These include *Campylobacter* in poultry; *Toxoplasma* in pork and beef; *Listeria* in deli meats and dairy products; *Salmonella* in poultry, eggs, produce, and complex foods; and *Norovirus* in complex foods.

#### **43. What counseling is appropriate for patients on prevention of acute diarrhea from domestic sources?**

Raw foods of animal origin are the most likely to be contaminated (e.g., raw meat and poultry, raw eggs, unpasteurized milk, and raw shellfish). Fruits and vegetables consumed raw are also of concern. Washing can decrease but not eliminate contamination. A few simple precautions are suggested to reduce the risk of foodborne illness.

- Cook meat, poultry and eggs thoroughly following temperature recommendations.
- Separate: Don't cross-contaminate one food with another. Avoid cross-contamination by washing hands, utensils, and cutting boards after they have touched raw meat and before they touch another food. Put cooked meat on a clean platter, rather than back on one that held the raw meat.
- Chill: Refrigerate leftovers promptly if they are not going to be eaten within 4 hours.
- Clean: Wash produce. Rinse in running tap water and remove the outermost leaves.
- Report: Report suspected cases of foodborne illness to your local health department. Calls from citizens are key to early detection of outbreaks and to understand risks to individuals and populations.

Please access ExpertConsult to view a **Clinical Vignette** for this chapter.

#### **BIBLIOGRAPHY**

- Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. Cochrane Database Syst Rev 2010 Nov;10(11):CD003048. <http://dx.doi.org/10.1002/14651858.CD003048.pub3>.
- American Society for Gastrointestinal Endoscopy (ASGE) Standards of Practice Committee. Shen B, Khan K, Ikenberry SO, Anderson MA, Banerjee S. The role of endoscopy in the management of patients with diarrhea. Gastrointest Endosc 2010 May;71(6):887–92. <http://dx.doi.org/10.1016/j.gie.2009.11.025>. Epub 2010 Mar 25.
- Aranda-Michel J, Giannella RA. Acute diarrhea: A practical review. Am J Med 1999;106(6):670–6.
- Atia AN, Buchman AL. Oral rehydration solutions in non-cholera diarrhea: A review. Am J Gastroenterol 2009;104 (10):2596–604, quiz 2605.
- Batz MB, Hoffmann S, et al. Ranking the disease burden of 14 pathogens in food sources in the United States using attribution data from outbreak investigations and expert elicitation. J Food Prot 2012;75(7):1278–91.
- DuPont HL. Traveller's diarrhoea: Contemporary approaches to therapy and prevention. Drugs 2006;66(3):9.
- Haley CC, Ong KL, et al. Risk factors for sporadic shigellosis, FoodNet 2005. Foodborne Pathog Dis 2010;7(7):741–7.
- Hannu T. Reactive arthritis. Best Pract Res Clin Rheumatol 2011;25(3):347–57.
- Hessen MT. In the clinic. *Clostridium difficile* infection. Ann Intern Med 2010;153(7), ITC41-15; quiz ITC416.
- Kaper JB, Nataro JP, et al. Pathogenic *Escherichia coli*. Nat Rev Microbiol 2004;2(2):123–40.
- Marshall JK, Thabane M, et al. Postinfectious irritable bowel syndrome after a food-borne outbreak of acute gastroenteritis attributed to a viral pathogen. Clin Gastroenterol Hepatol 2007;5(4):457–60.
- Marshall JK, Thabane M, et al. Incidence and epidemiology of irritable bowel syndrome after a large waterborne outbreak of bacterial dysentery. Gastroenterology 2006;131(2):445–50, quiz 660.
- Mintz ED, Weber JT, et al. An outbreak of Brainerd diarrhea among travelers to the Galapagos Islands. J Infect Dis 1998; 177(4):1041–5.
- Operario DJ, Houpt E. Defining the causes of diarrhea: Novel approaches. Curr Opin Infect Dis 2011;24(5):464–71.

15. Osterholm MT, MacDonald KL, et al. An outbreak of a newly recognized chronic diarrhea syndrome associated with raw milk consumption. *JAMA* 1986;256(4):484–90.
16. Pawlowski SW, Warren CA, et al. Diagnosis and treatment of acute or persistent diarrhea. *Gastroenterology* 2009; 136(6):1874–86.
17. Pfeiffer ML, DuPont HL, et al. The patient presenting with acute dysentery—a systematic review. *J Infect* 2012;64(4):374–86.
18. Porter CK, Gormley R, et al. The incidence and gastrointestinal infectious risk of functional gastrointestinal disorders in a healthy US adult population. *Am J Gastroenterol* 2010;106(1):130–8.
19. Porter CK, Thura N, Ranallo RT, Riddle MS, et al. The *Shigella* human challenge model. *Epidemiol Infect*. 2013;141(2):223–32.
20. Riddle MS, Arnold S, et al. Effect of adjunctive loperamide in combination with antibiotics on treatment outcomes in travelers' diarrhea: A systematic review and meta-analysis. *Clin Infect Dis* 2008;47(8):1007–14.
21. Riddle MS, Gutierrez RL, et al. The chronic gastrointestinal consequences associated with campylobacter. *Curr Gastroenterol Rep* 2012;14(5):395–405.
22. Scallan E, Griffin PM, et al. Foodborne illness acquired in the United States—Unspecified agents. *Emerg Infect Dis* 2011; 17(1):16–22.
23. Scallan E, Hoekstra RM, et al. Foodborne illness acquired in the United States—Major pathogens. *Emerg Infect Dis* 2011; 17(1):7–15.
24. Swindells J, Brenwald N, et al. Evaluation of diagnostic tests for *Clostridium difficile* infection. *J Clin Microbiol* 2010; 48(2):606–8.
25. Tarr PI, Gordon CA, et al. Shiga-toxin-producing *Escherichia coli* and haemolytic uraemic syndrome. *Lancet* 2005; 365(9464):1073–86.
26. Thielman NM, Guerrant RL. Clinical practice. Acute infectious diarrhea. *N Engl J Med* 2004;350(1):38–47.
27. Verdu EF, Mauro M, et al. Clinical onset of celiac disease after an episode of *Campylobacter jejuni* enteritis. *Can J Gastroenterol* 2007;21(7):453–5.
28. Yuki N, Hartung HP. Guillain-Barre syndrome. *N Engl J Med* 2012;366(24):2294–304.

#### Websites

- American College of Gastroenterology. Acute infectious diarrhea management guideline. Accessed September 22, 2014, from <http://s3.gi.org/physicians/guidelines/InfectiousDiarrhea.pdf>.
- Centers for Disease Control and Prevention. Travelers' diarrhea. Accessed September 22, 2014, from <http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-2-the-pre-travel-consultation/travelers-diarrhea>.

# CHRONIC DIARRHEA

*Lawrence R. Schiller, MD*

## 1. Define chronic diarrhea.

Diarrhea is defined as an increase in the frequency and fluidity of stools. For most patients, *diarrhea* means the passage of loose stools. Although loose stools are often accompanied by an increase in the frequency of bowel movements, most patients do not classify frequent passage of formed stools as diarrhea. Because stool consistency is difficult to quantitate, many investigators use frequency of defecation as a quantitative criterion for diarrhea. By this standard, passage of more than two “loose” bowel movements per day is considered abnormal ([Table 55-1](#)). Some authors also incorporate stool weight in the definition of diarrhea. Normal stool weight averages approximately 80 g/day in women and 100 g/day in men. The upper limit of normal stool weight (calculated as the mean plus two standard deviations) is approximately 200 g/day. Normal stool weight depends on dietary intake, and some patients on high-fiber diets exceed 200 g/day without reporting that they are having diarrhea. Thus stool weight by itself is an imperfect criterion for diarrhea.

**Table 55-1.** Criteria for Diagnosis of Diarrhea

CRITERION	NORMAL RANGE	DIARRHEA, IF:
Increased stool frequency	3 to 14 stools per week	>2 stools per day
More liquid stool consistency	Soft—formed stools	Loose—unformed
Increased stool weight		
Men	0 to 240 g/24 h	>240 g/24 h
Women	0 to 180 g/24 h	>180 g/24 h

## 2. What other disorder may be described as *diarrhea*?

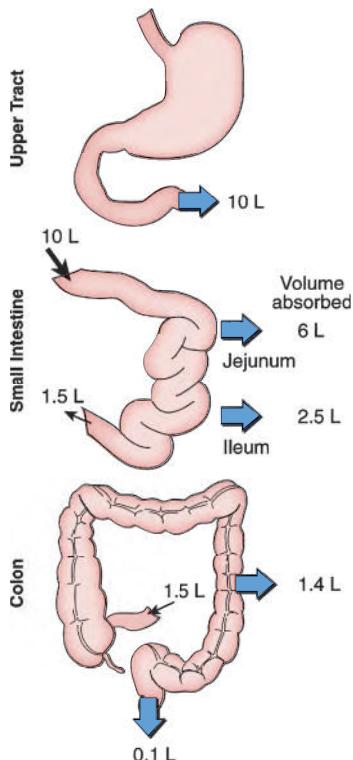
Occasionally patients with fecal incontinence describe that problem as *diarrhea*, even when stools are formed. Physicians must be careful to distinguish fecal incontinence from diarrhea, because incontinence is usually due to problems with the muscles and nerves regulating continence and not just to passage of unusually voluminous or liquid stools.

## 3. What is the basic mechanism of all diarrheal diseases?

Diarrhea is due to the incomplete absorption of fluid from luminal contents. Normal stools are approximately 75% water and 25% solids. Normal fecal water output is approximately 60 to 80 mL per day. An increase of fecal water output of 50 to 100 mL is sufficient to cause loosening of the stool. This volume represents approximately 1% of the fluid load entering the upper intestine each day; thus malabsorption of only 1% to 2% of fluid entering the intestine may be sufficient to cause diarrhea ([Figure 55-1](#)).

## 4. What pathologic processes can cause diarrhea?

Excessive stool water is due to the presence of some solute that osmotically obligates water retention within the lumen. This solute can be some poorly absorbed, osmotically active substance, such as magnesium ions, or can be an accumulation of ordinary electrolytes, such as sodium or potassium, that normally are absorbed easily by the intestine. When excess stool water is due to ingestion of a poorly absorbed substance, the diarrhea is called *osmotic diarrhea*. Examples of this include lactose malabsorption and diarrhea induced by osmotic laxatives. When the excessive stool water is due to the presence of extra electrolytes resulting from reduction of electrolyte absorption or stimulation of electrolyte secretion, the diarrhea is known as *secretory diarrhea*. Causes of secretory diarrhea include infection, particularly infections that produce toxins that reduce intestinal fluid electrolyte absorption; reduction of mucosal surface area resulting from disease or surgery; absence of an ion transport mechanism; inflammation of the mucosa; ingestion of drugs or poisons; endogenous secretagogues such as bile acids; dysfunction caused by abnormal regulation by nerves and hormones; and tumors producing circulating secretagogues.



**Figure 55-1.** Fluid loads through the intestine. Each day approximately 9 to 10 L of fluid pass into the jejunum. This consists of approximately 2 L of ingested food and drink, 1.5 L of saliva, 2.5 L of gastric juice, 1.5 L of bile, and 2.5 L of pancreatic juice. The jejunum absorbs most of this load as nutrients are taken up, and the ileum absorbs most of the rest. The colon absorbs more than 90% of the fluid load reaching it, leaving only 1% of the original fluid entering the jejunum excreted in stool. Substantial fluid malabsorption in the small bowel can overwhelm colonic absorptive capacity and may result in diarrhea. Less severe disruption of colonic absorption can lead to diarrhea because of the lack of any more distal absorbing segment. A reduction of absorptive efficiency of only 1% for the total intestine can result in diarrhea.

##### 5. List three classifications of diarrheal diseases.

Because the symptom of diarrhea has such a broad differential diagnosis, it is useful to classify the type of diarrhea to restrict the differential diagnosis to a more manageable number of conditions. Three helpful classification schemes include:

- Acute versus chronic (4 weeks or longer)
- Epidemiologic criteria (traveler's, epidemic or outbreak, acquired immune deficiency syndrome [AIDS], and institutional)
- Stool characteristics (watery, fatty, inflammatory)

Watery stools are typically runny and lack blood, pus, or fat. Watery diarrhea is subdivided into secretory and osmotic types, depending on stool electrolyte concentrations. Fatty stools have an excess of fat, which can be shown by qualitative testing with the Sudan stain or by quantitative analysis of a timed stool collection for fat. Inflammatory diarrheas typically contain blood or pus. If not grossly evident, these characteristics can be detected by a fecal occult blood test or by staining the stool for neutrophils.

Classifying diarrheas by stool characteristics enables the physician to sort quickly through more likely and less likely diagnoses (Table 55-2). This scheme is thus very useful in chronic diarrheas in which construction of a reasonable differential diagnosis can lead to more appropriate testing and more rapid diagnosis.

##### 6. What are the likely causes of diarrhea, according to epidemiologic characteristics?

###### Traveler's Diarrhea

- Bacterial infection (mostly acute)
- Protozoal infection (e.g., amebiasis, giardiasis)
- Tropical sprue

###### Epidemics and Outbreaks

- Bacterial infection
- Viral infection (e.g., rotavirus)

**Table 55-2.** Tests for Evaluation of Systemic Diseases Associated with Chronic Secretory Diarrhea

CATEGORY	CONDITION	DIAGNOSTIC TESTS
Endocrine diseases	Hyperthyroidism Addison's disease Panhypopituitarism Diabetes mellitus	Thyroid-stimulating hormone, T4 ACTH-stimulation test, cortisol ACTH-stimulation test, TSH Blood glucose, glycosylated hemoglobin
Endocrine tumor syndromes	MEN-1 (Wermer syndrome) Hyperparathyroidism Pancreatic endocrine tumors Pituitary tumors (Also may have adrenal cortical tumors, thyroid adenomas) MEN-2a (Sipple syndrome) Medullary thyroid cancer Pheochromocytoma Hyperparathyroidism MEN-2b (same as MEN-2a + neuromas, Marfanoid phenotype)	Parathormone Gastrin, VIP, insulin, glucagon Prolactin, growth hormone, ACTH Calcitonin Urine metanephrine Parathormone
Hematologic diseases	Leukemia, lymphoma Multiple myeloma	Complete blood count Serum protein electrophoresis
Immune system disorders	AIDS Amyloidosis Common variable immunodeficiency IgA deficiency	HIV serology Mucosal biopsy Immunoglobulin levels
Heavy metal poisoning		Heavy metal screen

ACTH, Adrenocorticotrophic hormone; AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; Ig, immunoglobulin; MEN, multiple endocrine neoplasia; T4, thyroxine; TSH, thyroid-stimulating hormone; VIP, vasoactive intestinal polypeptide.

- Protozoal infections (e.g., cryptosporidiosis)
- Brainerd's diarrhea (epidemic idiopathic secretory diarrhea)

#### **Patients with AIDS**

- Opportunistic infections (e.g., cryptosporidiosis, cytomegalovirus, herpes, *Mycobacterium avium* complex)
- Drug side effect
- Lymphoma

#### **Institutionalized Patients**

- *Clostridium difficile* toxin-mediated colitis
- Food poisoning
- Fecal impaction with overflow diarrhea
- Tube feeding
- Drug side effect

#### **7. What are the likely causes of osmotic watery diarrhea?**

Osmotic laxatives (e.g.,  $Mg^{2+}$ ,  $PO_4^{3-}$ ,  $SO_4^{2-}$ ) and carbohydrate malabsorption.

#### **8. List the likely causes of secretory watery diarrhea.**

- Bacterial toxins
- Ileal bile acid malabsorption
- Inflammatory bowel disease (ulcerative colitis, Crohn's disease, microscopic colitis [lymphocytic and collagenous colitis], diverticulitis)
- Vasculitis
- Drugs and poisons
- Stimulant laxative abuse

- Disordered motility or regulation (postvagotomy diarrhea, postsympathectomy diarrhea, diabetic autonomic neuropathy, amyloidosis, irritable bowel syndrome)
- Endocrine diarrhea (hyperthyroidism, Addison's disease, gastrinoma, vasoactive intestinal polypeptide tumor [VIPoma], somatostatinoma, carcinoid syndrome, medullary carcinoma of the thyroid, mastocytosis)
- Other tumors (colon cancer, lymphoma, villous adenoma)
- Idiopathic secretory diarrhea (epidemic secretory [Brainerd's] diarrhea, sporadic idiopathic secretory diarrhea)
- Congenital syndromes (e.g., congenital chloridorrhea)

#### **9. List the likely causes of inflammatory diarrhea.**

- Inflammatory bowel disease (ulcerative colitis, Crohn's disease, diverticulitis, ulcerative jeunoileitis)
- Infectious diseases (pseudomembranous colitis, invasive bacterial infections [tuberculosis, yersiniosis], ulcerating viral infections [cytomegalovirus, herpes simplex], invasive parasitic infections [amebiasis, strongyloides])
- Ischemic colitis
- Radiation colitis
- Neoplasia (colon cancer, lymphoma)

#### **10. List the likely causes of fatty diarrhea.**

##### **Malabsorption Syndromes**

- Mucosal disease (celiac disease, Whipple disease)
- Small bowel bacterial overgrowth
- Chronic mesenteric ischemia
- Short bowel syndrome
- Postgastrectomy syndrome

##### **Maldigestion**

- Pancreatic exocrine insufficiency
- Orlistat ingestion
- Inadequate luminal bile acid concentration

#### **11. Summarize the initial diagnostic scheme for patients with chronic diarrhea?**

The scheme in Figure 55-2 is based on obtaining a careful history, looking for specific physical findings, and obtaining simple laboratory data to help classify the diarrhea as watery, fatty, or inflammatory. The value of obtaining a quantitative (as opposed to a spot) stool collection is debated among experts. A quantitative collection over 48 or 72 hours permits a better estimation of fluid, electrolyte, and fat excretion, but is not absolutely necessary for the appropriate classification of diarrhea.

#### **12. How secretory and osmotic watery diarrhea distinguished?**

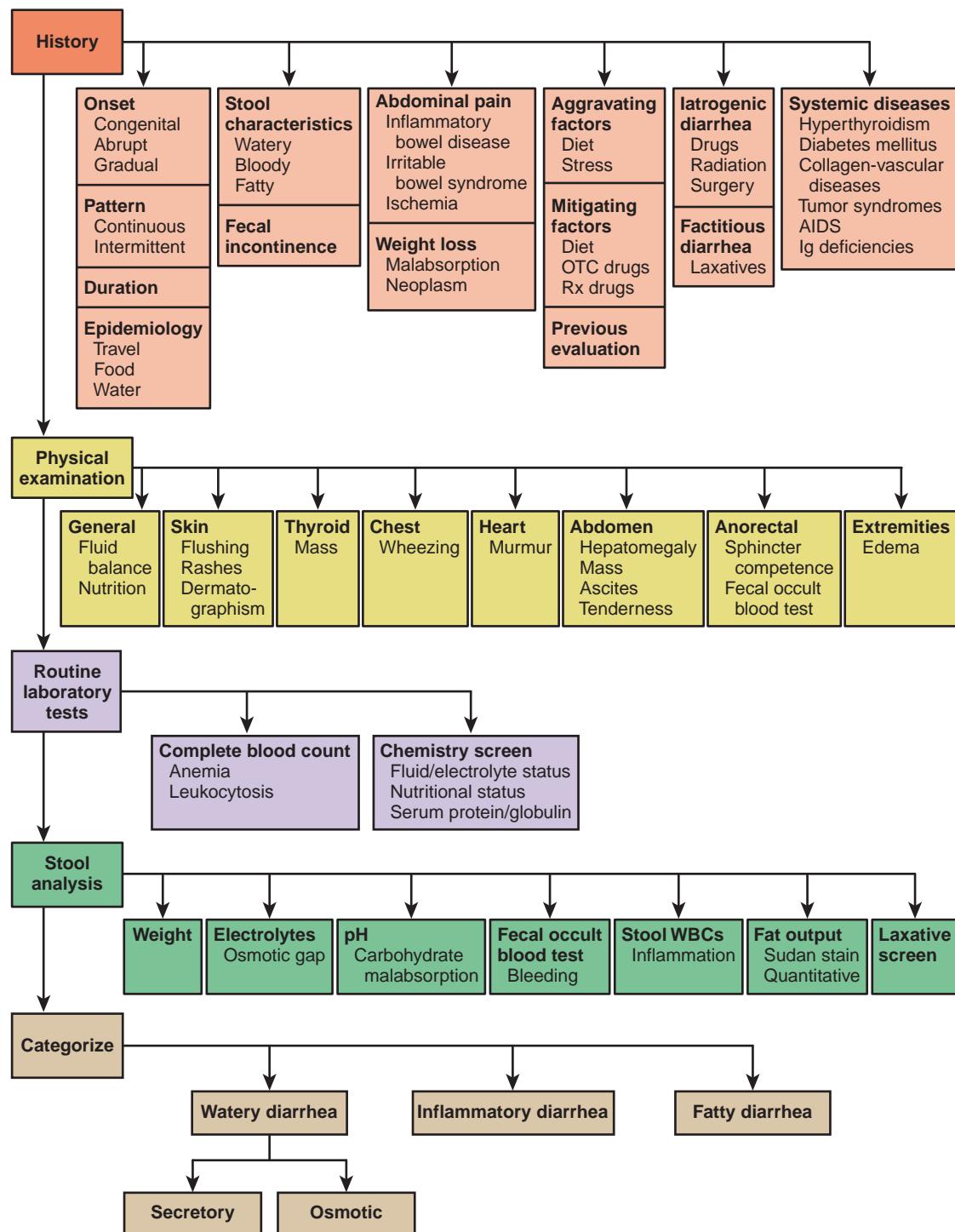
The most useful way to differentiate secretory and osmotic types of watery diarrhea is to measure fecal electrolytes and calculate the fecal osmotic gap. In many diarrheal conditions, sodium and potassium along with their accompanying anions are the dominant electrolytes in stool water. In secretory diarrhea, there is a failure to completely absorb electrolytes or actual electrolyte secretion by the intestine; sodium, potassium, and their accompanying anions are responsible for the bulk of osmotic activity in stool water and the retention of water within the gut lumen. In contrast, in osmotic diarrhea, ingestion of poorly absorbed, osmotically active substances is responsible for holding water within the gut lumen; electrolyte absorption is normal and thus sodium and potassium concentrations can become quite low (Figure 55-3). The fecal osmotic gap calculation takes advantage of these distinctions to differentiate the two conditions.

#### **13. How is the fecal osmotic gap calculated?**

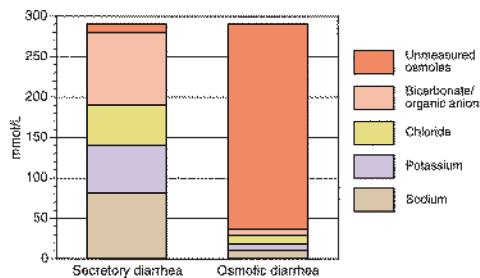
Fecal osmotic gap represents the osmotic activity in stool water not due to electrolytes. The sum of the concentrations of sodium and potassium in stool water is multiplied by 2 to account for the anions that are also present and this product is subtracted from 290 mOsm/kg, the approximate osmolality of luminal contents within the intestine. (This number is a constant in this calculation because the relatively high permeability of the intestinal mucosa beyond the stomach means that osmotic equilibration with plasma will have taken place by the time that luminal contents reach the rectum.) As an example, let us assume that a patient with watery diarrhea has a sodium concentration of 75 mmol/L and a potassium concentration of 65 mmol/L in stool water. Adding these together yields a concentration of 140 mmol/L. Doubling this to account for anions means that electrolytes account for 280 mOsm/kg of stool water osmolality. Subtracting this from 290 mOsm/kg yields an osmotic gap of 10 mOsm/kg. In contrast, if stool sodium was 10 mmol/L and potassium concentration was 20 mmol/L, the combined contribution of cations and anions in stool water would be only 60 mOsm/kg, yielding a fecal osmotic gap of 230 mOsm/kg. This represents the amount of some unmeasured substance that is contributing to fecal osmolality, presumably some poorly absorbed substance that is being ingested but not absorbed.

#### **14. How is the fecal osmotic gap interpreted?**

Fecal osmotic gaps less than 50 mOsm/kg correlate well with secretory diarrheas caused by incomplete electrolyte absorption. Fecal osmotic gaps greater than 50 mOsm/kg are associated with osmotic diarrheas.



**Figure 55-2.** The initial evaluation plan for patients with chronic diarrhea is aimed at assessing the severity of the problem, looking for clues to cause, and classifying the diarrhea as *watery* (with subtypes of *osmotic* and *secretory* diarrhea), *inflammatory*, or *fatty*. AIDS, Acquired immune deficiency syndrome; Ig, immunoglobulin; OTC, over the counter; Rx, prescription; WBC, white blood cell. (From Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. *Gastroenterology* 1999;116:1464-1486.)



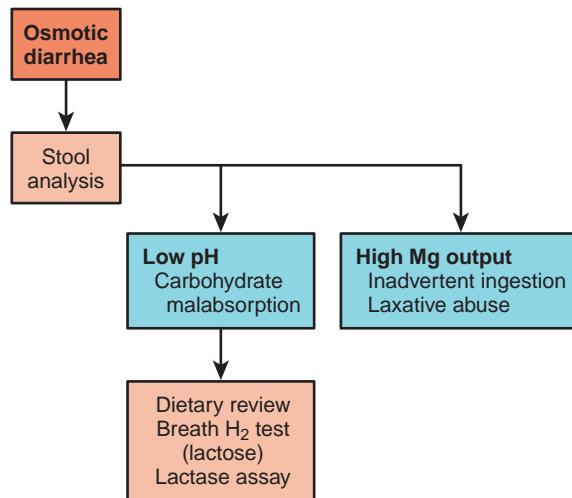
**Figure 55-3.** Electrolyte patterns differ between osmotic and secretory diarrhea. In secretory diarrhea, electrolytes account for the bulk of the osmotic activity of stool water. In contrast, in osmotic diarrhea electrolyte absorption is normal and therefore electrolyte concentrations are very low; most of the osmotic activity is due to unmeasured osmoles. (Bicarbonate concentrations are virtual and are not directly measurable in most circumstances because of reaction with organic acids generated by fermentation by colonic bacteria.)

### 15. What precautions are necessary when measuring fecal osmotic gaps?

Be certain that the stool has not been contaminated with either water or urine. Dilution by water or hypotonic urine will falsely lower fecal electrolyte concentrations and will elevate the calculated osmotic gap. This can be detected by actually measuring fecal osmolality; values that are substantially less than 290 mOsm/kg indicate dilution. Contamination with hypertonic urine may also affect fecal electrolyte concentrations, but is harder to detect unless the concentration of creatinine in stool water is measured or the sum of measured cations and assumed anions is much greater than 290 mmol/L.

### 16. How does one evaluate osmotic diarrhea?

Osmotic diarrheas are typically due to ingestion of poorly absorbed cations, such as magnesium, or anions, such as sulfate. In addition, carbohydrate malabsorption, such as that caused by ingestion of lactose in a patient with lactase deficiency, and ingestion of poorly absorbable sugar alcohols, such as sorbitol, can lead to an osmotic diarrhea. Measuring stool pH can help to distinguish between osmotic diarrheas caused by poorly absorbed cations and anions and those caused by ingestion of poorly absorbed carbohydrates and sugar alcohols. Carbohydrates and sugar alcohols are fermented by colonic bacteria, reducing fecal pH below 5 because of the production of short-chain fatty acids. In contrast, ingestion of poorly absorbed cations and anions does not affect stool pH much and stool pH is typically 7 in these circumstances. Once acidic stools have been discovered, check the diet and inquire about food additives and osmotic laxative ingestion. Specific testing for magnesium and other ions in stool is readily available to confirm any suspicions (Figure 55-4).

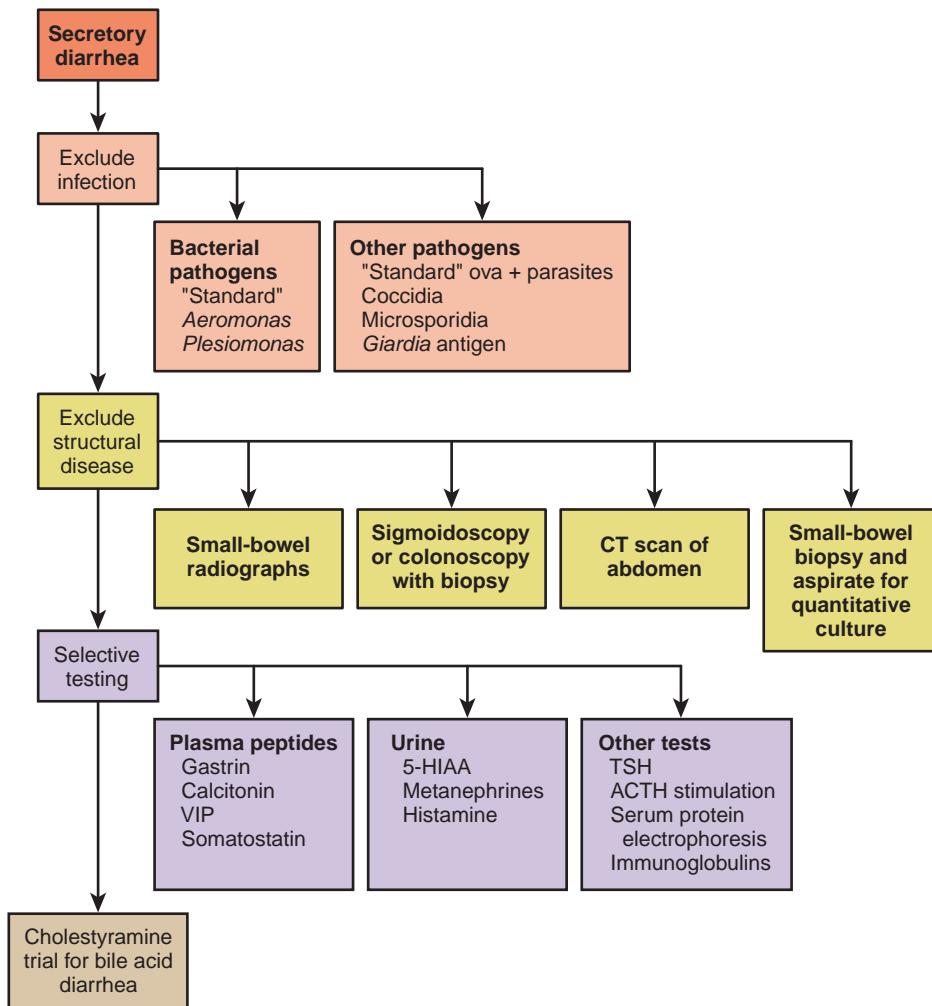


**Figure 55-4.** Once a diagnosis of osmotic diarrhea is made, evaluation is fairly straightforward; only a few causes are possible. H<sub>2</sub>, Hydrogen; Mg, magnesium. (From Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. Gastroenterology 1999;116:1464–1486.)

### 17. Describe the evaluation of chronic secretory diarrhea.

Because there are many causes of chronic secretory diarrhea, an extensive evaluation is necessary (Figure 55-5). Rare cases of infection should be excluded by bacterial culture and examination of stool for parasites or tests for protozoal antigens. Stimulant laxative abuse is best excluded by looking for laxatives in the urine or stool.

Structural disease and internal fistulas can be evaluated with small bowel radiography or computed tomography (CT) scanning of the abdomen and pelvis. Endoscopic examination of the upper gastrointestinal tract and colon is routine and should include biopsy of even normal-appearing mucosa, looking for microscopic evidence of disease. Systemic diseases such as hyperthyroidism, adrenal insufficiency, and defective immunity can be evaluated with appropriate tests (see Table 55-2).



**Figure 55-5.** Evaluation of secretory diarrhea can be very complex. This scheme can be used to guide the evaluation, depending on the specifics of each case. Not every test needs to be done in every patient. ACTH, Adrenocorticotrophic hormone; CT, computed tomography; 5-HIAA, 5-hydroxyindoleacetic acid; TSH, thyroid-stimulating hormone; VIP, vasoactive intestinal polypeptide. (From Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. *Gastroenterology* 1999;116:1464–1486.)

### 18. When should neuroendocrine tumors be suspected as a cause of chronic secretory diarrhea?

Neuroendocrine tumors are uncommon causes of chronic secretory diarrhea. For example, one VIPoma might be expected per 10 million people per year. Table 55-3 lists these tumors and their markers. Because of the rarity of these tumors as a cause for chronic diarrhea, other causes of secretory diarrhea should be considered first. If tumor is visualized by CT scan or if systemic symptoms (e.g., flushing) are present, evaluation for neuroendocrine tumors may have a better yield. Blanket testing for tumor-associated peptides is likely to yield many more false-positives than true-positives and therefore can be very misleading.

**Table 55-3.** Neuroendocrine Tumors Causing Chronic Diarrhea and Their Markers

TYPICAL SYMPTOMS	TUMOR	MEDIATOR AND TUMOR MARKER
Gastrinoma	Zöllinger-Ellison syndrome: pancreatic or duodenal tumor, peptic ulcer, steatorrhea, diarrhea	Gastrin
VIPoma	Verner-Morrison syndrome: watery diarrhea, hypokalemia, achlorhydria, flushing	Vasoactive intestinal polypeptide
Medullary thyroid carcinoma	Thyroid mass, hypermotility	Calcitonin, prostaglandins
Pheochromocytoma	Adrenal mass, hypertension	Vasoactive intestinal polypeptide, norepinephrine, epinephrine
Carcinoid	Flushing, wheezing, right-sided cardiac valvular disease	Serotonin, kinins
Somatostatinoma	Nonketotic diabetes mellitus, steatorrhea, diabetes, gallstones	Somatostatin
Glucagonoma	Skin rash (migratory necrotizing erythema), mild diabetes	Glucagon
Mastocytosis	Flushing, dermatographism, nausea, vomiting, abdominal pain	Histamine

VIPoma, Vasoactive intestinal polypeptide tumor.

#### 19. What is Bayes theorem? How does it relate to the diagnosis of peptide-secreting tumors?

Bayes theorem links the prevalence of the diagnosis to the positive predictive value of a diagnostic test. The positive predictive value of a test depends on the likelihood of the condition in the population to be tested, not only on the accuracy of the test. For example, peptide-secreting tumors are rare causes of chronic diarrhea with prevalences ranging from 1 per 5000 to 1 per 500,000 patients with chronic diarrhea, depending on tumor type. Bayes theorem can be expressed in the following simplified formula:

$$\text{Posttest odds of diagnosis} = \text{Pretest odds} \times \text{Likelihood ratio}$$

where the likelihood ratio = probability of true-positive result/probability of true-negative result.

Because the pretest odds of a peptide-secreting tumor are so long and the false-positive rate of serum peptide assays for that diagnosis is so high (approximately 45%), the positive predictive value for serum peptide assays is substantially less than 1%. An abnormal test result would be misleading more than 99% of the time.

#### 20. What is the likely outcome in patients with chronic secretory diarrhea in whom a diagnosis cannot be reached?

Diagnostic testing may fail to reveal a cause for chronic diarrhea in up to 25% of patients with chronic diarrhea depending on referral bias and the extent of evaluation.

Some patients with chronic secretory diarrhea that evades a serious diagnostic evaluation have a similar history of previous good health with the sudden onset of diarrhea, often accompanied by acute, but not progressive, weight loss. Although the acute onset suggests an acute infectious process, patients have negative microbiological studies and do not respond to empiric antibiotics. Diarrhea usually persists for 12 to 30 months and then gradually subsides. This condition can be sporadic or can occur in epidemics. The epidemic form (Brainerd's diarrhea) seems to be associated with ingestion of potentially contaminated food or drink, but no organism has been implicated. Management consists of the effective use of nonspecific antidiarrheals until the process subsides.

In other patients with chronic undiagnosed secretory diarrhea, a diagnosis will become apparent in time. Once a thorough evaluation has been concluded, it is therefore preferable to treat patients with undiagnosed secretory diarrhea symptomatically and follow them at intervals rather than to endlessly repeat diagnostic testing.

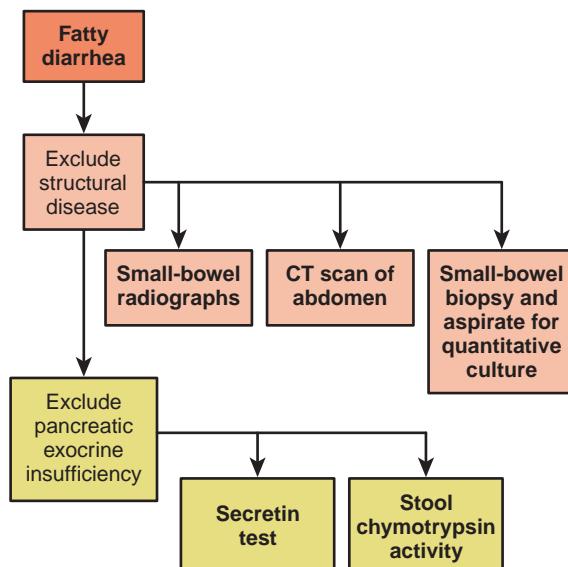
#### 21. Describe the evaluation of chronic fatty diarrhea.

Chronic fatty diarrhea is due to either maldigestion or malabsorption. Maldigestion can occur with pancreatic exocrine insufficiency, with ingestion of the lipase inhibitor orlistat, or if there is a bile acid deficiency, which reduces fat emulsification. Malabsorption typically is due to mucosal diseases such as celiac disease, small intestinal bacterial overgrowth, or small bowel fistula or resection.

Pancreatic exocrine insufficiency can be evaluated with a secretin test or measurement of chymotrypsin or elastase in stool. Because these tests are not widely available or have poor specificity

and sensitivity, clinicians often resort to a therapeutic trial of pancreatic enzymes. If this is done, the patient should be treated with a high dose of enzymes and the effect of this treatment on stool fat excretion as well as symptoms should be assessed.

Bile acid deficiency is a rare cause of maldigestion and is best assessed by direct measurement of duodenal bile acid concentration postprandially. Tests showing excess bile acid excretion in stool (radiolabeled bile acid excretion or total bile acid excretion tests) do not directly assess duodenal bile acid concentration, but if fecal bile acid excretion is high, reduced duodenal bile acid concentration can be inferred. Mucosal disease can be evaluated with small bowel biopsy and bacterial overgrowth can be assessed by breath hydrogen testing after an oral glucose load or by quantitative culture of intestinal contents (Figure 55-6).



**Figure 55-6.** Evaluation of chronic fatty diarrhea is designed to determine whether malabsorption or maldigestion is the cause of the excess fecal fat excretion. CT, Computed tomography. (From Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. *Gastroenterology* 1999;116:1464–1486.)

## 22. How does one make a diagnosis of celiac disease?

Celiac disease is a common cause of chronic fatty diarrhea, but may present without diarrhea. The population prevalence in the United States is estimated to be just less than 1%. Serologic testing for immunoglobulin A (IgA) antibodies against tissue transglutaminase is the preferred noninvasive test, but small bowel mucosal biopsy is the definitive test. If serologic testing is done, IgA levels should be measured because 10% of patients with celiac disease may have IgA deficiency, which would produce a false-negative test serologic result (see Chapter 40).

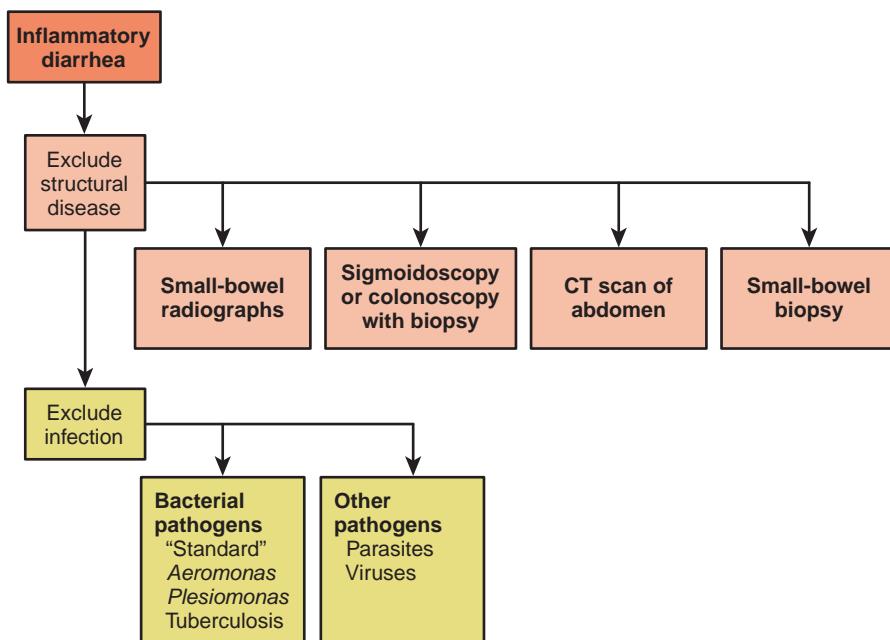
## 23. Describe the further evaluation of chronic inflammatory diarrhea.

Inflammatory diarrheas can be due to idiopathic inflammatory bowel diseases, such as ulcerative colitis or Crohn's disease; invasive chronic infectious diseases, such as tuberculosis or yersiniosis; ischemic colitis; radiation colitis; and some tumors. To sort through these diagnoses, the most appropriate tests include colonoscopy to inspect the colonic mucosa visually, colonic biopsy to look for microscopic evidence of inflammation, small bowel radiography or CT scanning of the abdomen; and special cultures for chronic infections, such as tuberculosis or yersiniosis. In most cases, the diagnosis will be apparent after these tests are completed (Figure 55-7).

## 24. How does one distinguish irritable bowel syndrome from chronic diarrhea?

The diagnosis of irritable bowel syndrome should be based on the presence of abdominal pain that is associated with defecation and abnormal bowel habits. Chronic continuous diarrhea in the absence of pain is not irritable bowel syndrome, although it may be functional in nature. Symptom criteria (Rome III criteria) have been published for clinical and research purposes and include the presence of at least 3 days per month of abdominal pain or discomfort in the last 3 months that is associated with at least two of the following three features:

- Relieved by defecation.
- Onset associated with a change in stool frequency.
- Onset associated with a change in stool form or appearance. Symptom onset must be at least 6 months prior to diagnosis.



**Figure 55-7.** Chronic inflammatory diarrhea has a diverse differential diagnosis. Structural evaluation with endoscopic or radiographic techniques often yields a diagnosis. Mucosal biopsy may be needed to confirm the diagnosis. CT, Computed tomography. (From Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. *Gastroenterology* 1999;116:1464–1486.)

## 25. What causes of chronic diarrhea may be difficult to diagnose?

- Fecal incontinence
- Iatrogenic diarrhea (drugs, surgery, radiation)
- Surreptitious laxative ingestion
- Microscopic colitis syndrome
- Bile acid-induced diarrhea
- Small bowel bacterial overgrowth
- Pancreatic exocrine insufficiency
- Carbohydrate malabsorption
- Peptide-secreting tumors
- Chronic idiopathic secretory diarrhea

These conditions are seen in referral centers after routine evaluation has failed to disclose a diagnosis. In general, the tests necessary to make these diagnoses are not difficult, but have not been done because physicians have not considered these diagnoses in the differential diagnosis of chronic diarrhea.

## 26. What are common causes of iatrogenic diarrhea?

Most iatrogenic diarrheas are due to ingestion of drugs, some of which may not be considered as common causes of diarrhea. Approximately two thirds of the drugs listed in the *Physician's Desk Reference* mention diarrhea as a possible side effect. Therefore the physician should obtain a history of all ingested drugs, including prescription medications, over-the-counter drugs, and herbal remedies (Box 55-1). Other causes of iatrogenic diarrhea include surgical operations, such as vagotomy, gastrectomy, and cholecystectomy, and radiation therapy, during which the intestine is exposed to high doses of ionizing radiation.

### Box 55-1. Drugs Associated with Diarrhea

- |   |  |
|---|--|
| <ul style="list-style-type: none"> <li>• Antibiotics (most)</li> <li>• Antineoplastic agents (many)</li> <li>• Antiinflammatory agents (e.g., NSAIDs, gold, 5-aminosalicylates)</li> <li>• Antiarrhythmics (e.g., quinidine)</li> <li>• Antihypertensives (e.g., <math>\beta</math>-receptor-blocking drugs)</li> </ul> | <ul style="list-style-type: none"> <li>• Antacids (e.g., those containing magnesium)</li> <li>• Acid-reducing agents (e.g., <math>H_2</math>-receptor antagonists, proton pump inhibitors)</li> <li>• Prostaglandin (e.g., misoprostol)</li> <li>• Vitamin and mineral supplements</li> <li>• Herbal products</li> </ul> |
|---|--|

### 27. What features should suggest surreptitious laxative ingestion?

Some patients who present with chronic diarrhea have diarrhea as a result of laxative abuse. In general, four groups of patients have this diagnosis:

- Bulimic patients: usually adolescent or young adult women concerned about body weight or with overt eating disorders
- Patients seeking a secondary gain: disability payments, concern or caring behavior by others
- Munchausen syndrome: peripatetic patients who relish being diagnostic challenges; may undergo extensive testing repeatedly
- Polle syndrome (Munchausen syndrome by proxy): dependent child or adult given laxatives by caregiver to show effectiveness as a caregiver or to gain sympathy from others; may have a history of a sibling who died with chronic diarrhea

Laxatives can be detected by chemical testing of stool or urine. The diagnosis should be confirmed before confronting the patient, and psychiatric consultation should be available to help with further management.

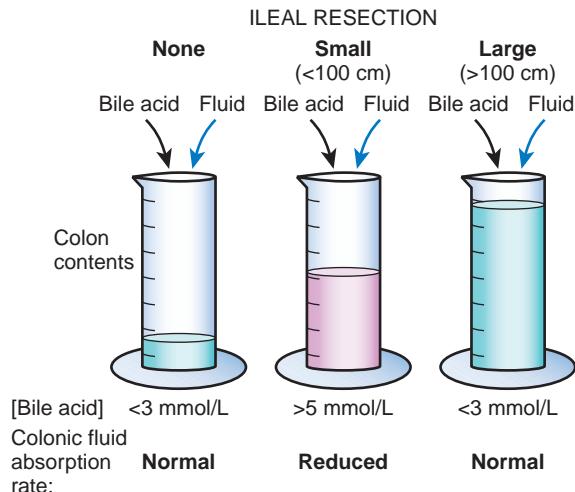
### 28. What is microscopic colitis syndrome?

Microscopic colitis is a syndrome characterized by chronic secretory diarrhea, a normal gross appearance of the colonic mucosa, and a typical pattern of inflammation in colon biopsy specimens. This pattern includes changes of the surface epithelium (flattening and irregularity), intraepithelial lymphocytosis, and an increased density of inflammatory cells in the lamina propria. There are two varieties. The first type is collagenous colitis in which the subepithelial collagen layer is thickened, and the second type is lymphocytic colitis in which the subepithelial collagen layer is of normal thickness. Microscopic colitis is as common as Crohn's disease in the general population. It occurs frequently in older patients and may be associated with fecal incontinence. In many cases, a rheumatologic or autoimmune disorder may be present. Treatment is variably effective: budesonide has the most evidence for efficacy; bile acid-binding drugs and bismuth subsalicylate have some efficacy.

### 29. Define bile acid diarrhea.

In patients with ileal resection or disease, the part of the small intestine with high-affinity bile acid transporters has been removed or is dysfunctional. Thus excessive bile acid finds its way into the colon. If the bile acid concentration in colonic contents reaches a critical level of approximately 3 to 5 mmol/L, salt and water absorption by the colonic mucosa is inhibited and diarrhea results. Patients who have had extensive small bowel resections (more than 100 cm) often have so much fluid entering the colon that this critical bile acid level is not reached, even though bile acid malabsorption may be extensive (*Figure 55-8*).

In addition to this classic form of diarrhea caused by bile acid malabsorption, some investigators have speculated that bile acid malabsorption causes chronic diarrhea in some patients with an intact ileum. Although tests of bile acid absorption frequently are abnormal in patients with idiopathic diarrhea, treatment with bile acid-sequestering resins, such as cholestyramine, is not often as effective in this group of patients as in those who have had surgical resection of the ileum.



**Figure 55-8.** Bile acid diarrhea occurs when bile acid malabsorption in the ileum is linked with relatively low fluid flows into the colon. As a result, the concentration of bile acid in the colon contents is greater than the cathartic threshold of 3 to 5 mmol/L. If fluid flows are high (as with substantial small bowel resection), bile acid malabsorption may be just as severe, but bile acid concentrations are not high enough to impair absorption by the colon.

### 30. What is the best nonspecific therapy for chronic diarrhea?

Because the evaluation of chronic diarrhea may extend over several weeks and because the diagnosis is not always forthcoming, patients may need symptomatic therapy. The most effective agents are opiates. Traditional antidiarrheal agents, such as diphenoxylate and loperamide, work well in many patients but should be given on a routine schedule in patients with chronic diarrhea rather than on an as-needed basis. Typical doses of one or two tablets or capsules of these agents before meals and at bedtime will improve symptoms in most people. When this therapy is ineffective, more potent opiates, such as codeine, opium, or morphine, can be used. With the stronger agents, doses should be low at first and increased gradually, so that tolerance to the central nervous system effects can develop. Fortunately, the gut does not become tolerant to these agents; thus one can usually find a dose that will control symptoms without producing severe side effects. Other agents that are sometimes used to manage chronic diarrhea include clonidine, octreotide, and cholestyramine, but they tend to be less effective than opiates and are often less well tolerated by patients, making them second-line agents in most circumstances ([Table 55-4](#)).

**Table 55-4.** Nonspecific Therapy for Chronic Diarrhea

DRUG CLASS	AGENT	DOSAGE
Opiates	$\mu$ -Opiate receptor selective Diphenoxylate Loperamide Codeine Morphine Opium tincture	2.5 to 5 mg qid 2 to 4 mg qid 15 to 60 mg qid 2 to 20 mg qid 2 to 20 drops qid
	$\delta$ -Opiate receptor selective Racecadotril (acetorphan) Adrenergic agonist Clonidine Somatostatin analogue Octreotide Bile acid-binding resin Cholestyramine	1.5 mg/kg tid* 0.1 to 0.3 mg tid 50 to 250 mcg tid (subcutaneously) 4 g qd to qid

*qid*, Four times daily; *qd*, every day; *tid*, three times daily.

\*Not yet approved in the United States.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

### BIBLIOGRAPHY

- Abraham BP, Sellin JH. Drug-induced, factitious, and idiopathic diarrhoea. Best Pract Res Clin Gastroenterol 2012;26:633–48.
- Fan X, Sellin JH. Review article: Small intestinal bacterial overgrowth, bile acid malabsorption and gluten intolerance as possible causes of chronic watery diarrhoea. Aliment Pharmacol Ther 2009;29:1069–77.
- Hammer HF, Hammer J. Diarrhea caused by carbohydrate malabsorption. Gastroenterol Clin North Am 2012;41:611–27.
- Li Z, Vaziri H. Treatment of chronic diarrhea. Best Pract Res Clin Gastroenterol 2012;26:677–87.
- Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterology 2006;130:1480–91.
- Murray JA, Ribio-Tapia A. Diarrhoea due to small bowel diseases. Best Pract Res Clin Gastroenterol 2012;26:581–600.
- Schiller LR. Diarrhea and malabsorption in the elderly. Gastroenterol Clin North Am 2009;38:481–502.
- Schiller LR. Chronic idiopathic diarrhea. In: Guandalini S, Vaziri H, editors. Diarrhea: Diagnostic and therapeutic advances. New York: Humana Press, Springer Science & Business Media. pp. 311–324.
- Schiller LR. Definitions, pathophysiology and diagnosis of chronic diarrhea. Best Pract Res Clin Gastroenterol 2012;26:551–62.
- Schiller LR. Malabsorption. In: Bope ET, Kellerman R, editors. Conn's current therapy 2013. Philadelphia: Elsevier Saunders; 2013. p. 547–53.
- Schiller LR, Pardi DS, Spiller R, et al. Gastro 2013 APDW/WCOG Shanghai Working Party Report: Chronic diarrhea: Definition, classification, diagnosis. Journal of Gastroenterology and Hepatology 2014;29:6–25.
- Schiller LR, Sellin JH. Diarrhea. In: Feldman M, Friedman L, Brandt LJ, editors. Sleisenger & Fordtran's gastrointestinal and liver disease. 9th ed. Philadelphia: Saunders Elsevier; 2010. p. 211–32.
- Scott IA, Greenberg PB, Poole PJ. Cautionary tales in the clinical interpretation of studies of diagnostic tests. Intern Med J 2008;38:120–9.
- Sellin JH. A practical approach to treating patients with chronic diarrhea. Rev Gastroenterol Disord 2007;7(Suppl. 3): S19S26.
- Steffe KJ, Santa Ana CA, Cole JA, Fordtran JS. The practical value of comprehensive stool analysis in detecting the cause of chronic diarrhea. Gastroenterol Clin North Am 2012;41:539–60.

**Websites**

- American College of Gastroenterology. Diarrheal diseases—Acute and chronic. Accessed September 22, 2014, from <http://patients.gi.org/topics/diarrhea-acute-and-chronic/>.
- Binder HJ. Causes of chronic diarrhea. N Engl J Med 2006;355:236–239. Accessed September 22, 2014, from <http://content.nejm.org/cgi/content/extract/355/3/236>.
- Centers for Disease Control and Prevention. Hygiene-related diseases: Chronic diarrhea. Accessed September 22, 2014, from [http://www.cdc.gov/healthywater/hygiene/disease/chronic\\_diarrhea.html](http://www.cdc.gov/healthywater/hygiene/disease/chronic_diarrhea.html).
- National Digestive Diseases Information Clearinghouse. Diarrhea. Accessed September 22, 2014, from <http://digestive.niddk.nih.gov/ddiseases/pubs/diarrhea/>.
- UpToDate. Patient information: Chronic diarrhea in adults. Accessed September 22, 2014, from <http://www.uptodate.com/patients/content/topic.do?topicKey=digestiv/4974>.

# AIDS AND THE GASTROINTESTINAL TRACT

C. Mel Wilcox, MD, MSPH, and Klaus E. Mönkemüller, MD, PhD

## 1. Describe the time course of opportunistic diseases in patients with human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS).

There is a stereotypical time course for the development of opportunistic processes in patients with HIV infection. *The risk for these disorders increases when the CD4 count falls to less than 200.* For some processes, such as lymphoma and tuberculosis, presentation may occur at a CD4 count of more than 200. Cytomegalovirus (CMV) infection, cryptosporidiosis, microsporidiosis, and *Mycobacterium avium* complex (MAC) occur when the CD4 count is less than 100 and often less than 50.

## 2. Is there a role for barium esophagogram in patients with HIV and esophageal symptoms?

Barium esophagogram has a limited role in patients with AIDS. Given that infections and neoplasms are the most common cause of disease in patients with significant immunodeficiency (CD4 count < 100), endoscopic inspection with tissue acquisition with biopsy or brushings is mandatory for a specific diagnosis. In addition, some of these disorders have a similar appearance radiographically, and toxicity can be associated with treatments directed at these infections. Thus a specific diagnosis is mandatory before empiric therapy is given. Motility disorders and reflux may be important to exclude in HIV-infected patients without immunodeficiency.

## 3. What are the implications of odynophagia in a patient with HIV infection?

Odynophagia, or painful swallowing, is an uncommon symptom. In patients with AIDS, this almost always represents an esophageal ulcer. In such patients, associated chest pain may be a concomitant complaint. Upper endoscopy is mandatory for a specific diagnosis. Rarely, *Candida* esophagitis may result in severe odynophagia, but more typically is milder and dysphagia is prominent.

## 4. What is the role of endoscopy in HIV-infected patients with upper gastrointestinal (GI) symptoms?

Patients with AIDS (CD4 count < 200) are at risk for opportunistic infections and neoplasms, particularly when the CD4 lymphocyte count falls to less than 100. Given the broad differential diagnosis of upper GI symptoms in these patients, generally upper endoscopy should be performed so all lesions can be biopsied for a definitive diagnosis.

## 5. How has highly active antiretroviral therapy (HAART) altered the incidence of opportunistic GI disorders?

Since the introduction of protease inhibitors and HAART in 1995, there has been a constant and dramatic decline of all GI opportunistic disorders (ODs) in AIDS patients. In addition, HAART has also been shown to indirectly treat many GI ODs. Once the immune status of the patient improves, the OD generally resolves. However, careful follow-up of patients receiving HAART early on is mandatory as their condition can decompensate as a result of immune reconstitution syndrome (IRIS).

## 6. What is the role of empiric therapy for new-onset esophageal symptoms in patients with HIV infection?

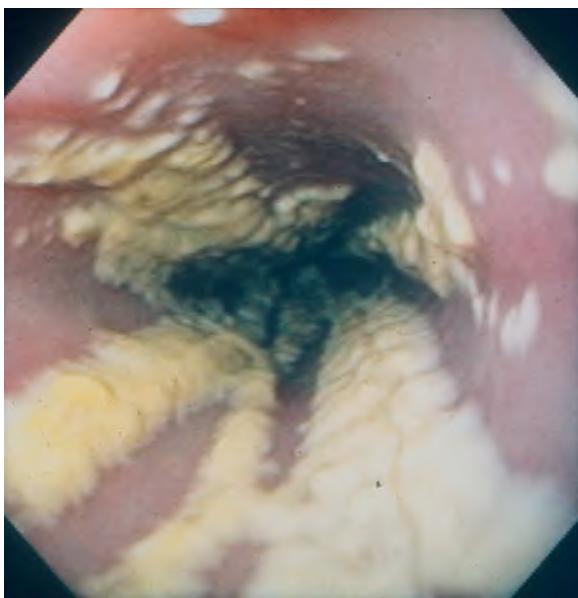
*Candida* esophagitis is the most common cause of esophageal disease in patients with AIDS presenting with dysphagia or odynophagia (Figure 56-1). Because of this high prevalence, an empiric approach to new-onset esophageal symptoms with potent antifungal therapy is commonly undertaken and accepted. A fluconazole loading dose of 200 mg followed by 100 mg/day for 10 days should be instituted. Because *Candida* esophagitis responds rapidly to fluconazole, patients who do not symptomatically improve within the first few days of treatment should undergo endoscopic evaluation to exclude other causes of disease (viral esophagitis). This is the only condition for which enough data exist to document empiric therapy. Empiric therapy for suspected viral, fungal, and parasitic diseases is not indicated.

## 7. What is the role of empiric therapy for upper GI symptoms in HIV-infected patients?

With improving HIV and AIDS therapies, patient commonly have CD4 counts higher than 200 cells/mL. In these patients, an empiric trial of a proton pump inhibitor is reasonable for symptoms consistent with gastroesophageal reflux disease (GERD) or other dyspeptic complaints. If symptoms do not improve within 1 or 2 weeks, endoscopic evaluation to exclude other causes of disease is mandatory.

## 8. What are the most common causes of esophageal ulceration in HIV-infected patients?

The most common causes are CMV and idiopathic esophageal ulcer (IEU). On endoscopy, CMV and IEU appear most often as multiple, large, well-circumscribed solitary ulcerations, with normal-appearing surrounding mucosa (Figure 56-2).



**Figure 56-1.** Candidal esophagitis. Yellow plaques coating the esophageal wall are typical for *Candida*. Note that on one portion of the wall, the material has been removed and the underlying mucosa is normal.



**Figure 56-2.** Ulcerative esophagitis in acquired immune deficiency syndrome. Cytomegalovirus (A), idiopathic esophageal ulcer (B), and herpes simplex virus (C).

Herpes simplex virus (HSV) is usually associated with multiple small, shallow esophageal ulcerations, often raised with a volcano crater appearance. GERD can also present with ulcerations of the distal esophagus generally involving the gastroesophageal junction; these lesions are generally linear and superficial. Neoplasms (e.g., lymphoma), parasites (e.g., leishmania), and fungal infections (e.g., histoplasmosis and *Candida* spp.) are rare causes of esophageal ulcers (Table 56-1).

**Table 56-1.** Reported Causes of Esophageal Ulcers in AIDS

Viruses	Cytomegalovirus, herpes simplex virus type II, Epstein-Barr virus, papovavirus, human herpes virus-6
Fungi	<i>Candida</i> spp., <i>Histoplasma capsulatum</i> , <i>Cryptococcus neoformans</i> , mucormycosis, aspergillosis, <i>Penicillium chrysogenum</i> , <i>Exophiala jeanselmei</i>
Bacteria	<i>Mycobacterium avium</i> -complex, <i>Mycobacterium tuberculosis</i> , <i>Bartonella henselae</i> , <i>Nocardia asteroides</i> , <i>Actinomyces israelii</i>
Protozoa	<i>Cryptosporidium</i> , <i>Leishmania donovani</i> , <i>Pneumocystis carinii</i>
Tumors	Non-Hodgkin's lymphoma, Kaposi sarcoma, cancer (squamous cell and adenocarcinoma), lymphoma
Pill-induced	Zalcitabine, zidovudine, other
Gastroesophageal disease, idiopathic	Idiopathic esophageal ulcer

AIDS, Acquired immune deficiency syndrome.

### **9. What biopsy technique should be used to sample an esophageal ulcer?**

The exact number of biopsies required for maximal sensitivity and specificity is not clearly established, but several studies suggest the range of 8 to 10. It is important to obtain biopsy samples from the ulcer margin and from the ulcer base. This is because biopsy of the ulcer edge reveals a cytopathic effect that is present in squamous epithelium associated with HSV; conversely, CMV resides in granulation tissue in the ulcer base. The role of culture and cytologic examination for esophageal ulcers is not settled. If all biopsies are negative for viral, bacterial, fungal, and parasitic infections, a diagnosis of IEU can be made.

### **10. What is AIDS cholangiopathy? How do patients present?**

AIDS cholangiopathy is a spectrum of biliary tract abnormalities resembling sclerosing cholangitis that can be caused by a wide array of microorganisms and neoplasms, usually in patients with advanced immunodeficiency (CD4 count <100 cells/mL). Patients generally present with epigastric or right upper quadrant pain, fever, and malaise. Although AIDS cholangiopathy is a cholestatic disease, jaundice and pruritus are uncommon.

### **11. What are the most common causes of AIDS cholangiopathy? How are they diagnosed?**

- A. *Cryptosporidium parvum*
- B. Microsporidia
  - Enterocytozoon bieneusi
  - Encephalitozoon intestinalis
  - Encephalocytotozoon cuniculi
- C. CMV
- D. MAC
- E. *Cyclospora cayetanensis*
- F. Non-Hodgkin's lymphoma
- G. Kaposi sarcoma (KS)

Despite its infectious origin, medical therapies aiming at the eradication of these organisms have not produced marked improvement in AIDS cholangiopathy. Conversely, treatment with HAART is associated with improvement of symptoms and decreased mortality.

### **12. How is AIDS cholangiopathy best diagnosed?**

The most common laboratory finding in this syndrome is a markedly elevated alkaline phosphatase, usually more than three times the upper limits of normal. Typically bilirubin is not elevated and rarely exceeds 3 mg/dL, and transaminases are only mildly elevated. Generally, these patients have a dilated bile duct that is identifiable on abdominal ultrasonography.

The diagnosis of AIDS cholangiopathy is best established by endoscopic retrograde cholangiopancreatography. The diagnosis is usually established by obtaining biopsy specimens of the ampulla or duodenal mucosa, bile duct biopsy, aspirated bile specimens, or biliary epithelial brush cytologic examination. Several cholangiographic patterns have been described, including papillary stenosis, sclerosing cholangitis, combined papillary stenosis and sclerosing cholangitis, isolated intrahepatic disease, and long extrahepatic bile duct strictures. The most common pattern is papillary stenosis with intrahepatic sclerosing cholangitis. Endoscopic sphincterotomy is appropriate for the relief of pain in patients with papillary stenosis and dilated ducts.

### **13. What are the most common causes of pancreatitis in HIV-infected patients?**

Several studies have documented chronic and recurrent elevations of serum amylase and lipase in up to 50% of patients with AIDS. The most common medications associated with pancreatitis in AIDS are pentamidine, didanosine (ddI), and zalcitabine (ddC). Protease inhibitors frequently cause hyperlipidemia. Ritonavir is associated with the most dramatic increases in serum triglycerides, with 10% of patients developing severe hypertriglyceridemia. Pancreatitis is well described in patients with elevations in triglycerides from protease inhibitors. Reported infectious causes of pancreatitis include CMV, HSV, MAC, and tuberculosis. An infectious cause of pancreatitis is difficult to establish and requires pancreatic biopsy.

### **14. What is the clinical presentation of diarrhea in AIDS?**

When evaluating an HIV-infected patient with diarrhea, careful attention should be directed to the history and physical examination. Enteritis (small bowel diarrhea) is associated with voluminous, watery bowel movements, abdominal bloating, cramping, borborygmi, and nausea. Abdominal pain, if present, tends to be periumbilical or diffuse. Abdominal examination reveals an increase in number and frequency of bowel sounds, which may be high-pitched. Conversely, colitis (large bowel diarrhea) is characterized by frequent, small bowel movements, with the presence of mucus, pus, or blood (dysentery). Patients with prominent involvement of the distal colon also have proctitis symptoms, such as tenesmus, dyschezia (pain on defecation), and proctalgia (rectal pain).

### **15. What is the approach to diarrhea in HIV-infected patients?**

It is important to consider patient exposures. A history of new medications or an alteration in a current regimen, such as antiretrovirals or antibacterials, is important because many protease inhibitors are associated with diarrhea and antibacterials are associated with *Clostridium difficile* colitis. In febrile patients, blood cultures should be obtained for common bacteria such as are mandatory. If stool and blood culture studies are negative, the next step is endoscopic evaluation with biopsy. In the presence of colitis symptoms, flexible sigmoidoscopy or colonoscopy is recommended. Table 56-2 summarizes the studies and laboratory tests used in the evaluation of diarrhea in AIDS.

**Table 56-2.** Studies and Laboratory Tests Used in the Evaluation of Diarrhea in AIDS

Stool	Cultures ( <i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter</i> spp.) Toxin ( <i>Clostridium difficile</i> ) Ova and parasites ( <i>Giardia lamblia</i> , <i>Entamoeba histolytica</i> , <i>Cryptosporidium</i> spp.) Modified Kinyoun acid-fast ( <i>Cryptosporidium</i> spp., <i>Isospora belli</i> ) Concentrated stool (zinc sulfate, Sheather sucrose flotation) (microsporidia)
Blood	Cultures ( <i>Mycobacterium avium</i> complex, <i>Salmonella</i> , <i>Campylobacter</i> spp.) Antibodies ( <i>Entamoeba histolytica</i> , CMV)
Gastrointestinal fluids	Duodenal aspirate ( <i>Giardia lamblia</i> , microsporidia) Electron microscopy ( <i>Cryptosporidium</i> spp., adenovirus)
Biopsy stains	Hematoxylin-eosin Gyms or methenamine silver (fungi) Methylene blue–azure II–basic fuchsin (microsporidia) Fite (mycobacteria)
Immunohistochemical stains (CMV), immunologic methods	In situ hybridization (CMV) DNA amplification (CMV) Culture of tissue CMV Herpes simplex virus Mycobacteria

AIDS, Acquired immune deficiency syndrome; CMV, cytomegalovirus.

**Table 56-3.** Infectious Causes of Diarrhea in AIDS

VIRUSES	BACTERIA	PARASITES	FUNGI
Cytomegalovirus	<i>Salmonella</i> spp.	<i>Giardia lamblia</i>	<i>Histoplasma capsulatum</i>
Astrovirus	<i>Shigella</i> spp.	<i>Entamoeba histolytica</i>	<i>Candida albicans</i>
Picornavirus	<i>Campylobacter jejuni</i>	<i>Microsporidia</i>	
Coronavirus	<i>Clostridium difficile</i>	<i>Enterocytozoon bieneusi</i>	
Rotavirus	<i>Mycobacterium avium</i>	<i>Encephalitozoon intestinalis</i> (formerly <i>Septata</i> )	
Herpesvirus	complex	<i>Cyclospora cayetanensis</i>	
Adenovirus	<i>Treponema pallidum</i>	<i>Cryptosporidium</i> spp.	
Small round virus	<i>Spirochetes</i>	<i>Isospora belli</i>	
HIV	<i>Neisseria gonorrhoeae</i>	<i>Blastocystis hominis</i> (?)	
	<i>Vibrio cholera</i>		
	<i>Aeromonas</i> spp.		
	<i>Pseudomonas</i> spp. (?)		
	<i>Staphylococcus aureus</i>		

AIDS, Acquired immune deficiency syndrome; HIV, human immunodeficiency virus.

**Table 56-4.** Sources of Infectious Diarrhea

INFECTIOUS AGENT	ASSOCIATION
<i>Clostridium difficile</i>	Recent antibiotics, nursing home or hospital exposures
<i>Cryptosporidiosis</i>	Recent visit to a farm, contact with farm animals, use of a public swimming pool
<i>Microsporidiosis</i>	
<i>Giardia</i>	Camping, stream water
<i>Mycobacterium avium</i>	CD4 count less than 50
<i>Cyclospora cayetanensis</i>	Common cause of diarrhea in South America
<i>Microsporidiosis</i>	Uncommon in the southern United States
<i>Rotavirus</i>	Common cause of diarrhea in Australia

### 16. Describe the clinical features of HSV proctitis in AIDS.

HSV proctitis is the most common cause of nongonococcal proctitis in sexually active homosexual men. HSV proctitis classically presents with tenesmus, purulent rectal discharge, severe proctalgia, fever, constipation, and anorectal bleeding. Painful inguinal lymphadenopathy is an almost universal finding. The pain tends to distribute in the region of the sacral roots (i.e., buttocks, perineal region, and posterior thigh). Because of the neural involvement by HSV and the presence of severe pain, patients may complain of impotence and difficulty in initiating micturition. Visual inspection and anoscopy commonly reveal the following lesions: vesicles, pustular rectal lesions, or diffuse ulcerations. HSV is a pathogen of the squamous mucosa; therefore diffuse proctitis involving the entire rectum is rare. In severe cases, the columnar rectal and sigmoid mucosa has been involved. The differential diagnoses of HSV proctitis include lymphogranuloma venereum (*Chlamydia trachomatis*), *Entamoeba histolytica*, *Salmonella* spp., and *Campylobacter jejuni*.

### 17. What is the preferred endoscopic procedure for the evaluation of diarrhea in AIDS?

The advantage of endoscopy is that it permits direct visualization of the mucosa and retrieval of tissue for histologic examination. The diagnostic yield of colonoscopy in HIV-infected patients with chronic diarrhea and negative stool studies ranges from 27% to 37%; in patients with AIDS, CMV is the most common etiologic factor identified (Figure 56-3). CMV colitis is usually present in the distal colon; however, isolated, right-sided CMV colitis has been reported. Therefore if CMV is suspected as the cause of diarrhea, a full colonoscopy is warranted, especially if sigmoidoscopy is negative. However, it is still not clear whether colonoscopy has a higher yield than flexible sigmoidoscopy for the detection of organisms other than CMV. Evaluation with colonoscopy is prudent if right-sided abdominal complaints are also reported. The value of upper endoscopy and small bowel biopsy in the evaluation of chronic diarrhea has also been demonstrated, although specific treatment options for most small bowel pathogens are limited. Some would obtain ileal biopsy at the time of colonoscopy rather than proceed with upper endoscopy and biopsy. The most commonly detected organisms involving the small bowel are cryptosporidia and microsporidia.

**Figure 56-3.** Cytomegalovirus colitis. Abdominal computed tomography scan shows colonic wall thickening most pronounced in the right colon.



### 18. What is the most common cause of viral diarrhea in AIDS?

CMV is one of the most common opportunistic infections in patients with AIDS, occurring late in the course of HIV infection when immunodeficiency is severe (CD4 lymphocyte count  $1 < 100/\text{mm}^3$ ). CMV has been identified in mucosal biopsy samples in as many as 45% of patients with AIDS and diarrhea, especially in those patients with negative stool studies. CMV causes both enteritis and colitis. A number of other viral pathogens—adenovirus, rotavirus, astrovirus, picobirnavirus, and coronavirus—have been reported to involve the GI tract in patients with AIDS, but their clinical importance remains to be determined. HSV can cause proctitis that mimics diarrhea because of the rectal mucous discharge. However, HSV does not cause enterocolitis because it invades the squamous mucosa, not the columnar epithelium, such as the one lining the colonic and small bowel mucosa.

### 19. What are the treatment options for CMV enterocolitis?

The natural history of CMV colitis is variable. In untreated patients, it usually has a chronic course characterized by progressive diarrhea and weight loss, although occasionally symptoms and histologic abnormalities remit spontaneously. Unlike CMV retinitis, for which strong evidence supports induction therapy followed by lifelong maintenance therapy, the optimal duration of therapy and the need for maintenance therapy in CMV colitis are undefined. Consensus guidelines recommend 3 to 6 weeks of induction therapy, typically ganciclovir, followed by maintenance therapy if there is a history of relapses. Valganciclovir can be given

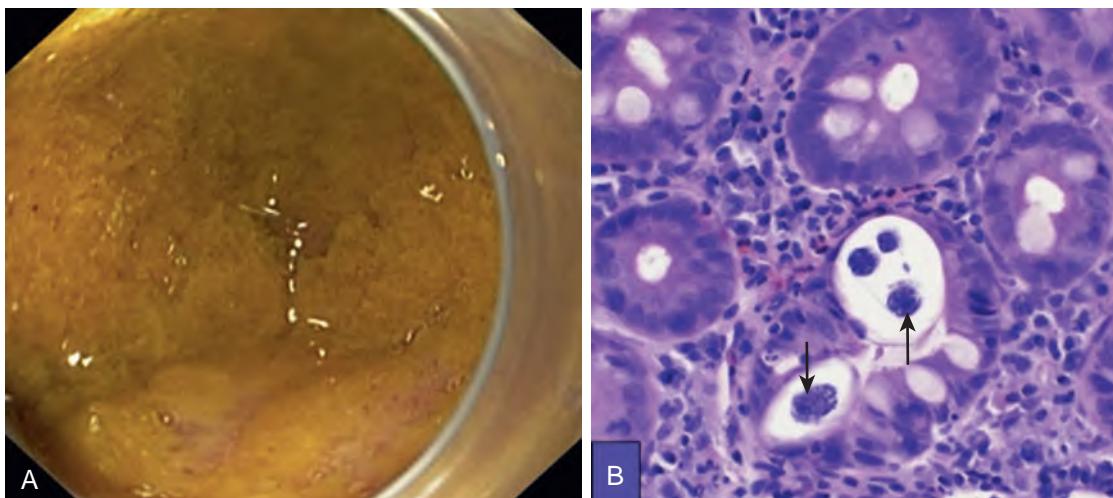
orally and achieves serum concentrations similar to intravenous ganciclovir. Studies for GI disease are limited. Funduscopic examination at the time of diagnosis of CMV enterocolitis is mandatory, because duration of therapy is considerably longer for disseminated diseases than for disease limited to the GI tract.

## 20. Name the common parasites that cause diarrhea in AIDS.

Among the protozoa, *C. parvum* is the most common parasite causing diarrhea in AIDS and has been identified in up to 11% of symptomatic patients. Although a cause of acute diarrhea, cryptosporidiosis is found most commonly in HIV-infected patients with chronic diarrhea. In some studies of HIV-infected patients with chronic diarrhea, microsporidia (*E. bieneusi* and *E. intestinalis*) are the most commonly identified pathogens. *Giardia* is also a consideration in patients with diarrhea, especially when chronic and associated with the upper GI symptoms of nausea and bloating. *Isospora belli* is a rare GI pathogen in HIV-infected patients in North America, whereas it is endemic in many developing countries, such as Haiti.

## 21. Is strongyloidiasis more prevalent in HIV infection?

*Strongyloides stercoralis* is an endemic parasite in the subtropical areas worldwide, including the southeastern United States. There is no clear evidence that HIV infection predisposes to strongyloidiasis. However, patients with HIV infection may be more prone to develop the *Strongyloides* hyperinfection syndrome. In addition, during therapy with HAART an IRIS with hyperinfection syndrome has been reported. Therefore it is important to keep this potentially life-threatening infection in mind when evaluating patients with HIV infection and GI symptoms such as diarrhea, abdominal pain, and dyspepsia. In HIV-infected patients with eosinophilia, empiric therapy with ivermectin is warranted while the work-up of eosinophilia is in progress. *Strongyloides* can infect any part of the GI tract. However, the classic finding is a “catarrhal” duodenitis, with edema of the villi and massive amounts of yellow exudate covering the mucosa (Figure 56-4).



**Figure 56-4.** *Strongyloides stercoralis* duodenitis in an HIV-infected patient with hyperinfection syndrome. The classic duodenal findings is a “catarrhal” duodenitis (A). Histologic examination is mandatory in the evaluation of strongyloidiasis (B). The preferred biopsy site is always the duodenum.

## 22. Compare the clinical features and therapies for cryptosporidiosis and microsporidiosis

GI microsporidial infection is generally attributed to two species: *E. bieneusi* and *E. intestinalis*. In general, intestinal disease is relatively mild in contrast to the severe diarrhea typical for cryptosporidiosis. Loose stools and mild weight loss are common, with colonic symptoms typically absent. GI bleeding suggests another diagnosis as this infection does not cause mucosal ulceration. Although stool studies can establish the diagnosis, small bowel biopsies, of either the duodenum or ileum, with special stains are more sensitive. Although there is no effective antimicrobial therapy for *E. bieneusi*, albendazole is highly effective for *E. intestinalis*. As with all opportunistic infections in AIDS, HAART may result in clinical remission.

Cryptosporidiosis are a common cause of chronic diarrhea in HIV-infected patients with severe immunodeficiency. There are at least 40 species of Cryptosporidium, but the most common cause of human disease is *Cryptosporidium muris*. The diarrhea is generally voluminous and watery. Dehydration and weight loss are common in patients with advanced immunodeficiency. Disease severity correlates with immune function. The disease may wax and wane, but persistent or progressive disease may be manifested by dehydration and electrolyte imbalances. Constitutional symptoms are prominent, including low-grade fever, malaise, anorexia, nausea, and vomiting. Both of these infections improve with reconstitution of the immune system following successful HAART.

**23. Which bacteria most commonly cause diarrhea in AIDS?**

*Campylobacter*, *Salmonella*, and *Shigella* spp. and *C. difficile* are the most common causes of diarrhea in AIDS. *Yersinia enterocolitica*, *Staphylococcus aureus*, and *Aeromonas hydrophila* have also been associated with severe enterocolitis in HIV-infected patients. *C. difficile* colitis has become the most frequent bacterial cause of diarrhea in HIV-infected patients, perhaps because of frequent exposure to antimicrobials and requirement for hospitalization. MAC is a common pathogen in patients with advanced immunosuppression (i.e., CD4 count < 50 cells/mm<sup>3</sup>). An incidence of 39% has been described when the CD4 count remains less than 10/mm<sup>3</sup>. Tuberculosis is most frequent in developing countries and is less likely to present with diarrhea alone, and can present at any level of immune dysfunction.

**24. What is bacillary peliosis hepatitis (BPH)?**

BPH produces multiple cystic blood-filled spaces in the liver. BPH is caused by an infection with the bacteria *Bartonella henselae* (formerly *Rochalimae*) and occurs in patients with advanced AIDS. Patients present with generalized and nonspecific symptoms, such as fever, weight loss, and malaise. Abdominal pain, nausea, vomiting, and diarrhea may be prominent. Skin manifestations include reddish vascular papules that can be confused with KS. On abdominal examination, hepatosplenomegaly and lymphadenopathy are the most prominent features. Histopathologic examination of the liver lesions shows multiple cystic blood-filled spaces within fibromyxoid areas. The treatment of choice is erythromycin for at least 4 to 6 weeks, but doxycycline is a safe alternative.

**25. When do you initiate hepatitis B virus (HBV) therapy in the setting of HIV?**

HBV-HIV coinfection represents a significant problem in HIV care. As HAART has improved the prognosis in HIV and AIDS, significant increases in morbidity and mortality resulting from liver disease have been observed. HBV and HIV are acquired by similar mechanisms and thus coinfection is common. Patients with coinfection of HIV and HBV have higher HBV DNA levels and are less likely to convert from hepatitis B e antigen-positive to hepatitis B e antibody-positive, indicating a poorer response to HBV therapy. *Patients with a HBV DNA greater than 2000 IU and F2 or greater fibrosis on biopsy should receive HBV treatment.* If a patient has cirrhosis, he or she should be treated if HBV DNA is greater than 200. For patients with a high CD4 count, HBV monotherapy that is not active against HIV should be first-line therapy. When initiating HAART, HBV also should be treated with two antiviral agents active against HBV. If CD4 counts are between 350 and 500 cells/mL, one can elect to treat both HIV and HBV. HAART with two agents active against HBV should be used instead of HBV monotherapy in these individuals.

**26. Why is it important to know the HBV treatments that are also active in treating HIV?**

Initiating HBV monotherapy that is also active in treating HIV can result in HIV resistance, potentially limiting HAART options. Furthermore, if HAART is initiated without concurrent HBV treatment, immune reconstitution can result in a potentially life-threatening flare of untreated HBV. Table 56-5 shows treatments active against HBV and HIV or HBV alone.

**Table 56-5. Hepatitis B Treatments and HIV Activity**

TREATS HIV AND HBV	TREATS HBV WITHOUT HBV RESISTANCE
Lamivudine	Interferon/PEG-IFN
Tenofovir	Adefovir (at 10-mg dosing)
Emtricitabine	Telbivudine (in vitro)
Entecavir (in vivo)	

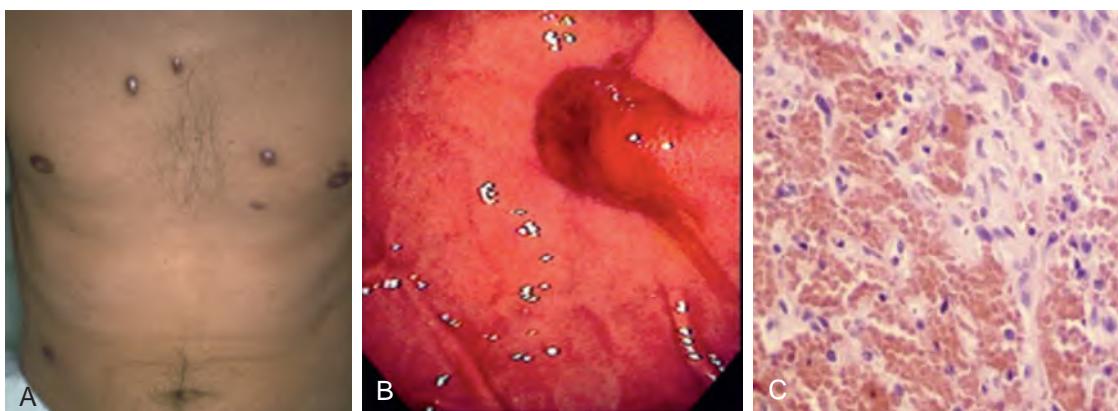
HBV, hepatitis B virus; HIV, human immunodeficiency virus; PEG-IFN, pegylated interferon.

**27. How is the natural history of hepatitis C virus (HCV) infection altered in patients with AIDS?**

HCV is common in HIV-infected patients given the similar routes of exposure. In the normal host, progression from infection to cirrhosis takes several decades. A number of studies now suggest that the progression rate is markedly accelerated in patients with AIDS. Indeed currently HCV infection-related cirrhosis is one of the most common causes of death in these patients. This alteration in natural history suggests that early diagnosis of HCV infection and treatment are important.

**28. What are the GI manifestations of KS in AIDS?**

KS is a vascular neoplasm caused by HSV-8, which is fairly prevalent in HIV infection, predominantly in homosexual men. HIV-infected patients are prone to develop KS at any stage of the disease. GI tract involvement occurs in up to 40% of patients. However, most cases of KS of the GI tract are asymptomatic. AIDS-related KS most frequently manifests with skin disease (Figure 56-5). However, cutaneous manifestation may be absent in visceral KS. Symptoms of GI KS are dyspepsia, diarrhea, GI bleeding, perforation, and ileus resulting from tumor obstruction (see Figure 56-5).



**Figure 56-5.** Kaposi sarcoma (KS) usually involves the skin (A). Any part of the gastrointestinal tract may be affected by KS (B). Histologic examination is important to confirm the diagnosis (C).

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

- Blanshard C, Francis N, Gazzard BG. Investigation of chronic diarrhoea in acquired immunodeficiency syndrome: A prospective study in 155 patients. *Gut* 1996;39:824–32.
- Bonacini M, Young T, Laine L. The causes of esophageal symptoms in human immunodeficiency virus infection: A prospective study of 110 patients. *Arch Intern Med* 1991;151:1567–72.
- Bush ZM, Kosmiski LA. Acute pancreatitis in HIV-infected patients: Are etiologies changing since the introduction of protease inhibitor therapy? *Pancreas* 2003;27:e1–5.
- Call SA, Heudebert G, Saag M, et al. The changing etiology of chronic diarrhea in HIV-infected patients with CD4 cell counts less than 200 cells/mm<sup>3</sup>. *Am J Gastroenterol* 2000;95:3142–6.
- Carr A, Marriott D, Field A, et al. Treatment of HIV-1-associated microsporidiosis and cryptosporidiosis with combination antiretroviral therapy. *Lancet* 1998;351:256–61.
- Cello JP. Acquired immunodeficiency syndrome cholangiopathy: Spectrum of disease. *Am J Med* 1989;86:539.
- Dore GJ, Marriott DJ, Hing MC, et al. Disseminated microsporidiosis due to *Septata intestinalis* in nine patients infected with the human immunodeficiency virus: Response to therapy with albendazole. *Clin Infect Dis* 1995;21:70–6.
- Goodgame RW. Understanding intestinal spore-forming protozoa: Cryptosporidia, microsporidia, isospora, and cyclospora. *Ann Intern Med* 1996;124:429–41.
- Iser DM, Sasadeusz JJ. Current treatment of HIV/hepatitis B virus coinfection. *J Gastroenterol Hepatol* 2008;23:699–706.
- Kearney DJ, Steuerwald M, Koch J, et al. A prospective study of endoscopy in HIV-associated diarrhea. *Am J Gastroenterol* 1999;94:556–9.
- Kulkarni S, Patsute S, Sane S, et al. Enteric pathogens in HIV infected and HIV uninfected individuals with diarrhea in Pune. *Trans R Soc Trop Med Hyg* 2013;107:648–52.
- Macías J, Márquez M, Téllez F, et al. Risk of liver decompensations among human immunodeficiency virus/hepatitis C virus-coinfected individuals with advanced fibrosis: Implications for the timing of therapy. *Clin Infect Dis* 2013;57:1401–8.
- Mohle-Boetani JC, Koehler JE, Berger TG, et al. Bacillary angiomatosis and bacillary peliosis in patients infected with human immunodeficiency virus: Clinical characteristics in a case-control study. *Clin Infect Dis* 1996;22:794–800.
- Mönkemüller KE, Call SA, Lazenby AJ, et al. Decline in the prevalence of opportunistic gastrointestinal disorders in the era of HAART. *Am J Gastroenterol* 2000;95:457–62.
- Mönkemüller KE, Wilcox CM. Diagnosis and treatment of colonic disease in AIDS. *Gastrointest Endosc Clin North Am* 1998;8:889.
- Mönkemüller KE, Wilcox CM. Diagnosis and treatment of esophageal ulcers in AIDS. *Semin Gastroenterol* 1999;10:1.
- Mönkemüller KE, Wilcox CM. Therapy of gastrointestinal infections in AIDS. *Aliment Pharmacol Ther* 1997;11:425–43.
- Schwartz DA, Straub RA, Wilcox CM. Prospective endoscopic characterization of cytomegalovirus esophagitis in patients with AIDS. *Gastrointest Endosc* 1994;40:481–4.
- Sullivan AK, Feher MD, Nelson MR, et al. Marked hypertriglyceridaemia associated with ritonavir therapy. *AIDS* 1998;12:1392–4.
- Wei-Fang K, Cello JP, Rogers SJ, et al. Prognostic factors for survival of patients with AIDS cholangiopathy. *Am J Gastroenterol* 2003;98:2176–81.
- Wilcox CM. Etiology and evaluation of diarrhea in AIDS: A global perspective at the millennium. *World J Gastroenterol* 2000;6:177–86.
- Wilcox CM, Clark WS, Thompson SE. Fluconazole compared with endoscopy for human immunodeficiency virus-infected patients with esophageal symptoms. *Gastroenterology* 1996;110:1803–8.
- Wilcox CM, Schwartz DA, Clark WS. Causes, response to therapy, and long-term outcome of esophageal ulcer in patients with human immunodeficiency virus infection. *Ann Intern Med* 1995;122:143–9.

# ISCHEMIC BOWEL DISEASE

*Siobhan Proksell, BS, MD, Amar R. Deshpande, MD, and Arvey I. Rogers, MD, FACP, MACG*

## 1. What is ischemic bowel disease?

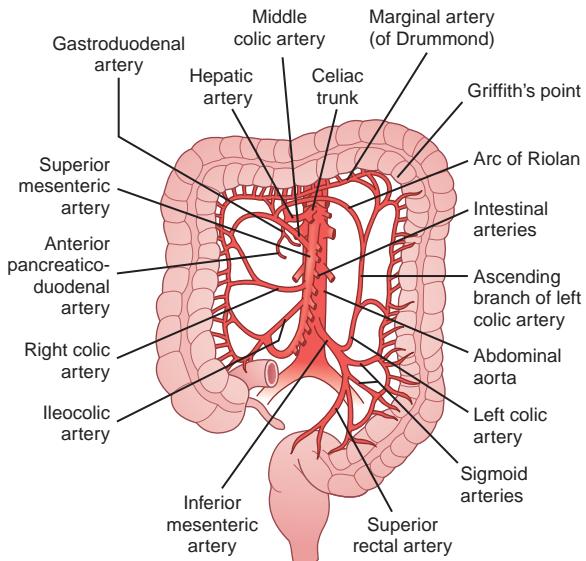
Ischemic bowel disease is caused by tissue hypoxia and ischemic injury of the small or large intestine as a result of a persistent decrease in mesenteric blood flow, decreased oxygen content of red blood cells, or mesenteric venous stasis. Ischemic bowel disease can manifest in numerous ways, such as acute or chronic midabdominal pain (meal-induced), vomiting, sitophobia (fear of eating), weight loss, diarrhea, ileus, gastrointestinal bleeding, intestinal infarction, peritonitis, or fibrotic strictures.

## 2. Describe the gross anatomy of the mesenteric vascular system

Three major arteries and two major veins compose the mesenteric circulation.

Arteries	Veins
<ul style="list-style-type: none"> <li>Celiac artery</li> <li>Superior mesenteric artery (SMA)</li> <li>Inferior mesenteric artery (IMA)</li> </ul>	<ul style="list-style-type: none"> <li>Superior mesenteric vein (SMV)</li> <li>Inferior mesenteric vein (IMV)</li> </ul>

The connection of major arteries and veins via capillaries, arterioles, and venules is known as the *splanchnic circulation* (Figure 57-1).

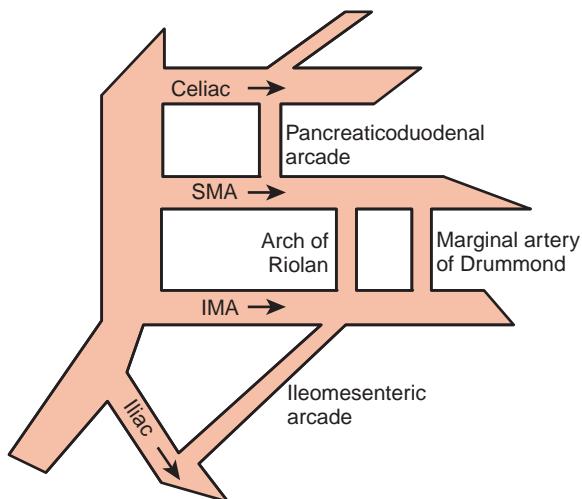


**Figure 57-1.** Mesenteric arterial anatomy. Three unpaired arterial branches of the aorta (celiac, superior mesenteric, and inferior mesenteric arteries) provide oxygenated blood to the small and large intestines. In most instances, veins parallel arteries. The superior mesenteric vein joins the splenic vein to form the portal vein, which enters the liver at its hilum. The inferior mesenteric vein joins the splenic vein near the juncture of the superior mesenteric and splenic veins. (Adapted from Rogers AI, Rosen CM. Mesenteric vascular insufficiency. In: Schiller LR, editor. *Small intestine, current medicine*. Philadelphia: Lange; 1997, with permission.)

The celiac artery provides blood to the stomach, proximal duodenum, part of the pancreas, spleen, liver, gallbladder, and biliary tree. The SMA provides blood to the rest of the duodenum and pancreas, the entire small intestine, and the large intestine up to the splenic flexure. The IMA supplies the remainder of the colon and rectum, with the latter receiving dual blood supply from internal iliac arteries as well. The IMV drains into the splenic vein, and the SMV and splenic vein anastomose to form the portal vein. Mirroring the arterial blood supply, there is dual venous drainage of the rectum into the systemic system through the inferior vena cava via the internal iliac veins and through the IMV to the portal circulation.

**3. An extensive collateral circulatory system exists between the systemic and splanchnic vascular networks. Describe this system.**

The several systemic-splanchnic and intersplanchnic collateral channels that connect the three major mesenteric arteries and their branches become apparent in the event of occlusion of one of the major branches ([Figure 57-2](#)):



**Figure 57-2.** Schematic representation of collateral channels between the three major mesenteric arteries. The development of alternative anastomoses and collateral flow makes it theoretically possible that any single artery could supply all of the abdominal viscera with arterial blood given sufficient time and opportunity, that is, gradual occlusion of one or two of the other major arterial vessels. One major anastomosis exists between the left branch of the middle colic artery (from the superior mesenteric artery [SMA]) and the left colic artery from the inferior mesenteric artery (IMA), forming the meandering mesenteric artery or the arc of Riolan. Its demonstration by angiography indicates occlusion of the SMA or IMA. The marginal artery of Drummond is an arterial connection that provides a continuous channel of collateral flow via the vasa recta to the small and large intestines. The ileomesenteric arcade establishes an important anastomosis between the mesenteric and systemic circulation between the superior hemorrhoidal artery, a branch of the IMA, and the hypogastric artery, a branch of the iliac artery. (Adapted from Rogers AI, Rosen CM. Mesenteric vascular insufficiency. In: Schiller LR, editor. *Small intestine, current medicine*. Philadelphia: Lange; 1997, with permission.)

- *Pancreaticoduodenal arcade* provides collateral channels between the celiac axis and SMA (the superior pancreaticoduodenal arteries of the celiac axis collateralize with the inferior pancreaticoduodenal arteries of the SMA).
- *Marginal artery of Drummond*, composed of branches of the SMA and IMA, is a continuous arterial pathway that runs parallel to the entire colon.
- The middle colic branch of the SMA and the left colic branch of the IMA are connected by the *arc of Riolan*.
- The IMA connects with the systemic circulation via the iliac artery by the *ileomesenteric arcade*.
- A slowly developing occlusion promotes the opening of these collateral channels; thus chronic mesenteric arterial insufficiency (e.g., abdominal angina) is unusual unless there is virtually complete occlusion of two of the three major mesenteric arteries, including the SMA.

**4. What is meant by autoregulation?**

Autoregulation is the concept by which blood flow remains relatively constant via the response of arterioles and venules to changes in perfusion. A steep gradient of pressure exists between the artery and proximal portion of the arteriole. If there is a decrease in arterial perfusion or an increase in oxygen demand (as in the postprandial state), arterioles dilate and additional capillaries are recruited to prevent tissue hypoxia. Additionally, adjustments in the resistance of the venous system are employed to maintain adequate cardiac output. For example, an increase in tone occurs in the setting of hypotension to enhance venous blood return to the heart ([Figure 57-3](#)).

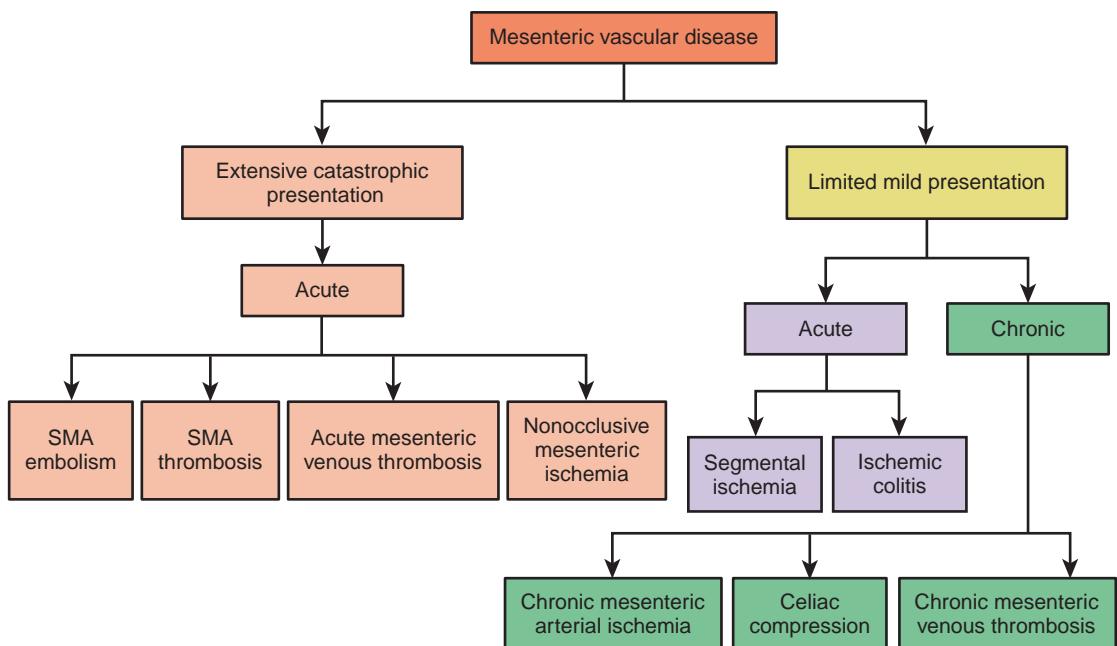
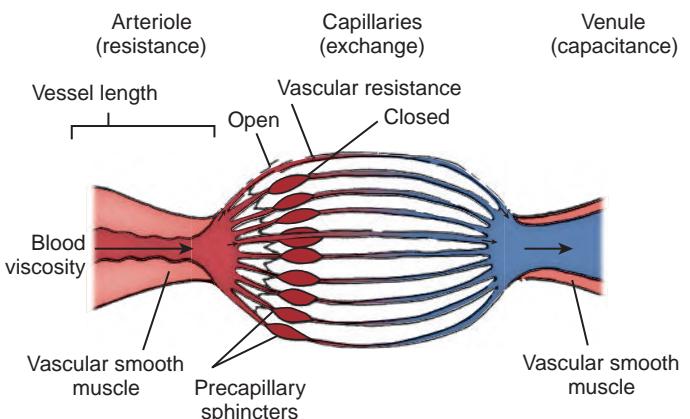
**5. What are the different varieties of ischemic bowel disease?**

Ischemic bowel disease can be sorted into various categories based on the vascular component affected (arterial or venous), the duration of reduction of blood flow through the vessel (acute or chronic), and the cause of the reduction in flow (occlusive or nonocclusive).

It can also be sorted into clinical entities:

- Acute mesenteric ischemia (AMI), usually due to emboli, thrombi, or vasoconstriction
- Chronic mesenteric ischemia, usually a result of atherosclerotic disease
- Colonic ischemia, most often secondary to transient hypoperfusion ([Figure 57-4](#))

**Figure 57-3.** Intramural vascular anatomy. The assured delivery of oxygen-rich arterial blood to the various layers of the small and large intestinal wall during basal, meal-stimulated, and stress states depends on the interplay between various anatomic and physiologic factors, including blood viscosity, red blood cell oxygen saturation, arteriole length and resistance to flow, tone of precapillary sphincters, tone of vascular smooth muscle, and venous capacitance. (Adapted from Rogers AI, Rosen CM. Mesenteric vascular insufficiency. In: Schiller LR, editor. Small intestine, current medicine. Philadelphia: Lange; 1997, with permission.)



**Figure 57-4.** Classification of mesenteric vascular disease based on the extent of resulting ischemia. This particular classification, proposed by Williams, may facilitate more effective evaluation and management by focusing on extent of gut involvement. SMA, Superior mesenteric artery. (From Williams LF. Mesenteric ischemia. *Surg Clin North Am* 1988;68:331–353.)

## 6. What clinical circumstances predispose to ischemic bowel disease?

### Arterial

#### Occlusive Mesenteric Ischemia

- **Embolus:** cardiac arrhythmias, valvular heart disease, myocardial infarction, mural thrombus, atrial myxoma, angiography, trauma
- **Thrombosis:** atherosclerosis, hypercoagulable states (e.g., pregnancy, hyperhomocysteinemia, antiphospholipid syndrome, birth control pills, neoplasms, polycythemia vera, essential thrombocythosis, and paroxysmal nocturnal hemoglobinuria), vascular aneurysms or dissections, vasculitides

#### Nonocclusive Mesenteric Ischemia

- Cardiac arrhythmias, hypoperfusion (cardiogenic shock, hypovolemia, sepsis), and vasoconstricting drugs (digoxin, cocaine)

#### Venous

- Hypercoagulable states (arterial causes, plus deficiencies of factor V Leiden, protein C and S, or antithrombin III), congestive heart failure, shock, portal hypertension, hepatic vein thrombosis (Budd-Chiari syndrome), malignancy, trauma, sclerotherapy, peritonitis, diverticulitis, pancreatitis, inflammatory bowel disease, intestinal obstruction, postoperative states, trauma

**7. Describe the pathophysiologic findings of occlusive AMI**

Intestinal ischemia results from tissue hypoxia, which can be secondary to a decrease in blood volume, red blood cell mass, flow rate, or oxygen content. As the radius of an artery decreases, the resistance to flow increases by a power of 4. Autoregulation (see Question 4) results in vasodilation to maintain flow up to a finite point, beyond which flow decreases. Examples of such instances are acute or chronic arterial thrombi, an embolus, or transient vasoconstriction.

**8. What is abdominal angina? What is its clinical significance?**

*Abdominal angina* refers to chronic, recurrent abdominal pain caused by a decrease in arterial blood flow through the mesenteric arteries, usually resulting from stenosis from atherosclerotic lesions. The postprandial state can be regarded as an exercise stimulus; food entering the stomach causes an increase in oxygen demand thereby decreasing blood flow to the intestines (steal phenomenon). Pain begins to occur within 30 to 90 minutes and can last for up to four hours. Initially, abdominal angina is usually minimal; however, it progressively increases in severity over weeks to months. Long-term hypoxia of the small intestinal mucosa can cause villous atrophy leading to diarrhea, protein-losing enteropathy, steatorrhea, weight loss, and malnutrition.

**9. Describe the pathophysiologic findings of nonocclusive mesenteric ischemia (NOMI).**

NOMI occurs, as the name implies, without the presence of an embolus or thrombus. The risk of intestinal hypoperfusion can increase with shock, severe hypovolemia, decreased cardiac output, and during major thoracic or abdominal surgery as the mesenteric vasculature vasoconstricts. It can also be seen in patients taking digoxin or cocaine as these aggravate mesenteric vasoconstriction.

**10. What should I know about mesenteric venous occlusion as a cause of ischemic bowel disease?**

Mesenteric venous occlusion is a rare cause of ischemic bowel disease, which requires an awareness of associated risk factors (often a hypercoagulable state) and a high index of suspicion for accurate diagnosis.

Patients with mesenteric venous occlusion generally present with severe midabdominal pain out of proportion to the minimal abdominal physical examination findings. Pain may be acute or subacute, occurring over weeks to months. *The gold standard for diagnosis is an abdominal CT with contrast, which reveals evidence of venous occlusion in more than 90% of patients.* These findings include thickening and contrast enhancement of the bowel wall (the result of delayed venous flow), enlarged SMV, thrombosis in the lumen of the SMV, and prominent collateral vessels.

If there is no sign of intestinal infarction, patients can be treated conservatively with anticoagulation and possibly thrombolytics. If infarction is suspected, immediate surgical intervention should be undertaken to avoid irreversible ischemia and subsequent bowel resection.

**11. What is focal segmental (short segment) ischemia?**

*Focal segmental ischemia* refers to ischemia that is confined to a short segment of bowel because it involves only a few small arteries or veins. This occurs by the same pathophysiologic processes that cause extensive bowel ischemia.

**12. What are the common symptoms of occlusive mesenteric ischemia?**

The common presenting symptoms of occlusive mesenteric ischemia vary by the cause of ischemia.

- Patients with **mesenteric ischemia** caused by an *acute embolus or thrombotic occlusion of the SMA* usually present with the abrupt onset of severe, colicky, midabdominal pain. These patients may also become incontinent of bowel function because of tonic contractions of smooth muscle provoked by ischemia. These contractions cause severe pain but produce few abdominal physical examination findings. It is important to note that late findings of abdominal distension and guaiac-positive stool may be the only presenting signs in patients who are unable to communicate (e.g., those who are sedated, demented, or with altered mental status).
- Patients with **mesenteric ischemia** caused by a *thrombotic occlusion* tend to present with a history consistent with mesenteric angina—recurrent postprandial mid or diffuse abdominal pain with or without radiation to the back. Associated weight loss is often present as a result of sitophobia. Additionally, patients may have diarrhea, steatorrhea, or protein-losing enteropathy, which can further complicate the chronically ischemic-induced atrophy of the small intestine.
- Patients with **venous occlusive disease** generally describe a more nonspecific, insidious onset of abdominal pain, diarrhea, and emesis. This occurs when massive influx of fluid into the bowel wall and lumen causes systemic hypotension and an eventual decrease in arterial flow. It should be suspected in the appropriate clinical settings such as abdominal sepsis, hypercoagulability, and the use of oral contraceptive pills.

**13. What are the physical findings in a patient with mesenteric ischemia?**

Again, the physical findings associated with mesenteric ischemia vary based on etiologic factors and duration of ischemia.

- The classic finding of a patient with an **acute occlusion of the SMA** is abdominal pain out of proportion to physical examination findings. Early in the course of the disease process the abdominal examination usually consists only of mild abdominal distension and normal or hypoactive bowel sounds. With progression of ischemic injury, bowel sounds decrease, ileus develops, and abdominal distension worsens. Stool becomes guaiac positive; sometimes grossly bloody stool may develop. Volume sequestration is manifested by hypotension and tachycardia, whereas fever and peritoneal signs are indications of transmural injury and likely infarction.

- Patients with **venous occlusive disease** present with physical examination findings based on the severity and etiologic characteristics of ischemia: congestive heart failure, abdominal mass, stigmata of chronic liver disease and portal hypertension, or hypercoagulability.
- **NOMI** (see Question 9) should be suspected in the correct clinical setting. Patients present with early complaints that are less dramatic than those of patients with acute arterial occlusion; however, a small proportion of patients do not have abdominal pain. Physical examination findings vary with the duration of ischemia. Patients usually describe chronic, recurrent abdominal pain secondary to compromised flow through the SMA. There are no specific physical examination findings. Of note, most patients have evidence of peripheral vascular disease and may also have weight loss.

#### 14. Do laboratory findings help at all?

In the early stages of mesenteric ischemia there are no specific abnormal laboratory values, only those that are associated with the underlying condition from which the ischemia developed. Nonspecific laboratory abnormalities that develop over the course of the disease process are a result of the consequence of ischemia (i.e., tissue hypoxia, inflammation, necrosis, and volume sequestration) and include hemoconcentration, leukocytosis, and lactic acidosis.

#### 15. What are the differential diagnostic considerations in a patient with suspected AMI, and how do plain abdominal radiographs help elucidate the disorder?

Flat and upright abdominal plain films should be obtained first in a patient complaining of abdominal pain unless a diagnosis of ischemia is clear. **Table 57-1** depicts differential diagnoses and associated findings on x-ray.

**Table 57-1.** Radiographic Clues to Diagnosis

DISORDER	FINDING ON PLAIN ABDOMINAL RADIOGRAPHS
Small bowel obstruction	Dilated loops of bowel with or without air-fluid levels Stair-step overlapping of loops of small bowel Termination of luminal small bowel air at transition point of obstruction
Pancreatitis	Sentinel loop of duodenum or colon cut-off sign
Volvulus	Characteristic jejunal, sigmoid, or cecal dilation (sigmoid volvulus—coffee bean sign)
Intraabdominal sepsis (appendicitis, diverticulitis)	Air in the hepatic or portal venous system (portal venous gas)
Perforation	Free air under the diaphragm Air dissecting between bowel loops or seen retroperitoneally
Bowel ischemia	Bowel wall thickening, loop separation, thumbprinting
Pneumatosis intestinalis and portal venous gas	Late signs and ominous for impending or frank infarction
Emphysematous cholecystitis	Air within the gallbladder wall, air-fluid level in the gallbladder (also caused by gas-forming organisms)

Numerous imaging modalities can be employed to further elucidate a diagnosis of mesenteric ischemia, including abdominal computed tomography (CT) with contrast, Doppler of mesenteric vessels, and mesenteric angiography. Laparoscopy and enteroscopy may also be indicated in the appropriate clinical setting.

In patients with bowel infarction, plain films and abdominal CT show nonspecific abnormalities in a minority of cases. Angiography is more effective than CT in identifying mesenteric arterial occlusion or NOMI. If venous occlusive disease is suspected, a dynamic abdominal CT with contrast can be a helpful diagnostic tool.

Of note, barium for small bowel study should be avoided if a contrast CT or angiogram is being considered as barium interferes with the completion and diagnostic interpretation of the aforementioned studies.

#### 16. What is the role of magnetic resonance angiography (MRA) in patients with suspected abdominal angina?

In patients with suspected abdominal angina, MRA may be helpful in those with a severe iodine allergy. Good correlation with CT angiography has been demonstrated, and three-dimensional reconstruction allows for visualization of splanchnic orifices.

Additionally, in patients with chronic kidney disease or impaired kidney function, gadolinium may not cause the contrast induced nephropathy seen with iodine. It can, however, uncommonly lead to nephrogenic systemic fibrosis, which is an irreversible condition.

**17. Describe the role of Doppler ultrasound studies in diagnosis**

Doppler ultrasound is a noninvasive test that evaluates the patency of and blood flow through the major mesenteric vessels. It should be performed while the patient is fasting and subsequently meal-stimulated. It is most helpful in diagnosing multivessel stenosis in suspected mesenteric angina by demonstrating narrowing or occlusion at a vessel origin and excessively turbulent flow.

Of note, duplex ultrasound has limited capabilities in obese patients as ultrasound waves must pass through body tissue prior to producing a diagnostic image.

**18. What is the diagnostic role of endoscopy (sigmoidoscopy, colonoscopy, enteroscopy) and laparoscopy?**

In spite of the fact that a small number of published case reports describe diagnostic findings of mesenteric ischemia via enteroscopy, this approach can be extremely dangerous because of the high risk of bowel perforation. Lower endoscopy, however, has been shown to be relatively safe and can aid in determining the diagnosis of a patient with suspected ischemic colitis (see Questions 24-28).

Laparoscopy, although invasive, has also been shown to be a relatively safe technique in assisting with diagnosis and assessing the degree of injury to the intestines. It can easily detect full-thickness mesenteric injury; however, it is limited in the fact that it will miss the earlier stages of potentially reversible ischemia because injury starts mucosally and then moves transmurally to the serosa. Additionally, when intraperitoneal pressure exceeds 20 mm Hg, a level often attained after insufflation during laparoscopy, splanchnic blood flow decreases.

**19. Why should you undertake invasive mesenteric angiographic studies?**

When the diagnosis and treatment of ischemic bowel disease is delayed and peritoneal signs and acidosis ensue, the mortality rate increases significantly.

Angiography is the gold standard for diagnosis of mesenteric arterial occlusion and can help to differentiate between embolic and thrombotic etiologic factors. The cutoff of a major artery in the absence of collateral vessel enlargement is indicative of an embolic cause, whereas vessel narrowing with the development of collaterals signifies thrombosis. Additionally, the venous phase of angiography may demonstrate venous occlusive disease. In NOMI, angiography may demonstrate vessel narrowing or spasm and arterial beading.

Angiography can also be used as a therapeutic modality by selectively infusing vasodilating drugs or thrombolytics, and aiding in the completion of angioplasty, balloon embolectomy, or stent placement. Because of the risks associated with the administration of thrombolytic agents, their use should probably be limited to poor surgical candidates without peritoneal signs, to those in whom the ischemic event is considered to be reversible or of short duration, and to tertiary care centers with technical expertise.

As with all procedures, angiography has associated risks. Atherosclerosis commonly involves the femoral artery, which is usually the site of entry for the angiographic catheter. This makes it harder to access the mesenteric system and can also cause emboli to distant arteries. Furthermore, iodine contrast increases the risk of developing renal insufficiency.

Angiography is the only technique other than exploratory surgery that can establish the diagnosis of and treat mesenteric occlusive disease and NOMI early in the course of the disease.

**20. Is there any medical treatment for mesenteric ischemia?**

Various measures can be employed to treat mesenteric ischemia:

- Management of the underlying disease process, including antiplatelet agents for vascular disease
- Anticoagulation for arterial thrombotic and venous occlusive disease
- Adequate pain control (avoiding opiates as they decrease peristalsis and aggravate ischemia)
- Theoretical treatments: small meals, smoking cessation, vasoconstrictors, and suppression of gastric acid secretion to decrease mucosal oxygen demand during meals

**21. What is the role of angioplasty and stenting in the management of ischemic bowel disease?**

Percutaneous transluminal angioplasty with or without stent placement can be considered as an alternative to surgery in patients with more distal lesions. Lesions located at the aortic orifices of mesenteric arteries may not be as amenable to dilation and angioplasty because of their fixed diameter.

**22. When should a patient with ischemic bowel disease be sent to the operating room?**

Initial clinical suspicion of acute ischemic bowel disease when other diagnoses have been excluded should prompt angiography. If findings are amenable to nonsurgical intervention (see Question 19) and there is no sign of bowel necrosis, patients can be managed medically.

Patients should be sent to the operating room for:

- Assessment of the degree and extent of injury
- Identification of the site of and relief of arterial occlusion
- Resection of irreversibly damaged bowel (Short gut syndrome is a possible consequence of resection)
- Revascularization

- Indications for revascularization include typical disabling signs of angina or angiographic evidence of occlusion of at least two major mesenteric arteries, one being the SMA. There is still controversy regarding whether or not only the SMA should be revascularized.

### **23. What is meant by a second-look operation?**

During initial surgery (whether or not revascularization has been attempted), some bowel may be left intentionally intact as the status of its viability may not be clear. Patients may undergo a second operation 24 to 48 hours later to assess viability.

### **24. Can ischemia be isolated to the colon?**

Ischemic colitis is the most common form of non-occlusive intestinal ischemia occurring in older adult patients with impaired cardiac output via a nonocclusive mechanism. In younger patients, however, the cause can be occlusive (sickle cell disease, hypercoagulable states) or nonocclusive (cocaine use, vasculitis, long-distance running).

### **25. How does ischemic colitis present clinically?**

Ischemic colitis most commonly presents with the sudden onset of cramping, mild left lower quadrant abdominal pain, and the urge to defecate. Additionally, patients may present with bright red blood per rectum or hematochezia. Palpation of the abdomen over the affected segment of bowel elicits tenderness. Differential diagnoses include infectious colitis, diverticulitis, and inflammatory bowel disease.

### **26. How do you confirm a suspected diagnosis of ischemic colitis?**

Abdominal plain films may demonstrate “thumbprinting” along the affected segment of colonic wall, often the splenic flexure, secondary to subepithelial edema and hemorrhage.

If ischemic colitis is suspected and there are no signs of peritoneal irritation, the patient should undergo colonoscopy for diagnostic confirmation. Any region of the colon may be involved, but the key feature is segmental distribution, classically at watershed areas between the SMA and IMA. The rectosigmoid (20%), descending colon (20%), splenic flexure (11%), and all three in combination (14%) are affected most commonly. A flexible sigmoidoscopy may be nondiagnostic in those with more proximal disease. The rectum is almost always spared because of its dual blood supply from the IMA and internal iliac artery branches.

Barium enema is less sensitive than colonoscopy but may reveal thumbprinting. Angiography is not indicated as predisposing nonocclusive vascular factors are often not demonstrated after ischemic injury has occurred ([E-Figure 57-5](#)).

### **27. What are the sequelae of ischemic colitis? Can anything be done to modify the course of the disease?**

Optimizing cardiac function is imperative; impaired cardiac output and cardiac arrhythmias should be corrected. Factors predisposing to vasoconstriction, digoxin therapy, vasopressor agents, and hypovolemia should be avoided when possible. Vasodilating agents are ineffective because low colonic blood flow has often already returned to normal by the time the ischemia has occurred. It is recommended that the patient be treated with intravenous fluids and bowel rest. A distended colon should be decompressed colonoscopically by placement of a rectal tube or by rolling the patient from a supine position to right and left lateral decubitus positions. If the precipitating event is occlusive in nature, the underlying cause should be corrected, possibly including prolonged anticoagulation. Thus far there is no objective evidence demonstrating the effectiveness of antibiotics.

Ischemic colitis is reversible in up to 70% of patients whose symptoms abate within 24 to 48 hours; in these patients, healing occurs without stricture in 1 to 2 weeks. Those with severe injury require 1 to 6 months to heal completely. Irreversible damage occurs in less than 50% of cases and can lead to toxic megacolon, gangrene and perforation, fulminant colitis, and ischemic strictures. Unfortunately, the course cannot be predicted at the time of initial presentation.

Isolated right-sided ischemic colitis has a higher mortality and need for surgery, as its pathophysiologic findings are closely related to AMI. The diagnosis and management of isolated right-sided ischemic colitis therefore mirrors that of AMI.

### **28. When is surgery indicated in patients with ischemic colitis?**

Surgery is indicated in patients who present with or develop peritoneal signs, massive bleeding, gangrene or perforation, evidence of toxic megacolon, or fulminant colitis. It should be considered even with apparent healing in patients who have recurrent bouts of sepsis and in patients who fail to respond to conservative measures over 2 to 3 weeks. Symptomatic colon strictures may also warrant surgical or endoscopic correction (e.g., balloon dilation or stent placement).

Please access ExpertConsult to view the E-Figure for this chapter.

### **BIBLIOGRAPHY**

1. Brandt LJ, Boley SJ. AGA technical review on intestinal ischemia. *Gastroenterology* 2000;118:954–68.
2. Brandt LJ, Boley SJ. Slesinger & Fordtran's gastrointestinal and liver disease. 7th ed. Philadelphia: Saunders; 2002.
3. Burns BJ, Brandt LJ. Intestinal ischemia. *Gastroenterol Clin North Am* 2003;32:1127–43.

4. Chang RW, Chang JB, Longo WE. Update in management of mesenteric ischemia. *World J Gastroenterol* 2006;2:3243–7.
5. Chang JB, Stein TA. Mesenteric ischemia: Acute and chronic. *Ann Vasc Surg* 2003;17:323–8.
6. Díaz Nieto R, Varcada M, Ogunbivi OA, Winslet MC. Systematic review on the treatment of ischaemic colitis. *Colorectal Dis* 2011;13(7):744–7.
7. Feuerstadt P. Colon ischemia: Recent insights and advances. *Curr Gastroenterol Rep* 2010;12:383–90.
8. Herbert GS, Steele SR. Acute and chronic mesenteric ischemia. *Surg Clin North Am* 2007;87:1115–34.
9. Jakribettuu VS, Levine JS. Ischemia and ischaemic colitis. In: Weinstein WM, Hawkey CJ, Bosch J, editors. *Clinical gastroenterology and hepatology*. Mosby: Spain; 2005.
10. Kim AY, Ha HK. Evaluation of suspected mesenteric ischemia: Efficacy of radiologic studies. *Radiol Clin North Am* 2003;41:327–42.
11. Kougias P, El Sayed HF, Zhou W, et al. Management of chronic mesenteric ischemia: The role of endovascular therapy. *J Endovasc Ther* 2007;14:395–405.
12. Kozuch PL. Review article: Diagnosis and management of mesenteric ischaemia with an emphasis on pharmacotherapy. *Aliment Pharmacol Ther* 2005;21:201–15.
13. Lefkovitz Z, Cappell MS, Lookstein R, et al. Radiologic diagnosis and treatment of gastrointestinal hemorrhage and ischemia. *Med Clin North Am* 2002;86:1357–99.
14. Mallick IH, Yang W, Winslet MC, et al. Ischemia-reperfusion injury of the intestine and protective strategies against injury. *Dig Dis Sci* 2004;49:1359–77.
15. Oldenburg WA, Lau LL, Rodenberg TJ, et al. Acute mesenteric ischemia: A clinical review. *Arch Intern Med* 2004;164:1054–62.
16. Payor AD, Tucci V. Acute ischemic colitis secondary to air embolism after diving. *Int J Crit Illn Inj Sci* 2011;1(1):73–8.
17. Sotiriadis J, Brandt LJ, Behin DS, et al. Ischemic colitis has a worse prognosis when isolated to the right side of the colon. *Am J Gastroenterol* 2007;102:2247–52.
18. Sreenarasimhaiah J. Chronic mesenteric ischemia. *Best Pract Res Clin Gastroenterol* 2005;19:283–95.
19. Sreenarasimhaiah J. Diagnosis and management of intestinal ischemic disorders. *BMJ* 2003;326:1372–6.
20. Van Bockel JH, Geelkerken RH, Kolkman JJ. Splanchnic vascular disorders. In: Weinstein WM, Hawkey CJ, Bosch J, editors. *Clinical gastroenterology and hepatology*. Mosby: Spain. pp. 479–484.
21. Williams LF. Mesenteric ischemia. *Surg Clin North Am* 1988;68:331–53.

**E-Figure 57-5.** Fluoroscopic view of thumbprinting in ischemic colitis. Note the appearance of thumbprints in the transverse colon (arrows) seen on barium enema. (From Brandt LJ. Intestinal ischemia. In: Feldman M, Friedman LS, Brandt LJ, editors. *Sleisenger & Fordtran's gastrointestinal and liver disease*. Philadelphia: Elsevier; 2006, pp. 2575–2576.)



# NUTRITION, MALNUTRITION, AND PROBIOTICS

Bonnie Jortberg, PhD, RD, CDE, and Peter R. McNally, DO, MSRF, MACG

## 1. What is meant by *nutritional status*?

Nutritional status reflects how well nutrient intake contributes to body composition and function in the face of the existing metabolic needs. The four major body compartments are water, protein, mineral, and fat. The first three compose the lean body mass (LBM); functional capacity resides in a portion of the LBM called the *body-cell mass*. Registered dietitians or registered dietitian nutritionists concentrate their efforts on preservation or restoration of this vital component.

## 2. Define *malnutrition*.

*Malnutrition* refers to states of overnutrition (obesity) or undernutrition relative to body requirements, resulting in dysfunction.

## 3. How do different types of malnutrition affect function and outcome?

- *Marasmus* is protein-calorie undernutrition associated with significant physical wasting of energy stores (adipose tissue and somatic muscle protein) but preservation of visceral and serum proteins. Patients are not edematous and may have mild immune dysfunction.
- *Hypoalbuminemic malnutrition* occurs with stressed metabolism and is common in hospitalized patients. They may have adequate energy stores and body weight, but have expanded extracellular space, depleted intracellular mass, edema, altered serum protein levels, and immune dysfunction.
- A similar state of relative protein deficiency occurs in classic *kwashiorkor*, in which caloric provision is adequate but quantity and quality of protein are not.

## 4. How is a simple nutritional assessment performed?

Simple bedside assessment may be as valuable for predicting nutrition-associated outcomes as sophisticated composition and function tests. Two popular methods, the Subjective Global Assessment (SGA) and the Mini Nutritional Assessment are simple-to-use validated nutritional assessment tools. Each incorporates basic questions about weight history, intake, gastrointestinal (GI) symptoms, disease state, functional level, and a physical examination to classify patients as well-nourished, mildly to moderately malnourished, or severely malnourished (Figure 58-1).

A weight history, estimate of recent intake, brief physical examination, consideration of disease stress and medications, and assessments of functional status and wound healing allow a good estimate of nutritional status. They predict the risk for malnutrition-associated complications as well as or better than laboratory data. Poor intake for longer than 1 to 2 weeks, a weight loss of more than 10%, or a weight less than 80% of desirable warrants closer nutritional assessment and follow-up.

## 5. Serum proteins are a marker of overall nutritional health. Which plasma proteins will have the most sensitive turnover rate?

Ferritin: 30 hours  
Retinol binding protein: 2 days  
Prealbumin: 2 to 3 days  
Transferrin: 8 days  
Albumin: 18 days

## 6. What simple blood tests offer an *instant* nutritional assessment?

Serum albumin → abnormal if <3.5 g%

Total lymphocyte count → abnormal if <1500/mm<sup>3</sup>

NESTLÉ NUTRITION SERVICES



## Mini Nutritional Assessment MNA®

Last name:	First name:	Sex:	Date:
Age:	Weight, kg:	Height, cm:	I.D. Number:

*Complete the screen by filling in the boxes with the appropriate numbers.  
Add the numbers for the screen. If score is 11 or less, continue with the assessment to gain a Malnutrition Indicator Score.*

<b>Screening</b>			
<p>A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?</p> <p>0 = severe loss of appetite 1 = moderate loss of appetite 2 = no loss of appetite</p> <input type="checkbox"/>		<p>J How many full meals does the patient eat daily?</p> <p>0 = 1 meal 1 = 2 meals 2 = 3 meals</p> <input type="checkbox"/>	
<p>B Weight loss during the last 3 months</p> <p>0 = weight loss greater than 3 kg (6.6 lbs) 1 = does not know 2 = weight loss between 1 and 3 kg (2.2 and 6.6 lbs) 3 = no weight loss</p> <input type="checkbox"/>		<p>K Selected consumption markers for protein intake</p> <ul style="list-style-type: none"> <li>• At least one serving of dairy products (milk, cheese, yogurt) per day? yes <input type="checkbox"/> no <input type="checkbox"/></li> <li>• Two or more servings of legumes or eggs per week? yes <input type="checkbox"/> no <input type="checkbox"/></li> <li>• Meat, fish or poultry every day yes <input type="checkbox"/> no <input type="checkbox"/></li> </ul> <p>0.0 = if 0 or 1 yes 0.5 = if 2 yes 1.0 = if 2 yes</p> <input type="checkbox"/> . <input type="checkbox"/>	
<p>C Mobility</p> <p>0 = bed or chair bound 1 = able to get out of bed/chair but does not go out 2 = goes out</p> <input type="checkbox"/>		<p>L Consumes two or more servings of fruits or vegetables per day?</p> <p>0 = no      1 = yes</p> <input type="checkbox"/>	
<p>D Has suffered psychological stress or acute disease in the past 3 months</p> <p>0 = yes      2 = no</p> <input type="checkbox"/>		<p>M How much fluid (water, juice, coffee, tea, milk...) is consumed per day?</p> <p>0.0 = less than 3 cups 0.5 = 3 to 5 cups 1.0 = more than 5 cups</p> <input type="checkbox"/> . <input type="checkbox"/>	
<p>E Neuropsychological problems</p> <p>0 = severe dementia or depression 1 = mild dementia 2 = no psychological problems</p> <input type="checkbox"/>		<p>N Mode of feeding</p> <p>0 = unable to eat without assistance 1 = self-fed with some difficulty 2 = self-fed with any problem</p> <input type="checkbox"/>	
<p>F Body Mass Index (BMI) (weight in kg) / (height in m)<sup>2</sup></p> <p>0 = BMI less than 19 1 = BMI 19 to less than 21 2 = BMI 21 to less than 23 3 = BMI 23 or greater</p> <input type="checkbox"/>		<p>O Self view of nutritional status</p> <p>0 = views self as being malnourished 1 = is uncertain of nutritional state 2 = views self as having no nutritional problem</p> <input type="checkbox"/>	
<p><b>Screening score</b> (subtotal max. 14 points)</p> <p>12 points or greater Normal – not at risk – no need to complete assessment 11 points or below Possible malnutrition – continue assessment</p>		<p>P In comparison with other people of the same age, how does the patient consider his/her health status?</p> <p>0.0 = not as good 0.5 = does not know 1.0 = as good 2.0 = better</p> <input type="checkbox"/> . <input type="checkbox"/>	
<p>G Lives independently (not in a nursing home or hospital)</p> <p>0 = no      1 = yes</p> <input type="checkbox"/>		<p>Q Mid-arm circumference (MAC) in cm</p> <p>0.0 = MAC less than 21 0.5 = MAC 21 to 22 1.0 = MAC 22 or greater</p> <input type="checkbox"/> . <input type="checkbox"/>	
<p>H Takes more than 3 prescription drugs per day</p> <p>0 = yes      1 = no</p> <input type="checkbox"/>		<p>R Calf circumference (CC) in cm</p> <p>0 = CC less than 31      1 = CC 31 or greater</p> <input type="checkbox"/>	
<p>I Pressure sores or skin ulcers</p> <p>0 = yes      1 = no</p> <input type="checkbox"/>		<p><b>Assessment</b> (max. 16 points)</p> <p><b>Screening score</b></p> <p><b>Total Assessment</b> (max. 30 points)</p> <p><b>Malnutrition Indicator Score</b></p> <p>17 to 23.5 points      at risk of malnutrition</p> <p>Less than 17 points      malnourished</p>	

Ref.: Guigoz Y, Vellas B and Barry PJ. 1994. Mini Nutritional Assessment: A practical assessment tool for grading the nutritional state of elderly patients. *Facts and Research in Gerontology*. Supplement #2:15-59.  
 Rubenstein LZ, Harker L, Guigoz Y and Vellas B. Comprehensive Geriatric Assessment (CGA) and the MNA: A New View of CGA. Nutritional Assessment, and Development of Shortened Version of the MNA. In: "Mini Nutritional Assessment (MNA): Research and Practice in the Elderly". Vellas B, Barry PJ and Guigoz Y, editors. Nestlé Nutrition Workshop Series. Clinical & Performance Programme, vol. 1. Karger, Basel, in press.  
 © Nestlé, 1994, Revision 1998. NG7200 12/99 10M

**Figure 58-1.** Mini nutritional assessment.

### 7. List desirable weights for men and women.

Body mass index (BMI) is calculated from a person's weight and height, and is a reliable indicator of body fatness. It is used to determine categories of disease risk based on weight status.

**Calculation of BMI** BMI is calculated the same way for both adults and children. The calculation is based on the following formulas ([Table 58-1](#)):

The standard weight status categories associated with BMI ranges for adults are shown in [Table 58-2](#).

BMI can be easily determined by using a BMI calculator (<http://www.cdc.gov/healthyweight/assessing/bmi>) or by referring to a BMI chart ([Figure 58-2](#)).

Basal energy expenditure in calories can be derived from the Harris Benedict equation:

$$\text{BEE for } \text{♂} : 66 + [13.7 \times \text{weight (kg)}] + [5.0 \times \text{height (cm)}] - [(6.8 \times \text{age})] = \text{kcal/day}$$

$$\text{BEE for } \text{♀} : 655 + [9.6 \times \text{weight (kg)}] + [1.8 \times \text{height (cm)}] - [(4.7 \times \text{age})] = \text{kcal/day}$$

$$\text{BEE} \times \text{Stress factor} = \text{daily caloric need}$$

**Table 58-1.** Calculation of BMI

MEASUREMENT UNITS	FORMULA AND CALCULATION
Kilograms and meters (or centimeters)	Formula: weight (kg) ÷ [height (m)] <sup>2</sup> With the metric system, the formula for BMI is weight in kilograms divided by height in meters squared. Because height is commonly measured in centimeters, divide height in centimeters by 100 to obtain height in meters. Example: Weight = 68 kg, Height = 165 cm (1.65 m) Calculation: $68 \div (1.65)^2 = 24.98$
Pounds and inches	Formula: weight (lb) ÷ [height (in)] <sup>2</sup> × 703 Calculate BMI by dividing weight in pounds (lb) by height in inches (in) squared and multiplying by a conversion factor of 703. Example: Weight = 150 lb, Height = 5'5" (65") Calculation: $[150 \div (65)^2] \times 703 = 24.96$

BMI, Body mass index.

**Table 58-2.** BMI Ranges for Adults

BMI	WEIGHT STATUS
Below 18.5	Underweight
18.5-24.9	Normal
25.0-29.9	Overweight
30.0 and above	Obese

BMI, Body mass index.

Centers for Disease Control and Prevention. How is BMI calculated and interpreted? Accessed September 22, 2014, from [http://www.cdc.gov/healthyweight/assessing/bmi/adult\\_bmi/index.html#Interpreted](http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html#Interpreted).

**Figure 58-2.** Body mass index chart.

Stress: Factor

Mild stress: ( $\times 1$  to 1.3)

Moderate stress: ( $\times 1.3$  to 1.4)

Severe stress: ( $\times 1.5$ )

See Table 58-3.

**Table 58-3.** Quick Formulas for Calculation of Protein and Caloric Requirements

ILLNESS SEVERITY	PROTEIN, G/KG/DAY	CALORIES, KCAL/KG/DAY
Minimal	0.8	20 to 25
Moderate	1 to 1.5	25 to 30
Severe	1.5 to 2.5	30 to 35

**8. Describe the types of commonly prescribed oral diets.**

The clear liquid diet supplies fluid and calories in a form that requires minimal digestion, stimulation, and elimination by the GI tract. It provides approximately 600 calories and 150 g carbohydrate but inadequate protein, vitamins, and minerals. Clear liquids are hyperosmolar; diluting the beverages and eating slower may minimize GI symptoms. If clear liquids are needed for longer than 3 days, a dietitian can assist with supplementation.

The full liquid diet is used often in progressing from clear liquids to solid foods. It also may be used in patients with chewing problems, gastric stasis, or partial ileus. Typically, the diet provides more than 2000 calories and 70 g protein. It may be adequate in all nutrients (except fiber), especially if a high-protein supplement is added. Patients with lactose intolerance need special substitutions. Progression to solid foods should be accomplished with modifications or supplementation, as needed.

**9. What is a hidden source of calories in the intensive care unit?**

Watch out for significant amounts of lipid calories from propofol, a sedative in 10% lipid emulsion (1.1 kcal/mL).

**10. Summarize the typical findings in deficiency or excess of various micronutrients.**

See Table 58-4.

**11. What are the nutritional concerns in patients with short bowel syndrome?**

Loss of bowel surface puts the patient at great risk for dehydration and malnutrition. The small bowel averages 600 cm in length and absorbs approximately 10 L/day of ingested and secreted fluids. A patient may tolerate substantial loss of small bowel, although preservation of less than 2 feet with an intact colon and ileocecal valve or less than 5 feet in the absence of the colon and ileocecal valve may make survival impossible when just the enteral route of nutrition is used. In addition, the loss of the distal ileum precludes absorption of bile acids and vitamin B<sub>12</sub>. Remaining bowel, especially ileum, may adapt its absorptive ability over several years, but underlying disease may hamper this process.

**12. Describe the management of nutritional problems in patients with short bowel syndrome.**

Therapy in the acute postsurgical phase is aimed at intravenous fluid and electrolyte restoration. Parenteral nutrition may be required while the remaining gut function is assessed and adaptation takes place. Attempts at oral feeding should include frequent, small meals with initial limitations in fluid and fat consumption. Osmolar sugars (e.g., sorbitol), lactose, and high-oxalate foods are best avoided. In patients with small bowel–colon continuity, increased use of complex carbohydrates may allow the salvage of a few hundred calories from colonic production and absorption of short-chain fatty acids (SCFAs). Antimotility drugs and gastric acid suppression should be used if stool output remains high. Oral rehydration with glucose- and sodium-containing fluids (e.g., sports drinks) may help prevent dehydration. Pancreatic enzymes, bile acid–binding resins (if bile acids are irritating the colon), and octreotide injections may play a role in selected cases. If oral diets fail, the use of elemental feedings may enhance absorption and nutritional state. Studies of gut rehabilitation with growth hormone and glutamine, as well as intestinal or combined intestinal-liver transplantation, are available at selected centers.

**13. Describe the approach to nutritional support in patients with acute pancreatitis.**

Pancreatitis can resemble other cases of stressed metabolism. If severe pancreatitis precludes the resumption of food intake beyond 4 to 5 days, consideration should be given to nutrition support. The route of feeding remains controversial; neither bowel and pancreatic rest nor nutritional support has been shown conclusively to alter the clinical course beyond improvement of the nutritional state. Several recent randomized trials suggest that distal (jejunal) enteral feeding may be tolerated as well as bowel rest and total parenteral nutrition (TPN), with fewer complications (Figure 58-3). The enteral route may be tried in the absence of GI dysfunction (e.g., ileus). Energy expenditure is variable, but most likely only 20% to 30% above basal. Use partial parenteral nutrition or TPN if the enteral approach fails. Experiments suggest that parenteral nutrition, including intravenous fat, elicits little significant pancreatic secretion; however, all patients with pancreatitis should be monitored to exclude severe hypertriglyceridemia.

**14. What adverse GI effects may be encountered in a patient using herbal supplements?**

It is estimated that one third to one half of the U.S. population uses herbal products in supplementary form and that 60% to 75% do not inform health care providers. Because herbal products are not regulated and their composition is not standardized, toxicity data are less clear than with regulated pharmaceuticals. However, popular products that may cause adverse GI effects include saw palmetto, *Ginkgo biloba* (nonspecific GI upset), garlic (nausea, diarrhea), ginseng (nausea, diarrhea), aloe (diarrhea, abdominal pain), and guar gum (obstruction). In addition, hepatotoxicity (ranging from asymptomatic enzyme elevation to fulminant necrosis)

**Table 58-4.** Vitamin and Mineral Deficiencies and Toxicities

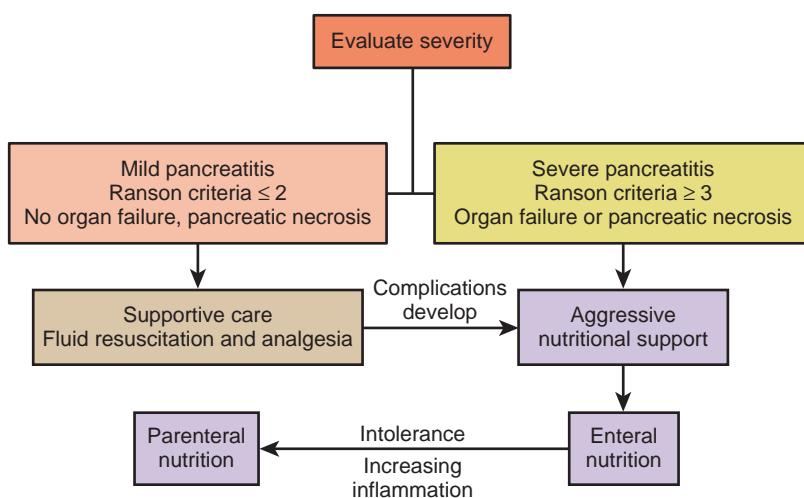
MICRONUTRIENT	DEFICIENCY	TOXICITY
Vitamin A	Follicular hyperkeratosis, night blindness, corneal drying, keratomalacia	Dermatitis, xerosis, hair loss, joint pain, hyperostosis, edema, hypercalcemia, hepatomegaly, pseudotumor
Vitamin D	Rickets, osteomalacia, hypophosphatemia, muscle weakness	Fatigue, headache, hypercalcemia, bone decalcification
Vitamin E	Hemolytic anemia, myopathy, ataxia, ophthalmoplegia, retinopathy, areflexia	Rare: possible interference with vitamin K, arachidonic acid metabolism, headache, myopathy
Vitamin K	Bruisability, prolonged prothrombin time	Rapid intravenous infusion: possible flushing, cardiovascular collapse
Vitamin C	Scurvy: poor wound healing, perifollicular hemorrhage, gingivitis, dental defects, anemia, joint pain	Diarrhea; possible hyperoxaluria, uricosuria; interference with glucose, occult blood tests; dry mouth, dental erosion
Vitamin B <sub>1</sub> (thiamine)	Dry beriberi (polyneuropathy): anorexia, low temperature Wet beriberi (high-output congestive heart failure): lactic acidosis Wernicke-Korsakoff syndrome: ataxia, nystagmus, memory loss, confabulation, ophthalmoplegia	Large-dose intravenous: anorexia, ataxia, ileus, headache, irritability
Vitamin B <sub>2</sub> (riboflavin)	Seborrheic dermatitis, stomatitis, cheilosis, geographic tongue, burning eyes, anemia	None
Vitamin B <sub>3</sub> (niacin)	Anorexia, lethargy, burning sensations, glossitis, headache, stupor, seizures Pellagra: diarrhea, pigmented dermatitis, dementia	Hyperglycemia, hyperuricemia, GI symptoms, peptic ulcer, flushing, liver dysfunction
Vitamin B <sub>6</sub> (pyridoxine)	Peripheral neuritis, seborrhea, glossitis, stomatitis, anemia, CNS/EEG changes, seizures	Metabolic dependency, sensory neuropathy
Vitamin B <sub>12</sub>	Glossitis, paresthesias, CNS changes, megaloblastic anemia, depression, diarrhea	None
Folic acid	Glossitis, intestinal mucosal dysfunction, megaloblastic anemia	Antagonizes antiepileptic drugs, decreases zinc absorption
Biotin	Scaly dermatitis, hair loss, papillae atrophy, myalgia, paresthesias, hypercholesterolemia	None
Pantothenic acid	Malaise, GI symptoms, cramps, paresthesias	Diarrhea
Calcium	Paresthesias, tetany, seizures, osteopenia, arrhythmia	Hypercalciuria, GI symptoms, lethargy
Phosphorus	Hemolysis, muscle weakness, ophthalmoplegia, osteomalacia	Diarrhea
Magnesium	Paresthesias, tetany, seizures, arrhythmia	Diarrhea, muscle weakness, arrhythmia
Iron	Fatigue, dyspnea, glossitis, anemia, koilonychia	Iron overload (hepatic, cardiac), possible oxidation damage
Iodine	Goiter, hypothyroidism	Goiter, hypo/hyperthyroidism

*Continued on following page*

**Table 58-4.** Vitamin and Mineral Deficiencies and Toxicities (Continued)

MICRONUTRIENT	DEFICIENCY	TOXICITY
Zinc	Lethargy, anorexia, loss of taste/smell, rash, hypogonadism, poor wound healing, immunosuppression	Impaired copper, iron metabolism, reduced HDL, immunosuppression
Copper	Anemia, neutropenia, lethargy, depigmentation, connective tissue weakness	GI symptoms, hepatic damage
Chromium	Glucose intolerance, neuropathy, hyperlipidemia	None
Selenium	Keshan's cardiomyopathy, muscle weakness	GI symptoms
Manganese	Possible weight loss, dermatitis, hair disturbances	Inhalation injury only
Molybdenum	Possible headache, vomiting, CNS changes	Interferes with copper metabolism, possible gout
Fluorine	Increased dental caries	Teeth mottling, possible bone integrity/fluorosis

CNS, Central nervous system; EEG, electroencephalography; GI, gastrointestinal; HDL, high-density lipoproteins.



**Figure 58-3.** Nutrition for pancreatitis.

has been documented with germander, chaparral, senna, *Atractylis*, and *Callilepis*. Hepatotoxicity associated with the use of valerian, mistletoe, skullcap, and various Chinese herbal mixtures has been noted but awaits a cause-and-effect confirmation. The pyrrolizidine alkaloids in *Crotalaria*, *Senecio*, *Heliotropium*, and comfrey have long been implicated in cases of venoocclusive liver disease.

## 15. How is obesity defined, and how common is it among U.S. residents?

BMI has become the standard of measurement for obesity.

$$\text{BMI} = \text{Weight (kg)} \times \text{body surface area (m}^2\text{)}.$$

A BMI higher than  $30 \text{ kg/m}^2$  is defined as obese (Table 58-5).

Although the number of adults has doubled since 1980, the number of obese adults has quadrupled; approximately 72 million adults in the United States are obese. According to the National Health and Nutrition Examination Survey from 2007 to 2010, among Americans age 20 and older, 154.7 million are overweight or obese: <http://apps.nccd.cdc.gov/brfss/> (Accessed September 22, 2014).

**Table 58-5.** BMI Data for Adults

	BMI CATEGORY	BMI, KG/M <sup>2</sup>
	<b>NORMAL</b>	<b>18.5 TO 24.9</b>
	<b>OVERWEIGHT</b>	<b>25 TO 29.9</b>
	<b>OBESITY</b>	<b>30 TO 39.9</b>
	<b>EXTREME</b>	<b>40+</b>
Adults	1998-1994	1995
Obese	22.9%	15.9%
Overweight	55.9%	35.5%
Extremely Obese	2.9%	4.7%
1999-2000	2000	2008
		2010

BMI, Body mass index.

#### 16. In 2007, what U.S. state had an obesity rate of less than 20%?

Colorado. However, the 2011 data shows that no state has an obesity rate less than 20% as Colorado's has risen to 20.7%. Open the link showing the percentage of each state's population that is obese: <http://www.cdc.gov/obesity/data/adult.html> (Accessed September 22, 2014).

#### 17. Does obesity carry a significant risk for death?

Yes. In the United States, 300,000 persons die annually from obesity-related diseases:

Cardiomyopathy	Degenerative joint disease (DJD)
Coronary artery disease	Immobility
Dyslipidemia	Depression
Hypertension	Low self-esteem
Diabetes	Malignancy
Infertility	Dyspnea
Fatty liver	Obstructive sleep apnea
Deep vein thrombosis	Obesity hypoventilation
Gallstones	Chronic fatigue
Pulmonary embolus	Venous stasis
Urinary stress incontinence	Gastroesophageal reflux disease (GERD)

#### 18. What are the medical therapies for obesity?

Dietary restriction of calories, while maintaining adequate protein, fluid electrolyte, mineral, and vitamin intake, is the key. A sensible weight reduction program targets gradual weight reduction by behavior modification, including dietary and activity changes. Numerous fad diets claim success, but key to the weight loss is patient commitment and total lifestyle modification. The U.S. Preventive Services Task Force 2012 recommendations include screening all adults for obesity. Clinicians should offer or refer patients with a BMI of 30 kg/m<sup>2</sup> or higher to intensive, multicomponent behavioral interventions.

Intensive, multicomponent behavioral interventions for obese adults include the following components:

- Behavioral management activities, such as setting weight-loss goals
- Improving diet or nutrition and increasing physical activity
- Addressing barriers to change
- Self-monitoring
- Strategizing how to maintain lifestyle changes

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to <http://www.uspreventiveservicestaskforce.org/> (Accessed September 22, 2014).

#### 19. What are the surgical options for obesity?

Bariatric surgery dates to the 1950s when intestinal bypass was first performed. The total weight lost correlates with the total length of bowel bypassed. Gastric bypass (GBP) is the most common weight loss surgery performed in the United States (see Chapter 77). The laparoscopic adjustable gastric banding procedure is the most common bariatric surgery in Australia and Europe. A recent systematic review concluded that weight loss outcomes strongly favored Roux-en-Y GBP over laparoscopic adjustable gastric banding.

**20. What are the National Institutes of Health consensus criteria thought to be viable indications for bariatric surgery?**

Failure of a major weight-loss program plus excessive obesity BMI of more than  $40 \text{ kg/m}^2$

or

Failure of a major weight-loss program plus BMI of more than  $35 \text{ kg/m}^2$   
and

Obesity-related comorbidities\*

**21. What is the operative mortality of GBP surgery?**

Operative mortality ranges from 0.3% to 1.6%, and perioperative complications occur in 10% of patients:

**Perioperative Complications**

- Splenic injury
- Pneumonia
- Wound infection
- Thrombotic events
- Anastomotic leaks
- Hemorrhage
- Pulmonary failure
- Cardiac events
- Wound dehiscence
- Thrombocytopenia
- Intraabdominal sepsis
- Death

**22. What are medical benefits of bariatric surgery?**

- **Diabetes:** 83% of patients with type 2 diabetes and 99% of those with glucose intolerance maintained normal levels of plasma glucose, glycosylated hemoglobin, and insulin; 88% of diabetics no longer required medication.
- **Cardiovascular:** 15% of patients experienced a decrease in cholesterol; 50%, a decrease in triglycerides; and prescription-treated hypertension was decreased from 58% to 14%.
- **Pulmonary:** 14% of patients have preoperative obstructive or hypoventilation syndrome, with most improved postoperatively.

**23. What nutritional deficiencies are seen with bariatric surgery?**

- Fat malabsorption
- $B_{12}$  deficiency: 37% develop  $B_{12}$  deficiency
- Folate deficiency
- Fat-soluble vitamin deficiency
- Iron deficiency and anemia seen in 33% and 30%, respectively

**Recommended Supplements**

- Iron 325 mg twice daily
- $B_{12}$  as part of a multivitamin
- Folate as part of a multivitamin
- 1200 to 1500 mg calcium in divided doses over the day. Calcium citrate is better absorbed in low acid environment.

**24. Is the number of bacteria populating the human intestine greater than the total number of cells in the human body?**

Yes. The average human body consists of approximately 10 trillion cells, whereas there are approximately 10 times that number of microorganisms in the gut.

**25. What value is gut microbiota to human existence?**

There are estimated to be 200 to 300 colonic species of bacteria in the gut, each with a unique function (Table 58-6).

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\*Hypertension, type 2 diabetes mellitus, DJD and disc disease, GERD, sleep apnea, obesity hypoventilation, severe venous stasis, abdominal wall hernias, and pseudotumor cerebri

**Table 58-6.** Commensal Effects of Gut Microbiota on Humans

ACTION	EFFECT
Carbohydrate fermentation	Reduction of intraluminal colonic pH
Protein fermentation	Production of NH <sub>4</sub> and sympathetic amines
Synthesis of short-chain free fatty acids	Main source of energy and nutrition for colon
Synthesis of vitamins K, B <sub>1</sub> , B <sub>61</sub> , and B <sub>12</sub> , folic acid, and pantothenic acid	Essential components for biologic processes
Deconjugation of bile salts, bilirubin, drugs, and steroid hormones	Biotransformation and absorption
Fat malabsorption	Regulation of plasma levels of cholesterol and triglycerides

**26. Is there a link between gut microbiota and obesity?**

Yes. Intestinal microbiota of obese (*ob/ob*) mice were examined and compared with wild-type (WT/WT) mice; it was found that *ob/ob* animals have a 50% reduction in the abundance of Bacteroidetes and a proportional increase in Firmicutes species that are more efficient in extracting calories from otherwise nondigestible polysaccharides in our diet and ultimately generating SCFAs.

**27. What is the definition of a probiotic?**

Probiotic refers to live microbial food supplements that beneficially affect the host by improving intestinal microbial balance and fulfill the following criteria:

- When ingested, they survive and colonize the gut, but rapidly disappear when discontinued.
- They are of human origin.
- They do not produce plasmids.

**28. What are some of the common probiotics?**

Probiotics are generally derived from four bacterial species: *Lactobacillus*, *Bifidobacter*, *Streptococcus*, and *Escherichia coli* (Table 58-7).

**Table 58-7.** Common Probiotics

LACTOBACILLUS (LAB)	BIFIDOBACTERIA	STREPTOCOCCUS	ESCHERICHIA COLI
<i>L. acidophilus</i>	<i>B. bifidum</i>	<i>S. thermophilus</i>	Nissle 1917
<i>L. casei GG</i>	<i>B. infantis</i>	<i>S. lactis</i>	Serotype
<i>L. rhamnosus</i>	<i>B. longum</i>	<i>S. salivarius</i>	06:K5:H1
<i>L. salivarius</i>	<i>B. thermophilum</i>		
<i>L. delbrueckii</i>	<i>B. adolescentis</i>		
<i>L. reuteri</i>			
<i>L. brevis</i>			
<i>L. plantarium</i>			

**29. Have probiotics been shown to benefit the treatment of GI disorders?**

Yes.

Disease State	Probiotic
Irritable bowel disease	<i>Bifidobacter</i> , VSL#3*
Ulcerative colitis	VSL#3*
Traveler's diarrhea	<i>Lactobacillus</i> , VSL#3*
Antibiotic-related diarrhea	Nonpathologic <i>E. coli</i> sero O6:K5:H1 Nissle 1917
Relapsing <i>Clostridium difficile</i> diarrhea	<i>Saccharomyces boulardii</i>
Recurrent <i>pouchitis</i>	VSL#3*

\*VSL#3 is a concentration of eight strains of bacteria.

### 30. How are probiotics believed to exert beneficial effect on the gut?

- Immune actions
  - Decrease tumor necrosis factor and interferon
  - Induce T reg cells
  - Induce T-cell apoptosis
  - Dendritic cell modulation
- Antimicrobial activity
  - Limited adhesion
  - Stimulated increased immunoglobulin A
  - Reduced chloride secretion
- Enhanced barrier integrity
  - Increase mucus secretion (increase in interleukins 10 and 12)
  - Enhance tight junctions

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

### BIBLIOGRAPHY

1. Buddeberg-Fischer B, Klaghofer R, Sigrist S, et al. Impact of psychosocial stress and symptoms on indication for bariatric surgery and outcome in morbidly obese patients. *Obes Surg* 2004;14:361–99.
2. Byrne TK. Complications of surgery for obesity. *Surg Clin North Am* 2001;81:1181–93.
3. Caba D, Ochoa JB. How many calories are necessary during critical illness? *Gastrointest Endosc Clin N Am* 2007;17:703–10.
4. De Legge MH, Drake LM. Nutritional assessment. *Gastroenterol Clin N Am* 2007;36:1–22.
5. Floch MH, Montrose DC. Use of probiotics in humans: An analysis of the literature. *Gastroenterol Clin N Am* 2005;34:547–70.
6. Francesco FW, Regano N, Mazzuoli S, et al. Cholestasis induced by total parenteral nutrition. *Clin Liver Dis* 2008;12:97–110.
7. Fuller R. Probiotics in man and animals. *J Appl Bacteriol* 1989;66:365–78.
8. Harrison GG. Height-weight tables. *Ann Intern Med* 1985;103:489–94.
9. Lee WJ, Wang W, Chen TC, et al. Clinical significance of central obesity in laparoscopic bariatric surgery. *Obes Surg* 2003;13:921–5.
10. Ley RE, Turnbaugh PJ, Klein S, et al. Microbial ecology: Human gut microbes associated with obesity. *Nature* 2006;444:1022–3.
11. Maroo S, Lamont JT. Recurrent *Clostridium difficile* related antibiotic diarrhea. *Gastroenterology* 2006;130:1311–6.
12. Nisha R, Punjabi NM. Sleep apnea and metabolic dysfunction: Cause or co-relation? *Sleep Med Clin* 2007;2:237–50.
13. Ochoa JB, Caba D. Advances in surgical nutrition. *Surg Clin N Am* 2006;86:1483–93.
14. Pai MP, Paloucek PP. The origin of the “ideal” body weight equations. *Ann Pharmacol* 2000;34:1066–9.
15. Pinkney J, Kerrigan D. Current status of bariatric surgery in the treatment of type 2 diabetes. *J Obes Rev* 2004;5:69–78.
16. Quigley EM. Bacteria: A new player in gastrointestinal motility disorders—Infections, bacterial overgrowth and probiotics. *Gastroenterol Clin N Am* 2007;36:735–48.
17. Shen B. Managing pouchitis. *Am J Gastroenterol* 2007;102:S60–4.
18. Singh VP, Sharma J, Babu S, Rizwanulla AS. Role of probiotics in health and disease: A review. *J Pak Med Assoc* 2013;63(2):253–7.
19. Skelton JA, DeMattia L, Miller L, et al. Obesity and its therapy: From genes to community action. *Pediatr Clin North Am* 2006;53:777–94.
20. Tenenhaus M, Rennekampff HO. Burn surgery. *Clin Plast Surg* 2007;34:697–715.
21. Tice JA, Karliner L, Walsh J, Petersen AJ. Gastric banding or bypass? A systematic review comparing the two most popular bariatric procedures. *Am J Med* 2008;121(10):885–93.
22. Tucker ON, Szomstein S, Rosenthal RJ, et al. Nutritional consequences of weight-loss surgery. *Med Clin N Am* 2007;91:499–514.

### Websites

- Centers for Disease Control and Prevention. Nutrition. Accessed September 22, 2014, from [www.cdc.gov/nccdphp/dnpa/nutrition/index.htm](http://www.cdc.gov/nccdphp/dnpa/nutrition/index.htm).
- Centers for Disease Control and Prevention. Overweight and obesity. Accessed September 22, 2014, from <http://www.cdc.gov/obesity/data/>.
- Halls.md. Set a realistic “ideal weight” goal for your body. Accessed September 22, 2014, from <http://www.halls.md/ideal-weight/body.htm>.
- Nestle Health Science. MNA (mini nutritional assessment). Accessed September 22, 2014, from [http://www.nestle-nutrition.com/Clinical\\_Resources/Default.aspx](http://www.nestle-nutrition.com/Clinical_Resources/Default.aspx).
- Nutrition.gov. Accessed September 22, 2014, from [www.nutrition.gov](http://www.nutrition.gov).

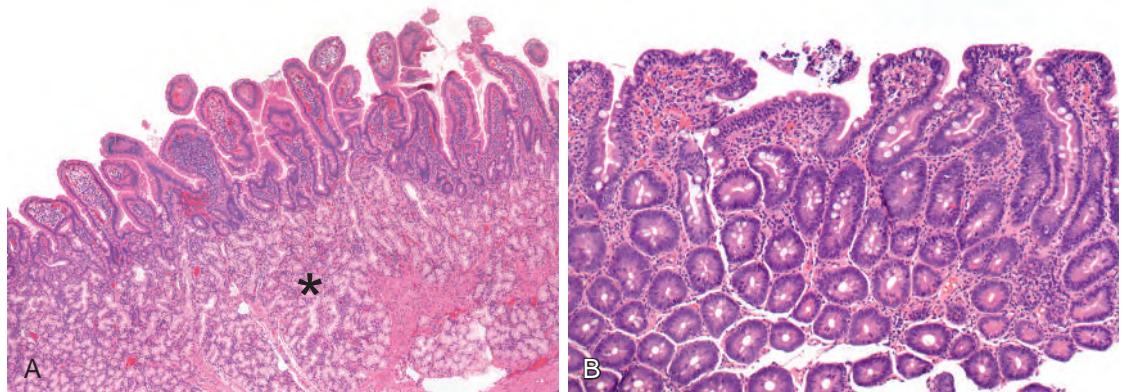
# SMALL BOWEL AND COLON PATHOLOGY

Shalini Taval, MD

## SMALL INTESTINE

### 1. What are the morphologic features of celiac disease?

The normal duodenal mucosa has numerous fingerlike projections, or villi, as shown in Figure 59-1A, whereas in celiac disease the normal villous architecture is lost (blunted villi and crypt hyperplasia) and intraepithelial lymphocytes (IELs) are increased, as shown in Figure 59-1B. Increased IELs are seen more toward the tips of the villi. These are T lymphocytes that can be highlighted by CD3 immunohistochemical stain.



**Figure 59-1.** A, Duodenum (normal) with underlying Brunner glands (asterisk). B, Celiac disease. Villous blunting with crypt hyperplasia and increased intraepithelial lymphocytes (tip heavy pattern). Hematoxylin and eosin stain.

The Marsh criteria represent a morphologic classification that defines the many histologic features of this entity. The modified classification (Marsh-Oberhuber) subdivides Marsh 3 into A, B, and C as partial, subtotal, or total villous atrophy, respectively. Corazza classification simplifies it further into Grade A, B1, and B2, representing Marsh type 1, 3a, and 3c, respectively. The comparison and summary of histologic classifications is depicted in Table 59-1.

Treated celiac disease may show normal villous architecture but the IELs are still increased.

**Table 59-1.** Histologic Classifications of Celiac Disease

MARSH MODIFIED (OBERHUBER)	HISTOLOGIC CRITERIA				CORAZZA
	IEL*	Crypt Hyperplasia	Villous Atrophy		
Type 0	No	No	No		None
Type 1	Yes	No	No		Grade A
Type 2	Yes	Yes	No		
Type 3a	Yes	Yes	Yes (partial)		Grade B1
Type 3b	Yes	Yes	Yes (subtotal)		
Type 3c	Yes	Yes	Yes (total)		Grade B2

IEL, Intraepithelial lymphocytes.

\*>40 IEL per 100 enterocytes for Marsh modified (Oberhuber); >25 IEL per 100 enterocytes for Corazza.

Adapted from Rubio-Tapia A, et al. ACG clinical guidelines: Diagnosis and management of celiac disease. *Am J Gastroenterol* 2013;108(5):656–676.

## 2. What is the differential diagnosis of the biopsy showing villous blunting?

- Allergy to other proteins (e.g., cow's milk in the pediatric population)
- Dermatitis herpetiformis
- Nonsteroidal antiinflammatory drugs (NSAIDs)
- Peptic duodenitis
- Giardiasis
- Tropical sprue
- Crohn's disease
- Severe malnutrition
- Bacterial overgrowth
- Common variable immunodeficiency
- Autoimmune enteropathy
- Graft-versus-host disease (GVHD)
- Zollinger-Ellison syndrome
- Chemotherapy effect

## 3. What are the complications of celiac sprue?

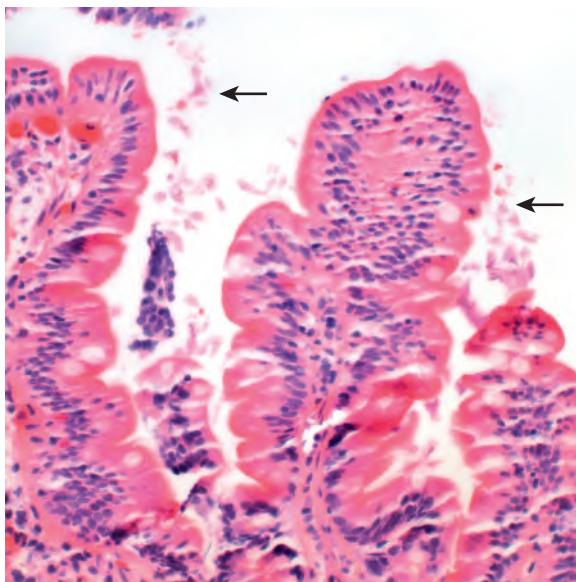
- *Collagenous sprue*: Some cases of longstanding sprue, unresponsive to gluten-free diet, exhibit a thickened subepithelial collagen table greater than 10 µm along with marked villous blunting.
- *Ulcerative jejunoileitis* is characterized by multiple transverse ulcers in the small intestine, predominantly in the jejunum.
- *Enteropathy-associated T-cell lymphoma* is mostly seen in older adult patients with celiac disease.
- *Carcinoma*: Increased incidence of small bowel adenocarcinoma and carcinoma at other GIT sites has been reported. Also reported are carcinomas of oropharynx, lung, breast, and ovary.

## 4. Histologically, what findings suggest peptic duodenitis?

Gastric foveolar metaplasia is seen in the villi (which may be focal or extensive), along with active lesions (i.e., cryptitis or crypt abscess) and increased chronic inflammation in the lamina propria ([E-Figure 59-2](#)). Rarely, *Helicobacter* organisms may be identified in cases with extensive foveolar metaplasia. The differential diagnosis includes gastric heterotopia.

## 5. Discuss a few causes of infectious enteritis.

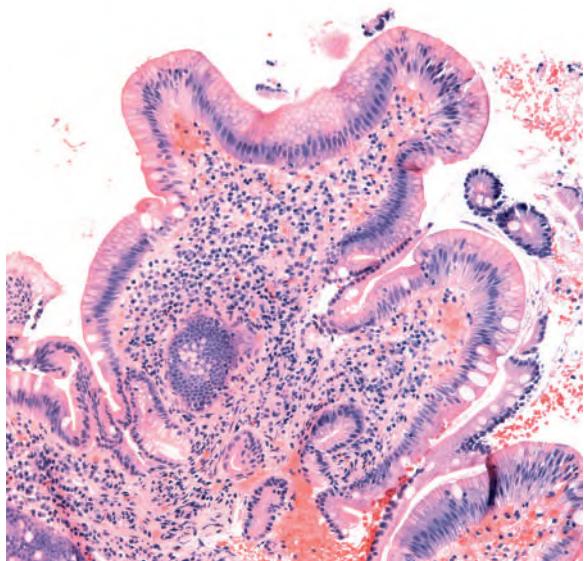
- *Giardiasis*: *Giardia lamblia* is seen as a pear-shaped organism, which resides in the upper small intestine (duodenum and jejunum) ([Figure 59-3](#)) and exists in two forms—trophozoite and cyst. The trophozoite form (7 µm wide, 14 µm long) shows two symmetrical nuclei with nucleoli and four pairs of flagella. On longitudinal sections, it appears as a long, curved organism.

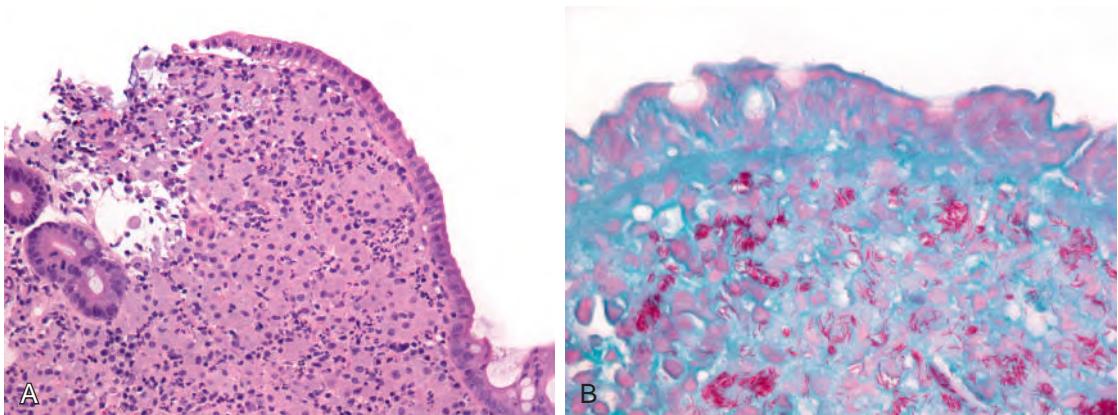


**Figure 59-3.** Photomicrograph of Giardiasis. Small bowel biopsy shows pear-shaped trophozoite forms (arrows) on the luminal surface. Hematoxylin and eosin stain. (Courtesy Dr. Loretta Gaido, Denver Health Medical Center, Denver, CO.)

- *Mycobacterium avium intracellulare* infection: This opportunistic infection affects both the small and large bowel in immunocompromised hosts in a patchy distribution. Histologic examination shows numerous histiocytes in the lamina propria ([Figure 59-4A](#)) that contain numerous acid-fast bacilli highlighted by Kinyoun stain (see [Figure 59-4B](#)). Granulomas may not be identified.

**E-Figure 59-2.** Photomicrograph of peptic duodenitis. Note the villous blunting with gastric foveolar metaplasia at the surface and increased chronic inflammation in the lamina propria. Hematoxylin and eosin stain.





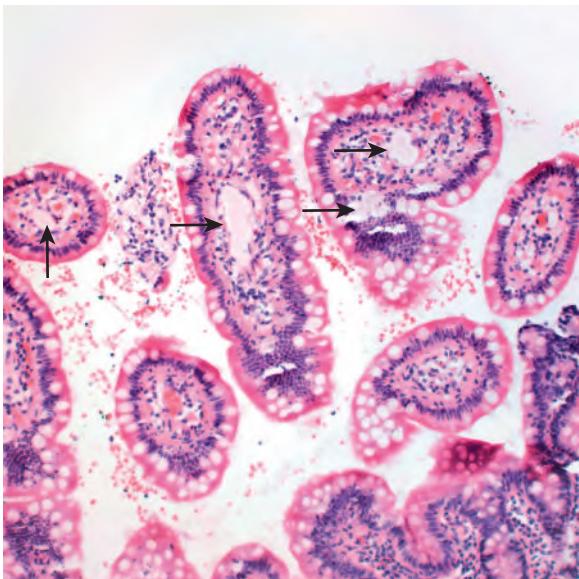
**Figure 59-4.** **A,** *Mycobacterium avium intracellulare*. There is marked expansion of the lamina propria by plump histiocytes (hematoxylin and eosin stain). **B,** *Mycobacterium avium intracellulare*. Acid-fast bacilli (magenta staining rods within histiocytes) highlighted by the Kinyoun stain. The *Tropheryma whipplei* organisms are not acid fast.

- **Whipple disease:** *Tropheryma whipplei* infects the small intestine, cardiac valves, nervous system, and lymph nodes. Histologic examination shows expansion of lamina propria by positive periodic acid–Schiff (diastase resistant) Whipple bacilli that are negative with acid-fast bacilli stain. The other feature that points to Whipple infection is the dilated lymphatics in the lamina propria caused by obstruction of the lymphatic ducts by bacilli. Other tests include polymerase chain reaction (PCR) assay and electron microscopy.
- Other infections include *cryptosporidium*, disseminated *histoplasmosis*, *Isospora belli*, *Microsporidium* spp. (*Enterocytozoon bieneusi*, *Enterocytozoon intestinalis*), *strongyloides*, and *Yersinia* spp.

#### Miscellaneous Conditions

- **Lymphangiectasia:** Primary lymphangiectasia presents in the pediatric age group generally before 3 years. The biopsy sample shows dilated lymphatics in the superficial lamina propria (Figure 59-5). Secondary causes will show similar histologic findings and include local inflammatory or a neoplastic process.

**Figure 59-5.** Photomicrograph of lymphangiectasia (secondary). Small bowel biopsy showing villi with dilated lacteals (arrows). Hematoxylin and eosin stain.

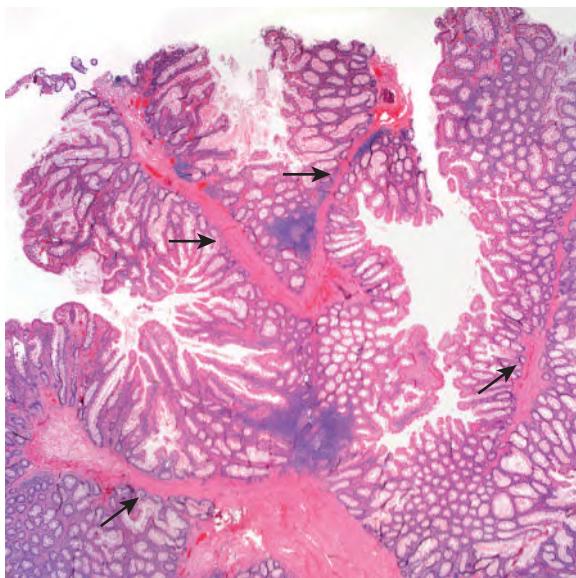


- **Ischemic enteritis:** This is often the result of mechanical obstruction and, histologically, shows hemorrhage in the lamina propria or transmural hemorrhage with mucosal sloughing.
- **GVHD:** Histologic findings are graded as follows:
  - Grade 1—Apoptosis (single cell necrosis) of the crypt epithelium
  - Grade 2—Apoptosis with crypt abscesses

- Grade 3—Individual crypt necrosis or crypt drop-out
- Grade 4—Total surface denudation of areas of bowel
- **Eosinophilic gastroenteritis:** The biopsy shows villous blunting with numerous eosinophils in the lamina propria forming clusters or sheets. The etiologic factors include food allergies, parasites, drugs, hypereosinophilic syndrome, and idiopathic disease.

### Small Intestinal Neoplasms

- **Peutz-Jeghers polyps:** The small intestine is the most common site for polyps in Peutz-Jeghers syndrome. Histologic examination shows arborizing smooth muscle bundles in the lamina propria without much expansion of lamina propria by inflammatory infiltrate (Figure 59-6). The overlying epithelium is that of small intestinal type and may show hyperplasia. Dysplasia can occasionally be seen in these polyps.



**Figure 59-6.** Photomicrograph of Peutz-Jeghers polyp. Note the arborizing smooth muscle bundles (arrows) traversing the lamina propria. Hematoxylin and eosin stain.

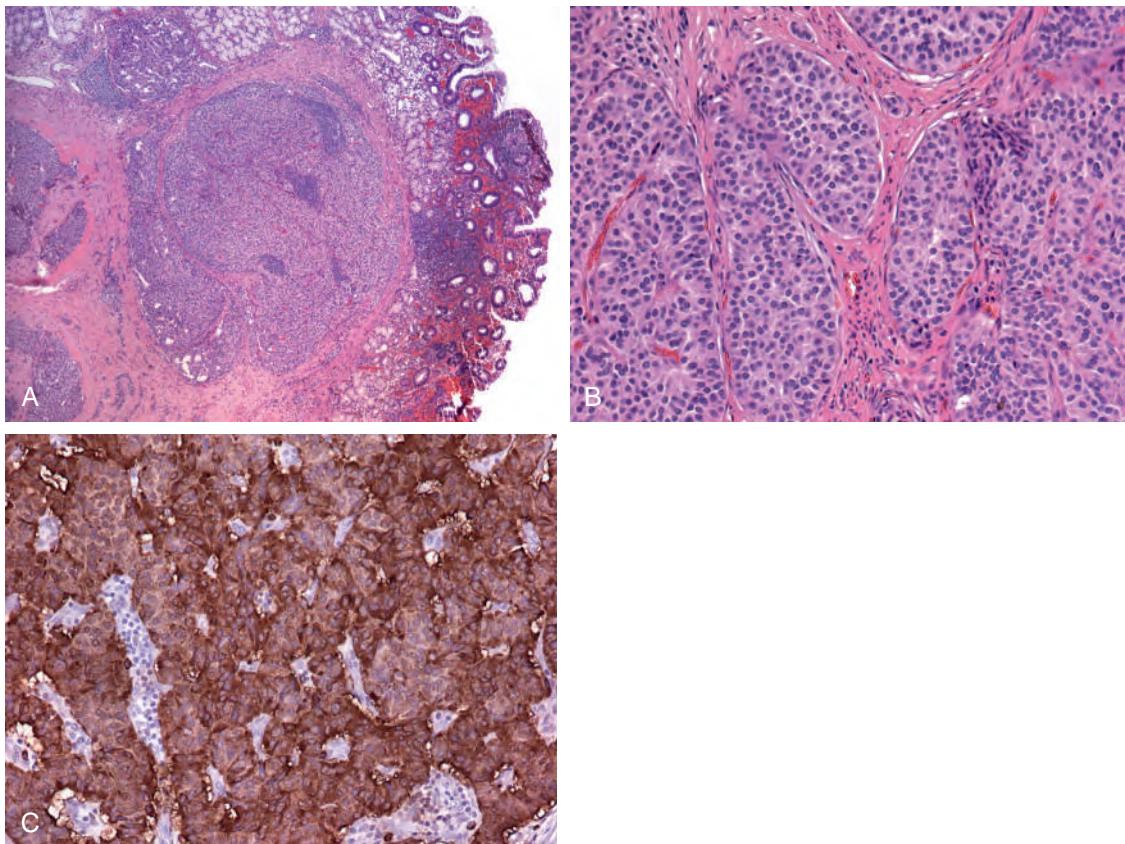
- **Adenomas:** Duodenum is the most common upper gastrointestinal (GI) site for an adenoma. The morphologic characteristics are similar to that in the colon: tubular, tubulovillous, or villous patterns are seen. Ampullary adenomas arise in the ampulla or periampullary region and are indistinguishable from each other based on morphologic examination.
- **Adenocarcinomas:** The primary adenocarcinoma of the small intestine is uncommon (2% of GI tract tumors), and the duodenum is the most common site. Usually, these arise from a sporadic adenoma. Histologic examination resembles colonic adenocarcinoma. Other predispositions include familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC), or hamartomatous polyp syndromes. Risk factors include chronic inflammatory conditions such as celiac disease, Crohn's disease, ileostomy, and protein-losing enteropathy.

### 6. Discuss the neuroendocrine tumors.

- **Carcinoid tumor** (Figure 59-7): The duodenum is the most common site of these well-differentiated neuroendocrine tumors. These can be functional or nonfunctional in the production of hormones. Serotonin production is common in ileal carcinoids.
- Gastrin production is common in duodenal carcinoids.

Immunohistochemical stains cannot be used to predict the functional status of the tumor. All carcinoids are considered to have metastatic potential. Histologic architecture varies from nested, trabecular, cords, or glandular morphologic characteristics and consists of cells with scant amphophilic cytoplasm that show a salt-and-pepper chromatin pattern in the round or ovoid nuclei with inconspicuous nucleoli. Mitotic figures are rare. Gastrin-producing, somatostatin cell, and serotonin-producing tumors have aggressive behavior and metastasize.

- **Gangliocytic paragangliomas** are usually benign infiltrative lesions and consist of ganglion cells, spindle cells (neural), and epithelial cells forming trabeculae, nests, and pseudoglandular architecture. Occasional large tumors (more than 2 cm) may spread to the lymph nodes.
- **Small cell carcinoma** is the other end of spectrum of neuroendocrine tumors. These are poorly differentiated neuroendocrine carcinomas with small cell morphologic characteristics, necrosis, and increased mitotic activity.



**Figure 59-7.** Photomicrograph of duodenal carcinoid tumor. **A**, Submucosal well-circumscribed nodule. **B**, Nested appearance of the tumor and cells with round-to-ovoid nuclei and salt-pepper chromatin. Hematoxylin and eosin stain. **C**, Same case of carcinoid tumor showing strong immunoreactivity with chromogranin stain.

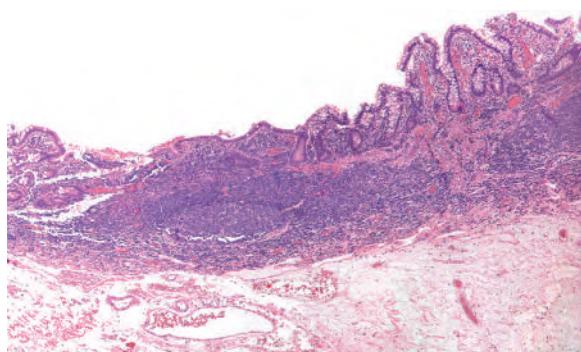
### Small Intestinal Lymphomas

- Small intestinal lymphomas are less common than gastric lymphomas and include extranodal marginal zone lymphoma (low-grade mucosa-associated lymphoid tissue [MALT], MALToma, or MALT lymphoma) ([E-Figure 59-8](#)), mantle cell lymphoma, Burkitt lymphoma, immunoproliferative small intestinal disease (IPSID), and enteropathy-like T-cell lymphoma (rare).
- IPSID is seen exclusively in Mediterranean and Middle Eastern regions. This is a variant of MALT lymphoma that secretes defective alpha heavy chains. The infiltrate consists of plasma cells with small lymphocytes, and monoclonal alpha heavy chain can be demonstrated in the cytoplasm of neoplastic cells. Transformation to large B-cell lymphoma is frequent in late stages.

## LARGE INTESTINE

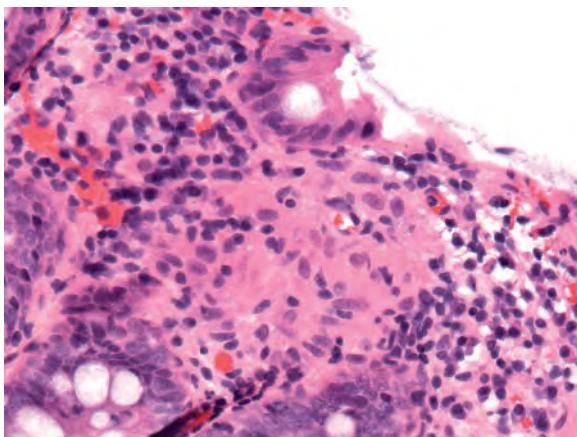
### 7. What are the histologic features of idiopathic inflammatory bowel disease (IBD)?

- **Chronic ulcerative colitis (UC):** Grossly, there is diffuse involvement of rectosigmoid and left-sided colon, and proximal extent of the disease varies. Infections such as *Cytomegalovirus*, *Salmonella*, *Shigella*, and *Clostridium difficile* can complicate UC. Toxic megacolon is a fulminant acute complication of the disease. Histologically, the features of acute disease include cryptitis (neutrophilic infiltration in the crypt epithelium), crypt abscesses (neutrophils in the crypt lumens), and mucosal erosions and ulcers. The features of chronicity include architectural distortion of crypts (crypt dropout, bifid crypts, crypt branching), mucin depletion (loss of goblet cells), Paneth cell metaplasia, basal plasmacytosis, increased eosinophils, and prominent lymphoid aggregates. These changes are diffuse except in the resolving phase, in which these may be focal (they should not be confused with Crohn's disease). Fibrosis is unusual in UC, in contrast to Crohn's disease. The differential diagnosis, especially in the acute disease process, includes infection, ischemic colitis, and Crohn's disease.
- **Quiescent colitis:** Histologically, mucosal atrophy (short crypts, loss of crypts, and crypt distortion), thickened muscularis mucosae, and normal inflammatory component in the lamina propria appear. Inflammatory pseudopolyps can be seen in longstanding cases.



**E-Figure 59-8.** Photomicrograph of mucosa-associated lymphoid tissue lymphoma in a resection specimen. Note the expansion of the lamina propria by the neoplastic lymphoid infiltrate extending into the adjacent submucosa. Hematoxylin and eosin stain.

- **Backwash ileitis:** Some patients with pancolitis demonstrate backwash ileitis, and the biopsy sample shows acute disease without features of chronicity.
- **Crohn's disease:** Colon biopsy samples show variable morphologic findings. Some foci may appear normal and the others show aphthous ulcers, cryptitis, glandular distortion and loss, and occasionally granulomas (Figure 59-9). Transmural inflammation is characteristic of Crohn's disease and distinguishes Crohn's from UC. The rectum is usually spared. The resection (done in complicated cases) specimen shows segmental involvement with *skip areas*, linear ulcers, cobblestoning, strictures, fissures and fistulas, inflammatory pseudopolyps, serosa with *creeping fat*, and a firm pipelike bowel resulting from fibrosis. Involvement of terminal ileum shows villous blunting and increased inflammation in the lamina propria.



**Figure 59-9.** Photomicrograph of Crohn's disease. A microgranuloma is seen in the lamina propria in this biopsy from transverse colon. Note the epithelioid histiocytes with ample eosinophilic cytoplasm and ovoid nuclei. Hematoxylin and eosin stain.

#### 8. Discuss colitis-associated dysplasia in IBD.

- Dysplasia can be flat or form a mass (dysplasia-associated lesion or mass [DALM]). Dysplasia in UC is graded as *negative, indefinite, low grade, or high grade*.
- The differential diagnosis of DALM is sporadic adenoma. The distinction between the two is difficult and requires clear communication between the pathologist and the endoscopist. If the lesion is isolated from the areas affected by colitis, then the diagnosis is usually a sporadic adenoma. A DALM lesion shows foci of dysplastic epithelium associated with areas of colitis. The pattern of dysplasia may not be uniform. Positive staining with beta-catenin may help in these cases that are negative for p53. Both DALM of any grade and flat, high-grade dysplasias are associated with the increased risk of invasive adenocarcinomas; total colectomy is usually recommended in UC cases.

#### 9. What is the differential diagnosis of focal active colitis?

- Infectious colitis
- Crohn's disease
- UC early or resolving
- Bowel preparation artifact

#### 10. What is the differential diagnosis of pseudomembranes?

- *Pseudomembranous colitis* is a complication of antibiotic-associated colitis caused by *C. difficile*. Not all *C. difficile* infections produce pseudomembranous colitis. Grossly, discrete gray-white patches of pseudomembranes are identified. The histologic features include loosely adherent fibrinopurulent exudate on the luminal surface (pseudomembrane) with associated superficial mucosal necrosis (E-Figure 59-10).
- Features of *Ischemic colitis* damage include mucosal necrosis, hemorrhage with congestion in the lamina propria, hyalinization of lamina propria, occasional fibrin thrombi, and pseudomembrane (neutrophilic-fibrinous exudate) formation. In longstanding ischemic bowel, mucin depletion, regenerative change, lymphoplasmacytic infiltrate, hemosiderin pigment, and fibrosis of lamina propria are seen. Systemic vasculitis should be considered in the differential diagnosis in these cases.

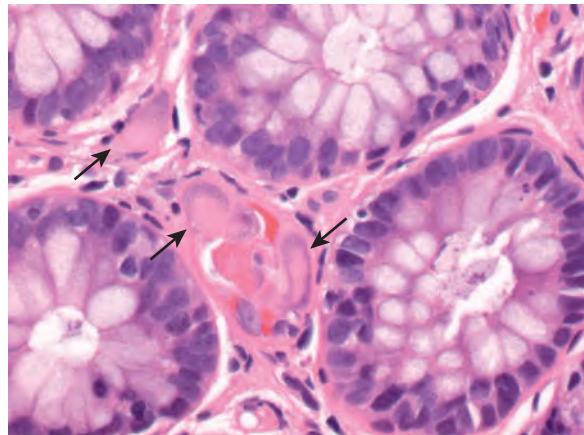
#### 11. Histologically, which findings help differentiate infectious colitis and NSAID-associated colitis?

- *Infectious colitis* on histologic examination shows acute inflammation in the lamina propria with cryptitis, crypt abscesses, and lack of prominent chronic inflammatory infiltrate or basal plasmacytosis (as seen in IBD). Chronic architectural changes may not be pronounced. Causative organisms include *Escherichia coli* O157:H7, *Salmonella*, *Shigella*, *Clostridium*, *Campylobacter*, *Yersinia*, cytomegalovirus colitis (Figure 59-11), amebic colitis, and histoplasmosis. Granulomas can be seen in tuberculosis, *Yersinia pseudotuberculosis*, and *Chlamydia* infections.

**E-Figure 59-10.** Microscopically, pseudomembrane (asterisk) is seen as necroinflammatory exudate on the luminal surface. Hematoxylin and eosin stain.

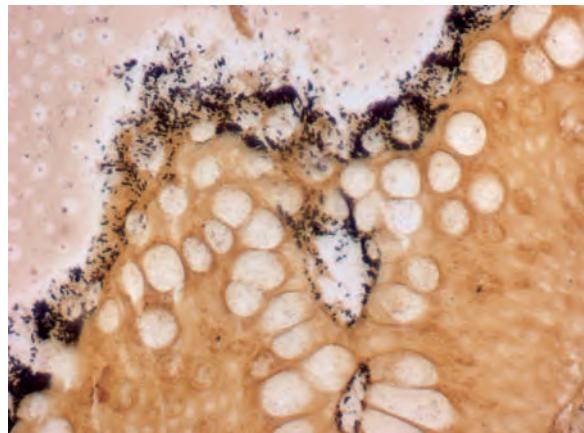


**Figure 59-11.** Photomicrograph of cytomegalovirus colitis. Note the large eosinophilic intranuclear viral inclusions (arrows). Hematoxylin and eosin stain.



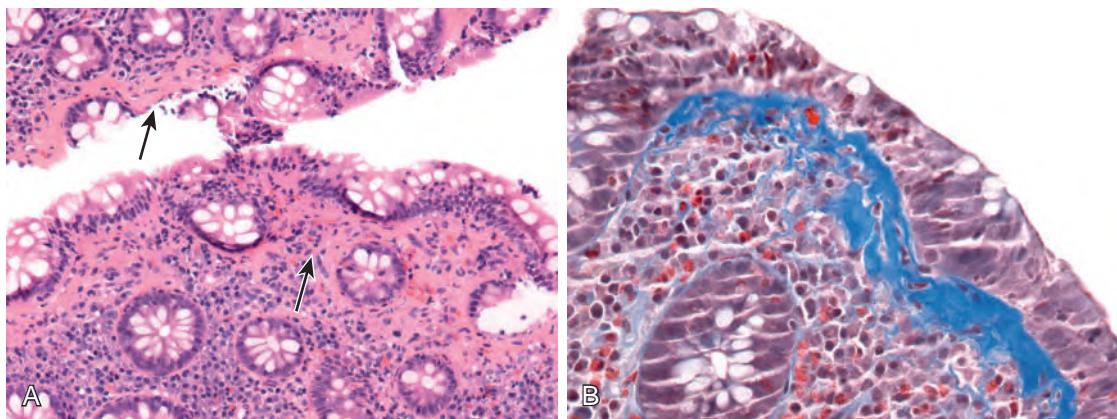
- *Intestinal spirochetosis* (Figure 59-12) shows organisms on the luminal surface that may not cause an active inflammatory response or injury in the mucosa. These anaerobic organisms belong to *Brachyspira* spp.
- *NSAID-associated colitis* changes are patchy, may involve any part of the colon, and histologically include focal active colitis, erosions and ulcers, increased apoptosis in crypts, and diaphragm strictures. *Diaphragm-like* strictures are formed as a result of repeated injury and repair and are seen microscopically as mucosal and submucosal fibrosis. These may cause luminal narrowing and occasionally serosal strictures. Thickened subepithelial collagen layer in longstanding cases has been associated with NSAIDs that can be confused with collagenous colitis and requires correlation with clinical history and endoscopic findings.

**Figure 59-12.** Photomicrograph of intestinal spirochetosis. Steiner stain highlights the spirochetes obscuring the luminal border. No significant inflammation was seen within crypts or lamina propria.



## 12. What are the histologic features of microscopic colitis?

- *Microscopic colitis* encompasses *collagenous* and *lymphocytic* colitis. Both of these conditions present as chronic watery diarrhea, are associated with autoimmune diseases, and show a near normal endoscopic examination. Histologically, *collagenous colitis* (Figure 59-13A) shows thickened subepithelial collagen layer that has irregular edges, is infiltrated by a few lymphocytes and eosinophils, and has dilated vessels. A few IELs may be seen. The collagen band can be highlighted by trichrome stain (Figure 59-13B). The differential diagnosis also includes ischemic colitis, NSAID-associated injury, IBD, diverticular disease, radiation injury, mucosal prolapse, and amyloidosis.
- *Lymphocytic colitis* shows increased IELs more on the surface epithelium. Both of the conditions show increased chronic inflammation in the lamina propria with increased eosinophils seen in collagenous colitis. An association between lymphocytic colitis and celiac disease is well known.



**Figure 59-13.** **A,** Collagenous colitis. Note the thickened subepithelial collagen table (arrows) with entrapped capillaries and inflammatory infiltrate. Hematoxylin and eosin stain. **B,** Collagenous colitis (trichrome stain). The stain highlights the thickened band that shows irregular edges.

### Miscellaneous Conditions

- **Irritable bowel syndrome:** Histologically, the biopsy samples do not show significant abnormality in these cases and appear normal.
- **Radiation colitis:** The histologic finding mimics ischemic colitis and shows enlarged nuclei and cells with hyalinization of lamina propria and vessel walls with scattered atypical stromal cells.
- **Eosinophilic colitis:** Microscopically, abundant eosinophils in the mucosa extending into submucosa are seen with minimal architectural distortion, if any.
- **Diversion colitis:** Mild cryptitis is seen on microscopic examination. Follicular lymphoid hyperplasia may be seen. The condition reverses on treatment with short-chain fatty acids.
- **Pouchitis:** This is a complication following ileal-pouch anal anastomosis for refractory UC. The pattern of inflammation mimics UC and there are no specific histologic criteria to distinguish recurrent UC from nonspecific inflammation of the pouch. Comparison with the biopsy samples from the nonpouch portion of the ileum may help.
- **Diverticular disease-associated colitis:** It is seen in the areas around diverticular orifices. Histologically, the findings are similar to those seen in IBD. Correlation with endoscopic findings and clinical history is essential.
- **Melanosis coli:** The biopsy sample shows numerous brown pigment-laden macrophages (lipofuscin) in the lamina propria (E-[Figure 59-14](#)). These are negative for staining with iron stain. There are no significant acute or chronic changes in the biopsy sample.
- **Endometriosis:** The common site in GI tract is the sigmoid colon. The biopsy sample shows endometrial glands and stroma with hemorrhage or hemosiderin pigment ([E-\[Figure 59-15\]\(#\)](#)). Any or all of the components may be present.

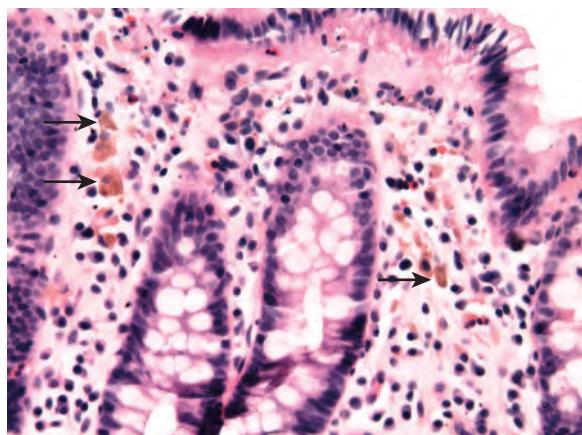
### 13. What is the differential diagnosis of polypoid lesions that can mimic adenoma?

- **Mucosal prolapse, solitary rectal ulcer syndrome, colitis cystica profunda, eroded polypoid hyperplasia:** These are seen in rectosigmoid colon as an ulcerated or a polypoid lesion in patients with history of constipation or straining during defecation. The histologic examination shows surface erosion, epithelial hyperplasia with distorted and dilated crypts, vertical stranding of muscle fibers in the lamina propria, fibrosis, and lymphoplasmacytic infiltrate. Inflammatory cloacogenic polyps are present at the anorectal junction and show similar histologic characteristics with both squamous and colonic epithelia.
- **Lymphoid polyps:** These are benign reactive lymphoid aggregates in the mucosa.
- **Inflammatory polyps:** Generally associated with IBD or diverticulitis and consist of marked inflammation in the lamina propria with granulation tissue and fibrosis. The mucosal lining may show regenerative change or erosions.

## POLYPS AND NEOPLASMS

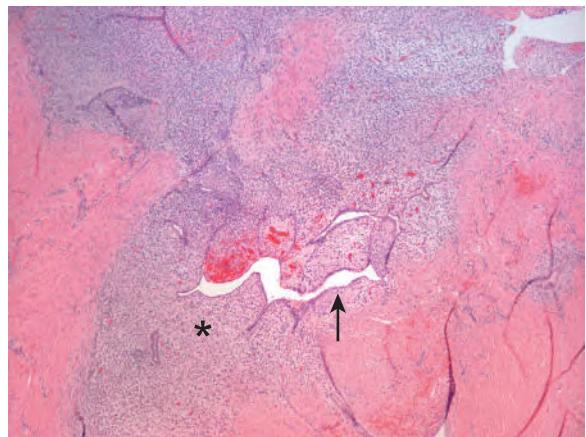
### 14. What are the histologic features of conventional adenomas?

Tubular adenomas ([Figure 59-16](#)) have a tubular architecture with the surface epithelium showing low-grade dysplasia that extends downward in the base. These can show focal areas of high-grade dysplasia with architectural complexity and marked cytologic atypia. Focal high-grade dysplasia does not have a metastatic potential. The *tubulovillous adenomas* ([Figure 59-17](#)) show a combination of tubular and villous architecture (villous component greater than 25%). *Villous adenoma* displays a predominant villous architecture (greater than 75%) and has a greater propensity for malignant transformation. All of these can have focal areas of

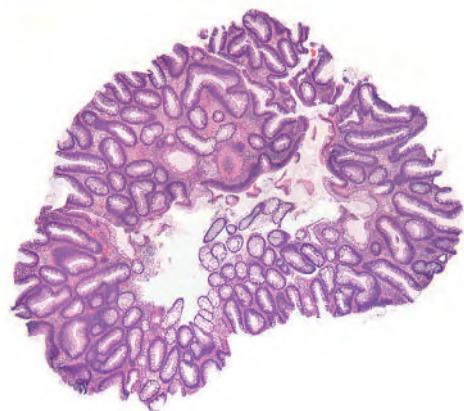


**E-Figure 59-14.** Photomicrograph of melanosis coli. Pigment laden macrophages in the lamina propria (arrows). Hematoxylin and eosin stain.

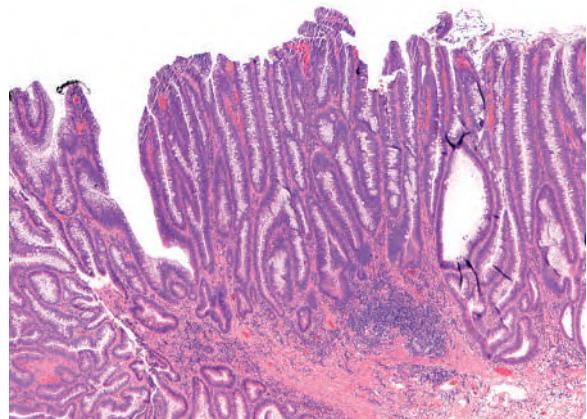
**E-Figure 59-15.** Photomicrograph of rectal endometriosis. Note the endometrial glands (arrow) surrounded by hemorrhage and stroma (asterisk). Hematoxylin and eosin stain.



**Figure 59-16.** Photomicrograph of tubular adenoma. Polyp showing tubular architecture lined by cells with nuclear stratification and hyperchromasia. Hematoxylin and eosin stain.



**Figure 59-17.** Photomicrograph of tubulovillous adenoma. Polyp showing villous architecture in addition to typical tubular areas. Hematoxylin and eosin stain.



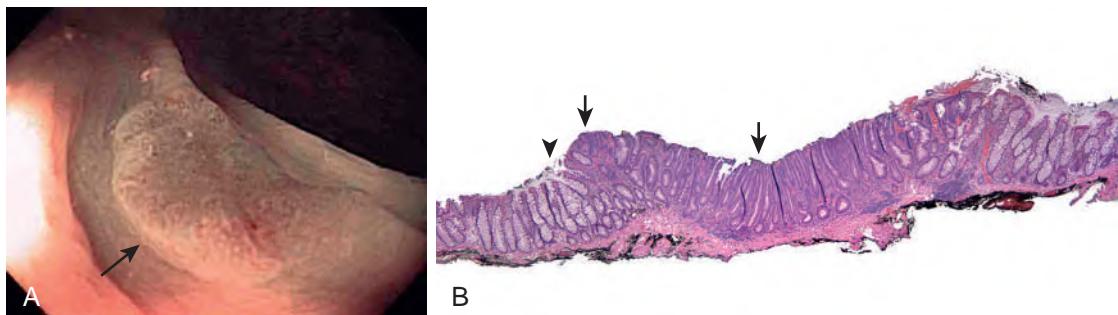
pseudoinvasion that should not be interpreted as intramucosal carcinoma. The conventional adenomas show KRAS mutations (BRAF negative).

#### 15. What is meant by *intramucosal carcinoma* in an adenoma?

Invasion of dysplastic glands into the lamina propria is intramucosal carcinoma. In the colon, it is equivalent to high-grade dysplasia, because it is not associated with metastatic potential and a polypectomy with negative margins should suffice.

#### 16. What is meant by the term *depressed or flat adenoma*?

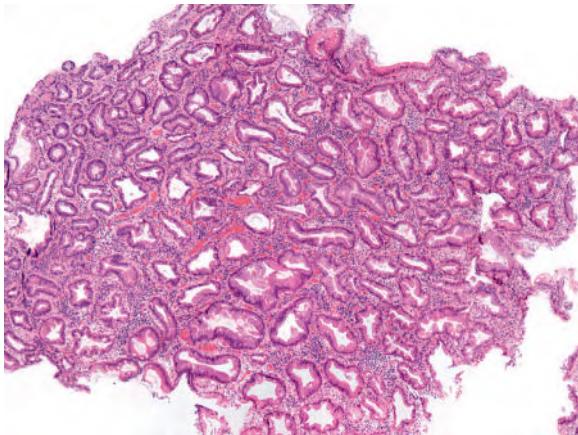
Endoscopically (Figure 59-18A), the adenoma shows subtle depression in the mucosa or may be flat. Histologically (see Figure 59-18B), the adenomatous glands show long, tubular architecture with a narrow opening at the surface and are lined by dysplastic epithelium. These tend to have high-grade dysplasia more often than the tubular adenomas and are more aggressive.



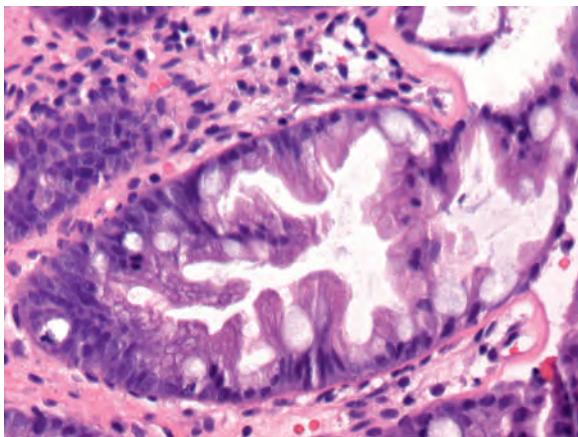
**Figure 59-18.** A, Depressed adenoma (arrow), endoscopic view. B, Photomicrograph of depressed adenoma, morphologic findings. Note the abrupt junction between normal (arrowhead) and abnormal (arrow) and the depression with tubular glands showing narrow openings at the surface (central arrow). Hematoxylin and eosin stain. (A, Courtesy Dr. Norio Fukami, University of Colorado Denver Health Sciences Center.)

**17 What is the difference between hyperplastic polyp (HP), traditional serrated adenoma (TSA), and sessile serrated adenoma (SSA)?**

- HPs are characterized by serrated crypt lumens that are lined by colonic epithelial cells that lack dysplasia (Figure 59-19).
- TSAs are polyps that show serrated crypt lumens with stratified *pencil-like* nuclei at the base of crypts (Figure 59-20) that resemble the ones seen in tubular adenoma. Some authors have described ectopic crypt formation in TSA. These are short crypts away from muscularis mucosae and are considered precursors to colorectal cancer (CRC).



**Figure 59-19.** Photomicrograph of hyperplastic polyp. Polyp with hyperplastic glands showing serrated lumens lined by epithelial cells without dysplasia. Hematoxylin and eosin stain.



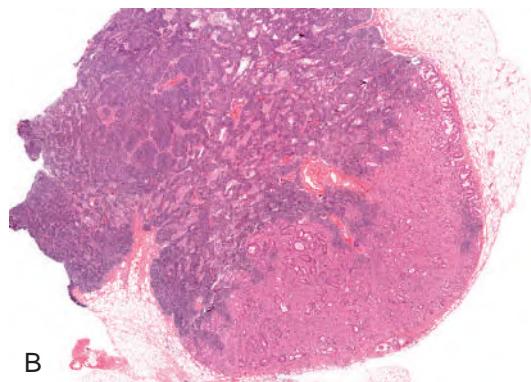
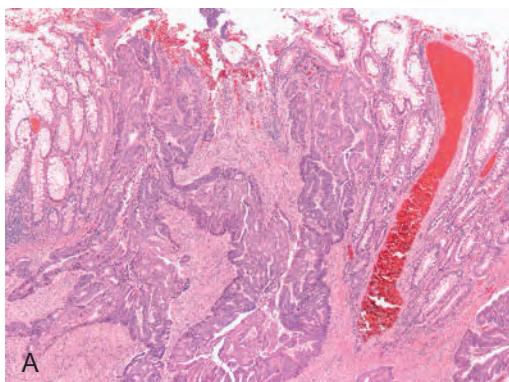
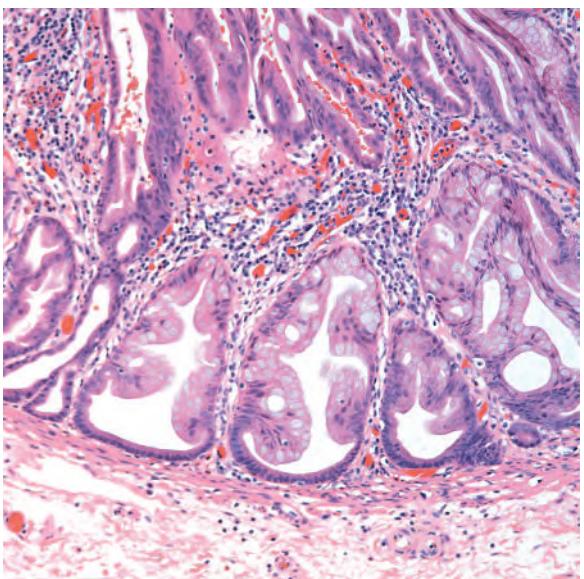
**Figure 59-20.** Photomicrograph of traditional serrated adenoma. Note the serrated lumens (as seen in hyperplastic polyps) lined by cells that show pencillate nuclei and stratification (as seen in tubular adenomas). Hematoxylin and eosin stain.

- SSAs are seen more on the right side of the colon in older adult women, and are always sessile. A few (10%) may occur in the left colon. In various studies, these account for 4% to 15% of serrated polyps. Architecturally, it differs and shows serrated lumens with a horizontal, broad or boat-shaped base (Figure 59-21). The lining epithelium is variable and shows goblet or mucinous cells or may be mucin depleted, and may show nuclear stratification. A subset of these polyps may show focal conventional dysplasia; however, architecture is the key finding. This adenoma has been associated with microsatellite instability-high (MSI-H)-related sporadic CRCs (hypermethylation of promoter gene). The majority of these show BRAF mutation, and approximately 1 in 25 (4%) of these may progress to cancer.
- Mixed polyps are HPs with typical adenoma foci.

**18. What are the genetic abnormalities in conventional CRCs?**

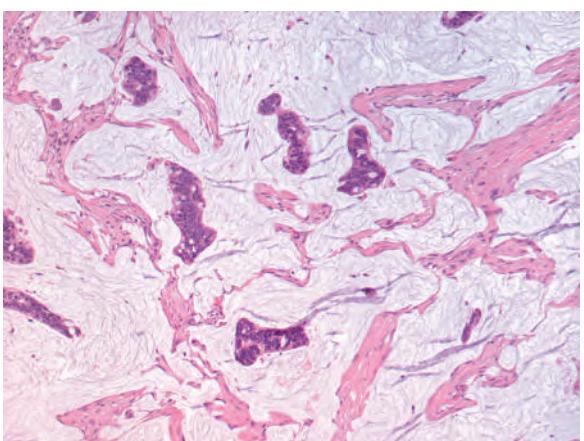
- Colorectal adenocarcinomas usually arise from adenomas and can be sporadic (85%) or syndromic. These are graded as *well*, *moderately*, or *poorly differentiated* based on the glandular differentiation (Figure 59-22). The variants include mucinous (greater than 50% mucinous morphologic characteristics) (Figure 59-23) and signet ring cell carcinomas (greater than 50% signet ring cell morphologic characteristics). Histologically, neoplastic glands with necrotic debris show invasion through the muscularis mucosa into the submucosa or beyond. On immunohistochemistry (IHC), these usually show staining with cytokeratin 20 and CDX2, and are usually

**Figure 59-21.** Photomicrograph of sessile serrated adenoma. Note the serrated lumens and broad (boat-shaped) base of the crypts in this polyp resected from cecum. Hematoxylin and eosin stain.



**Figure 59-22.** **A**, Colon adenocarcinoma, moderately differentiated. Note the infiltrating neoplastic glands with surface involvement in the center of the image and the nonneoplastic epithelium adjacent to it (for comparison). **B**, Lymph node with metastasis from colon adenocarcinoma (right). Hematoxylin and eosin stain.

**Figure 59-23.** Photomicrograph of mucinous adenocarcinoma. Note the mucin pools with floating neoplastic cell clusters. Hematoxylin and eosin stain.



negative for staining with cytokeratin 7. The most common genetic alteration (somatic) in sporadic CRCs is inactivation of APC/beta-catenin pathway that can have multiple consequences. Clonal accumulation of additional genetic alterations then occurs, including activation of proto-oncogenes such as *c-myc* and *ras* and inactivation of additional tumor suppressor genes (*TP53* on chromosome 17). These tumors are microsatellite stable (MSS). *BRAF* mutation is not common and seen in a few (less than 10%) conventional CRCs.

- *Small cell carcinoma* is a rare variant of CRC with poor prognosis, which shows small cell morphologic characteristics and positive immunostaining with neuroendocrine markers such as chromogranin, synaptophysin, and NCAM (CD56). These are not associated with carcinoid tumors (well-differentiated neuroendocrine tumors) and may be seen with conventional CRC.

#### **19. What genetic abnormalities point to HNPCC?**

HNPCC presents in a younger age group and has an autosomal dominant pattern of inheritance. Revised Bethesda Criteria are set to screen the patients for MSI. DNA mismatch repair (MMR) gene defect is tested for *hMLH1* (50%), *hMSH2* (39%), *hMSH6* (8%), and *hPMS2* (1%) genes. These defects result in insertion or deletion of nucleotides in the microsatellite sequences, which are tested using PCR and reported as high (MSI-H), low (MSI-L), or stable (MSS). At least five microsatellite sequences are tested and MSI-H is defined as instability in 30% to 40% of markers (two of five at least).

- Loss of *hMSH2* indicates HNPCC.
- Loss of *hMLH1* indicates HNPCC or sporadic CRC (loss caused by hypermethylation of *hMLH1* promoter in sporadic CRC).
- The IHC on paraffin sections (of normal and tumor) to test for mismatch repair is also done, which shows loss of staining in the tumor (caused by mutated gene) compared with the normal. Loss of *hMSH2* and/or *hMSH6* is highly associated with Lynch syndrome. Direct gene sequencing can be done in highly susceptible cases and to confirm the results of MSI and IHC. A negative test in an at-risk patient does not rule out other hereditary causes of CRC.

#### **20. What histologic features seen in CRCs can predict MSI-H?**

These tumors are usually right sided, show a medullary or syncytial growth pattern, have mucinous or signet ring cell features, are poorly differentiated, and show lymphocytic infiltration. Also, a Crohn-like reaction (nodular lymphoid aggregates) is seen beyond the advancing edge of the tumor. These features, along with the age at diagnosis, are used to determine the microsatellite instability by pathology score.

#### **21. What is the abnormality in MSI-unstable sporadic CRCs?**

These constitute approximately 12% to 15% of CRCs. The MSI-H is caused by somatic inactivation of *hMLH1* mismatch repair gene due to hypermethylation of the promoter region preceding the gene sequence, whereas in HNPCC, the instability is due to germline mutation in the MMR genes. Most of the sporadic ones show *BRAF* mutations (V600E mutation of *BRAF* oncogene). The histologic findings are similar to those seen in HNPCC.

### **POLYPOSISSYNDROMES**

#### **22. Name the hamartomatous polyp syndromes.**

- *Hamartomatous polyps* include juvenile hamartomatous polyp and the hamartomatous polyp of Peutz-Jeghers type.
- *Peutz-Jeghers syndrome* involves the entire GI tract (small intestine most common); there is a 93% lifetime risk of cancer. Sporadic Peutz-Jeghers polyps can occur but are extremely rare. Follow-up of these patients is warranted. Histologically, these typically show arborizing smooth muscle bundles in the lamina propria lined by normal or hyperplastic epithelium, occasionally with dysplastic foci.
- *Juvenile polyposis syndrome* involves the colon or entire GI tract (pedunculated polyps); the risk of CRC is approximately 30% to 40% and is less (10% to 15%) for upper GI cancer. This is the most common polyp in the juvenile population. Germline mutation in *SMAD4/DPC4* tumor suppressor gene accounts for half the cases. Histologically, these are lobulated polyps with cystically dilated crypt (mucus retention cysts) with inflamed edematous lamina propria and occasionally with superficial erosions. Other than juvenile polyp syndromes, juvenile polyps are seen in Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome.
- *Cowden syndrome* involves the entire GI tract from esophagus to rectum; the risk of developing CRC is generally not increased. The most commonly recognized cancer is breast, followed by thyroid. It arises from *PTEN* germline mutation. Histologically, juvenile polyps are common; also seen are HPs, adenomas, lipomas, and, rarely, ganglioneuromas.
- *Bannayan-Riley-Ruvalcaba syndrome* is a variant of Cowden syndrome with similar histologic features.
- *Cronkhite-Canada syndrome* occurs in any portion of the GI tract (sessile polyps); the risk of developing cancer is not well described. Histologically, the polyps seen are similar to juvenile-type (retention) polyps with marked edema in the lamina propria; the intervening mucosa shows similar changes in the lamina propria. Differential diagnosis includes Ménétrier disease and juvenile polyposis syndrome.
- *Hyperplastic polyposis* is a rare syndrome with an increased risk for CRC. It is characterized by the presence of HPs predominantly (adenomas—tubular or serrated also can be seen) in the colon proximal to sigmoid colon.

The number of polyps ranges from 5 to 100. Most of these are nonfamilial and the genetic abnormalities include BRAF and KRAS mutations.

All are hereditary except Cronkhite-Canada syndrome and hyperplastic polyposis.

### 23. Name the adenomatous polyp syndromes.

- FAP affects the entire colon and rectum; there is 100% risk of cancer. Histologically, tubular adenomas and occasionally tubulovillous and villous adenomas are identified.
- The variants include attenuated FAP, Gardner syndrome, Turcot syndrome, hereditary flat adenoma syndrome, and Muir-Torre syndrome.

All are hereditary syndromes.

### 24. How are neuroendocrine tumors classified?

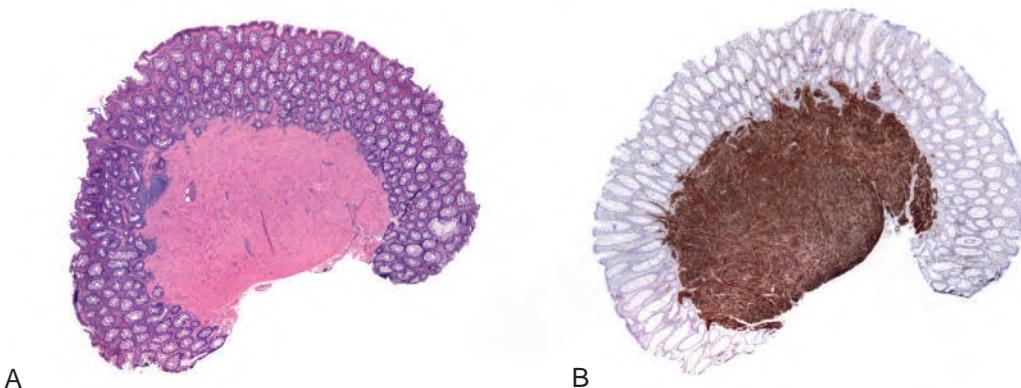
The spectrum ranges from well-differentiated neuroendocrine tumors (carcinoid tumors) to poorly differentiated (small cell carcinomas) and large cell neuroendocrine carcinomas. The common site of involvement is the rectum, followed by the cecum and sigmoid colon. The histologic characteristics are similar to those described in the small intestine section. These are sporadic tumors. The malignancy rate of 11% to 14% has been calculated for rectal carcinoids. The malignancy criteria include size greater than 2 cm, invasion into muscularis propria, and increased mitoses.

### 25. What are the most common primary tumor sites that can show colon metastases?

These include lung, stomach, breast, ovary, endometrium, and melanoma. These tumor cells creep under the surface epithelium or form submucosal nodules of varying sizes. More than one focus is generally seen. The surface epithelium lacks dysplasia (expected with primary colon adenocarcinomas). IHC may be helpful in poorly differentiated neoplasms. Usually primary colonic adenocarcinomas show immunoreactivity with cytokeratin 20 (95%) and CDX2 (intestinal epithelium marker). Difficulty arises in some poorly differentiated tumors that have lost antigenicity or show lineage infidelity.

### 26. What is the differential diagnosis of stromal tumors in colon?

- Gastrointestinal stromal tumors (GISTs) ([E-Figure 59-24](#)) in the GI tract most commonly occur in the stomach (50%), followed by the small bowel (25%), colon and rectum (10%), and, least commonly, esophagus (5%). Histologically, these can be spindled or epithelioid and show strong reactivity with CD117 (95%), and 60% to 70% show positive staining with CD34. These are also stain positive with DOG 1 antibody (including some of KIT negative tumors). Approximately one third can also show reactivity with smooth muscle markers (smooth muscle actin).

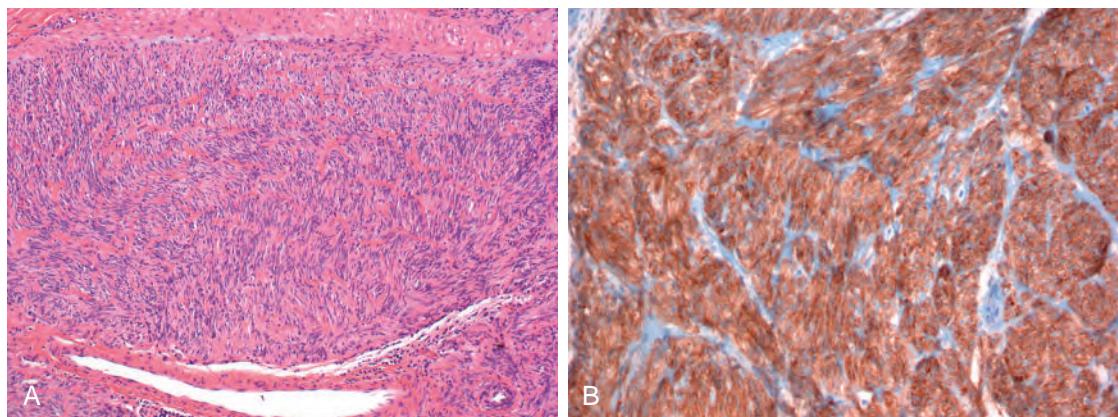


**Figure 59-25.** A, Leiomyoma. Submucosal spindle cell nodule (hematoxylin and eosin stain) (B) positive staining with smooth muscle actin immunostain.

These arise from interstitial cells of Cajal, and KIT mutations are seen in 85% to 90% of GISTs.

Approximately 5% show mutation within the PDGFRA gene and these are usually seen in gastric GISTs. These have epithelioid morphologic characteristics and a less aggressive clinical course. All the GISTs are potentially aggressive. The clinical behavior can be predicted on the basis of size, mitotic figures, and site. Gastric GISTs have a better prognosis than the small bowel GISTs. The GISTs with exon 11 mutation have a low risk for progressive disease (as opposed to exon 9 mutation) and respond better to imatinib mesylate in the metastatic disease setting.

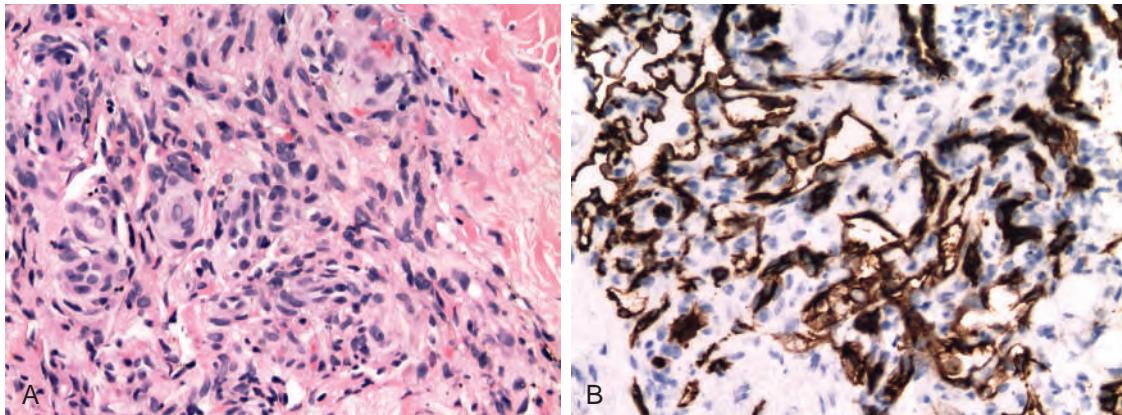
- *Schwannomas* are well-circumscribed, nonencapsulated spindle cell tumors with strong immunoreactivity with S100 protein. Dense lymphoid cuffing is seen around schwannomas.
- *Leiomyoma* ([Figure 59-25](#)) is another spindle cell tumor arising from the smooth muscle in muscularis mucosae that shows strong positive immunostaining with smooth muscle actin.
- *Lipoma* is a sporadic, benign, well-circumscribed submucosal lesion of adipose tissue.



**E-Figure 59-24.** A, Gastrointestinal stromal tumor (GIST). Spindle cell tumor in the submucosa (hematoxylin and eosin stain). B, GIST. CD117 immunostain showing strong staining in the spindle cells.

### Vascular Lesions

- Kaposi sarcoma shows proliferation of slitlike vascular channels, spindle cells, and inflammatory infiltrate (Figure 59-26). It is seen in some patients with human immunodeficiency virus infection and is associated with human herpesvirus 8.
- Other lesions include hemangiomas, lymphangiomas, vascular malformations, and, rarely, angiosarcomas.



**Figure 59-26.** Photomicrographs of Kaposi sarcoma. **A**, Proliferation of irregular, slitlike vessels (hematoxylin and eosin stain) highlighted by **(B)** the endothelial cell marker CD31.

## DISEASES OF THE APPENDIX

### 27. What is the effect of IBD on the appendix?

The appendix is involved in 50% of cases with ileal Crohn's disease and UC with cecal involvement. Isolated involvement is rare.

### 28. Describe the mucinous lesions of the appendix.

- *Mucocele* is a cystically dilated appendiceal lumen containing mucus. It can be nonneoplastic or neoplastic. Any obstruction of the lumen can give rise to mucocele.
- In *low-grade mucinous adenocarcinomas, with pseudomyxoma peritonei*, the mucin/tumor cells dissect through the wall of the appendix into the peritoneum. Most cases of synchronous tumors in the ovary and appendix are now considered metastases from the appendiceal tumor. Acellular pools of mucin pose a diagnostic problem. A diagnosis of adenoma (or cystadenoma) should be rendered only if the entire muscularis mucosae is intact. A diagnosis of "low-grade appendiceal mucinous neoplasm or LAMN" previously known as "uncertain malignant potential" is favored in the cases in which intact muscularis mucosae cannot be seen.
- *Mucinous adenocarcinomas with mucinous carcinomatosis* include signet ring cell carcinomas, invasive well-differentiated carcinomas, and cystadenocarcinoma.

### 29. What is the incidence of carcinoid tumors in appendectomy specimens (performed for appendicitis)?

Appendiceal carcinoid has been reported in 0.3% to 0.9% of appendectomy specimens. It is the most common appendiceal neoplasm. The functioning tumors are commonly serotonin-producing neoplasms. The risk factors for malignancy include size greater than 2 cm and invasion of mesoappendix.

### 30. What are the histologic types of mixed endocrine-exocrine neoplasms?

These include goblet cell carcinoid, tubular carcinoid, and mixed carcinoid-adenocarcinoma. Mixed carcinoid-adenocarcinoma carries the worst prognosis.

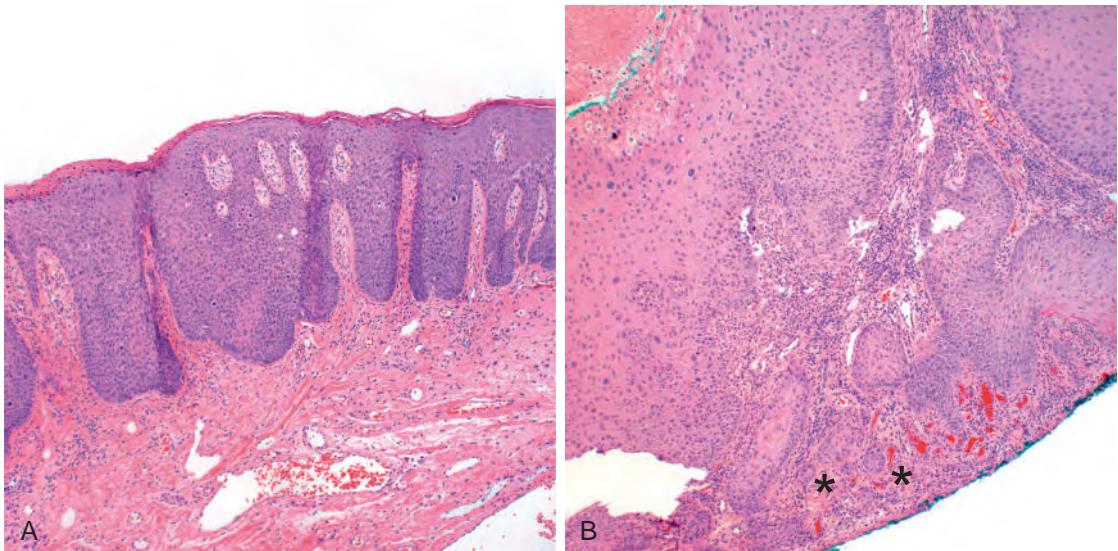
## DISEASES OF THE ANAL CANAL

### 31. The typical findings of Hirschsprung's disease include absence of ganglion cells. What other stain can help support the diagnosis, and what is the ideal site of biopsy?

Acetylcholinesterase stain highlights the proliferation of thickened nerve fibers in the lamina propria and muscularis mucosae. This stain is done on the frozen tissue. So, ideally, two biopsy samples are sent—one in formalin and another fresh for freezing. The site of biopsy is at least 2 cm above the dentate line. The lower rectum (adjacent to dentate line) is physiologically hypoganglionic. Also, submucosa should be included in the biopsy samples to assess nerves in both the lamina propria and muscularis mucosae.

**32. How is anal intraepithelial neoplasia (AIN) graded and what is the risk of progression to squamous cell carcinoma (SCC)?**

AIN is graded as low grade (AIN I or mild dysplasia) and high grade (encompasses AIN II and AIN III or moderate and severe dysplasia or carcinoma in situ, respectively). The term *Bowen disease* (Figure 59-27A) is used for lesions with severe dysplasia (carcinoma in situ) seen at the anal verge or perianal skin. The high-grade lesions are associated with high-risk human papillomavirus 16 and 18, among others. These lesions are known to recur after local treatment. The risk of progression to SCC (see Figure 59-27B) is low (approximately 5%).



**Figure 59-27.** A, Bowen disease. Note the thickened squamous epithelium showing severe full-thickness dysplasia. B, Squamous cell carcinoma (asterisks) at another focus within the same specimen. Hematoxylin and eosin stain.

**33. What are the cells of origin and the immunohistochemical profile of Paget disease?**

The Paget cells (intraepithelial large cells with pale pink cytoplasm and large nuclei) are believed to be of apocrine lineage and show immunoreactivity with low-molecular-weight keratins Cam 5.2, CK7, and carcinoembryonic antigen. Mucin stain may be positive. The differential diagnosis includes pagetoid spread from adjacent CRC and melanoma in-situ. The immunoprofile helps.

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#### BIBLIOGRAPHY

- Al-Daraji WI, Montgomery E. Serrated polyps of the large intestine: A practical approach. *Pathol Case Rev* 2007;12:129–35.
- Carvajal-Carmona LG, Howarth KM, Lockett M, et al. Molecular classification and genetic pathways in hyperplastic polyposis syndrome. *J Pathol* 2007;212:378–85.
- Check W. Lynch syndrome testing—When and how? *CAP Today* 2007. <http://www.cap.org>.
- Demetri GD, Benjamin RS, Blanke CD, et al. NCCN Task Force report: Management of patients with gastrointestinal stromal tumor (GIST)—Update of the NCCN clinical practice guidelines. *JNCCN* 2007;5(Suppl. 2):S1–S29.
- Hamilton SR, Altonen LA, editors. WHO classification of tumors: Pathology and genetics of the digestive system. Lyon: IARC Press; 2000. p. 96–8, 105–136.
- Issacson PG, Muller-Hermelink HK, Piris MA, et al. WHO classification of tumors: Tumors of hematopoietic and lymphoid tissues. Lyon: IARC Press, pp. 157–160.
- Jenkins MA, Hayashi S, O'Shea A, et al. Pathology features in Bethesda guidelines predict colorectal cancer microsatellite instability: A population-based study. *Gastroenterology* 2007;133:48–56.
- Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity (“celiac sprue”). *Gastroenterology* 1992;102:330–54.
- Rubio-Tapia A, Hill ID, Kelly CP, et al. ACG clinical guidelines: Diagnosis and management of celiac disease. *Am J Gastroenterol* 2013;108:656–76.
- Miettinen M, Lasota J. Gastrointestinal stromal tumors: Pathology and prognosis at different sites. *Semin Diagn Pathol* 2006;23:111–9.
- Montgomery EA. Biopsy interpretation of the gastrointestinal tract mucosa. Philadelphia: Lippincott Williams & Wilkins; 2006.
- Noffsinger A, Fenoglio-Presler C, Maru D, et al. Gastrointestinal diseases: Atlas of nontumor pathology, first series. Washington, DC: American Registry of Pathology in collaboration with Armed Forces Institute of Pathology, pp. 635–636.

13. Odze R. Diagnostic problems and advances in inflammatory bowel disease. *Mod Pathol* 2003;16(4):347–58.
14. Snover DC, Jass JR, Fenoglio-Preiser C, et al. Serrated polyps of the large intestine: A morphologic and molecular review of an evolving concept. *Am J Clin Pathol* 2005;124:380–91.
15. Snover DC, Weisdorf SA, Vercellotti GM, et al. A histopathologic study of gastric and small intestinal graft-versus-host disease following allogenic bone marrow transplantation. *Hum Pathol* 1985;16:387–92.
16. Tchana-Sato V, Detry O, Polus M, et al. Carcinoid tumor of appendix: A consecutive series from 1237 appendectomies. *World J Gastroenterol* 2006;12:6699–701.
17. Torlakovic EE, Gomez JD, Driman DK, et al. Sessile serrated adenoma (SSA) vs traditional serrated adenoma (TSA). *Am J Surg Pathol* 2008;32:21–9.

**Websites**

The Internet Pathology Laboratory for Medical Education. Accessed September 22, 2014, from <http://library.med.utah.edu/WebPath/webpath.html#MENU>.

[PathologyOutlines.com](http://www.pathologyoutlines.com). Esophagus chapter. Accessed September 22, 2014, from [www.pathologyoutlines.com/esophagusp.html](http://www.pathologyoutlines.com/esophagusp.html).

University of Iowa Histology Homepage. Accessed September 22, 2014, from [www.path.uiowa.edu/virtualslidebox/nlm\\_histology/content\\_index\\_db.html](http://www.path.uiowa.edu/virtualslidebox/nlm_histology/content_index_db.html).

# FOREIGN BODIES AND THE GASTROINTESTINAL TRACT

George Triadafilopoulos, MD, DSc

## 1. How common are foreign bodies in the gastrointestinal (GI) tract?

Every year, millions of foreign bodies enter the GI tract through the mouth or anus, and approximately 1500 to 3000 people die from their ingestion. However, only approximately 10% to 20% of foreign bodies require removal through some form of therapeutic intervention; the rest pass through the GI tract without incident.

## 2. Which populations are at risk for foreign-body ingestion?

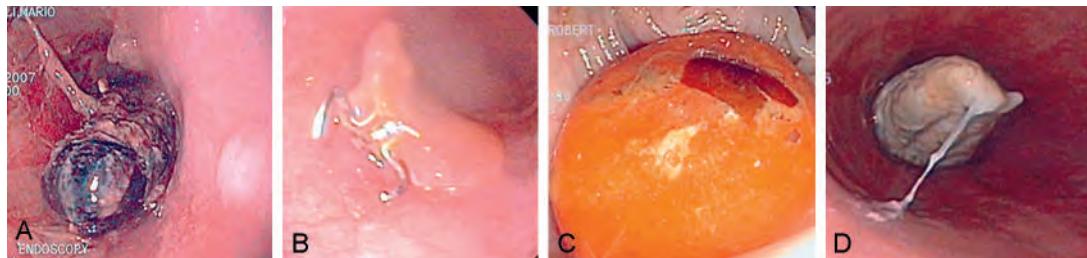
Eighty percent of foreign-body ingestions occur in children, whereas almost all foreign bodies inserted into the rectum are described in adults. Groups at increased risk for foreign-body ingestion include psychiatric patients, prisoners, and those who frequently and excessively use alcohol or sedative-hypnotic medications. Also at risk are older adult subjects, who may have poorly fitting dentures, impaired cognitive function resulting from medications, or dementia or dysphagia after stroke. Intentional ingestion of foreign objects is well described in smugglers of illicit drugs, jewelry, or other valuable items.

## 3. Which areas of the GI tract lead to problems in the passage of foreign bodies?

Several areas of anatomic or physiologic narrowing exist along the GI lumen and may compromise the spontaneous passage of foreign bodies: cricopharyngeal muscle, extrinsic compression of the middle esophagus from the aortic arch, lower esophageal sphincter, pylorus, ileocecal valve, rectal valves of Houston, and anal sphincters. In addition, numerous pathologic abnormalities, such as strictures or tumors, may impair spontaneous passage of foreign bodies (see [Question 12](#)).

## 4. What objects are commonly ingested?

The object ingested most commonly by children is a coin. Meat boluses impacted above an esophageal stricture, Schatzki ring, or eosinophilic esophagitis account for most adult cases ([Figure 60-1](#)). Accidental loss of sex stimulant devices account for more than one half of foreign objects introduced through the anus.



**Figure 60-1.** Several examples of foreign bodies in the gastrointestinal tract. **A**, Meat bolus (3 × 1 cm) impacted in the mid esophagus of a patient with diffuse esophageal spasm. **B**, Inadvertently swallowed partial denture (3 × 2 cm), with exposed hooks, in the esophagus of a patient without underlying esophageal pathologic findings. **C**, Dried apricot (2 × 2 cm) in the colon of a patient with intermittent abdominal pain. **D**, Chicken bolus (2 × 2 cm) impacted in distal esophagus of a patient with underlying eosinophilic esophagitis.

## 5. Describe the typical clinical presentation of foreign-body ingestion.

Adults trace the onset of symptoms to the ingestion of a specific meal or foreign body. Most commonly, acute dysphagia, odynophagia, and chest pain reflect underlying esophageal obstruction. Respiratory distress, stridor, and inability to handle oral secretions suggest the need for urgent intervention. Persons with developmental disabilities, psychiatric patients, or children may remain asymptomatic for months after ingestion, or they may not volunteer the history. Patients with impacted anorectal foreign bodies may relate a wide variety of medical histories to account for their predicament, ranging from accidents or assault to medical remedies.

## 6. What is suggested by respiratory symptoms related to foreign-body ingestion?

Patients with wheezing, stridor, cough, or dyspnea after foreign-body ingestion may have foreign-body entrapment in the hypopharynx, trachea, pyriform sinus, or Zenker diverticulum.

### 7. Do ingested sharp objects perforate the intestine?

On rare occasions, sharp objects, such as pins, needles, nails, and toothpicks, may perforate the intestine, but in 70% to 90% of cases they pass through the alimentary tract without complication. Two phenomena in the intestine allow safe passage: (1) foreign bodies pass with axial flow down the lumen, and (2) reflex relaxation and slowing of peristalsis cause sharp objects to turn around in the lumen so that the sharp end trails down the intestine. In the colon, the foreign object is centered in the fecal bolus, which further protects the bowel wall.

### 8. Why is it important to identify the type of foreign body ingested?

Although most foreign bodies traverse the GI tract without complication, specific exceptions require special attention. Button alkaline batteries may cause coagulation necrosis in the esophagus, but once they reach the stomach, gastric acid neutralizes their risk. Sharp objects can perforate any part of the alimentary tract. There is no known absolute size of a foreign body that dictates surgical intervention because the shape, composition, and sharpness of edges may play a key role. In general, inert, blunt objects measuring  $3 \times 3$  cm pass through the intestine, whereas objects longer than 6 cm may become lodged in the C-loop of the duodenum. Ingested magnets from magnetic toy sets may be attracted to one another across multiple loops of bowel and lead to intestinal perforation caused by bowel wall erosion and necrosis between the magnets.

### 9. How urgent is removal of a foreign body after ingestion?

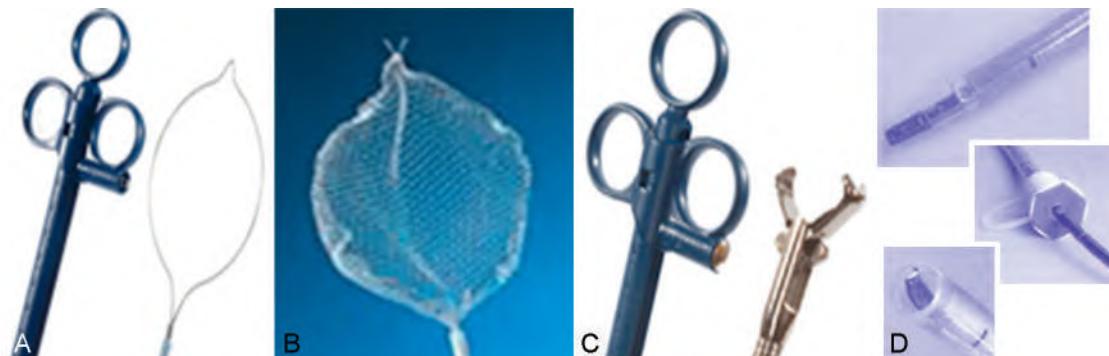
Button batteries or magnets, ingested typically by small children, need to be removed urgently because of the severe trauma that they may cause in the esophagus. Any sharp object that carries a high risk for perforation should be removed as soon as possible before it passes to a level that is beyond the reach of an endoscope. For the same reasons, long objects (larger than 6 cm) should be removed when identified. Finally, objects lodged in the esophagus that compromise ability to handle oral secretions should be removed urgently to reduce the risk of aspiration.

### 10. Describe the signs and symptoms of a complication related to foreign-body ingestion.

Respiratory symptoms suggest entrapment of the foreign body in the hypopharynx, trachea, pyriform sinus, or Zenker diverticulum (see Question 6). Sharp objects may penetrate, obstruct, or perforate the esophagus or intestine, presenting with chest, neck, or abdominal pain that varies from mild discomfort to symptoms and signs of acute abdomen. Injury to the esophagus can lead to hematemesis, fever, tachycardia, neck swelling, and crepitus. Excessive drooling and inability to swallow saliva suggest complete esophageal obstruction. Abdominal distention, vomiting, and hyperactive bowel sounds suggest intestinal obstruction. Hypoactive or absent bowel sounds, guarding, rebound, and abdominal pain are seen with wall penetration or free perforation. Aortoenteric fistula caused by ingestion of a sharp foreign body may cause massive hematemesis.

### 11. How should foreign bodies be removed?

Once identified, nearly all objects can be removed endoscopically. Other modalities have been used with variable success, although major complications have been reported. Prior to endoscopy, a rehearsal of what will be done using retrieval devices that would capture similar-shaped foreign objects is useful. Several endoscopic retrieval tools, such as rat tooth, grasping forceps, baskets, snares, Roth retrieval net, and overtube, are available (Figure 60-2). Protection of the airway, especially in children or combative or older adult patients with poor reflexes and cardiopulmonary reserve, is essential. Consultation with a surgeon is appropriate for cases in which perforation or other major complications are probable. Minimally invasive surgery alone or combined with endoscopy is used increasingly.



**Figure 60-2.** Several examples of foreign body removal tools: **A**, Standard polypectomy snare. **B**, Roth net. **C**, Rat-tooth grasper. **D**, Overtube for extraction of sharp foreign bodies.

**12. Which anatomic and functional defects of the GI tract contribute to foreign-body obstruction?**

See Table 60-1.

**Table 60-1.** Anatomic and Functional Defects of the Gastrointestinal Tract That Contribute to Foreign-Body Obstruction

INTESTINAL SITE	ANATOMIC DEFECT	FUNCTIONAL DEFECT
Esophagus	Stenosis, atresia, rings, webs, benign/malignant stricture, eosinophilic esophagitis, diverticula, vascular anomalies	Scleroderma, achalasia, Chagas disease
Stomach	Pyloric stenosis (congenital, malignancy, postoperative, gastroduodenal ulcer disease)	Gastroparesis (uremia, diabetes, hypothyroidism)
Intestine	Postoperative adhesion, Meckel diverticulum, strictures (ischemic, anastomotic, Crohn's disease), malignancy	Idiopathic intestinal pseudoobstruction, scleroderma
Colon	Strictures (ischemic, anastomotic, ulcerative colitis, Crohn's disease, radiation, trauma, infection, surgery), diverticular disease, malignancy	Cathartic colon, idiopathic constipation, familial megacolon, idiopathic intestinal pseudoobstruction
Anus	Stenosis (Crohn's disease, trauma, radiation, infection, surgery)	Hirschsprung's disease

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

#### BIBLIOGRAPHY

- Arana A, Hauser B, Hachimi-Idrissi S, et al. Management of ingested foreign bodies in childhood and review of the literature. *Eur J Pediatr* 2001;160:468–72.
- Barone JE, Yee J, Nealon Jr. TF. Management of foreign bodies and trauma of the rectum. *Surg Gynecol Obstet* 1983;156:453–7.
- Bounds BC. Endoscopic retrieval devices. *Tech Gastrointest Endosc* 2006;8:16–21.
- Busch DB, Starling JR. Rectal foreign bodies: Case reports and a comprehensive review of the world's literature. *Surgery* 1986;100:512–9.
- Caratozzolo E, Massani M, Antoniutti M, et al. Combined endoscopic and laparoscopic removal of ingested large foreign bodies: Case report and decisional algorithm. *Surg Endosc* 2001;15:1226.
- Cheng W, Tam PK. Foreign-body ingestion in children: Experience with 1,265 cases. *J Pediatr Surg* 1999;34:1472–6.
- Katsinelos P, Kountouras J, Paroutoglou G, et al. Endoscopic techniques and management of foreign body ingestion and food bolus impaction in the upper gastrointestinal tract: A retrospective analysis of 139 cases. *J Clin Gastroenterol* 2006;40:784–9.
- Li ZS, Sun ZX, Zou DW, et al. Endoscopic management of foreign bodies in the upper-GI tract: Experience with 1088 cases in China. *Gastrointest Endosc* 2006;64:485–92.
- Mehta D, Attia M, Quintana E, et al. Glucagon use for esophageal coin dislodgment in children: A prospective, double-blind, placebo-controlled trial. *Acad Emerg Med* 2001;8:200–3.
- Mosca S, Manes G, Martino R, et al. Endoscopic management of foreign bodies in the upper gastrointestinal tract: Report on a series of 414 adult patients. *Endoscopy* 2001;33:692–6.
- Pavlidis TE, Marakis GN, Triantafyllou A, et al. Management of ingested foreign bodies. How justifiable is a waiting policy? *Surg Laparosc Endosc Percutan Tech* 2008;18:286–7.
- Rodríguez-Hermosa JI, Codina-Cazador A, Ruiz B, et al. Management of foreign bodies in the rectum. *Colorectal Dis* 2007;9:543–8.

# FUNCTIONAL GASTROINTESTINAL DISORDERS AND IRRITABLE BOWEL

*Anthony Lembo, MD, and Vivian Cheng, MD*

## 1. What is irritable bowel syndrome (IBS)?

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by chronic or recurrent abdominal pain or discomfort, usually in the lower abdomen, that is associated with altered bowel habits (diarrhea, constipation or a combination of diarrhea and constipation). Bloating, distention, and disordered defecation are commonly associated features. IBS is a disorder of bowel function and is characterized by abnormalities in motility, sensation, and perception. The most commonly accepted criteria used to diagnosis IBS is the Rome III Criteria\* which is shown below:

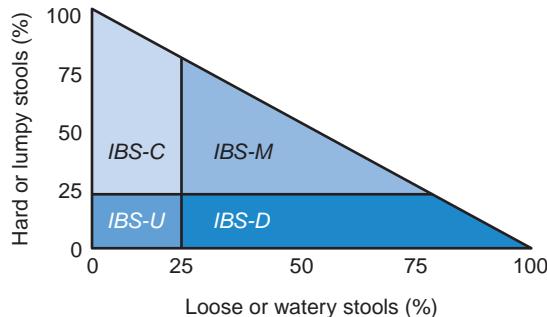
*Rome III Criteria Diagnostic criterion*

Recurrent abdominal pain or discomfort<sup>†</sup> at least 3 days/month in the last 3 months associated with *two or more* of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

## 2. How are the different IBS subtypes distinguished?

IBS subtypes are differentiated based on stool form and not stool frequency. Using the Rome III definition, subtypes are differentiated based on the percent of bowel movements with hard or lumpy stools versus those with loose or watery stools. It should be noted that patients frequently switch between subtypes. Approximately one third of patients with IBS have IBS with diarrhea (IBS-D), one third have IBS with constipation (IBS-C), and the remainder have IBS with mixed constipation and diarrhea (IBS-M) (Figure 61-1).



**Figure 61-1.** Irritable bowel syndrome (IBS) subtypes and stool form. IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed hard and loose stools over periods of weeks and months; IBS-U, unsubtyped IBS.

## 3. How common is IBS?

Approximately 10% to 15% of the population in Western societies report symptoms consistent with IBS. Younger individuals (25-45 years of age) are more likely to report IBS symptoms as compared with older individuals, although IBS can occur at any age. In some cases, symptoms of IBS date back to childhood.

Women report IBS symptoms more often than men. In particular, women with IBS tend to experience more symptoms of constipation and abdominal discomfort, especially bloating, whereas men with IBS report more symptoms of diarrhea. In primary care clinics in Western societies, the female-to-male ratio of IBS is 3-4:1, whereas in specialty clinics, it can be as high as 5-6:1. In contrast, in the general population, the female-to-male ratio is approximately 1.5-2:1. Thus not only do women have symptoms more frequently than men, but they are also more likely to seek medical attention for their symptoms.

\*Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

<sup>†</sup>Discomfort means an uncomfortable sensation not described as pain.

#### **4. What is the effect of IBS on quality of life?**

IBS can have a significant negative effect on health-related quality of life (HR-QOL). However, because IBS is not a life-threatening illness many clinicians underestimate its effect on individuals, family, and friends. Using the standard health-related questionnaire (SF-36), individuals with IBS symptoms report lower scores on all scales compared with the general population. Compared with other illnesses such as diabetes and depression, IBS patients have similar or significantly worse HR-QOL scores.

#### **5. What is the economic burden of IBS?**

Only approximately 25% to 50% of individuals with IBS symptoms ever seek health care. Nevertheless, given the prevalence of symptoms, IBS has a significant economic burden. IBS is one of the top 10 reasons for consultation with a primary care physician, and the most common reason for consulting a gastroenterologist. Nearly one third of all consultations by gastroenterologists are for IBS symptoms. In the United States alone, there are more than 3.5 million physician visits and more than 2.2 million prescriptions written for IBS. In addition, patients with IBS undergo a multitude of diagnostic and therapeutic procedures, which are often unnecessary and sometimes dangerous. The direct medical charges in the United States alone attributed to IBS have been estimated to be more than \$10 billion per year (excluding prescription and over-the-counter drug costs). In addition, the indirect costs associated with IBS are estimated to be significantly higher than direct medical costs.

#### **6. What is the current belief about the causes and risk factors for IBS?**

The pathogenesis of IBS appears to be multifactorial. Factors believed to play a role in the pathogenesis of IBS include heritability and genetics, environment and social learning, diet, intestinal microbiota, low-grade inflammation, central processing of visceral sensations, gut dysmotility, and disturbances in the neuroendocrine system of the gut.

IBS is the result of a complex interaction between psychosocial and physiologic factors via the brain-gut axis. Early life factors, such as family attitudes toward illness, major loss, or abuse history, or, possibly, genetic predisposition, may influence a person's psychosocial development (e.g., psychological state, coping skills, social support, or susceptibility to life stress) or gut dysfunction (e.g., gut dysmotility or hypersensitivity). Although closely interrelated, the importance of any one factor in the generation of IBS symptoms varies greatly between individuals.

#### **7. What is the role of intestinal dysmotility in IBS?**

Although abnormal motor patterns have been found in patients with IBS, these patterns are also found in healthy individuals and are therefore not diagnostic for IBS. IBS patients have both a reduction and an increase in the number of contractions per minute in IBS patients compared with healthy individuals. However, these abnormal motility patterns rarely correlate with IBS symptoms and thus are not sufficient to explain many of the symptoms associated with IBS.

#### **8. What is the role of abnormal central processing of pain?**

Abnormal central processing, such as down-regulation of incoming visceral sensations, has also been found in patients with IBS. In IBS patients, rectal distention fails to activate the perigenual anterior cingulate cortex (ACC), the area containing large amounts of B-endorphin activity, which may serve to down-regulate pain, but instead shows increased activation of the rostral ACC, an area associated with unpleasantness and attention. Also, patients with IBS and a history of abuse reported greater activation of the middle and posterior dorsal cingulate regions, and reduced activity of the supragenual anterior cingulate, and are implicated in pain inhibition and arousal. Therefore IBS patients may have an alteration of the pain modulatory system, as well as up-regulation of afferent signals at the primary splanchnic afferent or its spinal connections.

#### **9. What is the role of food in IBS?**

Most IBS patients report a worsening of symptoms following ingestion of certain foods. The most commonly implicated foods are milk and dairy products, wheat products, onions, peas and beans, hot spices, cabbage, certain meats, smoked products, fried food, and caffeine. However, the dietary composition of IBS patients is similar to the general community. There is no documented evidence showing that a food allergy or intolerance plays a role in IBS symptoms.

#### **10. What are FODMAPs?**

FODMAPs are fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. They include fructose, lactose, fructans, galactans, and sugar alcohols, such as sorbitol, maltitol, mannitol, xylitol, and isomalt. Fructose and lactose are present in apples, pears, watermelon, honey, fruit juices, dried fruits, milk, and dairy products. Polyols are used as a sugar replacement in low-calorie food products. Galactans and fructans are present in common dietary constituents, such as wheat, rye, garlic, onions, legumes, cabbage, artichokes, leeks, asparagus, lentils, inulin, soy, Brussels sprouts, and broccoli. Recent studies suggest that some patients with IBS have improvement in symptoms on a low FODMAP diet, although further studies are needed to determine which patients are most likely to improve.

#### **11. What is the role of fiber in IBS?**

Although increasing dietary fiber continues to be a standard recommendation for patients with IBS, clinical practice has shown that increased fiber intake in these patients increases abdominal pain, bloating, and

distention. IBS patients assigned to fiber treatment showed persistent symptoms or no improvement in symptoms after treatment compared with patients taking a placebo or a low-fiber diet. Other studies have shown that although water-insoluble fiber intake did not improve IBS symptoms, soluble-fiber intake was effective in improving overall IBS symptom. It is noteworthy that the role of FODMAPs and fiber on IBS symptoms is associated with intestinal flora. The presence of bacteria that break down FODMAPs and fiber and produce gas, such as *Clostridia spp.*, can cause distention of the large intestine with abdominal discomfort or pain.

## 12. What is the role of the intestinal microbiota in IBS?

Several studies have suggested that some differences exist in the intestinal microflora of IBS patients compared with healthy individuals. Using conventional microbiologic techniques, fecal microfloras of IBS patients have been shown to have higher numbers of facultative organisms, such as *Klebsiella* species and enterococci, and lower numbers of *Enterobacteriaceae*, *lactobacilli*, and *bifidobacteria*. Using more sophisticated DNA techniques, investigators have shown significant differences between IBS patients and controls for several bacterial genera, including *Coprococcus*, *Collinsella*, and *Coprobacillus*. In addition, IBS-D and IBS-C also appear to have distinct microbial populations.

## 13. What is the significance of visceral hypersensitivity in IBS?

IBS patients have lower pain thresholds to balloon-distention volumes specific to the GI tract (i.e., rectosigmoid, descending colon, small intestine, stomach, and esophagus) in comparison with healthy individuals.

The cause of visceral hypersensitivity in IBS is not completely understood. However, researchers now believe that noxious stimuli can change the synaptic efficiency of peripheral and central neurons. This may occur through altered release of serotonin (5-HT) from the enteroenteric cells in the myenteric plexus or release of inflammatory cytokines from activated immune or inflammatory cells in response to infection or injury. Through a process known as the *wind-up*, neurons can develop a *pain memory* that can persist long after the noxious stimulus is removed. IBS patients may also be prone to developing sensitization. Repetitive sigmoid contractions, such as those that may occur during intense stress, could induce sensitization in a person predisposed to developing IBS, thereby causing rectosigmoid hypersensitivity.

Although 95% of IBS patients have rectal sensory abnormalities, rectal sensitivity testing is not currently widely used in the diagnosis or management of IBS, partly because of the lack of standardization in balloon-distention protocols, the limited correlation between symptom severity or response to therapy, and the significant overlap with other GI diseases. Therefore, its clinical utility in making a definitive diagnosis of IBS is limited.

## 14. What is postinfectious IBS (PI-IBS)?

IBS symptoms develop in approximately 10% of healthy individuals after an infectious gastroenteritis. PI-IBS is most commonly reported after a bacterial infection such as *Campylobacter*, *Salmonella*, and *Shigella*, but has also been reported after viral, bacterial, protozoa, and nematode infections. Even after clearing the infection, there remains an increase in inflammatory (including CD3 lymphocytes, CD8 intraepithelial lymphocytes, and calprotectin-positive macrophages) and neuroendocrine cells that can release cytokines, serotonin, and other molecules that are capable of stimulating motor and sensory neurons in the GI tract.

Risk factors for developing PI-IBS in persons who have had gastroenteritis are (1) female gender, (2) age younger than 60 years, (3) absence of vomiting, and (4) prolonged diarrhea with the infection. Additionally, anxiety, neurosis, somatization, and stressful life events before or during the infection also appear to be risk factors for determining who will develop IBS.

## 15. What is the role of stress in IBS?

More than half of IBS patients associate the onset of their IBS symptoms with a stressful life event such as a family death, a surgical procedure, unemployment, financial problems, or marital difficulties. Although most people have experienced the effect of anxiety and stress on their GI tract with urgency, cramps, constipation, or diarrhea, IBS patients appear to have an exaggerated GI response (i.e., increased rectosigmoid contractions) to stress.

## 16. What are the common comorbid conditions associated with IBS?

Common comorbid conditions associated with IBS include fibromyalgia, chronic fatigue syndrome, chronic pelvic pain, dysmenorrhea or premenstrual syndrome, temporomandibular joint disorder, interstitial cystitis, gastroesophageal reflux disease, and functional dyspepsia. These comorbid conditions typically occur more often in women than in men.

## 17. How is IBS diagnosed?

IBS can generally be diagnosed based on symptoms without additional testing beyond a careful history, general physical examination, and routine laboratory studies in patients who meet the Rome criteria and who do not have alarm features.

## 18. What are the typical symptoms of IBS?

The key defining symptoms of IBS are abdominal pain or discomfort that is associated with alteration in bowel function. The abdominal symptoms are typically located in the lower abdomen, but frequently move throughout

the abdomen. These symptoms are often intermittent but can occur continuously. Although the Rome III criteria require these symptoms be present only 3 days per month, they often occur more frequently. Other symptoms that are common but not essential for the diagnosis include bloating or feeling of abdominal distention, urgency, and incomplete evacuation.

Individuals with IBS often have other GI and non-GI symptoms including upper GI symptoms (i.e., dyspepsia, heartburn, and nausea). Extraintestinal symptoms commonly present in patients with IBS, including urinary frequency and urgency (especially in women), sexual dysfunction, fibromyalgia and other rheumatologic conditions, dyspareunia, poor sleep, low back pain, headaches, chronic fatigue, loss of concentration, and insomnia. The number of these symptoms tends to increase with the severity of IBS. The presence of one or more of these intestinal or extraintestinal symptoms does not discriminate between IBS and organic intestinal diseases.

#### **19. When is a colonoscopy necessary in diagnosing IBS?**

A colonoscopy is routinely recommended only in patients older than 50 years of age as per the colon cancer screening guidelines. A colonoscopy for those younger than 50 years of age may be appropriate in patients with significant diarrhea or refractory symptoms or if other alarm features are present (see Question 20). It should be noted that if a colonoscopy is performed on a patient with suspected IBS with diarrhea, random biopsies should be obtained to exclude microscopic colitis, as a recent study found microscopic colitis present in 2.5% of patients older than the age of 35.

#### **20. What alarm features warrant further testing in diagnosing IBS?**

Alarm features such as rectal bleeding, unintended weight loss, fever, age greater than 50 years, nocturnal awakening from sleep, or a family history of colon cancer or inflammatory bowel disease may suggest the presence of an organic disease.

#### **21. What is the role of fructose intolerance?**

Fructose is the sweetest of the sugars and therefore is commonly used as a sweetener in soft drinks, chocolate, syrups, and jams. Its intake in Western diets has increased tenfold in the past 15 years. Fructose is also naturally present in many fruits and vegetables, and in honey. Up to one half of healthy adults have evidence of malabsorption after ingesting 25 g of fructose (10% concentration). Fructose intolerance can cause symptoms similar to those found in IBS; however, the prevalence of fructose malabsorption in IBS is similar to that in healthy individuals and is unlikely to be the cause of IBS in most patients. A fructose-free diet has been suggested to improve IBS symptoms in patients with fructose malabsorption. However, because of methodologic limitations, definitive conclusions cannot be made about the effectiveness of a fructose-free diet in IBS.

#### **22. What is the role of lactose intolerance?**

Lactose intolerance can cause symptoms similar to those associated with IBS. The prevalence of lactose intolerance is slightly higher in adults with IBS; however, lactose intolerance is not the cause of IBS in most patients. Nevertheless, because of the similarity in symptoms, patients with symptoms suggestive of lactose malabsorption should be given an empiric trial of a lactose-free diet or a lactose hydrogen breath test, which measures the exhaled hydrogen produced from colonic bacterial degradation of lactose.

Patients who respond to a lactose-free diet should be encouraged to gradually reintroduce lactose into their diet to determine if and when symptoms recur. Most people with lactose intolerance can consume up to 1.25 cups (280 mL) of milk per day without significant symptoms. Avoidance of lactose can lead to significant reduction in calcium intake, which may increase the risk of osteoporosis. Therefore patients on a restricted lactose diet should be advised to increase their calcium intake from other sources. Live-culture yogurt is another alternative source of calcium that is well tolerated by many patients with lactose intolerance.

#### **23. Should all patients with suspected IBS have celiac disease testing?**

It is recommended by the American College of Gastroenterology Task Force that serologic testing for celiac disease (i.e., tissue transglutaminase antibody) be performed on all patients with suspected IBS-D and IBS-M. Although previous studies have found an increased incidence of celiac disease among patients with IBS, a recent U.S. study found a similar incidence (0.4%) in IBS patients compared with healthy controls.

#### **24. What is the role of small intestinal bacterial overgrowth (SIBO) in IBS?**

SIBO is a condition in which excessive levels of bacteria, predominantly the colonic-type species, are present in the small intestine. SIBO appears to be more common in IBS, although the reported incidence of SIBO varies according to the detection method employed. A recent systematic review and metaanalysis found the rate of a positive breath test (lactulose and glucose) to be 54% (95% confidence interval [CI], 32%-76%) and 31% (95% CI, 14%-50%), respectively. The prevalence of a positive jejunal aspirate and culture was 4% to 12%. The odds ratio for any positive test for SIBO in IBS was 3.5 to 4.7, depending on the criteria used to define a positive test.

#### **25. How is SIBO tested?**

SIBO can be evaluated by breath testing and, more recently, small bowel culture. Although there are no definitive recommendations on the use of breath testing to diagnose SIBO, this test has become popular after evidence suggesting that IBS patients were more likely to have a positive SIBO breath test result. Breath

testing should be used to evaluate patients for SIBO if they report bloating and distention as a significant complaint. Breath testing for SIBO can be performed with different substrates, although lactulose, a nonabsorbed carbohydrate, is most commonly used (Figure 61-2).



**Figure 61-2.** Carbohydrate breath testing for small intestinal bacterial overgrowth.

#### 26. What is the treatment approach to IBS?

The first avenue of treatment in all IBS patients is lifestyle modification, including moderate or vigorous exercise (if tolerated), a well-balanced diet, stress reduction, and plenty of sleep. If unsuccessful, pharmacologic treatments based on the predominant symptom and severity should be considered. In patients with severe symptoms or psychological comorbidities (e.g., anxiety, depression), a multidisciplinary approach should be considered as many of these patients may also benefit from the addition of psychological intervention.

#### 27. Can diet modification improve IBS symptoms?

Most patients report that certain foods exacerbate their symptoms and some have adopted an inappropriately restrictive diet. Dietary history can help to determine if a significant correlation exists between a particular food and IBS symptoms. If a correlation exists, the offending food should be eliminated from the diet to discover if symptoms resolve. Resolution of symptoms suggests, but does not confirm, a diagnosis of a causal relationship between the food and IBS.

Diets deficient in fiber (e.g., fruits, vegetables, and grains) may help to explain constipation. Diets with excessive amounts of gas-producing foods (e.g., beans, cabbage, legumes, cauliflower, broccoli, lentils, and Brussels sprouts), poorly absorbed carbohydrates (e.g., fructose or sorbitol), or lactose in patients who are lactose intolerant, may explain excessive flatulence, bloating, or diarrhea. Excessive air swallowing, which commonly occurs in people who smoke, chew gum, or eat rapidly, may help explain excessive flatulence. Diets consisting of large fatty meals or caffeine may help explain postprandial rectal urgency and bowel frequency.

#### 28. What is the FODMAP diet?

FODMAPs are fermentable oligo-, di-, and monosaccharides and polyols that are poorly absorbed in the small intestine. A diet high in FODMAPs has been associated with higher levels of hydrogen produced in the breath in both IBS patients and healthy individuals as well as GI symptoms and lethargy in IBS patients, but not in healthy individuals. Conversely, a diet low in FODMAPs has been associated with lower levels of hydrogen production in both IBS patients and healthy individuals as well as a reduction in bloating,

abdominal pain, flatulence, and overall symptoms in IBS patients as compared with a normal diet. It is likely that a low FODMAP diet reduces the fermentation of these carbohydrates and subsequent hydrogen production, therefore reducing IBS symptoms such as bloating, abdominal pain, and flatulence (Table 61-1).

**Table 61-1.** The FODMAP diet

HIGH FODMAP FOODS	LOW FODMAP FOODS
High-fructose containing fruit Apples, pears, watermelon	Low-fructose containing fruit Bananas, grapes, strawberries
Fructan containing vegetables Onions, asparagus, artichokes	Low-fructan containing vegetables Spinach, carrots, eggplant
High-galactan containing foods Legumes, lentils, soy	Low-galactan containing foods Tofu, peanuts
Wheat-based products Bread, pasta, cereals	Wheat-free grains Oats, quinoa, corn
Sorbitol containing foods	Sucrose, glucose, pure maple syrup
Lactose containing foods Milk, ice cream, soft and fresh cheeses	Lactose free foods Lactose-free milk, rice milk, hard cheese

FODMAP, Fermentable oligo-, di-, and monosaccharides and polyols.

### 29. What is the role of gluten-free diet in IBS?

Although many IBS patients empirically report an improvement in symptoms on a gluten-free diet, rigorous evidence from controlled trials is lacking. After a 4-week trial in 45 IBS-D patients of a gluten-containing or a gluten-free diet, patients on the gluten-containing diet had more bowel movements per day as compared with patients on the gluten-free diet ( $P=0.04$ ) as well as higher small bowel permeability. However, in a separate study, 37 IBS patients were placed on a low FODMAP diet and then randomized to either a high-gluten, low-gluten, or gluten-free diet. All patients reported significant improvement in symptoms on the low FODMAP diet, but after introduction of the high-gluten, low-gluten, or gluten-free diet, all patients reported worsening of symptoms to a similar degree regardless of diet.

However, a recent metaanalysis found the pooled prevalence of IBS symptoms in patients with celiac disease to be 38% (95% CI, 27%-50%) and only 5.6% in controls (95% CI, 3.23%-9.7%). As compared with controls, among celiac disease patients who were not adherent to a gluten-free diet, IBS-type symptoms were more prevalent versus adherent celiac disease patients.

### 30. Can exercise improve IBS symptoms?

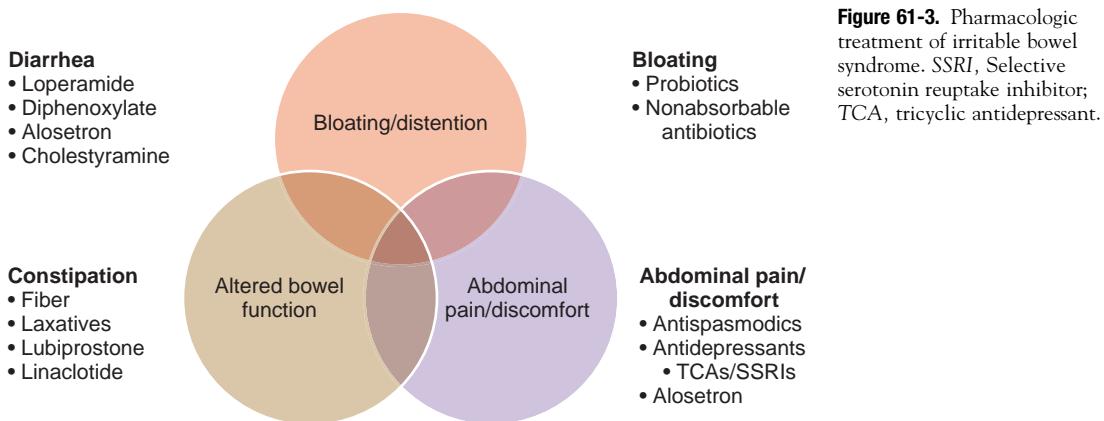
Physical activity has been shown to have a number of positive physiologic and psychological effects. In the GI tract, exercise can increase overall gut motility, including colonic motility and colon transit time. In a recent study, 12 weeks of moderate to rigorous exercise (20-60 minutes three times per week) resulted in significant improvement in IBS symptoms, although there were no differences in stool quality or characteristics, or in symptoms like bloating. Their overall quality of life scores did not improve, although their physical and cognitive skills did improve.

### 31. What is the pharmacologic approach in treating IBS?

Pharmacologic treatment of IBS has traditionally been aimed at treating and preventing the predominant symptoms, such as diarrhea, constipation, and abdominal pain. Pharmacologic treatment options for patients who report diarrhea as their predominant symptom include antidiarrheals, such as loperamide, diphenoxylate, cholestyramine, or alosetron. For patients who report constipation as their predominant symptom, treatment options include fiber, osmotic laxatives (i.e., sorbitol and lactulose), polyethylene glycol, lubiprostone, or linaclootide. For patients who report pain as the predominant symptom, treatment options include antispasmodics (i.e., dicyclomine), hyoscyamine, antidepressants (i.e., a tricyclic antidepressant [TCA] or a selective serotonin reuptake inhibitor [SSRI]) (Figure 61-3).

### 32. What is the role of alosetron in IBS?

Although alosetron was approved in 2000 by the Food and Drug Administration (FDA) in the United States for adult women with IBS-D, it was removed from the market later that year because of concerns about its safety, particularly severe constipation and ischemic colitis. However, as a result of public demand, the FDA in June 2002 reinstated alosetron for women with chronic, severe IBS-D unresponsive to conventional therapy. This required adherence to the manufacturer's prescribing program starting at a lower dose of 0.5 mg twice daily. This lower dose has been shown to be effective in achieving global improvement in bowel symptoms for women with severe IBS-D and produces less constipation, although the risk of ischemic colitis is similar (approximately 1 in 750-1000 patients).



**Figure 61-3.** Pharmacologic treatment of irritable bowel syndrome. SSRI, Selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

### 33. What is the role of loperamide in IBS?

Loperamide is a synthetic peripheral opioid agonist that reduces gut transit. By binding to the  $\mu$  opioid receptors on the myenteric neurons in the upper and lower bowel, loperamide reduces gut motility, which allows for greater fluid absorption and improved stool consistency. Loperamide does not cross the blood-brain barrier at standard doses, and therefore does not have central nervous system side effects, such as sedation or addiction. Most patients with IBS experience reduction in diarrhea and frequency, as well as improvement in stool consistency. Loperamide 2 to 4 mg each morning after the initial bowel movement and before social events can reduce undesirable urges to defecate, and increases confidence and willingness to engage in social activities.

### 34. What is the role of antidepressants in IBS?

Antidepressants are commonly used for moderate to severe abdominal symptoms associated with IBS. TCA medications are the most commonly used antidepressants for IBS symptoms. Typically the TCAs are administered in low doses (e.g., between 10-50 mg). The exact mechanism of action is not clear, but includes visceral analgesia, improvement in sleep, and normalization of the GI transit. Their effects in IBS appear to be independent of the TCAs' effects on depression or other psychological parameters. Data on the efficacy of TCAs in patients with IBS are inconsistent. However, in the largest published randomized, placebo-controlled trial to date, desipramine (escalating dose from 50 to 150 mg) was not superior to placebo in intention-to-treat analyses but in a per protocol analysis limited to patients with detectable plasma levels of desipramine showed a significant benefit over placebo.

Several small trials suggest that SSRIs may have beneficial effects in patients with IBS. These effects appear to be mostly limited to improvement in well-being and less so in abdominal pain. SSRIs may be particularly beneficial for patients with concomitant psychological disorders such as anxiety, panic, and depression. Because serotonin is associated with diarrhea, SSRIs may be better tolerated in IBS-C. SSRIs have been associated with agitation, nausea, and sleep disturbance, among other side effects.

### 35. What is the role of antispasmodics in IBS?

Antispasmodics decrease contractions or spasms in the GI tract, and thereby reduce abdominal cramps. IBS patients have exaggerated sigmoid contractions in response to meals and to stress, which may explain the postprandial discomfort and urgency in some patients. Antispasmodics can be classified into three major subclasses: anticholinergics, direct smooth muscle relaxants, and peppermint oil.

Anticholinergics work by blocking the acetylcholine mediated depolarization of intestinal smooth muscles. In the United States, the most commonly used anticholinergics are dicyclomine and hyoscyamine. Hyoscyamine and dicyclomine can be taken at regular intervals (four times daily) or intermittently for more episodic symptoms. For patients with postprandial symptoms, the medications can be taken 30 to 45 minutes before a meal. Hyoscyamine also comes in a long-acting form, which can be given twice daily. For patients with less predictable and more intermittent symptoms, hyoscyamine is preferable because it also comes in an easily dissolvable tablet, which can be taken sublingually and acts within minutes. Dicyclomine, an anticholinergic agent, is also a direct smooth muscle relaxant. Hyoscyamine is also available in combination with phenobarbital, scopolamine, and atropine. Although popular, these combination drugs have not been well evaluated in clinical trials and are probably best avoided because of their sedative and addictive potential.

Peppermint oil blocks entry of calcium into smooth muscle cells, whereas direct smooth muscle relaxants directly inhibit smooth muscle contractility by increasing cyclic adenosine monophosphate levels or by interfering with the intracellular calcium pool.

### **36. What is the role of antibiotics in IBS?**

The rationale for use of antibiotics in IBS is based on their ability to alter the intestinal microbiota. Alterations in the intestinal microbiota in IBS are supported from multiple lines of evidence. To date, most of the data on the treatment of IBS with antibiotics has been with neomycin and rifaximin.

Although neomycin has been shown to improve IBS symptoms, it has the potential to cause adverse reactions, including ototoxicity, nephrotoxicity, and neuromuscular blockade and respiratory paralysis, especially when given soon after anesthesia or muscle relaxants. Therefore neomycin should be used cautiously for the treatment of IBS.

Rifaximin is a minimally absorbed oral antibiotic with a broad spectrum of activity and a favorable tolerability profile. During the first 4 weeks after treatment with 2 weeks of rifaximin 550 mg three times daily, a greater percentage of rifaximin-treated IBS-D patients reported adequate relief of their global IBS symptoms (40.7% vs. 31.7%,  $P < 0.001$ ) and IBS-related bloating (40.2% vs. 30.3%,  $P < 0.001$ ) compared with placebo-treated patients.

Patients receiving rifaximin continue to report improvement in global symptoms after the treatment period as compared with placebo, although its efficacy declines over time. Although not contraindicated in IBS-C, rifaximin has not been well studied in this subgroup of IBS.

### **37. What is the role of probiotics in IBS?**

Probiotics are live organisms (bacteria) that are thought to exert a health benefit on the host. Probiotics exert their beneficial effects via several proposed mechanisms including modulation of bacterial flora, improvement of the barrier function of the epithelium, and alteration of the immune activity of the host. The mechanistic evidence for these hypotheses in IBS is still very limited.

Well-conducted large multicenter dose ranging studies are generally lacking. One of the few exceptions was performed in a primary care setting. Three hundred sixty-two women with IBS were randomized to three different doses of *Bifidobacterium infantis* 35624 or placebo. After 4 weeks of treatment, patients receiving *B. infantis* at a dose of  $1 \times 10^8$  colony-forming units were significantly superior to placebo and the other *bifidobacterium* doses. There was also significant decrease in abdominal pain and discomfort, bloating, and distention, as well as bowel function.

In another study, 274 IBS-C patients were randomized to placebo or fermented milk yogurt (Activia, Dannon), which contains *Bifidobacterium animalis (regularis)* DN-173 010 for 6 weeks. In the treatment group, the HR-QOL discomfort score improved, as did bloating symptoms. There was an increase in stool frequency only in patients with fewer than three stools per week.

A metaanalysis published in 2010 included 16 randomized, controlled trials evaluating the efficacy, safety, and tolerability of probiotics in IBS patients and found that only *B. infantis* 35624 showed any significant benefit in the composite symptom score of IBS patients.

### **38. What is the role of fiber in IBS?**

Fiber improves bowel function by limiting stool dehydration and normalizing stool consistency and stool volume. For every gram of fiber (e.g., wheat) ingested, approximately 2.7 g of stool is expelled. In general, fiber can improve symptoms associated with mild constipation. However, fiber is frequently associated with increased gas production, abdominal cramps, and bloating, which are frequently present in individuals with IBS.

A trial comparing 10 g of the soluble fiber psyllium (also known as *ispaghula*), 10 g of the insoluble fiber bran, and placebo found patients receiving psyllium husk had a mean improvement in IBS symptom severity, whereas bran was not significantly better than placebo. The improvement seen with psyllium was most notable during the first month of therapy. Approximately 40% of patients in this study stopped participation before the final visit because of worsening in their IBS symptoms. Not surprisingly, the highest dropout rate was among those patients receiving bran during the first month of treatment.

A prudent approach in IBS patients with mild to moderate IBS is to initially instruct them to gradually increase dietary fiber intake to approximately 20 to 25 g per day over several weeks. If adding fiber in the diet fails to relieve symptoms, psyllium should be tried next because of its ability to absorb water. If psyllium is not tolerated, then a trial with the semisynthetic fiber methylcellulose or the synthetic fiber polycarbophil should be considered. Patients who develop gas and distention with fiber should be instructed to reduce the dose of fiber and reduce their consumption of gas-producing foods, such as beans, cabbage, legumes, apples, grapes, and raisins.

### **39. What is the role of laxatives in IBS?**

When constipation associated with IBS does not improve with fiber, low-dose laxatives can improve bowel function. Osmotic laxatives should be tried first as they tend to be gentler and cause fewer side effects such as cramps and diarrhea. Although effective at improving bowel function, osmotic laxatives such as polyethylene glycol do not improve abdominal symptoms, including abdominal pain. In a recent study, patients with IBS-C were randomized to either polyethylene glycol or placebo for 28 days. Although both groups showed an increase in the mean weekly number of spontaneous bowel movements (SBMs) from baseline, the polyethylene glycol group had a statistically significant improvement ( $4.40 \pm 2.581$ ) as compared with placebo ( $3.11 \pm 1.937$ ). However, there was no difference in abdominal discomfort or pain with polyethylene glycol as compared with placebo.

It should be remembered that patients with constipation should be evaluated for pelvic floor dyssynergia, because many of these patients may respond to biofeedback therapy, a technique that retrains patients to relax their pelvic floor muscles when attempting defecation.

#### **40. What is the role of linaclotide in IBS?**

Linaclotide was recently approved by the FDA for adults with IBS-C and chronic idiopathic constipation. It is a minimally absorbed 14-amino-acid peptide that binds to and activates the guanylate cyclase C receptor. In two large, randomized trials, linaclotide resulted in improvement in abdominal pain, bowel function, and global outcomes in patients with IBS-C. The FDA endpoint for IBS-C (an increase from baseline of 1 or more complete SBMs per week and a 30% or more reduction from baseline in the weekly average of daily worst abdominal pain scores for 50% of the treatment weeks) was met by 49% to 50% of linaclotide-treated patients compared with 35% to 38% of placebo-treated patients with a number needed to treat (NNT) of 7. This, combined with a good safety and tolerability profile, suggests that linaclotide is an effective treatment for IBS-C.

#### **41. What is the role of lubiprostone in IBS?**

Lubiprostone is a chloride channel activator that increases secretions in the intestines, thereby increasing bowel transit. It acts locally on the epithelial cells that line the intestines and is rapidly metabolized, which leads to low systemic bioavailability. At a dose of 8 mcg twice daily, lubiprostone has been shown to improve bowel symptoms in women with IBS-C. The overall response to lubiprostone does not appear to be driven by one particular symptom; rather, improvement was associated with improvement in multiple symptoms.

#### **42. What is the role of cognitive-behavioral therapy in IBS?**

Cognitive-behavioral therapy is the best-studied psychological treatment for IBS. Cognitive techniques (typically administered over 4 to 15 sessions) are aimed at changing catastrophic or maladaptive thinking patterns underlying the perception of somatic symptoms. Behavioral techniques aim to modify dysfunctional behaviors through relaxation techniques, contingency management (rewarding healthy behaviors), or assertion training. Some randomized, controlled trials have also shown reductions in IBS symptoms with the use of gut-directed hypnosis (aimed at improving gut function), which involves relaxation, change in beliefs, and self-management.

A metaanalysis of 17 randomized trials of cognitive treatments, behavioral treatments, or both for IBS (including hypnosis), as compared with control treatments (including waiting list, symptom monitoring, and usual medical treatment), found patients treated with cognitive-behavioral therapy were significantly more likely to have a reduction in GI symptoms of at least 50% (odds ratio, 12; 95% CI, 6 to 260) with an NNT of 2.

Recently, a Swedish group developed an Internet-delivered cognitive behavioral treatment for IBS that includes 10 weeks of intervention, including contact with an online therapist. When compared with Internet-delivered stress management that emphasized symptom control through relaxation techniques, dietary adjustments, and problem-solving skills, the Internet-delivered cognitive behavioral treatment showed significant differences at posttreatment and 6-month follow-up as compared with Internet-delivered stress management (difference on GSRS-IBS of 4.8 at posttreatment and 5.9 at 6 months).

#### **BIBLIOGRAPHY**

1. American College of Gastroenterology Task Force on Irritable Bowel S, et al. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009;104(Suppl 1):S1–S35.
2. Cash BD, Schoenfeld P, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: A systematic review. *Am J Gastroenterol* 2002;97(11):2812–9.
3. Chey WD, et al. Linaclotide for irritable bowel syndrome with constipation: A 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol* 2012;107(11):1702–12.
4. Corney RH, Stanton R. Physical symptom severity, psychological and social dysfunction in a series of outpatients with irritable bowel syndrome. *J Psychosom Res* 1990;34(5):483–91.
5. Drossman DA, et al. AGA technical review on irritable bowel syndrome. *Gastroenterology* 2002;123(6):2108–31.
6. Drossman DA, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome—results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther* 2009;29(3):329–41.
7. Drossman DA, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Dig Dis Sci* 1993;38(9):1569–80.
8. Everhart JE, Renault PF. Irritable bowel syndrome in office-based practice in the United States. *Gastroenterology* 1991; 100(4):998–1005.
9. Gralnek IM, et al. The impact of irritable bowel syndrome on health-related quality of life. *Gastroenterology* 2000; 119(3):654–60.
10. Longstreth GF, Wolde-Tsadik G. Irritable bowel-type symptoms in HMO examinees. Prevalence, demographics, and clinical correlates. *Dig Dis Sci* 1993;38(9):1581–9.
11. Mayer EA. Clinical practice. Irritable bowel syndrome. *N Engl J Med* 2008;358(16):1692–9.
12. Mitchell CM, Drossman DA. Survey of the AGA membership relating to patients with functional gastrointestinal disorders. *Gastroenterology* 1987;92(5 Pt 1):1282–4.
13. Sandler RS. Epidemiology of irritable bowel syndrome in the United States. *Gastroenterology* 1990;99(2):409–15.
14. Talley NJ, Boyce PM, Jones M. Predictors of health care seeking for irritable bowel syndrome: A population based study. *Gut* 1997;41(3):394–8.
15. Whitehead WE, et al. Impact of irritable bowel syndrome on quality of life. *Dig Dis Sci* 1996;41(11):2248–80.

# ENDOSCOPIC CANCER SCREENING AND SURVEILLANCE

David P. Jones, DO, FACP, FACG, FASGE

## 1. What is endoscopic cancer screening and surveillance?

**Endoscopic screening** for premalignant or malignant conditions is the one-time application of a test to search for lesions in asymptomatic persons in the hope that an early diagnosis will have an effect on disease outcomes. **Endoscopic surveillance** is testing patients with known premalignant or malignant conditions repeatedly over time to search for additional lesions in patients at increased risk.

## 2. Why is endoscopic cancer screening and surveillance performed for gastrointestinal (GI) cancers?

GI cancers are annually reported as one of the most common causes of cancer death. Many if not all GI cancers begin on the mucosa and have well-defined premalignant lesions that are easily identified on endoscopy; examples include Barrett's esophagus (BE) and colorectal adenomas.

## ESOPHAGUS

### 3. Endoscopic cancer screening of the esophagus is primarily undertaken for what two types of esophageal cancers? What risk factors are associated with these two types of cancers?

- Esophageal adenocarcinoma (EAC) is the most common type of esophageal cancer in the United States; it is increasing in prevalence and is highly associated with BE, gastroesophageal reflux disease (GERD), and obesity.
- Squamous cell carcinoma (SCC) is a less frequent cause of esophageal cancer in the United States. The risk factors for esophageal SCC include alcohol, tobacco smoking, achalasia, caustic injury, tylosis, prior or concurrent head and neck SCC, and Plummer-Vinson syndrome. A new review links infection with human papillomavirus to a threefold greater chance of developing esophageal SCC.

### 4. What is Barrett Esophagus (BE, metaplasia)? Is endoscopic screening and surveillance for BE necessary?

BE is the development of specialized intestinal metaplasia (SIM) of the distal tubular esophagus, which has been identified as a premalignant precursor to EAC. The incidence of EAC is currently increasing at a rate greater than that of any other cancer in the Western world. The 5-year survival rate for late-stage EAC is poor and the only hope for improved survival is early detection. Screening for BE remains controversial, however, because of a lack of randomized controlled trials documenting a decreased effect on mortality.

### 5. Which patients should undergo endoscopic screening for BE?

Screening for BE in the general population is not recommended at this time but should be considered in selected male patients older than 50 with frequent heartburn (several times per week) and long-standing GERD. The primary purpose of surveillance of BE is to identify dysplasia and early EAC. Patients at increased risk for BE are typically white men older than 50 years and those with nocturnal reflux. After a negative screening examination, surveillance endoscopy is not indicated.

### 6. What techniques are used to perform endoscopic screening in BE?

A complete direct visual examination (esophagogastroduodenoscopy [EGD]) of the esophagus with high-resolution and high-definition white-light endoscopy is the standard for endoscopic screening of BE. Esophageal capsule endoscopy may provide a noninvasive assessment of suspected BE; however, studies demonstrate varying sensitivity with the device.

### 7. How is BE histologically graded?

BE is histologically graded as:

- Nondysplastic
- Indeterminate-grade dysplasia
- Low-grade dysplasia (LGD)
- High-grade dysplasia (HGD)

### 8. What is the rationale for endoscopic surveillance in BE?

Decisions about endoscopic surveillance and treatment for BE are based on the presumption that SIM may advance to LGD, that LGD may advance to HGD, and that HGD may progress to intramucosal carcinoma. BE surveillance programs attempt to detect adenocarcinoma or HGD at an earlier, potentially curable, stage and have been shown to significantly improve 5-year survival compared with similar patients not undergoing routine endoscopic surveillance.

### 9. What techniques are used to perform endoscopic surveillance in BE?

Surveillance endoscopy should only be performed after patients have their reflux aggressively controlled with a proton pump inhibitor because any inflammation may interfere with the endoscopic and microscopic identification of dysplasia. Endoscopic surveillance involves systematic four-quadrant biopsies at 1- to 2-cm intervals along the entire length of the Barrett segment. Biopsies should also specifically target any luminal irregularity in the Barrett segment (e.g., ulceration, erosion, nodule, or stricture) because there is an association of such lesions with underlying cancer. The use of jumbo biopsy forceps may improve the yield of the biopsies and should be considered, especially in patients with previous dysplasia. Newer brushing techniques (WATS, FISH etc) may provide greater sensitivity compared to biopsy for detecting high-grade lesions/dysplasia and neoplasia.

### 10. How often should patients with BE undergo endoscopic surveillance?

Endoscopic surveillance intervals are determined by the presence and grade of dysplasia found in patients with BE (Table 62-1).

**Table 62-1.** 2012 ASGE Guidelines: Endoscopic Management Strategies for Barrett's Esophagus

HISTOLOGIC CHARACTERISTICS	SURVEILLANCE	INTERVENTION OPTIONS
Nondysplastic Barrett's esophagus	Consider no surveillance. If surveillance is elected, perform EGD every 3 to 5 years with 4-quadrant biopsies every 2 cm.	Consider endoscopic ablation in select cases.
Indeterminate for dysplasia	Clarify presence and grade of dysplasia with expert GI pathologist. Increase antisecretory therapy to eliminate esophageal inflammation. Repeat EGD and biopsy to clarify dysplasia status.	No therapeutic intervention recommended
Low-grade dysplasia	Confirm with expert GI pathologist. Repeat EGD in 6 months to confirm LGD. Perform surveillance EGD every year, 4-quadrant biopsies every 1 to 2 cm.	Consider endoscopic resection or ablation.
High-grade dysplasia	Confirm with expert GI pathologist. Consider surveillance EGD every 3 months in select patients, 4-quadrant biopsies every 1 cm.	Consider endoscopic resection or mucosal ablation. Consider EUS for local staging and lymphadenopathy. Consider surgical resection.

EGD, esophagogastroduodenoscopy; EUS, endoscopic ultrasound; GI, gastrointestinal; LGD, low-grade dysplasia.

### 11. How is LGD managed in patients with BE?

LGD must be confirmed on a repeat EGD within 6 months, and an expert GI pathologist is also required to review the biopsy samples before the initiation of annual endoscopic surveillance. Surveillance endoscopy continues until there is no dysplasia on two consecutive endoscopic examinations. Some experts assert that aggressive ablation of LGD is an option and patients can be reassured that 60% of patients with LGD will regress to no dysplasia after a mean follow-up of 4 years.

### 12. How do you manage HGD in patients with BE?

HGD is associated with 30% risk of developing EAC. If HGD is confirmed by an expert GI pathologist, there is currently no agreement on the most appropriate management of these patients. Treatment options available to patients include intensive endoscopic surveillance with four-quadrant biopsies every 1 cm performed every 3 months, endoscopic ablation therapy, or surgical resection. All of these treatment options have produced similar outcomes for patients in retrospective cohort studies performed at expert centers. Optimal treatment is therefore determined on a case-by-case basis, taking into account the patient's age, comorbidities, and ability to comply with an aggressive surveillance program, as well as the available local endoscopic and surgical expertise.

### 13. What is the principal role of endoscopic ultrasound (EUS) in evaluating patients with HGD?

EUS can be used to exclude the presence of occult cancer, submucosal invasion, and malignant lymphadenopathy in patients with BE of HGD. This information is particularly important when determining the appropriate selection of patients if endoscopic management is considered. Routine application of EUS in BE with LGD or without dysplasia is not recommended because the risk of malignancy is so low.

**14. Describe the workup once EAC is identified while performing endoscopic surveillance for BE?**

Once EAC is confirmed by an expert GI pathologist, staging of the cancer is performed with a computed tomography (CT) scan, preferably with integrated positron emission tomography, to evaluate for the presence of metastatic disease. Next, patients without evidence of metastatic disease by CT would undergo EUS for regional staging to provide detailed images of the esophageal masses and their relationship within the structure of the esophageal wall. EUS with fine-needle aspiration (FNA) can also be used for lymph node staging. Finally, depending on the stage of the cancer, the patient should be referred to oncology, radiation oncology, or surgery for treatment. The use of endoluminal stenting may be considered.

**15. What other imaging modalities are available for BE endoscopic screening and surveillance?**

Confocal laser endomicroscopy (CLE) imaging of the GI mucosa enables endoscopists to obtain immediate real-time histologic images without biopsies as well as enhance the guidance of mucosal biopsies, leading to a higher dysplasia and neoplasia detection rate. BE and associated neoplasia can be predicted with a sensitivity of 98.1% and 92.9%, and a specificity of 94.1% and 98.4%, respectively, with CLE (overall accuracy: 96.8% and 97.4%), which may lead to decreased biopsies and lower associated cost.

Narrowband imaging (NBI) is a technique that filters the illuminating white light on the endoscope into two colors (blue and green), which are avidly absorbed by blood vessels to allow for better visualization of the mucosa. In one study of patients with BE, the sensitivity of NBI detection for an irregular mucosal pattern was 100% with a specificity of 98.7%. Chromoendoscopy has also been used to stain the esophagus with agents like methylene blue, crystal violet, indigo carmine, and acetic acid that are applied to the mucosa to enhance the detection of abnormal mucosal patterns in BE.

**16. Do patients with achalasia have an increased risk of esophageal cancer?**

Yes. Individuals with achalasia have as much as a thirty-threefold greater risk of developing SCC of the esophagus compared with the general population. On average, patients with achalasia will have had at least 15 years of symptoms prior to the diagnosis of esophageal cancer.

**17. What is the role of endoscopic cancer surveillance in patients with achalasia?**

Currently, there is insufficient data to support routine endoscopic surveillance in patients with achalasia. Endoscopic surveillance in patients with achalasia has not been found to be cost effective but may be considered 15 years after the onset of symptoms. All surface abnormalities of esophagus identified during the examination should undergo biopsy, and the recommended timing of any surveillance endoscopy has not been defined.

**18. Is there a link between caustic ingestion and the development of esophageal cancer?**

Yes. A caustic injury to the esophagus, most commonly after lye ingestion, appears to be associated with an increased risk of developing SCC of the esophagus. A history of caustic ingestion is present in 1% to 4% of patients with esophageal cancer.

**19. What are the clinical characteristics of patients who develop esophageal cancer after a caustic injury?**

- The mean age of onset is 35 to 51 years.
- The average interval between caustic injury and development of esophageal cancer is approximately 40 years.
- Cancers are located in the midesophagus.

**20. What rare genetic disorder is associated with a high incidence of SCC of the esophagus?**

Tylosis is an uncommon autosomal dominant disorder that is distinguished by thickening of the skin (hyperkeratosis) on the palms and soles. The syndrome is associated with a 27% incidence of SCC of the esophagus. The average age at onset of esophageal cancer is 45 years, and death from esophageal cancer can occur in patients as young as 30 years.

**21. What type of endoscopic surveillance is recommended in patients with tylosis?**

Patients with tylosis should begin endoscopic surveillance at the age of 30. Most cases of esophageal cancer in these patients have been noted in the distal esophagus, so attention should be focused in this area during the examination. Repeat endoscopy should not be conducted more frequently than every 1 to 3 years in these patients.

**STOMACH AND SMALL BOWEL****22. What is the malignant potential of gastric polyps?**

Gastric polyps are often found incidentally during endoscopy and are histologically classified as hyperplastic, fundic gland, or adenomatous polyps.

- *Hyperplastic polyps* are the most commonly encountered type of gastric polyp (70% to 90%) and may have malignant potential. Recent clinical studies have demonstrated dysplasia in up to 19% of hyperplastic polyps and there have been several reports of focal cancer.

- *Fundic gland polyps* have not been associated with an increased risk of gastric cancer but may develop in association with long-term use of proton pump inhibitors or may occur in association with familial adenomatous colorectal polyps.
- *Gastric adenomatous polyps* are rare but do have malignant potential, which correlates with the size of the polyp and the age of the patient.

**23. How are gastric polyps managed when encountered radiographically or endoscopically?**

Endoscopic evaluation is warranted for polyps of any size that are detected radiographically. During endoscopy, gastric polyps should be removed whenever possible because the gross appearance of polyps in most cases (typical small fundic-appearing glands excluded) cannot be used to differentiate the histologic subtypes. A representative biopsy should be performed on the largest polyp if multiple polyps are encountered or if a polypectomy is not possible. Surgical resection may be considered for any large adenomatous polyps or polyps containing dysplastic tissue. Care should be taken when resecting large gastric polyps as they may be very vascular.

**24. Is endoscopic surveillance required after the removal of a gastric polyp?**

Surveillance endoscopy is not necessary after the adequate sampling or the excision of a nondysplastic polyp. Gastric polyps with HGD or early gastric cancer necessitate individualized surveillance programs. Surveillance endoscopy should begin 1 year after removal of all adenomatous gastric polyps to assess for any recurrence or new or previously missed polyps. If the initial surveillance examination is negative, then repeat endoscopy should be repeated no earlier than every 3 to 5 years.

**25. What is gastric intestinal metaplasia (GIM)?**

GIM has been identified as a premalignant condition that may be the result of an adaptive response to a variety of environmental insults, such as *Helicobacter pylori* infection, smoking, or high salt intake. GIM is histologically identical to esophageal intestinal metaplasia.

**26. How common is GIM? What is its malignant potential?**

GIM is extremely common in Western countries; up to 25% to 30% of the population can be affected. Individuals with GIM, especially in certain geographical regions (e.g., Japan) and in those infected with *H. pylori*, have greater than a tenfold increased risk of developing gastric cancer. Patients found to have GIM with HGD are at a significant risk for developing gastric cancer and should proceed immediately to gastrectomy or endoscopic mucosal resection.

**27. What role does endoscopic surveillance have in GIM?**

Endoscopic surveillance is not uniformly recommended for GIM. GIM has not been extensively studied in the United States, and recent reports suggest that the risk of progression to cancer is low for most patients. Patients at increased risk for gastric cancer, based on ethnicity or family history, may benefit from surveillance. Topographic mapping of the entire stomach should be performed if endoscopic surveillance is to be undertaken.

**28. Are patients with pernicious anemia at an increased risk for gastric cancer? Is endoscopic screening or surveillance required?**

Yes. Individuals with pernicious anemia have an estimated two- to threefold increased risk of developing gastric cancer. The risk for developing gastric cancer in patients with pernicious anemia is highest within the first year of diagnosis, so a single endoscopy should be considered to identify prevalent neoplasia. There is insufficient data to support subsequent endoscopic surveillance.

**29. Is partial gastrectomy a risk factor for the development of gastric cancer?**

Yes. Patients with a history of benign gastric or duodenal ulcers requiring treatment with gastric surgery may be at an increased risk for neoplasia in the gastric remnant. Endoscopic surveillance studies have detected gastric cancer in 4% to 6% of these patients, but population-based studies have failed to confirm an increased risk.

**30. What are the endoscopic surveillance recommendations for postgastrectomy surgery patients?**

All postgastrectomy patients with a history of peptic ulcer disease should have an index endoscopy to assess for *H. pylori*, chronic gastritis, and intestinal metaplasia. Routine endoscopic surveillance is not recommended for these patients but may be considered after an interval of 15 to 20 years. During the endoscopic examination, multiple biopsy samples should be taken from the anastomosis and gastric remnant. In general, however, there should be a low threshold for endoscopy in postgastrectomy patients with upper GI symptoms.

**31. Who is at risk for ampullary and nonampullary duodenal adenomas?**

Ampullary and nonampullary duodenal adenomas can occur sporadically or in association with genetic syndromes such as familial adenomatous polyposis (FAP) or Peutz-Jeghers syndrome (PJS). Ampullary adenomas are considered premalignant lesions that can be treated surgically or endoscopically. Nonampullary duodenal adenomas have the potential for malignant transformation and are usually removed endoscopically.

**32. What are the endoscopic surveillance guidelines for sporadic duodenal adenomas?**

Sporadic duodenal adenomas are usually removed completely with endoscopic techniques, and surveillance endoscopy is usually performed to ensure complete tissue removal and to assess for recurrence. Currently, there is no established surveillance interval for patients with sporadic duodenal adenomas. Patients discovered to have advanced (stage IV) duodenal polyposis require surgical consultation for possible resection. All patients found to have duodenal adenomas should be offered colonoscopy because they are at increased risk for colorectal polyps.

**33. What is the upper GI tract endoscopic surveillance strategy for patients with FAP?**

Individuals with FAP should undergo endoscopic surveillance for duodenal adenomas with examinations beginning around the time the patient is being considered for colectomy or early in the third decade of life. The upper endoscopy needs to be performed with both end-viewing and side-viewing endoscopes. If no adenomas are found, then the examination should be repeated in 5 years.

**34. How often is surveillance endoscopy performed on patients who have undergone endoscopic resection of ampullary adenomas?**

Patients who have undergone endoscopic management of ampullary adenomas should have regular endoscopic surveillance for the detection of recurrent dysplasia with both a forward- and a side-viewing endoscope. Follow-up endoscopy and multiple biopsies should be performed every 6 months for a minimum of 2 years with repeated endoscopic examinations at 3-year intervals.

**35. When should surveillance endoscopy begin for patients with PJS?**

PJS places patients at 5% to 10% increased risk of gastric malignancy. The lifetime risk of developing small bowel cancer in PJS is 13%. Endoscopic surveillance of the stomach and duodenum with upper endoscopy should be performed every 2 years beginning at age 10. All visible polyps should be removed during the endoscopic examinations.

**36. What is the role of capsule endoscopy in small bowel surveillance for PJS?**

Patients with PJS have a significantly increased risk of developing dysplastic polyps and malignancies along the entire length of the small bowel. Capsule endoscopy is the method of choice for small bowel surveillance in PJS and should be performed every 2 years beginning at age 10.

**PANCREAS****37. Who should undergo endoscopic screening and surveillance for pancreatic cancer?**

Endoscopic screening and surveillance for pancreatic cancer are not recommended for the general population because of the overall low prevalence of the disease, the inaccuracy of available testing modalities, and the high expense. Some experts advocate that first-degree relatives of patients with familial pancreatic cancer and individuals with genetic syndromes associated with pancreatic cancer (such as hereditary nonpolyposis colorectal cancer [CRC], familial atypical mole melanoma, or PJS) undergo endoscopic screening and surveillance. CT scan or magnetic resonance imaging, combined with EUS, is considered to be the best available method for pancreatic cancer screening because of their high sensitivity and specificity and high negative predictive value for pancreatic malignancy.

**38. When should endoscopic screening begin for patients at increased risk for pancreatic neoplasia?**

No standardized recommendations are available for the endoscopic screening of individuals at high risk for pancreatic cancer. Small clinical studies have suggested some benefit with endoscopic screening with EUS for individuals with genetic syndromes associated with pancreatic cancer beginning at the age of 30. First-degree relatives of patients diagnosed with pancreatic cancer should begin endoscopic screening with EUS around the age of 40, or 10 years younger than the earliest age of pancreatic cancer development. Smokers should be screened at an earlier age because smoking decreases the age of onset for familial pancreatic cancer by 10 to 20 years.

**39. What is the recommended endoscopic surveillance interval for patients at high risk for pancreatic cancer?**

There is currently no consensus for the optimum endoscopic surveillance interval in individuals determined to be at increased risk for pancreatic neoplasia. Some medical centers advocate surveillance EUS in high-risk patients every 2 to 3 years, with the interval decreasing to every 12 months as the patient approaches the age when pancreatic cancer developed in the youngest affected relative.

**COLON****40. At what age is CRC screening recommended for average-risk patients? What are the preferred testing modalities for CRC screening?**

CRC screening should be offered to average-risk (asymptomatic) individuals beginning at the age of 50. It is recommended that blacks should start CRC screening at the age of 45. There is growing evidence that heavy cigarette smoking and obesity may be linked to an increased risk of CRC and to the development of CRC at an earlier age; however, there are no formal recommendations for earlier screening. The risks and benefits of each CRC screening method must be discussed between the physician and the individual patient (Table 62-2).

**Table 62-2.** CRC Screening Recommendations

PREFERRED METHOD	COLONOSCOPY EVERY 10 YEARS
Alternative methods	Annual FIT Flexible sigmoidoscopy every 5 years CT colonography every 5 years Double-contrast barium enema every 5 to 10 years

CT, Computed tomography; FIT, fecal immunochemical test.

**41. When should endoscopic screening begin for individuals with a family history of CRC? How often should endoscopic surveillance be performed in these individuals?**

Endoscopic screening for CRC should begin at age 40 or 10 years younger than the affected relative in individuals with a first-degree relative with CRC. Surveillance endoscopy should be scheduled every 3 to 5 years if the relative was younger than age of 60 at diagnosis. Individuals with a first-degree relative with CRC or advanced adenomas diagnosed at age 60 years or older can be screened like average-risk persons. Patients with a second- or third-degree relative with CRC should adhere to average-risk screening recommendations.

**42. What are the endoscopic surveillance guidelines for individuals with a personal history of colon cancer?**

If a complete endoscopic examination was not performed at the time of colon cancer diagnosis, a colonoscopy should be performed within 6 months after surgical resection. Endoscopic surveillance should begin 1 year after surgery and continue in 3- to 5-year intervals if the colonoscopy results are normal.

**43. Outline the endoscopic surveillance guidelines for individuals with a personal history of rectal cancer.**

- Colonoscopy at time of surgical resection
- Colonoscopy at 1 year and 4 years after resection and then at 5-year intervals
- Flexible sigmoidoscopy every 6 months for the first 2 years postoperatively for patients who did not receive pelvic radiation or those who underwent nonmesorectal resection

**44. What is the role of EUS in the endoscopic surveillance of individuals with a personal history of rectal cancer?**

After surgical resection, the local recurrence rate for advanced rectal cancer is approximately 25%, and the risk of recurrence is greatest in the first 2 years after surgery. EUS may be used to accurately detect recurrent rectal cancer and provide pathologic confirmation via FNA. The optimal interval for performing EUS following surgical resection has not been established. Currently, rectal EUS is recommended every 6 months for the first 2 years after low anterior resection or transanal excision to screen for recurrent rectal cancer.

**45. Do individuals with a first-degree relative diagnosed with adenomatous polyps require earlier screening for CRC? Do they have an increased risk for CRC?**

Yes. Persons with a first-degree relative diagnosed with advanced (high-risk adenoma [HRA]) adenomas (an adenoma  $\geq$  cm in size, or with HGD, or with villous elements) before the age of 50 should begin CRC screening at the age of 40 or 10 years younger than the affected relative. A first-degree relative with adenomatous polyps increases an individual's risk for CRC by two- to fourfold.

**46. What are the surveillance recommendations for a patient with a previous history of adenomatous colon polyps?**

After the removal of an adenomatous polyp, colonoscopy is the recommended method of surveillance because it has been shown to significantly reduce subsequent CRC incidence (Table 62-3).

**47. When should screening colonoscopy not be offered or surveillance stopped?**

Evidence suggests that the risks of colonoscopy increases with advancing age. Surveillance and screening should not be continued when risks outweigh the benefits. The United States Preventive Services Task Force (USPSTF) determined that screening should not be continued after age 85 years because the risk could exceed potential benefit. For patients aged 75 to 85 years, the USPSTF recommends against continued routine screening but argues for individualization based on comorbidities and findings of any prior colonoscopy. Patients with HRA are at higher risk for developing advanced neoplasia compared with average-risk patients and therefore the potential benefit of surveillance could be higher than for screening in these individuals.

**48. What is a serrated adenoma, and is there any increased risk of malignancy or need for surveillance?**

Sessile serrated adenomas are premalignant flat (or sessile), often mucus-covered lesions predominantly seen in the cecum and ascending colon, that are thought to lead to CRC through an (alternate) serrated pathway. This differs from most CRCs, which arise from mutations starting with inactivation of the adenomatous polyposis coli (APC) gene. The serrated pathway has a predilection for the proximal colon. These lesions may be associated with BRAF or k-ras mutations, and CPG island methylation, which can lead

**Table 62-3.** Colonoscopy Surveillance Recommendations

FINDINGS ON INDEX COLONOSCOPY	SURVEILLANCE RECOMMENDATION
≤2 small tubular adenomas (<1 cm) and only low-grade dysplasia	No earlier than 5 years
Advanced neoplasia or 3 to 10 adenomas	3 years
More than 10 adenomas	Within 3 years
Large, sessile polyp with incomplete excision	2 to 6 months
Negative surveillance colonoscopy	No earlier than 5 years
Distal small (<10 mm) hyperplastic polyps (no adenomas)	10 years
Sessile serrated polyp(s) <10 mm with no dysplasia	5 years
Sessile serrated polyp(s) ≥10 mm	3 years
Sessile serrated polyp with dysplasia or serrated polyposis syndrome	1 year

to silencing of mismatch repair genes (MLH1), which could result in more rapid progression to malignancy in some individuals.

#### 49. What is the definition of *serrated polyposis syndrome*?

The World Health Organization definition requires at least one of the following:

- At least five serrated polyps proximal to sigmoid, with two or more 10 mm or larger
- Any serrated polyps proximal to sigmoid with family history of serrated polyposis syndrome
- More than 20 serrated polyps of any size throughout the colon

#### 50. Define *familial adenomatous polyposis (FAP) syndrome*. What is the risk of developing CRC in patients with FAP syndrome?

FAP syndrome presents as more than 100 adenomas throughout the colon and is caused by mutations in the APC gene. The risk of developing CRC in patients with FAP is almost 100% by age 40 to 50 years. Total colectomy is indicated in patients with FAP who develop multiple, diffuse adenomas in the colon.

#### 51. When should endoscopic screening begin in patients with FAP?

Genetic testing should be offered to all patients at risk for FAP and to family members prior to endoscopic screening. Beginning at age 10 to 12, individuals at risk for FAP should undergo annual flexible sigmoidoscopy until 40 years of age and then every 3 to 5 years thereafter. Family members are assumed not to be affected if their genetic test is negative and the index case is positive but can be offered sigmoidoscopy every 7 to 10 years to account for any potential errors in the test.

#### 52. Do patients with PJS require endoscopic screening and surveillance for CRC?

CRC surveillance endoscopy is offered to patients with PJS syndrome because the lifetime risk of CRC for these individuals ranges from 10% to 20%. Several surveillance protocols have been published but the true efficacy of aggressive CRC surveillance for these patients has yet to be established. Most endoscopic surveillance protocols suggest colonoscopic examinations should begin around the age of 18 with 3-year surveillance intervals.

#### 53. What is hereditary nonpolyposis colorectal cancer syndrome (HNPCC)?

HNPCC syndrome is an autosomal dominant disorder distinguished by the early development of CRC (average age is 44). The diagnostic clinical criteria used to help establish the diagnosis of HNPCC include the Amsterdam (modified) and Bethesda classification systems.

#### 54. What are the endoscopic screening and surveillance guidelines for HNPCC?

Colonoscopy should be performed every 1 to 2 years in patients at risk for HNPCC, beginning at age 20 to 25 years or 10 years younger than the age of the earliest diagnosis of cancer in the family. The screening interval for endoscopic surveillance changes to yearly beginning at age 40.

#### 55. Do patients with ulcerative colitis (UC) and Crohn's disease require endoscopic surveillance?

Yes. Long-standing UC and extensive Crohn's disease increase an individual's risk for the development of dysplasia and CRC.

#### 56. Which clinical characteristics increase the risk of CRC in patients with UC and Crohn's disease?

In patients with UC and Crohn's disease, the risk of CRC increases with:

- Longer duration
- More extensive or severe colitis (more than one-third colonic involvement)

- Family history of CRC
- Young age at onset of disease
- Presence of backwash ileitis
- Personal history of primary sclerosing cholangitis.

The presence of isolated proctitis alone does not increase the risk for CRC.

### **57. How should endoscopic surveillance be performed in patients with UC and Crohn's disease?**

Surveillance colonoscopy should be performed in patients with UC or extensive Crohn's disease every 1 to 2 years beginning 8 to 10 years after the clear onset of disease symptoms. During the colonoscopy, four-quadrant biopsy samples should be obtained every 10 cm from the cecum to the rectum (minimum of 32 biopsy samples) in these patients. Biopsies targeted at macroscopically involved segments may be adequate for endoscopic surveillance in patients with less extensive colitis.

### **58. What is the treatment strategy for dysplasia in patients with UC or Crohn's disease?**

If dysplasia is identified during endoscopic screening, it should be confirmed by a second GI pathologist. HGD or multifocal LGD detected during endoscopy in an area of flat mucosa is an indication for colectomy. The management of unifocal LGD is controversial, as some experts recommend colectomy.

### **59. How are adenomatous-appearing polyps managed in patients with UC and Crohn's disease?**

Adenomatous-appearing polyps should be completely removed by polypectomy, and biopsy specimens should be obtained from the adjacent flat mucosa to determine the presence of dysplasia. If no dysplasia or inflammation is found in the surrounding mucosa, then this can be managed as a sporadic adenomatous polyp. Colectomy is indicated if dysplasia is identified in an area of active inflammation, also known as *dysplasia-associated lesion or mass*, and there is evidence of dysplasia in the adjacent mucosa. Repeat colonoscopy in 3 to 6 months and close follow-up are warranted when indefinite dysplasia is detected. Mucosal tattooing often assists in identifying the area in question on subsequent endoscopies.

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## **BIBLIOGRAPHY**

1. Adler DG, Qureshi W, Davila R, et al. The role of endoscopy in ampullary and duodenal adenomas. *Gastrointest Endosc* 2006;64:849–54.
2. Ahsan H, Neugut AI, Waye JD, et al. Family history of colorectal adenomatous polyps and increased risk for colorectal cancer. *Ann Intern Med* 1998;128:900–5.
3. Anandasabapathy S, Sontag S, Graham DY, et al. Computer-Assisted Brush-Biopsy Analysis for the Detection of Dysplasia in a High-Risk Barrett's Esophagus Surveillance Population. *Dig Dis Sci* 2011;56(3):761–6.
4. ASGE guideline: colorectal cancer screening and surveillance. *Gastrointest Endosc* 2006;63:546–57.
5. ASGE guidelines: the role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. *Gastrointest Endosc* 2012;76:1087–94.
6. Barr Fritchler EG, Brankley SM, et al. A comparison of conventional cytology, DNA ploidy analysis, and fluorescence in situ hybridization for the detection of dysplasia and adenocarcinoma in patients with Barrett's esophagus. *Hum Pathol* 2008;39(8):1128–35.
7. Brucher BL, Stein HJ, Bartels H, et al. Achalasia and esophageal cancer: incidence, prevalence, and prognosis. *World J Surg* 2001;25:745–9.
8. Burke CA, Santisi J, Church J, et al. The utility of capsule endoscopy small bowel surveillance in patients with polyposis. *Am J Gastroenterol* 2005;100:1498–502.
9. Buttar NS, Wang KK, Sebo TJ, et al. Extent of high grade dysplasia in Barrett's esophagus correlates with risk of adenocarcinoma. *Gastroenterology* 2001;120:1630–9.
10. Canto MI, Goggins M, Hruban RH, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. *Clin Gastroenterol Hepatol* 2006;4:766–81.
11. Corley DA, Levin TR, Habel LA, et al. Surveillance and survival in Barrett's adenocarcinomas: a population-based study. *Gastroenterology* 2002;122:633–40.
12. Dai Z, Xu YC, Niu L. Obesity and colorectal cancer risk: a meta-analysis of cohort studies. *World J Gastroenterol* 2007;13:4199–206.
13. Davila RE, Rajan E, Adler D, et al. ASGE guideline: the role of endoscopy in the diagnosis, staging, and management of colorectal cancer. *Gastrointest Endosc* 2005;61:1–7.
14. Erkal HS, Mendenhall WM, Amdur RJ, et al. Synchronous and metachronous squamous cell carcinomas of the head and neck mucosal sites. *J Clin Oncol* 2001;19:1358–62.
15. Fleischner DE, Sharma VK. Endoscopic ablation of Barrett's esophagus using the halo system. *Dig Dis* 2009;26(4):280–4.
16. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology* 2000;119:1447–53.
17. Ginsberg GG, Al-Kawas FH, Fleishcher DE, et al. Gastric polyps: relationship of size and histology to cancer risk. *Am J Gastroenterol* 1996;91:714–7.
18. Hirota EK, Zuckerman MJ, Adler DG, et al. The role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc* 2006;63:570–80.
19. Kimmey MB, Bronner MP, Byrd DR, et al. Screening and surveillance for hereditary pancreatic cancer. *Gastrointest Endosc* 2002;56:S82–6.
20. Kiviranta UK. Corrosion carcinoma of the esophagus. *Acta Otolaryngol* 1952;42:89–95.
21. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. *Gastroenterology* 2010;138:2088–100.

22. Leighton JA, Shen B, Baron TH, et al. ASGE guideline: endoscopy in the diagnosis and treatment of inflammatory bowel disease. *Gastrointest Endosc* 2006;63:558–65.
23. Leung WK, Sung JJY. Review article: intestinal metaplasia and gastric carcinogenesis. *Aliment Pharmacol Ther* 2002;16:1209–16.
24. Lieberman DA, Rex DK, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2012;143:844–57.
25. Lundergarth G, Adami HO, Helmick C. Stomach cancer after partial gastrectomy for benign ulcer disease. *N Engl J Med* 1988;319:195–200.
26. Maillefer RH, Greidanus MP. To B or not B: is tylosis B truly benign? Two North American genealogies. *Am J Gastroenterol* 1999;94:829–34.
27. Mäkinen MJ. Colorectal serrated adenocarcinoma. *Histopathology* 2007;50(1):131–50.
28. McGarry TJ, Kulin HE, Zaino RJ. Peutz-Jeghers syndrome. *Am J Gastroenterol* 2000;95:596–604.
29. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005;97:42–146.
30. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM. American college of gastroenterology guidelines for colorectal cancer screening. *Am J Gastroenterol* 2008;104(3):739–50.
31. Sharma P, Bansal A, Mathur S, et al. The utility of a novel narrow band imaging endoscopy system in patients with Barrett's esophagus. *Gastrointest Endosc* 2006;64:167–75.
32. Skacel M, Petras RE, Gramlich TL, et al. The diagnosis of low-grade dysplasia in Barrett's esophagus and its implications for disease progression. *Am J Gastroenterol* 2000;95:3383–7.
33. Terry P, Ekbom A, Lichtenstein P, et al. Long-term tobacco smoking and colorectal cancer in a prospective cohort study. *Int J Cancer* 2001;91:585–7.
34. Toh BH, van Driel IR, Gleeson PA. Pernicious anemia. *N Engl J Med* 1997;337:1441–8.
35. Wang KK, Sampliner RE. Updated guidelines for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol* 2008;103:788–97.

#### Websites

Websites that address general screening and surveillance include:

American College of Gastroenterology. <http://gi.org/> [Accessed September 22, 2014].

American Society for Gastrointestinal Endoscopy. <http://www.asge.org/publications/> [Accessed September 22, 2014].

# RHEUMATOLOGIC MANIFESTATIONS OF GASTROINTESTINAL DISEASES

Sterling G. West, MD, MACP, FACP

## ENTEROPATHIC ARTHRITIS

### 1. How often does an inflammatory peripheral or spinal arthritis occur in patients with idiopathic inflammatory bowel disease (IBD)?

Arthritis is the most common extraintestinal manifestation (EIM) of either type of IBD (Crohn's disease [CD] and ulcerative colitis [UC]) affecting up to 20% of patients (Table 63-1).

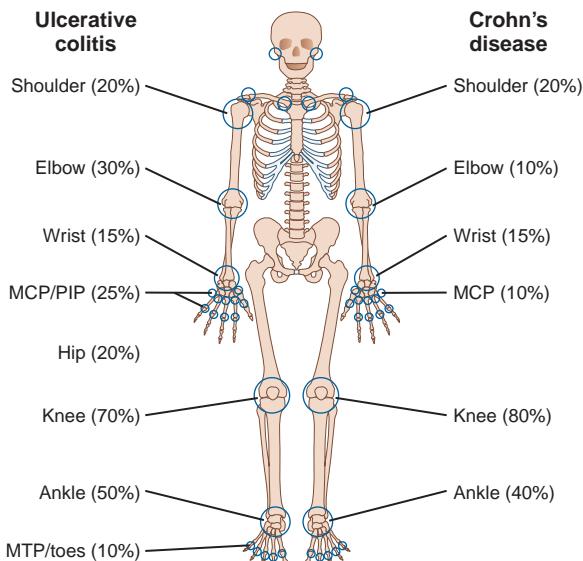
**Table 63-1.** Frequency of Peripheral or Spinal Arthritis in Inflammatory Bowel Disease

	ULCERATIVE COLITIS	CROHN'S DISEASE
Peripheral arthritis	5%-10%	10%-15%
Sacroiliitis/spondylitis*	5%-15%	10%-20%

\*Overall, 5% of ulcerative colitis patients and 10% of Crohn's disease patients develop ankylosing spondylitis, whereas 15%-20% of all inflammatory bowel disease patients have asymptomatic radiographic sacroiliitis.

### 2. What are the most common joints involved in UC and CD patients with an inflammatory peripheral arthritis?

Upper extremity and small joint involvement is more common in UC than in CD. Both UC- and CD-related arthritis affect the knee and ankle predominantly (Figure 63-1).



**Figure 63-1.** Joints commonly involved as an extraintestinal manifestation of ulcerative colitis and Crohn's disease. MCP, Metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

**3. Describe the clinical characteristics of the inflammatory peripheral arthritis associated with idiopathic IBD.**

**Type I** (*arthritis often parallels IBD activity*) occurs in 4% to 6% of patients with IBD. It affects both males and females equally. Children are affected as often as adults. The arthritis is typically acute (80%) in onset and asymmetric (80%). It usually involves fewer than five joints (i.e., oligoarticular), especially the knees or ankles. It occurs prior to (30% of cases) or early in the course of the bowel disease and is strongly associated (80%) with flares of IBD and other extraarticular manifestations (erythema nodosum, uveitis). Synovial fluid analysis reveals an inflammatory fluid with up to 50,000 white blood cells (WBC)/mm<sup>3</sup> (predominantly neutrophils) and negative findings on crystal examination and cultures. There is an increased prevalence of human leukocyte antigen (HLA)-B27, HLA-B35, and HLA-DRB1\*0103 in this type of arthritis. Most arthritic episodes are self-limited (80% within 3 months) and do not result in radiographic changes or deformities.

**Type 2** (*arthritis independent of IBD activity*) is less common, occurring in 3% to 4% of IBD cases. The arthritis tends to be symmetric (80%), polyarticular (metacarpophalangeal joints, knees, and ankles more than other joints), runs a course independent of the activity of IBD, and does not coincide with extraarticular manifestations (except uveitis). Active synovitis persists for months (90% of cases) and episodes of exacerbations and remissions may continue for years. Because of its chronicity, this type of arthritis can cause erosions and deformities. There is an association of this arthritis with HLA-B44 but not with HLA-B27.

**4. What other EIMs commonly occur in patients with idiopathic IBD and inflammatory peripheral arthritis?**

Approximately 25% of patients with IBD have a combination of EIMs. The development of one manifestation increases the risk of developing others. In IBD patients with arthritis, the following EIMs may be seen:

P = Pyoderma gangrenosum (less than 5%)

A = Aphthous stomatitis (less than 10%)

I = Inflammatory eye disease (acute anterior uveitis) (5%-15%)

N = Nodosum (erythema) (less than 15%)

**5. Does the extent and activity of IBD correlate with the activity of the peripheral inflammatory arthritis?**

Patients with UC and CD are more likely to develop a peripheral arthritis if the colon is extensively involved. In patients with type 1 arthritis, most arthritic attacks occur during the first few years following onset of the bowel disease, but late occurrences also occur. The episodes coincide with flares of bowel disease in 60% to 80% of patients. *The arthritis may precede symptoms of IBD in up to 30% of cases, especially in children with CD.* Consequently, lack of gastrointestinal (GI) symptoms and even a negative stool guaiac test do not exclude the possibility of occult CD in a patient who presents with a characteristic arthritis.

**6. Which points in the history and physical examination are helpful in separating inflammatory spinal arthritis from mechanical low back pain in an IBD patient?**

On the basis of history and physical examination, 90% of patients with inflammatory spinal arthritis can be differentiated from patients with mechanical low back pain (Table 63-2).

**Table 63-2.** Clinical Differentiation of Inflammatory Spinal Arthritis and Mechanical Low Back Pain

	INFLAMMATORY SA	MECHANICAL LBP
Onset of pain	Insidious	Acute
Duration of morning stiffness	>60 min	<30 min
Nighttime pain	Yes	Infrequent
Exercise effect on pain	Improvement	Worsen
Sacroiliac joint tenderness	Usually	No
Range of back motion	Global loss of motion	Abnormal flexion
Reduced chest expansion	Sometimes	No
Neurologic deficits	No	Possible
Duration of symptoms	>3 mo	<4 wk

LBP, Low back pain; SA, spinal arthritis.

**7. Does the activity of inflammatory spinal arthritis correlate with the activity of the IBD?**

No. The onset of sacroiliitis or spondylitis can precede onset of IBD by years, occur concurrently, or follow onset by years. Furthermore, the course of the spinal arthritis is completely independent of the course of IBD.

**8. What HLA occurs more commonly than expected in patients with inflammatory spinal arthritis associated with IBD?**

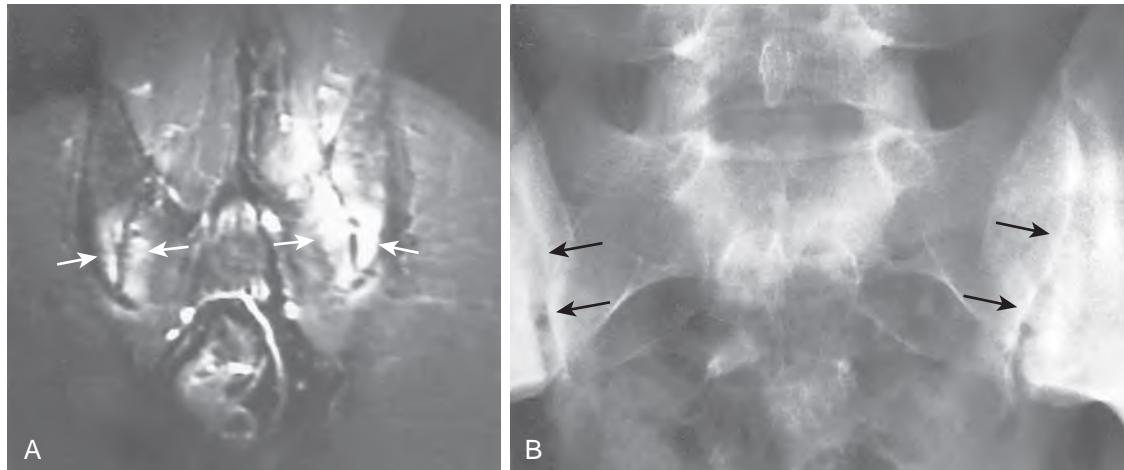
HLA-B27 is found in 55% of CD patients and 70% of UC patients with inflammatory sacroiliitis or spondylitis. This contrasts with an 8% frequency of HLA-B27 in a normal, healthy, white population. Thus a patient with IBD who possesses the HLA-B27 gene has 7 to 10 times increased risk of developing inflammatory sacroiliitis or spondylitis compared with IBD patients who are HLA-B27 negative.

**9. What serologic abnormalities are seen in patients with IBD?**

- Erythrocyte sedimentation rate (ESR) and C-reactive protein are elevated, whereas rheumatoid factor and antinuclear antibody are negative.
- Perinuclear antineutrophil cytoplasmic antibody is seen in more than 55% to 70% of UC patients and fewer than 20% of colon-predominant CD patients. It is usually directed against lactoferrin and less commonly bactericidal permeability increasing protein, cathepsin G, lysozyme, or elastase. It is never directed against myeloperoxidase.
- Anti-Saccharomyces cerevisiae is present in 40% to 70% of CD patients and rarely (<15%) in UC patients.

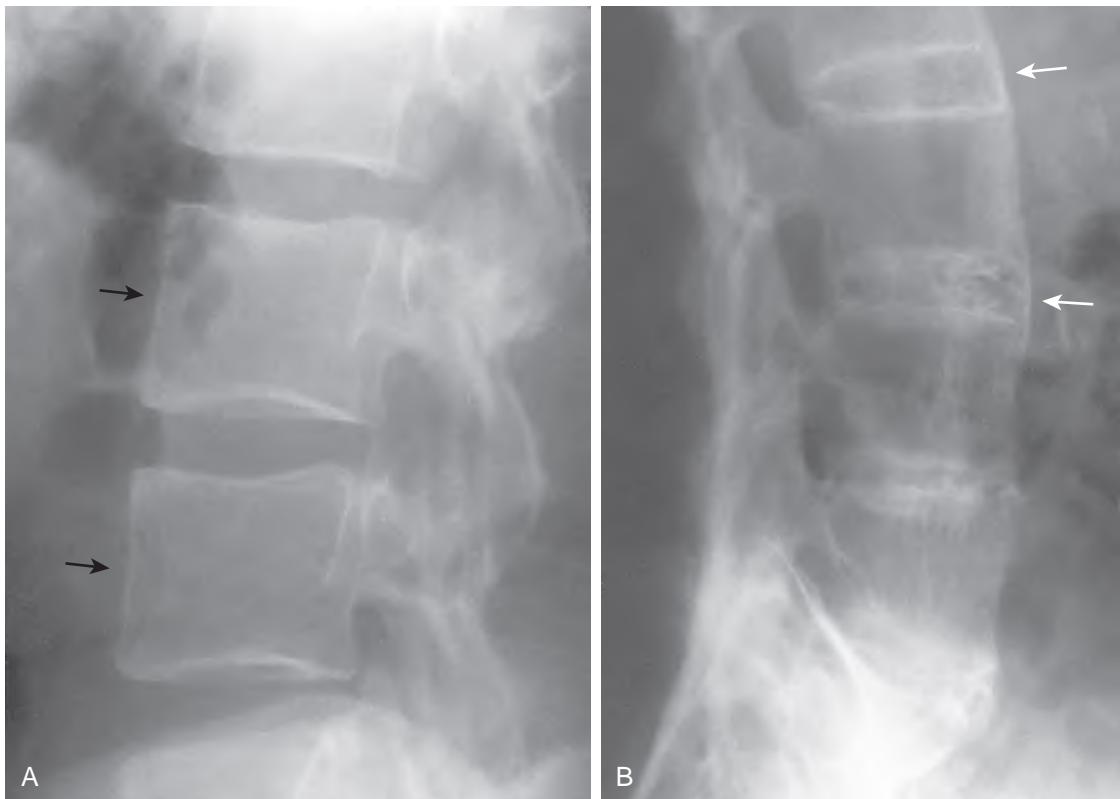
**10. Describe the typical radiographic features of inflammatory sacroiliitis and spondylitis in IBD patients.**

The radiographic abnormalities in IBD patients with inflammatory spinal arthritis are similar to those seen in ankylosing spondylitis. Patients with early inflammatory sacroiliitis frequently have normal plain radiographs. In these patients, magnetic resonance imaging of the sacroiliac joints demonstrates inflammation and edema (Figure 63-2A). Over several months to years, patients develop sclerosis and erosions in the lower two thirds of the sacroiliac joint (see Figure 63-2B). In some patients, these joints may completely fuse.



**Figure 63-2.** A, Magnetic resonance image of the sacroiliac joints showing inflammation (arrows) (T2-weighted image, TE50, TR2500). B, Radiograph showing early bilateral sacroiliitis (arrows).

Patients with early spondylitis may also have normal radiographs. Later, radiographs may show shiny corners at the insertion of the annulus fibrosis, anterior squaring of the vertebrae, and syndesmophyte formation (Figure 63-3A). Syndesmophytes (calcification of annulus fibrosis) are thin, marginal, and bilateral. A “bamboo spine” (bilateral syndesmophytes traversing the entire spine from lumbar to cervical) (see Figure 63-3B) occurs in 10% of patients. Patients who develop inflammatory hip disease are at increased risk for subsequently developing a bamboo spine.



**Figure 63-3.** A, Radiographs showing anterior squaring of the vertebrae in a patient with early inflammatory spondylitis. B, Radiograph showing thin, marginal syndesmophytes (*arrows*) causing bamboo spine in a patient with Crohn's disease with advanced inflammatory spondylitis.

**11. What other rheumatic problems occur with increased frequency in IBD patients?**

- Achilles tendon and plantar fascia enthesitis
- Clubbing of fingernails (5%, mostly CD)
- Hypertrophic osteoarthropathy (periostitis)
- Psoas abscess or septic hip from fistula formation (CD)
- Osteoporosis secondary to medications (i.e., prednisone)
- Granulomatous lesions of bone and joints (CD)
- Vasculitis (<5%)
- Amyloidosis

**12. Can treatment alleviate the symptoms of inflammatory peripheral arthritis or spinal arthritis in IBD patients?**

See Table 63-3.

**13. What rheumatic disorders are associated with pouchitis, lymphocytic colitis (LC), and collagenous colitis (CC)?**

Pouchitis is inflammation of the ileal pouch created following colectomy for UC. It occurs in up to 40% to 60% of patients having this surgery. Patients present with watery or bloody diarrhea. Some develop arthritic manifestations (Table 63-4). Treatment includes metronidazole and ciprofloxacin. Surgical revision may be necessary in treatment-resistant cases.

Microscopic colitis includes both LC and CC. Patients present with watery diarrhea and may develop arthritic manifestations (10%-20%) or autoimmune thyroiditis (see Table 63-4). Patients older than 65 years (80%) and females (60%) are most commonly affected. The diagnosis can only be made by tissue histologic examination obtained by colonoscopy. Budesonide is effective for inducing and maintaining clinical and histologic remission for CC and LC, and loperamide may ameliorate diarrhea. Evidence for benefit of bismuth subsalicylate and mesalamine with or without cholestyramine for treatment of CC or LC is weak.

**Table 63-3.** Alleviation of Arthritic Symptoms in Inflammatory Bowel Disease

	<b>PERIPHERAL ARTHRITIS</b>	<b>SACROILIITIS/Spondylitis</b>
NSAIDs*	Yes	Yes
Intra-articular corticosteroids	Yes	Yes (sacroiliitis)
Sulfasalazine	Yes	No
Immunosuppressives (MTX, 6-MP)	Yes	No
Anti-TNF $\alpha$	Yes	Yes
Bowel resection		
UC	Yes	No
CD	No	No

CD, Crohn's disease; FDA, Food and Drug Administration; IBD, inflammatory bowel disease; 6-MP, 6-mercaptopurine; MTX, methotrexate; NSAID, nonsteroidal antiinflammatory drug; TNF, tumor necrosis factor; UC, ulcerative colitis.

\*NSAIDs may exacerbate IBD. Sulfasalazine helps the peripheral arthritis in UC patients more than CD patients. Anti-TNF $\alpha$  agents that are FDA-approved and effective include infliximab, adalimumab, golimumab, and certolizumab pegol.

**Table 63-4.** Rheumatic Disorders Associated with Pouchitis, Lymphocytic Colitis, and Collagenous Colitis

	<b>POUCHITIS</b>	<b>LC</b>	<b>CC</b>
IBD-like peripheral inflammatory arthritis	Yes	Yes	Yes
Rheumatoid arthritis	No	Yes	Yes
Ankylosing spondylitis*	No	No	No
Thyroiditis or other autoimmune disease	No	Yes	Yes

CC, Collagenous colitis; IBD, inflammatory bowel disease; LC, lymphocytic colitis.

\*Up to 60% of patients with ankylosing spondylitis have asymptomatic Crohn-like lesions on right-sided colon biopsies. However, only 4% to 5% will evolve into overt inflammatory bowel disease.

#### 14. Why are patients with IBD more prone to develop an inflammatory arthritis?

The pathogenesis of gut-joint iteropathy is unknown. However, inflammation of the gut and joints appear to be tightly linked. When ileocolonoscopies are done on spondyloarthropathy (ankylosing spondylitis, reactive arthritis) patients without GI symptoms, up to 25% have macroscopic lesions and up to 60% have microscopic evidence of asymptomatic CD. Over time, 6% to 10% of these patients develop overt symptomatic CD. Alternatively, up to 10% of IBD patients without evidence of a spondyloarthropathy at onset of their GI symptoms will develop overt arthritis on followup.

Environmental antigens capable of inciting rheumatic disorders enter the body's circulation by traversing the respiratory mucosa, skin, or GI mucosa. The human GI tract has an estimated surface area of  $400 \text{ m}^2$  (200 times the body's skin surface area) and functions not only to absorb nutrients but also to exclude potentially harmful antigens. The gut-associated lymphoid tissue, which includes Peyer patches, the lamina propria, and intraepithelial T cells, constitutes 25% of the GI mucosa and helps to exclude entry of bacteria and other foreign antigens. Whereas the upper GI tract is normally exposed to  $10^3$  mucosa-adhering bacteria, the lower GI tract is constantly in contact with millions of bacteria (up to  $10^{12}/\text{g}$  of feces). The total number of bacterial cells called the *human microbiota* that we are exposed to is 10 times that of the number of cells of the body.

Inflammation, whether from idiopathic IBD or from infection with pathogenic microorganisms, can disrupt the normal integrity and function of the bowel, leading to increased gut permeability. This increased permeability may allow nonviable bacterial antigens in the gut lumen to enter the circulation more easily. These microbial antigens could either deposit directly in the joint synovia, leading to a local inflammatory reaction, or cause a systemic immune response, resulting in immune complexes that then deposit in joints and other tissues. Genetic susceptibility is required to develop the immunologic response in the gut and joint, which results in persistent inflammation and tissue injury.

## REACTIVE ARTHRITIS

### 15. What is reactive arthritis, and what are the most common GI pathogens that cause it?

A reactive arthritis is a sterile inflammatory arthritis that occurs within 1 to 3 weeks following an infection by an organism that infects mucosal surfaces, especially the urethra or large bowel. The most common GI pathogens causing reactive arthritis are:

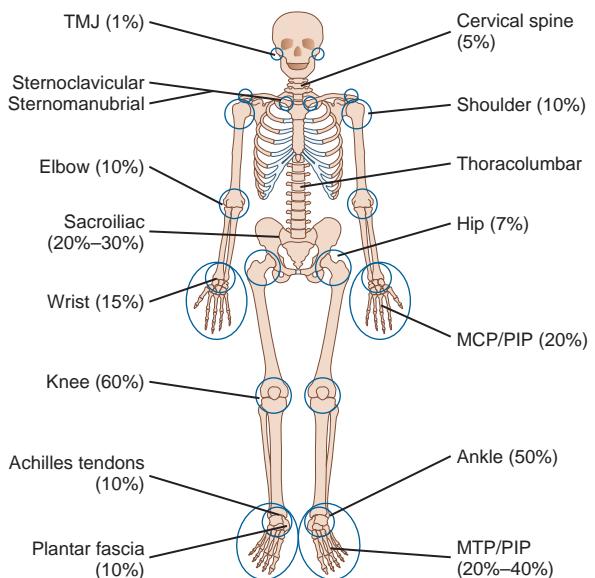
- *Yersinia enterocolitica* (0:3 and 0:9) or *Yersinia pseudotuberculosis*
- *Salmonella enteritidis* or *Salmonella typhimurium*
- *Shigella flexneri*, then *Shigella dysenteriae*, and occasionally *Shigella sonnei*
- *Campylobacter jejuni* or *Campylobacter coli*
- *Clostridium difficile*

Approximately 1% to 3% of patients who have an infectious gastroenteritis during an epidemic subsequently develop a reactive arthritis. It may be as high as 20% in *Yersinia*-infected individuals. Recently, joint pain following a diarrheal illness caused by pathogenic *Escherichia coli* has been reported.

### 16. Which joints are most commonly involved in a reactive arthritis following a bowel infection (i.e., postenteric reactive arthritis)?

See Figure 63-4.

**Figure 63-4.** Joints commonly involved in reactive arthritis after bowel infection. MCP, Metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal; TMJ, temporomandibular joint.



### 17. Describe the clinical characteristics of postenteric reactive arthritis.

- Demographically, males are affected more frequently than females; average age is 30 years old.
- Onset of arthritis is abrupt and acute.
- Distribution of joints is asymmetric and oligoarticular. A lower extremity is involved in 80% to 90%. Sacroiliitis occurs in 20% to 30%; enthesitis (Achilles tendon, plantar fascia attachments) and toe dactylitis occur.
- Synovial fluid analysis finds inflammatory fluid (usually 10,000-50,000 WBC/mm<sup>3</sup>), no crystals, and negative cultures.
- Course and prognosis finds that 80% resolve in 1 to 6 months; 20% have chronic arthritis with radiographic changes of peripheral and/or sacroiliac joints.

### 18. What extraarticular manifestations can occur in patients with postenteric reactive arthritis?

- Sterile urethritis (15% to 70%)
- Conjunctivitis
- Acute anterior uveitis (iritis)
- Oral ulcers (painless or painful)
- Erythema nodosum (5% of *Yersinia* infections)
- Circinate balanitis
- Keratoderma blennorrhagicum

**19. How commonly do patients with postenteric reactive arthritis have the clinical features of reactive arthritis (Reiter's syndrome)?**

The triad of inflammatory arthritis, urethritis, and conjunctivitis and uveitis with or without mucocutaneous lesions that characterize reactive arthritis (Reiter's syndrome) may develop 2 to 4 weeks after an acute urethritis or diarrheal illness. The frequency of the triad varies with the causative enteric organism:

- *Shigella*, 85%
- *Yersinia*, 10%
- *Salmonella*, 10% to 15%
- *Campylobacter*, 10%

**20. How do the radiographic features of inflammatory sacroiliitis and spondylitis caused by postenteric reactive arthritis differ from those in IBD patients?**

See Table 63-5 and Figure 63-5.

**Table 63-5. Radiologic Comparison of Spinal Arthritis in Postenteric Reactive Arthritis Versus Inflammatory Bowel Disease**

<b>REACTIVE ARTHRITIS</b>		<b>IBD</b>
Sacroiliitis	Unilateral, asymmetric	Bilateral, sacroiliac involvement
Spondylitis	Asymmetric, nonmarginal, jug-handle syndesmophytes	Bilateral, thin, marginal syndesmophytes

IBD, Inflammatory bowel disease.



**Figure 63-5.** A, Radiograph showing unilateral sacroiliitis (arrows) in a patient with reactive arthritis. B, Radiograph showing large, nonmarginal syndesmophytes (arrows) of the spine in a patient with reactive arthritis.

**21. Discuss the relationship of HLA-B27 positivity in patients with postenteric reactive arthritis compared with a normal healthy population.**

- Reactive arthritis patients, 60% to 80% HLA-B27 positive; normal healthy controls, 4% to 8% HLA-B27 positive.
- Caucasians and patients with radiographic sacroiliitis or uveitis are more likely to be HLA-B27 positive.
- A person who is HLA-B27 positive has a 30 to 50 times increased risk of developing reactive arthritis following an episode of infectious gastroenteritis compared with a person who does not have the HLA-B27 gene.
- Only 20% to 25% of all HLA-B27-positive individuals who get an infectious gastroenteritis from *Shigella*, *Salmonella*, or *Yersinia* go on to develop a postenteric reactive arthritis.

**22. Explain the current theory for the pathogenesis of a postenteric reactive arthritis.**

Bacterial lipopolysaccharide antigens (but not viable organisms or nucleotides) from the pathogens (*Yersinia*, *Shigella*, *Salmonella*) causing the infectious gastroenteritis have been shown to be deposited in the joints of patients who develop a postenteric reactive arthritis. These bacterial cell wall components are thought to incite inflammation in the joint. The role that *HLA-B27* plays in the pathogenesis is debated. One possibility is that recirculating *HLA-B27*-restricted T cells present bacteria-derived peptides with arthritogenic properties to the immune system in a unique way, leading to inflammation. Another postulate is that there is molecular mimicry between the *HLA-B27* molecule and the bacterial antigens, causing an aberrant immune response leading to altered or defective intracellular killing by *HLA-B27*-positive cells, resulting in persistence of arthritogenic pathogens. A third hypothesis relates to the tendency for the *HLA-B27* heavy chain to misfold when the cell is under stress. This results in heavy chains accumulating in the endoplasmic reticulum leading to an “unfolded protein response,” causing the release of inflammatory cytokines. The chronic persistence of bacterial antigens may stress the *HLA-B27*-positive cells, leading to B27 heavy chain misfolding and the unfolded protein response. However, because *HLA-B27* positivity is neither necessary nor sufficient to cause reactive arthritis, additional genetic (endoplasmic reticulum aminopeptidase-1 and interleukin 23R polymorphisms) and environmental factors likely play a role in the pathogenesis of postenteric reactive arthritis.

**23. Is any therapy beneficial for postenteric reactive arthritis?**

See Table 63-6.

**Table 63-6.** Treatment of Postenteric Reactive Arthritis

TREATMENT	ACUTE	CHRONIC	SACROILIITIS
NSAIDs	Yes	Yes	Yes
Corticosteroids	Yes	Yes	Yes
Intraarticular Oral only if used in high doses	No	No	
Antibiotics			
2-wk course	No	No	No
3-mo course	NA	No	No
Sulfasalazine	NA	Yes	No
Methotrexate	NA	Yes	No
Anti-TNF $\alpha$ *	NA	Yes	Yes

NA, Not applicable; NSAID, nonsteroidal antiinflammatory drug; TNF, tumor necrosis factor.

\*Anti-TNF $\alpha$  agents include etanercept, infliximab, adalimumab, golimumab and certolizumab pegol not FDA-approved.

## WHIPPLE DISEASE

**24. Who was Whipple?**

George Hoyt Whipple, MD, in 1907 reported the case of a 36-year-old medical missionary with diarrhea, malabsorption with weight loss, mesenteric lymphadenopathy, and migratory polyarthritis. He named this disease “intestinal lipodystrophy,” but it is now known as Whipple disease. Dr. Whipple also became a Nobel laureate in physiology in 1934 and was the founder of the University of Rochester Medical School.

**25. What are the multisystem manifestations of Whipple disease?**

W = Wasting and weight loss  
H = Hyperpigmentation (skin)  
I = Intestinal pain  
P = Pleurisy  
P = Pneumonitis  
L = Lymphadenopathy  
E = Encephalopathy  
S = Steatorrhea

D = Diarrhea  
I = Interstitial nephritis  
S = Skin rashes  
E = Eye inflammation  
A = Arthritis  
S = Subcutaneous nodules  
E = Endocarditis

**26. Describe the clinical characteristics of the arthritis associated with Whipple disease.**

Whipple disease occurs most commonly in middle-aged white men (male/female ratio, 8:1). Seronegative oligoarthritis or polyarthritis (knees, ankles, wrists) is the presenting symptom in 60% of patients and may

precede the intestinal symptoms by up to 5 years. More than 70% of patients will develop arthritis at some time during their disease course. The arthritis is inflammatory, is often migratory, and does not correlate with intestinal symptoms. Sacroiliitis or spondylitis occurs in 5% to 10% of patients, especially in those who are HLA-B27 positive (33% of patients). Synovial fluid analysis shows an inflammatory fluid with 5000 to 100,000 cells/mm<sup>3</sup> (predominantly neutrophils). Radiographs usually remain unremarkable.

#### **27. What are the etiologic factors of Whipple disease and how is the diagnosis made?**

Whipple disease is caused by a gram-positive actinomycete called *Tropheryma whipplei*. The diagnosis is made by demonstrating periodic acid-Schiff (PAS)-positive inclusions in macrophages of affected tissues, typically a small bowel or lymph node biopsy sample. These deposits contain the rod-shaped free *Tropheryma whipplei* bacilli seen on electron microscopy. The diagnosis can be confirmed by a polymerase chain reaction (PCR) of the DNA sequence of the 16S-ribosomal RNA gene sequence of *T. whipplei* in the PAS-positive tissue sample. PCR testing of cerebrospinal fluid has also been used to confirm central nervous system (CNS) Whipple disease. PCR testing of synovial fluid and blood can be performed but has limited sensitivity in patients with untreated Whipple disease.

#### **28. How is Whipple disease best treated?**

Initial treatment is ceftriaxone (or meropenem) for 2 weeks to ensure therapy of the CNS. Oral trimethoprim (TMP)-sulfamethoxazole (SMX) is subsequently used for more than 1 year. Tetracycline can be used in sulfa-allergic patients. Relapses can occur particularly in patients with CNS involvement (30%). These patients should be treated indefinitely with oral TMP/SMX.

### **OTHER GASTROINTESTINAL DISEASES**

#### **29. What rheumatic manifestations have been described in patients with celiac disease (CeD; gluten-sensitive enteropathy)?**

CeD is an enteropathy resulting from an autoimmune reaction to wheat gluten and gliadin by T lymphocytes in the gut in genetically predisposed individuals. It is primarily seen in white patients and is associated with HLA-DQ2 or HLA-DQ8, usually in linkage with HLA-DR3. Tissue transglutaminase (tTG) is the major autoantigen. Dietary gluten is partly digested by gastric enzymes to peptides including gliadin that is deaminated by tTG, which increases its immunogenicity. This immunogenic gliadin peptide is presented in the context of HLA-DQ2 or DQ8 to CD4+ T cells, resulting in interferon  $\gamma$  release and inflammation, altered gut permeability, and villous atrophy. The most frequent rheumatic manifestations include:

- Symmetric polyarthritis (4% to 26%) involving predominantly large joints (knees and ankles more frequently than hips and shoulders) occurs. Oligoarthritis and sacroiliitis can also occur. Importantly, the arthritis may precede enteropathic symptoms in 50% of cases.
- Osteomalacia is caused by steatorrhea from severe enteropathy causing vitamin D deficiency
- Dermatitis herpetiformis

CeD can be screened for by testing for immunoglobulin A antibodies against tTG (95% sensitivity/90% specificity) and confirmed by endoscopy with small bowel biopsy. The rheumatic manifestations can respond dramatically to a gluten-free diet but not always.

#### **30. Describe the intestinal bypass arthritis-dermatitis syndrome.**

In the past, this syndrome occurred in 20% to 80% of patients who had undergone intestinal bypass (jejunoleal or jejunocolic) surgery for morbid obesity. With newer techniques for bariatric surgery, this has been eliminated. Currently this is a rare complication occurring in GI diseases with defective peristalsis (systemic sclerosis, colorectal surgery) or a diverticular abscess. The arthritis is intensely painful, inflammatory, oligoarticular, and frequently migratory, affecting both upper and lower extremity small and large joints. Radiographic findings usually remain normal, despite 25% of patients having chronic recurring episodes of arthritis. Up to 80% develop dermatologic abnormalities, the most characteristic of which is a maculopapular or vesiculopustular rash.

The pathogenesis involves bacterial overgrowth in the blind loop, resulting in antigenic stimulation that purportedly causes immune complex formation (frequently cryoprecipitates containing secretory IgA and bacterial antigens) in the serum that deposits in the joints and skin. Treatment includes nonsteroidal antiinflammatory drugs and oral antibiotics, which usually improve symptoms. Only surgical reanastomosis of the blind loop or improvement in peristalsis can result in complete elimination of symptoms.

#### **31. What types of arthritis can be associated with carcinomas of the esophagus and colon?**

Carcinomatous polyarthritides can be the presenting feature of an occult malignancy of the GI tract. The arthritis is typically acute in onset and asymmetric and predominantly involves lower extremity joints while sparing the small joints of the hands and wrists. Patients have an elevated ESR and a negative rheumatoid factor. Another type of arthritis associated with colorectal malignancy is septic arthritis caused by *Streptococcus bovis*.

### 32. What are the clinical features of the pancreatitis, panniculitis, and polyarthritis (PPP) syndrome?

PPP syndrome is a systemic syndrome occurring in some patients with pancreatitis or pancreatic acinar cell carcinoma. Its clinical manifestations can be remembered by the following mnemonic:

**P** = Pancreatitis

**A** = Arthritis (60%) and arthralgias, usually of the ankles and knees (synovial fluid is typically noninflammatory and creamy in color as a result of lipid droplets that stain with Sudan black or oil red O)

**N** = Nodules that are tender, red, and usually on extremities (frequently misdiagnosed as erythema nodosum but really are areas of lobular panniculitis with fat necrosis)

**C** = Cancer of the pancreas (a more common cause than pancreatitis)

**R** = Radiologic abnormalities caused by osteolytic bone lesions from bone marrow necrosis (10%)

**E** = Eosinophilia

**A** = Amylase, lipase, and trypsin released by the diseased pancreas (causes fat necrosis in skin, synovium, and bone marrow)

**S** = Serositis, including pleuropericarditis, frequently with fever

### 33. What musculoskeletal problem can occur with pancreatic insufficiency?

Osteomalacia caused by fat-soluble vitamin D malabsorption.

### BIBLIOGRAPHY

1. Andras C, Csiki Z, Ponyi A, et al. Paraneoplastic rheumatic syndromes. *Rheumatol Int* 2006;26:376–82.
2. Carter JD, Hudson AP. Reactive arthritis: clinical aspects and medical management. *Rheum Dis Clin North Am* 2009;35:21–44.
3. Chand N, McDonald JW, Macdonald JK. Interventions for treating collagenous colitis. *Cochrane Database Syst Rev* 2008;16, CD003575.
4. Fenollar F, Puechal X, Raoult D. Whipple's disease. *N Engl J Med* 2007;356:55–66.
5. Gentile NM, Abdalla AA, Khanna S, et al. Outcomes of patients with microscopic colitis treated with corticosteroids: a population-based study. *Am J Gastroenterol* 2013;108(2):256–9. <http://dx.doi.org/10.1038/ajg.2012.416>.
6. Green PHR, Cellier C. Celiac sprue. *N Engl J Med* 2007;357:1731–43.
7. Holden W, Orchard T, Wordsworth P. Enteropathic arthritis. *Rheum Dis Clin N Am* 2003;29:513–30.
8. Lichtenstein GR, Sands BE, Pazianas M. Prevention and treatment of osteoporosis in inflammatory bowel disease. *Inflamm Bowel Dis* 2006;12:797–813.
9. Lubrano E, Cicacci C, Amers PR, et al. The arthritis of coeliac disease: prevalence and pattern in 200 adult patients. *Br J Rheumatol* 1996;35:1314–8.
10. Narvaez J, Bianchi MM, Santo P, et al. Pancreatitis, panniculitis, and polyarthritis. *Semin Arthritis Rheum* 2010;39:417–23.
11. Rodriguez-Reyna TS, Martinez-Reyes C, Yamamoto-Furusho JK. Rheumatic manifestations of inflammatory bowel disease. *World J Gastroenterol* 2009;15:5517–24.
12. Schiellerup P, Krogfelt KA, Locht H. A comparison of self-reported joint symptoms following infection with different enteric pathogens: effect of HLA-B27. *J Rheumatol* 2008;35:480–7.
13. Turner JR. Intestinal mucosal barrier function in health and disease. *Nat Rev Immunol* 2009;9:799–809.
14. Tysk C, Bohr J, Nyhlin N, et al. Diagnosis and management of microscopic colitis. *World J Gastroenterol* 2008;14:7280–8.
15. Zhiludev A, Zurkowski D, Young W, Leichtner A, Bousvaros A. Serologic testing with ANCA, ASCA, and anti-OmpC in children and young adults with Crohn's disease and ulcerative colitis: diagnostic value and correlation with disease phenotypes. *Am J Gastroenterol* 2004;99:2235–41.

### Website

Spondylitis Association of America. [www.spondylitis.org](http://www.spondylitis.org). [Accessed September 22, 2014].

# DERMATOLOGIC MANIFESTATIONS OF GASTROINTESTINAL DISEASE

James E. Fitzpatrick, MD, and Lori D. Prok, MD

## 1. At what serum level of bilirubin do adults and infants develop clinically noticeable jaundice?

Adults develop clinically detectable jaundice when serum levels of bilirubin reach 2.5 to 3 mg/dL, whereas infants may not demonstrate visually detectable jaundice (from the French word *jaune*, meaning yellow) until serum levels reach 6 to 8 mg/dL. Hyperbilirubinemia precedes jaundice by several days because the bilirubin has not yet bound to tissue. After serum levels of bilirubin normalize, patients may remain visually jaundiced, as it takes several days for tissue-bound bilirubin to be released.

## 2. Where is clinical jaundice first visible?

The mucosae of the soft palate and sublingual region are often the first mucocutaneous surfaces to appear yellow in response to hyperbilirubinemia. This is likely because of the thin mucosal surface in these anatomic locations. Bilirubin also has a strong affinity for elastin, which accounts for its early appearance in the sclera of the eye.

## 3. What other conditions produce yellowish discoloration of the skin?

Carotenoderma caused by excessive ingestion of carotene (e.g., yellow and orange vegetables such as carrots, sweet potatoes, and squash), lycopenodermia caused by excessive ingestion of lycopenes (e.g., red vegetables such as tomatoes and rose hips), and systemic administration of quinacrine can all cause yellowish skin discoloration unrelated to hyperbilirubinemia. The skin may also demonstrate a sallow, subtle yellowish hue in patients with profound hypothyroidism.

## 4. What are Terry nails and Muehrcke nails?

Terry nails are characterized by uniform white discoloration of the nail, with the distal 1 to 2 mm remaining pink. The white color results from abnormalities in the nail bed vasculature and is most commonly seen in patients with liver cirrhosis, heart disease, and diabetes. Muehrcke nails are characterized by double white transverse lines across the nails. They disappear when pressure is applied. These lines are also caused by abnormal vasculature of the nail bed. They are most commonly seen in liver disease associated with hypoalbuminemia.

## 5. What gastrointestinal (GI) disease is associated with blue lunulae?

The lunula is the moon-shaped white area present at the proximal nail plate. Blue lunulae are seen in Wilson disease (hepatolenticular degeneration), which is caused by an autosomal recessive defect in ATP7B and copper transport. Copper accumulates in the liver, brain, cornea, skin, nails, and other tissues. Patients may also demonstrate pretibial hyperpigmentation. Kayser-Fleischer rings (brown to green circle of pigment in Descemet membrane of the eye) are pathognomonic of Wilson disease.

## 6. What are spider angiomas? Why are they associated with liver disease?

Spider angiomas (nevus araneus) are vascular lesions characterized by a central arteriole and horizontal radiating thin-walled vessels that produce the legs of the vascular spider (Figure 64-1). The pulsation of the central, vertically oriented arteriole in larger lesions can be visualized with diascopy (observing the lesion through a glass slide firmly pressed on the lesion). The pathophysiologic mechanism is not proven, but the high incidence

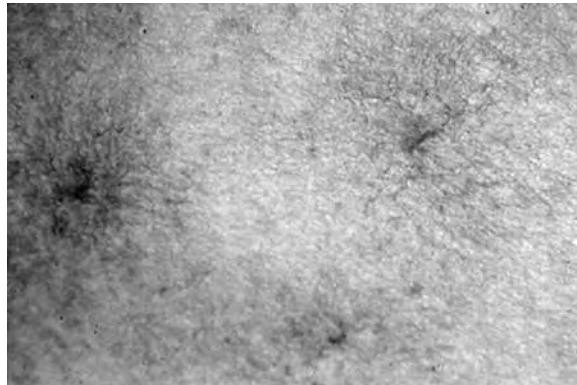


Figure 64-1. Three spider angiomas demonstrating central arteriole and radiating dilated blood vessels.

of spider angiomas in alcohol-associated hepatitis and pregnancy suggests that elevated levels of estrogens resulting from higher production or decreased metabolism is responsible. Patients with liver cirrhosis and spider angiomas have elevated plasma levels of vascular endothelial growth factor, which may play a role in the development of spider angiomas.

#### **7. Do the number of spider angiomas correlate with the severity of alcohol-induced liver disease?**

Yes, although there is some degree of individual susceptibility to spider angiomas. However, the correlation is high enough that one report suggests that barmaids in New York used to guess the degree of severity of liver cirrhosis of their customers based on the number of visible spider angiomas. The number of spider angiomas also correlates with the presence of esophageal varices. One study demonstrated that the presence of more than 20 spider angiomas correlated with a 50% chance of esophageal bleeding.

#### **8. Why do many patients with hepatobiliary disease itch?**

Approximately 40% of patients with hepatic cirrhosis demonstrate moderate to severe pruritus. The mechanism of pruritus associated with hepatobiliary disease has not been firmly established, but is likely caused by elevated levels of bile acids secondary to cholestasis. Serum bile acids are frequently elevated in patients with hepatobiliary disease and pruritus, and bile acid-binding resins relieve the pruritus. Studies on purified bile salts placed on blister bases have shown that all bile salts produced pruritus, but unconjugated chenodeoxycholate is the most potent.

#### **9. A 64-year-old alcoholic man presents with blisters on the dorsal hands and sclerotic changes of the facial skin. For what chronic liver disease should he be screened?**

This patient most likely has porphyria cutanea tarda (PCT), and he should be evaluated for hepatitis C virus (HCV) infection. Patients with hepatitis C can present with a variety of cutaneous eruptions, including pruritus, vasculitis, lichen planus, cryoglobulinemic purpura, and PCT. PCT is characterized by photosensitivity, skin fragility resulting in vesicles and bullae of sun-exposed skin, dyspigmentation, alopecia, hirsutism, and skin thickening. It is caused by reduced hepatic uroporphyrinogen decarboxylase activity, which results in overproduction of blood and urine porphyrins. HCV may cause hepatic iron overload in genetically susceptible individuals, leading to the clinical manifestations of PCT. Concomitant alcohol abuse, or other diseases or medications resulting in excess estrogens, increases the risk of developing PCT in these patients.

#### **10. List the GI diseases most commonly associated with pyoderma gangrenosum (PG).**

Like erythema nodosum, PG is associated with ulcerative colitis (most common), Crohn's disease, and chronic infectious hepatitis. One study reported that 50% all cases of PG are associated with ulcerative colitis but less than 10% of all patients with ulcerative colitis will develop PG. A separate study reported that one third of patients with PG had inflammatory bowel disease; ulcerative colitis and Crohn's disease were equally represented.

#### **11. What are the cutaneous manifestations of pancreatitis?**

Cutaneous manifestations of pancreatitis include Cullen sign, Grey Turner sign, and pancreatic fat necrosis. Cullen sign is a hemorrhagic discoloration of the umbilical area caused by intraperitoneal hemorrhage from any cause; one of the more frequent causes is acute hemorrhagic pancreatitis. Grey Turner sign is a discoloration of the left flank associated with acute hemorrhagic pancreatitis. Acute and chronic pancreatitis and pancreatic carcinoma may also produce pancreatic fat necrosis, which presents as very tender, erythematous nodules of the subcutaneous fat that may spontaneously drain necrotic material (Figure 64-2). Patients also often have associated acute arthritis that may be crippling. Histologically, pancreatic fat necrosis demonstrates diagnostic changes manifesting as necrosis and saponification of the fat associated with acute inflammation. The fat necrosis is thought to be due to release of lipase and amylase, which have been demonstrated to be elevated within lesions.



**Figure 64-2.** Pancreatic fat necrosis in a patient with alcohol-associated pancreatitis. Unlike erythema nodosum, epidermal changes (note scale) and ulceration are common.

**12. What GI disease is most commonly associated with dermatitis herpetiformis?**

Celiac disease (gluten-sensitive enteropathy). Although almost all patients demonstrate histologic findings of celiac disease in the gastrointestinal tract, only one-third demonstrate clinical symptoms of celiac disease. Both celiac disease and dermatitis herpetiformis respond to a gluten-free diet. Oral dapsone results in rapid improvement of the skin lesions and associated pruritus of dermatitis herpetiformis.

**13. What is Troussseau sign?**

Trousseau sign consists of superficial migratory thrombophlebitis associated with an underlying malignancy. Clinically it presents as erythematous linear cords that affect the superficial veins of the extremities and trunk. Patients typically continue to develop new lesions at multiple sites that may appear to *migrate*. Troussseau sign may be seen in association with many types of GI malignancies (e.g., gastric carcinoma, pancreatic adenocarcinoma) in addition to lung carcinoma, multiple myeloma, and Hodgkin's disease. The pathogenesis is not understood and the thrombophlebitis is notoriously resistant to anticoagulant therapy. It was a cruel coincidence that the physician who described this sign, Dr. Troussseau, was himself to develop Troussseau sign secondary to his underlying gastric carcinoma, which was ultimately fatal.

**14. Who was Sister Mary Joseph and what is a Sister Mary Joseph nodule?**

Sister Mary Joseph was the first surgical assistant to Dr. W. J. Mayo, who eventually became the superintendent of St. Mary's Hospital in Rochester, Minnesota. A Sister Mary Joseph nodule is an umbilical metastasis of an internal malignancy. In the largest series reported, the most common primary malignancies were stomach (20%), large bowel (14%), ovary (14%), and pancreas (11%). In 20% of cases, the primary could not be established. In 14% of cases, a Sister Mary Joseph nodule was the initial presentation of the internal malignancy. Umbilical metastases usually indicate advanced disease; the average survival is 10 months. Although it was Dr. Mayo who described the clinical features of nodular umbilical metastases, Sister Mary Joseph is credited with being the first to appreciate that patients with this finding had a poor prognosis.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

**BIBLIOGRAPHY**

1. Cacoub P, Bourlière M, Lübbe J, et al. Dermatological side effects of hepatitis C and its treatment: Patient management in the era of direct-acting antivirals. *J Hepatol* 2012;56:455–63.
2. Galossi A, Guarisco R, Bellis L, et al. Extrahepatic manifestations of chronic HCV infection. *J Gastrointestin Liver Dis* 2007;16:65–73.
3. Garcia-Romero D, Vanaclocha F. Pancreatic panniculitis. *Dermatol Clin* 2008;26:465–70.
4. Ghosn SH, Kibbi AG. Cutaneous manifestations of liver diseases. *Clin Dermatol* 2008;26:274–82.
5. Lee BA, Yu L, Ma L, et al. Sebaceous neoplasms with mismatch repair protein expressions and the frequency of co-existing visceral tumors. *J Am Acad Dermatol* 2012;67:1228–34.
6. Li CP, Lee FY, Hwang SJ, et al. Spider angiomas in patients with liver cirrhosis: Role of vascular endothelial growth factor and basic fibroblast growth factor. *World J Gastroenterol* 2003;9:2832–3.
7. Masmoudi A, Boudaya S, Charfeddine A, et al. Sister Mary Joseph's nodule: Report of five cases. *Int J Dermatol* 2008;47:134–6.
8. McDonald J, Bayrak-Toydemir P. Hereditary hemorrhagic telangiectasia. *Haematologica* 2005;90:728–32.
9. Thrash B, Patel M, Shah KR, et al. Cutaneous manifestations of gastrointestinal disease: Part II. *J Am Acad Dermatol* 2013;68:211.
10. Wahie S, Lawrence CM. Cutaneous signs as a presenting manifestation of alcohol excess. *Br J Dermatol* 2006;155:195–7.

**Website**

University of British Columbia Dermatology. Accessed September 22, 2014, from [www.derm.ubc.ca](http://www.derm.ubc.ca).

# ENDOCRINE ASPECTS OF GASTROINTESTINAL SYSTEM

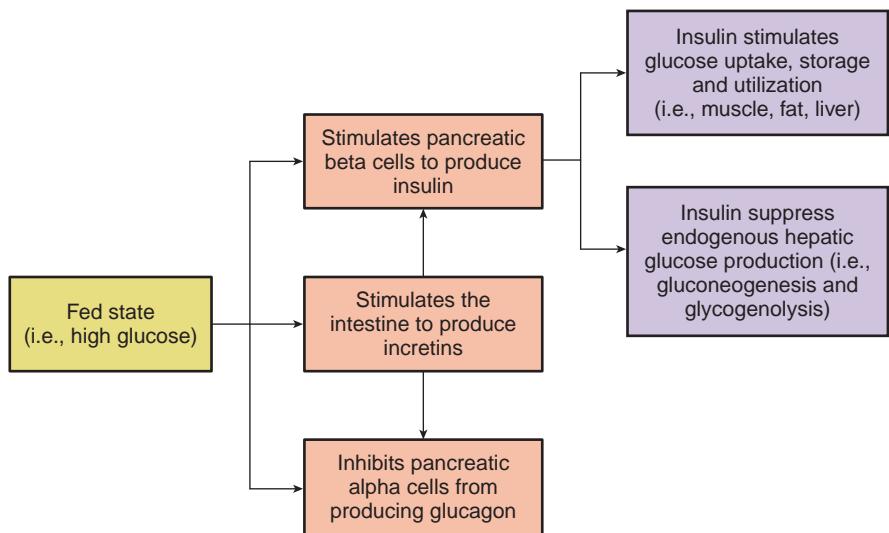
Geetha Gopalakrishnan, MD, and Harikrashna Bhatt, MD

## 1. Describe the general principles of glucose homeostasis.

Glucose is derived from dietary carbohydrates, glycogenolysis (breakdown of glycogen, which is a storage form of glucose), and gluconeogenesis (formation of glucose by the liver). Insulin, glucagon, and other hormones maintain normal plasma glucose levels.

High glucose stimulates insulin production. Insulin enhances glucose uptake, use, and storage. As a result, blood glucose returns to normal (Figure 65-1).

**Figure 65-1.** Algorithm of glucose-stimulated insulin production.



Fasting lowers blood glucose and insulin. It also results in the release of counter-regulatory hormones (i.e., glucagon, epinephrine, cortisol, and growth hormone). These hormones limit glucose use and stimulate hepatic glucose production. In addition, lack of insulin causes lipolysis in adipose tissue, proteolysis in muscle, and ketosis in the liver. Ketones are an alternative energy source and its formation is glucagon dependent (Figure 65-2).

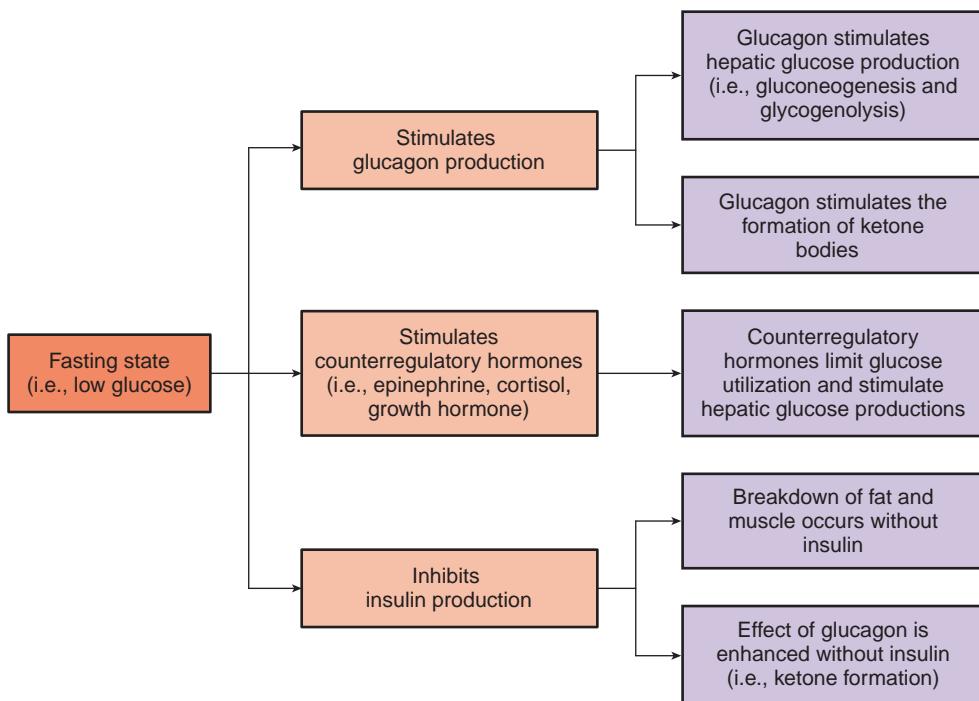
## 2. Describe the role of the pancreas and pancreatic hormones in glucose homeostasis.

Pancreatic islets (i.e., alpha and beta cells) are scattered throughout the pancreas. Beta cells secrete both insulin and amylin. Alpha cells produce glucagon. Figures 65-1 and 65-2 describe the role of insulin and glucagon. Amylin functions synergistically with insulin. It reduces plasma glucose by increasing satiety, delaying gastric emptying, and inhibiting glucagon.

## 3. Describe the role of pancreatic hormones in the development of diabetes.

Autoimmune destruction of pancreatic beta cells results in type 1 diabetes. These patients are deficient in both insulin and amylin. Peripheral insulin resistance (i.e., reduced insulin sensitivity) followed by beta cell failure is the predominate pathologic finding in type 2 diabetes. These patients have relative deficiency of both insulin and amylin. Both genetic and environmental factors (e.g., obesity) play a role in the development of type 2 diabetes.

Other types of diabetes include destruction of the pancreas (e.g., cystic fibrosis, pancreatitis), genetic disorders (e.g., maturity onset diabetes of the young, mitochondrial disorders) and medications (e.g., steroids). These disorders have varying effect on beta cell mass, beta cell function, or insulin action.

**Figure 65-2.** Algorithm of glucagon-dependent ketone formation.**4. Describe the role incretins play in glucose homeostasis and type 2 diabetes.**

Oral intake of food stimulates the intestine to produce incretins (i.e., glucagon-like peptide 1 [GLP-1] and gastric inhibitory peptide). These peptides enhance insulin release, reduce glucagon secretion, and delay gastric emptying (see [Figure 65-1](#)).

GLP-1 has a short half-life and is degraded within minutes by the enzyme dipeptidyl peptidase 4 (DPP-4). Two new classes of drugs for the treatment of type 2 diabetes were developed based on this mechanism ([Table 65-1](#)):

- GLP-1 analogues (resistant to DPP-4 degradation)
- Dipeptidyl peptidase inhibitors (delay GLP-1 degradation)

**Table 65-1.** Noninsulin Antidiabetic Agents

DRUG CLASS	MODE OF ACTION	Δ (%) HgbA1c Δ Wt.	HYPOLYCEMIA	SIDE EFFECTS, INCLUDING GI SYMPTOMS
Thiazolidinediones (e.g., pioglitazone)	↓ peripheral insulin resistance ↑ glucose disposal ↓ HGP	0.5-1.5↑	No	Transaminitis, hepatotoxicity, edema, CHF
Biguanides (e.g., metformin)	↓ HGP ↓ peripheral insulin resistance	1-2↓	No	Diarrhea, bloating, indigestion, lactic acidosis
Sulfonylureas (e.g., glipizide, glyburide)	↑ pancreatic insulin secretion	1-2↑	Yes	Rare symptoms of diarrhea, constipation, etc.
Meglitinides (e.g., repaglinide)	↑ pancreatic insulin secretion	1-2↑	Yes	Rare symptoms of diarrhea, constipation, etc.

**Table 65-1.** Noninsulin Antidiabetic Agents (*Continued*)

DRUG CLASS	MODE OF ACTION	$\Delta$ (%) HgbA1c $\Delta$ Wt.	HYPOLYCEMIA	SIDE EFFECTS, INCLUDING GI SYMPTOMS
D-phenylalanine derivatives (e.g., nateglinide)	↑ pancreatic insulin secretion	1-2↑	Yes	Rare symptoms of diarrhea, constipation, etc.
Incretin mimetics (e.g., exenatide, liraglutide)	↑ glucose-dependent insulin release ↓ glucagon secretion and HGP ↓ gastric emptying	0.5-1.5↓	Yes*	Nausea, vomiting diarrhea, constipation, hyperbilirubinemia, pancreatitis, pancreatic cancer, thyroid c-cell tumors, hypersensitivity reactions
DPP-4 inhibitors (e.g., sitagliptin, linagliptin)	↓ breakdown GLP-1 ↑ incretin effects ↑ insulin release, ↓ glucagon release, ↓ gastric emptying	0.5-1.5—	Yes*	Pancreatitis, pancreatic cancer, abnormal LFT, nasopharyngitis, URI, headache, hypersensitivity, skin reactions
Alpha-glucosidase inhibitors (e.g., acarbose)	↓ breakdown and absorption carbohydrates in the GI tract	0.5-1—	No	Abdominal pain, diarrhea, bloating, flatulence
Bile acid sequestrants (e.g., colesevelam)	↓ reabsorption of bile in GI tract	0.5-1—	No	Indigestion, nausea, constipation
Amylin mimetics (e.g., pramlintide)	↓ glucagon ↓ glucagon & ↓ HGP ↓ gastric emptying ↑ satiety	0.5-1↓	Yes	Nausea, indigestion, abdominal pain

\*Especially in combination with insulin or insulin secretagogues

CHF, Congestive heart failure; GI, gastrointestinal; GLP, glucagon-like peptide; HGP, hepatic glucose production; LFT, liver function test; URI, upper respiratory infection.

##### 5. What are the screening recommendations and criteria for the diagnosis of diabetes?

Universal screening is recommended at age 45 years. Younger individuals should be screened if they have risk factors for type 2 diabetes (i.e., obesity, family history of diabetes, hypertension, and hyperlipidemia). Prediabetes identifies individuals at high risk for developing diabetes (Table 65-2).

**Table 65-2.** American Diabetes Association Criteria for the Diagnosis of Diabetes

	PREDIABETES	DIABETES
HgA1c	5.7%-6.4%	>6.5%
Fasting blood glucose (8 hrs fast)	100-125 mg/dL	>126 mg/dL
Random blood glucose	—	>200 mg/dL with symptoms of hyperglycemia (i.e., polyuria, polydipsia)
2-h oral glucose tolerance test (75 g)	140-199 mg/dL	>200 mg/dL

HgA1c, Hemoglobin A1c.

##### 6. What are the therapeutic options available for the treatment of type 1 diabetes?

Patients with type 1 diabetes have deficiency of both insulin and amylin. Without insulin these patients develop hyperglycemia and ketosis (i.e., diabetic ketoacidosis). These patients typically require long-acting insulin (glargine, detemir, neutral protamine Hagedorn [NPH]) to cover basal needs and short acting insulin (i.e., lispro, aspart, glulisine, regular) to cover meals. Insulin can also be delivered via a pump devise in select patients. The predominant side effect is hypoglycemia.

Amylin analogues (i.e., pramlintide) can also be prescribed in type 1 diabetes to suppress glucagon mediated hepatic glucose production, improve satiety, and slow gastric emptying. Amylin injections are given in addition to insulin. Modest weight loss and improvements in hemoglobin A1c (<1%) are noted with treatment. Risk of hypoglycemia and the inconvenience of multiple daily injections limit the use of amylin.

#### **7. Disease of the exocrine pancreas (e.g., pancreatectomy, pancreatitis) can result in the development of diabetes. What are the characteristics of this type of diabetes?**

Both beta and alpha cells are affected, resulting in both insulin and glucagon deficiency. These patients require insulin and are at greater risk for hypoglycemia as a result of glucagon deficiency. Glucagon is also essential for the formation of ketone bodies. Without insulin, these patients develop hyperglycemia but are less likely to develop ketosis (i.e., diabetic ketoacidosis).

#### **8. What are the therapeutic options available for the treatment of type 2 diabetes?**

Patients with type 2 diabetes have relative deficiency of both insulin and amylin. Several oral agents have been approved for use in type 2 diabetes. These agents typically increase insulin secretion (i.e., sulfonylureas, GLP-1 analogues, DPP-4 inhibitors), improve insulin sensitivity at target tissues (i.e., thiazolidinediones, biguanides,) or decrease the absorption of glucose (i.e., alpha glucosidase inhibitors). The mechanism of action and side effects of available noninsulin antidiabetic agents are described [Table 65-1](#). Insulin can also be prescribed alone or in combination with these agents. Long (i.e., glargine, detemir), intermediate (i.e., NPH) and short (i.e., lispro, aspart, glulisine, regular) acting insulins are available on the market.

#### **9. What are the gastroenterological complications associated with diabetes?**

Diabetic complications related to the gastrointestinal (GI) system include constipation, heartburn (i.e., gastroesophageal reflux), delayed gastric emptying (i.e., gastroparesis), dyspepsia, abdominal pain, and watery diarrhea (i.e., diabetic enteropathy). Development of these symptoms is associated with longer duration of diabetes, poor glycemic control, and autonomic neuropathy of the enteric nervous system. Erratic absorption of food and wide blood sugar fluctuations are noted with gastroparesis and diabetic enteropathy.

Bacterial overgrowth and celiac disease can also contribute to the development of diarrhea in these patients. Celiac disease is typically associated with autoimmune conditions like type 1 diabetes. Diabetics are also at increased risk of certain types of cancers involving the GI system (i.e., liver, pancreas, colon, and rectum).

#### **10. How is hypoglycemia diagnosed in patients with and without diabetes?**

Hypoglycemia is defined by a blood glucose value of less than 70 mg/dL in patients with diabetes. Insulin therapy and other antidiabetic medications that cause low blood sugars (see [Table 65-2](#)) are the leading culprits.

In patients without diabetes, the following hypoglycemia triad (known as Whipple's triad) should be established:

- Symptoms of hypoglycemia (e.g., sweating, cognitive impairment, dizziness, palpitations)
- Measured low blood glucose (<70 mg/dL) at the time of hypoglycemic symptoms
- Resolution of symptoms with food intake (i.e., glucose)

#### **11. Describe the etiology and workup of hypoglycemia in non-diabetic patients?**

Several conditions that can precipitate hypoglycemia including medications (e.g. insulin, sulfonylurea), ethanol use (inhibits gluconeogenesis), malnutrition (lack of substrate), critical illness (increased glucose utilization), renal failure (decreased clearance of insulin) and adrenal insufficiency (loss of cortisol causes increased insulin sensitivity) must be ruled out based on medical history. Subsequent work-up for hypoglycemia includes plasma glucose, insulin, c-peptide (marker for endogenous insulin production) and urine sulfonylurea screen. Based on findings additional studies including IGF-II levels, insulin antibodies and imaging can be considered ([Table 65-3](#)).

#### **12. Describe the clinical presentation of neuroendocrine tumors.**

Neuroendocrine tumors are classified as well-differentiated (i.e., carcinoid tumors, pancreatic islet cell tumors) or as more aggressive, poorly differentiated tumors (i.e., carcinomas). Most are sporadic but can be associated with hereditary syndromes like multiple endocrine neoplasia 1 (MEN1). They typically secrete substances such as chromogranin A and pancreatic polypeptide. They can be further characterized based on their functional status (i.e., hormone secretion) and clinical manifestation ([Table 65-4](#) and [Table 65-5](#)). However, the majority of neuroendocrine tumors are nonfunctional. They present later in the disease process (i.e., larger tumors, metastasis) with symptoms of abdominal pain, weight loss, nausea, or obstructive symptoms.

#### **13. Describe the evaluation and management of neuroendocrine tumors.**

Hormone evaluation based on clinical presentation (see [Tables 65-4](#) and [65-5](#)). Computed tomography scan or magnetic resonance imaging can localize most tumors. Endoscopic ultrasound (i.e., pancreatic tumors) and octreotide scan can be used to localize small tumors. Treatment often involves resection of primary tumor and initiation of somatostatin analogs (i.e., octreotide, lanreotide). Interferon alpha and chemotherapy can be considered in refractory patients. Liver involvement may require liver resection, hepatic artery embolization, and transplantation.

**Table 65-3.** Hypoglycemia in Nondiabetic Patients

Etiology	Mechanism	History	Glc	INS	CP	Other Studies	CT Scan
Insulinoma	Insulin producing tumor of pancreas	Fasting hypoglycemia	↓	↑	↑	—	Pancreatic mass
Nesidioblastosis	Excessive insulin production by pancreas	Postprandial hypoglycemia	↓	↑	↑	—	No mass
Insulin overdose	Intentional or unintentional (hospital/pharmacy error)	Hypoglycemia duration varies	↓	↑	↓	—	—
Sulfonylurea overdose	Intentional or unintentional (hospital/pharmacy error)	Prolonged hypoglycemia	↓	↑	↑	Positive Urine Sulfonylurea	—
Non-islet cell tumors	Insulin like growth factor (IGF-II) secreted by tumors (e.g. liver or colon cancer)	Weight loss, fatigue, hypoglycemia	↓	↓	↓	Positive IGF-II	Solid tumor
Insulin antibody	Antibodies bind to insulin receptor or insulin	Erratic blood sugars (highs and lows)	↓	↓	↓	Positive Insulin antibodies	—

CT, Computed tomography; Glc, glucose; INS, insulin; CP, C-Peptide; IGF, insulin-like growth factor.

#### 14. What are the characteristics of carcinoid tumors?

Carcinoid tumors are neuroendocrine tumors of the lung, GI tract, or genitourinary system (see Table 65-5). They are classified based on their embryonic origin (i.e., foregut, midgut, and hindgut tumors). These tumors convert dietary tryptophan into serotonin. Serotonin is metabolized to 5-hydroxyindoleacetic acid (5-HIAA). Elevated levels of 5-HIAA are diagnostic. These tumors also secrete other vasoactive substances such as histamines, tachykinins, kallikrein, and prostaglandin. Clinical features associated with excess serotonin (i.e., diarrhea, valvular fibrosis) and histamine (i.e., flushing, bronchospasm) are referred to as *carcinoid syndrome*. The presence of these systemic features indicates the carcinoid tumor has extraintestinal tumor location or liver metastasis.

#### 15. What is the pathogenesis of obesity? How is it defined for clinical purposes?

Both genetic and environmental factors play a role in the development of obesity. In general, excess energy intake relative to expenditure results in the accumulation of body fat over time.

The regulation of adipose tissue is complex and involves the central and sympathetic nervous systems, hormones (e.g., ghrelin, leptin, and cortisol), and even the gut microbiome (increased concentrations of *Firmicutes* species).

The clinical definition of obesity is based on body mass index (BMI), calculated by the formula:

$$\text{BMI} = \frac{\text{body weight (in kg)}}{\text{height (in meters)}^2}$$

BMI classifications are as follows:

Normal: 18.5 to 24.9 kg/m<sup>2</sup>

Overweight: 25 to 29.9 kg/m<sup>2</sup>

Obese: 30 to 39.9 kg/m<sup>2</sup>

Morbid Obesity: >40 kg/m<sup>2</sup>

#### 16. What are specific GI manifestations of obesity?

The following GI disorders and cancers are potential complications of obesity:

- GI disorders: nonalcoholic fatty liver disease (NAFLD), gastroesophageal reflux disease (GERD), Barrett's esophagus, and gallstones
- GI cancers: esophagus, stomach, colon, rectal, liver, and pancreas

**Table 65-4.** Pancreatic Neuroendocrine Tumors

	HORMONE	CLINICAL MANIFESTATION	DIAGNOSIS	ADDITIONAL TREATMENT
Insulinoma	Insulin	Hypoglycemia	High insulin and C-peptide level associated with low glucose levels	Glucose to avoid hypoglycemia; diazoxide reduces insulin secretion
Gastrinoma (i.e., Zollinger-Ellison syndrome)	Gastrin	Peptic ulcer disease, secretory diarrhea	Elevated gastrin level $> 1000 \text{ pg/mL}$ Secretin stimulation test if gastrin level $< 1000 \text{ pg/mL}$ (i.e., gastrin increases with stimulation)	Proton pump inhibitors to block acid secretion
Glucagonoma	Glucagon	Necrolytic migratory erythema, cheilitis, diabetes, anemia, weight loss, diarrhea	Glucagon $> 500 \text{ pg/mL}$	Total parenteral nutrition to address catabolic state
Somatostatinomas	Somatostatin	Abdominal pain, weight loss, diabetes, diarrhea, and gallbladder stones	Fasting somatostatin level $> 160 \text{ pg/mL}$	—
VIPomas	VIP	Watery diarrhea, hypokalemia, and hypochlorhydria	VIP $> 75 \text{ pg/mL}$	Correct fluid loss and replace electrolytes; somatostatin analog to reduce VIP levels and improve diarrhea

VIP, Vasoactive intestinal peptide; VIPoma, vasoactive intestinal peptide tumor.

**Table 65-5.** Carcinoid Tumors

	LOCATION	HORMONE	CARCINOID SYNDROME	ASSOCIATED FEATURES
Foregut	Stomach Duodenum Pancreas Lung	Majority nonfunctional Elevated gastrin (5%) Histamine	Rare (associated with liver metastasis and bronchial carcinoids)	Atrophic gastritis Pernicious anemia Zollinger-Ellison syndrome MEN1
Midgut	Small intestine Proximal colon Appendix	Serotonin Vasoactive substances (i.e., histamines, tachykinins, kallikrein, prostaglandin)	Classic presentation (associated with liver metastasis)	Abdominal pain Obstruction Intussusception
Distal	Distal colon Rectum Genitourinary	Nonsecretory	Rare (associated with tumors of the ovary and testes)	Change in bowel habits Obstruction Bleeding

MEN, Multiple endocrine neoplasia.

### 17. Characterize NAFLD. How is it diagnosed and treated?

See Chapter 27. NAFLD represents a spectrum of liver abnormalities from steatosis (i.e., increased liver fat), nonalcoholic steatohepatitis, fibrosis, cirrhosis, and liver failure. Obesity, insulin resistance, hypertension, and dyslipidemia may contribute to the development of NAFLD. Most patients are asymptomatic, but others can present with right upper quadrant pain, hepatomegaly, jaundice, encephalopathy, and other signs of liver disease. Abnormal liver function studies and fatty liver on abdominal ultrasound is diagnostic. Weight loss can reverse pathologic conditions of the liver, and therefore lifestyle modification is the first step in the management of NAFLD. Insulin sensitizer (i.e., metformin and thiazolidinediones) and vitamin E can be considered, but benefits are equivocal.

### 18. What are the treatment options for obesity?

Obesity is associated with increased morbidity (i.e., diabetes mellitus, dyslipidemia, hypertension, sleep apnea, coronary artery disease) and mortality. Weight loss (i.e., 5%-10% loss) can modify metabolic parameters and reduce the risks associated with obesity. Lifestyle modification (i.e., diet and exercise) is the cornerstone of treatment. For individuals who fail lifestyle measures, pharmacologic (Table 65-6) and surgical therapy can be considered.

**Table 65-6.** Pharmacologic Therapy for Obesity

DRUG	MECHANISM OF ACTION	SIDE EFFECT
Orlistat	Reduces fat absorption by inhibiting pancreatic lipase	Cramps, flatulence, fecal incontinence, reduced absorption of fat-soluble vitamins, liver injury, calcium oxalate stones
Lorcaserin	Stimulates serotonin receptor 2C, which reduces appetite	Headache, nasopharyngitis, nausea Contraindicated: liver disease, renal failure, use with other serotonergic agents
Sympathomimetic drugs (i.e., phentermine, diethylpropion, benzphetamine, phendimetrazine)	Stimulates norepinephrine release or prevents reuptake of norepinephrine into the nerve terminal, which causes early satiety	Increased heart rate, increased blood pressure, insomnia, dry mouth, constipation, nervousness, potential for abuse (duration of use limited to 12 weeks only)
Topiramate	Antiepileptic drug	Paresthesia, somnolence, metabolic acidosis

### 19. What are the medications available for the treatment of obesity?

Pharmacologic therapy (see Table 65-6) can be offered to individuals with BMI greater than  $30 \text{ kg/m}^2$  or BMI greater than  $27 \text{ kg/m}^2$  and comorbid conditions (e.g., diabetes, dyslipidemia, hypertension). Weight loss of 4 to 6 kg is noted with most agents. Orlistat is typically the first-line choice, followed by lorcaserin. For obese patients with diabetes, antidiabetic agents associated with weight loss (see Table 65-1) can be considered.

### 20. What are the indications for bariatric surgery? Describe the types of procedures and potential complications.

Bariatric surgery is reserved for individuals with a BMI of more than  $40 \text{ kg/m}^2$  or a BMI of more than  $35 \text{ kg/m}^2$  and comorbid conditions. Weight loss of 50% to 70% is reported after surgery. There are three bariatric surgical techniques for weight loss (see Chapter 77):

- restrictive (i.e., gastric banding and sleeve gastrectomy)
- malabsorptive (i.e., biliopancreatic diversion)
- combination of restrictive and malabsorptive (i.e., Roux-en-Y)

Restrictive procedures result in gradual weight loss as a result of reduced stomach capacity. Malabsorptive procedures reduce the absorption of food and produce even greater weight loss. However, these patients are at risk for severe malnutrition and micronutrient deficiencies (i.e., iron, folate, thiamine,  $\text{B}_{12}$ , vitamin D).

Roux-en-Y is the most common bariatric procedure. The procedure results in reduced stomach capacity and malabsorption of nutrients, as well as alterations in gut hormones that decrease appetite (i.e., ghrelin, peptide YY, GLP-1).

**21. What are the mechanisms for hypoglycemia in patients following gastric bypass surgery?**

- Dumping syndrome occurs following gastric bypass patients after ingestions of simple carbohydrates. Rapid emptying of food into the small bowel results in fluid shifts and insulin release, resulting in hypotension, diarrhea, tachycardia, and hypoglycemia. Treatment entails small frequent meals and avoidance of simple carbohydrates.
- Islet cell hyperplasia may develop following gastric bypass, or an underlying defect may be unmasked. Patients are at risk for nesidioblastosis and even insulinoma in rare cases. Refer to [Table 65-3](#).

**22. What is dyslipidemia?**

Defects in the production or removal of lipoproteins results in dyslipidemia. Both genetic (i.e., lipoprotein lipase deficiency, low-density lipoprotein [LDL] receptor defect) and acquired conditions (e.g., obesity, diabetes) have been implicated in the pathogenesis of lipid disorders. Dyslipidemia is characterized by total cholesterol, triglyceride (TG), or LDL level above the 90th percentile or high-density lipoprotein (HDL) level below the tenth percentile for the general population. It plays a significant role in the development of coronary heart disease. Clinical manifestations of excess LDL include atheroma, skin and tendon xanthomas, eyelid xanthelasma, and iris corneal arcus. Marked hypertriglyceridemia ( $>1000$  mg/dL) is associated with chylomicronemia syndrome. It is characterized by pancreatitis, eruptive skin xanthomas, and lipemia retinalis.

**23. How and when is dyslipidemia treated?**

Treatment is aimed at reducing LDL cholesterol to less than 160 mg/dL in most individuals. Lower targets are recommended in high-risk conditions like diabetes ( $<100$  mg/dL) and coronary heart disease ( $<70$  mg/dL). Target TG of less than 200 mg/dL and HDL more than 40 mg/dL is also recommended. Pharmacologic agents are recommended if target goals are not achieved with lifestyle measures. Lipid effects and potential GI side effects described in [Table 65-7](#).

**Table 65-7.** Treatment of Dyslipidemia

DRUG CLASS	MECHANISM OF ACTION	HDL	TG	LDL	GI AND OTHER SIDE EFFECTS
Bile acid sequestrants	Binds bile acid in the intestine and enhances fecal excretion of cholesterol	↑	—	↓↓	Nausea, bloating, cramping, interferes with the absorption of other drugs
Fibrates	Reduces VLDL production by the liver	↑↑	↓↓↓	↓	Hepatotoxicity, cramping, nausea, myalgias
Nicotinic acid	Reduce free fatty acid transport to the liver and VLDL production by the liver	↑↑	↓↓	↓↓	Vomiting, diarrhea, hepatotoxicity, flushing, and pruritus
HMG CoA inhibitors	Inhibits HMG CoA reductase, an enzyme necessary in de novo cholesterol synthesis	↑	↓	↓↓↓	Hepatotoxicity, myositis
Omega 3 fatty acids	Reduces VLDL production	↑	↓	↓	Taste altered, indigestion
Cholesterol absorption inhibitors	Inhibits the absorption of cholesterol in the intestine	—	—	↓↓	Pancreatitis, hepatitis

TG, triglycerides.

**24. Which commonly prescribed hepatitis C treatment is associated with hypothyroidism?**

Pegylated interferon- $\alpha$ 2b causes or worsens underlying autoimmune thyroid disease. Hypothyroidism can be seen in upward of 5% of treated patients. In addition, tyrosine kinase inhibitors (e.g., sunitinib, imatinib), which are used to treat hepatocellular carcinoma, are also noted to cause hypothyroidism.

**25. What are the common GI side effects of oral bisphosphonates, routinely prescribed for osteoporosis?**

GERD, dyspepsia, esophageal ulcers, and gastritis have been reported with oral bisphosphonates. Their use is contraindicated in Barrett's esophagus.

**26. What are the GI manifestations associated with common endocrine conditions?**

See [Table 65-8](#).

**Table 65-8.** GI Manifestations of Common Endocrine DISORDERS

ENDOCRINE DISORDER	GI MANIFESTATION
Hypothyroidism	Weight gain, reduced taste sensation, constipation, ascites in severe hypothyroidism
Hyperthyroidism	Weight loss, increased appetite, hyperdefecation
Papillary thyroid cancer (cribiform morular variant)	Familial adenomatous polyposis, increased risk of colorectal cancer
Hypercalcemia	Constipation, nausea, peptic ulcer disease, pancreatitis
Adrenal insufficiency	Nausea, vomiting, abdominal pain, weight loss, diarrhea
Cushing's syndrome	Abdominal striae, central obesity, rarely oral candidiasis
Acromegaly	Colonic polyp, diverticula, colon cancer

GI, Gastrointestinal.

### 27. What are the GI side effects of exogenous oral corticosteroids?

GI side effects of steroids include oral and esophageal fungal infection, esophagitis, peptic ulcer, GI bleeding, and rarely pancreatitis. Transaminitis can also occur. Such symptoms usually occur if steroid administration is prolonged and at high doses.

### 28. What are the GI manifestations of endocrine syndromes and neoplastic disorders?

Autoimmune polyglandular syndromes and multiple endocrine neoplasias affect various endocrine systems, but they also affect the GI tract. Table 65-9 provides a summary.

**Table 65-9.** GI Manifestations of Common Endocrine SYNDROMES

	GI MANIFESTATIONS	NON-GI MANIFESTATIONS
APS Type 1	Oral candidiasis, pernicious anemia, celiac disease	Hypoparathyroidism Adrenal insufficiency Hypogonadism Autoimmune thyroid disease Alopecia
APS Type 2	Type 1 diabetes (pancreatic failure)	Autoimmune thyroid disease Adrenal insufficiency
MEN Type 1	Pancreatic tumors (e.g., insulinoma, gastrinoma)	Hyperparathyroidism Pituitary tumor
MEN Type 2A	Hirschsprung's disease (colonic obstruction and megacolon)	Medullary thyroid cancer Pheochromocytoma Hyperparathyroidism
MEN Type 2B	Mucosal neuromas affecting tongue and intestines	Medullary thyroid cancer Pheochromocytoma

APS, Autoimmune polyglandular syndrome; GI, gastrointestinal; MEN, multiple endocrine neoplasia.

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

### BIBLIOGRAPHY

- American Diabetes Association. Standards of Medical Care in Diabetes 2013. *Diabetes Care* 2013;36(1):S11–66.
- Bradley D, Magkos F, Klein S. Effects of bariatric surgery on glucose homeostasis and type 2 diabetes. *Gastroenterology* 2012;143(4):897–912.
- Bray GA, Ryan DH. Medical therapy for the patient with obesity. *Circulation* 2012;125(13):1695–703.
- Bytzer P, Talley NJ, Hammer J, Young LJ, Jones MP, Horowitz M. GI symptoms in diabetes mellitus are associated with both poor glycemic control and diabetic complications. *Am J Gastroenterol* 2002;97(3):604.
- Dixon JB, le Roux CW, Rubino F, Zimmet P. Bariatric surgery for type 2 diabetes. *Lancet* 2012;379(9833):2300–11.

6. Gopalakrishnan G, Smith RS. Disorders of lipid metabolism. In: Andrreoli T, Benjamin I, Griggs R, Wing E, editors. *Cecil essentials of medicine*. 8th ed. Philadelphia: WB Saunders Elsevier; 2012. p. 643–50.
7. Burra P. Liver abnormalities and endocrine diseases. *Best Pract Res Clin Gastroenterol* 2013;27(4):553–63.
8. Lu YY, Zhu F, Jing DD, Wu XN, Lu LG, Zhou GQ, et al. Multiple endocrine neoplasia type 1 with upper gastrointestinal hemorrhage and perforation: A case report and review. *World J Gastroenterol* 2013;19(8):1322–6.
9. Maser C, Toset A, Roman S. Gastrointestinal manifestations of endocrine disease. *World J Gastroenterol* 2006;2(20):3174–9.
10. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. Current status of gastrointestinal carcinoids. *Gastroenterology* 2005;128(6):1717–51.
11. Syro LV, Scheithauer BW, Kovacs K, et al. Pituitary tumors in patients with MEN1 syndrome. *CLINICS* 2012;67(S1):43–8.

# PLAIN FILM, BARIUM, AND VIRTUAL RADIOGRAPHY

Michael Reiter, DO

## 1. When requesting an imaging examination, what information should a clinician provide for a radiologist?

By communicating the following information, a clinician helps ensure that an imaging examination will be conducted and interpreted optimally for each patient.

- Provide pertinent or significant medical history and clinical information related to the examination: (a) key findings from history, physical examination, and laboratory tests that suggest the diagnoses in question; and (b) any surgical alteration of the anatomy to be examined with imaging.
- Explain the purpose of the examination, including possible diagnoses, potential complications from a recently performed procedure or an established diagnosis or finding to follow for change. A specific explanation of how the imaging findings may alter management decisions (i.e., follow-up vs. surgery) or confirm a notorious diagnostic dilemma is useful as the radiologist may not be aware of specific treatment algorithms.
- Never hesitate to visit with the radiologist and discuss the case. Effective dialogue and communication between clinician and radiologist leads to more accurate and diagnostic radiologic imaging.

## ABDOMINAL RADIOGRAPHY

### 2. What is the optimum radiographic evaluation for pneumoperitoneum?

- Ideally, a frontal radiograph of the lower chest and upper abdomen with the patient in the **upright** position should be obtained to identify free air under the diaphragm.
- If there is an equivocal finding for pneumoperitoneum, then lateral decubitus views can be performed, as this is the most sensitive plain radiographic technique to detect intraabdominal free air.
- Supine frontal abdominal radiographs are insensitive for the detection of pneumoperitoneum, but these examinations are performed frequently so awareness of the diverse imaging manifestations of free air is important. The radiologic diagnosis of pneumoperitoneum is one of the most important findings to make in all of radiology as it may be subtle and, if missed, could result in significant morbidity and mortality. Abdominal computed tomography (CT) is the most sensitive test to detect pneumoperitoneum and should be considered in cases in which clinical suspicion is high and plain radiographs are indeterminate or negative.

### 3. Name and describe several of the supine radiographic signs of pneumoperitoneum.

- Doges cap sign ([E-Figure 66-1A](#))
- Rigler's sign ([E-Figure 66-1B](#))
- Continuous diaphragm sign ([E-Figure 66-1C](#))
- Football sign ([E-Figure 66-1D](#))
- Cupola sign
- Triangle sign

### 4. What is the key radiographic finding of bowel obstruction?

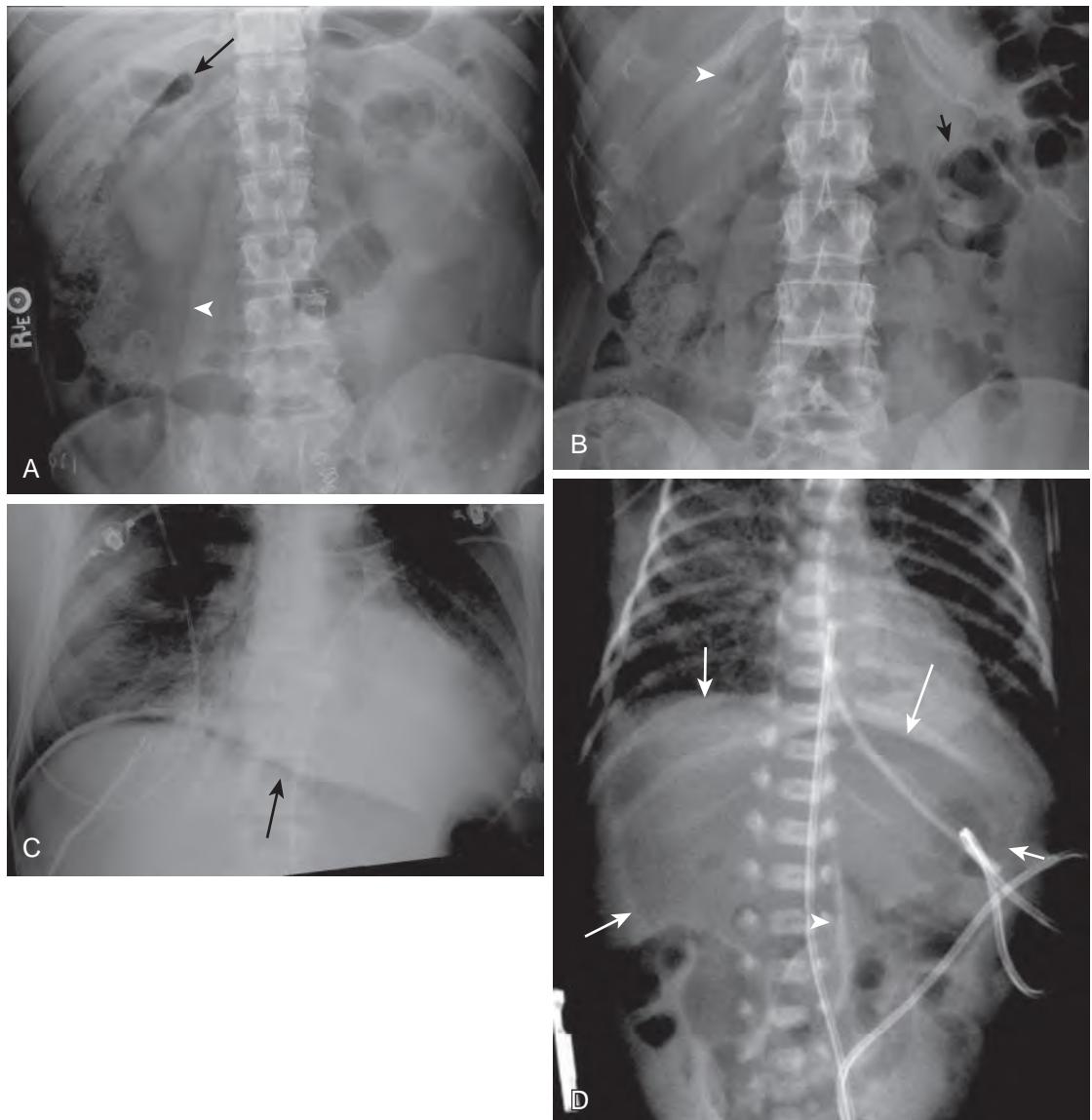
The hallmark of obstruction, whether mechanical or functional, is dilatation of bowel. The rule of “3s” defines abnormal dilation of the intestine:

- Small bowel 3 cm or larger
- Transverse colon 6 cm or larger
- Cecum 9 cm or larger

Differentiating bowel obstruction from paralytic ileus may be challenging, but several signs are suggestive: prominent abdominal distention, small bowel dilatation, and absence of large bowel dilatation all favor the diagnosis of small bowel obstruction ([Figure 66-2](#)). A “stepladder” configuration of dilated small bowel loops extending from the left upper to the right lower quadrants is highly suggestive. Although previously considered a reliable sign, air fluid levels in the same loop of small bowel at differing heights are not as dependable in diagnosing mechanical small bowel obstruction as initially thought.

### 5. Where in the algorithmic approach for the work-up of small bowel obstruction does abdominal radiography lie?

Abdominal radiography is the preferred initial radiologic examination for patients with suspected small bowel obstruction, primarily because of its widespread availability and low cost. However, it is only diagnostic in 50% to 60% of cases ([Figure 66-3](#)) so if clinical suspicion for obstruction is high, abdominal CT should be considered the most definitive test.



**E-Figure 66-1.** Supine radiographic signs of pneumoperitoneum. **A**, Doges cap sign represents free air within Morrison's pouch and manifests as a triangular shaped lucency within the right upper quadrant (black arrow). Note also the relative hyperlucency of the right hemiabdomen compared with the left in addition to increased conspicuity of the lateral edge of the right psoas muscle (white arrowhead) caused by pneumoperitoneum. **B**, Rigler's sign represents air outlining the bowel wall in the left upper quadrant (black arrow), present both intraluminally (normal) as well as within the peritoneal space (abnormal). Doges cap sign is also present (white arrowhead). **C**, Central diaphragm sign refers to free intraperitoneal air, which outlines the entirety of the diaphragm, the central portion of which (black arrow) is not normally visualized because of contact with the heart. **D**, Football sign refers to a collection of intraperitoneal air anterior to the abdominal viscera, which is ovoid in shape (arrows). When seen in combination with the falciform ligament (arrowhead), which is normally invisible on radiographs unless outlined by air, the latter represents the laces of the football.



**Figure 66-2.** Supine abdomen radiograph. Multiple dilated loops of small bowel are present throughout the abdomen without significant colonic distension. Small bowel mechanical obstruction was found at surgery secondary to ventral abdominal hernia.



**Figure 66-3.** Portable supine abdomen radiograph. Because dilatation of small bowel does not reach the right lower quadrant, mechanical obstruction of small bowel substantially upstream of the terminal ileum is probable. This obstruction, however, was functional, a result of acute pancreatitis.

#### 6. What are the hallmark features of gallstone ileus?

Although representing an infrequent cause of small bowel obstruction, gallstone ileus has significant associated mortality if the diagnosis is delayed. The characteristic imaging findings are referred to as *Rigler's triad*: pneumobilia; small bowel obstruction; and an ectopic, intraabdominal, radiodense gallstone (most often lodged at the ileocecal valve).

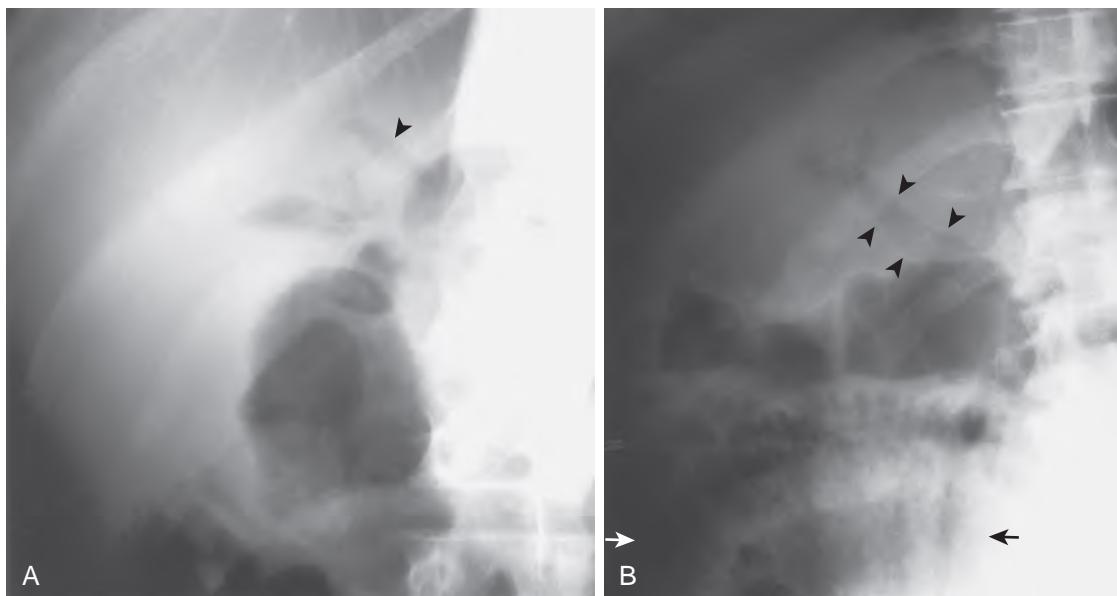
#### 7. Is ascites detectable on abdominal radiography?

Abdominal radiographs are insensitive for identification of ascites and should never be used as a diagnostic test for that indication. However, there are several findings that suggest the presence of ascites on supine radiography, such as centrally located, air-filled loops of bowel and lack of visualization of the abdominal contents, to include the liver, spleen, psoas, and urinary bladder outlines. There may also be a hazy density overlying the majority of the abdomen. For cases of suspected ascites, ultrasound is the most appropriate modality as it is not only sensitive for the detection of ascites but also can assist with guiding the site chosen for paracentesis.

#### 8. What distinguishes portal venous gas from "septic" pneumobilia?

Although in both conditions gas is in a branching, tapering pattern, the location within the liver of the gas is usually distinctive. Because portal venous blood normally flows toward the periphery, gas in portal veins tends to accumulate in the periphery of the liver. Because bile normally flows toward the hilum, biliary gas tends to accumulate near the hilum. These rules occasionally fail, however, because at the instant the radiograph is exposed the location of the constantly moving gas may transiently be atypical (Figure 66-4). Diligent inspection of the radiograph for secondary signs such as pneumatosis intestinalis is helpful because, if present, it is indicative of bowel ischemia and indicates the intrahepatic gas is within the portal system.

**Important Pearl** Pneumobilia is most commonly seen due to ampullary sphincterotomy or choledocoenterotomy. This is a benign finding. Pneumobilia caused by bacterial gas production within the biliary tree is uncommon and the patient is usually septic. It is imperative that the radiologist be provided with clinical information to make this distinction.



**Figure 66-4.** A branching and tapering gas pattern in the liver, if predominantly near the hilum (arrowheads), usually is biliary (A) but occasionally is in portal veins. B, Bubbly and linear pneumatisos (arrows) below the liver is consistent with bowel ischemia.

#### 9. Which types of foreign bodies are encountered on abdominal radiographs?

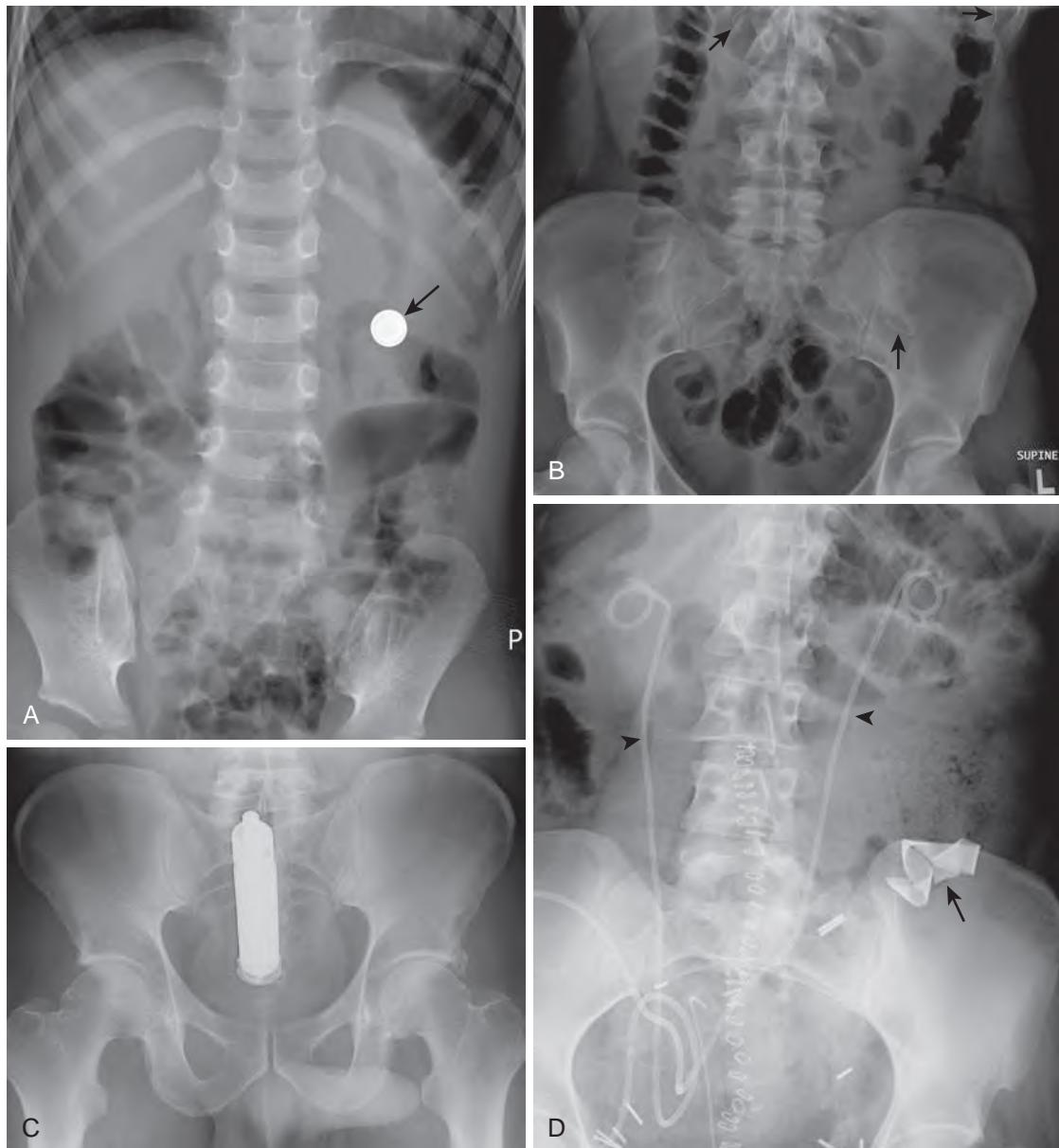
A wide range of foreign bodies are radiopaque and therefore visible at abdominal radiography (Figure 66-5). They can be categorized as intraluminal or extraluminal for logistical purposes (Table 66-1).

**Table 66-1. Common Causes of Radiopaque Foreign Bodies**

INTRALUMINAL	EXTRALUMINAL
Bezoars	Surgical clips (either in expected or migrated position)
Markers for measurement of colonic transit (Sitz-marks)	Migrated intrauterine devices
Packages of illegal narcotics ("body packing")	Retained surgical materials (e.g., inadvertent clamp or surgical sponge; latter typically occurs in setting of incorrect sponge count)
Dislodged tubes from prior procedures (e.g., feeding tubes and biliary stents)	Intentionally placed surgical materials (e.g., surgical sponge used to control bleeding in traumatic liver laceration—clinical history helps to distinguish from the inadvertent variety)
Ingested or inserted items (coins, batteries, and endoscopic capsules used for work-up of small bowel disease)	

#### 10. What are causes of intraabdominal calcification?

- Renal calculi (80% radio dense) and bladder calculi
- Cholelithiasis (10%-15% radio dense) and "milk of calcium"
- Porcelain gallbladder (20% risk for cancer)
- Pancreas (usually chronic pancreatitis, includes cancer, vessels and cysts)
- Calcified lymph nodes (chronic inflammation, includes spleen)
- Vascular calcifications (aortic aneurysm or dissection)
- Appendicoliths (plus acute right lower quadrant pain very predictive of appendicitis)



**Figure 66-5.** Examples of various abdominal foreign bodies. **A**, Round metallic structure (arrow) overlies the left hemiabdomen in a 3-year-old girl; in cases of suspected but not witnessed foreign body ingestion, a lateral view can be helpful to confirm the intraabdominal location. This was confirmed to be button battery ingestion. **B**, Three curvilinear radiodense structures (arrows) project over the abdomen on this frontal supine view of a 24-year-old woman. Patient initially denied ingestion of foreign bodies but subsequently admitted to swallowing numerous staples. **C**, Cylindrical radiopaque structure overlying the midline pelvis represents a vibrator inserted in the rectum. Rectal foreign bodies are typically oriented in the craniocaudal direction. **D**, Inadvertent laparotomy sponge (arrow) is present within the abdominal cavity following surgery. This portable supine radiograph was obtained after recognition of an incorrect sponge count. The laparotomy sponge itself is radiolucent; however, they are detectable because of an incorporated radiopaque marker. Bilateral ureteral stents are also present (arrowheads).

## CONTRAST MEDIA

### 11. What are the roles of barium and water-soluble (iodinated) contrast media for opacification of the lumen of the gastrointestinal (GI) tract?

Barium contrast media, which consist of barium sulfate particles suspended in water, are usually preferred over water-soluble iodinated agents because they produce better images as a result of greater mucosal detail, are more resistant to dilution, and are less costly. Currently, iodinated contrast media use is primarily limited to situations in which barium is contraindicated, as with cases of potential intestinal perforation or leak, cases

prior to surgical procedures involving the bowel, and cases for confirmation of the position of a percutaneously placed bowel catheter. Water-soluble contrast is ideally suited for use in patients with suspected perforation of a hollow viscus as it is rapidly absorbed from all extraluminal spaces. No untoward effects have been reported from the presence of iodinated contrast in the mediastinum, pleural cavity, or abdomen. Barium, on the other hand, has a propensity to incite an inflammatory reaction if it leaks into the peritoneal cavity, resulting in granulomatous peritonitis. In cases of aspirated barium, serious consequences may result, particularly in patients with pneumonia or adult respiratory distress syndrome (Figure 66-6).



**Figure 66-6.** Barium aspiration. Barium contrast is seen coating the trachea, mainstem bronchi, and bilateral lower lobe bronchi following accidental aspiration. A large quantity of contrast is retained with the piriform sinuses (arrow), which predisposes to aspiration.

## 12. What is the ideal choice of contrast media for the detection of perforation or postoperative anastomotic leak?

Water-soluble contrast agents are the medium of choice for the radiographic evaluation of patients with suspected upper GI perforation or postoperative leak. However, water-soluble media are less sensitive in the detection of leaks in comparison with barium because they are less radiopaque. In cases in which an initial study using iodinated contrast medium fails to demonstrate a suspected perforation, a repeat study using barium should be performed because small leaks may go undetected.

## SWALLOWING STUDIES

### 13. What information does a barium swallow provide?

Barium swallow, also referred to as *esophagram*, is the general term for a fluoroscopic-radiographic examination of oral, pharyngeal, and esophageal swallowing. For the evaluation of dysphagia, a barium swallow study has a few advantages over endoscopy, primarily its ability to diagnose disorders of motility in addition to structural abnormalities. Conversely, endoscopy is superior in detecting milder grades of esophagitis, permits tissue sampling, and does not expose the patient to ionizing radiation. Barium swallow provides assessment of esophageal motility and emptying, type of hiatal hernia if present, presence of a stricture or mucosal injury, and detection of esophageal reflux.

### 14. In patients with gastroesophageal reflux disease (GERD), is there a role for barium swallow?

A barium esophagram plays a key role prior to antireflux surgery for patients with GERD. This examination allows for assessment of esophageal emptying, identifies the presence and type of hiatal hernia as well as the presence of a foreshortened esophagus, evaluates esophageal motility, and may detect and qualify the amount of reflux. The caveat with reflux is that its absence at the time of the barium swallow

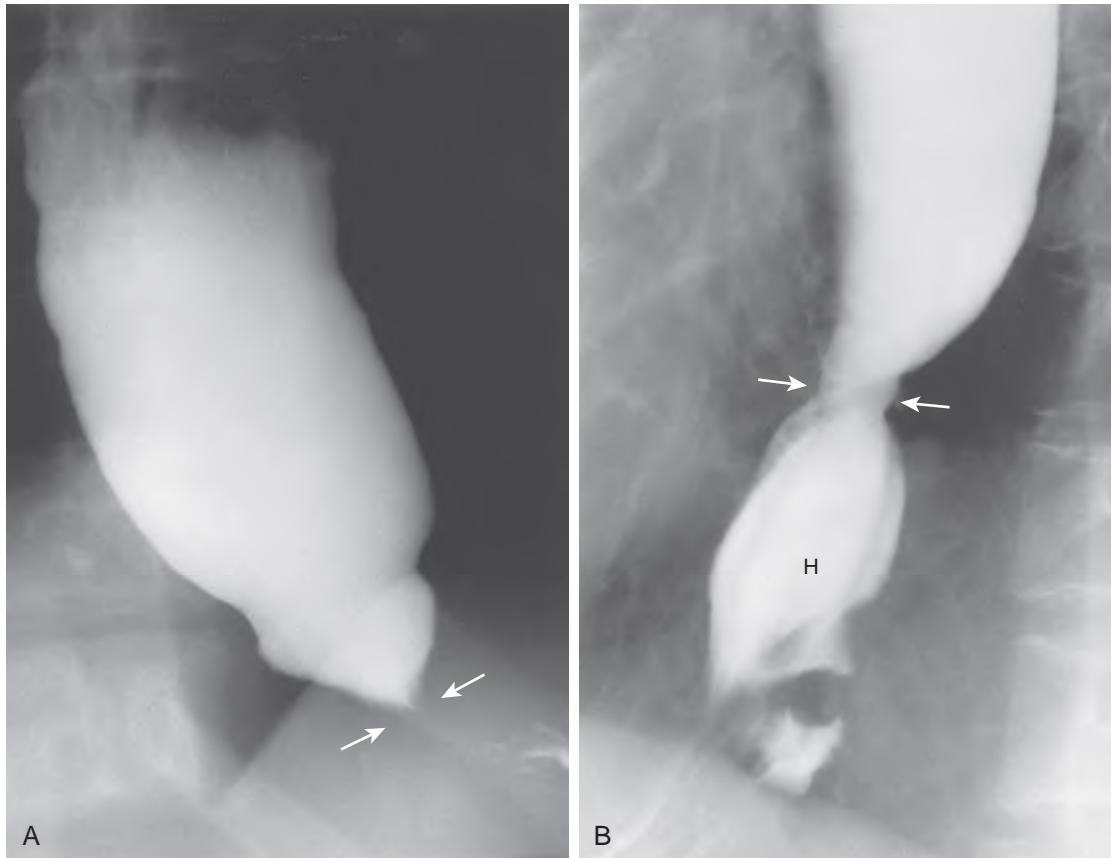
does not exclude this diagnosis; therefore this examination should never be performed solely to detect or exclude reflux.

**15. Which esophageal motility disorders are diagnosable by barium swallow?**

Of the five primary esophageal motility disorders, three may be diagnosed by barium swallow: achalasia, esophageal spasm, and ineffective esophageal motility. The two primary motility disorders that cannot be diagnosed by barium swallows are “nutcracker esophagus” and hyperactive lower esophageal sphincter (LES).

**16. How can a barium swallow distinguish achalasia from scleroderma?**

If the condition results in dysmotility that is at least moderate in severity, barium swallow abnormalities are usually different in these two conditions (Figure 66-7 and Table 66-2).



**Figure 66-7.** Lower esophagus. **A**, Achalasia. Dilatation is marked above a “beak” (arrows), formed by the closed lower sphincter. **B**, Scleroderma. Dilatation is moderate above a cylindrical reflux esophagitis stricture (arrows), below which is a sliding hiatus hernia (H).

**Table 66-2.** Achalasia versus Scleroderma

	ESOPHAGEAL DILATATION	PERISTALSIS IN PURE SMOOTH MUSCLE PART OF ESOPHAGUS	ESOPHAGOGASTRIC JUNCTION
Achalasia	May be marked	Absent	Beak: smooth, concentric, tapered, flexible No hiatus hernia
Scleroderma	Minimal or moderate	Weak, incomplete, or absent	Stricture from esophagitis: cylindrical, rigid, sometimes irregular or ulcerated Often a sliding hiatus hernia

**17. What findings help distinguish achalasia secondary to cancer from primary achalasia?**

- Features suggestive for secondary achalasia (cancer):
- LES “beak” is irregular, eccentric, or abruptly marginated.
  - LES “beak” is long, 3.5 cm or longer.
  - Esophageal body is relatively narrow, caliber 4 cm or smaller.

**18. What is the difference between barium swallow, upper GI series, and small bowel follow-through (SBFT)?**

All three refer to a radiographic examination in which the patient ingests a radiopaque contrast medium, typically barium. Unlike a barium swallow, an upper GI series does not evaluate swallowing and also includes evaluation of the stomach and duodenum in addition to the esophagus. A SBFT solely focuses on the duodenum, jejunum, and ileum without evaluation of the esophagus or stomach.

**19. Can benign and malignant gastric ulcers be distinguished?**

Imaging features allow an estimate of the likelihood of malignancy. A malignant or possibly malignant appearance warrants endoscopy and biopsy. For unequivocally benign radiographic features, radiologic follow-up is a less costly and less invasive alternative. If features equivocal for malignancy develop during follow-up or if healing fails despite adequate medical therapy, endoscopy and biopsy are indicated ([Table 66-3](#)).

**Table 66-3.** Gastric Ulcers on Upper Gastrointestinal Series: Benign and Malignant Features

FINDINGS	BENIGN	MALIGNANT
Location in stomach	Other than upstream half of stomach along greater curvature	Upstream half of stomach along greater curvature
Profile view: relationship of ulcer to lumen	Beyond expected lumen	Within expected lumen
Radiating folds	Regular To margin of ulcer or to ulcer mound (of edema)	Nodular, irregular, fused, clubbed, or amputated May not reach ulcer margin
If ulcer is within a mass	Ulcer location in mass: central Mass: smooth Junction with wall: obtuse angle	Ulcer location in mass: eccentric Mass: irregular Junction with wall: acute angle
Surrounding mucosa	Intact	Distorted or obliterated
Ulcer shape	Round, oval, or linear	Angular
Other	Hampton line	
Healing	Complete	Usually incomplete Occasionally complete, but scar Radiating folds with malignant characteristics

**20. What are indications for either SBFT or enteroclysis?**

In the past, SBFT and enteroclysis (also known as *small bowel enema* because it involves injection of contrast medium directly into the small bowel) have been employed in the evaluation of seemingly any type pathologic condition of the small bowel, including inflammatory bowel disease, neoplasm, and obstruction. With the technologic advances of both CT and magnetic resonance imaging, however, the current roles of SBFT and enteroclysis have significantly diminished. Crohn's disease represents one of the few remaining indications for SBFT or enteroclysis. Today, neither examination plays a role in cases of suspected bowel obstruction or GI bleeding as they have been supplanted by other imaging modalities.

## COLON AND RECTUM

**21. What are indications for either single- or double-contrast techniques of a barium enema examination?**

- Single contrast: for fistula or sinus tract evaluation, anastomotic integrity prior to ileostomy closure, and obstruction (predominantly colonic volvulus)
- Double contrast: for colorectal cancer and colitis

There has been a substantial decline in the use of double-contrast barium enema as a screening tool for colorectal cancer detection, as it has been largely replaced in favor of optical or virtual colonoscopy. Although once touted as an effective test in this manner because of its relative low cost, minimal risk, and ability to evaluate the entirety of the colon, double-contrast barium enema has been shown to be less sensitive for polyp detection compared with optical colonoscopy, which has emerged as the accepted gold standard.

## 22. What is the role of defecography (evacuation proctography)?

Defecography may identify the cause and help direct therapy if there is anorectal dysfunction. It may also show one or more of the following: rectocele, rectal intussusception (rectorectal or intraanal), external rectal prolapse, and enterocele. Optimal diagnosis and management require correlation of defecography findings with history, physical examination, nonimaging tests of anorectal function, and often endoanal ultrasound.

## CHOLANGIOPANCREATOGRAPHY

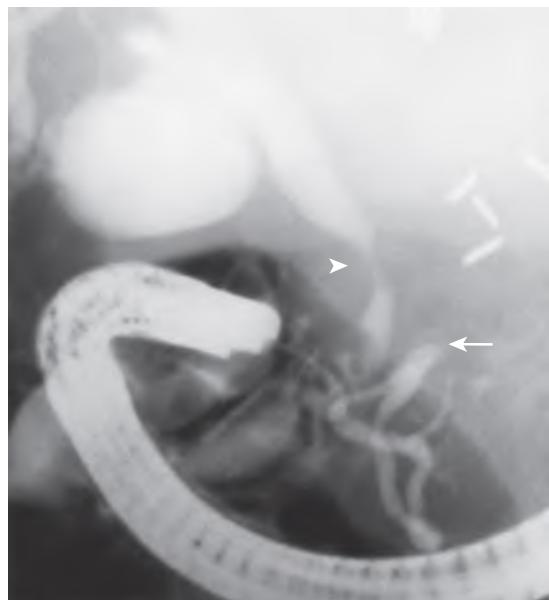
### 23. What is the double duct sign of cholangiopancreatography?

A stricture or complete obstruction of the intrapancreatic common bile duct and another stricture or complete obstruction of the main pancreatic duct nearby (Figure 66-8) constitute the double duct sign. The most common malignant cause is adenocarcinoma of the pancreatic head; cholangiocarcinoma, lymphoma, and metastasis are occasional causes. The most common benign cause is chronic pancreatitis.

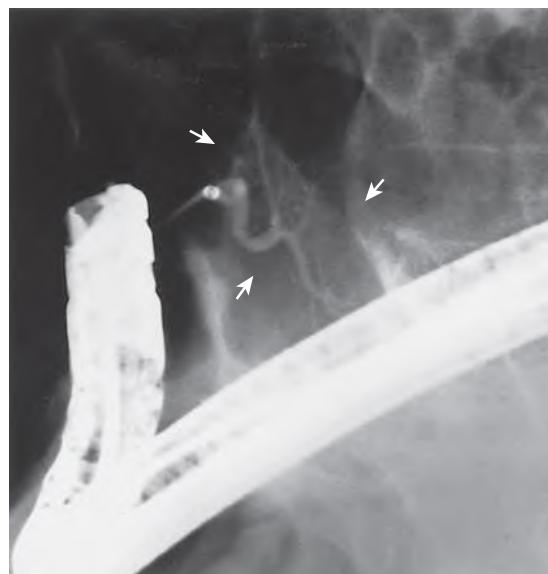
### 24. What pancreatographic features distinguish pancreas divisum from complete obstruction of the main pancreatic duct?

Although the main duct opacified via the major papilla is shorter than normal in both conditions, their pancreatographic appearances are usually distinctive.

- With obstruction (see Figure 66-8), the main duct appears truncated. Caliber of the opacified part of the main duct and its branches is normal, and upstream termination of the main duct is abrupt. Two other conditions—traumatic disruption of the main duct and excision of the pancreatic tail and body—can have this same appearance.
- In divisum (Figure 66-9), the ductal system appears minified. Caliber of the main duct is small, and the main duct terminates upstream not abruptly but by branching and tapering.



**Figure 66-8.** Double duct sign. The stricture (arrowhead) of the intrapancreatic common bile duct, although smooth and predominantly tapered, is probably malignant because it is short and eccentric. Nearby is a complete obstruction (arrow) of the pancreatic duct. No abnormalities of chronic pancreatitis involve the truncated opacified part of the pancreatic duct. Diagnosis is ductal adenocarcinoma of the pancreatic head.



**Figure 66-9.** Pancreas divisum. This short pancreatic ductal system (arrows), opacified via the major papilla, is minified.

## VIRTUAL COLONOSCOPY

### 25. Describe the primary differences between virtual colonoscopy, also referred to as computed tomographic colonography (CTC), and optical colonoscopy.

Technologic advances over the past few years have allowed CTC to evolve into the premiere radiologic method to investigate colonic neoplasia, surpassing double-contrast barium enema. However, optical colonoscopy continues to be the primary tool used for colorectal cancer screening. There are several inherent differences between these two modalities, and each has its own advantages and disadvantages (Table 66-4). Although it is necessary for physicians to be cognizant of the unique features of both CTC and optical colonoscopy, the most important fact is that they are equivalent in their ability to detect colorectal cancer and large polyps (>10 mm).

**Table 66-4.** Virtual Colonoscopy versus Optical Colonoscopy

	VIRTUAL COLONOSCOPY (CTC)	OPTICAL COLONOSCOPY
Safety profile	Less complications, including lower rate of bowel perforation	More frequent incidence of bowel perforation Less well tolerated than CTC
Complete colonic wall visualization	Better complete colonic wall visualization (4% for CTC versus 7% for optical colonoscopy in one large series of direct comparison*)	Higher rate of incomplete examination
Bowel prep	Potential for no bowel prep (laxative-free CTC) with use of fecal tagging	Required
Radiation exposure	Uses ionizing radiation, although dose to the patient is not significantly different from that of a routine abdominal CT scan	None
Ability to perform procedures	Unable to perform interventions	Able to perform procedure (biopsy or polypectomy) at same time lesions are identified
Extracolonic findings	Ability to visualize the colon wall, in addition to detect incidental findings of the abdomen and pelvis	Can only visualize colonic lumen

CTC, Computed tomographic colonography.

Halligan S, Taylor SA. CT colonography: results and limitations. Eur J Radiol. 2007 Mar;61(3):400-8.

### 26. Do guidelines exist for the appropriate management of CTC findings?

- If a mass is detected, surgical consultation is recommended.
- For a polyp 10 mm or greater in size, or if there are three or more polyps 6 mm or larger, endoscopic resection is recommended.
- If less than three polyps measuring 6-9 mm are detected (Figure 66-10), recommendations are less clear with some advocating shorter interval follow-up CTC, possibly in 3 years, while others suggest optical colonoscopy should be performed.
- For polyps 5 mm or less in size, continued routine screening with CTC is recommended in 5 years.



**Figure 66-10.** CT colonography demonstrating a 6.9 mm sessile colon polyp.

The author would like to acknowledge the contributions of Dr. Zeligman, who was the author of this chapter in the previous edition, and provided many of the images.

Please access ExpertConsult to view the E-Figures and a Clinical Vignette for this chapter.

## BIBLIOGRAPHY

1. Baker ME, Einstein DM, Herts BR, et al. Gastroesophageal reflux disease: Integrating the barium esophagram before and after antireflux surgery. *Radiology* 2007;243:329–39.
2. Baker SR. Pneumoperitoneum—The radiographic and clinical virtues of the supine abdominal film. *Emerg Radiol* 2012;19:547–8.
3. Gayer G, Petrovitch I, Jeffrey RB. Foreign objects encountered in the abdominal cavity at CT. *Radiographics* 2011;31:409–28.
4. Interactive radiology cases. Accessed September 22, 2014, from <http://www.radrounds.com>.
5. Johnson CD, Chen MH, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med* 2008;359:1207–17.
6. Levine MS, Creteur V, Kresel HY. Benign gastric ulcers: Diagnosis and follow-up with double-contrast radiography. *Radiology* 1987;164:9.
7. Siewert B, Kruskal JB, Eisenberg R, Hall F, Sosna J. Quality initiatives: Quality improvement grand rounds at Beth Israel Deaconess Medical Center: CT colonography performance review after an adverse event. *Radiographics* 2010;30:23–31.
8. Swanson JO, Levine MS, Redfern RO, Rubesin SE. Usefulness of high density barium for detection of leaks after esophagogastrectomy, total gastrectomy, and total laryngectomy. *AJR Am J Roentgenol* 2003;181:415–20.
9. Woodfield CA, Levine MS, Rubesin SE, et al. Diagnosis of primary versus secondary achalasia: Reassessment of clinical and radiographic criteria. *Am J Roentgenol AJR* 2000;175:727–31.

# INTERVENTIONAL RADIOLOGY I: CROSS-SECTIONAL IMAGING PROCEDURES

Kimi L. Kondo, DO, and Paul D. Russ, MD

## IMAGE-GUIDED PERCUTANEOUS BIOPSIES AND FLUID ASPIRATION AND DRAINAGE

### 1. What are the indications for image-guided percutaneous needle biopsy (PNB)?

- Establish a benign or malignant diagnosis of a lesion.
- Stage patients with known or suspected malignancy when metastasis is suspected.
- Obtain material for microbiological analysis in patients with known or suspected infection.
- Determine the nature and extent of diffuse parenchymal diseases (e.g., cirrhosis, organ transplant rejection, glomerulonephritis).

### 2. What are the indications for image-guided percutaneous fluid aspiration (PFA) and percutaneous catheter drainage (PCD)?

- Obtain a sample for fluid characterization.
- Remove fluid suspected to be infected or the result of an abnormal fistulous connection.
- Remove a fluid collection suspected to be the cause of symptoms sufficient to warrant drainage.
- Perform an adjunctive procedure necessary to facilitate the improved outcome of a subsequent intervention (e.g., drainage prior to sclerotherapy).
- Perform a temporizing maneuver to stabilize the patient's condition before definitive surgery (e.g., drainage of diverticular abscess to allow primary reanastomosis).

### 3. Name contraindications (absolute or relative) for image-guided PNB and PFA/PCD.

- A competent patient who does not give consent
- A patient who is unwilling or unable to cooperate with or to be positioned for the procedure (e.g., a retroperitoneal abscess is only accessible percutaneously via the back but the patient is unable to lie prone because of pain from an anterior abdominal wound or recent surgical incision)
- Uncorrectable coagulopathy
- Severely compromised cardiopulmonary function or hemodynamic instability
- Lack of a safe percutaneous "window" or pathway to the target
- Inability to visualize the target with available imaging modalities
- Pregnancy in cases in which imaging guidance uses ionizing radiation (the potential risks to the fetus and the clinical benefits of the procedure should be considered before proceeding)

### 4. When is an image-guided percutaneous core biopsy required as opposed to a percutaneous fine-needle aspiration (FNA)?

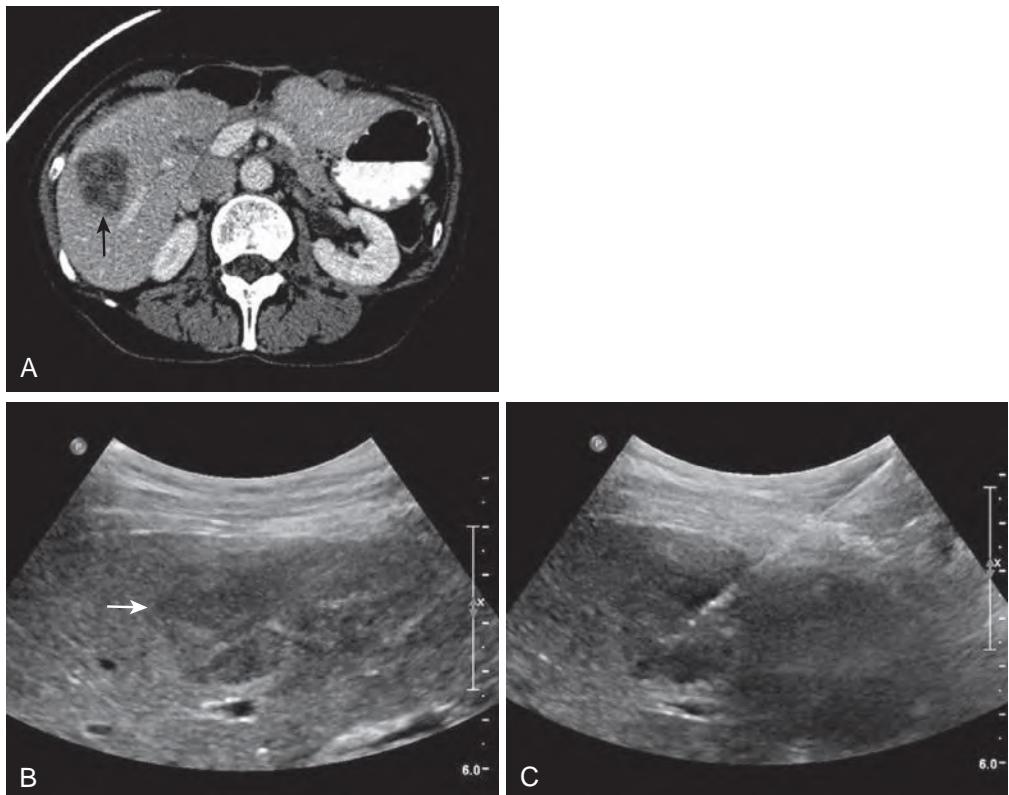
When architectural detail is needed for histopathologic diagnosis (e.g., well-differentiated neoplasms) and staging (e.g., staging fibrosis of diffuse liver diseases), a core biopsy is required. FNA specimens are usually obtained using 22- to 25-gauge needles and yield clusters of cells and occasionally small tissue fragments for cytopathologic examination. Core biopsies are performed using disposable, spring-loaded, automated devices (20 gauge or larger) and yield cylinders of tissue 1 to 2 cm long.

### 5. Which imaging modalities are used to guide interventional procedures?

Fluoroscopy, ultrasound (US) (Figure 67-1), computed tomography (CT), and magnetic resonance imaging (MRI) can be used to guide interventions. US and CT are used most often.

### 6. What five conditions must be satisfied before a percutaneous procedure can be performed?

- The patient or patient representative must provide written, informed consent for the procedure, intravenous conscious sedation (if applicable), and potential administration of blood or blood products.
- Code status during the procedure and postprocedural recovery period must be determined if the patient has do not attempt resuscitation orders.
- The patient's coagulation profile must be determined and any coagulopathies corrected.
- The patient must be fasting if conscious sedation will be used during the procedure. Exact times vary depending on institutional protocols and guidelines. Typical guidelines are fasting for at least 2 hours for "clear" liquids and at least 6 hours for "solids" or food.
- Appropriate antibiotic coverage must be administered if there is any possibility that the lesion or fluid collection is infected.



**Figure 67-1.** Metastatic cholangiocarcinoma to the liver. **A**, Contrast-enhanced axial computed tomography scan of the liver demonstrates a 3.6 cm heterogenous hypodense mass (arrow). **B**, Ultrasound of the liver demonstrates the mass to be heterogeneously hypoechoic (arrow). **C**, The needle is echogenic and well visualized during percutaneous ultrasound-guided biopsy.

#### 7. What coagulation parameters are assessed before a percutaneous procedure?

The patient history should be reviewed for bleeding risks, such as anticoagulant (warfarin [Coumadin], low-molecular-weight heparin) or platelet-inhibitor (aspirin, clopidogrel [Plavix]) agents, uremia, or hepatocellular disease. Routinely assessed parameters include hematocrit, prothrombin time, international normalized ratio (INR), partial thromboplastin time (PTT), and platelet count.

#### 8. How and when should coagulopathies be corrected?

Coagulopathies should be corrected with appropriate transfusions of packed red blood cells or hemostatic agents such as platelets, fresh-frozen plasma, vitamin K, cryoprecipitate, protamine, and recombinant factor VIIa. Institutional guidelines vary, but an INR greater than 2, a PTT greater than 1.5 times normal, or a platelet count less than 50,000/ $\mu$ L are each a relative contraindication for most procedures. Recent Society of Interventional Radiology guidelines offer useful coagulation and transfusion parameters for percutaneous procedures based on low, moderate, and significant risk of bleeding and ease of bleeding detection and controllability. If the patient has a coronary stent, a cardiology consult may be necessary prior to discontinuing antiplatelet agents to avoid stent complications.

#### 9. What pharmacologic agents can be injected into septated or viscous abdominal fluid collections to improve drainage?

Intracavitary fibrinolysis therapy with tissue plasminogen activator (tPA) can be performed through the drainage catheters to shorten treatment time and improve the clinical course of patients treated with percutaneous drainage catheters. Optimal dosing regimens have not been determined. Typical doses of tPA range from 2 to 6 mg of tPA diluted in 10 to 50 mL saline. The total volume of fluid depends on the size of the cavity. The dose is injected into the catheter, which is clamped for 1 to 2 hours after the dose is administered. After unclamping, the dose is allowed to drain spontaneously. The dose can be administered 1 to 3 times daily. Total number of doses varies depending on output response. Caution should be used with hepatic abscesses or in patients who are coagulopathic because of the potential increased risk of bleeding.

#### 10. What should you suspect if the drainage catheter has persistently elevated outputs?

If a catheter has persistently elevated outputs, a sudden increase in drainage, or a change in the composition of the effluent, a fistula should be suspected. Injection of contrast into the catheter under fluoroscopy often demonstrates the fistula, which can be to the gastrointestinal tract, pancreatic duct, biliary system, or to the

genitourinary tract. Occasionally, an alternative study is necessary such as a small bowel follow-through if the fistula acts as a one-way valve and is not demonstrated by injection of the drainage catheter. Often the fistula will heal but prolonged drainage is required and can last as long as 2 to 4 weeks or more. The catheter should not be removed until the fistula has healed or has been repaired.

#### **11. When should you remove the drainage catheter?**

If the catheter output is less than 10 to 20 mL per 24 hours, there are no other reasons for the decreased outputs (e.g., catheter clogged, kinked, or malpositioned), and the patient has clinically improved, the catheter can be removed. Repeat imaging with US, CT, or contrast injection under fluoroscopy is not necessary unless the patient has a known fistula or is still clinically symptomatic, or unless the overall output is less than expected. An exception to these criteria for catheter removal is percutaneous cholecystostomy catheters. Percutaneous cholecystostomy catheters require an epithelialized tract to form before removal to prevent bile leakage and bile peritonitis. This usually requires a minimum of 3 weeks' time, but if the patient is immunocompromised or in the intensive care unit, the process can take even longer.

#### **12. What are the major complications of image-guided PNB?**

Major complications are defined as those that result in an unplanned increase in the level of care, prolonged hospitalization (in-patients), admission to the hospital for therapy (out-patients), permanent adverse sequelae, and death. The complications of PNB can be stratified as general or organ-specific. Major general complications include hemorrhage, infection, solid organ injury, bowel perforation, and pneumothorax. Reported rates of major complications range from 0.1% to 10% with infection as a result of a biopsy being uncommon. Clinically significant bleeding requiring blood transfusion or intervention is infrequent, but the reported rates increase with larger needles sizes, use of cutting needles, and the vascularity of the organ or lesion biopsied.

#### **13. Does seeding of the needle tract occur during routine tumor biopsy?**

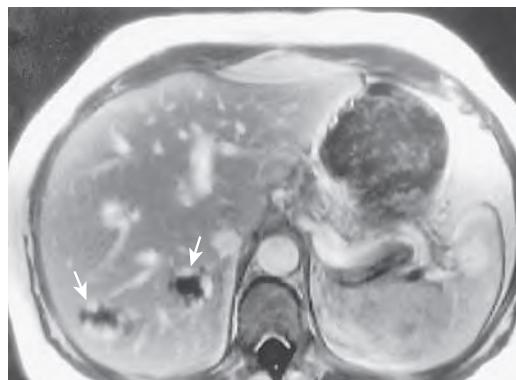
Case reports of tumor spread along the needle tract as a result of percutaneous biopsy are described in the medical literature. Overall, seeding the needle tract is uncommon and the reported rates vary according to organ biopsied. For masses suspected to be hepatocellular carcinoma (HCC), needle track seeding can be a potentially devastating complication in transplant candidates in whom immunosuppression may predispose to seeded tumor growth; however, the American Association for the Study of Liver Diseases believes the risk has been overstated in earlier literature. Needle gauge sizes, number of needle passes, and coaxial versus single-needle systems are believed to influence the risk of tumor seeding, but robust evidence is still lacking. Although this potential complication should be discussed with the patient prior to the procedure, it should not be considered a contraindication to FNA or core biopsy in patients in whom the diagnosis is in question and when knowledge of a specific diagnosis is likely to alter clinical management.

Cystic lesions like suspected cystadenomas or cystadenocarcinomas of the ovary or pancreas should not be sampled percutaneously, even with small, skinny needles. This is associated with a significant risk of postprocedure needle-tract seeding and subsequent pseudomyxoma peritonei or peritoneal carcinomatosis.

### **HEPATIC INTERVENTIONS**

#### **14. Is FNA or core biopsy safe or necessary for all hepatic masses?**

Benign masses such as hemangiomas (Figure 67-2), focal nodular hyperplasia, and adenomas often have distinguishing characteristics on high-quality cross-sectional imaging modalities. When these masses are present in patients with classic corresponding clinical features, obtaining specimens for cytologic or histologic examination is usually not necessary. If any imaging or clinical features are not characteristic, biopsy can be performed safely.



**Figure 67-2.** Dynamic, gadolinium-enhanced. T1-weighted magnetic resonance (MR) scan of the liver shows two lesions (arrows) with perfusion patterns characteristic of hemangiomas. Their distinctive MR features allow conservative management with surveillance imaging, obviating biopsy. Incidental note is made of a nonspecific hyperintensity in the spleen.

Carcinoid crisis characterized by profound hypotension can be precipitated by FNA of hepatic carcinoid metastases. Patients with carcinoid tumors typically present with characteristic clinical symptoms and can be confirmed biochemically. If biopsy of a suspected hepatic carcinoid metastasis must be performed for diagnosis, appropriate preparatory measures should be taken and resuscitative equipment needs to be readily available.

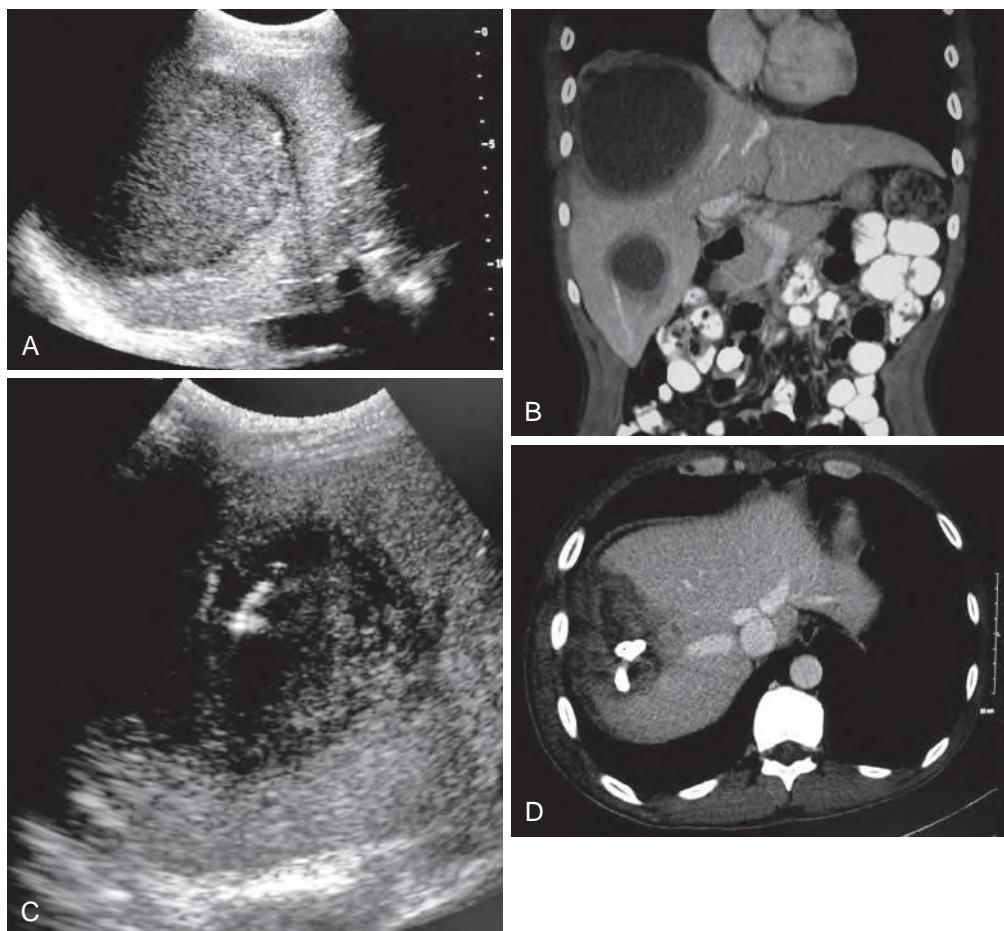
### 15. How are pyogenic hepatic abscesses treated?

At least 90% of pyogenic hepatic abscesses can be successfully drained percutaneously. Most pyogenic abscesses smaller than 3 cm in diameter are treated with antibiotics either alone or in combination with needle aspiration, with excellent success rates. For pyogenic abscesses larger than 4 cm in diameter, image-guided PCD is required. The size of the self-retaining, pigtail catheter inserted often depends on the viscosity of the fluid encountered.

The possibility of an abscess complicating an underlying hepatic neoplasm should always be considered. Follow-up imaging should be obtained to document eventual complete resolution of the lesion. FNA or core biopsy of any persistent abnormality may be necessary to exclude occult hepatic tumor.

### 16. When is image-guided PFA/PCD indicated for treatment of amebic abscesses (Figure 67-3)?

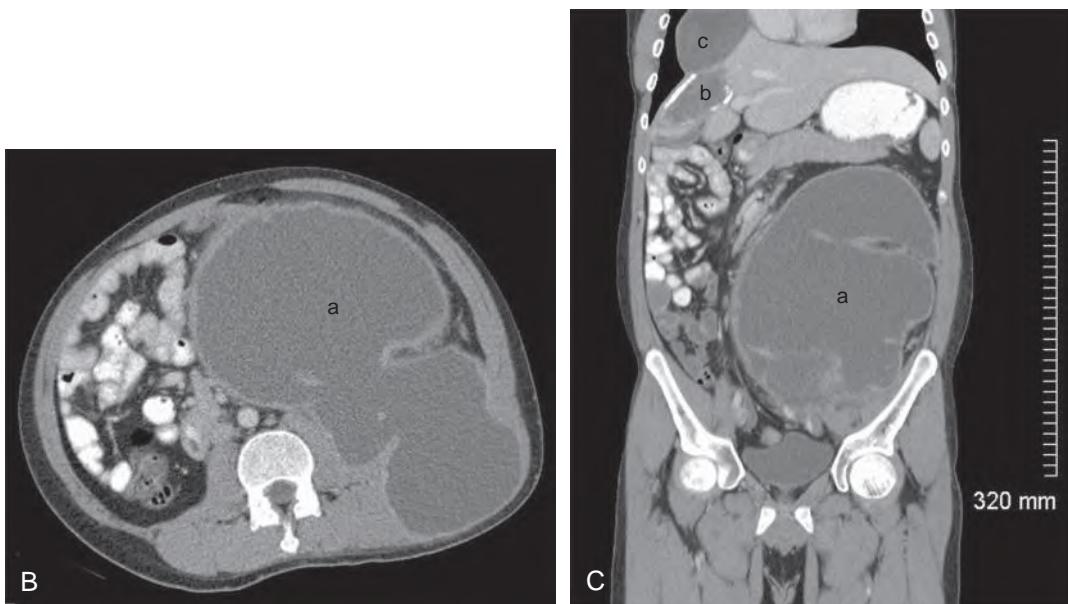
Amebic abscesses respond well to appropriate antibiotic treatment regardless of size, and PCD is usually not required unless response to medical treatment is inadequate. PCD should be considered for large amebic abscesses in a peripheral location or in the left hepatic lobe as these sites are prone to rupture into the peritoneum, pericardium, or pleural space.



**Figure 67-3.** Percutaneous drainage of an amebic abscess in a 43-year-old Mexican immigrant who presented with abdominal pain, vomiting, night sweats, and fever. **A**, Ultrasound of the liver demonstrates a  $9 \times 10$  cm well-defined, homogeneously echogenic abscess. **B**, Coronal image from a contrast-enhanced computed tomography (CT) scan of the abdomen obtained 9 hours later for worsening right upper quadrant pain and fever despite intravenous metronidazole. The large abscess in the right hepatic dome has increased to  $9.6 \times 13$  cm, concerning for imminent rupture. A second smaller abscess is in the inferior right lobe. **C**, Ultrasound-guided placement of 14-Fr pigtail catheter. The echogenic puncture needle is well visualized in the center of the abscess at sonography, and 500 mL of thick, brownish material was evacuated with immediate pain relief. **D**, CT scan obtained 1 week later demonstrates significant decrease in the size of the abscess.

### 17. Is image-guided PFA/PCD indicated for treatment of hydatid cyst disease?

Cystic echinococcosis is caused by *Echinococcus granulosus*. Previously PFA/PCD of a suspected echinococcal cyst or hydatid cyst disease was an absolute contraindication because of fatal anaphylaxis from spillage of the scolices. However, published series describe favorable results with oral albendazole treatment combined with PCD or with the puncture, aspiration, injection, reaspiration (PAIR) technique. The cyst contents are aspirated via the percutaneous puncture. Contrast is injected under fluoroscopic guidance to ensure there is no communication with the bile ducts and then a protoscolicide such as hypertonic saline or ethanol is injected, allowed to sit, and then reaspirated. Modified PAIR uses placement of a catheter, which allows more complete evacuation of the endocyst and repeat injections of protoscolicide, and is especially useful for treating large cysts. Oral albendazole treatment must be started *at least 4 hours prior* to percutaneous intervention. Caution: The risk of fatal anaphylaxis is not entirely eliminated and thus appropriate emergency medical treatment and resources must be readily available (Figure 67-4B and C and E-Figure 67-4A and D).



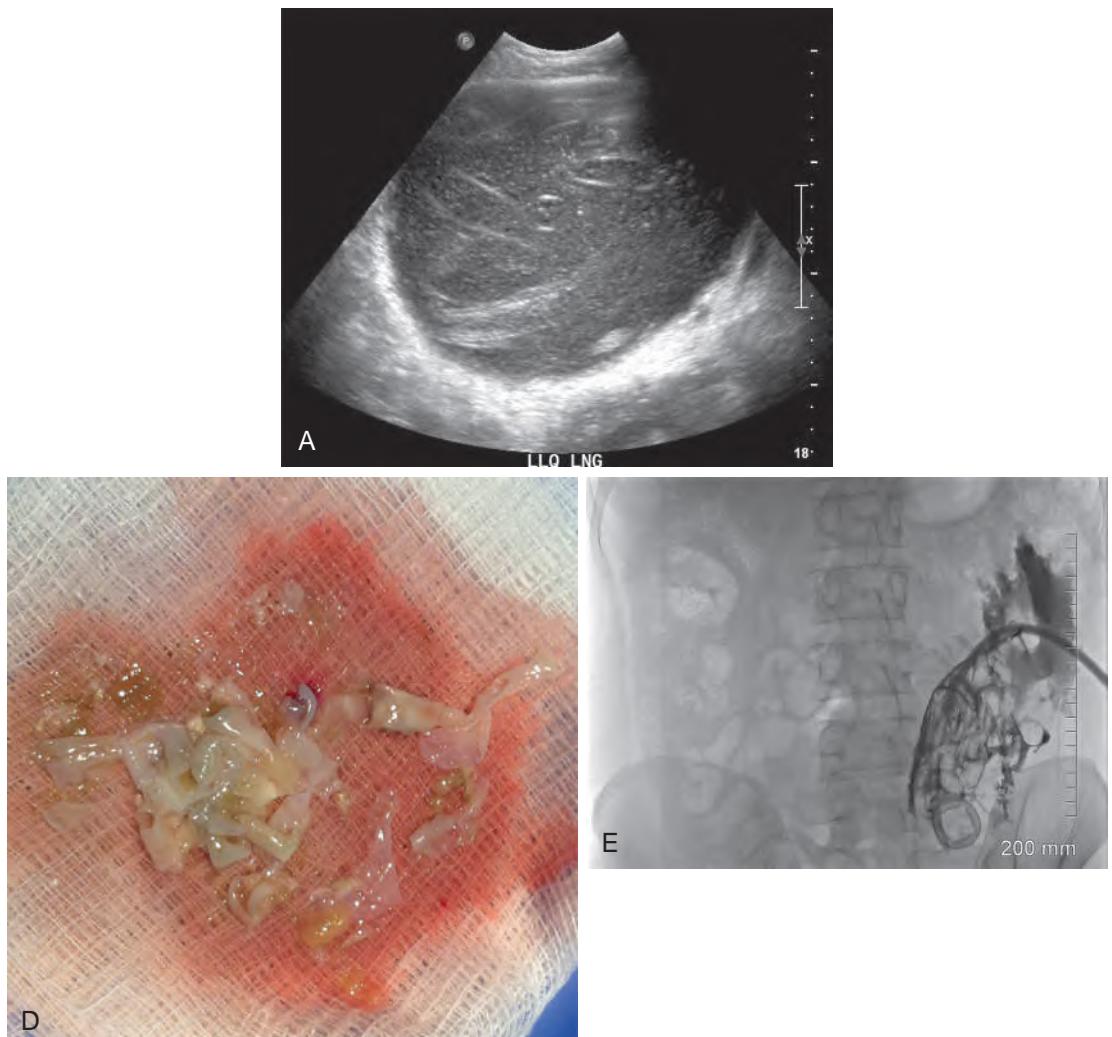
**Figure 67-4.** Hydatid cyst disease in a 26-year-old man who immigrated to the United States 11 years ago from Ethiopia. He presented to the outpatient medicine clinic with complaints of left back swelling and mild pain for 7 days. Axial (B) and coronal (C) images from a contrast-enhanced computed tomography (CT) scan demonstrates the  $27 \times 16 \times 25$  cm (a) well-circumscribed fluid collection in the left abdomen and extending to the left flank. Also shown on the coronal (C) CT image are the  $8 \times 6$  cm (b) collection with irregular calcifications in the right hepatic lobe and the subdiaphragmatic  $9 \times 7$  cm (c) collection in the hepatic dome.

### 18. Describe the treatment of simple, benign, epithelialized hepatic cysts.

Epithelialized hepatic cysts can be drained successfully and obliterated with sclerotherapy. A self-retaining, pigtail catheter can be used. After catheter placement with US or CT guidance, and complete cyst aspiration, samples are sent for culture and cytologic examination. Contrast is injected through the catheter under fluoroscopic guidance to ensure that there is no communication with the biliary tree. If no connection to the bile ducts is demonstrated, then 33% to 50% of the original cyst volume is replaced with a sclerosant. Sclerosants used to treat hepatic cysts include ethanol (not to exceed 100 mL), tetracycline, doxycycline, and povidone-iodine. The patient is rotated into multiple positions until the entirety of the cyst wall has been in contact with the sclerosing agent for 60 minutes. The entire volume of sclerosant and residual cyst contents are then completely aspirated through the catheter. Large cysts may require repeat treatments. After the final treatment and aspiration, the catheter is removed.

### 19. Can cysts in patients with polycystic liver disease be treated with sclerotherapy?

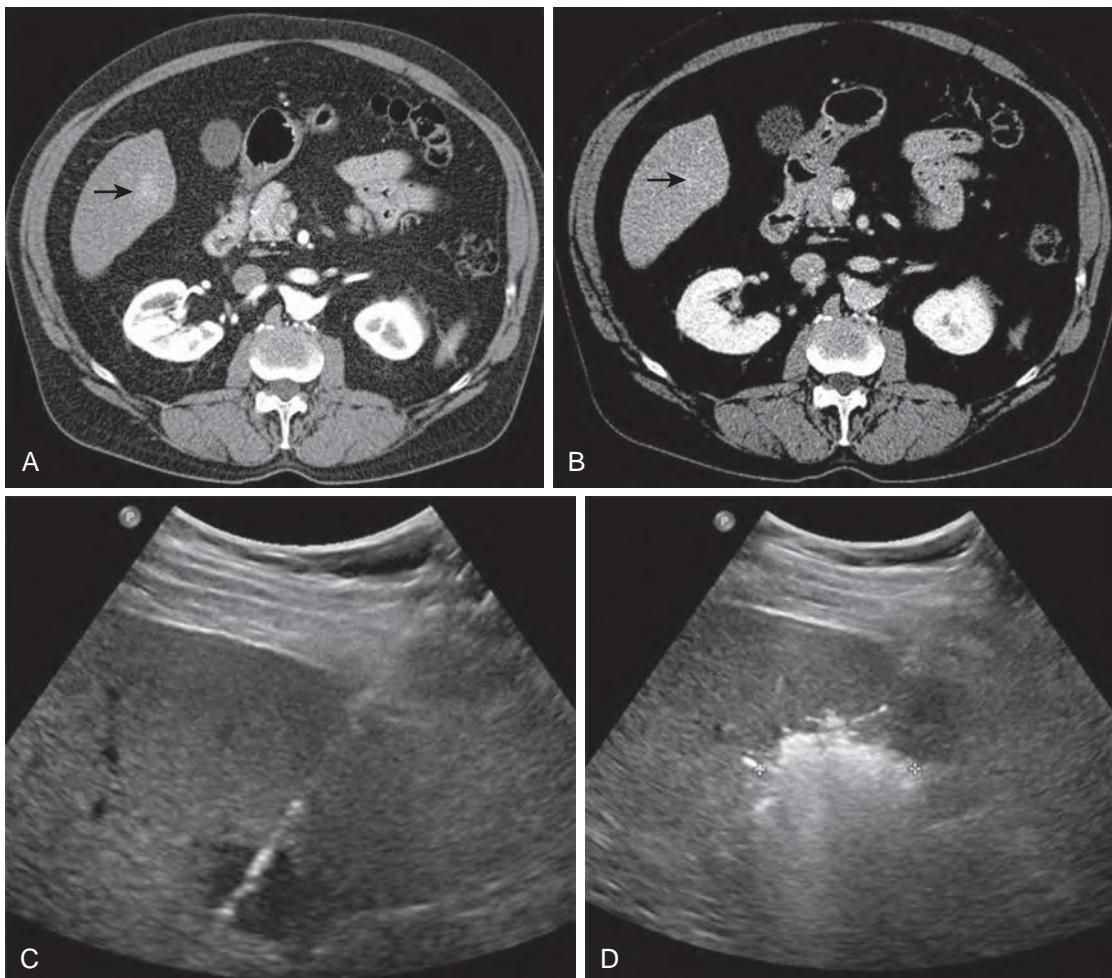
Yes, although solitary hepatic cysts are more often successfully sclerosed than cysts in patients with polycystic liver disease. In polycystic liver disease, cysts tend not to collapse, presumably because the surrounding liver is less pliable, making cyst wall apposition and subsequent scarring of the cavity less likely. Surgical or laparoscopic unroofing, fenestration, or removal of cysts may be needed when percutaneous treatment fails.



**E-Figure 67-4.** A, Ultrasound of the abdomen demonstrates a large complex fluid collection in the left flank containing mobile debris and linear membranes. D, Photograph of debris removed from the left peritoneal echinococcal cyst after treatment with hypertonic saline. E, Injection of contrast into the drainage catheter under fluoroscopy demonstrates the markedly smaller sized cavity of the left peritoneal echinococcal cyst after repeated treatments with hypertonic saline and prolonged catheter drainage.

**20. Name the minimally invasive percutaneous ablative therapies for HCC.**

Percutaneous ablative techniques for local control of HCC can be divided into two categories: thermal ablation and chemical ablation. Thermal ablation techniques alter the temperature of the tumor to cause cell death and include heat-based methods (radiofrequency ablation [RFA], microwave ablation ([Figure 67-5A-D](#) and [E-Figure 67-5E](#)), laser ablation, high-intensity focused US) and cold-based methods (cryoablation). Chemical ablation involves injecting substances such as ethanol or acetic acid directly into the tumor to produce tissue necrosis.



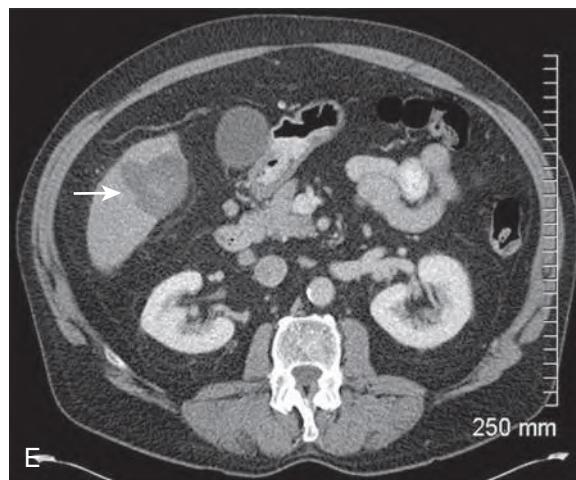
**Figure 67-5.** Microwave ablation of hepatocellular carcinoma (HCC). **A**, Arterial phase contrast-enhanced computed tomography (CT) scan demonstrates a 2.5-cm hypervascular mass (arrow) in the right hepatic lobe of a patient with hepatitis C. **B**, There is washout (arrow) on the portal venous phase consistent with HCC. **C**, Ultrasound image shows the hypoechoic mass with placement of the echogenic microwave probe in the mass. **D**, Ultrasound image during microwave ablation depicts the hyperechoic zone of ablation.

**21. What temperatures must be achieved to be cytotoxic for tumor destruction?**

Irreversible damage with cellular protein denaturation, cell membrane dysfunction, and coagulation necrosis occurs at temperatures between 60 °C and 100 °C. Above 100 °C to 110 °C, tissue carbonization and charring occurs which results in diminished volume of the ablation zone from less effective energy transmission. In cryotherapy, irreversible damage from cellular dehydration, membrane rupture, and ischemic microvascular thrombosis occurs at temperatures between -20 °C and -40 °C. For adequate tumor destruction, the entire target volume must be subject to cytotoxic temperatures and thus the zone of ablation must be larger than the size of the tumor itself to achieve tumor-free margins.

**22. What are the advantages of RFA and other methods of percutaneous thermal ablation?**

- Low mortality and complication rates (Multicenter surveys report mortality rates ranging from 0.1% to 0.5%, major complication rates ranging from 2.2% to 3.1%, and minor complication rates ranging from 5% to 8.9%).



**E-Figure 67-5.** E, Contrast-enhanced CT scan (portal venous phase shown) 4 weeks later shows the nonenhancing, mainly hypodense area of thermocoagulation (*arrow*), which encompasses the HCC with a margin of treated tissue around the tumor.

- Repeatability
- Minimally invasive and shorter recovery times compared with surgery
- Can be used in combination with other treatment therapies
- Less destruction of nonneoplastic tissue than surgery

#### **23. What are the contraindications of RFA or percutaneous thermal ablative techniques?**

The only absolute contraindications are uncorrectable coagulopathy or a noncompliant patient. RFA and other percutaneous ablative techniques are local treatments and are usually not performed in patients with vascular invasion or extrahepatic metastases. Patients with colonization of the biliary tract from bilioenteric anastomoses, endoscopic sphincterotomy, or bilioenteric fistula are at increased risk of postablation liver abscess. Some liver transplant centers may exclude patients from transplant consideration who have had percutaneous tumor ablation because of concerns of tumor recurrence from tract seeding, so it is important to discuss treatment options with referral hepatologists and surgeons who are experts in liver transplantation.

#### **24. Describe the risks of thermal ablation related to the anatomic location of the tumor.**

Superficial tumors adjacent to the gastrointestinal tract are at risk for thermal injury to the bowel wall. The colon appears to be at greater risk for perforation than the stomach and small bowel because of the thinner wall thickness and its lesser mobility. The gallbladder and biliary tract are also at risk for thermal injury. Perforation of the gallbladder is rare, but ablation of tumors adjacent to the gallbladder can be associated with iatrogenic cholecystitis, which is usually self-limited. Bilomas and biliary stenoses can also occur. Lesions in the dome of the liver can result in thermal injury to the diaphragm, pneumothorax, or hemothorax. Vessels in the vicinity or adjacent to lesions are usually protected because of the “heat or cold sink” effect of flowing blood. However, if the vessel is very small or the flow is decreased for any reason, thrombosis can occur. The *heat or cold sink* effect may also result in incomplete ablation of the neoplastic tissues adjacent to the vessel from temperature loss.

#### **25. In the treatment of HCC, how do survival outcomes of RFA compare with surgical resection?**

Most studies evaluating surgical resection and RFA show similar long-term outcomes for HCC smaller than 3 cm. In a randomized control trial of 112 patients with a solitary HCC less than 5 cm by Chen et al., there were no significant differences in local recurrence, overall survival, or disease-free survival between the two groups.

#### **26. What other liver tumors have been treated with percutaneous thermal ablative techniques?**

Liver metastases from neuroendocrine, gastric, pancreatic, pulmonary, renal, uterine, or ovarian cancer and melanoma have all been successfully treated with RFA. Besides HCC, the majority of percutaneous thermal ablative procedures are performed for the treatment of colorectal liver metastases. Percutaneous RFA has also been used to successfully treat symptomatic giant cavernous hemangiomas in patients choosing not to undergo surgical resection.

### **SPLENIC INTERVENTIONS**

#### **27. What cross-sectional image-guided interventions are possible in the spleen?**

When clinically indicated given the increased risk of complications such as bleeding, percutaneous image-guided biopsy and catheter drainage can be performed safely in the spleen. Focal splenic masses are uncommon, so splenic biopsy is rarely performed. Splenic abscesses also are not common although the incidence is thought to be growing because of the increasing number of immunocompromised patients. If a percutaneous procedure is attempted, the size of the needle or catheter should be conservative because of the risk of hemorrhage.

### **PANCREATIC PROCEDURES**

#### **28. What procedures are appropriate for solid pancreatic masses?**

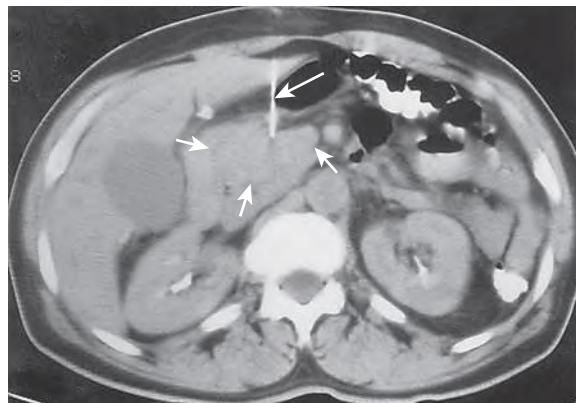
Solid masses, usually suspected tumors, can be aspirated percutaneously (Figure 67-6). Only FNAs should be performed; core biopsies should be avoided, because the use of cutting needles can result in severe pancreatitis. As noted previously, percutaneous biopsy of suspected cystadenomas or cystadenocarcinomas should be avoided.

#### **29. Can FNA be performed for solid pancreatic masses completely surrounded by the bowel?**

If a skinny needle (<20 gauge) is used and the lesion is solid, any organ, including the stomach, small bowel, and colon, can be traversed. Antibiotic coverage is recommended for procedures through the bowel. Major blood vessels should be avoided. The diagnosis of pancreatic adenocarcinoma often can be established by cytopathologic examination alone; a negative result must be interpreted with caution and assumed to be a sampling error until proved otherwise.

#### **30. What procedures are used for pancreatic and peripancreatic collections?**

Various acute and chronic pancreatic and peripancreatic collections can be percutaneously aspirated and drained using image guidance if clinically indicated. According to the revised Atlanta classification system for acute pancreatitis, collections should be defined as acute peripancreatic fluid collection (APFC), pancreatic



**Figure 67-6.** Fine-needle aspiration of pancreatic head carcinoma. Computed tomography scan shows mild fullness of the pancreatic uncinate process (small arrows). A skinny needle (large arrow), passed through the liver and bowel wall without complication, was used to obtain cellular material diagnostic of pancreatic adenocarcinoma.

pseudocyst, acute necrotic collection (ANC), or walled-off necrosis (WON). The term *pancreatic abscess* is not used in the current classification. These collections can be aspirated to determine whether they are sterile or infected. In this setting, bowel should not be crossed with the aspiration needle to avoid contaminating and superinfecting otherwise sterile fluid.

### 31. Do APFCs require percutaneous image-guided treatment?

APFCs are adjacent to the pancreas and extrapancreatic only. They occur during the first 4 weeks, have no discernible wall, and do not contain debris or necrosis. Most usually resolve spontaneously without intervention and do not become infected. Percutaneous image-guided drainage is only indicated if infected. The presence of infection can be presumed when there is the presence of extraluminal gas or when percutaneous image-guided FNA is positive for bacteria or fungi on gram stain and culture.

### 32. When is drainage indicated for treatment of pancreatic pseudocysts?

Pancreatic pseudocysts usually occur 4 weeks after the onset of interstitial edematous pancreatitis, have a well-defined wall, and no nonliquid component. Drainage is indicated when pseudocysts are infected, rapidly enlarging, painful, obstructing, or large ( $\geq 5$  cm). Drainage can be achieved via percutaneous image guidance, endoscopic US guidance, or surgically; the optimal technique depends on the clinical situation and the decision should be made after multidisciplinary consultation with interventional radiologists, gastroenterologists, and surgeons.

### 33. What are the similarities and differences between an ANC and WON?

Both collections can be intrapancreatic or extrapancreatic, associated with necrotizing pancreatitis, and contain variable amounts of fluid and solid necrotic tissue. An ANC occurs within the first 4 weeks and does not have a definable wall encapsulating the collection. WON occurs 4 weeks or more after the onset of necrotizing pancreatitis and is a mature, encapsulated collection with a well-defined inflammatory wall.

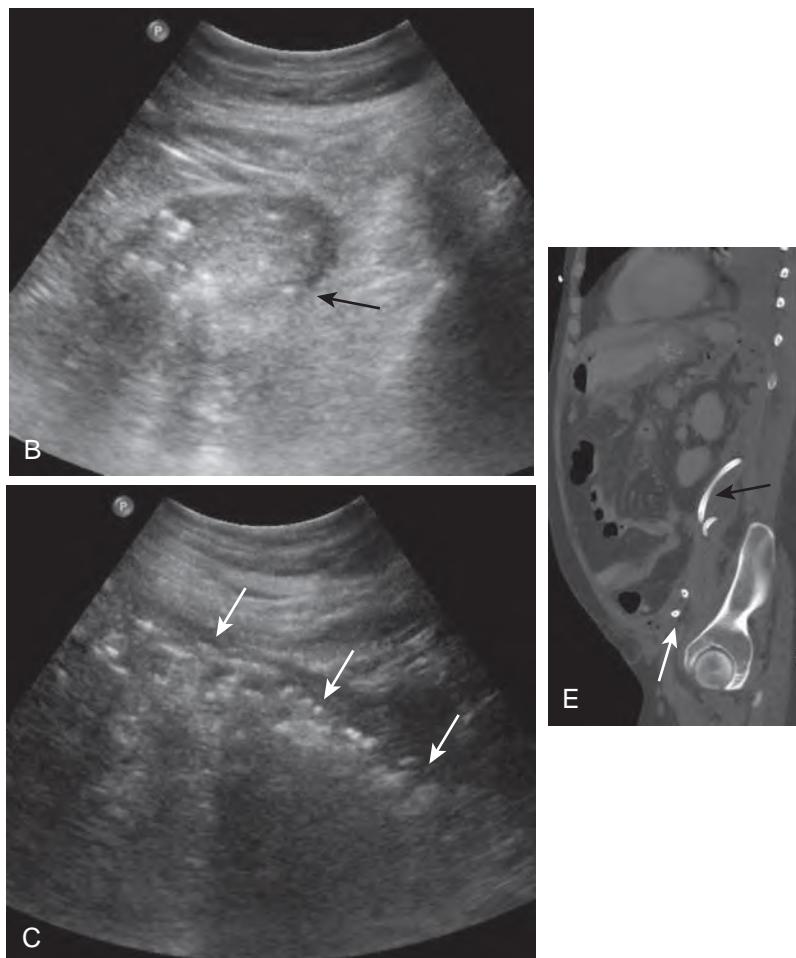
### 34. What is the role of image-guided PCD in the treatment of infected ANC and WON?

The role of PCD in the management of infected ANC and WON is controversial. Open surgical necrosectomy is still considered the gold standard treatment in infected pancreatic necrosis, because it involves nonliquefactive tissue that is difficult to remove with percutaneous drainage catheters. However, open necrosectomy is associated with a high mortality rate and significant morbidity. Image-guided PCD generally has a lower morbidity and mortality rate and can be considered in patients with appropriate percutaneous access either as potential definitive treatment or as a bridge to surgery. It is not uncommon for drains to be left in place for a month or longer. Effective percutaneous drainage also requires vigorous catheter irrigation and frequent catheter upsizing and exchange (Figure 67-7A and D and E-Figure 67-7B, C, and E).

## ADRENAL BIOPSY

### 35. When is adrenal gland biopsy indicated?

In patients with no history of malignancy, most incidentally discovered adrenal masses less than 4 cm in diameter are benign and should be evaluated with CT scans or MRI. For adrenal masses greater than 4 cm and not typical for adenoma, myelolipoma, hemorrhage, or simple cysts, surgical resection should be considered. In patients with histories of malignancy, an incidental adrenal mass is more often malignant and even small lesions are suspect. In these situations, a biopsy is indicated when noninvasive tests are inconclusive unless the presence of widespread nonadrenal metastases makes the presence or absence of adrenal metastases



**E-Figure 67-7.** Transverse (B) and longitudinal (C) ultrasound images demonstrate a heterogeneous collection containing gas (arrows). E, Coronal image from CT scan 1 week later demonstrates the catheter (black arrow) within the collection that has decreased in size. A second drainage catheter (white arrow) is within the loculated portion of the collection in the pelvis.



**Figure 67-7.** Infected, walled-off necrosis in a 53-year-old man with elevated white blood cell count and fever. His onset of necrotizing pancreatitis was 6 weeks ago. **A**, Sagittal image from a contrast-enhanced computed tomography (CT) scan demonstrates a left retroperitoneal collection with a well-defined inflammatory wall containing fluid and gas (arrows). **D**, Fluoroscopic image of a multihole drainage catheter placed using ultrasound and fluoroscopic guidance. Contrast outlines the cavity.

unlikely to change patient management. Adrenal biopsies are also indicated when enlarging masses are seen on follow-up imaging and the imaging characteristics are suspicious for malignancy.

### 36. What adrenal lesions should NOT be biopsied?

Because of the risk of hypertensive crisis, possible pheochromocytomas in any of the above situations should not be needleled. Pheochromocytomas do not have specific imaging features and thus must be suspected clinically with confirmation testing for urine or serum catecholamines.

*The authors would like to acknowledge the contribution of Dr. Stephen Subber, who was an author of this chapter in the previous edition.*

Please access ExpertConsult to view the E-Figures for this chapter.

### BIBLIOGRAPHY

1. American College of Radiology ACR Appropriateness Criteria. Radiologic management of infected fluid collections. Accessed September 22, 2014, from <http://www.acr.org/Quality-Safety/Appropriateness-Criteria~/media/7A5A6BA0A47C406884C17C5F96A416AC.pdf>.
2. American College of Radiology ACR Appropriateness Criteria: Incidentally discovered adrenal mass. Accessed September 22, 2014, from <http://www.acr.org/~/media/ACR/Documents/AppCriteria/Diagnostic/IncidentallyDiscoveredAdrenalMass.pdf>.
3. Aryafar H, Kinney TB. Percutaneous biopsy. In: Valji K, editor. The practice of interventional radiology with online cases and videos. Philadelphia: Elsevier Saunders; 2012. p. 84–105.
4. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: Revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–11.
5. Brunetti E, Kern P, Vuitton DA. Writing Panel for the WHO-IWGE. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop 2010;114:1–16.
6. Cheng D, Nagata KT, Yoon HC. Randomized prospective comparison of alteplase versus saline solution for the percutaneous treatment of loculated abdominopelvic abscesses. J Vasc Interv Radiol 2008;19:906–11.
7. Hickey R, Vouche M, Sze DY, et al. Cancer concepts and principles: Primer for the interventional radiologist—part II. J Vasc Interv Radiol 2013;24:1167–88.
8. McWilliams JP, Yamamoto S, Raman SS, et al. Percutaneous ablation of hepatocellular carcinoma: Current status. J Vasc Interv Radiol 2010;21:S204–S213.
9. Meza-Junco J, Montano-Loza AJ, Liu DM, et al. Locoregional radiological treatment for hepatocellular carcinoma: Which, when and how? Cancer Treat Rev 2012;38:54–62.
10. Nair AV, D'Agostino HR. Transcatheter fluid drainage. In: Valji K, editor. The practice of interventional radiology with online cases and videos. Philadelphia: Elsevier Saunders; 2012. p. 106–25.
11. Patel IJ, Davidson JC, Nikolic B, et al. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. J Vasc Interv Radiol 2012;23:727–36.
12. Robertson EG, Baxter G. Tumour seeding following percutaneous needle biopsy: The real story!. Clin Radiol 2011;66:1007–14.
13. Rockey DC, Caldwell SH, Goodman ZD, et al. Liver biopsy AASLD position paper. Hepatology 2009;43:1017–44.
14. Shenoy-Bhangale AS, Gervais DA. Use of fibrinolytics in abdominal and pleural collections. Semin Intervent Radiol 2012;29:264–9.
15. Silva MA, Hegab B, Hyde C, et al. Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: A systematic review and meta-analysis. Gut 2008;57:1592–6.

16. Sinha V, Dyer P, Roy-Choudhury S, et al. Case of carcinoid crisis following a fine-needle biopsy of hepatic metastasis. *Eur J Gastroenterol Hepatol* 2009;21:101–3.
17. Wronski M, Cebulski W, Karkocha D, et al. Ultrasound-guided percutaneous drainage of infected pancreatic necrosis. *Surg Endosc* 2013;27:2841–8.

**Websites**

American Association for the Study of Liver Disease. Accessed September 22, 2014, from [www.aasld.org](http://www.aasld.org).

American College of Radiology. Accessed September 22, 2014, from [www.acr.org](http://www.acr.org).

Society of Interventional Radiology. Accessed September 22, 2014, from [www.sirweb.org](http://www.sirweb.org).

# INTERVENTIONAL RADIOLOGY II: FLUOROSCOPIC AND ANGIOGRAPHIC PROCEDURES

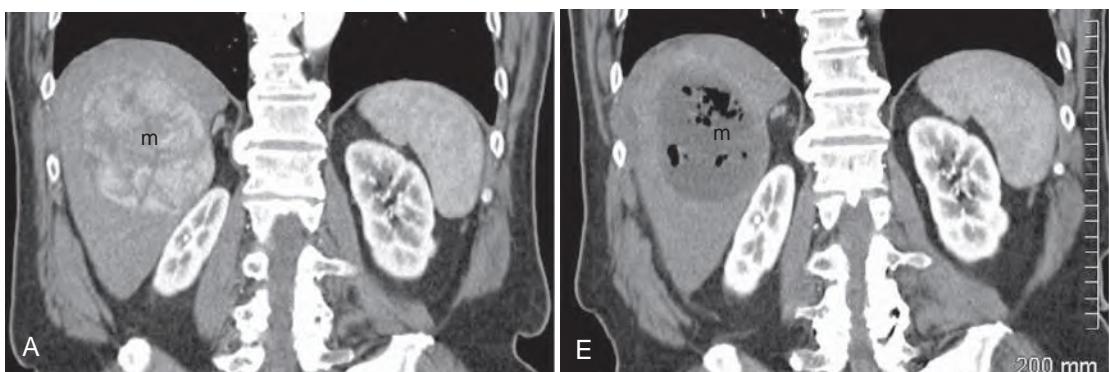
Kimi L. Kondo, DO, and Paul D. Russ, MD

## 1. Name the current radiologic methods of treating hepatic malignancies.

Transarterial chemoembolization (TACE), transarterial embolization (TAE), selective internal radiation therapy (SIRT), percutaneous image-guided chemical ablation, percutaneous image-guided thermal ablation, TACE combined with ablation, and hepatic arterial chemotherapy infusion are the current radiologic methods. Hepatic arterial chemotherapy infusion has been used for treatment of colorectal cancer metastases to the liver but remains unpopular because of cost, complexity of arterial pump placement, and concerns of liver toxicity.

## 2. What are the indications for TACE?

Chemoembolization is indicated in patients with liver-dominant hepatic malignancies who are not candidates for curative resection. In patients with hepatocellular carcinoma (HCC), TACE has been used as palliative treatment or as a bridge to liver transplantation. It is considered standard of care for intermediate stages of HCC according to the Barcelona Clinic Liver Cancer staging system. TACE has also been used as a palliative treatment for patients with unresectable cholangiocarcinoma, and hepatic metastases from neuroendocrine tumors, colorectal carcinoma, breast carcinoma, as well as soft-tissue sarcomas. The injection of the chemotherapeutic agent mixed with ethiodized oil followed by embolization with particles is considered conventional TACE as opposed to a more recent refinement of the technique using drug-eluting beads (Figure 68-1A and E and E-Figure 68-1B-D) to both deliver the chemotherapy and act as the embolic agent.



**Figure 68-1.** Chemoembolization of a hepatocellular carcinoma (HCC). **A**, Coronal arterial phase contrast-enhanced computed tomography (CT) scan demonstrates an 8-cm hypervascular mass (m) in the right lobe of the liver. **E**, Coronal arterial phase contrast-enhanced CT scan performed 4 weeks later demonstrates the hypodense, nonenhancing HCC (m) consistent with complete devascularization and response to chemoembolization. The gas bubbles are a result of sterile tumor necrosis from injection of polyvinyl alcohol particles in addition to the doxorubicin drug-eluting beads. (see E-Figure 68-1B-D)

## 3. What is the expected median survival for intermediate HCC patients after TACE?

For intermediate HCC patients the expected median survival is 16 months. After TACE, it is approximately 20 months. This fulfills standard oncological criteria for treatment efficacy.

## 4. Describe exclusion criteria/contraindications for TACE in HCC patients.

Contraindications for TACE can be categorized based on tumor status, liver disease, patient performance status, procedural aspects, and chemotherapy characteristics (Table 68-1). Exclusion criteria based on laboratory values are not definitively established. Greater than 50% liver replacement with tumor, bilirubin level of more than 2 mg/dL, a lactate dehydrogenase level of more than 425 mg/dL, and an aspartate aminotransferase level of more than 100 IU/L have been reported to be strongly associated with increased postprocedural mortality. However, individual abnormalities of these four parameters have not been shown to predict adverse outcome from TACE. A total bilirubin cutoff value of more than 3 mg/dL has been described in the literature, although some operators have performed TACE in patients with total bilirubin of more than 3 mg/dL if they are listed for liver transplantation. Portal vein thrombosis is no longer considered an absolute contraindication; however, highly selective embolization and adjustment of the chemotherapy dose may minimize liver damage.



**E-Figure 68-1.** **B**, Coronal portal venous phase contrast-enhanced CT scan depicts washout (m) diagnostic of HCC. **C**, Hypervascularity and tumor blush of the HCC on hepatic arteriography. **D**, Absence of tumor blush and arterial flow to the mass on hepatic arteriography after chemoembolization with 100-300  $\mu\text{m}$  and 300-500  $\mu\text{m}$  drug-eluting beads loaded with doxorubicin.

**Table 68-1.** Exclusion Criteria and Contraindications for TACE

CATEGORY	CRITERIA
Tumor status	Single resectable tumor BCLC class D
Liver disease	Child-Pugh class C Active gastrointestinal bleeding
Patient performance status	ECOG >2
Procedural	Renal insufficiency/failure Uncorrectable coagulopathy Intractable systemic infection Severe anaphylactic/anaphylactoid contrast reaction
Doxorubicin related	WBC <3000 cells/mm <sup>3</sup> ; neutrophils <1500 cells/mm <sup>3</sup> Left-ventricular ejection fraction <50%

BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; WBC, white blood cell.

### 5. Describe postembolization syndrome (PES).

PES is an expected side effect of liver embolization and can occur after TAE, TACE, and SIRT. It is characterized by fever, abdominal pain, anorexia, nausea, vomiting, and fatigue. PES occurs in up to 90% of patients. The severity of symptoms is variable and is usually a self-limited event that is managed supportively. Occasionally it can require an extended hospital admission. The etiologic factors are not fully understood but PES is thought to be caused by a combination of liver tissue ischemia, inflammatory response, and tumor necrosis.

### 6. How is response to TAE and TACE monitored?

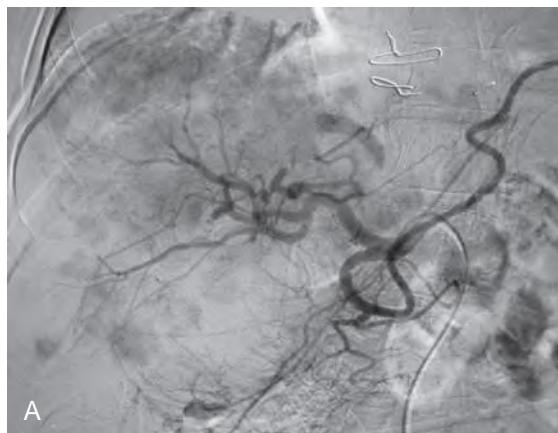
Posttreatment monitoring is performed with contrast-enhanced multiphase computed tomography (CT) or dynamic magnetic resonance imaging (MRI) 4 to 6 weeks after all tumor-bearing areas are treated. If treatment of both lobes of the liver is planned, imaging between sessions may be performed based on operator preference. Signs of tumor necrosis on CT include uptake of ethiodized oil (conventional TACE only) and absence of arterial-phase enhancement when present prior to therapy (see [Figure 68-1](#)). The principal determinant of tumor necrosis on MRI is also the absence of arterial enhancement when present prior to treatment.

### 7. What is SIRT or radioembolization?

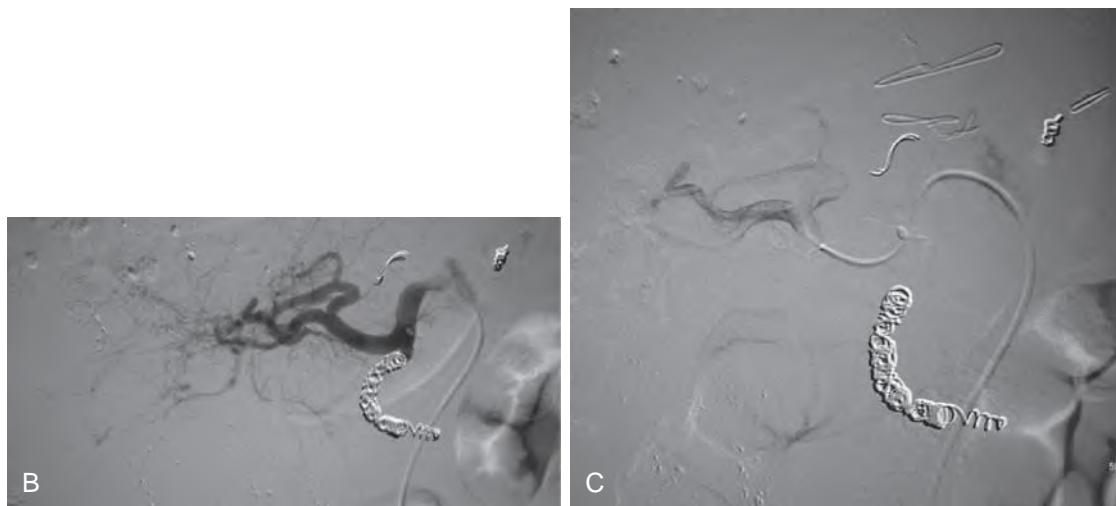
SIRT, or radioembolization, is a transarterial method for treating hepatic malignancies that involves selective intraarterial delivery of microspheres loaded with a radioisotope. It is a form of intraarterial brachytherapy. The primary mode of action is the emission of radiation and the second mode of action is the embolization of the vasculature. Yttrium-90 (<sup>90</sup>Y) is the most common radioisotope used for radioembolization. It is a beta emitter, has a mean tissue penetration of 2.5 mm and a maximum penetration of 11 mm, and a half-life of 64.2 hours.

### 8. Name the two Food and Drug Administration (FDA)-approved and commercially available radioactive microspheres and describe their differences.

SIR-Spheres are nonbiodegradable resin spheres with a median size of 32 µm and are FDA approved for the treatment of unresectable colorectal liver metastases. TheraSphere therapy consists of nonbiodegradable glass spheres with a median size of 25 µm and is FDA approved for the treatment of unresectable HCC ([Figure 68-2A](#) and [E-Figure 68-2B](#) and C). The activity per particle is higher with TheraSphere, which



**Figure 68-2.** TheraSphere yttrium-90 (<sup>90</sup>Y)-radioembolization of multifocal hepatocellular carcinoma. **A**, Common hepatic arteriogram demonstrates multiple hypervascular masses throughout the liver. (see [E-Figure 68-2B](#))



**E-Figure 68-2.** **B**, Postembolization arteriogram confirms complete occlusion of the right gastric artery and gastroduodenal artery prior to radioembolization of the right hepatic lobe. Prophylactic embolization is performed to avoid complications of nontarget embolization via intestinal vessels. **C**, Injection of TheraSphere  $^{90}\text{Y}$  glass beads through a microcatheter in the distal right hepatic artery.

measures 2500 Bq as opposed to 50 Bq for SIR-Spheres. The number of particles delivered per treatment and the embolization effect with TheraSphere is less compared with SIR-Spheres.

#### **9. What are the indications for $^{90}\text{Y}$ radioembolization?**

$^{90}\text{Y}$  radioembolization is indicated for treatment of unresectable or medically inoperable primary or secondary liver malignancies. The tumor burden should be liver dominant but does not have to be exclusive to the liver. The Eastern Cooperative Oncology Group performance status should be 0 to 1 and life expectancy should be at least 3 months.

#### **10. In the pretreatment workup of patients considered for $^{90}\text{Y}$ radioembolization, what imaging procedures besides cross-sectional imaging must occur?**

Prior to  $^{90}\text{Y}$  radioembolization, diagnostic visceral arteriography with injection of the celiac, superior mesenteric, left gastric, gastroduodenal, proper hepatic, and right and left hepatic arteries should be performed. Embolization of the gastroduodenal artery as well as any right gastric or other gastric arteries should be considered to redistribute the flow of blood and prevent potential ulcerations from nontarget embolization. After embolization of these extrahepatic pathways, technetium-99 macroaggregated albumin is injected into the hepatic artery. Nuclear medicine scanning is performed to determine pulmonary shunt fraction and nontarget embolization. If the percentage of pulmonary shunting is high, there is a risk of radiation pneumonitis.

#### **11. What are the contraindications of $^{90}\text{Y}$ radioembolization?**

- Uncorrectable coagulopathy
- Severe anaphylactic or anaphylactoid contrast reaction
- Severe liver or renal dysfunction
- Lung or gastrointestinal (GI) shunts that cannot be corrected
- Untreated varices at high risk of bleeding
- Bilirubin greater than 2 mg/dL in the absence of a reversible cause
- Greater than 70% tumor replacement of liver unless synthetic function (prothrombin time and albumin) is maintained
- Prior radiation therapy to the liver or upper abdomen that included a significant volume of the liver
- Systemic chemotherapy agents in the preceding 4 weeks not known to be used safely concurrently with radioembolization
- Granulocyte count less than  $1.5 \times 10^9/\text{L}$

#### **12. Discuss potential advantages of $^{90}\text{Y}$ radioembolization compared with TACE.**

$^{90}\text{Y}$  radioembolization has a decreased incidence and severity of PES and thus can be performed as an outpatient procedure without the need for hospitalization. Recent studies suggest better disease control (longer time to progression) with less toxicity with  $^{90}\text{Y}$  radioembolization than TACE, although no survival differences between the two treatments have been demonstrated. Additionally,  $^{90}\text{Y}$  radioembolization for HCC (TheraSpheres) is a microembolic procedure causing minimal occlusion of the hepatic arteries and may be safely used in the setting of portal vein thrombosis.

#### **13. Define preoperative portal vein embolization (PVE).**

PVE is an image-guided procedure performed prior to resection of liver malignancies to increase the size of the future liver remnant (FLR) or the liver segments that will remain after surgery. By embolizing the portal vein branches supplying the tumor-bearing segments, flow is redirected to the non-tumor-bearing segments, resulting in hypertrophy of the FLR.

#### **14. In major hepatic resection candidates with normal liver function, what is the standardized future liver remnant (sFLR) cutoff for PVE?**

The size of the FLR needs to be standardized to patient size as larger patients require a larger liver mass to support their essential functions compared to smaller patients. sFLR is expressed as a percentage of FLR in relation to total functioning liver volume. The cutoff for PVE is an sFLR less than 20%. Studies have shown significantly higher rates of postoperative liver insufficiency and death from liver failure in patients with sFLR of less than 20% compared with patients with an sFLR of 20% or more.

#### **15. Is PVE indicated for patients with HCC and clinically evident portal hypertension?**

No. Clinically evident portal hypertension is a contraindication to hepatectomy, so these patients are not candidates for major hepatic resection.

#### **16. When might PVE be indicated in patients with cirrhosis?**

PVE is considered in patients with well-compensated cirrhosis (i.e., Child-Pugh [CP] class A), who are surgical resection candidates, and who have an sFLR of less than 40%. Patients with cirrhosis often demonstrate attenuated rates and degrees of hypertrophy, so it is not uncommon that PVE might be performed in combination with other techniques such as TACE. TACE is performed prior to PVE and may prevent disease progression that could result in the patient no longer being eligible for resection.

**17. What are the indications for transjugular intrahepatic portosystemic shunt (TIPS)?**

- Uncontrollable variceal hemorrhage
- Acute or prior variceal bleeding not controlled with initial or continued endoscopic therapy (Figure 68-3A and B and E-Figure 68-3C and D)
- Refractory ascites
- Prophylaxis against recurrent variceal bleeding in high-risk patients
- Portal hypertensive gastropathy
- Hepatic hydrothorax
- Budd-Chiari syndrome or other venoocclusive diseases
- Hepatorenal syndrome
- Hepatopulmonary syndrome
- Decompression of portosystemic collaterals prior to abdominal surgeries



**Figure 68-3.** Creation of a second parallel transjugular intrahepatic portosystemic shunt (TIPS) in a 64-year-old woman with nonalcoholic steatohepatitis and recurrent small bowel variceal bleeding. **A**, Superior mesenteric venography (SMV) demonstrates the presence of small bowel varices (arrows). **B**, Fluoroscopic image demonstrates the existing TIPS (\*) and contrast in the portal vein from injection through a colapinto needle (arrow). (See E-Figure 68-3C)

**18. What are contraindications to performing the TIPS procedure?**

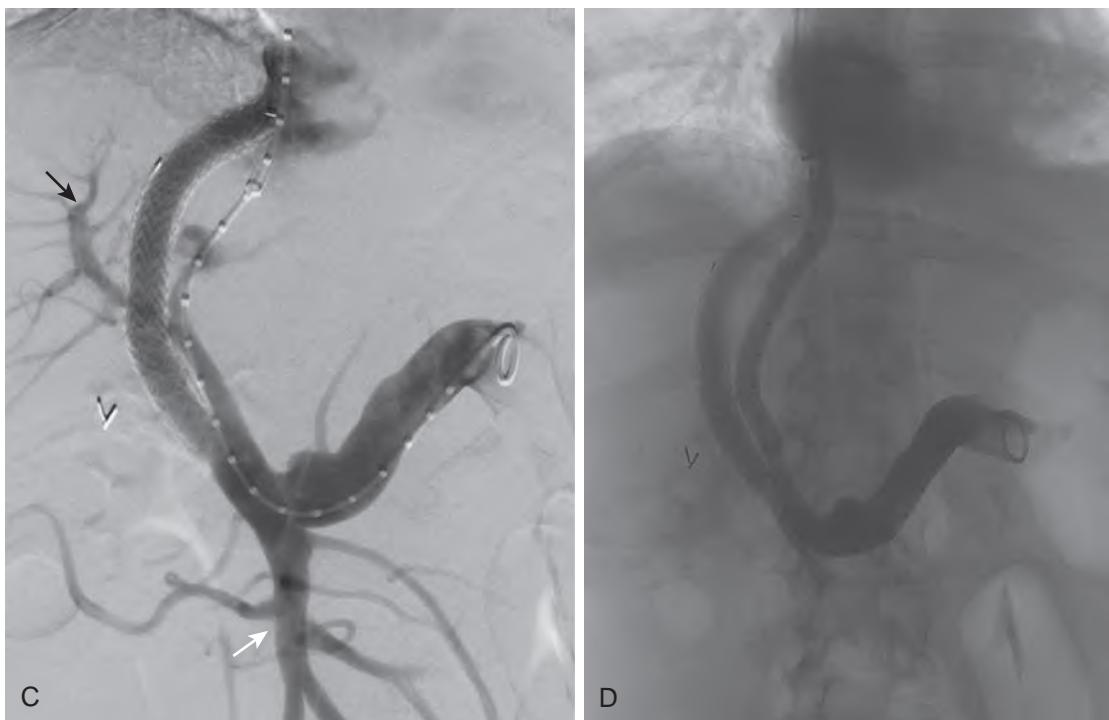
- Elevated right or left heart pressures
- Heart failure or cardiac valvular insufficiency
- Marked pulmonary hypertension
- Rapidly progressing liver failure
- Clinically significant hepatic encephalopathy
- Uncontrolled sepsis or systemic infection
- Unrelieved biliary obstruction
- Severe, uncorrectable coagulopathy
- Extensive hepatic malignancy (primary or secondary)

**19. What should the portosystemic pressure gradient (PSG) be reduced to for TIPS placed for variceal bleeding as opposed to TIPS placed for refractory ascites?**

The post-TIPS PSG should be reduced to less than 12 mm Hg to prevent rebleeding episodes. The degree of PSG reduction to control ascites is unclear but a PSG of 12 mm Hg or less is considered an acceptable goal. Gradients of less than 5 mm Hg have been associated with an increased risk of liver failure and severe hepatic encephalopathy requiring an intervention such as TIPS reduction or occlusion.

**20. Which liver disease scoring system, CP or Model for End-Stage Liver Disease (MELD), more effectively predicts survival after TIPS creation?**

MELD score is superior to CP score at predicting post-TIPS mortality. A MELD score of more than 18 predicts a significant higher 30-day and 90-day mortality after TIPS compared with patients with a MELD score of 18



**E-Figure 68-3.** C, Portal venography depicts reversal of flow in the SMV (white arrow) and intrahepatic portal vein flow (black arrow) despite the presence of the patent TIPS. D, Absence of reversed flow in the SMV and intrahepatic portal vein flow after creation of second TIPS.

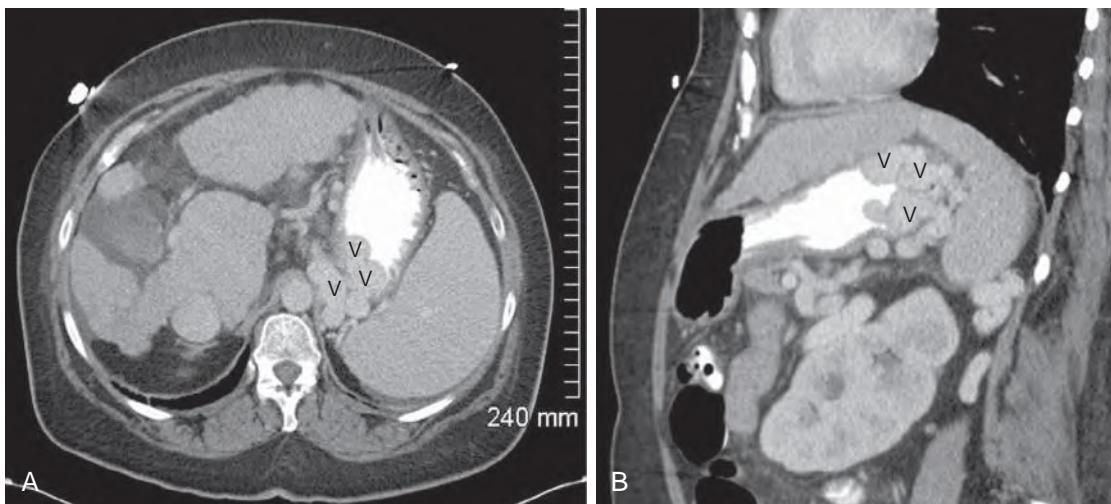
or less. A study by Gaba et al. demonstrated 30-day mortality rates reaching 39% for patients with MELD scores of more than 18. In patients with MELD scores of more than 25, 30-day and 90-day mortality rates were more than 70%.

#### 21. How is TIPS patency followed?

TIPS patency can be followed noninvasively by color Doppler ultrasound or venography. Protocols differ among institutions. Two-year primary patency rates with the use of the Viatorr stent graft are 76% to 84%, and thus the need for frequent routine ultrasound surveillance is in question. If an early ultrasound evaluation is performed, it should be done at least 5 days after TIPS creation because air bubbles in the expanded polytetrafluoroethylene fabric create gas artifacts, which do not allow complete visualization and evaluation in the first 2 to 4 days. If the patient becomes symptomatic (e.g., variceal bleeding or ascites) or if significant interval change is demonstrated by ultrasound, venography with therapeutic intervention should be performed to restore normal shunt function.

#### 22. Define balloon-occluded retrograde transvenous obliteration (BRTO).

BRTO is an endovascular technique used as a therapeutic adjunct or alternative to TIPS in the management of gastric varices. It involves the use of occlusion balloons to occlude the outflow veins of a portosystemic shunt and endovascular injection of a sclerosing agent directly into the varix. BRTO is the primary method used in Japan and Korea for the management of gastric varices as opposed to the United States and Europe where the primary management of gastric varices has been portal decompression with TIPS. Its use is growing in the United States (Figure 68-4A and B and E-Figure 68-4C-F).



**Figure 68-4.** Balloon-occluded retrograde transvenous obliteration treatment of bleeding gastric varices in a 62-year-old man with primary biliary cirrhosis. A, Axial and sagittal (B) contrast-enhanced computed tomography (CT) scan demonstrates large gastric varices (v). (see E-Figure 68-4C-F)

#### 23. Name the most common portosystemic shunt occluded during a BRTO procedure.

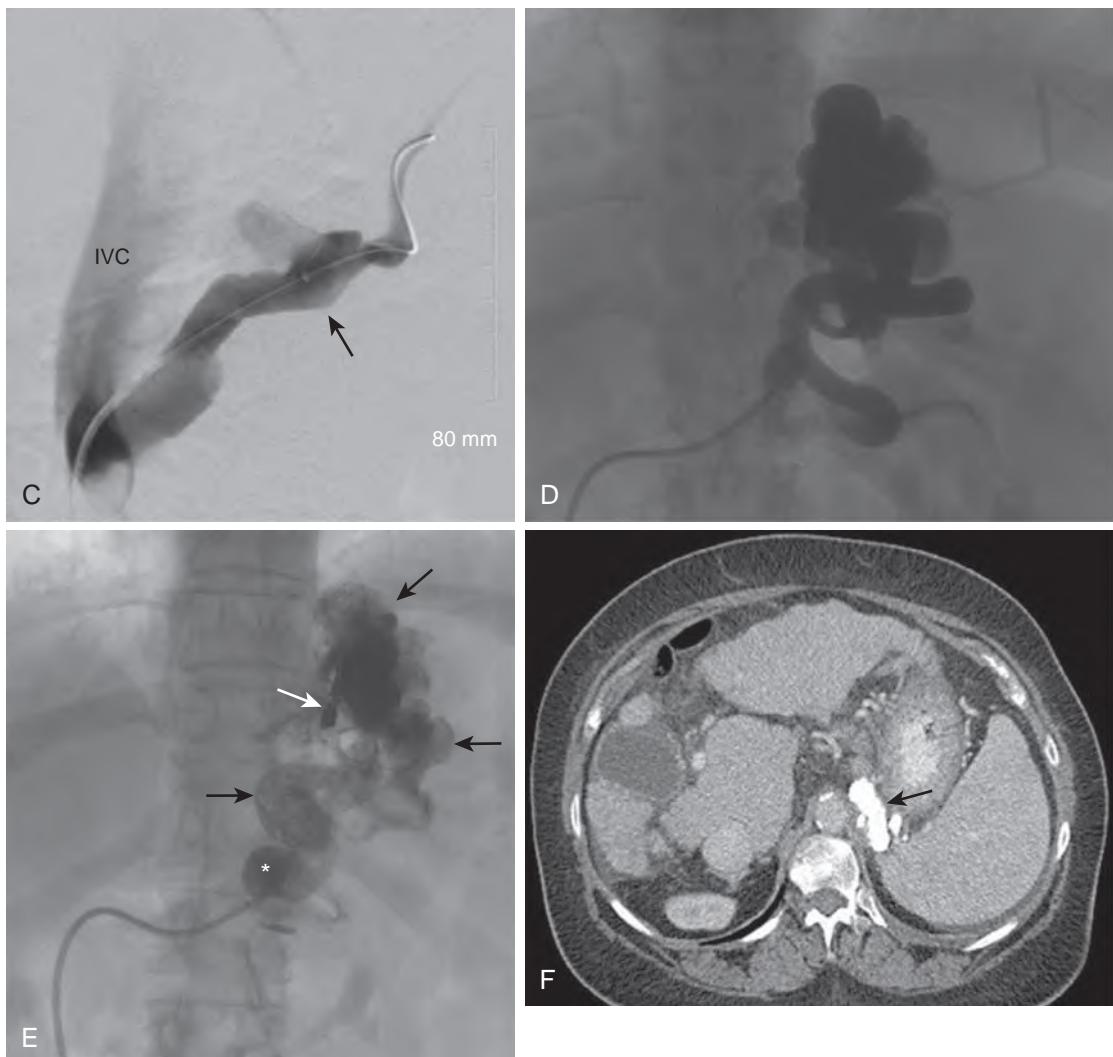
A gastrorenal shunt is the most common type to be occluded during a BRTO procedure because a gastrorenal shunt provides venous outflow in 90% of gastric varices cases with the remaining 10% draining via a gastrocaval shunt.

#### 24. When might BRTO rather than TIPS be indicated to treat gastric varices?

BRTO is indicated in patients with a large gastrorenal or gastrocaval shunt who have hepatic encephalopathy, poor hepatic reserve, or a low portal pressure. With TIPS, portal flow is diverted away from the liver and through the shunt; thus there is a risk of hepatic encephalopathy and deterioration of hepatic function. With BRTO, the portal flow is often diverted toward the liver, which can potentially reduce hepatic encephalopathy and improve hepatic function. In patients with a decompressive gastrorenal or splenorenal shunt, the portal pressure might already be lower than the traditional hemodynamic endpoint of the TIPS procedure (<12 mm Hg) and there is little gain to further lower the gradient by creating a TIPS.

#### 25. Postprocedurally, what condition can BRTO aggravate?

Portal hypertension can increase after BRTO. As a result of increased portal hypertension, there can be aggravation of nongastric (esophageal or duodenal) varices, development of portal hypertensive gastropathy, ascites, and hydrothorax or pleural effusion.



**E-Figure 68-4.** C, Venography demonstrates the large gastrorenal shunt (arrow) draining into the inferior vena cava. D, Injection of contrast through the inflated balloon occlusion catheter demonstrates the large gastric varices. E, Sclerosis of the gastric varices (black arrows) with injection of air-sodium tetradeccyl (Sotradecol)-lipiodol mixture through a microcatheter distal to the inflated balloon occlusion catheter (\*). An accessory gastrorenal shunt (white arrow) was coil embolized prior to sclerosis. F, Follow-up contrast-enhanced CT scan depicts the decompressed and sclerosed gastric varices (arrow).

**26. What are the specific indications for transjugular liver biopsy?**

- Coagulopathy
- Need for hepatic venous pressure gradient (HVPG)
- Massive obesity
- Ascites?

Ascites is often listed as an indication for transjugular liver biopsy and a contraindication for percutaneous liver biopsy. However, several studies have demonstrated no significant difference in minor or major complication rates with percutaneous liver biopsies in patients with or without ascites and normal coagulation.

**27. How is the HVPG measured?**

Access into the hepatic veins can be obtained via the more common transjugular approach or via a transfemoral approach. A balloon occlusion catheter is placed into a hepatic vein 2 to 3 cm from the hepatic vein ostium and a free hepatic vein pressure (FHVP) measurement is obtained with the balloon deflated. A wedged hepatic vein pressure (WHVP) measurement is obtained with total occlusion of the hepatic vein on inflation of the balloon. The HVPG is the difference between WHVP and FHVP.

**28. Is percutaneous transhepatic biliary drainage (PTBD) the most appropriate initial method to treat biliary obstruction?**

The selection of the most appropriate modality (percutaneous, endoscopic, or surgical) to provide biliary drainage depends on the interventional options available, the location and extent of the obstructing lesion, and the expertise of the operator. Currently, endoscopic drainage is the initial procedure of choice for biliary decompression, because of its reported lower complications and better patient tolerance compared with the transhepatic approach. However, not all endoscopic drainages are successful, and PTBD continues to play an important role in the management of biliary disease. Biliary disease is best managed by a team that includes an endoscopist, interventional radiologist, and surgeon.

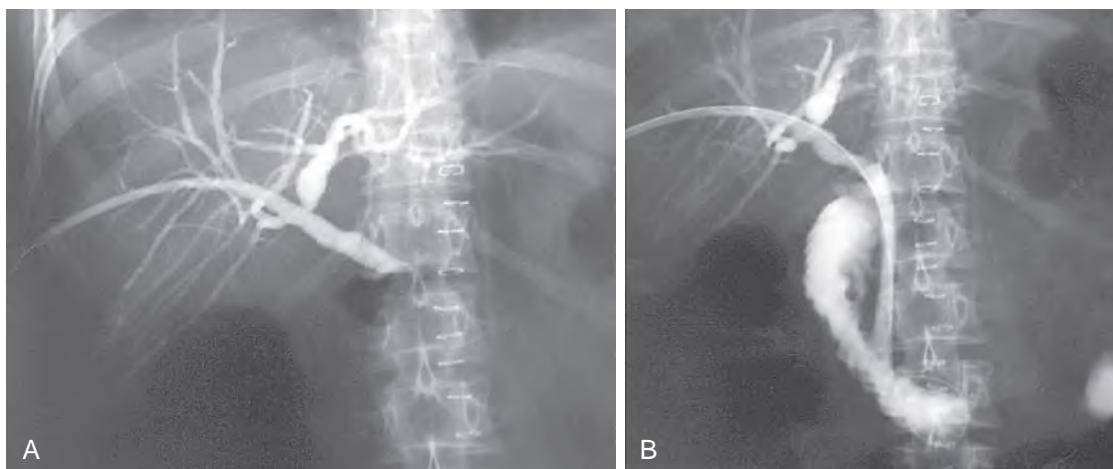
**29. What are the indications for PTBD?**

- Unsuccessful endoscopic drainage
- Biliary obstruction at or above the level of the porta hepatis
- Biliary obstruction following biliary-enteric anastomosis
- Bile duct injuries after laparoscopic cholecystectomy

The most common of these indications is failed endoscopic drainage for any reason.

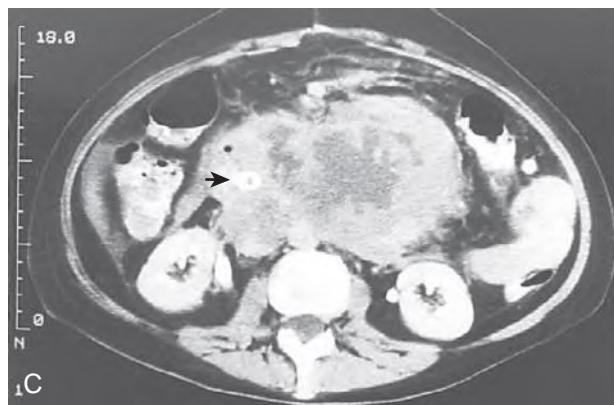
**30. Discuss the role of metallic stents for the treatment of biliary obstruction.**

The use of permanent metallic stents for the treatment of malignant biliary obstruction is well accepted, especially for inoperable patients whose life expectancies are 6 to 12 months ([Figure 68-5A and B](#) and [E-Figure 68-5C](#)). In these patients, metallic stents have been shown to be cost effective and provide a better quality of life than external catheters. Long-term patency of noncovered metallic stents is poor, with an occlusion rate of 30% to 60% by 6 months, and nearly all patients require reintervention within 1 year. The use of metallic stents in benign disease remains highly controversial.



**Figure 68-5.** A 58-year-old woman presented with jaundice and an abdominal mass. **A**, A cholangiogram performed after percutaneous transhepatic biliary drainage shows complete obstruction of the common bile duct (CBD). **B**, After placement of a metallic stent, the CBD is widely patent. (see [E-Figure 68-5C](#))

**E-Figure 68-5.** C, CT scan of the abdomen shows the large, poorly differentiated lymphoma encasing the biliary stent (arrowhead).



### 31. When is percutaneous cholecystostomy indicated?

Its two primary indications are:

- Persistent and unexplained sepsis in critically ill patients with acalculous cholecystitis
- Acute cholecystitis in patients too ill to undergo surgery

In unstable patients, it can be performed at the bedside, if necessary.

Less frequent indications include temporary treatment for gallbladder perforation, drainage for distant malignant biliary obstruction, and transcholecystic biliary intervention.

### 32. When do diagnostic angiography and percutaneous transcatheter therapy play a role in the management of GI bleeding?

Acute GI bleeding that is refractory to conservative management or invasive endoscopic techniques requires angiographic evaluation. For the interventional radiologist to identify the bleeding site, the following conditions must be met:

- The patient must be actively bleeding at the time of the study unless a structural lesion is the cause of intermittent bleeding.
- The bleeding must be brisk enough to be detectable during the arteriogram, usually more than 0.5 mL/min.
- The bleeding must be arterial or capillary bleeding; venous bleeding is rarely detected on the venous phase of an arteriogram.

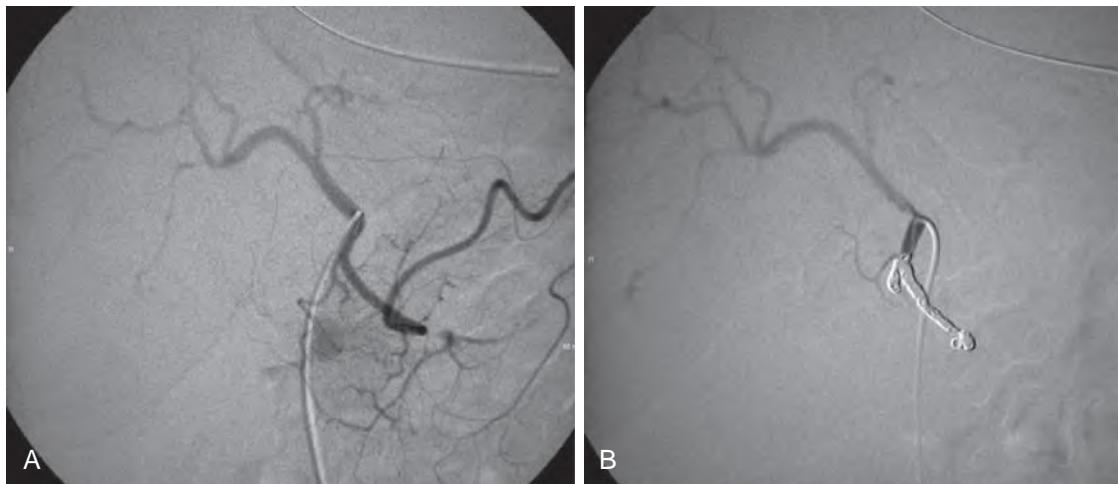
Once the bleeding site is identified, transcatheter embolization is a treatment option.

### 33. How important is localization of the bleeding site before angiography?

Preangiographic localization of the GI bleeding site is extremely helpful. A visceral arteriogram involves evaluation of the celiac, superior mesenteric, and inferior mesenteric arteries; selective catheterization of these vessels and the multiple angiographic projections needed when looking for a bleeding site can make this a tedious and time-consuming procedure, requiring large contrast volumes. Localization of a bleeding vessel or even distinguishing an upper from a lower GI source is helpful, can guide the interventionalist in choosing which vessel should be studied first, and can shorten the procedure.

### 34. What two types of transcatheter therapy are used for GI bleeding?

Selective embolization and vasopressin (Pitressin) infusion. Vasopressin infusion is rarely used today because of the cardiovascular complications (myocardial ischemia, arrhythmias, visceral ischemia), high rate of rebleeding after discontinuation of the infusion, difficulty in maintaining catheter position, and the long treatment times of 12 to 24 hours. Modern coaxial systems and microcatheters permit superselective catheterization with accurate deposition of embolic material at the bleeding site ([Figure 68-6](#)). These advances have decreased the risk of bowel infarction, making transcatheter embolization a relatively safe procedure even in the small bowel and colon.



**Figure 68-6.** A 52-year-old man with upper GI bleeding from a duodenal ulcer after failed endoscopic treatment. **A**, Selective gastroduodenal (GDA) artery arteriogram demonstrates active bleeding and contrast extravasation from a branch of the superior pancreaticoduodenal arcade. **B**, Cessation of bleeding after particle and coil embolization of the GDA and superior pancreaticoduodenal arcade.

### 35. Describe the role of conventional (catheter-based) angiography in a patient with acute, nonocclusive mesenteric ischemia.

Conventional arteriography is considered the gold standard test for diagnosis and it also enables therapy with catheter-directed infusion of a vasodilator. However, multidetector CT angiography is fast and noninvasive, and

diagnostic sensitivity and specificity continues to improve with technological advances. In a patient not clinically stable to undergo angiography or who is critically ill, rapid diagnosis with multidetector CT angiography and initiation of systemic intravenous pharmacotherapy may be beneficial.

### **36. What is the role of endovascular therapy in patients with acute occlusive mesenteric ischemia?**

The primary goal of any treatment is revascularization of the affected bowel to restore normal function and prevent infarction. Open surgery has traditionally been the standard of care. Endovascular techniques including aspiration embolectomy, thrombolysis, and stenting have been successfully described in the literature to treat acute occlusive mesenteric ischemia but most are case reports and small series. If there are no indications of bowel infarction (peritoneal symptoms, pneumoperitoneum, or intramural air on CT), then endovascular treatment may be considered but this should be a multidisciplinary decision based on local expertise with involvement of a vascular surgeon, interventional radiologist, and intensivist.

### **37. Compare open surgical versus percutaneous endovascular treatment for patients with chronic mesenteric ischemia.**

Endovascular treatment with percutaneous angioplasty and stenting is minimally invasive and thus has better short-term morbidity and mortality than open surgical repair. Open surgical repair, however, is more durable and has a decreased reintervention rate compared with endovascular therapy.

*The authors would like to acknowledge the contribution of Dr. Stephen Subber, who was an author of this chapter in the previous edition.*

Please access ExpertConsult to view the E-Figures for this chapter.

### **BIBLIOGRAPHY**

1. American College of Radiology ACR Appropriateness Criteria. Radiologic management of benign and malignant biliary obstruction. 2013 [Accessed September 22, 2014]. <http://www.acr.org/Quality-Safety/Appropriateness-Criteria/~/media/0DAC29F1768642B0821E8B9B271A08BC.pdf>.
2. American College of Radiology ACR Appropriateness Criteria. Radiologic management of gastric varices. 2013 [Accessed September 22, 2014]. <http://www.acr.org/Quality-Safety/Appropriateness-Criteria/~/media/1BB847EFAD1B4FBF9B6A3AEA7BE729A1.pdf>.
3. American College of Radiology ACR Appropriateness Criteria. Radiologic management of hepatic malignancy. 2013 [Accessed September 22, 2014]. <http://www.acr.org/Quality-Safety/Appropriateness-Criteria/~/media/68FFA493F4994FAF88191F8CD36D6834.pdf>.
4. American College of Radiology ACR Appropriateness Criteria. Radiologic management of lower gastrointestinal tract bleeding. 2013 [Accessed September 22, 2014]. <http://www.acr.org/Quality-Safety/Appropriateness-Criteria/~/media/5F9CB95C164E4DA19DCBCFBA790BB3C.pdf>.
5. American College of Radiology ACR Appropriateness Criteria. Radiologic management of upper gastrointestinal bleeding. 2013 [Accessed September 22, 2014]. <http://www.acr.org/Quality-Safety/Appropriateness-Criteria/~/media/319829D25E5942FA91FE70BB473BE92A.pdf>.
6. Brown DB, Nikolic B, Covey AM, et al. Quality improvement guidelines for transhepatic chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancies. *J Vasc Interv Radiol* 2012;23:287–94.
7. Bruix J, Sherman M. AASLD practice guideline management of hepatocellular carcinoma: An update. *Hepatology* 2011;53:1020–1022. 2013 [Accessed September 22, 2014]. <http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf>
8. Fidelman N, Kwan SW, LaBerge JM, et al. The transjugular intrahepatic portosystemic shunt: An update. *AJR* 2012;199:746–55.
9. Gaba RC, Couture PM, Bui JT, et al. Prognostic capability of different liver disease scoring systems for prediction of early mortality after transjugular intrahepatic portosystemic shunt creation. *J Vasc Interv Radiol* 2013;24:411–20.
10. Liapi E, Geschwind JF. Transcatheter arterial chemoembolization for liver cancer: Is it time to distinguish conventional from drug-eluting chemoembolization? *Cardiovasc Intervent Radiol* 2011;34:37–49.
11. Mammen T, Shyamkumar NK, Eapen CE, et al. Transjugular liver biopsy: A retrospective analysis of 601 cases. *J Vasc Interv Radiol* 2008;19:351–8.
12. May BJ, Talenfeld AD, Madoff DC. Update on portal vein embolization: evidence-based outcomes, controversies, and novel strategies. *J Vasc Interv Radiol* 2013;24:241–54.
13. Memon K, Lewandowski RJ, Kulik L, et al. Radioembolization for primary and metastatic liver cancer. *Semin Radiat Oncol* 2011;21:294–302.
14. Meza-Junco J, Montano-Loza AJ, Liu DM, et al. Locoregional radiological treatment for hepatocellular carcinoma: Which, when and how? *Cancer Treat Rev* 2012;38:54–62.
15. Upponi S, Harvey JJ, Uberoi R, et al. The role of radiology in the diagnosis and treatment of mesenteric ischaemia. *Postgrad Med J* 2013;89:165–72.

### **Websites**

Society of Interventional Radiology. Accessed September 22, 2014, [www.sirweb.org](http://www.sirweb.org).

American College of Radiology. Accessed September 22, 2014, from [www.acr.org](http://www.acr.org).

American Association for the Study of Liver Diseases. Accessed September 22, 2014, from [www.aasld.org](http://www.aasld.org).

# NONINVASIVE GI IMAGING: ULTRASOUND, COMPUTED TOMOGRAPHY, AND MAGNETIC RESONANCE IMAGING

Michael G. Fox, MD, and Ryan Kaliney, MD

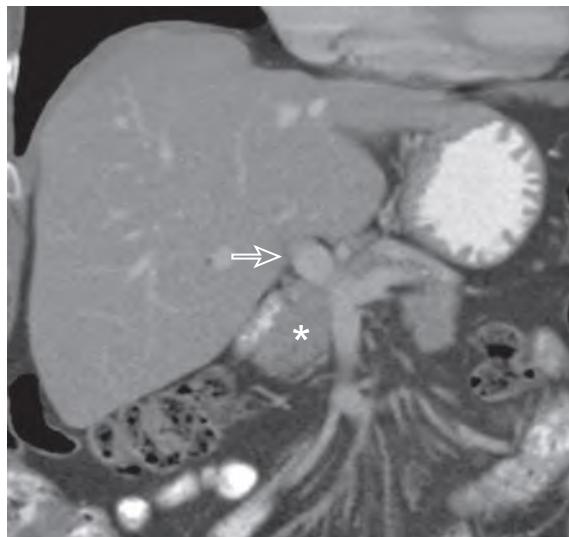
## GENERAL

### 1. How has multidetector computed tomography (MDCT) changed the evaluation of the liver, pancreas, and biliary system?

MDCT allows for the rapid acquisition of images using very thin collimation (0.6 mm) and reconstruction intervals (0.5 mm). Using these true isotropic volumetric data sets, exquisite multiplanar reformations (MPR) in the coronal, sagittal, or any other imaging plane can be created ([Figure 69-1](#)).

Imaging can be performed in the noncontrast computed tomography (NCCT) phase, early hepatic arterial phase (HAP), late HAP, and the portal venous phase (PVP) depending on the clinical indication. The early HAP is approximately 20 seconds after injection, the late HAP is 35 to 40 seconds after injection and the PVP is 60 to 70 seconds after injection, with the dominant contrast effect in the liver occurring in the PVP. This ability to image rapidly can take advantage of the dual blood supply of the liver—75% from the portal vein (PV) and 25% from the hepatic artery.

MDCT improves the imaging of the hepatic vasculature. It is very helpful in preoperative or preintraarterial chemotherapy planning and for the detection of hepatic infarctions, aneurysms and pseudoaneurysms, PV thrombosis, or strictures. Liver volumes prior to hepatic resection can also be estimated using volume-rendered images.



**Figure 69-1.** Multiplanar reformats. Coronal reformatted image from axial computed tomography data set allows for multidimensional evaluation. Open arrow marks the main portal vein with the pancreatic head (\*) inferior.

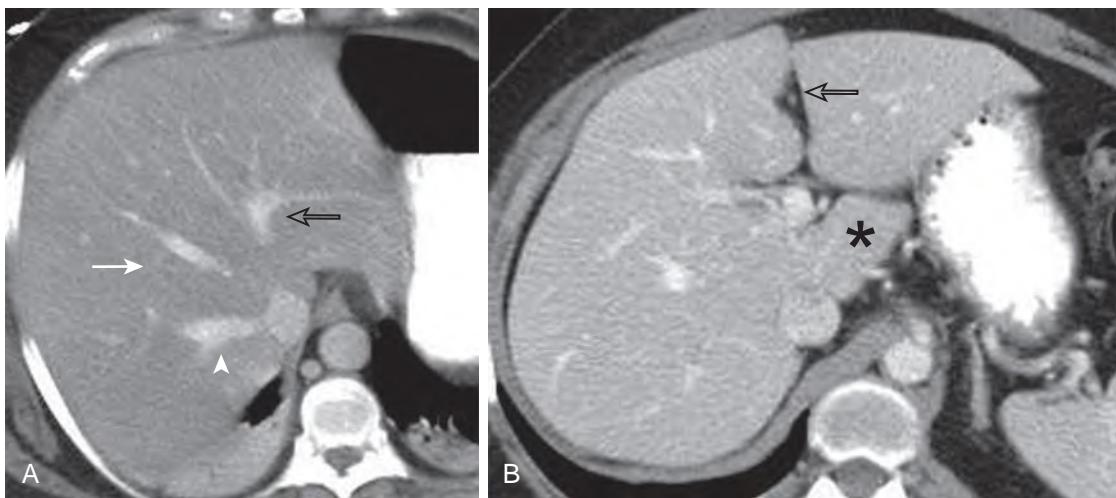
## LIVER IMAGING

### 2. How is segmental liver anatomy defined?

The liver is divided into four lobes based on the surface configuration and the hepatic veins (HVs). The different hepatic segments are divided by intersegmental fissures, which are traversed or are in the same plane as the HVs.

The main lobar fissure divides the liver into right and left lobes and is represented by a line extending from the gallbladder recess through the inferior vena cava (IVC). It is represented by the middle HV. The right intersegmental fissure divides the right lobe of the liver into anterior and posterior segments and is approximated by the right HV. The left intersegmental fissure divides the left lobe of the liver into medial and lateral segments. It is marked on the external liver margin by the falciform ligament, and it is represented by the left HV. The caudate lobe is the portion of liver located between the IVC and the fissure of the ligamentum venosum ([Figure 69-2A and B](#)).

Couinaud's anatomy further subdivides the liver into eight segments, each with its own blood supply. The eight segments are the caudate lobe (I), the left superior (II) and inferior (III) lateral segments, the left superior (IVa) and inferior (IVb) medial segments, the right anterior (V) and posterior (VI) inferior, and the right posterior (VII) and anterior (VIII) superior segments.



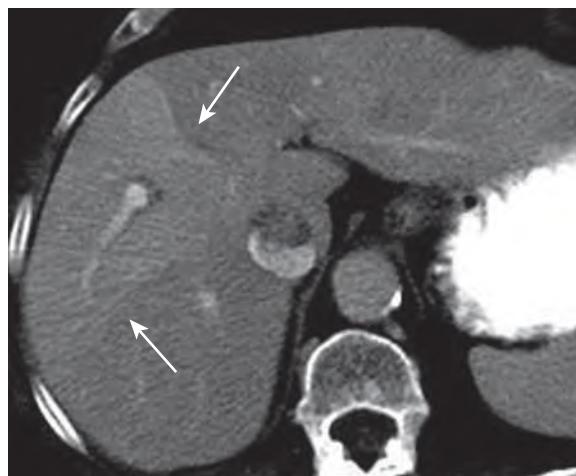
**Figure 69-2.** Hepatic vascular anatomy. **A**, Computed tomography image depicts the right hepatic vein (arrowhead) that divides the anterior and posterior segments of the right lobe of the liver. The middle hepatic vein (arrow) divides the right lobe from the left lobe. The left hepatic vein (open arrow) divides the medial and lateral segments of the left lobe of the liver. **B**, The falciform ligament (open arrow) divides the medial and lateral segments of the left lobe of the liver. The caudate lobe is marked by the \*.

### 3. Describe the ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) findings of fatty infiltration of the liver.

**US:** Fatty infiltration is seen as areas of focal or diffuse increased echogenicity that do not demonstrate mass effect on adjacent biliary structures or blood vessels. Fatty infiltration may limit or prevent visualization of intrahepatic vessels, the deeper posterior portion of the liver, and the diaphragm posterior to the liver.

Hepatitis or cirrhosis can also present with diffusely increased liver echogenicity.

**CT:** On NCCT, the liver is normally 8 Hounsfield units (HU) greater in density than the spleen. In fatty infiltration, the spleen is 10 HU more dense than the liver. In diffuse fatty infiltration, the hepatic vessels are more conspicuous and may appear as if they contain contrast even on a NCCT scan. In focal fatty infiltration, the normal hepatic vessels traverse the area of decreased attenuation, a finding not usually present in malignancy. Focal fatty infiltration tends to be in a lobar distribution (wedge shaped) with linear margins ([Figure 69-3](#)). Areas where fatty infiltration or sparing typically occur include the gallbladder fossa, subcapsular, left lobe medial segment near the fissure for the ligamentum teres, anterior to the porta hepatis, and around the IVC.



**Figure 69-3.** Computed tomography (CT) image of fatty infiltration in a 66-year-old woman with lung carcinoma. A large geographic area of focal fatty sparing (arrows) extending to the liver capsule with fatty replacement of the remainder of the liver parenchyma is noted on this axial CT image.

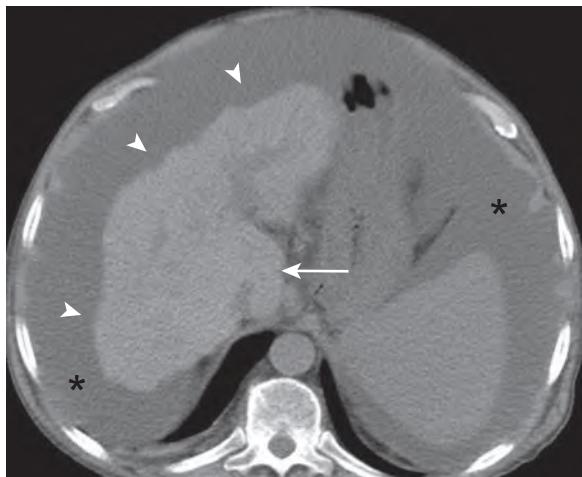
**MRI:** Signal differences in focal fatty infiltration of the liver may be subtle. As with CT, vessels should course normally through the area of signal abnormality without mass effect on adjacent structures. MRI with fat suppression is more sensitive than T1-weighted (T1-w) and T2-weighted (T2-w) imaging for fatty infiltration, with fatty infiltration having decreased signal intensity compared with normal liver. Areas of fatty infiltration will also reliably demonstrate decreased signal on opposed-phase T1-w imaging.

#### 4. Describe the US, CT, and MRI findings in cirrhosis.

**US:** The hepatic parenchyma in cirrhosis is typically heterogeneous and hyperechoic with “coarsened” echoes and poorly defined intrahepatic vasculature. Unfortunately, these findings are nonspecific, with increased parenchymal echogenicity also present in fatty infiltration, and parenchymal heterogeneity also present in infiltrating neoplasms. Sonographic features with greater specificity for cirrhosis include nodularity of the liver surface and relative enlargement of the caudate lobe. A caudate-to-right lobe volume ratio of more than 0.65 is highly specific but not sensitive in diagnosing cirrhosis.

**MDCT:** In cirrhosis, the caudate lobe and left-lateral segment typically enlarge, and the right lobe and left-medial segment typically atrophy, resulting in an enlarged gallbladder fossa. Enlargement of the hilar periportal space, as a result of atrophy of the left lobe medial segment, is more than 90% sensitive and specific for early cirrhosis. In advanced cirrhosis, liver volume usually decreases and periportal fibrosis and regenerative nodules can compress the portal and hepatic venous structures, which may result in altered hepatic perfusion and portal hypertension. The presence of isodense regenerating nodules can often only be inferred from the nodular contour of the liver edge. Complications of portal hypertension, especially varices, are exquisitely demonstrated with MDCT; however, unlike sonography, CT cannot determine the direction of vascular flow (Figure 69-4). Increased attenuation of the mesenteric fat is also noted.

**Figure 69-4.** Computed tomography images of cirrhosis in a 67-year-old man with renal failure. The liver margin is nodular in contour (arrowheads). The caudate lobe (arrow) is hypertrophied as compared with the right and left lobes. Perihepatic and perisplenic ascites (\*) is present.



**MRI:** MRI findings in cirrhosis are similar to those on MDCT, with early changes manifesting as enlargement of the hilar periportal space as a result of atrophy of the left lobe medial segment and later findings presenting as a caudate/right hepatic lobe ratio of more than 0.65 and an expanded gallbladder fossa sign. Regenerative nodules are usually smaller than 1 cm in diameter, have variable T1-w signal, and usually iso to decreased T2-w and gradient-recalled echo (GRE) signal. Regenerative nodules are usually isointense to liver following contrast.

Dysplastic nodules are considered premalignant and are usually larger than regenerative nodules. They often demonstrate increased T1-w and decreased T2-w signal; however, there is overlap with hepatocellular carcinoma (HCC). Imaging findings of portal hypertension are similar to those on MDCT and initially include dilation of the portal and splenic veins with later occlusion and cavernous transformation of the PV and development of portosystemic collaterals and ascites.

#### 5. Which is the most sensitive examination for detecting hemochromatosis?

**MRI:** Because many patients with hemochromatosis will develop cirrhosis and 25% will develop HCC, it is important to diagnose early.

**US:** US examination is normal despite iron deposition, unless underlying cirrhosis is present.

**NCCT:** Liver attenuation is typically more than 70 HU in hemochromatosis, compared with a normal level of approximately 45 to 60 HU.

**MRI:** More sensitive and specific than CT in detecting hemochromatosis. On MRI, the paramagnetic effects caused by iron deposition result in decreased T2-w and GRE signal intensity (Figure 69-5).

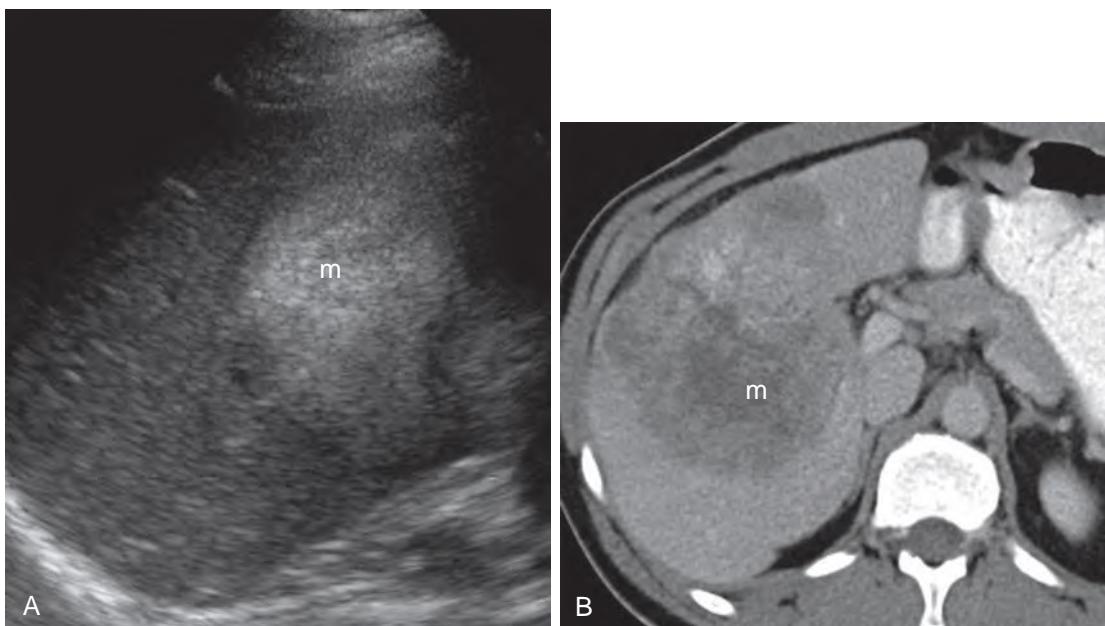


**Figure 69-5.** Axial T2-weighted (T2-w) magnetic resonance image of a 53 year old male with hepatic encephalopathy, pre liver transplant demonstrates a small cirrhotic liver having markedly decreased T2-w signal consistent with hemochromatosis (white \*). Also noted is extensive ascites (black \*).

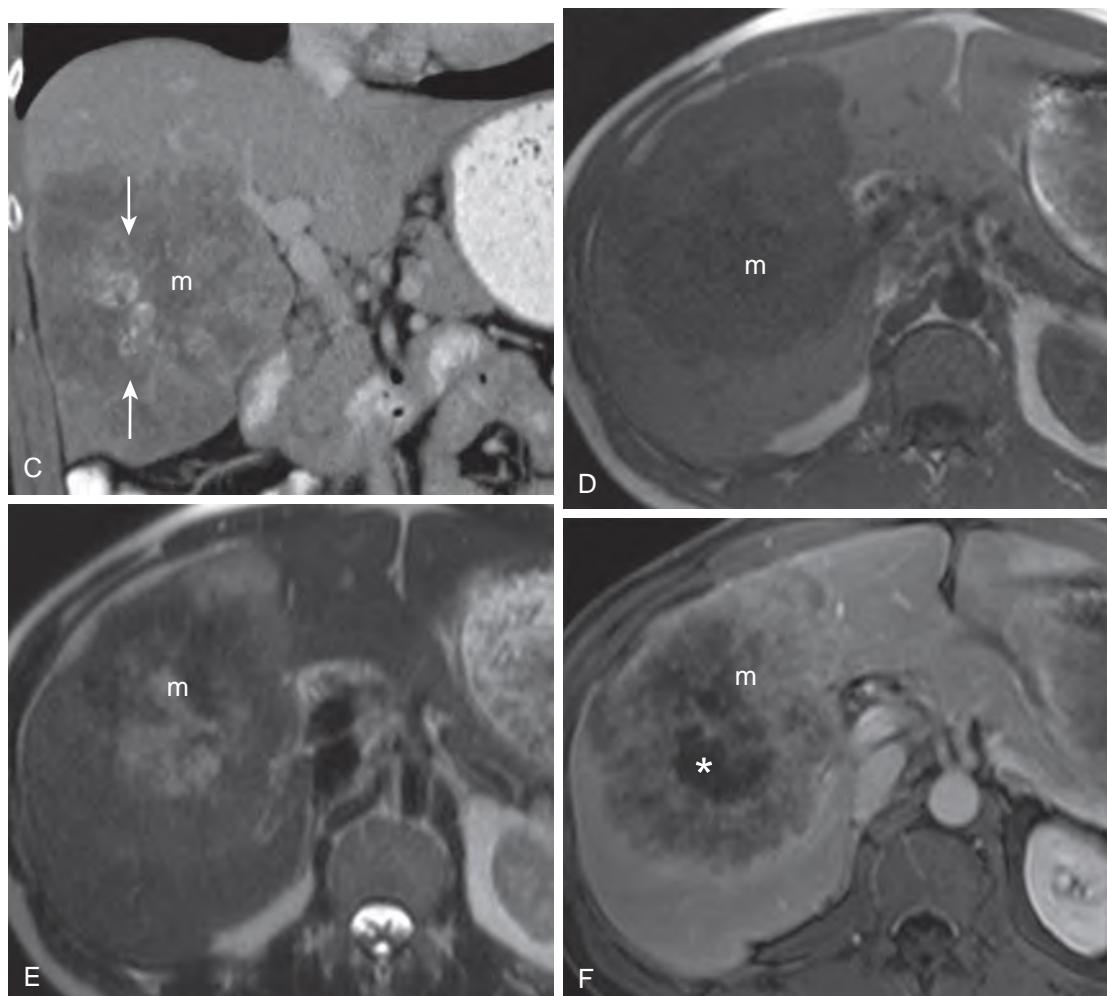
## 6. How do liver metastases appear on US, CT, and MRI?

**US:** Appearance is variable. Gastrointestinal and more vascular tumors (e.g., islet cell, carcinoid, choriocarcinoma, renal cell carcinomas) tend to produce hyperechoic metastases, which may mimic a hemangioma ([Figure 69-6A](#)). Hypoechoic lesions are also common, particularly with lymphoma, breast, lung, and cystic or necrotic metastases. Hypoechoic halos surrounding liver masses produce the nonspecific but common “bull’s-eye” appearance often seen with malignant lesions; these require additional work-up.

**MDCT:** Most liver metastases have decreased attenuation compared with the surrounding parenchyma on NCCT. Most metastases are hypovascular (e.g., colon adenocarcinoma) and are best imaged in the PVP. Hypervascular metastases (i.e., renal cell, carcinoid, thyroid, melanoma, and neuroendocrine tumors) are best imaged during the HAP, which should be added to PVP imaging to increase lesion detection ([Figure 69-6B](#) and [E-Figure 69-6C](#)). Calcified metastases are most commonly seen with mucinous colon carcinoma.



**Figure 69-6.** Ultrasound, computed tomography (CT), and magnetic resonance images of hepatic metastases (m) from colonic adenocarcinoma in a 43-year-old man. **A**, Rounded, hyperechoic mass (m) on this longitudinal ultrasound image is a typical appearance for a metastatic lesion from a gastrointestinal tract malignancy or other hypervascular metastatic lesion. **B**, Axial CT image of heterogeneous metastasis (m) with hypodense areas of necrosis centrally (see [E Figure 69-6C-F](#)).



**E-Figure 69-6.** **C**, Coronal CT image demonstrates internal calcifications (arrows) within the metastatic lesion (*m*). This can be seen in metastases from mucinous colonic adenocarcinoma, as well as treated metastases from breast cancer. **D**, Magnetic Resonance axial T1-weighted (T1-w) image demonstrating low signal, and, **E**, axial T2-weighted image demonstrating heterogeneously increased signal within the metastasis (*m*). Commonly seen with colonic adenocarcinoma metastases (*m*) are nonenhancing areas of central necrosis (\*) as demonstrated on this postcontrast T1-w image (**F**).

**MRI:** In general, metastases are hypointense on T1-w and hyperintense on T2-w images (E-Figure 69-6D, E, F). However, hemorrhagic and melanoma metastases are hyperintense on T1-w images. Dynamic gadolinium enhanced MRI increases the sensitivity for the detection of liver metastasis.

## 7. What are the three growth patterns of HCC?

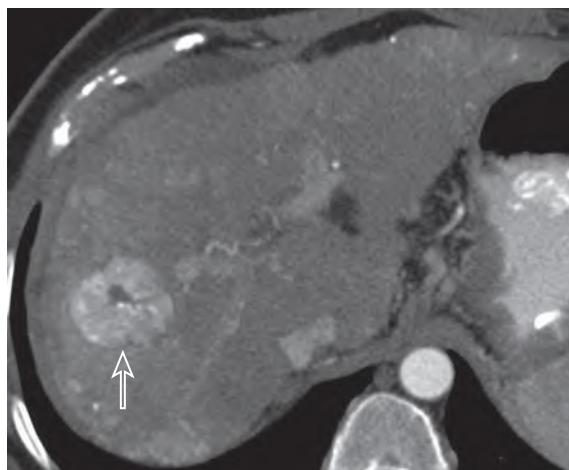
- Large solitary mass (50%)
- Multifocal HCC (40%)
- Diffuse infiltration (10%)

## 8. How does HCC appear on US, CT, and MRI?

**General:** In the United States, more than 80% of patients with HCC have underlying liver disease (e.g., cirrhosis). Men are three times more commonly affected.

**US:** Appearance is variable, sometimes simulating metastatic disease. HCCs smaller than 5 cm are often hypoechoic, whereas larger lesions have mixed echogenicity. Fat within the tumor may cause internal hyperechoic foci. Vascular invasion is common; PV invasion is more common than HV invasion. Doppler US can depict tumor thrombus, which typically has an arterial waveform.

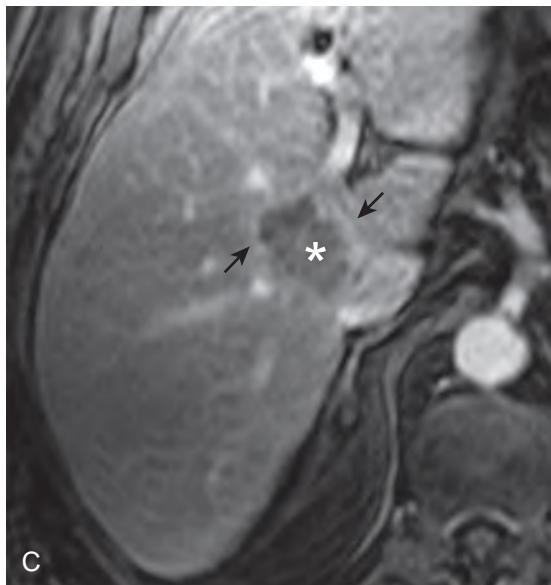
**MDCT:** On NCCT, HCCs are typically hypodense but may appear hyperdense in fatty livers, with 5% to 10% containing calcification. In the HAP, small HCCs (<3 cm) typically demonstrate homogeneous and large HCCs heterogeneous enhancement, often with central necrotic areas of low attenuation. Imaging in the HAP allows detection of up to 30% more tumor nodules compared with NCCT and PVP imaging alone (Figure 69-7). In the PVP, HCC is usually iso- to hypodense in appearance. Even so, sometimes contour deformity, mass effect, or vascular, especially venous, invasion might be the only clues to detection. Hemoperitoneum, caused by rare spontaneous rupture, and intratumoral hemorrhage may also occur.



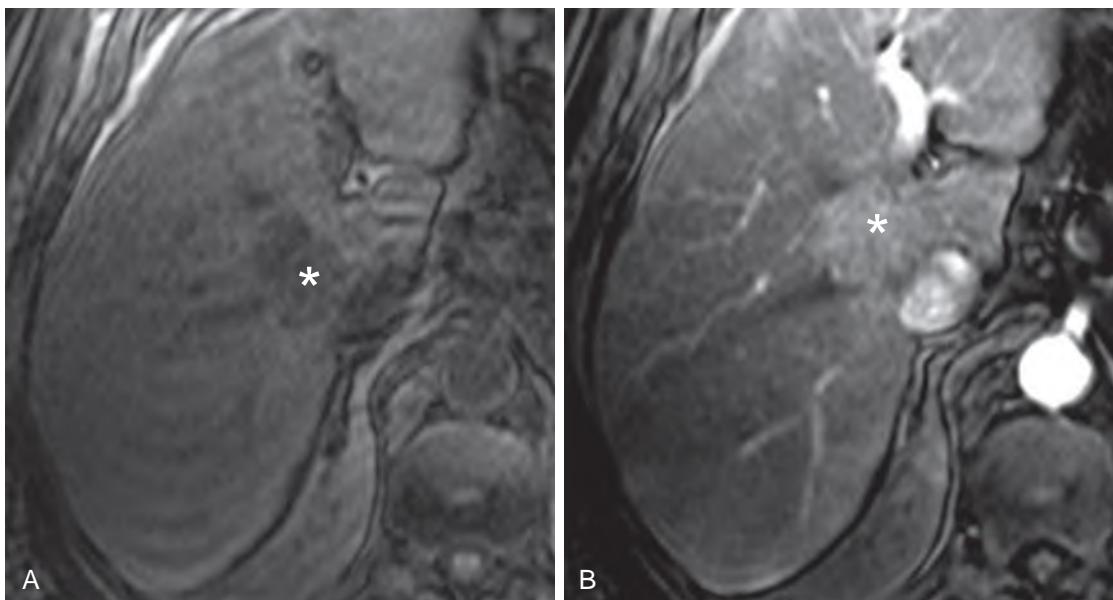
**Figure 69-7.** Computed tomography image of hepatocellular carcinoma (HCC) in a 55-year-old woman with cirrhosis. During the arterial phase of contrast enhancement, HCC appears as a focus of early arterial enhancement (open arrow) and can be delineated from the surrounding hepatic parenchyma.

**MRI:** MRI can usually distinguish between regenerative nodules, dysplastic nodules, and HCC. HCC is usually hypointense on T1-w images, but HCC may be iso- or hyperintense depending on the degree of fatty change and internal fibrosis. Findings that suggest HCC include increased T2-w signal (in more than 70% of HCCs) and a diameter of more than 2 to 3 cm. A “nodule within a nodule” appearance (increased T2-w nodule within a decreased T2-w mass) is highly suggestive of HCC within a dysplastic nodule. Gadolinium-enhanced images increase the detection of HCC as HCC has marked enhancement in the HAP phase, late washout, and a peripherally enhancing pseudocapsule on PVP images. As the degree of malignancy increases, there is increased hepatic arterial and decreased portal flow to the nodules (Figure 69-8A and B and E-Figure 69-8C). HCC may also enhance after gadoxetic acid administration.

Both fibrolamellar HCC and focal nodular hyperplasia (FNH) have a central scar with multiple fibrous septa; however, fibrolamellar HCC has a high prevalence of calcification. The central scar in fibrolamellar HCC is typically T2-w hypointense and calcified, whereas in FNH the central scar is T2-w hyperintense and not calcified. Fibrolamellar HCC occurs at a younger age, has equal male to female incidence, and a better prognosis.



**E-Figure 69-8. C,** On delayed contrast enhanced on T1-w images, there is persistent peripheral enhancement (*arrows*) of the lesion with central washout (\*).



**Figure 69-8.** Magnetic resonance images of hepatocellular carcinoma (HCC) in a 73-year-old man. **A**, Rounded intrahepatic mass (\*) near the inferior vena cava (IVC) demonstrates low signal intensity on unenhanced T1-weighted (T1-w) images. **B**, Early arterial enhancement of this mass (\*) on T1-w images is consistent with HCC (see [E-Figure 69-8C](#)).

#### 9. What MRI contrast agents are commercially available in the United States for use in hepatobiliary imaging?

Gadobenate diglumine (Multihance, Bracco Diagnostics) and gadoxetic acid (Eovist, Bayer Healthcare Pharmaceuticals) are both conventional, nonspecific extracellular as well as hepatocyte-specific contrast agents (outside the United States, Eovist is marketed as Primovist). The hepatocyte-specific contrast agent mangafodipir trisodium and the superparamagnetic iron oxide ferumoxides and carboxydextrans-coated particles are not currently available in the United States.

Gadobenate diglumine is taken up by functioning hepatocytes and excreted in the bile in addition to being in the extracellular space. The maximal benefit in the detection of lesions with this agent occurs with imaging 1 to 2 hours after injection, which is the time of peak liver-to-lesion contrast. Imaging in the hepatobiliary phase can differentiate between FNH (with biliary ducts) and hepatocellular adenoma (HCA).

Gadoxetic acid is similar to gadobenate diglumine except that the time of peak liver-to-lesion contrast occurs 20 to 45 minutes after injection. Recently, studies have shown that Gadobenate diglumine is more accurate than CT arterial portography (CTAP) in detecting even small HCC lesions. In addition, imaging with Gadobenate is noninvasive and does not require radiation, unlike CTAP.

#### 10. What is the most common benign neoplasm of the liver?

Cavernous hemangioma is the most common benign liver neoplasm.

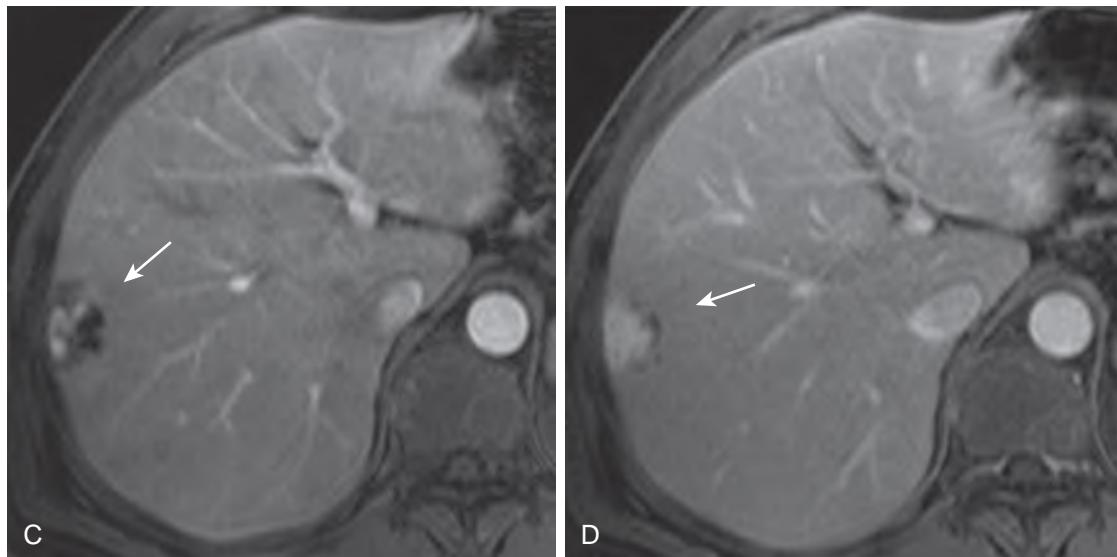
#### 11. Describe the US, CT, and MRI characteristics of hepatic hemangiomas.

**US:** Cavernous hemangiomas appear as well-defined hyperechoic masses in a normal liver. Doppler and color flow imaging usually demonstrate no detectable flow within the mass as blood flow is usually very slow; however, a feeding vessel may sometimes be detected. Occasionally hemangiomas have a mixed or hypoechoic appearance, especially in the setting of a fatty liver.

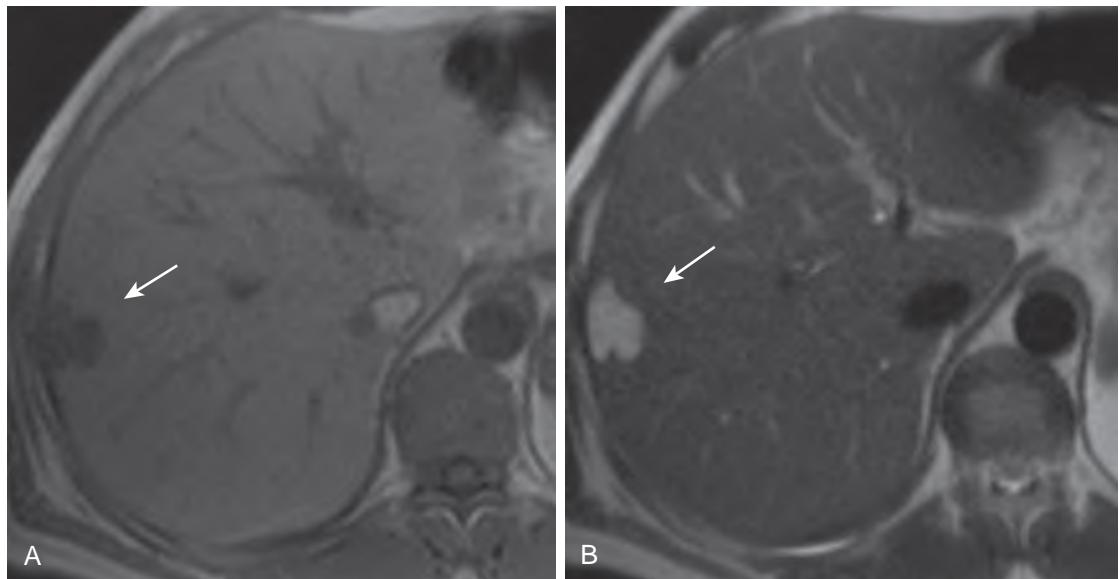
**MDCT:** On NCCT, hemangiomas are usually isodense to blood vessels, with 20% containing calcifications.

A characteristic peripheral nodular enhancement pattern, isodense to the aorta, is present on HAP imaging; followed by slow central filling of the lesion, which becomes isodense to the blood pool in the PVP. The enhancement typically persists; however, large lesions may not completely enhance. Less frequently, hemangiomas may initially have central or uniform enhancement, similar to the pattern present in malignant lesions.

**MRI:** Hemangiomas are usually well defined and have decreased T1-w and increased T2-w signal compared with the normal liver. The signal increases on more heavily T2-w images equal to or greater than the signal of bile. Using dynamic contrast-enhanced MRI, the enhancement pattern is similar to the pattern on CT (Figure 69-9A and B, [E-Figure 69-9C and D](#)).



**E-Figure 69-9.** C and D, Serial images of the mass (arrows) following administration of intravenous gadolinium contrast material demonstrates the progressive centripetal enhancement of the hemangioma, from the classic appearance of peripheral, nodular discontinuous enhancement (C) to near complete enhancement on the more delayed image (D).



**Figure 69-9.** Magnetic resonance images of a hepatic cavernous hemangioma in 57-year-old man. **A**, Cavernous hemangioma (arrow) has decreased signal compared with liver parenchyma on unenhanced T1-weighted image. **B**, Increased T2-weighted signal, classic for cavernous hemangioma, is evident within the lobulated mass (arrow) (See E-Figure 69-9C and D).

### 12. Describe the appearance of FNH on US, CT, and MRI.

**General:** FNH is the second most common benign hepatic tumor and it is more common in women. FNH contains all of the normal liver elements, but in an abnormal arrangement. It is typically smaller than 5 cm in diameter and solitary. The characteristic feature of FNH is the central scar, containing radiating fibrous tissue with vascular and biliary elements. The central scar may be seen with other lesions such as fibrolamellar HCC. Therefore, although a characteristic feature of FNH, it is not specific for FNH.

**US:** Often subtle; therefore, minimal contour abnormalities or vascular displacement should raise the possibility of FNH. A well-demarcated hypo- to isoechoic mass, possibly demonstrating a central scar, may be identified. Doppler images, especially if a stellate arterial pattern is present, are suggestive of FNH.

**MDCT:** FNH is hypo- to isodense on NCCT and without calcifications. FNH is hyperdense on HAP images because it is supplied by the hepatic artery. On PVP images, it is isodense to normal liver with a hyperdense pseudocapsule. The central scar is present in 35% of lesions smaller than 3 cm and 65% of lesions larger than 3 cm. The scar has lower attenuation than the normal liver on HAP and PVP images, but becomes hyperdense on 5- to 10-minute delayed images. Enlarged feeding arteries and draining veins may be seen, especially with the use of MPRs.

**MRI:** FNH is T1-w hypo- to isointense and T2-w iso- to hyperintense to liver. The central scar is T1-w hypointense and T2-w hyperintense, unlike HCC in which the central scar is T2-w hypointense. The lesion demonstrates diffuse enhancement in the HAP except for the central scar, which demonstrates delayed enhancement similar to CT. Unlike HCC and HCAs, capsular enhancement is not identified in FNH. FNH has delayed enhancement with gadoteric acid.

### 13. How does HCA appear on US, CT, and MRI?

**General:** HCAs are more common in women and are associated with oral contraceptive use. HCAs can cause morbidity and mortality because of their propensity for hemorrhage and rare malignant degeneration to HCC. HCAs are often 8 to 15 cm in diameter when diagnosed. HCAs contain few if any bile ducts or Kupffer cells, but they are more likely to demonstrate calcification or fat than FNH.

**US:** Typically shows a heterogeneous, hyperechoic mass caused by internal hemorrhage and high lipid content.

**MDCT:** A hypodense mass is typically seen on NCCT resulting from intratumoral fat. Internal areas of higher attenuation may be present as a result of recent hemorrhage, a key distinguishing feature from FNH. Contrast-enhanced CT (CECT) may show centripetal enhancement similar to a hemangioma. In contrast to hemangiomas, the enhancement is transient.

**MRI:** HCA is commonly heterogeneous as a result of necrosis and internal hemorrhage. HCA is usually T2-w iso- to slightly hyperintense. The T1-w signal is variable, but often hyperintense because of fat or hemorrhage, although similar findings may be seen in HCC. HCA can demonstrate decreased signal on opposed-phase T1-w imaging because of the high lipid content. Enhancement is most pronounced in the HAP with rapid washout in the PVP. The presence of hemorrhage helps differentiate HCA from HCC.

#### 14. Describe the appearance of a hepatic abscess on US, CT, and MRI.

**General:** Hepatic abscesses can develop from (1) biliary, (2) portal venous, (3) arterial, (4) local extension, and (5) traumatic etiologic factors.

**US:** A hepatic abscess appears as a complex fluid collection, typically with septations, an irregular wall, and internal debris or air. Air is seen as a focal area of echogenicity with posterior shadowing. An abscess can also appear as a simple fluid collection, similar to a cyst.

**MDCT:** CT is the most sensitive imaging modality; however, the CT findings vary with the size and age of the abscess. Generally, an abscess is a well-defined, low-attenuating uni- or multilocular mass with a well-defined enhancing wall that may contain internal septations. Air bubbles within the abscess cavity, although present in a minority of cases, are the most specific sign for an abscess (Figure 69-10).



**Figure 69-10.** 74 year old male with abnormal liver function tests and a large hepatic abscess. Axial contrast-enhanced computed tomography image demonstrates a large nonenhancing liver mass (\*) with minimal peripheral enhancement. Subsequent percutaneous drainage confirmed an hepatic abscess.

**MRI:** An abscess appears as a well-defined homogeneous or heterogeneous lesion with decreased T1-w and increased T2-w signal. The cavity may contain septations and is surrounded by a low-signal enhancing capsule. Other complex cystic lesions, such as necrotic or hemorrhagic neoplasms, may have a similar appearance.

#### DOPPLER LIVER IMAGING

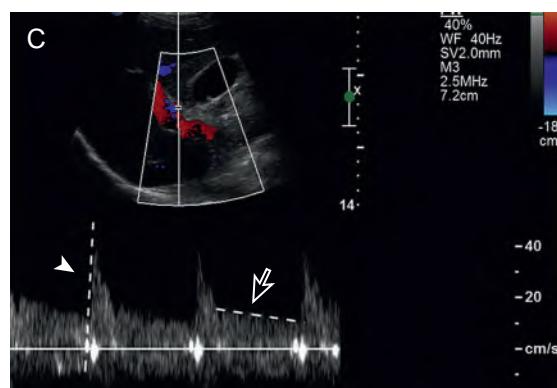
##### 15. What is a “normal” Doppler waveform?

The “normal” Doppler waveform depends on the vessel being imaged. In general, veins have continuous low-velocity flow that varies with respiration. The PV normally has hepatopetal flow (flow toward the liver) that ranges from 15 to 18 cm/sec (Figure 69-11A). The HVs have triphasic and pulsatile flow directed away from the liver into the IVC (see Figure 69-11B). Arterial flow varies dramatically with the cardiac cycle, with high-velocity flow during systole and relatively high flow (i.e., low resistance) during diastole (E-Figure 69-11C).

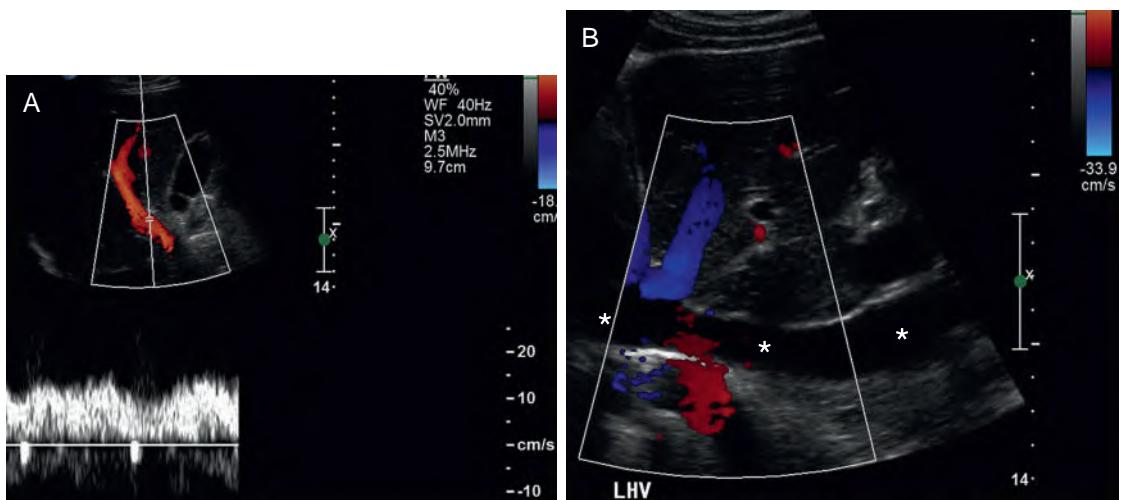
The change in frequency of reflected sound waves from flowing blood (the Doppler frequency shift) and the angle at which the US beam interfaces with the flowing blood (the Doppler angle) are used to calculate the velocity and direction of blood flow. The Doppler angle should be less than 60 degrees to avoid erroneous velocity calculations. The operator determines whether flow directed toward the transducer is displayed above or below the baseline on grayscale imaging and whether blood flowing toward the transducer is blue or red on color imaging, with flow in arteries and veins normally assigned a different color.

##### 16. Describe the sonographic findings of portal hypertension.

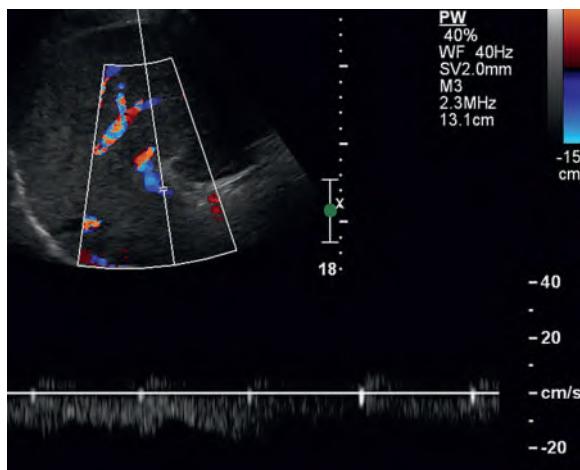
Portal hypertension can be suggested when (1) PV diameter is larger than 13 mm, (2) there is less than 20% increase in the PV diameter with deep inspiration, (3) a monophasic waveform is present, and (4) flow velocity is decreased. Specific measurements may be unreliable given PV diameter variability and the formation of portosystemic collaterals, which often develop in response to portal hypertension, reducing the PV diameter. Common collaterals include (1) a recanalized paraumbilical vein, which runs in the falciform ligament to the abdominal wall and drains the left PV; (2) splenorenal shunts; (3) retroperitoneal veins; (4) hemorrhoidal veins; and (5) the coronary vein, which connects with the portosplenic confluence and ascends to the gastroesophageal junction, producing esophageal varices. A coronary vein diameter larger than 7 mm is highly associated with severe portal hypertension. Retrograde (hepatofugal) PV flow indicates advanced disease and is a useful but late finding (Figure 69-12).



**E-Figure 69-11. C,** The hepatic artery (calipers) possesses a low resistance arterial waveform, with continuous forward flow throughout diastole (open arrow). Note the sharp upstroke of the normal systolic peaks (arrowhead).



**Figure 69-11.** Normal Doppler ultrasound images of the hepatic vasculature. **A**, Spectral Doppler ultrasound of the right portal vein (red) demonstrates subtle, phasic undulations in the waveform caused by cardiac and respiratory variations. Flow is hepatopetal, or into the liver. **B**, A normal left hepatic vein with blood flowing away from the liver (blue) into the inferior vena cava (\*) is depicted on this longitudinal image (see E-Figure 69-11C).



**Figure 69-12.** Hepatofugal flow. Color Doppler ultrasound image of the portal vein in the setting of cirrhosis and portal hypertension demonstrates flow away from the transducer (hepatofugal flow) manifested by blue color in the main portal vein and a waveform below the baseline or away from the periphery of the liver.

### 17. How are Doppler waveforms altered in PV thrombosis?

In acute PV thrombosis, flow in the PV is markedly diminished or absent, with no Doppler waveform or color flow. Cavernous transformation of the PV, manifested by multiple tubular channels in the porta hepatis demonstrating Doppler and color flow with nonvisualization of the native PV, may develop within 12 months. Echogenic material representing thrombus is usually seen in the PV. An arterial waveform within the thrombus is highly specific for malignancy.

### 18. How does Budd-Chiari syndrome affect Doppler waveforms?

Budd-Chiari syndrome refers to obstruction of hepatic venous outflow. It can occur anywhere from the small hepatic venules to the IVC. It is diagnosed when echogenic thrombus or absent flow is present in one or more of the HVs or the suprahepatic IVC. Intrahepatic collaterals extending from the HVs to the liver surface are common, and the liver parenchyma is usually diffusely heterogeneous. Associated PV thrombosis is present in 20% and ascites is often present. The caudate lobe is frequently spared as it has separate drainage to the IVC.

## BILIARY TRACT IMAGING

### 19. Describe the CT findings in acute cholecystitis.

Findings are similar to those of US; wall thickening, pericholecystic fluid, and gallstones are seen. CT is better than US at detecting stranding in the adjacent tissues. CECT can also demonstrate enhancement in the adjacent liver. CT can depict intramural gas in emphysematous cholecystitis.

### 20. What other conditions can result in gallbladder wall thickening?

Numerous conditions exist. These are (1) congestive heart failure; (2) constrictive pericarditis; (3) hypoalbuminemia; (4) renal failure; (5) portal venous congestion or portal hypertension; (6) hepatic venoocclusive disease; (7) chronic cholecystitis; (8) acquired immune deficiency syndrome-related cholangitis; (9) adenomyomatosis; (10) primary sclerosing cholangitis; (11) leukemic infiltration; and (12) inflammation from hepatitis, pancreatitis, and colitis.

Gallbladder carcinoma also causes wall thickening but is usually differentiated from other causes by a masslike appearance, adenopathy, and liver metastases.

### 21. Describe the differential imaging features seen in the common causes of biliary obstruction.

- A. Intrahepatic ductal dilatation ( $>2$  mm) with a normal common bile duct (CBD) suggests an intrahepatic mass or abnormality. Dilatation of the pancreatic duct typically localizes the obstruction to the pancreatic or ampullary level.
- B. An abrupt transition from a dilated to a narrowed or obliterated CBD is more characteristic of a neoplasm or stone. Gradual tapering of the CBD at the pancreatic head is more typical of fibrosis associated with chronic pancreatitis, but chronic pancreatitis also can present as a focal mass, and biopsy may be required for differentiation.
- C. Cholangiocarcinoma often arises around the liver hilum (Klatskin tumor). It should be suspected when abrupt biliary obstruction is present but no mass or stone is identified.

**US:** The primary mass is difficult to identify.

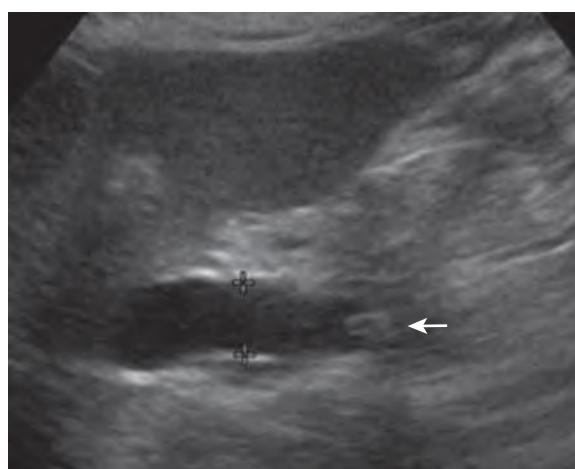
**MDCT:** Low-attenuating mass with mild delayed (10-20 minutes postinjection) peripheral enhancement is typical. Unlike HCC, cholangiocarcinoma usually encases but does not invade adjacent vessels.

**MRI:** Usually has low T1-w and high T2-w signal and progressive delayed enhancement caused by fibrous tissue. This can help determine the area to biopsy.

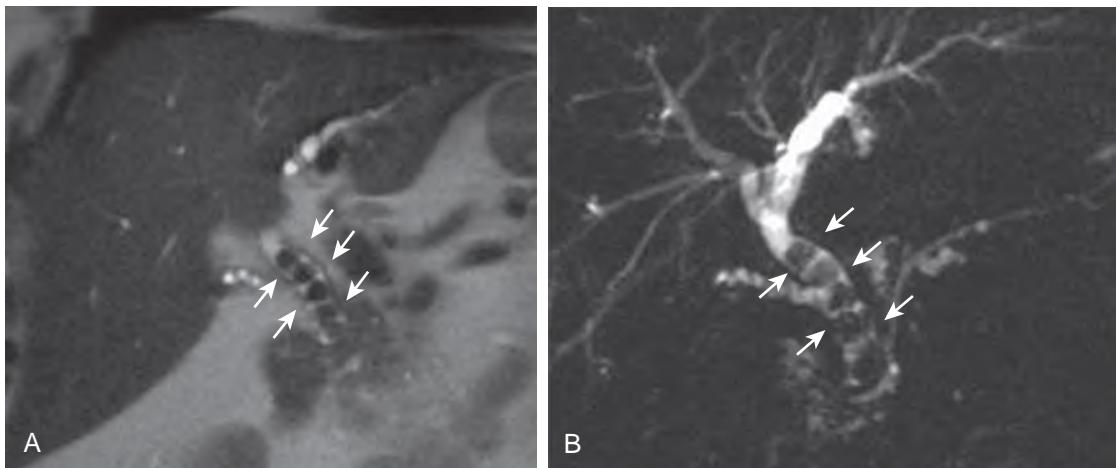
### 22. What is magnetic resonance cholangiopancreatography (MRCP) and how does it compare to endoscopic retrograde cholangiopancreatography (ERCP)?

MRCP is a noninvasive way to evaluate the hepatobiliary tract using heavily T2-w images. MRCP can reliably demonstrate the CBD, the pancreatic duct, the cystic duct, and aberrant hepatic ducts, and can differentiate dilated from normal ducts. MRCP exceeds the accuracy of CT and US in detecting choledocholithiasis, because CBD stones do not always exhibit acoustic shadowing. This is one reason why US is only 60% to 70% accurate in detecting CBD stones (Figure 69-13).

MRCP is comparable to ERCP in detecting choledocholithiasis and extrahepatic strictures, and in diagnosing extrahepatic biliary and pancreatic duct abnormalities (Figure 69-14A and B).



**Figure 69-13.** Choledocholithiasis in an 81-year-old woman with elevated liver function tests. Sonographic image demonstrates markedly dilated common bile duct (calipers) with obstructing echogenic stone (arrow).



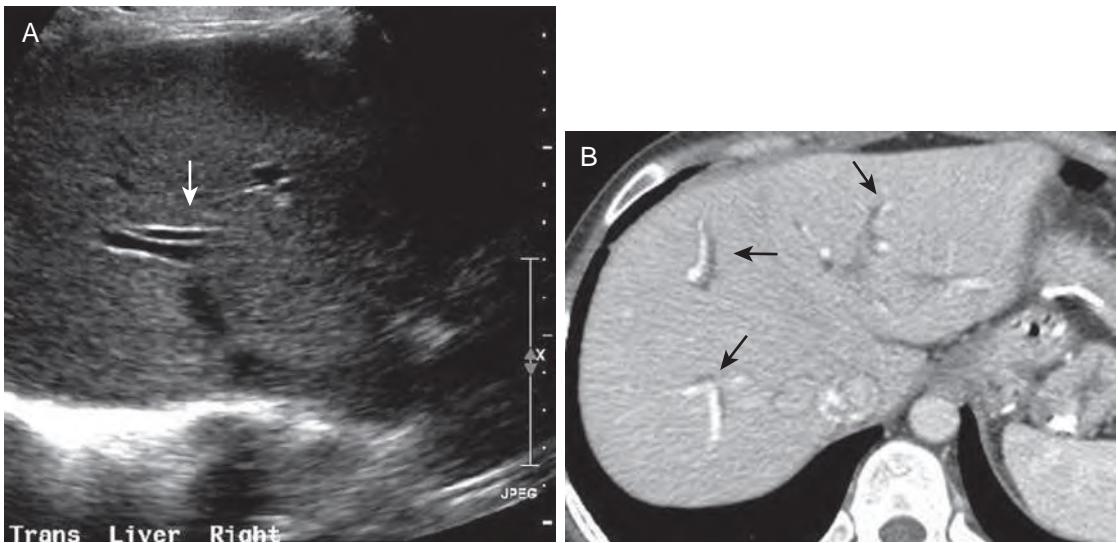
**Figure 69-14.** Choledocholithiasis in an 83-year-old woman with fever, elevated white blood cell count, elevated total bilirubin and prior cholecystectomy. **A**, Coronal T2-weighted magnetic resonance image demonstrates numerous gallstones (arrows) within the common bile duct. **B**, Magnetic resonance cholangiopancreatography depicts choledocholithiasis (arrows) in same patient.

### 23. Describe the radiologic work-up of suspected biliary tree obstruction.

**US:** US is the screening examination of choice for suspected biliary ductal disease. Doppler can readily differentiate biliary ducts from vasculature in the portal triad. A CBD diameter larger than 6 mm is more sensitive than dilated intrahepatic ducts in assessing early or partial biliary obstruction; however, the extrahepatic ductal diameter may increase with age, following cholecystectomy or previous resolved obstruction. Normal intrahepatic ducts are smaller than 2 mm in diameter and less than 40% of the diameter of the adjacent PV. With intrahepatic ductal dilatation ( $>2$  mm), tubular, low-echogenicity structures are seen to parallel the PVs, producing the “too many tubes” sign (Figure 69-15A).

**MDCT and MRI/MRCP:** Once biliary disease is detected, MDCT or MRI are more efficacious in depicting the degree, site, and cause of obstruction because bowel gas commonly obscures US visualization of the distal CBD (see Figure 69-15B). MDCT and MRI/MRCP also provide more complete delineation of the entire CBD, especially with the use of coronal imaging.

**ERCP or percutaneous transhepatic cholangiography:** These imaging methods provide a more detailed evaluation than US, MDCT, or MRI/MRCP, but both modalities are invasive.



**Figure 69-15.** Intrahepatic ductal dilatation. **A**, Sonographic image demonstrates the “double duct” sign (arrow) consistent with intrahepatic ductal dilatation. **B**, Contrast-enhanced axial computed tomography image in a 41-year-old woman with a gastrointestinal bleed demonstrates nonenhancing dilated ducts (arrows).

## PANCREATIC IMAGING

### 24. How can acute pancreatitis be distinguished from chronic pancreatitis on imaging?

#### Acute

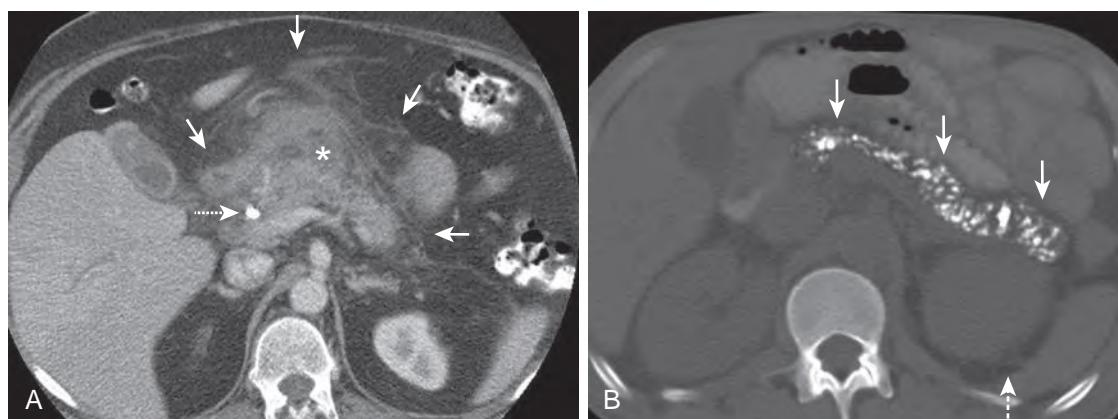
**US:** US may be limited in the initial evaluation of acute pancreatitis because of overlying bowel gas, resulting in incomplete visualization of the pancreas and underestimation of the extent of peripancreatic fluid collections compared with CT. If pancreatic visualization is not impeded by bowel gas, early or mild pancreatitis often appears normal. In more severe cases of pancreatitis, the pancreas may appear enlarged and hypoechoic.

**MDCT:** CT is not performed to diagnose early or mild pancreatitis as it may be normal. Occasionally, the pancreas may appear enlarged and slightly heterogeneous, with increased attenuation in the peripancreatic fat ("dirty fat") caused by inflammation. CT with MPR is the preferred study for patients with clinically severe pancreatitis, especially to evaluate for necrosis or other complications. NCCT is initially performed to detect pancreatic ductal or parenchymal calcifications and hemorrhage, and to provide a baseline HU for any masses. Imaging in the late HAP and the PVP is then performed. In more severe disease, intraglandular extravasation of pancreatic fluid causes intrapancreatic fluid collections. Extravasation of fluid results in peripancreatic inflammation, thickened fascial planes, and peripancreatic fluid collections, most commonly in the anterior pararenal space (left greater than right) and lesser sac (Figure 69-16A). Fluid extending into the pararenal space can result in the Grey Turner sign (flank ecchymosis) and fluid extending into the gastrohepatic and falciform ligaments can result in Cullen sign (periumbilical ecchymosis). Posterior leakage of fluid can present with a pleural effusion, classically on the left.

#### Chronic

**US:** Calcifications, ductal dilatation, heterogeneous hyperechoic echotexture, focal mass lesions, and pseudocysts may be present. The gland usually atrophies with focally enlarged areas.

**MDCT:** Intraductal calcifications are the most reliable CT indicator of chronic pancreatitis (see Figure 69-16B). The gland size is variable, but focal enlargement caused by a chronic inflammatory mass may necessitate biopsy to exclude carcinoma. The pancreatic duct can be dilated ( $>3$  mm) to the level of the papilla and may appear beaded, irregular, or smooth. Pseudocysts may be seen within or adjacent to the gland.



**Figure 69-16.** Pancreatitis. **A,** Contrast-enhanced computed tomography (CT) image in patient with acute pancreatitis caused by obstruction from pancreatic carcinoma. Extensive stranding in the peripancreatic fat (arrows), a nonenhancing pseudocyst anterior to the pancreatic body (\*) and a common bile duct stent (dotted arrow) are noted. **B,** Noncontrast CT image demonstrates numerous calcifications (arrows) within the pancreas consistent with chronic pancreatitis. Left perinephric fat stranding (dotted arrow) caused by pyelonephritis.

### 25. Describe the role of CT and US in assessing the delayed complications of pancreatitis.

- Ten percent to 20% of patients with acute pancreatitis and fluid collections develop pseudocysts after 4 to 6 weeks. Most pseudocysts smaller than 5 cm in diameter regress spontaneously. Drainage may be indicated for pseudocysts (1) failing to resolve after 6 weeks; (2) remaining larger than 5 cm in diameter; or (3) causing pain, infection, hemorrhage, bowel obstruction, or fistula.

**US:** Pseudocysts appear as anechoic fluid collections with or without internal debris surrounded by a thin wall. May appear complex or even solid because of the debris.

**CECT:** Pseudocysts appear as well-defined fluid collections with a uniformly thin, enhancing wall. Gas bubbles inside a pseudocyst relate to infection or enteric fistula formation.

- Acute peritonitis may occur if a pseudocyst ruptures into the peritoneal cavity.

- C. Necrosis is diagnosed by a lack of contrast enhancement within the pancreatic tissue. It is best demonstrated by MDCT in the PVP with an accuracy of 85%. CT evidence of necrosis correlated to morbidity/mortality is as follows:
- No necrosis: mortality rate (0%) and morbidity rate (6%)
  - Mild (<30% of the total gland) necrosis: mortality rate (0%) and morbidity rate ( $\approx 50\%$ )
  - Severe (>50% of the total gland) necrosis: mortality rate (11%-25%) and morbidity rate (75%-100%)
- If secondarily infected, gas may be present in the area of necrosis (i.e., emphysematous pancreatitis). Infected areas usually do not contain gas, and a percutaneous aspirate is needed to confirm the diagnosis and identify the organism.
- D. Abscesses result from liquefactive necrosis with subsequent infection and usually occur 4 weeks after the onset of acute pancreatitis. Rate of abscess formation varies with the amount of necrosis.
- US:** Abscesses appear as a hypo- to anechoic masses, sometimes containing hyperechoic gas, surrounded by a thickened wall.
- MDCT:** Abscesses appear as focal low-attenuation fluid collections with thick enhancing walls. If gas is present, an abscess needs to be excluded. The distinction between abscess and infected necrosis is difficult, but important because a pancreatic abscess often requires more aggressive treatment.
- E. Enzymatic breakdown of the arterial wall can result in a pseudoaneurysm, most commonly in the (1) splenic, (2) gastroduodenal, or (3) pancreaticoduodenal arteries. Up to 10% of pseudoaneurysms rupture, usually into a pseudocyst, but occasionally into the retroperitoneum, peritoneum, pancreatic duct, or bowel. This results in massive hemorrhage.
- US:** Color Doppler US is sensitive in detecting pseudoaneurysms and their complications.
- MDCT:** MDCT is best at identifying pseudoaneurysms, which usually present as densely enhancing structures in close proximity to a pseudocyst.
- F. Splenic vein thrombosis increases the risk of bleeding gastric varices. It is detected by absence of enhancement in the expected region of the splenic vein on MDCT in the PVP. It is present in up to 45% of cases of chronic pancreatitis. Color Doppler can also make the diagnosis.

#### 26. What are the imaging findings of pancreatic ductal adenocarcinoma?

- A. Pancreatic enlargement is usually focal and best appreciated in the pancreatic body and tail. Diffuse enlargement is often secondary to pancreatitis caused by the neoplasm.
- B. Enlargement and distortion of the pancreatic contour or shape are the most frequent findings of pancreatic cancer.
- C. Difference in density or echogenicity are present.
- US:** US usually detects a hypoechoic mass, compared with a normal pancreas, with ill-defined borders.
- CT:** Pancreatic ductal adenocarcinoma usually appears hypodense compared with a normal pancreas, especially on CECT.
- D. Pancreatic duct dilatation (>2-3 mm in diameter) may be the only indirect evidence of a small neoplasm. Dilatation is more common when the neoplasm is located in the pancreatic head and can result in both CBD and pancreatic duct dilatation ("double duct" sign). This sign may also be present in chronic pancreatitis.
- E. Biliary tract dilatation is more commonly seen with neoplasms in the head of the pancreas. Isolated intrahepatic biliary ductal dilatation may be seen with pancreatic cancer that has spread to the porta hepatis.
- F. Local invasion is most commonly into the peripancreatic fat, but occasionally into the porta hepatis, stomach, spleen, and adjacent bowel loops.
- G. Regional lymph node enlargement occurs, including nodes in the porta hepatis, paraaortic region, and area around the celiac and superior mesenteric artery axis.
- H. Liver metastasis occurs as pancreatic metastases that usually are low-density lesions.

#### 27. Which imaging modality is best for detecting and staging pancreatic cancer?

MDCT obtained in the pancreatic parenchymal phase with MPRs is the best imaging modality for detecting lesions as small as 2-3 mm and providing a detailed evaluation of the pancreatic duct. MDCT is better than US at evaluating adjacent spread or nodal involvement. Overlying bowel gas may limit evaluation of the pancreas with US; however, if the pancreas can be completely imaged with US, carcinoma can reliably be excluded. More recently, dual-energy CT obtained with a lower tube voltage (kVp) has been shown to increase detection of adenocarcinoma. Dynamic MRI with gadolinium can be performed in patients with iodine contrast allergy.

#### 28. What are the characteristic features of the four major cystic pancreatic neoplasms?

- A. Serous cyst adenoma (SCA) is more common in women older than 60, is overwhelmingly benign, and is often in the pancreatic head. SCA is composed of numerous cysts smaller than 2 cm. It calcifies more commonly than other pancreatic tumors.
- US:** Often appears solid and hyperechoic because of multiple small cysts that may not be individually resolved. A hyperechoic central stellate scar and calcifications suggest the diagnosis.
- MDCT:** Innumerable minute cysts may appear solid, whereas multiple small but visible cysts may have a honeycomb or "Swiss-cheese" appearance. A central stellate scar and calcifications suggest the diagnosis.

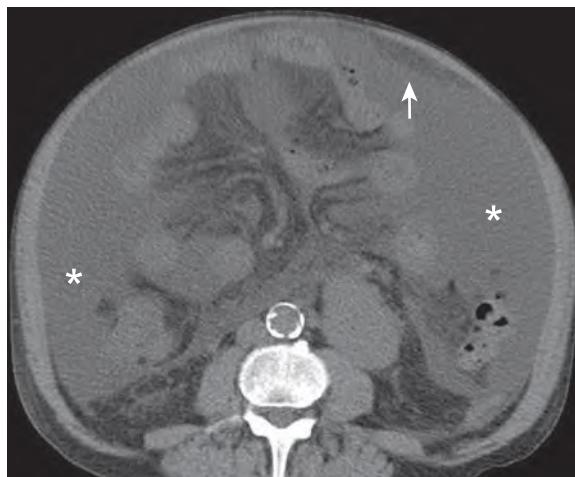
- B. Mucinous cystic neoplasms
  - a. Female predominance (9:1)
  - b. Patients 40 to 60 years old
  - c. Strong predilection for the pancreatic tail (85%)
  - d. Peripherally calcify in 10% to 25% of cases
  - e. Considered malignant
  - f. Larger than 5 cm in diameter
  - g. Composed of unilocular or multilocular cysts larger than 2 cm
- US:** Better depicts solid excrescences and internal septations of variable number and thickness; usually thicker than septations in SCA tumors.
- MDCT:** Better demonstrates tumor wall and organ of origin.
- C. Intraductal papillary mucinous tumors (IPMT) are rare but are most prevalent in men older than 60 years of age. They produce large amounts of mucin, which can result in ductal dilatation caused by mucin plugs. ERCP is best for diagnosis. IPMTs are usually (40%-80%) malignant. Findings associated with malignancy include (1) ductal dilatation larger than 10 mm, (2) large mural nodules, (3) intraductal calcifications, (4) bulging duodenal papilla, and (5) diffuse or multifocal involvement. Intraductal papillary nodules and a prominent duodenal papilla can distinguish this tumor from chronic pancreatitis.
- D. Solid pseudopapillary tumor of the pancreas is most often seen in younger ( $\approx$ 25-year-old) black or Asian women and is characteristically present in the pancreatic tail. They are often large (9 cm) at presentation and have a low malignant potential. On CT, fluid-debris levels can be present because of hemorrhage.

## PERITONEAL IMAGING

### 29. How is simple ascites distinguished from complicated ascites?

#### Simple Ascites

- A. Watery transudate is usually caused by major organ failure (e.g., hepatic, renal, or cardiac).
- B. CT density is similar to water (0-20 HU); HU is higher as the fluid protein content increases.
- US:** Simple ascites is anechoic, with increased through transmission and no internal septations. Ascites is “free-flowing” and located in the dependent portions of the abdomen and pelvis (i.e., Morison’s pouch, paracolic gutters, and pelvis). US demonstrates a sharp, smooth interface with other intraabdominal contents (Figure 69-17). Bowel seems to “float” within the fluid, usually in the center of the abdomen, if large amounts of ascites are present.



**Figure 69-17.** Ascites in a 67-year-old man with renal failure and cirrhosis. Noncontrast computed tomography image demonstrates marked ascites (\*) with elevation of the omental fat (arrow).

#### • Loculated Ascites

Loculated ascites is formed by adhesions, either benign (i.e., prior surgery), infectious, or malignant in etiologic origin. Loculated ascites is typically (1) nondependent, (2) stable when patient changes position, and (3) may displace adjacent bowel loops.

#### • Complex Ascites

Complex ascites is usually secondary to an infectious, hemorrhagic, or neoplastic process. Findings include internal debris or septations, a thick or nodular border or capsule, and HU of more than 20. Aspiration may be required to determine whether a collection is simple or complex.

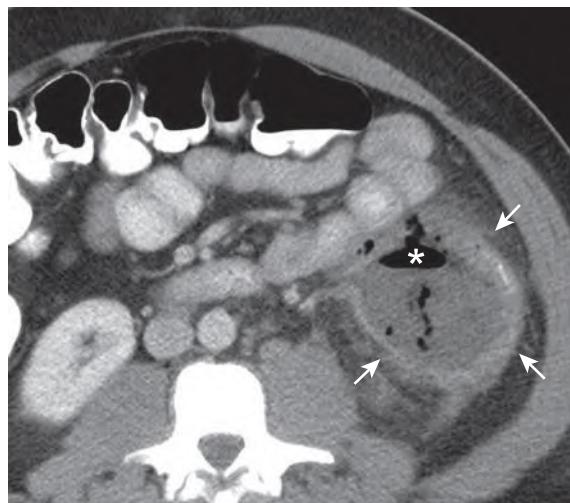
### 30. How is ascites differentiated from pleural effusion on CT?

1. Ascites is located anterior and pleural fluid posterior to the diaphragmatic crus.
2. Pleural effusion can appear to contact the spine.
3. Ascites has a sharper interface with intraabdominal organs than pleural fluid.
4. Unlike pleural fluid, ascites spares the bare area of the liver, which lies along the posterior border of the right hepatic lobe.

### 31. Discuss the role of imaging in the assessment of intraabdominal abscess.

**US:** US is best suited for evaluating pelvic and right and left upper quadrant abscesses, where the bladder, liver, and spleen provide acoustic windows for sound transmission. Abscesses vary in appearance but commonly are irregularly marginated and hypoechoic, with internal areas of increased echogenicity.

**MDCT:** CT is the first choice for detecting abscess in acutely ill patients. The CT appearance of an abscess depends on its maturity. Initially, an abscess may appear as a soft-tissue density mass. As it matures and undergoes liquefactive necrosis, the central region develops a near-water attenuation, possibly with internal air bubbles or an air-fluid level (Figure 69-18). The abscess wall typically enhances, increased density in the adjacent fat is common, and mass effect on the surrounding structures may be seen.



**Figure 69-18.** 23 year old male with left pericolonic abscess. Axial computed tomography image demonstrates an abscess (arrows) likely resulting from diverticulitis. Gas (\*) is present within the abscess cavity.

## BOWEL IMAGING

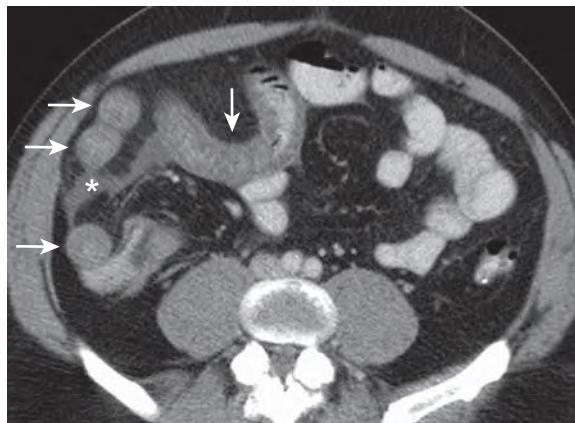
### 32. How has MDCT changed small bowel evaluation?

MDCT with coronal and sagittal MPRs can image the entire abdomen in a single breath-hold acquisition, facilitating small bowel evaluation. Ideal small bowel imaging requires intraluminal and intravenous (IV) contrast and bowel distention to best evaluate the mucosa, bowel wall, and surrounding structures, including adjacent fat. Neutral contrast agent use, such as dilute 0.1% barium sulfate mixed with sorbitol (VoLumen), allows better depiction of the bowel wall and mucosa compared to positive contrast agents such as meglumine diatrizoate (Gastrografin). If the intraluminal contrast is administered orally, the procedure is termed *CT enterography*, but if the intraluminal contrast is administered via a nasojejunal tube, the procedure is termed *CT enteroclysis*.

### 33. What are causes of small bowel wall thickening (>3 mm) on MDCT?

Smooth and concentric bowel wall thickening is typical for nonmalignant disease (e.g., Crohn's; ulcerative colitis; and ischemic, infectious, or radiation enteritis). Extraintestinal findings are important. In acute Crohn's, MDCT is the best initial examination to evaluate for associated abscesses, fibrofatty proliferation, fistulas, mesenteric inflammation, and engorged vasa recta ("comb sign") (Figure 69-19). However, small bowel follow-through remains more sensitive for subtle mucosal changes and should be performed if suspicion for Crohn's remains after a normal MDCT. MRI is excellent at diagnosing perianal disease, including fistulas.

Eccentric and irregular bowel wall thickening of more than 2 cm, especially if confined to a short segment, is suspicious for malignancy. Carcinoid is the most common primary malignant small bowel tumor. Carcinoid is typically located in the ileum; however, the actual tumor is often small and not visible on CT. A surrounding desmoplastic reaction with spiculated, often calcified mesenteric lymph nodes suggests the diagnosis. Adenocarcinoma is the most common primary malignant proximal small bowel tumor. It often presents as a mass or annular stricture that may obstruct. B-cell lymphoma occurs in the distal small bowel (2%) and T-cell lymphoma in the proximal small bowel (1%). Massive mesenteric or retroperitoneal adenopathy is

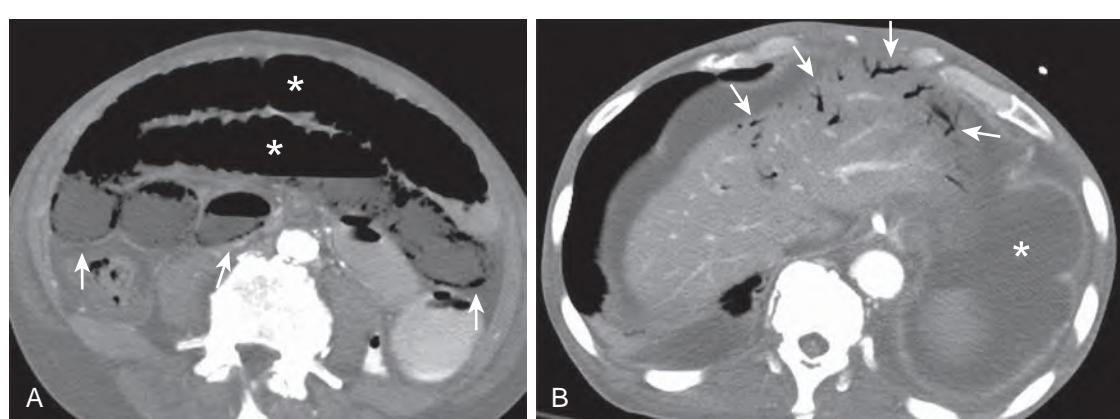


**Figure 69-19.** Crohn's. Computed tomography image depicts small bowel wall thickening (arrows) in this patient with Crohn's. Adjacent fluid within the mesentery is noted (\*).

often present. Lipomas are easily recognized by their low attenuation ( $\approx -100$  HU). The most common metastatic tumors to the small bowel include lung and melanoma.

#### 34. How does MDCT assist in diagnosing small bowel obstruction?

MDCT is useful for evaluating small bowel obstruction; however, supine and erect abdominal radiographs should remain the initial diagnostic examination. MDCT with MPRs can determine the cause and level of obstruction, especially when high-grade. CT enteroclysis is the best imaging modality for low-grade obstruction. The site of obstruction or "transition zone" is the location in which the bowel proximal is dilated and bowel distal is decompressed. MDCT has a high specificity and negative predictive value, but low specificity for detecting ischemia. Bowel ischemia should be considered when wall thickening, mesenteric stranding, and mesenteric fluid are present. Pneumatosis, PV gas, and intramural hemorrhage are present in severe cases (Figure 69-20A and B). MDCT can also diagnose closed-loop obstructions.



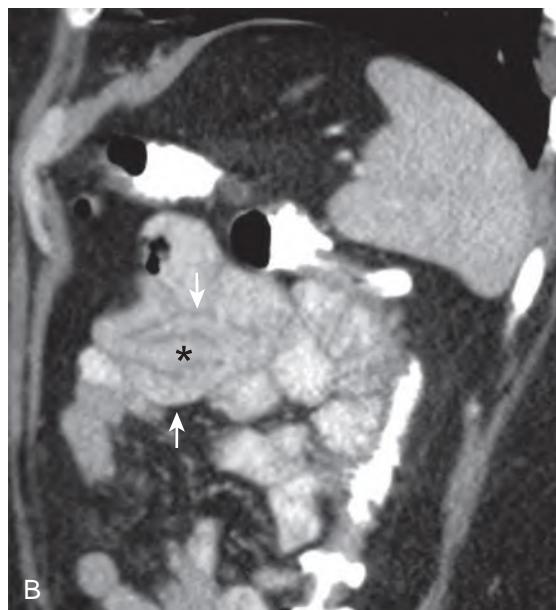
**Figure 69-20.** Ischemia. **A**, Computed tomography (CT) image demonstrates dilated air and fluid-filled small bowel loops (\*). Air is present in the nondependent walls of multiple small bowel loops (arrows). **B**, CT image demonstrates intrahepatic air within multiple branches of the portal vein (arrows). Ascites is also noted (\*).

#### 35. What is the significance of entero-enteric intussusception in adults?

Entero-enteric intussusception is usually considered incidental in adults when found on MDCT if there is no proximal bowel dilatation and if the intussusception is less than 3.5 cm in length. Intussusceptions are easily defined by the invaginated, low-density mesenteric fat situated between the higher density of the inner intussusceptum and the outer intussuscipiens (Figure 69-21A and E-Figure 69-21B).

#### 36. How is MDCT used to evaluate the large bowel?

Optimal evaluation of the colon requires bowel preparation and luminal distention with rectal contrast or air to evaluate the true wall thickness. Normal wall thickness of a distended colon is smaller than 4 mm. The addition of IV contrast facilitates the evaluation of the bowel wall and improves the evaluation of solid organs and vascular structures.



**E-Figure 69-21.** Sagittal (B) multiplanar reformatted computed tomography image demonstrating an asymptomatic enteric intussusception (white arrows) in the left upper quadrant. The inner intussusceptum (\*) and the outer intussuscipiens (arrows) are clearly identified.



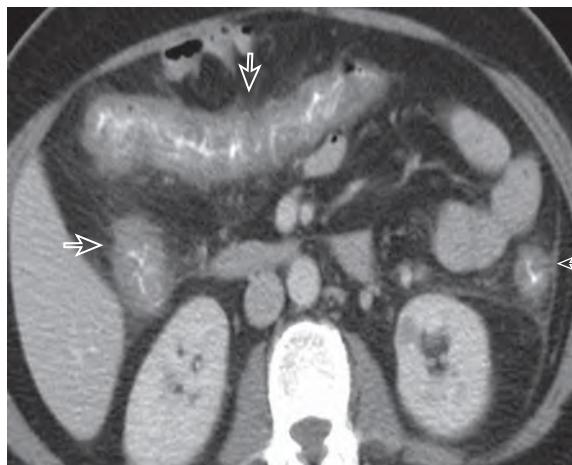
**Figure 69-21.** Enter-enteric intussusception. Coronal (A) multiplanar reformatted computed tomography image demonstrates an asymptomatic enter-enteric intussusception (white arrows) in the left upper quadrant. The invaginated low-density mesenteric fat and vessels (dotted arrows) are seen extending into the intussusception. The inner intussusceptum (\*) and the outer intussusciens (arrows) are clearly identified (see E-Figure 69-21B).

### 37. What are the causes of large bowel wall thickening on MDCT?

Wall thickening is present in numerous conditions, including Crohn's, ischemic colitis, pseudomembranous colitis, radiation colitis, neutropenic colitis, and infectious (cytomegalovirus or *Campylobacter*) colitis (Figure 69-22). On CECT, wall thickening can present either as homogeneous enhancing soft-tissue density or as concentric rings of high attenuation from hyperemic enhancement of the mucosa and serosa surrounding the low attenuation of the nonenhancing submucosa, termed the *halo* or *target sign*.

The cause of wall thickening sometimes can be determined by location or associated findings. For example, wall thickening in the splenic flexure region suggests ischemic disease from hypoperfusion in the superior mesenteric artery (SMA) and inferior mesenteric artery watershed area. Inflammation from a ruptured appendix can produce wall thickening mimicking a primary cecal process, and severe pancreatitis can cause transverse colon wall thickening if inflammatory changes spread through the transverse mesocolon.

Adenocarcinoma can present with an annular narrowing, an intraluminal polypoid mass, or eccentric lobulated wall thickening. Findings of regional or retroperitoneal adenopathy or liver or lung metastases help confirm the diagnosis of carcinoma. Signs of extracolonic extension include strands of soft tissue extending into the pericolonic fat, loss of fat planes between the colon and surrounding structures, and a masslike appearance. CT is useful in evaluating anastomotic recurrence from colorectal carcinoma, which occurs in the serosa, beyond the reach of the endoscope.

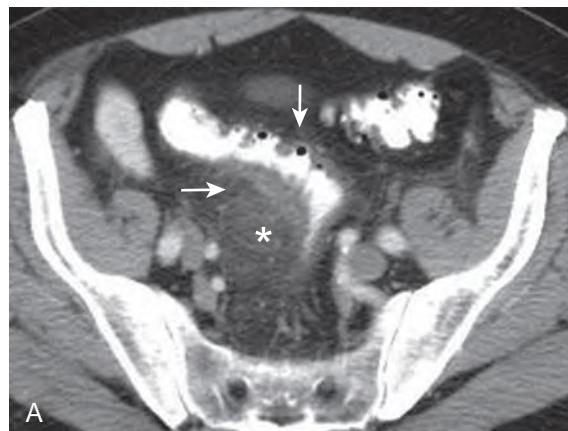


**Figure 69-22.** Pseudomembranous colitis in a man who presented with diarrhea and fever. CT image demonstrates marked circumferential colon wall thickening (open arrows) in patient with pseudomembranous colitis.

### 38. Describe the optimal radiographic work-up of diverticulitis.

MDCT is more than 95% accurate in the diagnosis of diverticulitis. It is superior to other modalities because it directly depicts the severity of the pericolic inflammation and the full intraperitoneal or retroperitoneal extension. It is more sensitive than a barium study in detecting abscesses and fistulas. The CT assessment of the colon is improved with adequate colonic opacification and distention with oral contrast.

The CT hallmark of acute diverticulitis is increased attenuation in the pericolic fat or “dirty fat.” (Figure 69-23A). A phlegmon or abscess, possibly containing air may be seen (E Figure 69-23B). With perforation, air may be seen in the peritoneum or retroperitoneum. Diverticula and a thickened bowel wall are usually present, but these findings are nonspecific. The bowel wall thickening occasionally may be difficult to distinguish from colon cancer. Findings that suggest tumor include a short segment ( $<10$  cm), an abrupt transition zone, wall thickness larger than 2 cm, lymphadenopathy, and metastases.



**Figure 69-23.** Diverticulitis. A, Computed tomography (CT) image demonstrates thickened wall of the sigmoid colon (arrows) with stranding in the adjacent fat (\*) indicative of diverticulitis.

### 39. What are the CT and US findings of acute appendicitis?

**US:** A distended ( $>6$  mm), noncompressible appendix with or without an adjacent fluid collection, an appendicolith, peritoneal fluid, abnormal flow in the wall of the appendix and a focal mass representing a phlegmon or abscess.

**MDCT:** The hallmark findings are a distended ( $>6$  mm), thick-walled appendix with abnormal enhancement and inflammatory changes in the periappendiceal fat. An appendicolith may be seen in 25% of cases. Additional signs of inflammation include focal thickening of adjacent fascia, focal fluid collections, and adjacent phlegmon or abscess (Figure 69-24). Findings that suggest perforation include (1) abscess, (2) extraluminal air, (3) extraluminal appendicolith, (4) phlegmon, and (5) focal defect in the enhancing wall. If all findings are present, perforation can be diagnosed with 95% sensitivity and specificity.



**Figure 69-24.** Appendicitis. Computed tomography image demonstrates dilated fluid-filled appendix (dotted arrow) with minimal surrounding fat-stranding and an appendicolith (arrow).



**E-Figure 69-23. B,** CT image slightly more caudal demonstrates an air-filled abscess cavity (*arrows*) with adjacent thickened sigmoid colon wall.

#### 40. Which examination is better for diagnosing acute appendicitis?

The sensitivity and specificity of CT is slightly superior to that of US, and CT is better at demonstrating both a normal appendix and the extent of adjacent inflammatory changes. The disadvantages of CT are higher cost and the use of ionizing radiation and contrast material. US is highly operator dependent, but is usually a good first choice in children, pregnant women, and thin people. CT should be used for all other types of patients and is more effective in obese patients.

#### 41. What is CT or "Virtual Colonoscopy"?

Optimal performance of MDCT Colonoscopy (CTC) requires thin-section (2-3 mm) images using a low dose technique with additional dedicated CT colonography software. Typical CT scan time is 5-7 seconds and both prone and supine images are obtained. Bowel preparation requires catharsis usually with magnesium citrate or sodium phosphate. The addition of dilute 2% CT barium to tag residual stool and/or diatrizoate (gastrograffin) to opacify luminal fluid helps differentiate stool from polyps. Distension is performed with either room air or automated CO<sub>2</sub> delivery via a small-caliber flexible catheter. Advantages over optical colonoscopy are that sedation is NOT required and other areas of the abdomen can be evaluated; however, CTC exposes the patient to radiation.

#### 42. How effective is CT or "Virtual Colonoscopy" in screening for polyps?

Most studies suggest that the accuracy of CTC is greater than barium enemas and approaches optical colonoscopy, especially for polyps >10 mm if the colon is properly prepped and distended. However, interpretation of CTC exams requires the review of both 2D and 3D images and it is recommended that only radiologists with experience evaluating 50 or more CTC exams should provide the interpretation.

*The authors would like to acknowledge the previous contributions of Dr. David Bean, Dr. Steven H. Peck, and Dr. Kevin Rak to this chapter.*

Please access ExpertConsult to view the E-Figures and [Clinical Vignette](#) for this chapter.

#### BIBLIOGRAPHY

1. Ba-Salamah A, Baroud S, Bastati N, Qayyum A. MR imaging of benign focal liver lesions. Magn Reson Imaging Clin N Am 2010;18:403-19.
2. Bashir MR, Gupta RT. MDCT evaluation of the pancreas: nuts and bolts. Radiol Clin N Am 2012;50:365-77.
3. Kamel IR, Liapi E, Fishman EK. Liver and biliary system: evaluation by multidetector CT. Radiol Clin N Am 2005;43:977-97.
4. Khatri G, Merrick L, Miller FH. MR imaging of hepatocellular carcinoma. Magn Reson Imaging Clin N Am 2010;18:421-50.
5. Lee JKT, Sagel SS, Stanley RJ, Heiken JP, editors. Computed body tomography with MRI correlation. 4th ed. Philadelphia: Lippincott-Williams Wilkins; 2006.
6. Lee SS, Park SH. Computed tomography evaluation of gastrointestinal bleeding and acute mesenteric ischemia. Radiol Clin N Am 2013;51:29-43.
7. Maglinte DDT. Fluoroscopic and CT enteroclysis: evidence-based clinical update. Radiol Clin N Am 2013;51:149-76.
8. Motohara T, Semelka RC, Bader TR. MR cholangiopancreatography. Radiol Clin N Am 2003;41:89-96.
9. Ooka Y, Kanai F, Okabe S, et al. Gadoxetic acid-enhanced MRI compared with CT during angiography in the diagnosis of hepatocellular carcinoma. Magn Reson Imaging 2013;31:748-54.
10. Pickhardt PJ, Kim DH. CT colonography: pitfalls in interpretation. Radiol Clin N Am 2013;51:69-88.
11. Rumack CM, Wilson SR, Charboneau JW, Levine D, editors. Diagnostic ultrasound. 4th ed. St. Louis: Elsevier Mosby; 2011.
12. Sano K, Ichikawa T, Motosugi U, et al. Imaging study of early hepatocellular carcinoma: usefulness of gadoxetic acid-enhanced MR imaging. Radiology 2011;261(3):834-44.
13. Santillan CS. Computed tomography of small bowel obstruction. Radiol Clin N Am 2013;51:17-27.
14. Tonan T, Fujimoto K, Qayyum A. Chronic hepatitis and cirrhosis on MR imaging. Magn Reson Imaging Clin N Am 2010;18:383-402.
15. Umphrey H, Canon CL, Lockhart ME. Differential diagnosis of small bowel ischemia. Radiol Clin N Am 2008;46:943-52.
16. Yee J. CT colonography: techniques and applications. Radiol Clin N Am 2009;47:133-45.
17. Zamboni GA, Ambrosetti MC, D'Onofrio M, Mucelli RP. Ultrasonography of the pancreas. Radiol Clin N Am 2012;50:395-406.

# NUCLEAR IMAGING

Won S. Song, MD

**1. Outline the general advantages of nuclear medicine procedures compared with other imaging modalities.**

- Provide functional information that is either not available by other modalities or is obtained at greater expense or patient risk.
- High-contrast resolution (target-to-background ratio) can be achieved in many instances by nuclear medicine techniques, allowing diagnostic studies despite poor spatial resolution.
- Relatively noninvasive studies are the rule in nuclear medicine. They require only injection of a radioactive dose or swallowing of a substance, followed by imaging.

**2. What are the disadvantages of nuclear medicine procedures compared with other radiographic studies?**

- Spatial resolution, usually on the order of 1 to 2 cm, is inferior to that of other imaging modalities.
- Imaging times can be long, sometimes up to 1 hour or more.
- Radiation risk is obviously greater than with magnetic resonance imaging (MRI) or ultrasound (US). However, the radiation risk from most nuclear medicine studies is usually less than that of an average computed tomography (CT) study. Gallium-67 and indium-111 white blood cell studies are the exceptions; they involve an average of two to four times more radiation exposure than other nuclear medicine studies. Positron emission tomography (PET) with CT has the radiation dose of a CT in addition to the radiation from the PET scan. In some studies, such as gastric emptying and esophageal transit studies, radiation risk is insignificant compared with traditional imaging methods, such as fluoroscopy.
- Availability may be limited. Specialized procedures require radiopharmaceuticals or interpretive expertise not available in all centers.

**3. What nuclear medicine tests are most helpful in gastrointestinal (GI) medicine?**

Nuclear medicine procedures have been used in the evaluation of nearly every GI problem (Table 70-1). Current improvements in and widespread use of endoscopy, manometry, pH monitoring, and diagnostic radiologic imaging techniques (CT, MRI, US) have limited the use of nuclear medicine to specific clinical problems.

**Table 70-1. Uses of Nuclear Medicine Procedures in Gastrointestinal Diseases**

TEST OR STUDY	USEFUL IN DIAGNOSIS/EVALUATION
Cholescintigraphy (hepatobiliary imaging)	Acute cholecystitis Gallbladder dyskinesia Common duct obstruction Biliary atresia Sphincter of Oddi dysfunction Hepatic mass Biliary leak Choleangiointestinal anastomosis patency
Gastric emptying	Quantification of gastric motility
Esophageal motility/transit	Quantification of esophageal transit Evaluation/detection of reflux Detection of pulmonary aspiration
<sup>14</sup> C-urea breath test	Identification of <i>Helicobacter pylori</i> infection
Liver/spleen scan	Hepatic mass lesions Accessory spleen/splenosis
Heat-damaged RBC scan	Accessory spleen/splenosis
<sup>67</sup> Gallium scan	Staging of abdominal malignancies Abdominal abscess

**Table 70-1.** Uses of Nuclear Medicine Procedures in Gastrointestinal Diseases (Continued)

TEST OR STUDY	USEFUL IN DIAGNOSIS/EVALUATION
$^{111}\text{In}$ -pentetreotide	Neuroendocrine tumor staging/recurrence
$^{111}\text{In}$ WBC scan	Evaluation of abdominal infection/abscess Evaluation of active inflammatory bowel disease
$^{99\text{m}}\text{Tc}$ -HMPAO WBC scan	Evaluation of active inflammatory bowel disease
$^{99\text{m}}\text{Tc}$ -RBC scan	GI bleeding localization Hepatic hemangiomas
Pertechnetate ( $\text{NaTcO}_4$ ) scanning	Meckel diverticulum
$^{99\text{m}}\text{Tc}$ -sulfur colloid dynamic imaging	GI bleeding localization
Hepatic arterial perfusion with $^{99\text{m}}\text{Tc}$ MAA	Hepatic intraarterial catheter perfusion
$^{90}\text{Y}$ microspheres	Treatment of unresectable hepatocellular carcinoma Treatment of hepatic metastatic lesions
$^{18}\text{F}$ -FDG PET and PET/CT	Evaluation of various malignancies Assessment of inflammatory bowel disease

$^{14}\text{C}$ , Carbon-14; CT, computed tomography;  $^{18}\text{F}$ -FDG,  $^{18}\text{F}$ -fluorodeoxyglucose; GI, gastrointestinal; HMPAO, hexamethylpropyleneamine-oxime;  $^{111}\text{In}$ , indium-111; MAA, macroaggregated albumin; PET, positron emission tomography; RBC, red blood cell;  $^{99\text{m}}\text{Tc}$ , technetium-99m; WBC, white blood cell;  $^{90}\text{Y}$ , yttrium-90.

#### 4. How is cholescintigraphy (hepatobiliary imaging) performed? What is a normal study?

The technique for a basic cholescintigraphic study is the same for nearly all of its clinical indications (see Question 3). The patient is injected with a technetium-99m-labeled iminodiacetic acid (IDA) derivative. Although commonly referred to as a *HIDA scan*, hepatic IDA is no longer used in imaging. Disofenin and mebrofenin are used currently because of improved pharmacokinetics. High bilirubin levels (greater than 5 mg/dL for disofenin and greater than 10 mg/dL for mebrofenin) can cause a competitive inhibition of radiopharmaceutical uptake; however, administering a higher dose can overcome this impediment.

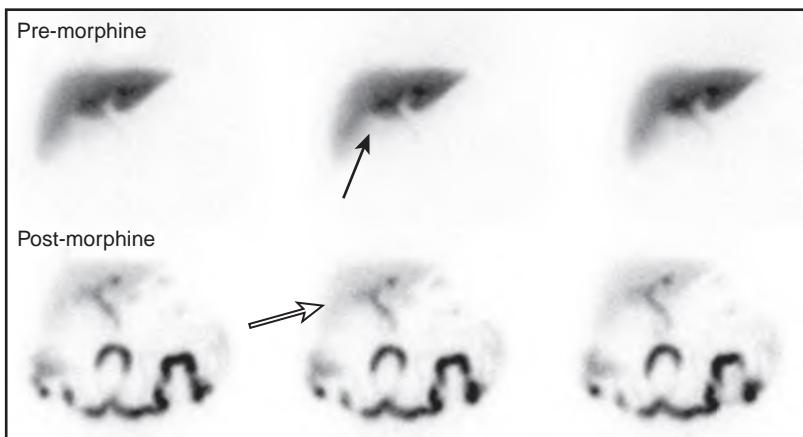
After injection, sequential images, usually 1 minute in duration, are routinely obtained for 60 minutes. Normally, the liver rapidly clears the radiopharmaceutical. On images displayed at normal intensity, blood pool activity in the heart is faint or indiscernible by 5 minutes after injection. Persistent blood pool activity and poor liver uptake are indications of hepatocellular dysfunction. Right and left hepatic ducts, the common bile duct, and small bowel are typically visualized within 30 minutes. The gallbladder usually is seen within 30 minutes but can still be considered normal if visualized within 1 hour, provided the patient has not eaten within 4 hours. By 1 hour, nearly all the activity is in the bile ducts, gallbladder, and bowel; the liver is seen faintly or not at all. In all of the studies listed in Question 3, failure to see an expected structure at 1 hour (e.g., gallbladder in acute cholecystitis, small bowel in biliary atresia) requires delayed imaging (4 hours for evaluation for acute cholecystitis, 24 hours for biliary atresia). In some cases, various manipulations, such as sincalide infusion or morphine injection, are performed after the initial 60-minute images.

#### 5. How should patients with acute cholecystitis be prepared? What manipulations are used to shorten the study or increase its reliability?

Traditionally, acute cholecystitis is diagnosed on functional cholescintigraphy by noting a lack of filling of the gallbladder on both the initial 60-minute study and subsequent 4-hour delayed images. Patient preparation is vital in ensuring that lack of gallbladder visualization is a true-positive finding. Instead of 4-hour delayed images, morphine can be used to shorten the time needed to complete this study.

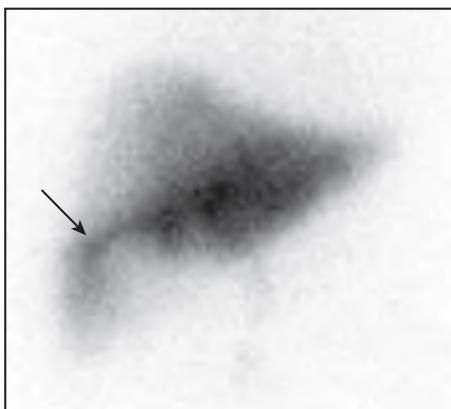
Because food is a potent and long-lasting stimulus for endogenous cholecystokinin (CCK) release, the patient should not eat for 4 hours prior to the study because endogenous CCK will prevent normal gallbladder relaxation and consequently impair normal filling, leading to a false-positive study. These patients should wait 4 hours to ensure an optimal study. On the other hand, patients who have had a prolonged fast (longer than 24 hours), are receiving intravenous hyperalimentation, or are severely ill can develop viscous bile formation, which may not be adequately emptied out of a normal gallbladder. This can impair radiopharmaceutical filling of the gallbladder, which in turn can also cause a false-positive study. In these patients at risk for viscous bile formation, the short-acting CCK analog sincalide can be administered (0.02 mcg/kg intravenously in 20-30 minutes), prior to cholescintigraphy. This ensures proper emptying of the gallbladder before the radiopharmaceutical is administered and will prevent a false-positive event from occurring.

Despite these manipulations, the gallbladder may not be visualized during the initial 60 minutes of the study. Rather than reimage at 4 hours, the study can be expedited using morphine (0.04 mg/kg intravenously), provided small bowel activity is seen within the initial 60 minutes. After morphine administration, imaging



**Figure 70-1.** Acute cholecystitis. Premorphone images: After injection with  $^{99m}\text{Tc}$  mebrofenin, selected 1-minute static images during the initial 60-minute images demonstrate absence of radiotracer in the expected location of the gallbladder (black arrow). Despite 60 minutes of imaging, the gallbladder was not visualized. Postmorphine images: To expedite the examination, morphine was administered; however, continued imaging for 30 minutes did not demonstrate gallbladder filling (white arrow).

is continued for another 30 minutes. Because morphine causes sphincter of Oddi contraction, the resultant increased biliary tree pressure will overcome a functional obstruction of the cystic duct. If the gallbladder is still not seen, delayed imaging is not necessary and acute cholecystitis is diagnosed (Figure 70-1). Overall, the sensitivity for acute calculous cholecystitis is 97% with a specificity of 85%. The sensitivity and specificity are slightly lower in acute acalculous cholecystitis with a sensitivity and specificity of 79% and 87%, respectively. If there is pericholecystic hepatic activity with a subsequent *rim sign*, the potential for a complicated cholecystitis (i.e., gangrenous or perforated gallbladder) is significantly higher (Figure 70-2). In adults, absence of activity in the intrahepatic ducts or small bowel can represent a high grade obstruction (Figure 70-3). In the early stages, conventional imaging will be normal. Fortunately, scintigraphy will demonstrate abnormal excretion before anatomic abnormalities are detectable.



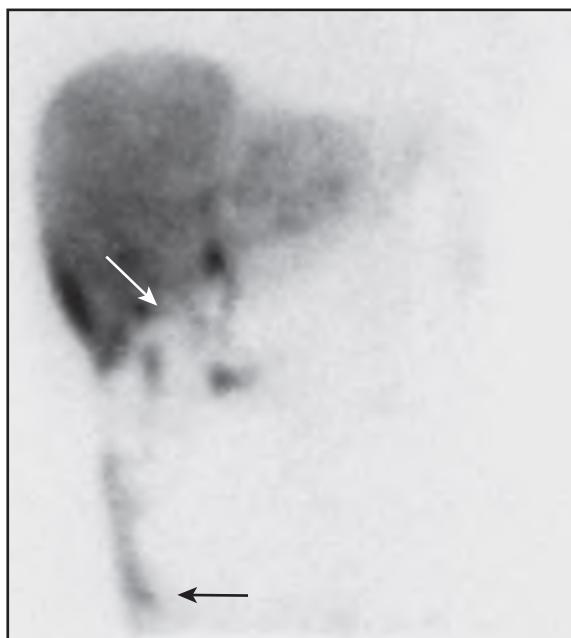
**Figure 70-2.** Acute gangrenous cholecystitis. During the initial 60 minutes of hepatobiliary imaging, pericholecystic hepatic activity (rim sign) is noted without visualization of the gallbladder. The rim sign is thought to be secondary to regional hyperemia, which increases delivery of the radiopharmaceutical to this area, in addition to localized hepatic dysfunction, which prevents efficient excretion of the radiopharmaceutical. Approximately 40% of patients with this type of activity have a perforated or gangrenous gallbladder.



**Figure 70-3.** High-grade biliary obstruction. After injection of  $^{99m}\text{Tc}$  mebrofenin, there is no visible activity in the intrahepatic ducts or small bowel in the initial 60 minutes of images. Additional 4- and 24-hour images (not shown) did not demonstrate activity in the small bowel.

## 6. How is cholescintigraphy used to diagnose and manage biliary leak?

Cholescintigraphy is highly sensitive and specific for detecting biliary leak. Nonbile fluid collections are common after surgery and can significantly limit the specificity of anatomic studies. In cases of a postcholecystectomy bile leak, cholescintigraphy can demonstrate accumulation of activity in the gallbladder fossa with progressive activity in dependent regions, commonly the right paracolic gutter (Figure 70-4). Additional delayed images up to 24 hours after injection can demonstrate small leaks. Because cholescintigraphy has poor spatial resolution, the exact origin of the leak may not be determined and endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography may be necessary for further anatomic assessment. Cholescintigraphy can also be used noninvasively to document resolution of a bile leak. Bilomas can also be detected if there is a focus of increased activity that correlates with a fluid collection noted on previous cross-sectional imaging.



**Figure 70-4.** Bile leak. After laparoscopic cholecystectomy, the patient developed severe right upper quadrant pain. Injection of  $^{99m}\text{Tc}$  mebrofenin was followed with acquisition of 1-minute sequential images. There is accumulation of the radiopharmaceutical in the gallbladder fossa (white arrow) as well as activity in the right paracolic gutter “tail sign” (black arrow) consistent with bile leak.

## 7. What is the role of cholescintigraphy in diagnosing biliary atresia?

If the patient is properly prepared for the examination, cholescintigraphy can be helpful in excluding the diagnosis of biliary atresia. The other primary differential diagnostic possibility in neonates is severe neonatal hepatitis. The role of scintigraphy is not to diagnose biliary atresia but rather to rule out biliary atresia as a possible diagnosis. To improve the sensitivity of the study, premedication of the neonate with oral phenobarbital (5 mg/kg/day in divided doses for 5 days) is imperative, because it stimulates hepatic activity and increases the ability of the liver to extract the radiopharmaceutical. The importance of therapeutic serum levels of phenobarbital cannot be overemphasized because a scan resulting from poor preparation is indistinguishable from a scan consistent with biliary atresia or neonatal hepatitis. If the radiotracer is not seen in the small bowel, delayed images must be obtained and if small bowel is visualized, biliary atresia is ruled out.

Unfortunately, severe hepatic dysfunction and hepatitis may have a similar appearance to biliary atresia. Additional delayed images should be obtained to assess for activity in the small bowel, which excludes the diagnosis of a high-grade obstruction or biliary atresia.

## 8. What is gallbladder dyskinesia? How does cholescintigraphy evaluate the emptying of the gallbladder?

A significant number of patients with normal conventional imaging and clinical evaluation have pain referable to the gallbladder, as evidenced by relief of symptoms after cholecystectomy. The poorly understood and

heterogeneous entity of gallbladder dyskinesia has been proposed as the cause of this pain. It is thought that poorly coordinated contractions between the gallbladder and cystic duct can cause pain. Gallbladder dyskinesia may be manifested by an abnormally low ejection of bile under the stimulus of CCK (sincalide).

After the gallbladder has filled during cholescintigraphy, gallbladder contraction is stimulated by an infusion of sincalide, 0.02 mcg/kg in 30 minutes. The amount of gallbladder emptying in 30 minutes reflects the gallbladder ejection fraction (GBEF), normal being greater than 35%. This protocol has demonstrated correlation of both normal and abnormal GBEF with surgical and medical follow-up.

#### **9. What nuclear medicine esophageal studies are available? How are they used?**

- **Esophageal motility study:** The evaluation of esophageal dysmotility should begin with assessment for anatomic abnormalities using endoscopy, barium swallowing study, or CT. This is typically followed by manometry if an anatomic cause is not identified. A nuclear medicine study is performed if a diagnosis is still uncertain. Rapid sequential imaging in either the supine or upright position after ingestion of  $^{99m}\text{Tc}$  sulfur colloid in water is performed with additional subsequent dry swallows during imaging. Esophageal motility studies are also useful in evaluation of response to therapy for dysmotility and achalasia.
- **Esophageal reflux study:** This study is performed by serial imaging of the esophagus after the patient drinks acidified orange juice containing  $^{99m}\text{Tc}$ -sulfur colloid with subsequent serial inflation of an abdominal binder. Although less sensitive than 24-hour pH monitoring, the test is more sensitive than barium studies and can be used as a screening study or evaluation of response to therapy.
- **Pulmonary aspiration studies:** These studies are performed by imaging the chest after oral administration of  $^{99m}\text{Tc}$ -colloid in water or formula in infants. Activity in the lungs is diagnostic of aspiration. Although sensitivity is low, it is likely higher than that of radiographic contrast studies. The test has the advantage of easy serial imaging to detect intermittent aspiration.

#### **10. What is a nuclear medicine gastric emptying study?**

Either liquid or solid-phase gastric emptying studies can be performed. Liquid studies are typically conducted on infants. After the infant receives a mixture of  $^{99m}\text{Tc}$ -sulfur colloid with milk or formula at the normal feeding time, imaging is performed and an emptying half-time is calculated. In adults, a solid-phase emptying study usually is performed after an overnight fast and subsequent ingestion of  $^{99m}\text{Tc}$ -sulfur colloid-labeled scrambled eggs as part of a standard meal. Anterior and posterior imaging is obtained with either dynamic imaging in 90 minutes or static images at 0, 1, 2, and 4 hours. The percentage of emptying is calculated based on the geometric mean of the anterior and posterior counts. A consensus statement by the Society of Nuclear Medicine has recommended the use of a low-fat, egg-white meal, although this is not necessarily used at every clinic and normal values are institution dependent and will obviously vary with different meal compositions. Using a 285-calorie meal of scrambled eggs, bread, and jam, normal  $t_{1/2}$  gastric emptying time (time at which 50% of the gastric contents is emptied) is less than 135 minutes ([E-Figure 70-5](#)).

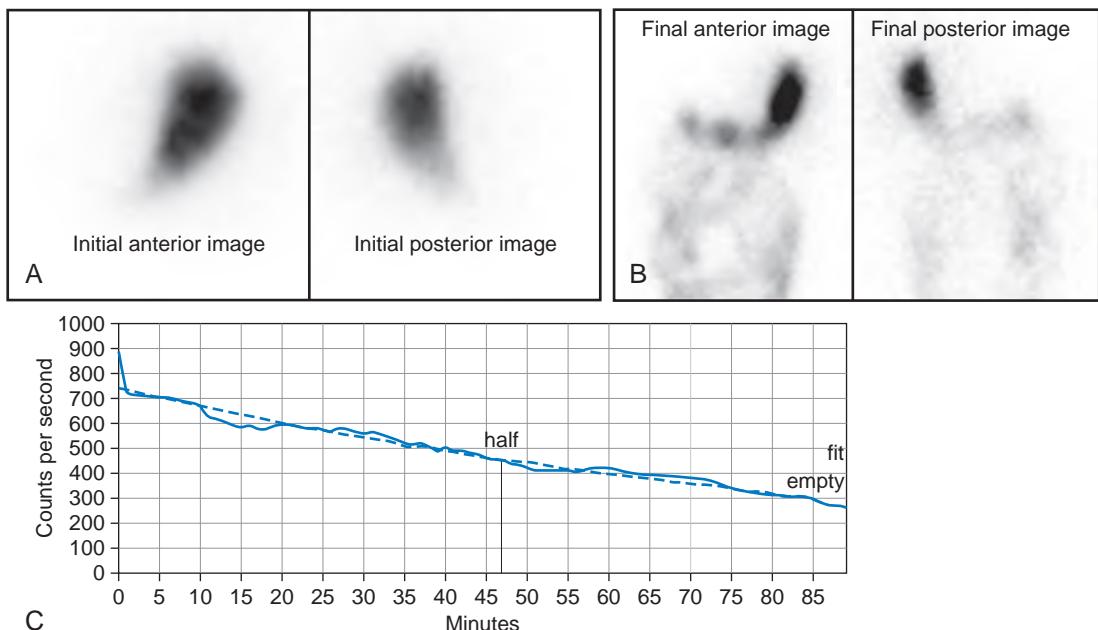
#### **11. What is the role for nuclear medicine studies in evaluating hepatic mass lesions?**

The traditional liver and spleen scan using an intravenous injection of  $^{99m}\text{Tc}$ -sulfur colloid has largely been replaced by US and dynamic multiphase CT and MRI. In addition to superior resolution with CT and MRI, adjacent structures can also be evaluated. If results are inconclusive, nuclear medicine testing can provide additional information, which can lead to the proper diagnosis.

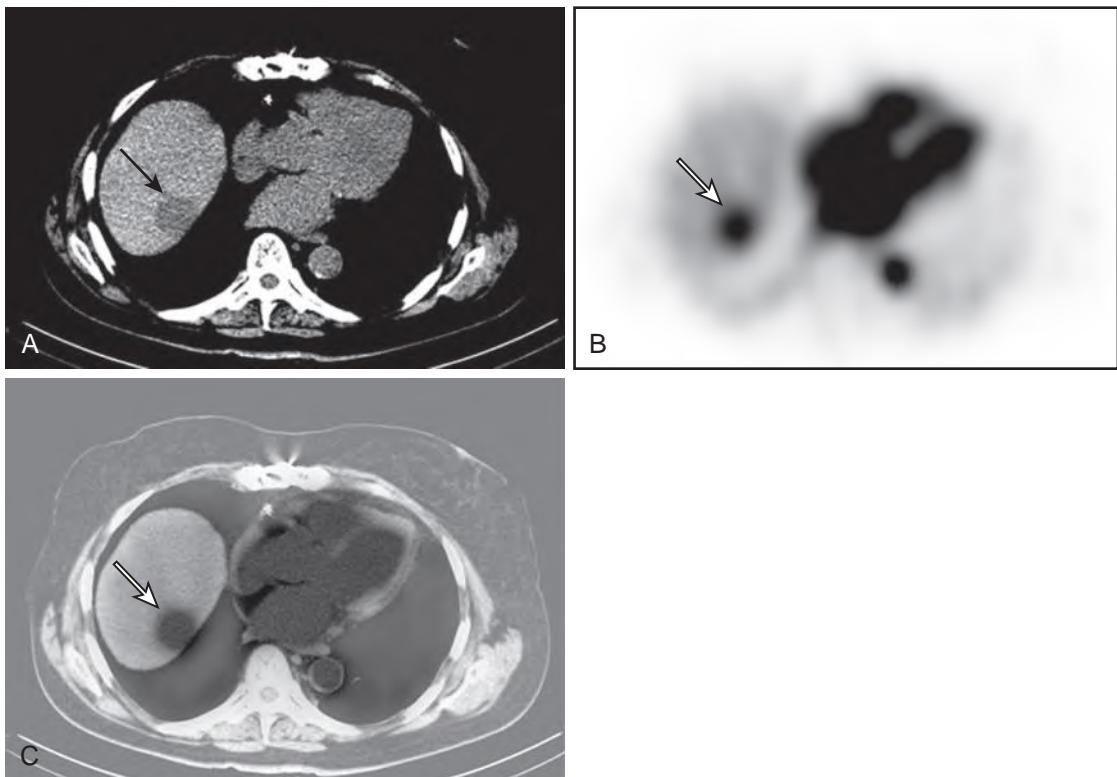
Sulfur colloid is composed of small particles (0.3 to 1  $\mu\text{m}$ ) that are phagocytosed by the reticuloendothelial systems, including Kupffer cells in the liver. Lesions that lack Kupffer cells in the liver will not accumulate sulfur colloid. Virtually all neoplasms, including metastasis, focal inflammatory and infectious diseases of the liver, and vascular malformations, manifest as decreased radionuclide activity (cold) on both liver-spleen and hepatobiliary imaging. However, focal nodular hyperplasia (FNH) can demonstrate a nonspecific appearance on CT, MRI, and US. If a lesion appears isointense (warm) or hyperintense (hot) compared with the rest of the liver, it can be presumed to be FNH because no other hepatic lesion contains a sufficient number of Kupffer cells to concentrate sulfur colloid. Occasionally, FNH can appear cold if there are not enough Kupffer cells to accumulate a sufficient amount of sulfur colloid, which unfortunately does not differentiate it from other hepatic masses. Additional imaging with cholescintigraphy will demonstrate early and prolonged uptake of the radiopharmaceutical because of the presence of hepatocytes in FNH with impaired clearance of the radiopharmaceutical from these lesions.

The evaluation of hepatic lesions is limited on planar imaging to approximately 1 to 2 cm. To evaluate smaller lesions, single-photon emission computed tomography (SPECT) imaging, which is produced using rotating gamma camera heads and reconstructing the data into three dimensions, can be used in the evaluation of lesions in the subcentimeter range.

Using multiphasic imaging with CT or MRI, evaluation for hepatic hemangiomas is excellent. However, if atypical features are noted, imaging using SPECT with  $^{99m}\text{Tc}$ -labeled red blood cells (RBCs) can provide additional information for hemangiomas larger than 2 cm and close to the hepatic surface ([Figure 70-6](#)), frequently at lower cost and without intravenous contrast injection. Additional SPECT imaging also improves the ability to evaluate smaller hemangiomas.



**E-Figure 70-5.** Normal gastric emptying. After ingestion of  $^{99m}\text{Tc}$ -sulfur colloid in two scrambled eggs, 1-minute images were obtained for 90 minutes in the anterior (A) and posterior (B) projections. Gastric emptying is calculated using the decay correct geometric mean of the counts on the anterior and posterior images. C, The emptying curve demonstrates normal gastric emptying with a half-life of 47 minutes and 60% emptying at 90 minutes.



**Figure 70-6.** Evaluation of mass lesion. Single-photo emission computed tomography (SPECT)/computed tomography (CT) scan of the liver using in vitro tagged  $^{99m}\text{Tc}$  red blood cells (RBCs). **A**, Initial CT evaluation of the hepatic mass (black arrow) demonstrated findings that were suggestive of an atypical hemangioma. Additional evaluation was suggested. **B**, SPECT imaging (using CT attenuation correction from SPECT/CT) demonstrates normal blood pool activity of  $^{99m}\text{Tc}$  RBC with an additional intense focus (white arrow) that corresponds to the hepatic mass. **C**, Fused images of simultaneously acquired SPECT and CT images reveals the intense focus to be in the exact region of the hepatic mass consistent with hemangioma.

## 12. How can nuclear medicine procedures assist in detecting ectopic gastric tissue?

As a source of pediatric GI bleeding, a Meckel diverticulum invariably contains ectopic gastric mucosal tissue. Because  $^{99m}\text{Tc}$ -pertechnetate is concentrated and extracted by gastric tissue, it is an ideal agent to localize sources of GI bleeding caused by a Meckel diverticulum, which can be difficult to detect with traditional radiographic studies.

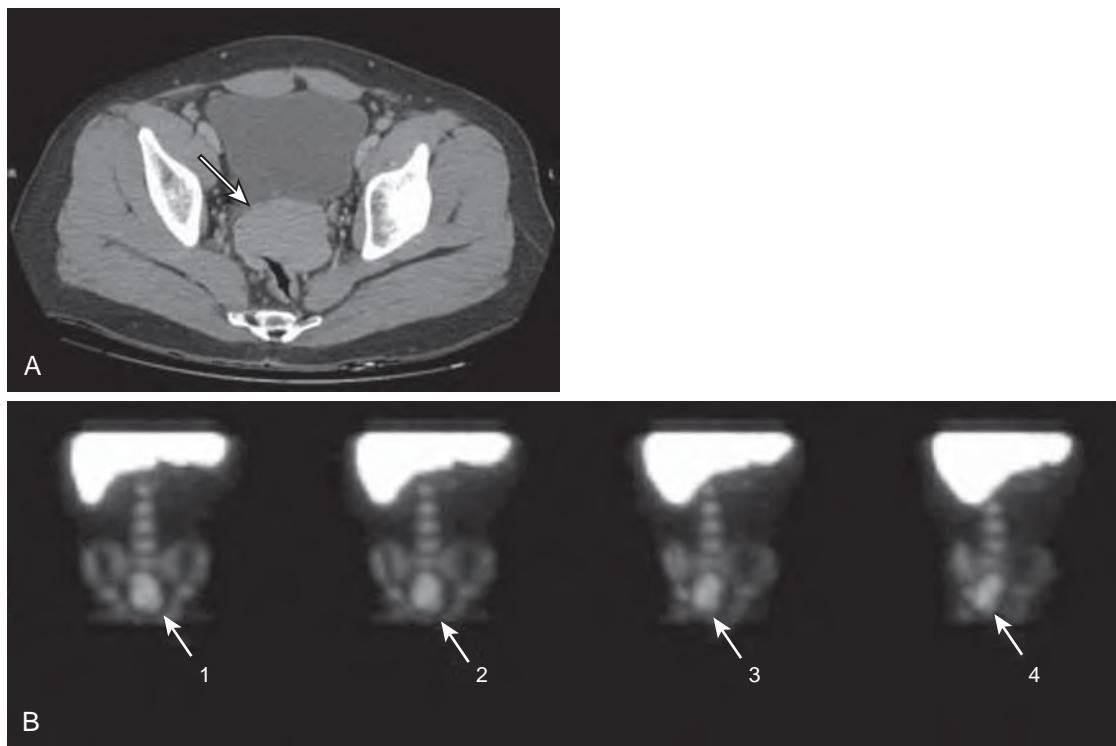
The study is performed by injecting pertechnetate intravenously and imaging the abdomen for 60 minutes. Typically, ectopic gastric mucosa appears at the same time as gastric mucosa and does not move during imaging. Sensitivity is 85% for detection of bleeding from a Meckel diverticulum. Manipulations to increase the sensitivity of the study may include additional pharmaceuticals such as cimetidine (to block pertechnetate release from ectopic mucosa), pentagastrin (to enhance mucosal uptake), and glucagon (to inhibit bowel motility and prevent movement of the radiopharmaceutical).

## 13. Can accessory splenic tissue or splenosis be detected via nuclear medicine procedures?

After splenectomy as treatment of idiopathic thrombocytopenia, approximately 30% of adult patients can result in treatment failure, which may be secondary to an accessory spleen or splenosis. Unrecognized splenosis may also be a cause of unexplained abdominal pain or present as an abdominal or pelvic mass on CT. The most sensitive imaging procedure for localization of small foci of splenic tissue is the heat-damaged  $^{99m}\text{Tc}$ -RBC scan, because damaged RBCs localize in splenic tissue intensely and specifically. This is the procedure of choice, especially if SPECT is used. However, the RBC-damaging process requires additional laboratory manipulation and may not be readily available in many clinics. It is therefore reasonable to perform a liver-spleen scan as an initial study and, if it is positive for splenic tissue, to institute appropriate therapy (E-Figure 70-7). If it is negative or inconclusive, a heat-damaged RBC study should be performed.

## 14. Which nuclear medicine procedures are useful in localizing lower GI bleeding?

The difficulty of localizing acute lower GI bleeding is well recognized. Even acute and rapid bleeding can be intermittent and not detected on angiography. Alternatively, the culprit lesion can be obscured by luminal blood

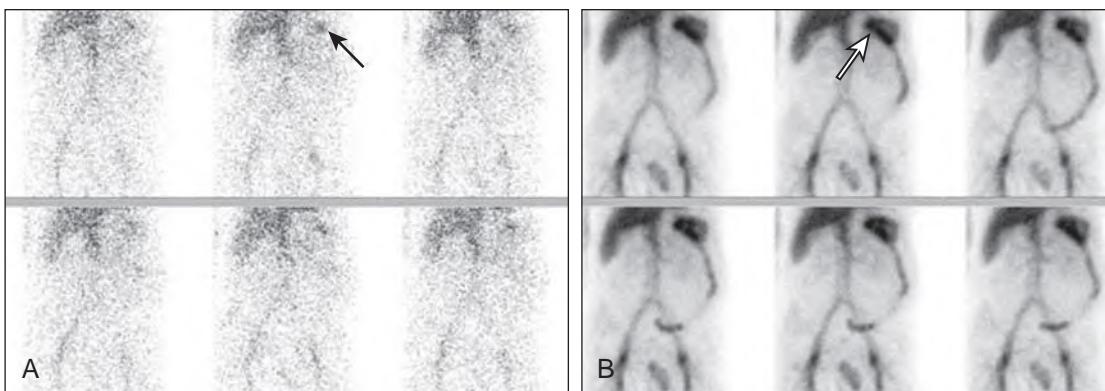


**E-Figure 70-7.** Splenosis. **A**, Computed tomography image of the pelvis demonstrates a large soft tissue mass (black arrow) in the pelvis of a patient with a remote history of trauma that eventually led to splenectomy. **B**, Single-photon emission computed tomography imaging with  $^{99m}\text{Tc}$ -sulfur colloid demonstrates increased activity in the pelvis (white arrows) that correlates with the pelvic mass, consistent with splenosis.

during endoscopy. Small bowel bleeding distal to areas accessible by upper endoscopy is notoriously difficult to localize.

Two nuclear procedures have been used to localize GI bleeding sources: short-term imaging with  $^{99m}\text{Tc}$ -sulfur colloid injection and extended imaging using  $^{99m}\text{Tc}$ -tagged RBC injection. Despite the theoretical advantage of  $^{99m}\text{Tc}$ -sulfur colloid in being able to detect smaller bleeds, this technique shares the limitation of angiography: a short intravascular residence time, which mandates the bleed to be active at the exact point of imaging. In addition, the normal biodistribution of sulfur colloid to the liver and spleen limits the evaluation of possible bleeds around the hepatic and splenic flexures.  $^{99m}\text{Tc}$ -RBC imaging has assumed dominance because the long intravascular residence time allows detection of intraluminal radioactive blood accumulation if extended imaging is necessary.

The first step is performing an in vitro tagging of RBCs with  $^{99m}\text{Tc}$ -pertechnetate, which provides the highest RBC tagging efficiency. In vitro tagging of radiolabeled RBCs involves obtaining a small blood sample (1 to 3 mL) from the patient and using  $^{99m}\text{Tc}$ -pertechnetate to label the RBCs in reaction vials. The radiolabeled RBCs are injected back into the patient and dynamic 1- or 2-second flow images are obtained in 60 seconds. In the case of a brisk bleed, the flow images will allow for better localization because delayed images will demonstrate significant radiotracer spread through the bowel (Figure 70-8). Immediately after dynamic flow images are obtained, sequential 1-minute images are acquired for 90 minutes. The use of dynamic imaging is important because sensitivity for localization is higher when the study is displayed in a cine-loop. If the patient has an intermittent bleed and the initial study is negative, images can be acquired up to 24 hours later if the patient actively bleeds again without reinjecting additional tagged RBCs. Unfortunately, delayed images will have a significant disadvantage in localizing the area of active bleeding because of normal peristaltic activity and the additional time from the beginning of the bleed to the time of imaging.



**Figure 70-8.** Gastrointestinal bleed. **A**, After injection of in vitro labeled  $^{99m}\text{Tc}$  red blood cells, 1-second-per-frame flow images were obtained, which demonstrate a focus of increasing activity (black arrow) at the splenic flexure. Because of the brisk nature of this bleed, the flow images were useful in localizing the origin of the bleed. **B**, Additional 1-minute-per-frame images demonstrate significant radiotracer uptake at the splenic flexure (white arrow) and extending activity moving anterograde down the descending colon and into the sigmoid colon. The patient subsequently had a colectomy performed.

#### 15. Are nuclear medicine procedures clinically useful in localizing GI bleeding, or are simpler techniques adequate?

$^{99m}\text{Tc}$ -RBC studies are more sensitive than both colonoscopy and angiography in detecting intermittent bleeding. Upper endoscopy would be a better choice if an upper GI bleed is suspected because tagged RBC studies are limited in the assessment of the stomach as a result of physiologic splenic activity. In addition to better visualization, upper endoscopy can also provide therapeutic options. One advantage of the tagged RBC study is that it allows for a survey of both the small and large bowel during a much longer time frame. Once the bleed is localized, therapeutic options with interventional radiology can be facilitated because less time is required to find which vessel to treat.

#### 16. Is nuclear medicine helpful in placement of arterial perfusion catheters?

The use of hepatic arterial infusion chemotherapy can serve as an adjuvant treatment following surgery or may be used for patients with unresectable disease. Occasional unrecognized systemic shunting, catheter dislodgment, and unintended perfusion of an area not suitable for highly toxic chemotherapeutic drugs hamper placement of hepatic arterial perfusion catheters. Arterial catheter injection of  $^{99m}\text{Tc}$ -macroaggregated albumin (MAA) results in temporary microembolization and provides an imaging map of the true area of perfusion of the catheter. After a baseline scan, if there has been a significant change in perfusion, further therapy with chemotherapy would entail significant risk for GI toxicity.

### 17. Are there additional minimally invasive treatments for unresectable malignant liver masses?

Use of yttrium-90 ( $^{90}\text{Y}$ ) microspheres is a newer treatment option that delivers concentrated radiation to unresectable hepatocellular carcinoma and metastatic disease.  $^{90}\text{Y}$ , with a half-life of 64.5 hours, releases beta particles that radiate adjacent soft tissue with an average penetration of 2.5 mm.  $^{90}\text{Y}$  microspheres have a diameter of 20 to 30  $\mu\text{m}$ , which become trapped in the capillary beds of the intended masses and deliver a substantial dose of radiation specifically to these regions without the dangers of systemic radiation.

To safely deliver the dose of radiation to the targeted disease, hepatic angiography via the femoral artery is performed first. To safely map the perfusion and subsequent delivery area of  $^{90}\text{Y}$  microspheres,  $^{99\text{m}}\text{Tc}$ -MAA is administered directly to the hepatic artery in the identical manner that the  $^{90}\text{Y}$  microspheres will be delivered. Because  $^{99\text{m}}\text{Tc}$ -MAA particles are similarly sized compared with  $^{90}\text{Y}$  microspheres, the biodistribution of these radiopharmaceuticals should be nearly identical. Using the images from  $^{99\text{m}}\text{Tc}$ -MAA, the biodistribution is assessed and a shunt fraction is calculated to assess potential unwanted systemic distribution, particularly to the lungs. If these images and calculations demonstrate a safe delivery of  $^{99\text{m}}\text{Tc}$ -MAA, then treatment with  $^{90}\text{Y}$  microspheres is possible.

### 18. Can abdominal malignancies be evaluated with nuclear medicine studies?

$^{111}\text{In}$  pentetreotide is a somatostatin analog that targets a variety of neuroendocrine tumors including carcinoid tumors, pancreatic islet cell neoplasm, gastrinoma, pheochromocytoma, neuroblastoma, and paraganglioma. Whole-body planar and SPECT imaging are performed at 4 and 24 hours. The additional anatomic information provided by CT images, by fusion software, or with simultaneous acquisition with SPECT and CT provides localization of disease. In addition, if performed as SPECT/CT, the use of attenuation correction can improve detection of lesions deep within the body (E-Figure 70-9).

### 19. What is PET and how does it work?

PET uses specialized positron-emitting radiopharmaceuticals and equipment to detect areas of increased metabolic activity, a characteristic commonly seen in malignancies. The most commonly used radiopharmaceutical in PET imaging is  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG), which is a marker for glucose metabolism. Unlike other commonly used radiopharmaceuticals in nuclear medicine,  $^{18}\text{F}$ -FDG has a short half-life (110 minutes) and requires a cyclotron for production. Because of the complexity and cost of operating a cyclotron, the vast majority of nuclear medicine clinics do not have an on-site cyclotron and require the use of a separate PET radiopharmacy to provide the PET radiopharmaceutical. In addition, the short half-life of  $^{18}\text{F}$ -FDG and the need to transport the  $^{18}\text{F}$ -FDG from an outside facility to the imaging site can limit the overall accessibility of PET imaging.

Tumors demonstrate increased  $^{18}\text{F}$ -FDG avidity because of increased expression of glucose transporters and hexokinase, which is responsible for phosphorylating normal glucose and radioactive  $^{18}\text{F}$ -FDG. After  $^{18}\text{F}$ -FDG is phosphorylated, it is not metabolized any further and becomes effectively trapped intracellularly.

Patient preparation for a study using  $^{18}\text{F}$ -FDG entails fasting for 4 to 6 hours prior the examination to optimize the uptake of  $^{18}\text{F}$ -FDG into malignant cells. At the time of the administration of  $^{18}\text{F}$ -FDG, blood glucose levels less than 150 mg/dL are optimal, although images obtained in patients with blood glucose levels up to 200 mg/dL can still yield diagnostic results. Use of insulin can interfere with the biodistribution of  $^{18}\text{F}$ -FDG, which can complicate the preparation of insulin-dependent diabetics.

### 20. What malignancies can PET and PET/CT be used for?

PET is a proved modality in the evaluation of various malignancies, including esophageal, gastric, pancreatic, and colon cancers, as well as GI stromal tumors (GISTs), carcinoid tumors, and lymphoma. In addition, PET/CT has demonstrated utility in the assessment of inflammatory bowel disease.

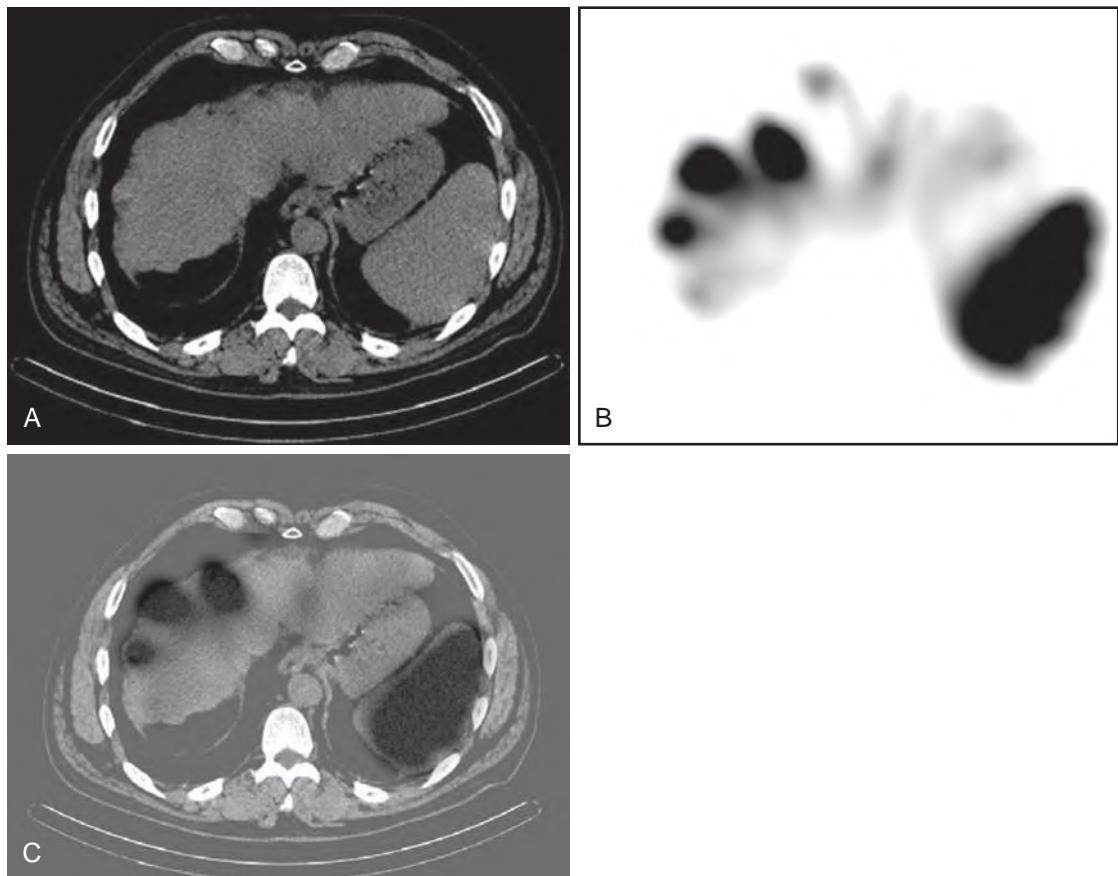
Combined with CT, PET/CT exemplifies the value of combined metabolic and anatomic imaging. The most common scenarios in which PET and PET/CT have been useful are staging and surveillance of malignancies and evaluation of postoperative sites.

Although routine staging of colon cancer is not recommended,  $^{18}\text{F}$ -FDG PET/CT has demonstrated significant benefit in assessing recurrence and restaging (E-Figure 70-10). Studies with  $^{18}\text{F}$ -FDG have been useful in patients with increasing carcinoembryonic antigen levels without anatomic abnormalities and in the evaluation of liver metastases, which are often underestimated with other radiologic modalities.

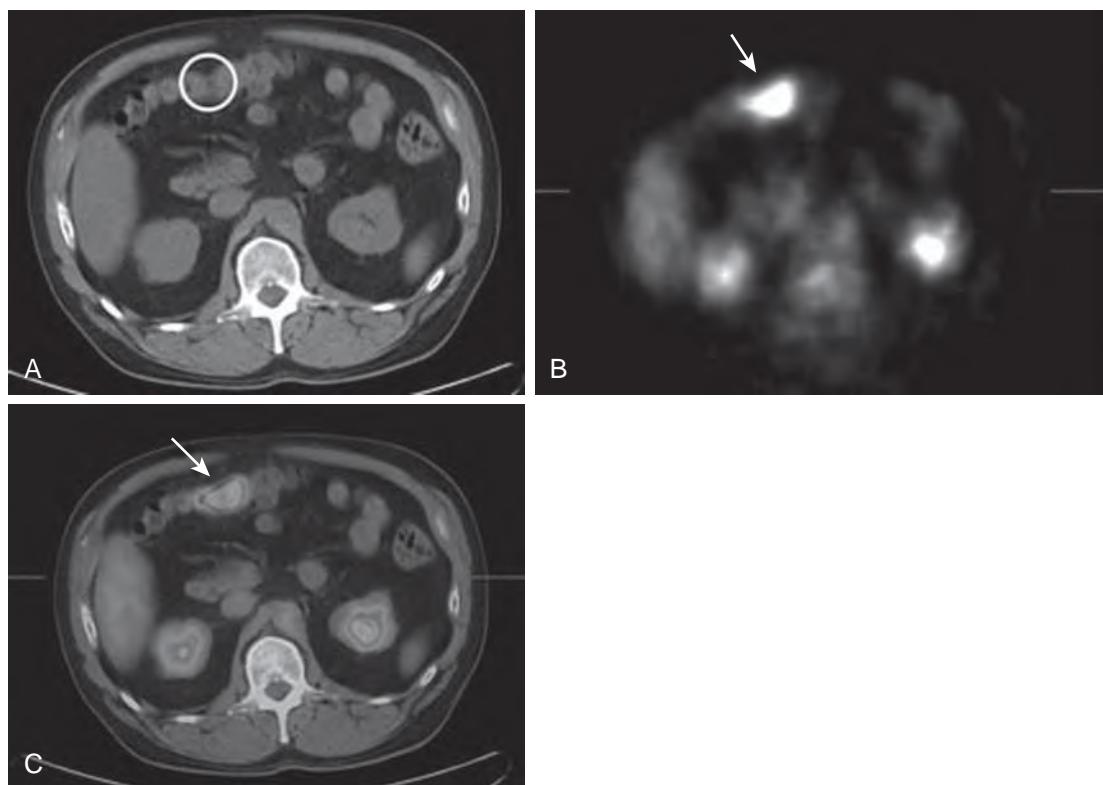
Detection of primary and metastatic pancreatic cancer using  $^{18}\text{F}$ -FDG PET/CT has been proven as well. Unfortunately, there are some lesions that are not  $^{18}\text{F}$ -FDG avid and the sensitivity of this test has been limited in detecting cystic pancreatic malignancies, mucinous tumors, and low cellular density lesions. In addition, pancreatitis and inflammatory pseudotumors can be falsely positive for malignancy and demonstrate FDG avidity.

GISTs typically have a rounded, exophytic appearance with well-defined borders on CT imaging.  $^{18}\text{F}$ -FDG PET imaging demonstrates intense activity in malignant GISTs, with lower metabolic activity in non-malignant GISTs.  $^{18}\text{F}$ -FDG PET can also serve in predicting response to therapy.

One malignancy that has a low sensitivity on  $^{18}\text{F}$ -FDG PET is hepatocellular carcinoma. Typically, poorly differentiated HCC will be  $^{18}\text{F}$ -FDG avid. Well-differentiated HCC can have higher levels of glucose-6-phosphatase, which will dephosphorylate the phosphorylated  $^{18}\text{F}$ -FDG and permit it to leach out of the cell.



**E-Figure 70-9.** Metastatic carcinoid. Single-photon emission tomography (SPECT)/computed tomography (CT) images were obtained after injection of 6 mCi  $^{111}\text{In}$ -pentetretide. **A**, Noncontrast CT image demonstrates a nodular appearance of the hepatic dome. **B**, Multiple areas of increased uptake are noted in the reconstructed axial image from the CT attenuation-corrected SPECT images of  $^{111}\text{In}$ -pentetretide. **C**, Fusion of the SPECT and CT images demonstrates anatomic and metabolic correlation of the metastatic carcinoid tumors.



**E-Figure 70-10.** Colon cancer imaged with  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) positron emission tomography (PET)/computed tomography (CT). **A**, CT image demonstrate a soft tissue lesion in the transverse colon (white circle). **B**, Simultaneously acquired PET images reveal focal increased FDG activity (striped arrow). **C**, Fusion of these two images demonstrates that the increased FDG activity overlies the transverse colon soft tissue lesion (white arrow), consistent with malignancy.

Alternative PET radiotracers such as  $^{11}\text{C}$ -choline and  $^{11}\text{C}$ -acetate have been shown to have better avidity for well-differentiated HCC but are not as widely available as  $^{18}\text{F}$ -FDG.

Please access ExpertConsult to view the E-Figures for this chapter.

## BIBLIOGRAPHY

1. Annovazzi A, Bagni B, Burroni L, et al. Nuclear medicine imaging of inflammatory/infective disorders of the abdomen. *Nucl Med Commun* 2005;26:657–64.
2. Banks KP, Song WS. Role of positron emission tomography-computed tomography in gastrointestinal malignancies. *Radiol Clin North Am* 2013;51:799–831.
3. Biancone L, Schillaci O, Capoccetti F, et al. Technetium-99m-HMPAO labeled leukocyte single photon emission computerized tomography (SPECT) for assessing Crohn's disease extent and intestinal infiltration. *Am J Gastroenterol* 2005;100:344–54.
4. Choi B, Nguyen M. The diagnosis and management of benign hepatic tumors. *J Clin Gastroenterol* 2005;39:401–12.
5. Ell PJ, Gambhir SS. Nuclear medicine in clinical diagnosis and treatment. 3rd ed. Edinburgh: Churchill Livingstone; 2004, p. 789–818, 837–846.
6. Howarth D. The role of nuclear medicine in the detection of acute gastrointestinal bleeding. *Semin Nucl Med* 2006;36:133–46.
7. Huynh L, Kim S, Murphy T. The typical appearance of focal nodular hyperplasia in triple-phase CT scan, hepatobiliary scan, and Tc-99m sulfur colloid scan with SPECT. *Clin Nucl Med* 2005;30:736–9.
8. Ikeda O, Kusunoki S, Nakaura T, et al. Comparison of fusion imaging using a combined SPECT/CT system and intra-arterial CT: assessment of drug distribution by an implantable port system in patients undergoing hepatic arterial infusion chemotherapy. *Cardiovasc Intervent Radiol* 2006;29:371–9.
9. Kehagias D, Moulopoulos L, Antoniou A, et al. Focal nodular hyperplasia: imaging findings. *Eur Radiol* 2001;11:202–12.
10. Malfertheiner P, Megraud F, O'Morain C, et al. Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III consensus report. *Gut* 2006;56:772–81.
11. Mariani G, Pauwels E, AlSharif A, et al. Radionuclide evaluation of the lower gastrointestinal tract. *J Nucl Med* 2008;49:776–87.
12. Maurer A. Consensus report on gastric emptying: what's needed to prevent tarnishing a gold standard? *J Nucl Med* 2008;49:339.
13. Maurer A, Parkman H. Update on gastrointestinal scintigraphy. *Semin Nucl Med* 2006;36:110–8.
14. Mettler FA, Guiberteau MJ. Essentials of nuclear medicine. 5th ed. Philadelphia: WB Saunders; 2006, p. 203–210, 215–220.
15. Pelosi E, Masaneo I, Clara R, et al. Technetium-99m labeled macroaggregated albumin arterial catheter perfusion scintigraphy: prediction of gastrointestinal toxicity in hepatic arterial chemotherapy. *Eur J Nucl Med* 2000;27:668–75.
16. Stasi R, Evangelista M, Stipa E, et al. Idiopathic thrombocytopenic purpura: current concepts in pathophysiology and management. *Thromb Haemost* 2008;99:4–13.
17. Vilaichone R, Varocha M, Graham D. *Helicobacter pylori* diagnosis and management. *Gastroenterol Clin N Am* 2006;35:229–47.
18. Ziessman H. Acute cholecystitis, biliary obstruction, and biliary leakage. *Semin Nucl Med* 2003;33:279–96.

# ENDOSCOPIC ULTRASOUND

Linda S. Lee, MD

## 1. How does ultrasound work?

Sound waves are vibrations that occur at a specific frequency, are transmitted through a medium, and can be reflected off objects. Information about the direction from which the sound waves are reflected and the time taken for the sound to return from the object can be used to locate the object. Sound waves used in ultrasonography occur at frequencies of more than 20,000 Hz, which is beyond the range of human hearing. The ultrasound transducer both generates and receives sound waves to create images. Sound travels readily through liquid, whereas air causes distortion and reverberation of ultrasound waves. The ultrasound transducer at the tip of the echoendoscope must be immersed in a water-filled lumen or covered with a water-filled balloon to transmit and receive defined images.

## 2. Define the terminology used to describe endoscopic ultrasound (EUS) findings and name examples of corresponding structures.

See Table 71-1.

**Table 71-1.** Definitions to Describe EUS Findings and Examples of Corresponding Structures

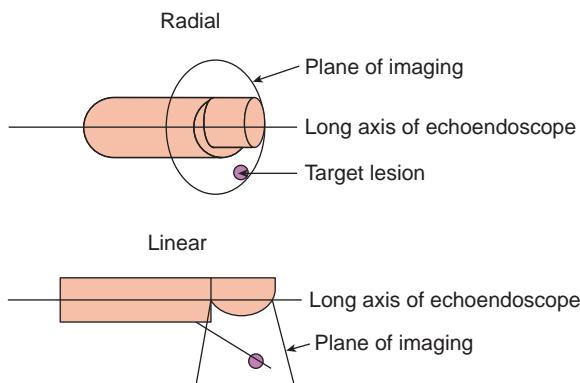
TERMINOLOGY	ECHOGENICITY	EXAMPLES OF STRUCTURES
Anechoic	Black	Fluid (e.g., blood, bile, pancreatic juice)
Hypoechoic	Gray (darker than surrounding structures)	Lymph node, muscle
Hyperechoic	Bright (light gray to white)	Fat, bone

## 3. What is the relationship between the frequency of ultrasound, depth of penetration, and resolution?

There is an inverse relationship between the frequency of the ultrasound probe and depth of penetration. Standard echoendoscopes typically have a frequency ranging from 5 to 10 mHz, which allows a depth of penetration of 8 and 4 cm, respectively. High-frequency ultrasound probes that can be passed through the biopsy channel of a standard gastroscope or colonoscope have higher frequencies up to 30 mHz with corresponding decreased depth of penetration. The higher the frequency, the greater the resolution (image clarity or ability to differentiate two adjacent objects).

## 4. What is the major difference between the radial and linear echoendoscopes?

See Figure 71-1. The major difference between the radial and linear echoendoscopes is in the way images are acquired. The ultrasound transducer at the tip of the radial echoendoscope rotates 360 degrees and acquires

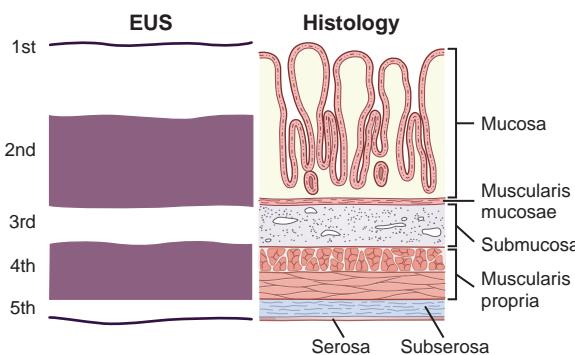


**Figure 71-1.** Plane of imaging of radial and linear echoendoscopes.

cross-sectional images in a plane perpendicular to the long axis of the echoendoscope. On a linear echoendoscope, the transducer does not rotate and provides a 120-degree image parallel to the shaft of the echoendoscope. This enables visualization of a needle passing through the biopsy channel of the echoendoscope into the targeted tissue, allowing fine needle aspiration (FNA) unlike with a radial echoendoscope.

### 5. What is the EUS anatomy of the normal gastrointestinal (GI) tract?

See Figure 71-2. The intestinal wall has five sonographic layers.



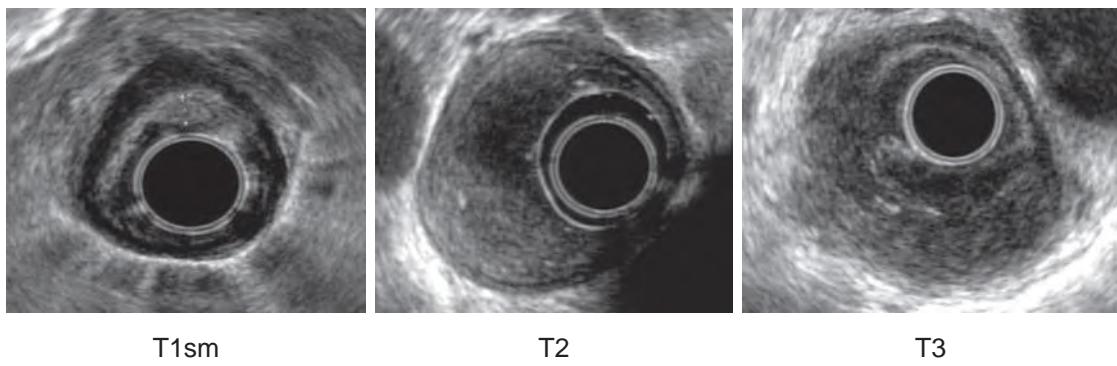
**Figure 71-2.** Correlation of endoscopic ultrasound (EUS) image to the histologic composition of the bowel wall.

### 6. Describe generic T staging for luminal GI cancers.

See Table 71-2 and Figure 71-3.

**Table 71-2.** Generic T Staging for Gastrointestinal Luminal Cancers

T STAGE	DEFINITION
T1m	Invades mucosa or deep mucosa.
T1sm	Invades submucosa.
T2	Invades muscularis propria.
T3	Invades adventitia or serosa.
T4	Invades surrounding structures.



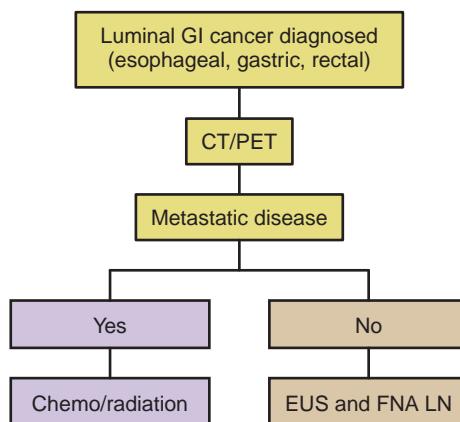
**Figure 71-3.** Endoscopic ultrasound for T staging of esophageal cancer.

### 7. List the most common indications for EUS.

- Staging GI cancers, including esophageal, gastric, pancreatic, ampullary, rectal, and cholangiocarcinoma
- Staging lung cancer
- Evaluating subepithelial lesions; thick gastric folds; chronic pancreatitis (CP) and idiopathic recurrent pancreatitis; pancreatic lesions, including cysts and masses; and hepatobiliary lesions, including stones, strictures, and masses.

### 8. How does EUS fit into esophageal cancer staging?

See Figure 71-4. EUS provides the most accurate method of T and N staging for esophageal cancer with overall accuracy 80% to 90%. If there is no evidence of distant metastatic disease on radiologic imaging, EUS should be performed to provide locoregional staging.



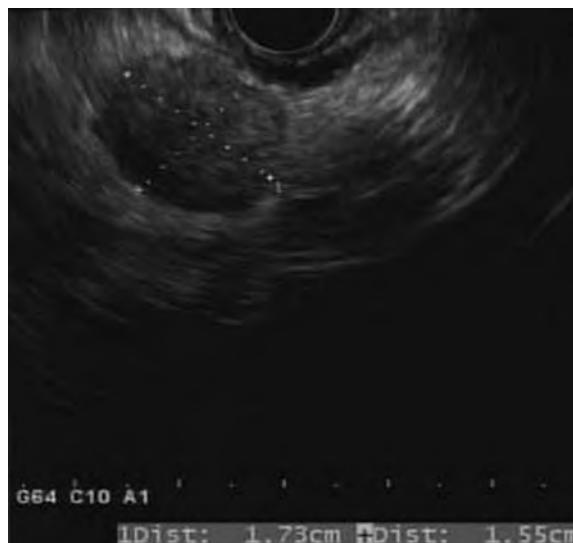
**Figure 71-4.** Algorithm for staging luminal gastrointestinal (GI) cancers. CT, Computed tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; LN, lymph node; PET, positron emission tomography.

### 9. What are the recent changes to esophageal cancer staging?

- Staging applies to masses that arise within the first 5 cm of the stomach that extend into the esophagus.
- T4 is divided into T4a, in which the tumor invades the pleura, pericardium, or diaphragm and is potentially resectable, whereas T4b tumors are unresectable with invasion into other adjacent structures, including the aorta, vertebral body, and trachea.
- Regional nodal staging is no longer binary, but classified as N0 through N3: N0 with no lymph node (LN), N1 with one or two LNs, N2 with three to six LNs, and N3 with seven or more LNs.
- Regional lymphadenopathy includes LNs in the chest, around the esophagus, and celiac axis.
- Celiac axis lymphadenopathy no longer qualifies as metastatic disease.

### 10. How is malignant lymphadenopathy determined in esophageal cancer?

See Figure 71-5. The presence of four EUS criteria (size >1 cm, round, well-defined, and hypoechoic) predicts a malignant LN in nearly 100% of cases. However, only 20% to 40% of all malignant LNs have all four



**Figure 71-5.** Endoscopic ultrasound of malignant periesophageal lymph node.

EUS criteria. Therefore, when possible, FNA of LN should be performed. The addition of FNA to EUS increases sensitivity and specificity to nearly 90% and 100%, respectively.

#### **11. Discuss some of the limitations of EUS in esophageal cancer staging.**

The accuracy of T staging by EUS varies with the actual stage of the tumor, with the least accurate being T1 tumors.

Strictures occur in approximately 30% of esophageal masses. Accuracy for staging is higher for traversable tumors compared with tumors occluding the lumen. Older literature suggested high perforation rates approaching 25% following dilation to allow passage of an echoendoscope, with recent studies suggesting the safety of pre-EUS dilation. Alternatively, a high-frequency ultrasound probe may be carefully advanced through a stricture.

EUS following chemoradiation is inaccurate with a tendency to overstage. Accuracy of EUS for T and N staging ranges from 50% to 60%.

#### **12. How does EUS affect management of esophageal cancer?**

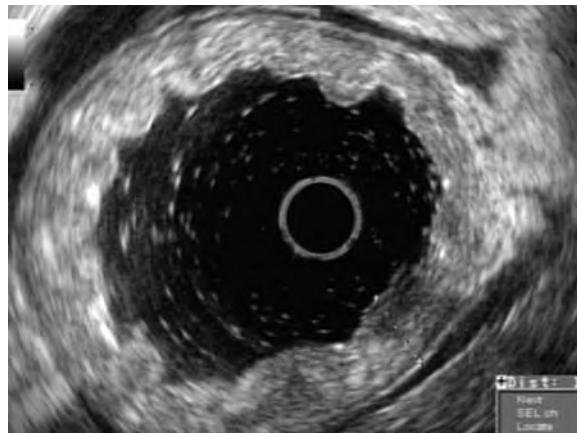
In 29% to 56% of cases, EUS findings changed management of esophageal cancer by determining candidates for surgical and endoscopic resection versus neoadjuvant chemoradiation.

#### **13. What is the role of EUS in gastric cancer staging?**

Treatment for gastric cancer is stage dependent with endoscopic mucosal resection and submucosal dissection an option for T1N0 cancers and neoadjuvant treatment administered for T3/T4 and nodal positive cancers. Therefore accurate staging is important. If no distant metastatic disease is visible on computed tomography (CT) or positron emission tomography scan, EUS is the next step for locoregional staging. Overall EUS sensitivity and specificity for T staging are 86% and 91%, respectively. For N staging, EUS sensitivity and specificity are 69% and 84%. CT and magnetic resonance imaging (MRI) appear comparable to EUS for T and N staging.

#### **14. What EUS findings predict malignancy in thickened gastric folds?**

See [Figure 71-6](#). Definitive diagnosis of thickened gastric folds is difficult despite the use of EUS. These EUS findings are more predictive of malignancy: thickened submucosa, muscularis propria, or serosa; presence of ascites or lymphadenopathy. The etiologic factors of gastric wall thickening caused by thickened mucosa or deep mucosa can be diagnosed by biopsy or snare resection.



**Figure 71-6.** Endoscopic ultrasound of thickened gastric wall caused by submucosal thickening.

#### **15. Discuss the accuracy of EUS and endorectal coil MRI in staging rectal cancer.**

EUS and MRI appear overall comparable with T stage accuracy for both, ranging from 65% to 95% and nodal stage accuracy of approximately 75%. However, MRI cannot reliably identify T1 tumors, whereas EUS tends to understage T4 tumors. The addition of FNA may increase the accuracy of N staging.

#### **16. What are the EUS characteristics for a malignant LN in rectal cancer?**

EUS characteristics are the same as for esophageal cancer with the exception of a size larger than 5 mm.

#### **17. List some of the limitations of EUS for rectal cancer staging.**

- Invasion into the mesorectal fascia cannot be evaluated.

- Distinguishing peritumoral inflammation from tumor extension may be difficult.
- Staging stenotic rectal masses may be limited.
- Posttreatment staging is inaccurate.
- Endosonographer experience affects accuracy of staging.

#### **18. How is EUS used in the diagnosis and staging of pancreatic cancer?**

EUS-FNA is the preferred diagnostic procedure for pancreatic cancer with a sensitivity of 80% to 85% and specificity near 100%. This compares favorably with CT-guided FNA, with a sensitivity of 62% to 81%. Accuracy of locoregional staging is comparable for CT, MRI, and EUS. EUS is superior for detection of portal vein invasion, whereas pancreatic protocol CT better visualizes superior mesenteric artery (SMA) and superior mesenteric vein (SMV) involvement.

#### **19. What are the limitations of EUS in pancreatic cancer?**

In CP, the diagnostic accuracy of EUS-FNA for pancreatic masses falls to approximately 54% to 73%. As mentioned previously, visualization of SMA and SMV invasion is limited with EUS.

#### **20. What is the role of EUS in pancreatic neuroendocrine tumors (PNETs)?**

EUS is an integral part of both detecting and diagnosing PNETs with 77% to 94% sensitivity for detecting them. When abdominal CT scan is negative for PNET, EUS is more than 70% sensitive for detecting it. EUS is superior to CT scan for small (<2 cm) PNETs and insulinomas. EUS-FNA is nearly 90% sensitive for diagnosing these tumors.

#### **21. What are common subepithelial lesions and their EUS characteristics?**

See Table 71-3 and Figure 71-7.

EUS features concerning for malignancy in subepithelial lesions include size larger than 3 cm, irregular margins, and internal cystic spaces.

**Table 71-3. Common Subepithelial Lesions and EUS Characteristics**

SUBEPITHELIAL LESION	EUS CHARACTERISTIC
Gastrointestinal stromal tumor	Hypoechoic, second or fourth layer
Lipoma	Hyperechoic, third layer
Carcinoid	Mildly hypoechoic, second or third layer
Cyst	Anechoic, second or third layer
Pancreatic rest	Hypoechoic or heterogeneous, second, third, or fourth layer
Granular cell tumor	Hypoechoic, second or third layer
Varices	Anechoic, serpiginous, second or third layer
Inflammatory fibroid polyp	Hypoechoic, second or third layer

#### **22. Compare the diagnostic yield of EUS-FNA in subepithelial lesions to other diagnostic techniques.**

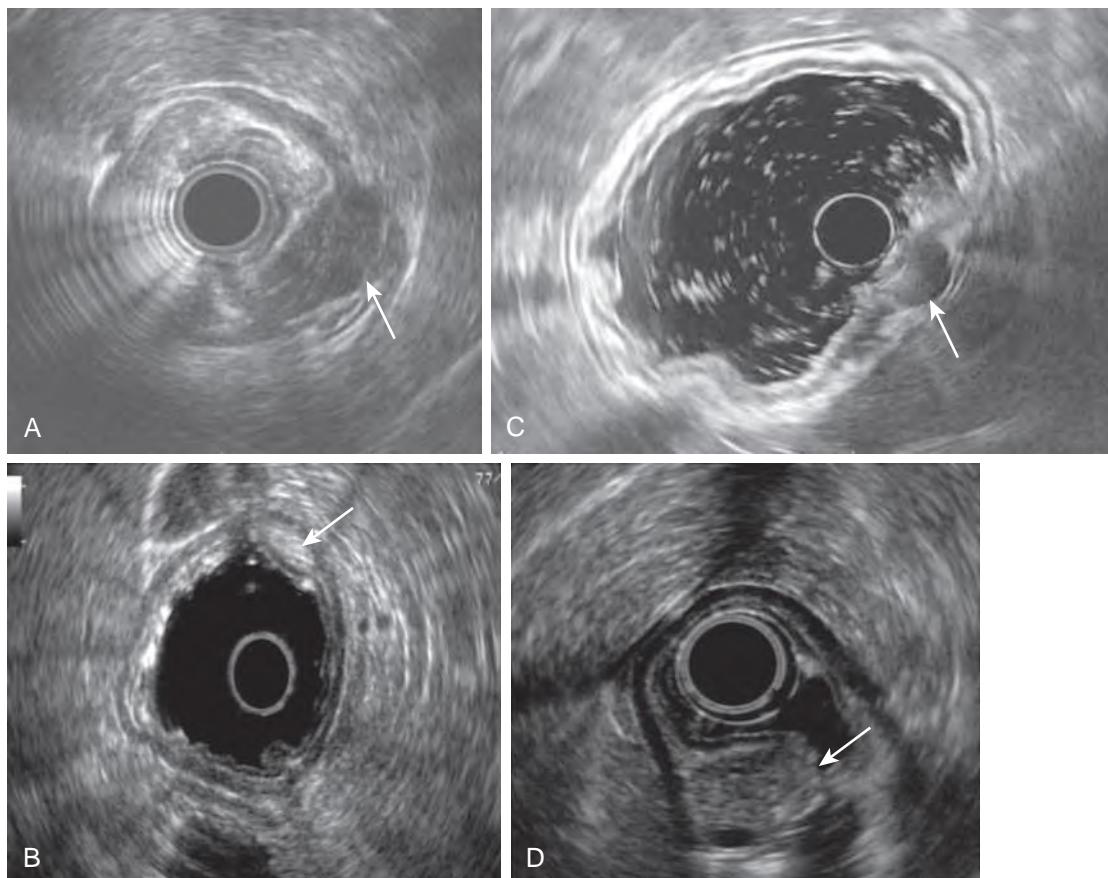
EUS-FNA has modest diagnostic yield in subepithelial lesions of approximately 60%. Endoscopic mucosal resection has high diagnostic yield (87%) with standard forcep bite-on-bite biopsies having the lowest yield (38%). Performing five FNA passes and having an on-site cytologist present may increase yield of EUS-FNA. It is unclear whether performing Trucut biopsy using larger cutting needles to obtain larger tissue samples increases diagnostic yield.

#### **23. How does EUS compare with endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), and abdominal ultrasound for detection of choledocholithiasis?**

ERCP, MRCP, and EUS have comparable sensitivity and specificity for choledocholithiasis (85%-95%, 92%-98%, respectively). Although the overall accuracy of EUS is comparable to MRCP for choledocholithiasis, EUS is superior for stones smaller than 5 mm and intraspincteric stones. All are superior to abdominal ultrasound, which has poor sensitivity of 20% to 55% and 83% specificity.

#### **24. What is the role of EUS in suspected choledocholithiasis?**

See Figure 71-8. This depends on the probability of choledocholithiasis being present based on clinical and imaging findings. In patients with high probability of choledocholithiasis (total bilirubin >4 mg/dL or common bile duct (CBD) stone seen on radiologic imaging, or both dilated CBD with bilirubin 1.8-4 mg/dL), ERCP should be performed without further testing, whereas patients with low probability of stones may be managed conservatively. EUS is indicated in patients with intermediate probability of choledocholithiasis (abnormal liver function tests other than bilirubin, clinical gallstone pancreatitis, age >55 years).



**Figure 71-7.** Endoscopic ultrasound of subepithelial lesions. **A**, Gastrointestinal stromal tumor. **B**, Lipoma. **C**, Carcinoid. **D**, Pancreatic rest.



**Figure 71-8.** Endoscopic ultrasound of choledocholithiasis (hyperechoic with shadowing).

**25. Discuss the accuracy of EUS imaging and cytologic examination in diagnosing pancreatic cystic lesions.**

EUS imaging differentiates mucinous from nonmucinous cysts with 50% accuracy. Sensitivity of EUS-FNA cytologic examination for distinguishing mucinous from nonmucinous cysts is less than 50%.

**26. How do cyst fluid carcinoembryonic antigen and amylase help differentiate among the common pancreatic cystic lesions?**

See Table 71-4.

**Table 71-4.** Levels of CEA and Amylase in Pancreatic Cystic Lesions

TYPE OF CYST	CEA	AMYLASE
Pseudocyst	↓ (<192 ng/mL)	↑ (>250 U/L)
Serous cystadenoma	↓	↓
Mucinous cystic neoplasm	↑	↓
Intraductal papillary mucinous neoplasm	↑	↑

CEA, Carcinoembryonic antigen.

## 27. What are the standard nine EUS criteria for CP?

See Box 71-1 and Figure 71-9.

### Box 71-1. Standard EUS Criteria for CP

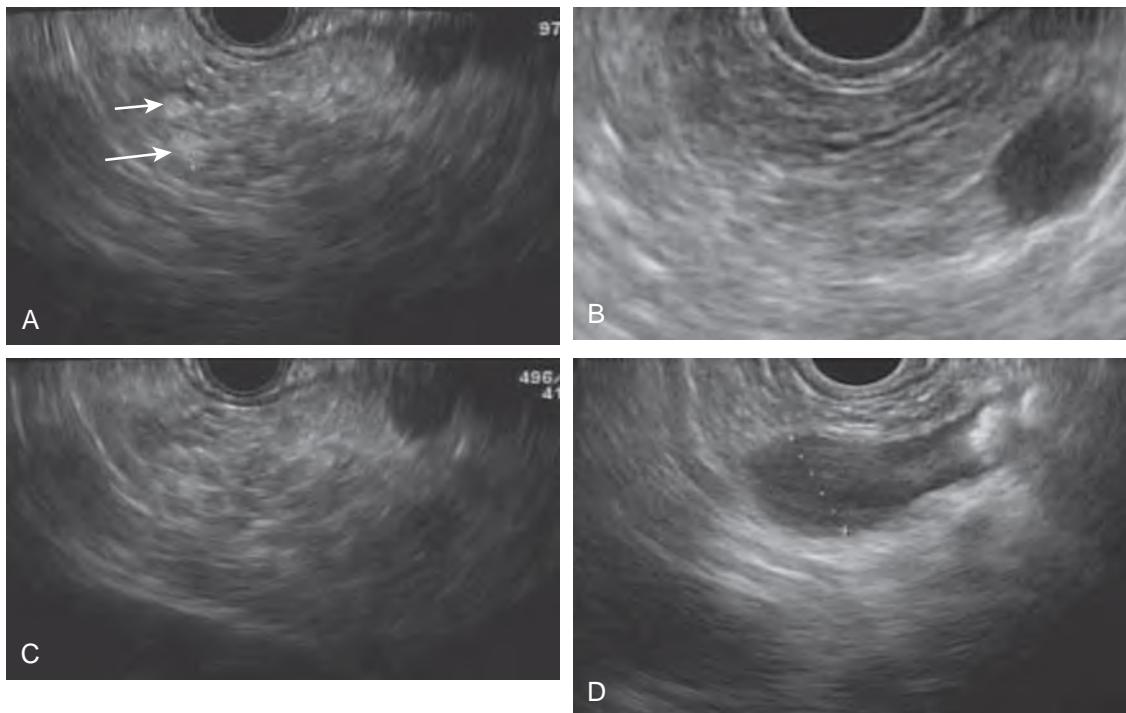
#### Parenchymal criteria

- Hyperechoic foci: small distinct reflectors
- Hyperechoic strands: small, stringlike hyperechoic structures
- Lobularity: containing lobules—rounded homogeneous areas separated by strands of another echogenicity
- Cysts: abnormal anechoic round or oval structure
- Calcifications: hyperechoic lesion with acoustic shadowing

#### Ductal criteria

- Main pancreatic duct dilation: >3.5 mm in body or >1.5 mm in tail
- Dilated side branches: at least three anechoic structures, >1 mm in width communicating with main pancreatic duct
- Irregular pancreatic duct: uneven outline of duct
- Hyperechoic duct wall: at least 50% of length of main pancreatic duct in body and tail with hyperechoic wall

Adapted from The International Working Group for Minimal Standard Terminology in Gastrointestinal Endoscopy. Minimal standard terminology in gastrointestinal endosonography. *Dig Endosc* 1998;10:159–184; and Catalano MF et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. *Gastrointest Endosc* 2009;69:1251–1261.



**Figure 71-9.** Endoscopic ultrasound findings in chronic pancreatitis. **A**, Hyperechoic foci. **B**, Hyperechoic strands, irregular pancreatic duct, hyperechoic duct wall. **C**, Lobularity. **D**, Parenchymal calcifications.

## 28. What is the accuracy of EUS for diagnosing CP?

When using the standard EUS criteria for CP, the diagnosis of CP depends on the presence of varying numbers of EUS criteria. Increasing the threshold improves the specificity of EUS while sacrificing sensitivity. The presence of at least five EUS criteria is commonly used to diagnose CP, which yields sensitivity and specificity of 76% and 91%, respectively.

## 29. What are the limitations of EUS in diagnosing CP?

Interobserver agreement for the diagnosis of CP is moderate with kappa of 0.45; for the individual EUS features of CP, there is poor to moderate agreement, with the highest agreement for ductal dilation and lobularity.

Determination of whether EUS findings are pathologic or represent asymptomatic fibrosis, normal age-related changes, or normal variant is not possible. Asymptomatic EUS changes of CP have been reported in alcoholics, patients of advanced age, and patients who smoke without clinical CP.

## 30. How is EUS helpful in idiopathic recurrent pancreatitis?

EUS can provide an etiologic factor for 40% to 80% of idiopathic recurrent pancreatitis cases with negative abdominal ultrasound and CT scan. More than 60% of the EUS findings are biliary pathologic conditions (microlithiasis, sludge, or stone).

*The author would like to acknowledge the contributions of Dr. Peter McNally, who was the author of this chapter in the previous edition.*

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

## BIBLIOGRAPHY

1. Caletti G, Fusaroli P. The rediscovery of endoscopic ultrasound (EUS) in gastric cancer staging. *Endoscopy* 2012;44:553–5.
2. Cantor MJ, Davila R, Faigel DO. Yield of tissue sampling for subepithelial lesions evaluated by EUS: a comparison between forceps biopsies and endoscopic submucosal resection. *Gastrointest Endosc* 2006;64:29–34.
3. Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. *Gastrointest Endosc* 2009;69:1251–61.
4. Fernandez-Esparrach G, Ayuso-Colella JR, Sendino O, et al. EUS and magnetic resonance imaging in the staging of rectal cancer: a prospective and comparative study. *Gastrointest Endosc* 2011;74:347–54.
5. Gleeson FC, Clain JE, Papachristou GI, et al. Prospective assessment of EUS criteria for lymphadenopathy associated with rectal cancer. *Gastrointest Endosc* 2009;69:896–903.
6. Gleeson FC, Topazian M. Endoscopic retrograde cholangiopancreatography and endoscopic ultrasound for diagnosis of chronic pancreatitis. *Curr Gastroenterol Rep* 2007;9:123–9.
7. Horwitz JD, Paulson EK, McGrath K, et al. A randomized comparison of EUS-guided FNA versus CT or US-guided FNA for the evaluation of pancreatic mass lesions. *Gastrointest Endosc* 2006;63:966–75.
8. Hwang SW, Lee DH, Lee SH, Park YS, Hwang JH, Kim JW, et al. Preoperative staging of gastric cancer by endoscopic ultrasonography and multidetector-row computed tomography. *J Gastroenterol Hepatol* 2010;25:512–8.
9. Karakan T, Cindoruk M, Alagozlu H, et al. EUS versus endoscopic retrograde cholangiography for patients with intermediate probability of bile duct stones: a prospective randomized trial. *Gastrointest Endosc* 2009;69:244–52.
10. Lee LS. Diagnosis of pancreatic neuroendocrine tumors and role of endoscopic ultrasound. *Gastroenterol Hepatol* 2010;6:520–2.
11. Lee LS. Endoscopic ultrasound. In: Greenberger N, editor. *Current diagnosis and treatment in gastroenterology*. New York: McGraw-Hill; 2011. p. 416–30.
12. Lee LS, Clancy T, Kadiyala V, Suleiman S, Conwell DL. Interdisciplinary management of cystic neoplasms of the pancreas. *Gastroenterol Res Pract* 2012;2012:513163. <http://dx.doi.org/10.1155/2012/513163>.
13. Lee LS, Conwell DL. Updates on advanced endoscopic techniques for the pancreas: ERCP, drainage and biopsy, and endoscopic ultrasound. *Radiol Clin N Am* 2012;50:547–61.
14. Maker AV, Lee LS, Raut CP, et al. Cytology from pancreatic cysts has marginal utility in surgical decision-making. *Ann Surg Oncol* 2008;15:3187–92.
15. Maple JT, Ikenberry SO, Anderson MA, et al. The role of endoscopy in the management of choledocholithiasis. *Gastrointest Endosc* 2011;74:731–44.
16. Moon JS. Endoscopic ultrasound-guided fine needle aspiration in submucosal lesion. *Clin Endosc* 2012;45:117–23.
17. National Cancer Institute. Stage information for esophageal cancer. <http://www.cancer.gov/cancertopics/pdq/treatment/esophageal/HealthProfessional/page3> [Accessed September 22, 2014].
18. Petrone MC, Arcidiacono PG, Testoni PA. Endoscopic ultrasonography for evaluating patients with recurrent pancreatitis. *World J Gastroenterol* 2008;14:1016–22.
19. Pfau PR, Perlman SB, Stanko P, et al. The role and clinical value of EUS in a multimodality esophageal carcinoma staging program with CT and positron emission tomography. *Gastrointest Endosc* 2007;65:377–84.
20. Ribeiro A, Franceschi D, Parra J, et al. Endoscopic ultrasound restaging after neoadjuvant chemotherapy in esophageal cancer. *Am J Gastroenterol* 2006;101:1216–21.

21. Shimpi RA, George J, Jowell P, Gress FG. Staging of esophageal cancer by EUS: staging accuracy revisited. *Gastrointest Endosc* 2007;66:475–82.
22. Soriano A, Castellis A, Ayuso C, et al. Preoperative staging and tumor resectability assessment of pancreatic cancer: prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography. *Am J Gastroenterol* 2004;99:492–501.

**Website**

Krinsky ML, Binmoeller K. Endoscopic ultrasound for the characterization of subepithelial lesions of the upper gastrointestinal tract. UpToDate. <http://www.uptodate.com/contents/endoscopic-ultrasound-for-the-characterization-of-subepithelial-lesions-of-the-upper-gastrointestinal-tract> [Accessed September 22, 2014].

# ADVANCED THERAPEUTIC ENDOSCOPY

Daphne Antillon, MPH, and Mainor Antillon, MD, MBA, MPH

## 1. What is advanced therapeutic endoscopy?

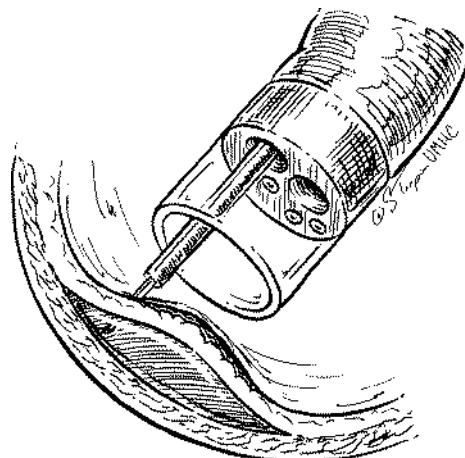
Advanced therapeutic endoscopy is a group of techniques that are minimally invasive and organ sparing, and yet can diagnose, remove, and treat benign lesions and early malignancies of the gastrointestinal (GI) tract without need of traditional surgery using endoscopy.

## 2. What are the major advanced therapeutic endoscopy techniques?

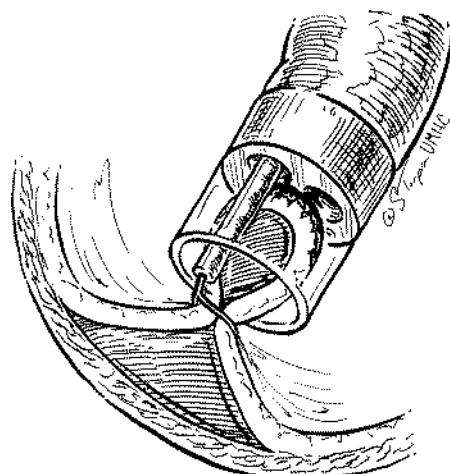
A. Endoscopic mucosal resection (EMR) can remove mucosal lesions of the GI tract en bloc that are less than 2 cm (or piecemeal if larger than 2 cm). The EMR technique may employ the use of a cap at the tip of the scope and suction to retract the lesion into the cap and subsequent removal by electrocautery snare or submucosal injections with various solutions (Table 72-1) to raise the lesions to provide fluid cushion for safe dissection (Figure 72-1 and Figure 72-2).

**Table 72-1.** Submucosa Injection Solutions

SOLUTION	CUSHION DURABILITY	COMMENTS
Normal saline	Short	Easy to inject, cheap, dissipates quickly
Hypertonic saline 3%	Moderate	Easy to inject, cheap, tissue damage
Hydroxypropyl methylcellulose 0.83%-1.25%	Extended	Long lasting, relatively cheap, safe and effective, may cause tissue damage
Hyaluronic acid 1%	Extended	Long lasting, expensive, safe and effective, special storage
Dextrose 50%	Moderate	Easy to inject, cheap, tissue damage
Albumin 25%	Moderate	Easy to inject, expensive, safe

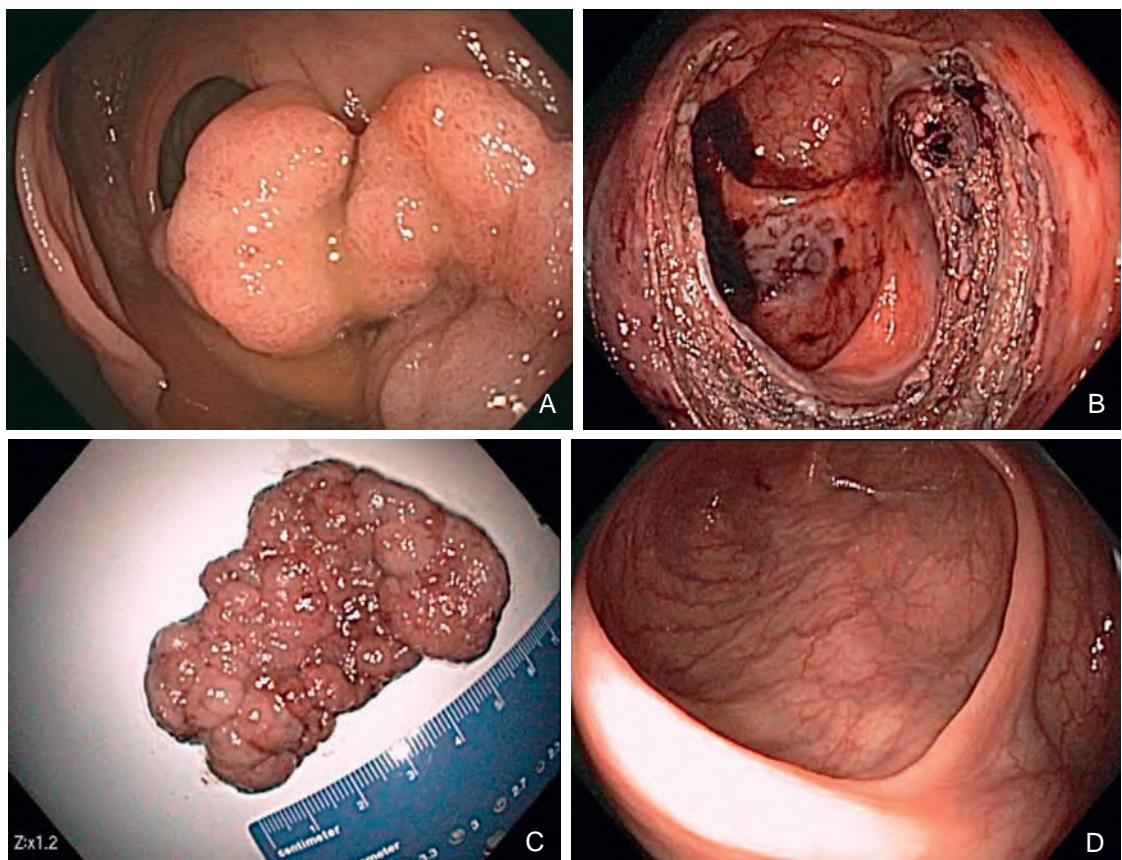


**Figure 72-1.** Endoscopic mucosal resection cap with submucosal injection.

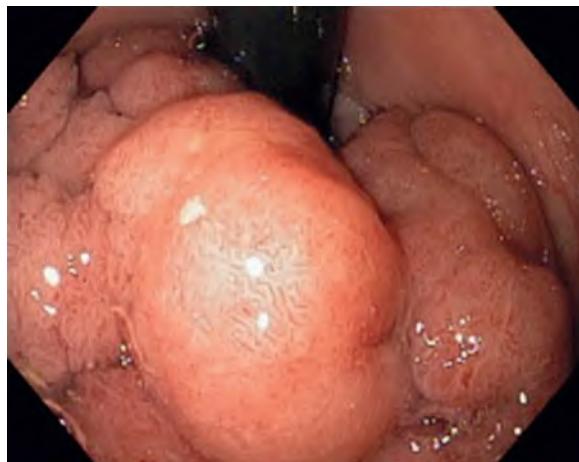


**Figure 72-2.** Endoscopic mucosal resection technique to remove lesion with snare.

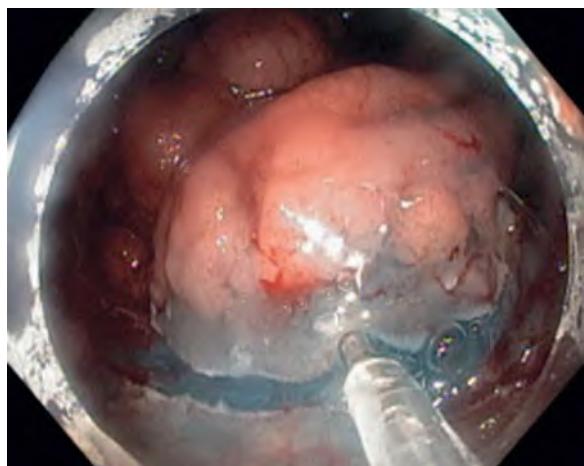
- B. Endoscopic submucosal dissection (ESD) can remove mucosal lesions en bloc that are larger than 2 cm, that are flat, or that are in the deeper layers (submucosa) of the GI tract and cannot be removed by other endoscopic methods. It uses an electrocautery needle knife with high cutting power to make a circumferential cut around the lesion and dissect the base of the lesion through the deeper submucosal layer. Submucosal injections are used to provide fluid cushion for dissection. Adding dye (indigo carmine or methylene blue) to injection solutions helps to identify the submucosal layer to determine margins of dissection ([E-Figure 72-3](#), [E-Figure 72-4](#), and [E-Figure 72-5](#)). An example of the ESD technique to remove a large sessile mass in the cecum is demonstrated in [Figure 72-6](#).



**Figure 72-6.** A, Endoscopic view of a large polypoid mass in the colon. B, Endoscopic view after endoscopic submucosal dissection (ESD) of this large polypoid colon mass. C, Gross anatomic specimen of the polypoid colon mass removed by ESD. D, Endoscopic appearance of the ESD site after healing.



**E-Figure 72-3.** Giant 14-cm rectal mass planned for endoscopic submucosal dissection. (From Antillon MR, Bartalos CR, Miller ML, et al. En bloc endoscopic submucosal dissection of a 14-cm laterally spreading adenoma of the rectum with involvement to the anal canal: expanding the frontiers of endoscopic surgery (with video). *Gastrointest Endosc*. 2008 Feb;67(2):332-7.



**E-Figure 72-4.** Dissection of mass with needle knife during endoscopic submucosal dissection. (From Antillon MR, Bartalos CR, Miller ML, et al. *En bloc endoscopic submucosal dissection of a 14-cm laterally spreading adenoma of the rectum with involvement to the anal canal: expanding the frontiers of endoscopic surgery (with video)*. Gastrointest Endosc. 2008 Feb;67(2):332-7.)

**E-Figure 72-5.** Mass removed en bloc by endoscopic submucosal dissection. (From Antillon MR, Bartalos CR, Miller ML, et al. En bloc endoscopic submucosal dissection of a 14-cm laterally spreading adenoma of the rectum with involvement to the anal canal: expanding the frontiers of endoscopic surgery (with video). Gastrointest Endosc. 2008 Feb;67(2):332-7.)



C. Advanced endoscopic ultrasound (EUS) is used to diagnose and treat lesions within the GI tract and in close proximity to the GI tract by making use of ultrasound for guidance. Some indications for advanced EUS include sampling of suspected malignant lesions or lymph nodes with EUS-guided fine-needle aspiration (FNA), drainage of pancreatic or peripancreatic fluid collections, such as pancreatic pseudocysts. With EUS-guided fine-needle injection (FNI) celiac plexus neurolysis (CPN) (block for pain control) for pancreatic cancer or chronic pancreatitis can be performed. Other applications of EUS-FNI include botulinum injection for achalasia, and EUS-FNI of antitumor agents for locally advanced pancreatic cancer.

### 3. What are the applications of EMR and ESD?

These techniques provide definite therapy for benign lesions, premalignant lesions, and early malignancies (Tis and T1N0M0). EUS and Kudo's mucosal pit pattern analysis may be used to assess the tumor-node-metastasis (TNM) staging and invasiveness and removability of the lesion. Lesions in the mucosa, lesions with minimal submucosal invasion up to 1000 µm with tumor-free margins, and lesions that are well differentiated and moderately without lymphovascular involvement can be considered cured. The rationale for EMR and ESD in early malignancy is that there is very low probability for lymph node involvement in Tis and T1 stage (Table 72-2). Furthermore, when accessible, EUS can determine the status of Tis and T1 with 91% to 94% accuracy. A few examples include adenocarcinoma of the esophagus and colon, flat polyps, gastric nodules, and duodenal adenomas.

**Table 72-2.** Stage of Cancer and Lymph Node Involvement Status

STAGE	N	%N1
Tis	29	0%
T1mucosal	38	2.6%
T1submucosal	27	22.2%
T2	37	42.3%
T3	219	77.2%

Rice TW, Zuccaro G Jr, Adelstein DJ, et al. Esophageal carcinoma: depth of tumor invasion is predictive of regional lymph node status. Ann Thorac Surg 1998; 65: 787-92.

### 4. How is EMR performed?

Various commercially available EMR kits can be used. The EMR cap is made of clear plastic that can be soft or hard and straight or oblique in various sizes up to 18 mm. Larger caps are soft to allow easier passage into the GI tract. The oblique caps are helpful in the esophagus and straight caps are helpful in the stomach. The target lesion is raised with submucosal injection to form a cushion. An EMR cap of desired size is affixed to the tip of the endoscope. The electrocautery snare is opened and positioned on the distal internal circumferential ridge of the cap. The scope is advanced and placed over the lesion. Suction is applied to retract the lesion into the cap. Once the lesion is well positioned in the cap, the snare is closed and the lesion is captured with the snare. The suction is released. The lesion is then resected like a polyp. The lesion can be retrieved in the cap using suction. In addition to the previously discussed EMR cap technique, there are several variations on EMR techniques, such as "inject, lift, and cut," and a newer banding device for mucosectomy can be used. (See the website at the end of the chapter for a link about how to perform EMR.)

### 5. How is ESD performed?

The lesion is located and raised with submucosal injections. The borders of the lesion are defined using narrow band imaging or adding a dye to the surface of the lesion (chromoendoscopy). The needle knife is passed through the instrument channel of the scope and a circumferential submucosal cut is first made using fine movements and maneuvers. Subsequently the base of the lesion is dissected with multiple cuts. Multiple submucosal injections are needed as the submucosal cushion tends to dissipate with time. One modified needle knife (ERBE Hybrid knife) allows injection and cutting using the same needle. Once the lesion is freed from the base, it can be retrieved with a Roth net or a spider net. The specimen is immediately mounted on polystyrene foam with pins and oriented for pathologic examination. In addition to the previously discussed technique, there are other variations to the ESD such as magnetic anchor-guided ESD. (See the website at the end of the chapter for a link about how to perform ESD.)

### 6. What are the differences and limitations of the EMR and ESD?

The EMR is limited by the largest suction cap size of 18 mm to accommodate the narrow passages in the GI tract. This can be overcome by ESD. EMR and ESD cannot be performed in areas such as the distal small bowel that are not accessible by traditional endoscopes. These procedures are technically difficult, time consuming, and labor intensive, and specialized training is needed.

## 7. What are the complications of EMR and ESD?

The major complications include bleeding (average 10% in various series) and perforation (4% to 10% for ESD) and (0.3% to 0.5% rate for EMR). Table 72-3 lists gastric ESD complications. Most bleeding can be handled endoscopically using coagulation graspers and endoscopic clips without surgery. Most perforations can be handled endoscopically using endoscopic clips and loops without surgery. Box 72-1 describes nonsurgical treatment of ESD perforations. In certain instances, especially when the perforation is large, surgical repair is needed. In our own series for colorectal ESD using the new modified needle knives, bleeding rate was 1.8% and perforation rate was 1.8% ( $n=220$ ). Other complications include stricture (esophageal or pyloric) and infections.

## 8. What are some investigational applications of EMR and ESD?

These techniques used in combination with EUS aid in accessing lesions outside of the GI tract such as mediastinal lymph nodes and intraabdominal organs such as the gall bladder. Once the technique to create and then close an endoscopic transluminal opening (perforation) is mastered.

Therefore EMR and ESD facilitate the development of other techniques such as natural orifice transluminal endoscopic surgery and mediastinoscopy. Full-thickness endoscopic resection has been performed using modified needle knives for the therapy of gastrointestinal stromal tumors (GISTs). Results from our series are demonstrated in Video 72-1. (Please access ExpertConsult to view the Video.)



## 9. What are some investigational applications of advanced EUS?

- EUS-guided pancreatic necrosectomy and drains with large-bore plastic or metal stents
- EUS-guided antitumor therapy
- EUS-guided nonpapillary pancreatic and bile duct drainage

## 10. What is the role of EUS-guided FNA biopsy in tissue sampling and sampling of nodes?

EUS-FNA has been shown to aid in the diagnosis of primary lesions within or close to the GI tract such as rectal, esophageal, pancreatic, and lung cancers. The EUS-FNA of lymph nodes has overall sensitivity of 84%, specificity of 92%, positive predictive value of 88%, and negative predictive value of 89%. The sensitivity and specificity vary with the type and location of lesion being evaluated. The sensitivity and specificity of EUS-FNA is higher for lesions such as pancreatic neuroendocrine tumors and pancreatic cancer, and lower for submucosal lesions such as GISTs. The main utility of EUS-FNA is in nodal staging of these lesions, allowing not only imaging of lymph nodes but also providing samples of these nodes (Figure 72-7).

**Table 72-3. Gastric ESD Complications**

STUDY AUTHOR	N	LESION SIZE MM	ENBLOC RATE %	BLEED %	PERFORATION %
Kakushima	334	3-85	95	3.4	3.9
Imagawa	185	5-70	84	0	6.1
Onozato	160	24	94	7.6	0
Imaeda	25	10-25	100	0	0
Yonezawa	20	18	95	2.5	2.5
Neuhaus	10	20-45	100	0	20

ESD, Endoscopic submucosal dissection.

*Endoscopic Dissection. Endoscopy. 2006;38 (10):980-1028 (entire issue).*

## Box 72-1. Nonsurgical Treatment of ESD Perforations

27 perforations in 528 resections (5.1%)

Various regions: esophagus: 4, gastric: 14, colon: 9

Nonsurgical methods: clips in most, NG tube, IV antibiotics, and pneumoperitoneum relieved by 18-gauge needle

Mean antibiotic duration 6.7 days

Mean NPO period of 5.3 days

Mean admission time 12.1 days after ESD

Median follow-up duration for no sequels or tumor spread for 36 months

ESD, Endoscopic submucosal dissection; IV, intravenous; NG, nasogastric; NPO, nothing by mouth.

Rice TW, Zuccaro G Jr, Adelstein DJ, Rybicki LA, Blackstone EH, Goldblum JR. Esophageal carcinoma: depth of tumor invasion is predictive of regional lymph node status. *Ann Thorac Surg* 1998; 65: 787-92.



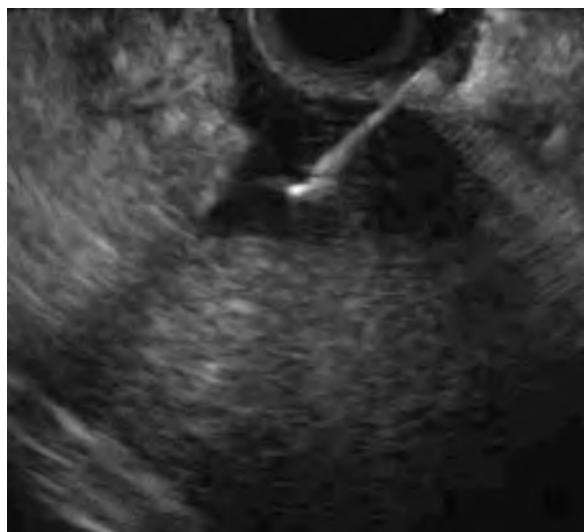
**Figure 72-7.** Endoscopic ultrasound–guided fine-needle aspiration of a lymph node.

### 11. How is EUS-FNA performed?

EUS is performed with a linear array scope, which provides an image along the long axis of the scope. This allows the endoscopist to visualize the exact position and action of the needle in sonographic real time. The flow and Doppler capability of this instrument allow for visualization of vascular structures that need to be avoided to perform a safe tissue sampling. The 19- to 24-gauge aspiration needle, with a stylet, is introduced through the scope channel and under direct ultrasound visualization is advanced into the area to be sampled. Once the lesion has been entered, the stylet is advanced to the original position to clear any nonlesional tissue possibly adherent from the passage of the needle through the GI tract. Suction is then applied with a syringe to the proximal end of the needle. Sometimes several passes are performed to ensure that enough material is obtained.

### 12. What are the advantages of EUS-FNA over other sampling modalities?

EUS-FNA allows definitive cytologic diagnosis of both primary and metastatic lesions and thus permits staging of the primary tumor, regional lymph nodes, and metastatic lesions (the TNM system). Patients undergoing evaluation of a suspected GI wall malignancy often require an EUS examination to obtain tumor staging information (depth of penetration of lesion through the GI wall) of the lesion. Nodal (N) staging with tissue acquisition can be performed in the same setting. EUS-FNA can also be useful in determining the presence of distal metastasis (M) such as to the liver. In addition, EUS-FNA allows the sampling of extremely small lesions, including pleural and ascitic fluid collections that cannot be obtained by other means (such as computed tomography [CT]–guided biopsy). In general, EUS staging accuracy appears to be better than all modalities except surgical exploration (Figure 72-8).



**Figure 72-8.** Endoscopic ultrasound–guided fine-needle aspiration of malignant ascites (not seen on computed tomography scan).

### 13. What is the sensitivity and specificity of EUS-FNA for the diagnosis of malignancy?

The sensitivity and specificity of EUS-FNA for diagnosis of malignancy depends on the type of tissue being sampled (Table 72-4 and E-Figure 72-9).



**E-Figure 72-9.** Endoscopic ultrasound-guided fine-needle aspiration of neuroendocrine tumor in the tail of the pancreas.

**Table 72-4.** Sensitivity and Specificity of EUS-FNA

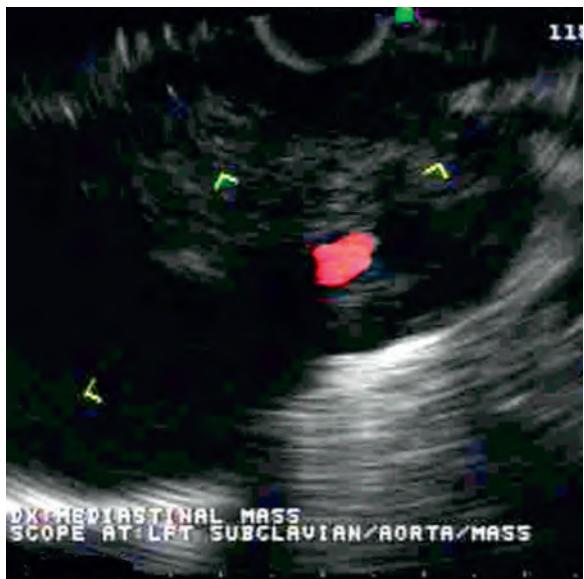
TISSUE	SENSITIVITY	SPECIFICITY
Pancreatic cancer	90%-95%	90%-100%
Mediastinal lymphadenopathy	88%	90%-100%
Periintestinal lymphadenopathy	70%-90%	93%-100%
Mucosal and submucosal lesions	50%-90%	80%-100%

EUS, Endoscopic ultrasound; FNA, fine-needle aspiration.

#### 14. What is the role of EUS-FNA in the evaluation of mediastinal lymphadenopathy?

EUS with FNA is the diagnostic test of choice for evaluating mediastinal lymphadenopathy. It has been found to be particularly useful in patients who have non–small cell lung cancer (NSCLC). In patients with NSCLC, the most significant predictor of long-term survival is the presence of metastasis within regional bronchopulmonary or mediastinal lymph nodes. In a large metaanalysis, EUS-FNA sensitivity in mediastinal nodes was 88% (95% CI: 85.8%-90%), and specificity was 96.4% (95% CI: 95.3%-97.4%). EUS-FNA is safer and more cost-effective than other more invasive methods of sampling, such as mediastinoscopy or thoracotomy (Figure 72-10).

**Figure 72-10.** Mediastinal mass invading the left subclavian artery.



#### 15. What are the risks of EUS-FNA?

The risks of EUS-FNA are thought to be extremely low, given the small diameter of the aspiration needle. In addition to the usual risks of any endoscopic procedure (bleeding, perforation, sedation risk) a 0.5% overall complication rate was reported in a multicenter trial predominantly from infectious or hemorrhagic events. EUS-FNA of the pancreas has a very small risk of acute pancreatitis, probably less than 1%.

#### 16. What is the role of EUS in sampling pancreatic cystic neoplasms?

EUS with FNA can be used to obtain diagnosis in the case of suspected cystic neoplasms. Additional analysis of aspirated fluid can also be of value, such as a mucin stain (positive in intraductal papillary mucinous tumor, mucinous cystadenoma, and mucinous cystadenocarcinoma), determination of amylase level (suggestive of a pseudocyst), and carcinoembryonic antigen (CEA) level (a high CEA level suggests the presence of mucinous cystadenoma with malignant potential, but a normal CEA level suggests the presence of a serous cystadenoma or pseudocyst with no malignant potential) (Figure 72-11).

#### 17. Is there a risk of biopsy tract seeding when EUS-FNA of a suspected malignancy is sampled?

Yes, although the amount of risk has been found to be very low. Comparative studies have found that there is less risk of seeding with EUS-FNA when compared with percutaneous CT-guided FNA biopsy.

#### 18. How is EUS-guided transmural pseudocyst drainage performed?

Transmural EUS guided pseudocyst drainage can be performed by a multistep or single-step procedure. The multistep procedure involves EUS localization of the pseudocyst, followed by transmural drainage using a



**Figure 72-11.** Septated cystic mass in the pancreas: biopsy.

side-viewing endoscope (duodenoscope). Presence of gastric or duodenal varices and lack of bulging of the stomach or duodenum produced by the pseudocyst are contraindications to using a duodenoscope for transmural drainage.

The single-step procedure allows the endoscopist to achieve drainage of the pseudocyst with a single linear array EUS scope. This technique allows continued EUS imaging during the whole procedure. Presence of varices or the lack of a bulge does not preclude the performance of transmural drainage with this technique. The placement of large-bore endoprostheses (10 Fr double pigtail stents) requires the use of a therapeutic EUS scope. After the needle pathway is found to be safe (flow or Doppler interrogation), a 19-gauge FNA needle is advanced into the pseudocyst and cyst fluid is aspirated. A 0.035-inch guidewire is subsequently introduced through the needle into the pseudocyst cavity. Fluoroscopy can be used for guidance. After the guidewire is coiled into the cyst, the FNA needle is removed, leaving the guidewire in place. Opening of the gut-cyst wall is performed by cutting with the needle knife, which is subsequently removed, leaving the guidewire in place. Dilatation of the gut-cyst opening is performed using a 10-mm biliary balloon dilator over the guidewire. Dilatation is followed by the placement of the first 10 Fr 2- to 3-cm double pigtail stent into the cyst. The original guidewire is removed from the cyst. Placement of the second 10 Fr 2- to 3-cm double pigtail stent is performed over the wire after recannulation of the opening next to the first stent with the sphincterotomy.

**Single-Step EUS-Guided Pseudocyst Drainage** See [Figure 72-12](#), [Figure 72-13](#), [Figure 72-14](#), [E-Figure 72-15](#), [E-Figure 72-16](#), and [Figure 72-17](#).



**Figure 72-12.** Bulge in gastric wall from pseudocyst seen endoscopically (bulge visualization is not necessary for single-step endoscopic ultrasound-guided pseudocyst drainage).

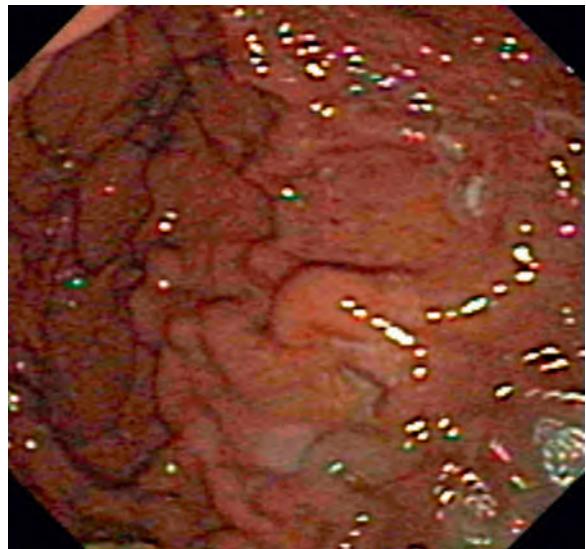
**E-Figure 72-15.** Transgastric placement of wire into cyst cavity.





**E-Figure 72-16.** Fluoroscopic view of wire in cyst cavity and dilation of tract.

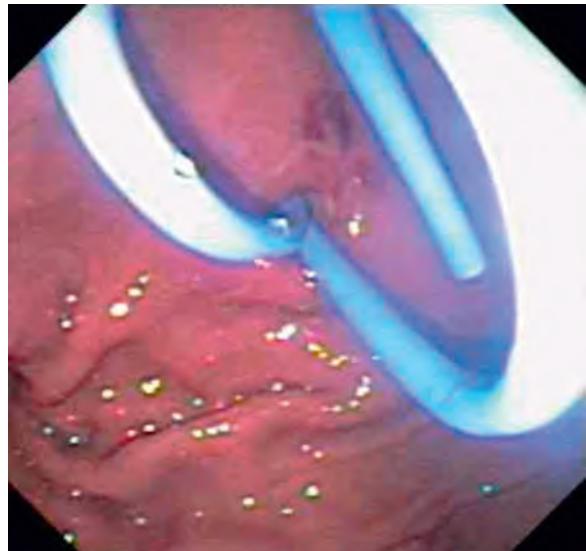
**Figure 72-13.** No bulge, but endoscopic presence of gastric varices in a patient with pseudocyst. Endoscopic ultrasound-guided pseudocyst drainage can still safely be performed.



**Figure 72-14.** Visualization of pseudocyst with endoscopic ultrasound.



**Figure 72-17.** Final view of drainage stents.



**19. What are the indications for EUS-guided celiac plexus block (CPB) and CPN? What is the difference? Why do they work?**

The celiac plexus transmits pain sensations from the pancreas and most of the abdominal organs. As a result, blockage of this transmission has been found to be effective in the therapy of pain. CPB refers to the use of steroid or local anesthetics to temporarily inhibit celiac plexus function in patients with uncontrolled pain secondary to chronic pancreatitis. CPN refers to the use of alcohol or phenol to produce neurolysis in patients with uncontrolled pain secondary to pancreatic cancer.

**20. How are EUS-guided CPB and neurolysis performed?**

The celiac trunk is easily identified with EUS, because it is located in close proximity to the posterior gastric wall. Because of its close proximity EUS-FNI is easily performed. A 22-gauge needle is advanced into the area and bupivacaine (an anesthetic) is injected to reduce discomfort. Next, alcohol (for pancreatic cancer) or steroids (for chronic pancreatitis) is injected to the plexus (Figure 72-18).



**Figure 72-18.** Celiac axis identified by endoscopic ultrasound.

**21. What is the success rate of CPN and CPB?**

The success rates of CPN and CPB differ. A CPN performed for pain from pancreatic cancer has a reported sustained response of 78% at 2 weeks with a sustained response for up to 24 weeks independent of narcotic use or adjuvant therapy. A CPB performed for pain secondary to chronic pancreatitis has a lower success rate.

**22. What are the potential complications of CPN?**

There is a 1% to 2% risk of major complications. Neurologic complications include lower extremity weakness, paresthesia, or paralysis. The artery of Adamkiewicz runs along the spine between T8 and L4, and perfuses the lower two thirds of the spinal cord. Spasm or thrombosis of this artery can lead to spinal cord ischemia. In addition, direct damage to the spinal cord or somatic nerves can cause neurologic deficits. Chronic gastroparesis or diarrhea may also occur. Bleeding, infection, and inadvertent organ puncture are also recognized complications.

**23. Is EUS-FNI cholangiography or pancreatography possible? When are they indicated?**

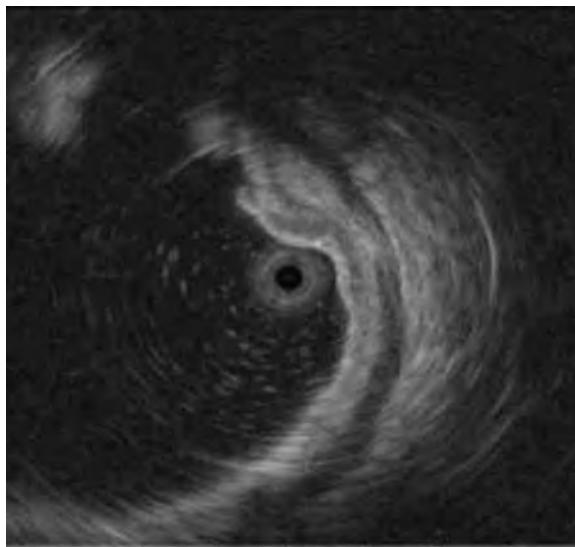
Yes. EUS-guided pancreatography and cholangiography can be easily achieved because of the ability of EUS to image the common bile duct and pancreatic duct. Injection of contrast into the ducts can be performed. These techniques are used when ERCP fails to gain access. This might be an issue in the case of tumor obstruction or surgically altered anatomy (Billroth II or gastrectomy with Roux-en-Y). EUS-guided transduodenal and transgastric placement of the stents into the pancreatic duct or biliary system is possible. This can be a viable alternative to percutaneous biliary drainage. EUS-guided pancreatic duct drainage has been performed via a transgastric route (pancreaticogastrostomy) to alleviate pain associated with chronic pancreatitis and ductal disruption and obstruction.

**24. What is high-frequency ultrasound probe sonography-assisted EMR?**

A high-frequency ultrasound probe uses a frequency of 20 or 30 mH, rather than 7.5- or 12-mH frequencies used in a conventional EUS transducer. The probe is introduced through the working channel of a standard therapeutic endoscope. The advantage of this probe is that it can be placed directly on a lesion with direct endoscopic guidance. This allows one to evaluate the depth of invasion of a mucosal lesion, whether in the esophagus, stomach, or colon, and determine whether it can be appropriately and safely removed by EMR after submucosal injection (Figure 72-19 and Figure 72-20).



**Figure 72-19.** Submucosal mass seen on endoscopy.



**Figure 72-20.** High-frequency ultrasound probe: Hyperechoic lesion arising from submucosa consistent with lipoma.

Please access ExpertConsult to view the Video and E-Figures for this chapter.

#### BIBLIOGRAPHY

1. Antillon MR, Bartalos CR, Miller ML, et al. En bloc endoscopic submucosal dissection of a 14-cm laterally spreading adenoma of the rectum with involvement to the anal canal: expanding the frontiers of endoscopic surgery (with video). *Gastrointest Endosc* 2008;67:332–7.
2. Antillon MR, Shah RJ, Stiegmann G, Chen YK. Single-step EUS-guided transmural drainage of simple and complicated pancreatic pseudocysts. *Gastrointest Endosc* 2006;63:797–803.
3. Burmester E, Niehaus J, Leineweber T, et al. EUS-cholangio-drainage of the bile duct: report of 4 cases. *Gastrointest Endosc* 2003;57(2):246–51.
4. Francois E, Kahaleh M, Giovannini M, Matos C, Deviere J. EUS-guided pancreaticogastrostomy. *Gastrointest Endosc* 2002;51(1):128–33.
5. Gotoda T, Oda I, Tamakawa K, et al. Prospective clinical trial of magnetic-anchor-guided endoscopic submucosal dissection for large early gastric cancer (with videos). *Gastrointest Endosc* 2009 Jan, 69(1):10–5.

6. Gunaratnam NT, Sarma AV, Norton ID, et al. A prospective study of EUS-guided celiac plexus neurolysis for pancreatic cancer pain. *Gastrointest Endosc* 2001;54(3):316–24.
7. Hawes RH, Fockens P. Endosonography. Philadelphia: Saunders Elsevier; 2006, p. 265–271.
8. Ho JM, Darcy SJ, Esselein VE, et al. Evolution of fine needle aspiration cytology in the accurate diagnosis of pancreatic neoplasms. *Am Surg* 2007;73:941–4.
9. Iwatate M, Ikumoto T, Sano Y, et al. Diagnosis of neoplastic and non-neoplastic lesions and prediction of submucosal invasion of early cancer during colonoscopy. *Rev Col Gastroenterol* 2011;26(1). [Accessed September 22, 2014]. [http://www.scielo.org.co/scielo.php?pid=S0120-99572011000100008&script=sci\\_arttext&tlang=en](http://www.scielo.org.co/scielo.php?pid=S0120-99572011000100008&script=sci_arttext&tlang=en).
10. Kantsevoy SV, Alder DG, Conway JD, et al. Endoscopic mucosal resection and endoscopic submucosal dissection. *Gastrointest Endosc* 2008;68:11–8.
11. Levy MJ, Topazian MD, Wiersema MJ, et al. Initial evaluation of the efficacy and safety of endoscopic ultrasound-guided direct Ganglia neurolysis and block. *Am J Gastroenterol* 2008;103:98–103.
12. Levy MJ, Wiersema MJ. EUS-guided celiac plexus neurolysis and celiac plexus block. *Gastrointest Endosc* 2003;57(7):923–30.
13. Naini BV, Apple SK, Presley M, et al. A correlation study on diagnostic endoscopic ultrasound-guided fine-needle aspiration of lymph nodes with histological and clinical diagnoses, the UCLA Medical Center experience. *Diagn Cytopathol* 2008;36:460–6.
14. Peng HQ, Greenwald BD, Tavora FR, et al. Evaluation of performance of EUS-FNA in preoperative lymph node staging of cancers of esophagus, lung, and pancreas. *Diagn Cytopathol* 2008;36:290–6.
15. Prasad P, Wittmann J, Pereira SP. Endoscopic ultrasound of the upper gastrointestinal tract and mediastinum: diagnosis and therapy. *Cardiovasc Intervent Radiol* 2006;29:947–57.
16. Puli SR, Batapati Krishna Reddy J, Bechtold ML, et al. Endoscopic ultrasound: its accuracy in evaluating mediastinal lymphadenopathy? A meta-analysis and systematic review. *World J Gastroenterol* 2008;21:3028–37.

**Website**

<http://www.youtube.com/watch?v=zVuTEpTjVf0>

# ESOPHAGEAL SURGERY

Theodore N. Pappas, MD, and Georgios Kokosis, MD

## ACHALASIA

### 1. Define achalasia. What are the classic findings of esophageal achalasia?

Achalasia is a primary motility disorder of the esophagus characterized by a loss of enteric neurons leading to absence of peristaltic waveform in the body and impaired relaxation of the lower esophageal sphincter (LES) in response to swallowing. The condition is relatively rare, occurring at an incidence of 0.5 to 1 per 100,000 of the population per year, yet it is the most commonly diagnosed primary esophageal motility disorder. Peak incidence is between 20 and 50 years of age, and it typically has an insidious onset.

### 2. What are the most common symptoms of achalasia?

The nonrelaxing LES causes a functional outflow obstruction to the lower esophagus, resulting in progressive dysphagia, regurgitation, weight loss, and chest pain.

### 3. What is pseudoachalasia? How is it diagnosed?

Pseudoachalasia, or secondary achalasia, is an esophageal motility disorder caused by a distal esophageal obstruction from an infiltrating tumor that may directly intrinsically or extrinsically compress the esophagus. Patients exhibit symptoms typical of achalasia, including dysphagia, regurgitation, chest pain, and weight loss. Conventional manometry, endoscopy, and radiologic examination cannot distinguish pseudoachalasia from achalasia. Endoscopy helps rule out the possibility of pseudoachalasia but cannot diagnose a mural or extramural tumor. When this is suspected, based on a history of substantial weight loss (more than 20 lb in 6 months), endoscopic ultrasonography or computed tomography is recommended. The main distinguishing feature is the complete reversal of pathologic motor phenomena following successful therapy of the underlying disorder.

### 4. What is vigorous achalasia?

Vigorous achalasia is a variant of achalasia in which the esophageal body responds to a swallow with normal or less often high-amplitude contractions that may be multiphasic, but as with classic achalasia, there are no progressive peristaltic waves. Patients with vigorous achalasia are usually younger and have chest pain as a prominent symptom. Additionally, in vigorous achalasia the LES pressure is higher and repetitive waves are more common than in classic achalasia. Most investigators believe that vigorous achalasia is an early form of the disease that presents in some patients.

### 5. What are the nonsurgical options for treatment of achalasia?

- Smooth muscle relaxants (nitrates, calcium channel blockers)
- Botulinum toxin
- Pneumatic dilatation of the LES

### 6. What are the basic components of laparoscopic Heller myotomy for achalasia?

Surgical treatment of achalasia consists of a longitudinal myotomy of the distal esophagus and gastroesophageal (GE) junction, first described by Ernest Heller in 1913. Most myotomies were performed through the chest before the advent of minimally invasive surgery. The transabdominal laparoscopic approach is currently the procedure of choice with good long-term results in 84% to 94% of patients.

Five trocars are placed in the upper abdomen in an arrangement similar to that of a laparoscopic antireflux operation. A myotomy roughly 6 to 8 cm in length is performed, 3 cm below the GE junction. The myotomy is carried down to the level of the mucosa. Intraoperative manometry is then used to confirm successful ablation of the pathologic high-pressure zone. A partial fundoplication is performed after the completion of the myotomy around a 52-Fr bougie. There is a general consensus that a complete 360-degree wrap may cause significant obstruction at the distal end of the esophagus and lead to worsening of esophageal function in patients with already impaired peristalsis. The Toupet fundoplication (partial posterior wrap) and Dor fundoplication (partial anterior wrap) are equally popular among surgeons. With the addition of a Dor antireflux wrap, the incidence of gastroesophageal reflux disease (GERD) decreases from 47.6% to 9.1%. A randomized trial compared Heller myotomy and Dor fundoplication with Heller myotomy and Nissen fundoplication; the recurrence rate in the Nissen group was significantly higher than the Dor group (15% vs. 2.8%, respectively) supporting the addition of Dor fundoplication to the Heller

myotomy as the preferred method to prevent GERD. Patients with mild to moderate reflux after addition of a potential fundoplication can be easily managed medically.

#### **7. How do long-term results of Heller myotomy compare with mechanical esophageal dilatation?**

On the basis of excellent results with laparoscopic Heller myotomy, it is largely considered the optimal treatment for severe symptoms of achalasia. Several large retrospective series have compared the two treatments and favor operative myotomy over pneumatic dilatation. With the introduction of the minimally invasive approach, the historical concerns about the morbidity associated with open surgical techniques have essentially disappeared and the morbidity and mortality of both surgical and nonsurgical options are now nearly identical. The long-term success and safety of laparoscopic myotomy have completed the shift in favor of surgery as the primary therapeutic option for patients with achalasia. *However, a recent randomized controlled trial that compared laparoscopic Heller myotomy (with Dor fundoplication added) with pneumatic dilatation revealed that the two techniques are equally effective in a 2-year follow up.*

#### **8. Describe the complications of Heller myotomy.**

The most common complication of a surgical myotomy is esophageal perforation, which is reported in 0% to 4.6% of patients. Previous pneumatic dilatation and botulinum toxin injection increase the technical difficulty in performing a myotomy and may increase the rate of perforation. Mucosal injuries detected during surgery may be repaired primarily. An unrecognized esophageal perforation may present as persistent fever, tachycardia, or left-sided pleural effusion. These patients require close observation and may need reoperation if conservative measures fail.

Early postoperative dysphagia results usually from an incomplete myotomy, whereas causes of late dysphagia also include healing of the myotomy or, more rarely, a reflux-induced peptic stricture. Incomplete myotomy responds usually to extension of the myotomy. However, in patients in whom the first myotomy was complete, a second myotomy is less likely to be successful and such patients may require esophageal resection.

#### **9. Summarize the treatment algorithm for patients with achalasia.**

In summary, the treatment options for achalasia are initially medical (nitrates, calcium channel blockers), botulinum toxin injection, and pneumatic dilation. Surgical treatment (laparoscopic Heller myotomy, with Dor fundoplication) is reserved for patients with severe symptoms.

Patients who are unwilling to undergo any procedure should be treated with medications. Botulinum toxin injection should be reserved for patients who are unable to tolerate surgery because of significant comorbidities, or patients whose clinical presentation is complicated, putting the diagnosis of achalasia in doubt.

Overall, younger patients may choose early surgical intervention to avoid the need for multiple pneumatic dilatations. The decision for either of these two approaches will eventually be based on the medical specialist's experience and the patient's preference. Peroral endoscopic myotomy has also been gaining popularity as a means of treating achalasia.

#### **10. What is the association between achalasia and esophageal cancer?**

Patients with achalasia are thought to be at *increased risk for the development of squamous cell carcinoma, with risk as high as 140-fold reported.* The risk is elevated because of food retention, chronic chemical irritation, and bacterial growth, as well as the associated esophagitis and Barrett's formation, the latter resulting in adenocarcinoma. Tumors develop at an age 10 years younger than in the general population and carry a worse prognosis because of late diagnosis. The effect of surgical treatment on the incidence of cancer is not known and surveillance endoscopy is recommended every 2 years.

## **ESOPHAGEAL CANCER**

#### **11. What is the incidence of esophageal cancer?**

Cancer of the esophagus accounts for 1% of all newly diagnosed cancers in the United States, and the incidence has continued to rise in the last 30 years. An estimated 13,000 new cases of carcinomas of the esophagus were diagnosed in men and 3500 new cases in women in 2009. Approximately 11,500 men and 3000 women will die from the disease. It is seven times more common in men than women and is the seventh leading cause of death from cancer among men. Whereas squamous cell carcinoma accounted for most cancers of the esophagus 40 years ago, adenocarcinoma now represents more than 70% of such tumors in the United States. This is primarily caused by the striking increase in incidence of adenocarcinoma among white men older than 60 years. The cause for the rising incidence and changing demographics is unknown, although part of the rise is due to the increasing incidence of Barrett's esophagus and resulting adenocarcinoma in the distal esophagus.

#### **12. What are the risk factors of esophageal cancer?**

Risk factors for squamous cell carcinoma include tobacco use and excessive alcohol consumption, which appear to have a synergistic effect in its pathogenesis. Additionally, N-nitroso food compounds, achalasia, caustic injury, low socioeconomic status, and prior thoracic irradiation have been associated with an increased risk of the

disease. Risk factors for the development of distal esophageal adenocarcinoma are less clear. The presence of Barrett's esophagus is associated with an increased risk of developing adenocarcinoma, and recently a population-based case-control study from Sweden has demonstrated that symptomatic chronic GE reflux is also a risk factor.

### **13. Describe the relationship of Barrett's esophagus to esophageal cancer.**

Barrett's columnar-lined esophagus is an acquired condition of the distal esophagus occurring in 10% to 15% of individuals with chronic GE reflux and in 6.8% of the general population. The incidence of adenocarcinoma increases nearly fortyfold in patients with Barrett's esophagus. It is *estimated that 5% of patients with Barrett's esophagus will eventually develop invasive cancer*, and patients with histologically proven Barrett's esophagus require lifelong surveillance with endoscopic four-quadrant biopsies every 2 cm (1 cm if known dysplasia) because of this risk. It is also important that two different pathologists review the slides to increase the yield of the histologic diagnosis per the American Gastroenterological Association 2011 guidelines. It is generally believed that disease progresses from Barrett's metaplasia to low-grade dysplasia to high-grade dysplasia (HGD) to adenocarcinoma.

### **14. Can Barrett's esophagus regress after antireflux therapy?**

Recent publications have suggested that curtailing reflux may decrease the tendency of GERD patients without Barrett's epithelium to develop Barrett's esophagus. In addition, reflux control may diminish the tendency toward dysplastic or malignant degeneration of existing Barrett's epithelium. That can be accomplished by either medical or surgical management, with the latter shown to be more effective. This effect is manifested by:

- Inducing actual regression of dysplastic to nondysplastic Barrett's epithelium
- Stabilizing the Barrett's epithelium in a nondysplastic state
- Allowing a return to normal squamous epithelium

The majority of regression occurs within 5 years after surgery.

### **15. Discuss the surgical management of patients with HGD.**

HGD is defined as the detection in the Barrett's epithelium of epithelial abnormalities that could equally be described as carcinoma in situ (markedly enlarged nuclei at the surface, pronounced pleomorphism and focal loss of nuclear polarity). Many large surgical series document that following esophageal resection, between 20% and 40% of patients with Barrett's esophagus who have severe dysplasia will be found to actually have invasive carcinoma in the specimen. Although this does not imply that the majority of the patients will have invasive carcinoma, the inability to reliably distinguish the two groups preoperatively means that every patient with HGD should be thought of as having a probable carcinoma. In addition, the likelihood of developing cancer in the first 3 to 5 years once severe dysplasia has been identified is 25% to 50%. This increases to 80% risk of adenocarcinoma development in 8 years. Therefore the finding of HGD is an extremely strong indication for surgical resection. Although there are recommendations for less invasive therapy modalities, as ablation (photodynamic therapy, cryotherapy, radiofrequency [RF] ablation) and endoscopic mucosal resection, the most definitive treatment is esophagectomy. The latter is challenged with increased morbidity and mortality rates. Recently minimally invasive approaches as vagal sparing esophagectomy have gained popularity for treatment of HGD to decrease the rates of morbidity and mortality associated with resection.

### **16. What are the surgical approaches to the patient with esophageal cancer?**

Surgery is the primary treatment modality for esophageal cancer. In the United States, esophageal resection is most commonly performed, using one of the following approaches:

- *Transhiatal esophagectomy* involves both a midline laparotomy and left cervical incision. The short gastric and left gastric arteries are ligated, whereas the right gastric artery and right gastroepiploic arcade are carefully preserved to allow a well vascularized gastric conduit to reach to the neck. The esophagus is resected through the abdominal and neck incisions. A cervical GE anastomosis is performed through the cervical incision. The main advantage of this approach is avoidance of a thoracic anastomosis because a cervical leak carries much less morbidity than for a thoracic leak.
- *Ivor-Lewis esophagectomy* requires a midline laparotomy and a right posterolateral thoracotomy. En bloc resection is performed from the hiatus to the apex of the chest just above the azygos vein. A GE anastomosis is performed in the right chest.
- *Multi-incision esophagectomy* is performed less often and requires a midline laparotomy, right thoracotomy, and cervical incision.
- *Left thoracoabdominal esophagectomy* involves one incision extended across the abdomen and posterolateral chest for en block resection of the GE junction.
- *Minimally invasive esophagectomy* involves right thoracoscopic esophageal and lymph node bearing tissue mobilization, laparoscopic mobilization of the stomach, and a high intrathoracic or cervical anastomosis. Regardless of the incision approach, the same operative procedure is performed, that is, esphagogastrectomy with regional lymph node resection. Although each approach has its proponents, transhiatal esophagectomy is

the most common procedure performed, with a decreased incidence of pulmonary complications, the reduced morbidity and mortality of an anastomotic leak, and no evidence that a radical lymphadenectomy benefits overall survival cited as the most compelling arguments.

#### **17. When is neoadjuvant therapy appropriate in the treatment of patients with esophageal carcinoma?**

At most institutions, neoadjuvant treatment is currently recommended for stage III esophageal cancer or greater. There are different modalities of neoadjuvant therapy for esophageal cancer treatment, including either radiation alone (dose used 50 Gy), chemotherapy alone (chemotherapeutic agents used are cisplatin, 5-fluorouracil, carboplatin, paclitaxel, etoposide, or epirubicin), or chemoradiation prior to surgery. Preoperative radiation alone was found to have no significant benefit compared with surgery alone. Clinical trials have shown that *neoadjuvant chemoradiation or chemoradiation were found to have statistically significant benefits for survival compared with surgery alone*. Chemotherapy versus chemoradiation have been compared in clinical trials but no statistical difference was shown. Potential advantages of neoadjuvant therapy include cancer down-staging, increased resectability, and reduction in micrometastasis. In addition, the chemotherapeutic agents used all possess radiosensitizing properties. However, more studies are needed to verify the effectiveness of this treatment strategy.

#### **18. Describe nonsurgical options for treatment of esophageal cancer.**

Nonsurgical options for treatment of esophageal cancer can be divided into interventions for palliation and those for cure. Precancerous lesions or superficial cancers confined to the mucosa without evidence of metastatic spread can be cured with local therapy. Appropriate candidates include patients with limited HGD and carcinoma in situ associated with Barrett's esophagus. In these cases, alternative therapies, such as endoscopic mucosal resection, endoscopically applied laser, photodynamic therapy, or argon plasma coagulation, are ablative therapies that have been curative in certain cases. When curative treatment is not possible, in addition to systemic chemotherapy, palliative care measures have included external beam radiation, endoluminal brachytherapy, endoluminal stenting, laser ablation, and photodynamic therapy.

#### **19. What is the survival of patients with esophageal cancer?**

The overall 5-year survival in patients with esophageal cancer is reported between 13% and 17%. Those patients with stage I disease have an excellent 5-year survival, approximately 80%. The 5-year survival for stage II and stage III disease is 20% to 30% and 10%, respectively. Those with stage IV disease live rarely beyond 18 months. Unfortunately, most esophageal cancers present at later stages with locally advanced disease or metastases, when cure is not possible and palliation is the only treatment option.

## **GASTROESOPHAGEAL REFLUX AND ESOPHAGEAL HERNIAS**

### **GASTROESOPHAGEAL REFLUX DISEASE**

#### **20. Define GERD.**

GERD is defined as symptoms or mucosal injury caused by the abnormal reflux of gastric contents into the esophagus. It involves typical symptoms (see Question 2 for definition of typical symptoms) occurring two or more times weekly, or symptoms perceived as problematic to patients, or resulting in complications. *One third of the U.S. population suffers from symptoms of GERD at least once monthly, 10% to 20% once weekly, and 4% to 7% daily.* Although there is a high prevalence of heartburn, not everyone with heartburn has GERD.

#### **21. Describe the typical and atypical symptoms of GERD.**

The typical symptoms of GERD include heartburn, regurgitation, or water brash (in which the oral cavity suddenly fills with fluid, usually clear and perhaps acidic) or dysphagia (the blockage to the passage of food in the lower substernal area). Classic heartburn is defined as the substernal burning "rising from the stomach or lower chest towards the neck" that lasts for a few moments to several minutes, that is relieved by antacids or food, and that occurs a half hour or an hour after meals. Atypical or extraesophageal symptoms include cough, asthma, hoarseness, laryngitis, dental erosions, and noncardiac chest pain. Atypical symptoms are the primary complaint in 20% to 25% of patients with GERD and are secondarily associated with heartburn and regurgitation in many more. Nearly 50% of patients with chest pain and negative coronary angiograms, 75% with chronic hoarseness, and up to 80% with asthma have a positive 24-hour esophageal pH test, indicating abnormal acid reflux into the esophagus. Although many patients with atypical symptoms benefit from antireflux surgery, it is not as effective as for those patients with typical symptoms.

#### **22. What factors play a role in altering the GE barrier?**

The two most important are hypotension of the LES and loss of the angle of His as a result of hiatal hernia. Either may contribute to loss of competency of the sphincter and thus abnormal reflux. Physiologic reflux or reflux in early disease results from the transient loss of the high-pressure zone normally created by the tonic contraction of the smooth fibers of the LES. In severe GERD, the high-pressure zone is permanently reduced or nonexistent.

A large hiatal hernia alters the geometry of the GE junction, and the angle of His is lost. There is a close relationship between the degree of gastric distention necessary to overcome the high-pressure zone and the morphologic characteristics of the gastric cardia. In patients with an intact angle of His, more gastric dilatation and higher intragastric pressure are necessary to overcome the sphincter than in patients with a hiatal hernia. Furthermore, a hiatal hernia may also result in hypotension of the LES. However, every patient with a hiatal hernia does not have GERD, and the presence of a small, sliding hiatal hernia without GERD is not an indication for medical or surgical intervention.

### **23. Describe the workup of patients with suspected GERD.**

The four tests performed when GERD is suspected are barium swallow and upper gastrointestinal (GI) series, esophagogastroduodenoscopy (EGD), esophageal manometry, and 24-hour pH test, with the latter being the gold standard for a diagnosis of GERD.

- *Barium esophagram* provides both a functional and structural information. It is most useful in assessing the size and reducibility of a hiatal hernia and presence of esophageal shortening. A large, fixed hiatal hernia or paraesophageal hernia and a short esophagus are evidence of advanced disease and may predict a long, difficult operation.
- *EGD* helps to identify the presence of esophagitis and Barrett's esophagus. It can also be used to evaluate response to treatment and to detect complications of GERD, including peptic stricture and shortened esophagus. Furthermore, endoscopy provides valuable information about the absence of other lesions in the upper GI tract that can produce symptoms identical to those of GERD.
- *Esophageal manometry* evaluates the peristaltic function of the esophagus and the pressure and relaxation of the LES. It is not a diagnostic test but provides information about the severity of the underlying physiologic defects of the LES and esophageal body. Furthermore, *manometry helps rule out achalasia or other esophageal motility problems*. A normal manometric test includes a resting basal LES of 10 to 45 mm Hg.
- *Esophageal 24-hour pH monitoring* is the most direct method for assessing the presence and severity of GERD and, because it has the highest sensitivity and specificity of all available tests, has become the gold standard for the diagnosis of GERD. It is very useful in the evaluation of patients with atypical symptoms and patients with typical symptoms but with no evidence of esophagitis on endoscopy. The test also measures the correlation between symptoms and episodes of reflux in the supine or erect position. It is also used to determine if there is adequate acid suppression when patients are on medical treatment. It should be performed in every patient before surgical repair and with patients off acid suppression. A new device, the BRAVO probe, is a miniaturized pH probe that is attached 5 cm above the lower esophagus (as determined by manometry) during EGD that transmits pH data to a recording device that the patient wears. It stays in the esophagus for 3 to 5 days and is then spontaneously excreted in the stool. The advantage of the probe is that it is much better tolerated than the standard nasoesophageal probes. Newer techniques currently being tested, use 3-hour instead of 24-hour pH monitoring.

### **24. What is the significance of a defective LES?**

The finding of a *permanently defective LES (pressure less than 6 mm Hg)* has several implications. First, it is almost always associated with esophageal mucosal injury and predicts that symptoms will be difficult to control with medical therapy alone. A defective LES results in an increased GE junction diameter and progressively leads to loss of the acute angle of His and the development of a hiatal hernia. It is a signal that surgical therapy is probably needed for consistent, long-term control as the condition is irreversible, even when the associated esophagitis has healed. The worse the esophageal injury, the more likely it is that the LES is defective. Approximately 40% of patients with pH-positive GERD and no mucosal injury have a mechanically defective LES, whereas nearly 100% of patients with long-segment Barrett's esophagus have a defective LES.

### **25. What is the significance of abnormal esophageal motility in patients with GERD?**

Long-standing, severe GERD can lead to deterioration of esophageal body function. Abnormalities of esophageal body function include a lack of peristalsis, severely disordered peristalsis (*more than 50% simultaneous contractions*), or ineffective peristalsis (*the amplitude of the contractions in one or more of the lower esophageal segments is less than 30 mm Hg*), also called *ineffective esophageal motility*. Dysphagia is generally a prominent symptom in patients with defective peristalsis.

### **26. What is Barrett's esophagus and what are the risk factors?**

Barrett's esophagus is defined as the metaplasia of the normally squamous epithelium of the esophagus into columnar epithelium with intestinal metaplasia (presence of goblet cells). Barrett's esophagus is a premalignant condition and the incidence of esophageal adenocarcinoma increases nearly fortyfold in patients with Barrett metaplasia.

### **27. What are the indications for an antireflux operation?**

The introduction of minimally invasive procedures to surgically treat GERD has increased the frequency of these operations. The ability to permanently stop GE reflux and rid patients of dependence on expensive

medications has prompted gastroenterologists to refer patients for surgical therapy more readily. Indications for surgery include:

- Patient's wish to control symptoms without medication
- Persistent symptoms despite maximal medical therapy (most common)
- GERD with prominent regurgitation component
- Paraesophageal hiatal hernia
- Reflux complications (esophagitis, Barrett's esophagus, bleeding, stricture, mucosal ulceration, Cameron ulcer—chronic iron-deficiency anemia caused by slow bleeding from the point where the herniated stomach rubs against the diaphragm)

Surgery may be the treatment of choice in patients who are at high risk of progression despite medical therapy. The risk factors for progression include:

- Nocturnal reflux on 24-hour esophageal pH study
- Structurally deficient LES (pressure less than 6 mm Hg)
- Mixed reflux of gastric and duodenal juice
- Mucosal injury at presentation

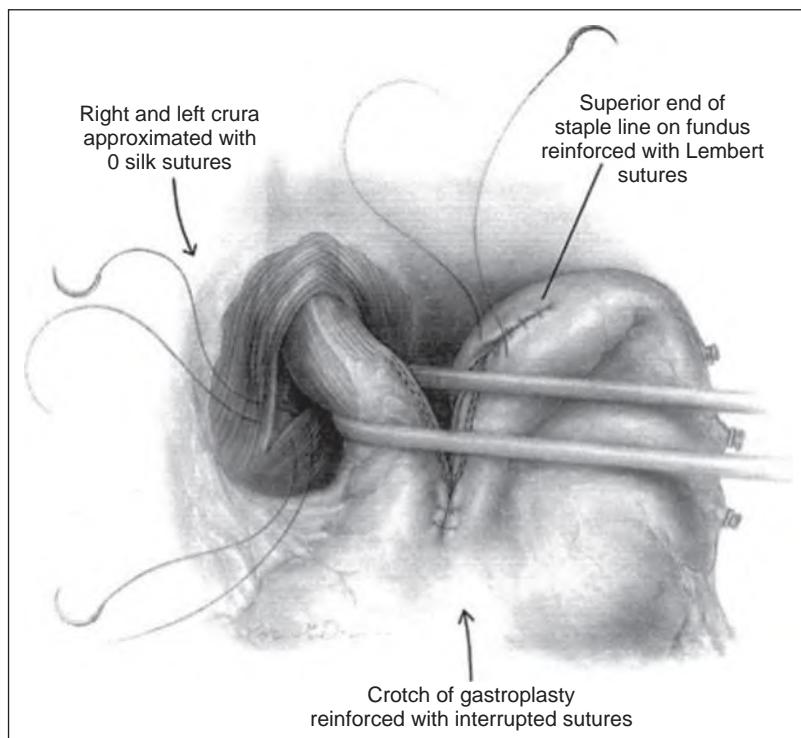
GERD in lung transplant patients is associated with decreased survival and attenuated allograft function. Early Nissen fundoplication has been safely performed in this subset of patients with improved outcomes from a lung transplant standpoint, as evidenced by 1-year forced expiratory volume in the first second of expiration measurements.

## 28. What are the surgical options to relieve GERD?

All of the successful surgical procedures for GERD have certain characteristics in common. All create an intraabdominal segment of esophagus, prevent recurrence of the hiatal hernia if present, and create an antireflux valve.

- Dor fundoplication: partial 270-degree anterior fundoplication
- Belsey Mark IV: partial 270-degree anterior fundoplication via thoracic approach
- Toupet fundoplication: partial 270-degree posterior fundoplication
- Nissen fundoplication: total 360-degree fundoplication
- Thal fundoplication: 90-degree anterior fundoplication
- Watson: 120-degree anterolateral fundoplication

The approach to the repair can be abdominal (open or laparoscopic), thoracic (open or video-assisted thoracic surgery), and even thoracoabdominal. None of the operations or approaches is perfect for all patients. If the esophagus is shortened, consider approaching from the chest and performing a Collis gastroplasty in which a portion of the lesser curvature is stapled and divided to create extra esophageal length ([Figure 73-1](#)).



**Figure 73-1.** Thoracoscopic view of Collis gastroplasty, which is necessary in patients with a short esophagus. (From Cameron JL: Current surgical therapy. Philadelphia: Mosby; 2004.)

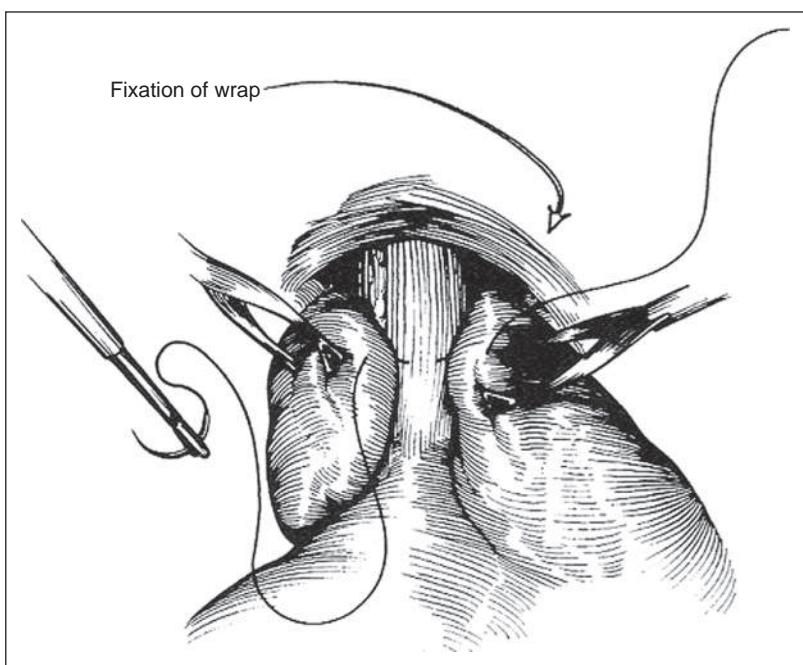
If esophageal motility is an issue, consider a partial wrap so as not to produce severe dysphagia. Additionally, robot-assisted Nissen has been widely performed with similar outcomes to conventional laparoscopic Nissen repair.

The newest techniques include minimally invasive approaches that involve either endoluminal suturing for plication at the level of the GE junction (Esophyx, EndoCinch suturing system, full thickness NDO plicator) or application of RF energy to this area. The long-term benefits of these novel therapies have not been well documented.

### 29. What are the important technical steps of a Nissen fundoplication?

Despite the caveats in Question 28, laparoscopic Nissen fundoplication is now the procedure of choice for most patients requiring an antireflux operation. Five trocars are inserted in the upper abdomen to provide access for the laparoscope and instruments. Both the right and the left vagus nerves are identified and preserved. The short gastric vessels are divided in the proximal part of the stomach, thereby mobilizing the fundus so that it can be placed around the distal esophagus without tension (the “shoeshine” maneuver). Dissection is performed to identify the right and left crura of the diaphragm. The distal esophagus is mobilized so that at least 3 cm of the distal esophagus lies without tension in the abdomen. The crura are approximated with nonabsorbable sutures (Figure 73-2). A bougie (range, 48- to 60-Fr depending on the size of the patient) is placed in the esophagus to prevent an excessively tight fundoplication. Some surgeons anchor the wrap to the crura of the diaphragm and to the esophagus to help prevent it from herniating into the chest. If there is a large hiatal hernia or if closure of the crura appears under tension, reinforcing the crural sutures with absorbable mesh reduces the rates of herniation.

**Figure 73-2.** Laparoscopic view of the placement of the first fundoplication stitch. (From Cameron JL: Current surgical therapy. Philadelphia: Mosby; 2004.)



### 30. What are the predictors of successful antireflux surgery?

Predictors of successful antireflux surgery include typical symptoms of GERD (heartburn and regurgitation), an abnormal score on 24-hour esophageal pH monitor, and symptomatic improvement in response to acid suppression therapy before surgery.

### 31. What are the predictors of poor outcome after antireflux surgery?

The presence of GI symptoms other than typical GERD symptoms predicts less than optimal results. A large hiatal hernia, stricture with persistent dysphagia, and Barrett are characteristics of advanced GERD and may predict less than ideal results.

### 32. Explain the benefits of surgical treatment of GERD.

Antireflux procedures performed by experienced esophageal surgeons provide several benefits that cannot be accomplished with antacid medications. A successful operation augments the LES and repairs the hiatal hernia if present. It prevents the reflux of both gastric and duodenal juice, thus preventing aspiration. Antireflux operations also improve esophageal body motility and speed gastric emptying, which is often subclinically

delayed in patients with GERD. More than 90% of patients are relieved of symptoms, eat unrestricted diets, and are satisfied with the surgical outcome.

### 33. What are the complications of laparoscopic fundoplication?

A laparoscopic antireflux operation is associated with significantly reduced postoperative pain, shorter hospitalization, quicker recovery, and improved cosmesis when compared with the open approach. The overall incidence of complications after laparoscopic Nissen fundoplication is between 2% and 13%. Most complications are minor and include urinary retention, postoperative gastric distention, and superficial wound infections. Mild early dysphagia may be found in 15% to 20% of patients, but the incidence of residual dysphagia after 3 months is less than 5%. Less than 1% of these patients need intervention to treat dysphagia. Splenectomy may be required in rare circumstances. Conversion rate of laparoscopic to open fundoplication is 1% to 2%. The major morbidity rate (esophageal, stomach injury and leak, pneumothorax) is 2% to 10% and mortality rate is 0.0% to 0.5%, making it a relatively safe procedure for alleviating GERD.

## PARAESOPHAGEAL HERNIAS

### 34. Define the four types of hernias occurring at the hiatus.

- Type I is a *sliding* hiatal hernia in which the GE junction migrates through the hiatus into the posterior mediastinum as a result of laxity of the phrenoesophageal ligament. This is the most common type of hiatal hernia (95%).
- Type II is a true paraesophageal hernia, characterized by an upward dislocation of the fundus of the stomach alongside a normally positioned GE junction. This is the least common type of hiatal hernia.
- Type III is a combination of types I and II, characterized by cephalad displacement of both the GE junction and typically a large portion of the fundus and body of the stomach into the chest. Type III hernias probably start as a sliding hernia, and as the hiatus enlarges over time, a progressively greater portion of the fundus and body of the stomach herniate through the defect. When more than 30% of the stomach is herniated in the stomach, the term *giant paraesophageal hernia* is used. An *intrathoracic stomach* is used to describe the condition in which all of the stomach is within the chest.
- Type IV are type III hernias in which other viscera such as the colon or spleen are included in the hernia sac. These are quite uncommon and represent only 2% to 5% of all paraesophageal hernias (Table 73-1).

**Table 73-1.** Types of Hernias Occurring at the Hiatus

HERNIA TYPE	LOCATION OF GASTROESOPHAGEAL JUNCTION	HERNIA CONTENTS	SPONTANEOUS REDUCIBILITY
Type I (Sliding)	Intrathoracic	Fundus	Usually reducible
Type II (True paraesophageal)	Intraabdominal	Fundus ± body	Often fixed
Type III (Mixed)	Intrathoracic	Fundus + body	Fixed
Type IV (Type III with other viscera included)	Intrathoracic	Fundus + body + other organ	Fixed

### 35. What causes a hiatal hernia?

The precise cause of a hiatal hernia is unknown. Its pathogenesis is thought to involve at least two important factors, including increased intraabdominal pressure and a progressive enlargement of the diaphragmatic hiatus. The increased incidence with age suggests that these hernias are acquired.

### 36. What are the signs and symptoms of a paraesophageal hernia?

Many hiatal hernias are asymptomatic and are first recognized on chest radiography. Type I is often associated with reflux but does not cause direct symptoms. Paraesophageal hernias classically cause symptoms of substernal chest pain, often thought to be cardiac in origin, and shortness of breath after eating. Shortness of breath is secondary to loss of vital capacity caused by impingement of hernia contents on the lung. Other symptoms, which may or may not be present, include dysphagia, early satiety, abdominal bloating, and GE reflux, as well as aspiration manifested by chronic cough, dyspnea, and wheezing. Cameron ulcers are often the cause of unexplained microcytic anemia in older adults with otherwise normal upper and lower endoscopy. Rarely, acute herniation occurs, causing sudden pain and symptoms of gastric outlet obstruction. Strangulation can cause gastric necrosis, resulting in rapid decompensation, shock, and death.

### 37. How are hiatal and paraesophageal hernias diagnosed and evaluated?

Paraesophageal hernias are often first suspected because of a *chest radiograph* abnormality. Classically a retrocardiac air bubble with or without an air-fluid level will be present. Confirmation can be obtained with a *barium swallow*, which shows the typical appearance of a large intrathoracic stomach and evaluates the motility

of the esophagus simultaneously. *Upper endoscopy* is useful to evaluate the distal esophagus and stomach for ulcers, erosions, Barrett's esophagus, or neoplasms in this generally older population. An *esophageal motility study* is recommended in patients being considered for elective surgical correction of a paraesophageal hernia both to determine the status of the LES and to assess the function of the esophageal body. This is particularly true in any patient with symptoms of dysphagia. A 24-hour pH test is usually not necessary because a fundoplication is recommended as part of the procedure to correct this defect.

### **38. What are the indications for surgical repair of paraesophageal hernias?**

In most patients with a paraesophageal hernia, it is the hernia itself that is responsible for symptoms and imparts the risk of life-threatening complications. There is no medical medication appropriate for treating a paraesophageal hernia. The only therapy for the hernia is surgical, and there used to be a controversy about which patients should have an operation and which procedure and approach are most appropriate. A prophylactic paraesophageal hernia repair is now rarely performed as the mortality rate after elective hernia repair in an asymptomatic patient ranges between 0.5% and 1.4%, whereas the probability of developing acute symptoms that will require emergent surgery is estimated to be 1.1%. However, all patients with symptoms or signs associated with the paraesophageal hernia should undergo repair in the absence of prohibitive surgical risk. Also, patients with gastric volvulus, obstruction, strangulation, perforation, and bleeding should undergo emergent paraesophageal hernia repair.

### **39. What is the operative strategy of a paraesophageal hernia repair?**

The key steps of paraesophageal hernia repair are:

- Return stomach and esophagus to their normal intraabdominal positions.
- Remove the hernia sac.
- Close the hiatus.
- Anchor the stomach below the diaphragm.

In most circumstances, a fundoplication is added both to augment the LES and to aid in stabilizing the repair below the diaphragm. Many recent studies also advocate the use of a mesh to reduce the recurrence rate. There are three approaches for the surgical repair of paraesophageal hernias: transabdominal, transthoracic, and laparoscopic. Traditionally, a transthoracic repair has been advocated because of the relative ease of mobilizing the esophagus and dissecting out the hernia sac and its contents. However, as the stomach is reduced blindly into the abdomen, an organoaxial rotation of the stomach could persist or redevelop and lead to an intraabdominal gastric volvulus. The abdominal approach is now preferred with the main advantage being the ability to place the stomach into the appropriate anatomic orientation. Laparoscopic repair offers the advantages of decreased length of postoperative discomfort, earlier return to regular activities, and shorter hospital stay.

## **BIBLIOGRAPHY**

1. American Gastroenterological Association, Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology* 2011;140:1084–91.
2. Biere SS, van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *Lancet* 2012;379:1887–92.
3. Bittner HB, Meyers WC, Brazer SR, Pappas TN. Laparoscopic Nissen fundoplication: operative results and short-term follow-up. *Am J Surg* 1994;167:193–8, discussion 199–200.
4. Boeckxstaens GE, Zaninotto G, Richter JE. Achalasia. *Lancet* 2013;383:83–93.
5. Brucher BL, Stein HJ, Bartels H, et al. Achalasia and esophageal cancer: incidence, prevalence, and prognosis. *World J Surg* 2001;25:745–9.
6. Burmeister BH, Thomas JM, Burmeister EA, et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. *Eur J Cancer* 2011;47:354–60.
7. Camacho-Lobato L, Katz PO, Eveland J, et al. Vigorous achalasia: original description requires minor change. *J Clin Gastroenterol* 2001;33:375–7.
8. Chen D, Barber C, McLoughlin P, Thavaneswaran P, Jamieson GG, Maddern GJ. Systematic review of endoscopic treatments for gastro-oesophageal reflux disease. *Br J Surg* 2009;96:128–36.
9. Gockel I, Eckardt VF, Schmitt T, et al. Pseudoachalasia: a case series and analysis of the literature. *Scand J Gastroenterol* 2005;40:378–85.
10. Kahrilas PJ, et al. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. *Gastroenterology* 2008;135:1392–413, 1413 e1–5.
11. Larusson HJ, Zingg U, Hahnloser D, Delport K, Seifert B, Oertli D. Predictive factors for morbidity and mortality in patients undergoing laparoscopic paraesophageal hernia repair: age, ASA score and operation type influence morbidity. *World J Surg* 2009;33:980–5.
12. Lundell L. Therapy of gastroesophageal reflux: evidence-based approach to antireflux surgery. *Dig Dis* 2007;25:188–96.
13. O'Halloran EK, Reynolds JD, Lau CL, et al. Laparoscopic Nissen fundoplication for treating reflux in lung transplant recipients. *J Gastrointest Surg* 2004;8:132–7.
14. Rastogi A, Puli S, El-Serag HB, et al. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. *Gastrointest Endosc* 2008;67:394–8.
15. Rebecchi F, Giaccone C, Farinella E, et al. Randomized controlled trial of laparoscopic Heller myotomy plus Dor fundoplication versus Nissen fundoplication for achalasia: long-term results. *Ann Surg* 2008;248:1023–30.

16. Simonka Z, Paszt A, Abraham S, et al. The effects of laparoscopic Nissen fundoplication on Barrett's esophagus: long-term results. *Scand J Gastroenterol* 2012;47:13–21.
17. Smith G. Mesh repairs in hiatal surgery. The case for mesh repairs in hiatal surgery. *Ann R Coll Surg Engl* 2007;89:481–3.
18. Swanstrom LL, Kurian A, Dunst CM, et al. Long-term outcomes of an endoscopic myotomy for achalasia: the POEM procedure. *Ann Surg* 2012;256:659–67.
19. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006;101:1900–20, quiz 1943.
20. Van Hagen P, Hulshof MC, van Lanschot JJ, et al. Group C. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074–84.

**Websites**

Visible Human Journal of Endoscopy. <http://www.vhjoe.org> [Accessed September 22, 2014].  
<http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-achalasia?source=machineLearning&search=achalasia&selectedTitle=1%7E72&sectionRank=1&anchor=H34211525#H34211525>

# SURGERY FOR PEPTIC ULCER DISEASE

Theodore N. Pappas, MD, and Georgios Kokosis, MD

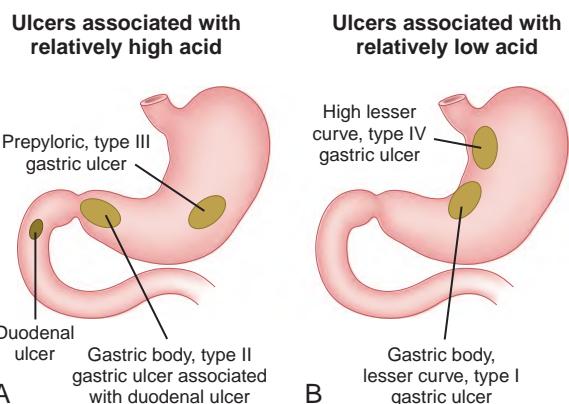
**1. Describe the five types of gastric ulcers in terms of location, gastric acid secretory status, incidence, and complications.**

Peptic ulcers are a common cause of upper gastrointestinal (GI) symptoms with peak incidence in middle-aged men (55-65). They arise at various locations, including the stomach (gastric ulcer), duodenum (duodenal ulcer), and esophagus (esophageal ulcer). Gastric ulcers are further divided into five types based on location, secretory status, and cause (Table 74-1 and Figure 74-1).

**Table 74-1.** The Five Types of Gastric Ulcers by Location, Gastric Acid Secretory Status, Complications, and Incidence

Type	Location	Acid Hypersecretion	Complications	Incidence
I	Gastric body, lesser curvature	No	Bleeding uncommon	55%
II	Body of stomach + duodenal ulcer	Yes	Bleeding, perforation, obstruction	20%
III	Prepyloric	Yes	Bleeding, perforation	20%
IV	High on lesser curvature	No	Bleeding	<5%
V	Anywhere (medication induced)	No	Bleeding, perforation	<5%

**Figure 74-1.** The four types of gastric ulcers and their association with either high acid (A) or low acid (B). (From Sabiston DC Jr. *Textbook of surgery: The biologic basis of modern surgical practice*. Philadelphia: WB Saunders; 1997.)



**2. Describe the classic indications and goals for peptic ulcer surgery.**

Since the introduction of H<sub>2</sub>-receptor antagonists and proton pump inhibitors (PPIs) and the identification of *Helicobacter pylori* as an ulcerogenic cofactor, the frequency of elective operations for peptic ulcer disease (PUD) has decreased by more than 90%. Currently, surgery for duodenal and gastric ulcers is reserved for the management of complications of PUD, the most common being stricture or perforation (10-35% of patients). The classic indications for peptic ulcer surgery are:

- Intractability of symptoms
- Suspicion of malignancy (peptic ulcer failed to heal after 12 weeks, even with negative biopsies)
- Perforation
- Bleeding (with two failed endoscopic attempts to control hemorrhage and increased transfusion requirements, >6 units the first 24 hours or >3 units per day)
- Gastric outlet obstruction (GOO)

The main goals of surgery are to:

- Treat any complications of PUD
- Eliminate the factors that contribute to ulcer occurrence

### 3. What are the three classic operations used for PUD?

Truncal vagotomy and drainage

Truncal vagotomy and antrectomy

Highly selective vagotomy (parietal cell vagotomy or proximal gastric vagotomy)

### 4. Describe the truncal vagotomy, selective vagotomy, and highly selective vagotomy.

*Truncal vagotomy* involves the division of both anterior and posterior vagal trunks at the esophageal hiatus above the origins of the hepatic and celiac branches. Periesophageal dissection must include the distal 6 to 8 cm of the esophagus to ensure division of gastric vagal branches that arise from the trunks above the level of the hiatus. Thus truncal vagotomy results in denervation of all vagal nerve-supplied viscera. A drainage procedure, usually a pyloroplasty, must be performed with truncal vagotomy, because denervation of the pylorus results in impaired gastric emptying.

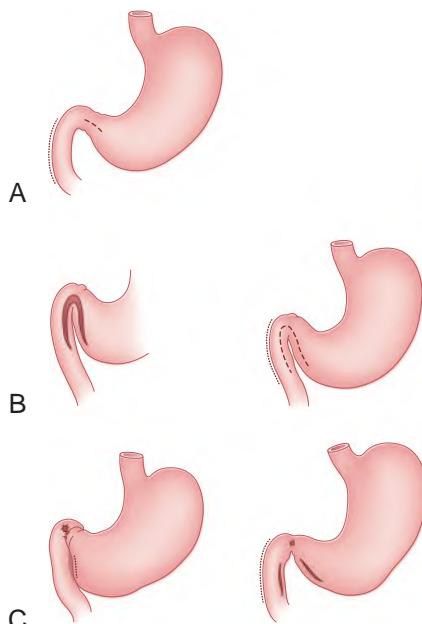
*Selective vagotomy* involves division of the vagal trunks distal to the hepatic and celiac branches, thereby preserving vagal innervation to the gallbladder and celiac plexus. This reduces the incidence of gallbladder dysmotility, gallstones, and diarrhea. However, selective vagotomy also results in complete gastric vagotomy, necessitating a drainage procedure. Selective vagotomy is not the operation of choice, as it is needlessly complex and not superior to truncal vagotomy; it is rarely used and only of historic importance.

*Highly selective vagotomy* (parietal cell vagotomy or proximal gastric vagotomy) involves selective division of the vagal fibers to the acid-producing parietal cell mass of the gastric fundus, while maintaining vagal fibers to the antrum and distal gut. The anterior and posterior neurovascular attachments are divided along the lesser curvature of the stomach, beginning approximately 7 cm from the pylorus and progressing to the gastroesophageal junction, with additional skeletonization of the distal 6 to 8 cm of the esophagus to ensure division of the *criminal nerve of Grassi*. Innervation of the antrum and pylorus is maintained because the two terminal branches of the anterior and posterior nerves of Latarjet are left intact.

### 5. Why is an outlet or drainage procedure added to truncal vagotomy? What are the surgical options?

Truncal vagotomy involves division of both anterior and posterior vagal trunks at the esophageal hiatus.

This procedure results in denervation of the acid-producing mucosa of the gastric fundus as well as the pylorus and antrum, causing an alteration of normal pyloric coordination and impaired gastric emptying. Thus a procedure to eliminate function of the pyloric sphincter must be performed to allow gastric drainage. There are four primary options for an outlet procedure (Figure 74-2):



**Figure 74-2.** A, Heineke-Mikulicz pyloroplasty, B, Finney pyloroplasty, and C, Jaboulay gastroduodenostomy are the primary options for an outlet or drainage procedure after truncal vagotomy.

**Heineke-Mikulicz pyloroplasty:** a longitudinal incision of the pyloric sphincter, extending into the duodenum and antrum, is closed transversely. This is the most commonly performed technique.

**Finney pyloroplasty:** a U-shaped incision crossing the pylorus is made and a gastroduodenostomy is created; used in cases of extensive duodenal scarring to create a wider gastroduodenal opening.

**Jaboulay gastroduodenostomy:** a side-to-side gastroduodenostomy is created in which the incision does not cross the pyloric sphincter. Although it is rarely necessary, it is used when severe pyloric scarring precludes division of the pyloric channel.

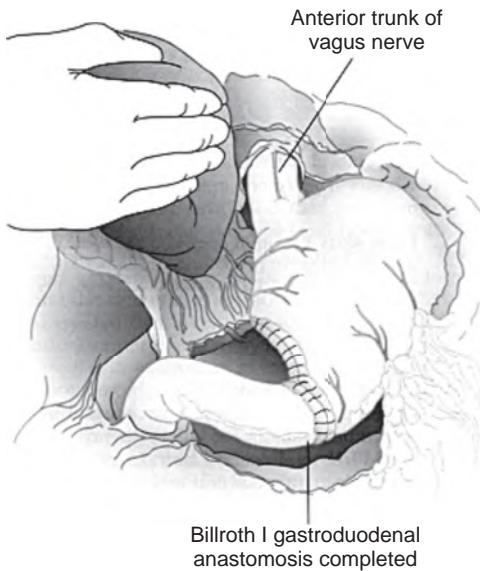
**Gastrojejunostomy:** Billroth II or Roux-en-Y anastomosis is reserved for significant duodenal bulb scarring that makes pyloroplasty more challenging.

## 6. What are the relative indications and contraindications to highly selective vagotomy?

Highly selective vagotomy is indicated for the treatment of intractable duodenal ulcers because, unlike truncal vagotomy, it does not require a drainage procedure, because antral peristalsis and sphincter function are preserved. It has also been used in the emergent treatment of bleeding or perforated duodenal ulcers in stable patients. It reduces the basal and stimulated acid secretion by more than 75% and 50% respectively. Highly selective vagotomy is contraindicated in patients with prepyloric ulcers or with GGO because they demonstrate high rates of recurrent ulceration. The ulcer recurrence rate is closely tied to the surgeon's experience with this operation and in the PPI era should only be performed by an experienced GI surgeon well versed in the technique. Because of its high recurrence rate, and the fact that most surgeons have very little experience with this procedure, it is rarely used today.

## 7. What are the surgical options for reconstruction after antrectomy?

Billroth I reconstruction consists of a gastroduodenostomy in which the anastomosis is created between the gastric remnant and the duodenum (Figure 74-3).



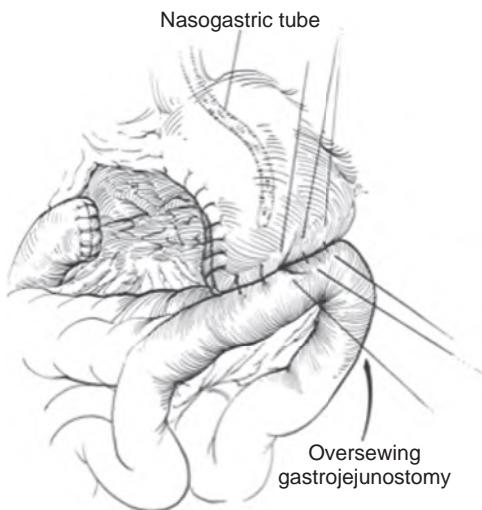
**Figure 74-3.** Hemigastrectomy with Billroth I anastomosis. (From Townsend CM. Sabiston textbook of surgery, ed 18. Philadelphia: WB Saunders; 2008.)

Billroth II reconstruction consists of a gastrojejunostomy in which a side-to-side anastomosis is created between the gastric remnant and a loop of jejunum, with closure of the duodenal stump (Figure 74-4).

Roux-en-Y reconstruction involves the creation of a jejunoojejunostomy (forming a Y-shaped figure of small bowel) downstream from the anastomosis of the free jejunal end to the gastric remnant (gastrojejunostomy).

## 8. How is the type of reconstruction determined for a given patient?

The decision of which type of reconstruction to perform is determined, in large part, by the extent of duodenal scarring caused by PUD and the ease with which the duodenum and the stomach can be brought together. Severely scarred duodenum cannot be used for a Billroth I anastomosis. The Billroth I reconstruction, however, offers the most physiologic anastomosis because it restores normal continuity of the GI tract. The Billroth II reconstruction may be complicated by afferent loop syndrome in which obstruction of the afferent limb results in accumulation of bile and pancreatic secretions, causing right upper quadrant abdominal pain that is alleviated by bilious vomiting. Roux-en-Y reconstruction allows diversion of bile and pancreatic secretions away from the gastric outlet, thereby reducing the risk of bile reflux gastritis. However, it can result in a delay in gastric emptying.



**Figure 74-4.** Hemigastrectomy with Billroth II anastomosis. (From Sabiston DC. *Atlas of general surgery*. Philadelphia: WB Saunders; 1994.)

**9. Define *intractability* in terms of the medical treatment of PUD.**

Intractability is defined as mucosal healing refractory to maximal medical therapy. The following three criteria define a refractory ulcer and are generally indications for operative intervention:

Ulcer persistence after 2 months of PPI or 3 months of H<sub>2</sub>-antagonist treatment

Ulcer recurrence within 1 year, despite maintenance medical therapy

Ulcer disease in which cycles of prolonged activity are interrupted by brief or absent remissions

**10. Describe the most appropriate elective operative procedure for duodenal ulcers and each type of gastric ulcer.**

The choice of operation for gastric ulcers depends on several factors: ulcer location, acid secretory status, and presence of a coexistent duodenal ulcer. In general, gastric ulcers should be included with the resection while duodenal ulcers heal after acid suppression.

**Type I:** antrectomy with inclusion of the ulcer and Billroth I or II reconstruction. Although type I gastric ulcers are associated with low to normal acid secretion, most surgeons include a truncal vagotomy, unless achlorhydria is demonstrated. It is associated with excellent symptomatic relief and low recurrence rates.

**Type II and III:** truncal vagotomy, antrectomy with inclusion of the gastric ulcer and Billroth I reconstruction.

Type II (gastric body) and III (prepyloric) gastric ulcers are associated with high rates of acid secretion and therefore the goal of the surgery is removal of the gastric mucosa at risk for ulceration and reduction of acid secretion. Highly selective vagotomy has been associated with poor results and high recurrence rates.

**Type IV:** distal gastrectomy with resection proximally to include the ulcer high on the lesser curvature and Billroth I anastomosis. Because type IV ulcers are located high on the lesser curvature, they are surgically challenging.

**Type V:** surgery is reserved for treatment of complications. Type V gastric ulcers generally heal rapidly with cessation of aspirin or a nonsteroidal antiinflammatory drug (NSAID) and institution of an H<sub>2</sub>-receptor antagonist or PPI. An intractable type V gastric ulcer should raise suspicion for underlying malignancy.

**Duodenal ulcer:** historically, the highly selective vagotomy has been the mainstay of treatment. However, the intractable duodenal ulcer is a rare entity in the PPI era and may represent a more resistant variant with a higher rate of recurrence. Therefore truncal vagotomy with pyloroplasty is predominantly used today.

**11. Describe the presentation of a patient with a perforated peptic ulcer.**

Patients usually describe a prodrome of gnawing localized pain in the epigastric region prior to perforation. With acute perforation, the epigastric pain becomes diffuse as a result of release of acidic fluid in the peritoneal cavity and the resulting release of vasoactive mediators, and is often associated with fever, tachycardia, tachypnea, and hypotension. Patients with a perforated posterior duodenal ulcer will often present with upper GI bleeding secondary to erosion into the gastroduodenal artery. On examination, the patient with peptic ulcer perforation lies immobile. Bowel sounds are typically absent, and the abdomen is diffusely tender and rigid. The white blood cell count is elevated, and, in 70% of cases, free intraperitoneal air is found on upright abdominal radiographs. Although computed tomography (CT) scan is the most sensitive radiologic test for free intraperitoneal air, it is rarely indicated because patients with perforated peptic ulcers usually present with classic signs and symptoms, and CT scanning only serves to delay an operation.

## 12. Why do almost all perforated gastric ulcers require an operation?

Perforated gastric ulcers constitute 40% of overall perforated peptic ulcers, and duodenal ulcers the remaining 60%.

- Unlike perforated duodenal ulcers, which may be treated nonoperatively if the ulcer has sealed itself as demonstrated on Gastrograffin swallow, perforated gastric ulcers usually fail to heal spontaneously.
- They are associated with a risk of adenocarcinoma.
- Gastric ulcer disease produces a hypoacidic environment with resultant bacterial overgrowth and abscess formation with perforation.

## 13. What are the contraindications to medical management of perforated PUD?

Concurrent use of corticosteroids, which makes healing unlikely

Continued leak, as demonstrated by a contrast radiograph

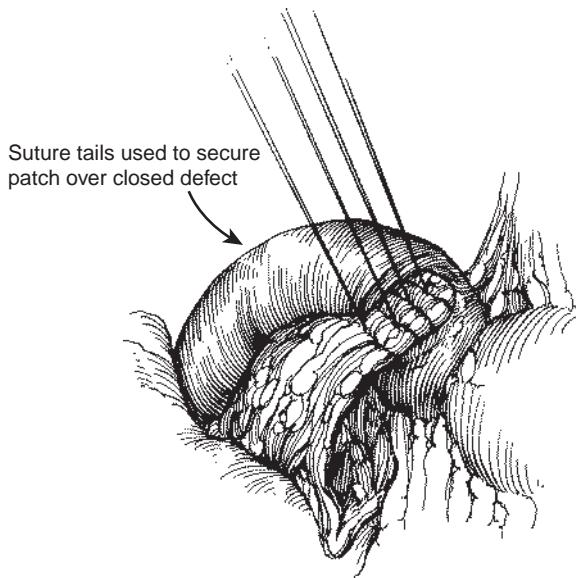
Perforation in a patient taking an H<sub>2</sub>-receptor antagonist or a PPI. A definitive ulcer operation is necessary to allow ulcer healing and to reduce the risk of recurrence

## 14. What are the three major goals of operation for perforated PUD?

Repair of the perforation is usually performed by suturing the perforation closed and buttressing the repair with omental fat as a Graham patch (Figure 74-5).

The abdominal cavity is copiously irrigated.

Definitive ulcer operation is performed. A patient who has had a perforation for less than 24 hours and is hemodynamically stable without significant comorbidities should undergo a definitive ulcer operation if he or she has known PUD, has been receiving medical therapy for PUD, or is taking medication that increases the risk of PUD.



**Figure 74-5.** Omental patching of a perforated peptic ulcer.

## 15. What is the preferred operation for treatment of perforated gastric ulcer?

Excision of the ulcer with or without vagotomy and drainage. The major distinction between surgical management of perforated duodenal and perforated gastric ulcers is that in all cases of perforated gastric ulcers, carcinoma must be excluded. Thus all perforated gastric ulcers must undergo biopsy or resection. One option is to perform a wedge resection as diagnostic biopsy. Controversy exists as to whether a definitive ulcer operation should be added to this procedure, with most surgeons in favor of a definitive acid-reducing procedure in type II or III variant. An alternative for perforated antral ulcers is antrectomy (with inclusion of the ulcer in the resection), to which truncal vagotomy may be added if the patient is an acid hypersecretor. The decision for the type of operation should be based on an individual patient, taking into account the patient's comorbidities, age, and severity at presentation.

## 16. What is the preferred operation for treatment of a perforated duodenal ulcer?

The preferred operation is a simple patch (Graham patch) of the perforation, especially in the setting of shock or in patients with multiple comorbidities undergoing an emergent operation, when prolonged operative time can be detrimental. In patients who have undergone medical therapy to eradicate *H. pylori*, a reasonable approach for a perforated duodenal ulcer is truncal vagotomy and pyloroplasty, with incorporation of the perforation into the pyloroplasty closure. This relatively simple procedure requires a short operative time. In the ideal surgical

candidate, highly selective vagotomy with patch closure of the perforation is recommended, although this procedure requires a high degree of surgical expertise. Patients who have not been treated for *H. pylori* prior to perforation should undergo repair and Graham patch of a perforated duodenal ulcer as stated previously with postoperative *H. pylori* eradication therapy, in lieu of a definitive ulcer operation.

### **17. What are the major risk factors for mortality in the surgical treatment of perforated PUD?**

Severe comorbidities

Perforation present for longer than 24 hours

Hemodynamic instability on presentation

Patients with one of these risk factors have a mortality rate of approximately 10%; with two risk factors, the mortality rate increases to 46%. Patients with all three risk factors have a mortality rate of nearly 100%.

### **18. Discuss the role for laparoscopy in the management of perforated PUD and the indications for conversion to an open operation.**

The surgical goals in the laparoscopic management of a perforated peptic ulcer are similar to those of open surgical management:

Repair of the perforation

Copious irrigation of the abdominal cavity

Addition of a definitive ulcer operation, which depends on the skill of the surgeon and may involve either laparoscopic truncal vagotomy and pyloroplasty or on rare occasion laparoscopic highly selective vagotomy. The relative indications for conversion to an open procedure include posterior location of the ulcer and inadequate localization. The presence of a perforated gastric ulcer with its suspicion for malignancy may necessitate conversion for definitive diagnosis.

### **19. In patients with GI bleeding caused by PUD, what are the predictors for rebleeding in the hospital? What is the Forrest classification?**

- Hemodynamic instability (systolic blood pressure <100 mm Hg, heart rate >100-110 beats per minute)
- Large ulcer size (>1-2cm)
- Ulcer location (posterior duodenal wall, high lesser curvature)
- Active bleeding during endoscopy
- Hematocrit less than 30
- Multiple comorbidities
- Coagulopathy
- Hematemesis
- Inability to clear the stomach with aggressive lavage

The Forrest classification describes endoscopic risk factors for rebleeding; see [Chapter 50](#).

### **20. What are the classic indications for operation for rebleeding after endoscopic therapy?**

After two attempted endoscopic therapeutic interventions for a bleeding peptic ulcer, patients who have already required six units of blood should be strongly considered for surgical intervention.

In general, the indications for surgical treatment of a bleeding peptic ulcer are:

- Hemodynamic instability as a result of massive hemorrhage (after cardiovascular stabilization)
- Need for multiple transfusions caused by continued bleeding
- Failure of nonsurgical therapy to prevent re-bleeding

### **21. What are the operative options for control of a bleeding gastric ulcer?**

The best option is excision. *Bleeding gastric ulcers require excision and biopsy to rule out malignancy.* Small gastric ulcers (less than 2 cm) can usually be excised easily and safely, with the addition of an ulcer operation for patients who are acid hypersecretors. Large gastric ulcers, lesser curvature ulcers, bleeding ulcers associated with gastritis, and gastric ulcers that penetrate into the pancreas often require a more radical and technically demanding operation (subtotal, 75% resection, or near total, 95% resection, gastrectomy) to control hemorrhage.

### **22. What is the most appropriate surgical procedure for a bleeding duodenal ulcer?**

The best option is simple oversew of the bleeding ulcer. Control of the ulcer bed is attained by performing a duodenotomy with direct ligation of the bleeding vessel or complete plication of the ulcer bed. Three-point suture ligation takes place in the superior, inferior, and medial aspect of the vessel. If a posterior duodenal ulcer has eroded into the gastroduodenal artery, bleeding may be profuse. If a patient has ulcer disease refractory to medical management or is on chronic NSAID therapy, a definitive ulcer operation is then performed. This may consist of either truncal vagotomy and pyloroplasty or a truncal vagotomy and antrectomy. An alternative approach is to attain control of the bleeding duodenal ulcer through a pyloroplasty incision, in which case a truncal vagotomy completes the definitive ulcer operation. Patients who have not been treated for *H. pylori* prior to bleeding should undergo ligation of the bleeder only, with postoperative *H. pylori* eradication therapy, in lieu of a definitive ulcer operation.

### **23. How is GOO caused by PUD surgically managed?**

GOO can result from an acute exacerbation of PUD in the setting of chronic pyloric and duodenal scarring. Classically, patients with GOO present with nausea, emesis, early satiety, and weight loss. Although radiologic

contrast studies are useful in evaluation, upper endoscopy is critical to rule out a malignant cause of the obstruction. Although in *H. pylori*-positive patients a trial of medical management may be successful, operative intervention is necessary in more than 75% of patients presenting with GOO. The two main goals of surgery are to relieve the obstruction and to perform a definitive ulcer operation. Truncal vagotomy and antrectomy with Billroth II reconstruction is performed if the duodenal stump can be safely closed. If the stump cannot be closed, a tube duodenostomy is left in place for control of secretions until the stump closes by secondary intention. An alternative is to perform a truncal vagotomy and pyloroplasty, which often requires the Finney pyloroplasty or Jaboulay gastroduodenostomy because of severe scarring. Truncal vagotomy and gastrojejunostomy may be performed if the severe scarring precludes an adequate drainage procedure via the duodenum. In patients with a prolonged history of obstruction, postoperative gastric atony can be expected, so placement of a gastrostomy tube may be helpful in postoperative care. Also, the nutritional status of the patient should be taken into account (albumin <3 mg/dL is associated with higher rates of morbidity and mortality) and a feeding jejunostomy at the time of the operation may be deemed necessary.

#### **24. Discuss the role for endoscopic and laparoscopic management of GOO secondary to PUD.**

Patients treated with balloon dilatation, without treatment of *H. pylori* infection have a higher rate of failure and recurrent obstruction. Patients who are negative for *H. pylori* do not respond favorably to balloon dilatation and should be considered for surgical treatment early in the process.

Laparoscopic truncal vagotomy and drainage procedure, either pyloroplasty or jejunostomy, has been described successfully with low morbidity. The choice of open or laparoscopic management depends on the skill and experience of the surgeon.

#### **25. What are the long-term outcomes and risks for complications after truncal vagotomy and drainage, truncal vagotomy and antrectomy, and highly selective vagotomy?**

Truncal vagotomy and antrectomy, although having the lowest recurrence rate, also has the highest morbidity and mortality (Table 74-2). Highly selective vagotomy, although having the lowest morbidity and mortality, has the highest recurrence rate. The surgeon must balance these issues, patient preference, and the pathophysiology of the ulcer type in question when choosing an operative plan.

**Table 74-2.** Comparison of Surgical Options for Peptic Ulcer Disease

	TRUNCAL VAGOTOMY AND ANTRECTOMY	TRUNCAL VAGOTOMY AND DRAINAGE	HIGHLY SELECTIVE VAGOTOMY
Mortality rate	1% to 2%	0.5% to 0.8%	0.05%
Recurrence rate	Low	Moderate	High
Dumping	10% to 15%	10%	1% to 5%
Diarrhea	20%	25%	1% to 5%

#### **26. What are the Visick criteria?**

The Visick criteria are used to grade outcome after surgery for PUD:

Grade I—No symptoms

Grade II—Mild symptoms that do not affect daily life

Grade III—Moderate symptoms that affect daily life and require treatment but are not disabling

Grade IV—Recurrent ulceration or disabling symptoms

Grades I and II are considered adequate results. Most poor outcomes fall into grade III.

#### **27. How should postoperative gastroparesis be managed?**

Postoperative gastroparesis typically occurs in patients who undergo surgery for GOO. Evaluation should begin with esophagogastroduodenoscopy, upper GI series with small bowel follow-through, and gastric emptying scan. Once mechanical obstruction has been ruled out, medical treatment is successful in most cases.

Prokinetic agents such as erythromycin and metoclopramide may be helpful. The indications for reoperation are:

Early marginal ulcers refractory to medical management

Anatomic abnormalities of the gastric outlet

Recurrent bezoar associated with weight loss

Intractable gastroparesis following vagotomy and drainage may be treated with subtotal gastrectomy and Roux-en-Y reconstruction. If the gastric remnant is large, a Billroth II reconstruction may be preferable to Roux-en-Y reconstruction because the latter option may be associated with persistent gastric emptying problems. Gastroparesis may be managed with preoperative nasogastric tube decompression for the severely dilated stomach.

**28. Describe the management of duodenal stump disruption (*blow-out*) after truncal vagotomy, antrectomy, and Billroth II reconstruction.**

Patients presenting with postoperative localized right upper quadrant tenderness are managed by aggressive percutaneous drainage of the abscess under radiologic guidance. An acute abdomen with free perforation and leakage of duodenal contents into the peritoneal cavity may require surgical management. This includes reclosure of the duodenal stump over a tube duodenostomy as well as wide external drainage. Mortality from stump blowout approaches 10%.

**29. What is dumping syndrome? Describe the pathophysiologic findings and treatment.**

The dumping syndrome, occurring in 20% of patients after vagotomy and gastrectomy, consists of tachycardia, diaphoresis, hypotension, and abdominal pain after meals in patients who have undergone ulcer operations, such as truncal vagotomy. Its pathophysiologic characteristic is loss of receptive relaxation of the fundus in response to a gastric load. Thus gastric pressure increases during a meal, and rapid decompression through the gastric outlet causes release of vasoactive hormones (serotonin, vasoactive intestinal peptide) and the resulting classic signs and symptoms. The constellation of symptoms occurring hours after meals is described as *late dumping syndrome* and is due to hypoglycemia resulting from postprandial insulin peak. Symptoms improve typically with time and can be alleviated in some patients by separation of solids and liquids during meals, as well as the introduction of small and frequent meals high in protein and fat and low in carbohydrates. Conversion of a Billroth II to a Billroth I or a Billroth operation to a Roux-en-Y reconstruction can improve symptoms but is rarely necessary. Octreotide, a somatostatin analog administered on a monthly basis, has been proven to alleviate symptoms and improve quality of life, but is indicated only if symptoms are severe.

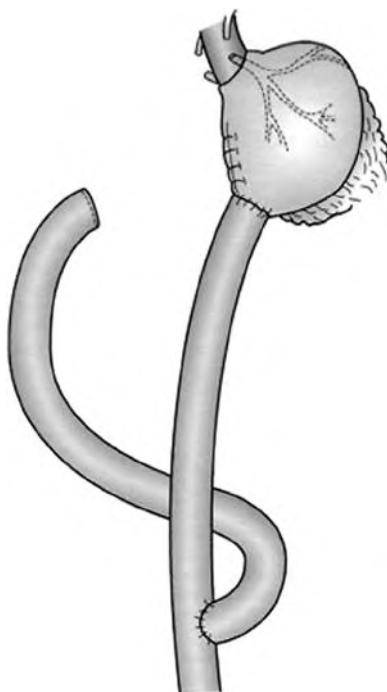
**30. Describe the pathophysiologic findings of bile reflux gastritis. How is it managed?**

Bile reflux gastritis occurs when ablation or dysfunction of the pylorus results in stasis of bile in the stomach. The diagnosis is made with the following triad of findings:

- Postprandial epigastric pain accompanied by nausea and bilious emesis
- Evidence of bile reflux into the stomach or gastric remnant
- Biopsy-proved gastritis

Bile reflux gastritis can occur after truncal vagotomy and pyloroplasty or truncal vagotomy and antrectomy with Billroth reconstruction. Although up to 20% of patients who undergo these operations may have transient bile reflux gastritis postoperatively, symptoms resolve in all but 1% to 2%.

Treatment of bile reflux gastritis requires revision of the pyloroplasty or the Billroth reconstruction to a Roux-en-Y gastrojejunostomy with a 50- to 60-cm limb (Figure 74-6). Bilious emesis resolves in nearly 100% of patients who undergo revision. The symptoms of bile reflux gastritis may be indistinguishable from those



**Figure 74-6.** Conversion of Billroth I or Billroth II reconstruction to a Roux-en-Y anastomosis. (From Cameron JL. Current surgical therapy. Philadelphia: Mosby; 2004.)

of gastroparesis. Because the Roux-en-Y gastrojejunostomy worsens the symptoms of gastroparesis, care must be taken to exclude the diagnosis of gastroparesis preoperatively.

### **31. What is the presentation of Zollinger-Ellison syndrome?**

Most patients with Zollinger-Ellison syndrome are between 20 and 50 years old and present with PUD or diarrhea. Ulcers are typically duodenal. The diarrhea resembles steatorrhea and results from a combination of high volumes of acid and neutralization of pancreatic enzymes. The syndrome is either sporadic or associated with multiple endocrine neoplasia (MEN) syndrome I. In patients with Zollinger-Ellison syndrome associated with MEN I, signs and symptoms may be related to parathyroid or pituitary disease.

### **32 How is Zollinger-Ellison syndrome diagnosed?**

A high level of suspicion is required for the diagnosis of gastrinoma. Serum gastrin should be measured in all patients undergoing peptic ulcer surgery. *If the gastrin level is in the range of 1000 to 2000 pg/mL, gastric pH analysis demonstrating acid production confirms the diagnosis.* If the gastrin level is minimally elevated, the patient should undergo gastric pH analysis and a secretin test. The secretin test is performed by comparison of basal serum gastrin level with gastrin level after the administration of secretin. Gastrinoma is suspected in patients with an *increase in the serum gastrin level of 200 pg/mL after secretin administration.* Normal patients have no change or a reduction in serum gastrin after secretin administration. Because achlorhydria is more common than gastrinoma, an elevation in serum gastrin is due more commonly to lack of acid as opposed to ectopic gastrin production. Therefore measurement of acid production is also essential in making the appropriate diagnosis. Serum chromogranin A is a general marker for neuroendocrine tumors, and although it does not differentiate between the various types, it is also elevated in Zollinger-Ellison syndrome.

### **33. For which patients with Zollinger-Ellison syndrome is operative intervention indicated?**

Surgery is the treatment of choice for patients with nonmetastatic sporadic gastrinoma. In addition, patients with metastatic gastrinoma who are unable to tolerate or are refractory to medical management should be considered for operative intervention. Sporadic gastrinomas are often solitary and located in the pancreas or duodenum, but not both, and are amenable to surgical resection and cure. Although gastrinomas seen with MEN syndrome are usually multiple, virtually always in the duodenum, and often multicentric, they are also found in the pancreas and are more difficult to cure surgically. Gastrinoma associated with hypercalcemia should suggest MEN syndrome complicated by hyperparathyroidism, and parathyroidectomy is essential for management of gastric acid hypersecretion. Elevated serum gastrin levels postoperatively after gastrinoma surgery indicate residual gastrinoma(s) that should be treated medically. Medical management is also generally indicated for patients with metastatic gastrinoma. Medical management consists of high-dose PPIs with the goal of reducing gastric acid output to less than 10 mEq/h for the hour that immediately precedes the next scheduled dose of antisecretory medication.

### **34. Describe the preoperative evaluation for gastrinoma.**

CT scan with intravenous and oral contrast is routine in the preoperative evaluation for gastrinoma resection to rule out metastatic disease, and its accuracy depends on the size of the gastrinoma. In some cases, magnetic resonance imaging (MRI) is used because it is more sensitive than CT scan for liver metastases. The advent of somatostatin receptor scintigraphy (octreotide) scan has greatly improved the preoperative localization of gastrinomas. This study relies on the high density of somatostatin receptors on gastrinomas and uses the radiolabeled synthetic somatostatin analog, iodine-125—[<sup>125</sup>I]octreotide—to identify primary as well as metastatic gastrinomas.

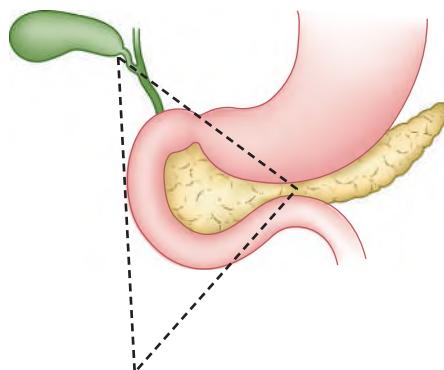
Recent studies have demonstrated that somatostatin receptor scintigraphy has high sensitivity and specificity for detection of primary and metastatic gastrinomas and is the initial imaging modality of choice for localization. It also evaluates the extent of somatostatin receptors and addresses the need for somatostatin-based therapies. Endoscopic ultrasound has recently been used to localize gastrinomas; however, it is highly operator dependent and does not reliably identify small tumors in the duodenum. Intraoperative upper endoscopy with transillumination or intraoperative ultrasound may also help to localize small duodenal gastrinomas. More recently, a modification of octreotide scanning has become available as an adjunct to intraoperative localization. A handheld gamma-detecting probe is used intraoperatively to localize gastrinomas after the injection of [<sup>125</sup>I]octreotide.

### **35. Where is the gastrinoma triangle? What percentage of tumors occur in this area?**

The apex of the gastrinoma triangle is at the cystic duct–common bile duct junction, and the triangle is bounded by the border of the second and third portions of the duodenum and the junction of the neck and body of the pancreas (Figure 74-7). Approximately 60% to 75% of gastrinomas are found within this triangle.

### **36. Describe the operative scheme for exploration, localization, and removal of gastrinoma.**

If no tumor is obvious on preoperative CT scan, and other preoperative localization studies have failed, exploration begins with exposure of the anterior surface of the pancreas by mobilization of the transverse colon. A Kocher maneuver is then performed to mobilize the duodenum, allowing complete bimanual palpation of the pancreas. Intraoperative ultrasound is concentrated in the gastrinoma triangle. Biopsy of lymph nodes should be



**Figure 74-7.** The gastrinoma triangle.

performed because, occasionally, the gastrinoma is localized to a solitary node. If ultrasound of the pancreas does not reveal the tumor, duodenal gastrinoma should be suspected. A pyloroplasty incision is made, and the duodenal wall is visually inspected and manually palpated. An alternative method of localizing duodenal gastrinomas is to transilluminate the wall with intraoperative endoscopy. Gastrinomas in the duodenal wall or pancreas may be enucleated, but solitary lesions in the pancreatic tail are often treated by distal pancreatectomy.

If no lesion is found or if the disease is found to be multicentric or metastatic, an ulcer operation may be performed as palliation. This procedure often consists of a truncal vagotomy and pyloroplasty. Alternatively, the patient may be maintained on a PPI. In rare cases, a total gastrectomy may be performed for control of acid production in patients who are refractory to medical therapy or unable to tolerate the side effects of the medication.

### 37. Describe the risk of gastric stump cancer after partial gastrectomy for duodenal and gastric ulcer.

Gastric stump carcinoma is defined as adenocarcinoma of the stomach that occurs at least 5 years after partial gastric resection for benign disease. In patients who have had a partial distal gastrectomy for gastric ulcer, the relative risk is no different than in the general population in the first 20 years but rises to 3-fold after 20 years. Annual screening gastroscopy and biopsy should be performed in patients who underwent gastric resection at least 15 years earlier and have moderate to severe dysplasia on biopsy.

#### BIBLIOGRAPHY

1. Anlauf M, Gabrech N, Henopp T, et al. Sporadic versus hereditary gastrinomas of the duodenum and pancreas: distinct clinico-pathological and epidemiological features. *World J Gastroenterol* 2006;12:5440–6.
2. Ashley SW, Daly JM, editors. *Principles of surgery*. Columbus, OH: McGraw-Hill; 1999.
3. Arts J, Caenepeel P, Bisschops R, Dewulf D, Holvoet L, Piessevaux H, et al. Efficacy of the long-acting repeatable formulation of the somatostatin analogue octreotide in postoperative dumping. *Clin Gastroenterol Hepatol* 2009;432–7.
4. Azimuddin K, Chamberlain RS. The surgical management of pancreatic neuroendocrine tumors. *Surg Clin North Am* 2001;81:511–25.
5. Behrman SW. Management of complicated peptic ulcer disease. *Arch Surg* 2005;140:201–8.
6. Hadzibulic E and Govendarica S. Significance of forrest classification, rockall's and blatchford's risk scoring system in prediction of rebleeding in peptic ulcer disease. *Acta Med Median* 2007;46(4):38–43.
7. Hansson LE. Risk of stomach cancer in patients with peptic ulcer disease. *World J Surg* 2000;24:315–20.
8. Harbison SP, Dempsey DT. Peptic ulcer disease. *Curr Probl Surg* 2005;42:346–454.
9. Jamieson GG. Current status of indications for surgery for peptic ulcer disease. *World J Surg* 2000;24:256–8.
10. Lipof T, Shapiro D, Kozol RA. Sporadic versus hereditary gastrinomas of the duodenum and pancreas: distinct clinico-pathological and epidemiological features. *World J Gastroenterol* 2006;12:3248–52.
11. Millat B, Fingerhut A, Borie F. Surgical treatment of complicated duodenal ulcers: controlled trials. *World J Surg* 2000;24:299–306.
12. Noguiera C, Silva AS, Santos JN, et al. Perforated peptic ulcer: main factors of morbidity and mortality. *World J Surg* 2003;27:782–7.
13. Norton JA, Fang TD, Jensen RT. Surgery for gastrinoma and insulinoma in multiple endocrine neoplasia type 1. *J Natl Cancer Inst* 2006;4:148–53.
14. Rockall TA. Management and outcome of patients undergoing surgery after acute upper gastrointestinal haemorrhage. Steering Group for the National Audit of Acute Upper Gastrointestinal Haemorrhage. *J R Soc Med* 1998;91(10):518.
15. Shroder VT, Pappas TN, Vaslef SN, Scarborough JE. Peptic ulcer surgery in the modern era. *J Surg Res* 2013;179:234–5.
16. Testini M, Portincasa P, Piccini G, et al. Significant factors associated with fatal outcome in emergency open surgery for perforated peptic ulcer. *World J Gastroenterol* 2003;9:2338–40.

#### Website

<http://www.uptodate.com/contents/surgical-management-of-peptic-ulcer-disease/abstract/6?utdPopup=true>

# SURGICAL APPROACH TO THE ACUTE ABDOMEN

Kevin Rothchild, MD, and Jonathan A. Schoen, MD

## 1. What is meant by the term *acute abdomen*?

The classic definition refers to the sudden onset of severe abdominal pain of unclear cause. *Acute abdomen* refers to any abdominal condition that requires prompt diagnosis. Often acute abdomen is equated with inflammation of the peritoneum or peritonitis, but they are not identical. Although many cases may ultimately require surgical intervention, it is not inherently implied by the term.

## 2. What elements of a patient's history are most important?

- Age
- Location of pain (what quadrant)
- Character (sharp, stabbing, dull, burning)
- Onset and duration
- Past surgical history and medical comorbidities

## 3. Which disorders are associated with specific age groups?

- Neonates: intussusception, appendicitis, Meckel's diverticulitis, mesenteric adenitis, midgut volvulus, malrotation, hypertrophic pyloric stenosis, small bowel atresia
- Adults: cholecystitis, diverticulitis, gynecologic disorders, peptic ulcer disease (PUD), incarcerated hernia, ruptured spleen, renal or biliary stones, pancreatitis, small bowel obstruction
- Older adults: diverticulitis, colon cancer (perforation), appendicitis, aortic aneurysm, colonic (cecal or sigmoid) and small bowel volvulus, mesenteric ischemia

## 4. Pain in each of these locations is often associated with which disorders?

- Right upper quadrant: biliary tract disease, hepatitis, PUD, pneumonia
- Right flank: hepatitis, pyelonephritis, appendicitis
- Right lower quadrant: appendicitis (late), ectopic pregnancy, incarcerated inguinal hernia, rectus sheath hematoma, ovarian torsion, pelvic inflammatory disease, ruptured ovarian cyst, Meckel's diverticulitis, Crohn's disease
- Epigastrium: pancreatitis, PUD, cardiac disease, esophageal disease
- Central abdomen: bowel obstruction, bowel ischemia, midgut volvulus, appendicitis (early)
- Left upper quadrant: splenic rupture or infarct, PUD, pneumonia, leaking abdominal aortic aneurysm
- Left lower quadrant: diverticulitis, incarcerated inguinal hernia, ovarian torsion, pelvic inflammatory disease, colon cancer (perforated)

## 5. What associated problems can help to pinpoint the diagnosis?

A complete medical, surgical, and family history are essential. For example, in premenopausal women, pelvic inflammatory disease and pregnancy-related issues must be screened as part of the initial assessment. Risk factors will often narrow a wide differential, such as chronic nonsteroidal antiinflammatory drug use in a patient with epigastric pain (peptic ulcer), or history of inflammatory bowel disease in a patient with obstipation and right lower quadrant pain (Crohn's ileocecal stricture).

## 6. Describe the innervation of the peritoneum. What are peritoneal signs?

The peritoneum is derived from the mesoderm. It consists of two double-layered sheets of cells that form the visceral and parietal layers, each with their own sensory innervation. The visceral layer covers the organs and has autonomic innervation. These slow C fibers can respond to various stimuli such as mechanical stretch or hypoxia, and produce dull, often crampy midline pain of insidious nature (a patient will often wave his or her hand over the umbilicus when asked to localize). The parietal layer covers the inner surface of the abdominal cavity and has somatic innervation from the corresponding spinal nerves, each producing a sensation of pain in the local area from which it originates. These are fast transmitters and they lead to pain that is sharp and easier to localize. *Peritonitis* refers to any inflammation of these peritoneal layers. This inflammation leads to guarding or spasm of the muscle when it is palpated. *Voluntary guarding* is defined as when the patient can consciously eliminate the muscular spasm, and *involuntary guarding* refers to a guarding response that cannot be repressed. The latter is more foreboding; a tense and boardlike abdomen often is associated with diffuse peritonitis.

**7. What is the significance of rebound pain, and should it be elicited?**

If one palpates deeply with the fingers and suddenly releases the manual pressure, often this may elicit severe pain on the rebound in patients with peritoneal irritation. Many surgeons believe that this sign does not convey any more information than can be obtained with gentle, deep palpation, and it often causes unexpected and unnecessary pain, in addition to voluntary guarding that will make further examinations less reliable.

**8. What is the nature of intestinal pain?**

The intestines themselves are insensate to direct pain from traumatic injury or inflammation. However, intense pain can be elicited from stretching or distention, as well as contraction against resistance, as is seen in colicky pain from obstruction.

**9. What is meant by the term “referred pain”?**

Referred pain is a phenomenon whereby pain is felt at a location other than the site of painful stimulus. Classic examples are pain in the left arm or jaw with a myocardial infarction, or pain at the tip of the scapula with liver or gallbladder pathologic conditions (see later in this chapter). The mechanism is poorly understood but several theories exist, including *convergence-projection*, which hypothesizes that separate afferent axons converge on the same spinal neuron, producing the disturbed sensation.

**10. Is acute abdomen ruled out by absence of fever or leukocytosis?**

No. Fever and leukocytosis are often late occurrences. Older and immunocompromised patients may be unable to mount an immune response even late in the course of the disease process.

**11. What is the significance of bowel sounds?**

Bowel sounds are notoriously inaccurate in the surgical evaluation of the abdomen. Their absence may be indicative of ileus or peritonitis, whereas loud borborygmi, tinkling, or rushes may be suggestive of an obstructive process.

**12. What is the most important part of the abdominal examination?**

Palpation is a key component of the abdominal examination, which permits assessment of localized tenderness, guarding, or diffuse peritonitis. One should attempt to begin palpation away from the area of expected maximal tenderness. A rectal examination is also essential. A pelvic examination can also be invaluable in female patients of childbearing age with abdominal pain.

**13. What are the psoas and obturator signs?**

Inflammation of the psoas muscle causes pain on hip flexion-extension, whereas inflammation of the internal obturator muscle causes pain on internal rotation and flexion of the hip. A retrocecal appendicitis or, on occasion, diverticulitis may be responsible for these signs.

**14. What is Rovsing sign?**

Palpation of the *left* lower quadrant can elicit pain in the *right* lower quadrant, often seen in appendicitis. Neils Thorkild Rovsing was a Danish surgeon who described this pathologic condition in 1908.

**15. What is Kehr's sign?**

Pain in the left upper quadrant radiates to the *top* of the left shoulder secondary to diaphragmatic irritation. Kehr's sign often indicates hematoma from splenic injury or can be seen in perforated peptic ulcer. The eponym is attributed to Johannes Kehr, a German surgeon who also developed a biliary T-tube.

**16. Define mittelschmerz.**

Mittelschmerz is lower abdominal pain that occurs during the middle of the menstrual cycle secondary to ovulation, often perceived in the lower midline.

**17. How does urinalysis help in the assessment?**

White blood cells in the urine may indicate urinary tract infection. Hematuria may suggest ureteral stones or tumor. Glucose or ketones may reveal diabetic ketoacidosis. An inflamed appendix abutting an adjacent ureter may lead to the finding of white or red blood cells in the analysis.

**18. What should be the first imaging study obtained?**

An acute abdominal series consists of an upright, supine, and lateral decubitus abdominal film. It is quick and inexpensive, yet can provide vital information. Upright chest radiograph may reveal free air under the diaphragm or suggest a pulmonary process. Free air may also be seen over the liver in a left lateral decubitus abdominal film. Air-fluid levels on the upright film may suggest bowel obstruction, whereas lack of air in the rectum may indicate a complete obstruction. Only 10% of gallstones are radiopaque, but 90% of ureteral calculi are visualized. Appendiceal fecalith may suggest appendicitis in the setting of right lower quadrant pain. Air in the biliary tree may be seen with biliary-enteric fistula or pelvic pyelophlebitis.

**19. How is ultrasound (US) used?**

US helps to evaluate the gallbladder and biliary tree, to assess for free peritoneal fluid, and can visualize the female adnexa (in the setting of possible ectopic pregnancy or ovarian cyst or mass). Unfortunately, abdominal US examination is limited in the setting of obesity as well as bowel distention.

**20. What additional imaging studies may help in the diagnosis?**

Computed tomography (CT) scan of the abdomen and pelvis with oral and intravenous contrast is useful in the setting of intraabdominal abscess, pancreatitis, aortic aneurysm or dissection, arterial and venous occlusive disease, hepatic, splenic, retroperitoneal, and renal disorders. Upper and lower gastrointestinal (GI) series may pinpoint the level of bowel obstruction or establish the diagnosis if CT is inconclusive. Angiography or US (less sensitive) can be used to assess mesenteric arterial flow.

**21. If the diagnosis is in doubt, what other procedure should be done?**

Surgical exploration of the abdomen is the next step if diagnostic studies are equivocal, and it is mandatory if the patient's condition worsens despite aggressive resuscitation. In many centers laparoscopy has widely supplanted laparotomy for exploration, even with suspected pathologic conditions such as perforated peptic ulcer, diverticulitis, and appendicitis.

**22. Is exploratory laparotomy justified, even if it produces no significant findings?**

Yes. Despite the risk of general anesthesia, postoperative pain, risk of wound infection, and a small lifetime risk of bowel obstruction from adhesions (less than 5%), it is still safer to undergo a surgical exploration than to miss the diagnosis of appendicitis or bowel infarction.

**23. In blunt trauma, CT scan of the abdomen and pelvis reveals free peritoneal fluid collections. When is observation appropriate instead of immediate surgical exploration?**

In the setting of trauma, any free fluid seen on CT should be concerning for possible bowel injury, for which CT is notoriously insensitive. Any patient must be hemodynamically stable for observation to be appropriate. Small lacerations to the liver or spleen are readily identifiable and should be treated with aggressive resuscitation. Escalating pain, fluid requirements, or need for blood transfusion should prompt an immediate exploration.

**24. Do all penetrating injuries to the abdomen require laparotomy?**

No. In the era of CT scanning, a hemodynamically stable patient with a negative CT can be observed. Many stab wounds and low-velocity firearm injuries are tangential and do not penetrate the abdominal fascia. However, observation in the setting of multiple trauma can be time-consuming and immediate exploration to rule out injury can be beneficial at times. High-velocity bullet wounds almost always require exploration because of the high likelihood of associated bowel and adjacent organ injury.

**25. What is the role of laparoscopy in trauma?**

Laparoscopy can be a useful adjunct to assess for diaphragmatic injuries or when penetration of the abdominal fascia cannot be ascertained. The classic example is a stab wound to the left upper quadrant, where CT or US might not be helpful.

**26. When is surgery indicated for PUD?**

- Perforation: Closure with an omental or a Graham patch is acceptable for patients without previous history of PUD and for hemodynamically unstable patients. Definitive antiulcer surgery is indicated in hemodynamically stable patients with a prior history or chronic PUD. Resection of the ulcer crater with adequate margins should be performed for gastric ulcers. Definitive gastrectomy is undertaken after recovery if carcinoma is found in the specimen.
- Obstruction: If duodenal obstruction from an ulcer is not relieved by 7 days, surgery is generally indicated. Balloon dilation and stenting are alternatives in patients who are poor surgical candidates.
- Bleeding: Surgery is indicated in any hemodynamically unstable patient or in those requiring greater than 6 units of packed red blood cells within a 24-hour period. Esophagogastroduodenoscopy (EGD) as well as angiography can be very useful in this setting prior to operative intervention.
- Intractability: Despite benign biopsies, recurrent or nonhealing gastric ulcers should be resected because of the risk of underlying carcinoma.

**27. When is cholecystectomy optimal for acute pancreatitis, presumably caused by gallstone disease?**

Classically, patients with gallstone pancreatitis would undergo cholecystectomy 4 to 6 weeks following their initial hospitalization; however, more recent studies show high recurrence rates with this delay. In addition, early surgery (i.e., during the same hospitalization, after pain has resolved) has shown similar complication and conversion rates compared with the delayed approach.

**28. When is surgery indicated for severe acute pancreatitis?**

Patients with progressively hemorrhagic or necrotizing infected pancreatitis should undergo surgery when resuscitative measures fail. Both CT-guided catheter drainage of well-localized pancreatic abscesses as well as endoscopic decompression of well-formed pseudocysts may be an alternative. Despite aggressive surgery, mortality rates are still in excess of 40% in some series.

**29. What are omental infarction and epiploic appendagitis and how are they related?****What is the ideal treatment of these processes?**

Spontaneous torsion or infarction of either the omentum or epiploic appendages of the colon can mimic either appendicitis or other acute abdominal pathologic conditions based on their location. For both, the process is generally self-limiting, with conservative (nonsurgical) care recommended. CT is the mainstay of diagnosis and can avoid unnecessary surgery.

**30. What is the best method to diagnose pain secondary to mesenteric ischemia?**

Despite multiple modalities (CT, US, angiography) to assess intestinal vascular flow, high index of suspicion, a careful history, and physical examination remain the best method to diagnose mesenteric ischemia. Pain out of proportion to physical examination is a classic finding. Atrial fibrillation, recent cardiac surgery, and any hypercoagulable state should arouse suspicion. Base deficit from arterial blood gas may reflect ischemia or necrosis, but a normal blood gas or lactate should not delay exploration. Laparoscopy can be helpful if there is not excessive bowel dilation.

**31. Describe the surgical strategy for the treatment of Crohn's disease.**

Because of the chronicity of the disease, any surgical strategy should be to maximize small bowel length. Strictureplasty has been shown to be an effective measure with multiple Crohn's strictures and maintains small bowel length. In the setting of long segments of disease, resection is generally limited to areas of grossly diseased bowel (not microscopically normal).

**32. When should surgery be offered for uncomplicated acute diverticulitis? What is laparoscopic peritoneal lavage?**

The classic surgical tenet that patients with two or more attacks should undergo colectomy has been challenged, as has the concept that patients at the ends of the age spectrum should have more aggressive surgical intervention. Newer data suggests that it is safe to consider intervention on a case-by-case basis and offer colectomy based on symptoms. Free perforation with peritonitis, bowel obstruction, and severe bleeding are indications for immediate surgery. Catheter drainage of a localized abscess can often postpone surgery and may often obviate the need for acute colostomy formation (Hartmann procedure) or allow a laparoscopic approach.

Peritoneal lavage or washout consists of a laparoscopic procedure to wash out the abdominal cavity in the setting of purulent (not feculent) peritonitis caused by acute diverticulitis. Saline is used to irrigate the abdomen and drains are placed. Several large-scale prospective studies are under way to assess whether this procedure can reduce overall colectomy and morbidity rates.

**33. Should older adult patients with sigmoid or cecal volvulus undergo surgery?**

Yes. After immediate reduction with barium enema or endoscopy, the recurrence rate may be as high as 50% to 90%. Unless the patient cannot tolerate an operation or is in a moribund state, surgery should be offered during the same hospitalization.

**34. How should toxic megacolon in the setting of ulcerative colitis be managed?**

Aggressive fluid resuscitation, bowel rest, broad-spectrum antibiotics, and intravenous corticosteroids are the mainstays of medical therapy. Serial abdominal examinations and plain films are mandatory to assess for colonic distention or impending perforation. Total abdominal colectomy with end-ileostomy is often required if there is no improvement in 48 hours.

**35. How should Ogilvie's syndrome be managed?**

The vast majority of patients improve with bowel rest and removal of narcotics; however, colonic decompression is indicated in the presence of pain or significant distention (more than 12 cm). Intravenous neostigmine as a prokinetic agent has a high success rate (greater than 80%–90% in some small series), although cardiac risk must be assessed prior to administration. Tube cecostomy can be considered in moribund patients.

**36. After endoscopic retrograde cholangiopancreatography (ERCP), a patient develops upper abdominal and back pain. What steps should be considered?**

CT scan or upper GI series can usually pinpoint an injury to the duodenum after ERCP or polypectomy. Repeat EGD can provide the option of endoscopic repair, but is less reliable for localization, especially with a small injury. The main focus should be on the location of the leak—is it the biliopancreatic system or the duodenum? Bile duct injury may be treated by endoscopic stent placement with percutaneous drainage of any biloma or exploration (open or laparoscopic) if the injury is complex. Pancreatitis is not uncommon and should be treated expectantly. A contained, small leak in the posterior duodenum (retroperitoneal) may be treated with bowel rest and gastric decompression; however, laparotomy is indicated in the presence of ongoing pain or signs of diffuse peritonitis.

**37. How should colonic perforation be managed after colonoscopy?**

The risk of perforation of the colon is 0.19% to 0.4% after diagnostic colonoscopy and 0.3% to 1% with polypectomy. In a well-prepped colon, bowel rest, antibiotics, and observation are often appropriate, provided there is no evidence of diffuse peritonitis. For small perforations, early (within 24 hours) laparoscopic repair is a viable alternative, with resection and primary anastomosis reserved for large injuries or devitalized tissue. Other complications such as bleeding or even splenic rupture have rarely been reported after colonoscopy.

**38. What are some other nonsurgical causes of acute abdomen?**

The list of medical causes of acute abdominal pain is long and can often cause diagnostic dilemmas if the index of suspicion is low. It includes diabetic ketoacidosis, hypercalcemia, myocardial infarction, pneumonia, ureteral calculi, and gastroenteritis. Careful history, repeat examinations, and judicious use of diagnostic imaging are paramount to avoid unnecessary surgery.

**BIBLIOGRAPHY**

1. Ahmed A, Eller PM, Schiffman FJ. Splenic rupture: an unusual complication of colonoscopy. *Am J Gastroenterol* 1997;92:1201–4.
2. Anderson ML, Pasha TM. Endoscopic perforation of the colon: lessons from a 10-year study. *Am J Gastroenterol* 2000;95:3418–22.
3. Arendt-Nielsen L, Svensson P. Referred muscle pain: basic and clinical findings. *Clin J Pain* 2001;17(1):11–9.
4. Bretagnol F, et al. Emergency laparoscopic management of perforated diverticulitis: a promising alternative to more radical procedures. *J Am Coll Surg* 2008;206:654–7.
5. Chae FH, Stiegmann GV. Current laparoscopic gastrointestinal surgery. *Gastrointest Endosc* 1998;47:500–11.
6. Cope Z. Cope's early diagnosis of the acute abdomen. New York: Oxford University Press; 1921.
7. Marco CA, Schoenfeld CN, Keyl PM, et al. Abdominal pain in geriatric emergency patients: variables associated with adverse outcomes. *Acad Emerg Med* 1998;5:1163–8.
8. McKellar DP, Reiling RB, Eiseman B. Prognosis and outcomes in surgical disease. St Louis: Quality Medical Publishing; 1999.
9. Murinson BB, Griffin JW. C-fiber structure varies with location in peripheral nerve. *J Neuropathol Exp Neurol* 63(3):246–54.
10. Norton LW, Stiegmann GV, Eiseman B. Surgical decision making. Philadelphia: WB Saunders; 2000.
11. Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med* 1999;341:137–41.
12. Pritchard JR, Schoetz DJ. Strictureplasty of the small bowel in patients with Crohn's disease: an effective surgical option. *Arch Surg* 1990;125(6):715–7.
13. Singh AK, Novelline RA. Acute epiploic appendagitis and its mimics. *Radiographics* 2005;25:1521–34.

# COLORECTAL SURGERY: POLYPOSIS SYNDROMES AND INFLAMMATORY BOWEL DISEASE

Martin D. McCarter, MD

## 1. Identify four different classes of intestinal polyps.

- Neoplastic (adenomatous, tubular, villous, tubulovillous, serrated)
- Hamartomatous
- Inflammatory and lymphoid
- Hyperplastic

## 2. What is a hamartoma?

A hamartoma is an exuberant growth of normal tissue in an abnormal amount or location. An isolated hamartomatous polyp has no malignant potential.

## 3. Which intestinal polyposis syndromes are associated with hamartomatous polyps?

- Peutz-Jeghers syndrome (PJS)
- Juvenile polyposis (familial or generalized)
- Cronkhite-Canada syndrome (hamartomatous polyps with alopecia, cutaneous pigmentation, and toenail and fingernail atrophy)
- Intestinal ganglioneuromatosis (isolated or with von Recklinghausen disease or multiple endocrine neoplasia type 2)
- Ruvalcaba-Myhre-Smith syndrome (polyps of colon and tongue, macrocephaly, retardation, unique facies, pigmented penile macules)
- Cowden disease (gastrointestinal [GI] polyps with oral and cutaneous verrucous papules [tricholemmomas], associated with breast cancer, thyroid neoplasia, and ovarian cysts)

## 4. How is PJS manifested?

This autosomal dominant trait is often heralded by the presence of melanin spots on the lips and buccal mucosa. Hamartomas are almost always present on the small intestine and occasionally on the stomach and colon. Previously considered a benign process, patients with PJS are at increased risk for multiple cancers: breast (50%), GI (50%), pancreatic (35%), gynecologic (10%-20%), and testicular (<10%). Aggressive cancer screening programs are recommended for persons with PJS.

## 5. Describe the manifestation of familial adenomatous polyposis (FAP).

FAP is an autosomal-dominant, non-sex-linked disease in which more than 100 adenomatous polyps affect the colon and rectum. FAP is caused by mutation in the adenomatous polyposis coli (APC) gene on the long arm of chromosome 5 at the 5q21-q22 locus. The APC protein is a tumor suppressor that, when mutated, fails to bind beta-catenin and allows for unregulated cellular growth. One third of patients present as the propositus case (presumed mutation) with no prior family history. The disease invariably leads to invasive colon cancer if not treated. The average age at diagnosis of colon cancer is 39 years compared with 65 years for routine colon cancer.

## 6. What is Gardner syndrome?

Gardner syndrome is a phenotypic variant of FAP manifest by colonic polyposis plus fibromas of the skin, osteomas (typically of the mandible, maxilla, and skull), epidermoid cysts, desmoid tumors, and extra dentition.

## 7. How does one screen for FAP?

When family history is positive, children should undergo annual sigmoidoscopic surveillance beginning at age 10 to 12 years. When polyps are identified, a full colonoscopy is recommended. Once multiple adenomas are documented, colectomy is recommended. Mutational analysis of the APC gene is the most accurate diagnosis. Ophthalmoscopic examination for congenital hypertrophy of the retinal pigment epithelium (CHRPE) can detect involved patients as early as 3 months of age with a 97% positive predictive value for developing FAP. CHRPE is present in 55% to 100% of FAP patients.

## 8. What are the surgical indications for ulcerative colitis?

- Intractability or failure of medical management
- Fulminant colitis (toxic megacolon, bleeding, diarrhea)
- Prophylaxis of carcinoma (presence of high-grade dysplasia)
- Treatment of carcinoma

**9. What are the elective surgical options for FAP and chronic ulcerative colitis?**

- Total proctocolectomy with end (Brooke) ileostomy
- Total proctocolectomy with continent ileostomy reservoir (Kock pouch)
- Abdominal colectomy with ileorectal anastomosis
- Near-total proctocolectomy ± rectal mucosectomy and ileal pouch-anal anastomosis (IPAA)

**10. Can one always tell the difference between Crohn's disease and ulcerative colitis?**

No. Colitis that cannot be categorized as definitely Crohn or ulcerative colitis is called *indeterminate colitis* and may account for 5% to 10% of cases referred for surgical consideration.

**11. What is pouchitis?**

Pouchitis, one of the most frequent long-term complications of IPAA, is a nonspecific acute or chronic inflammation of the reservoir. Pouchitis is found in 7% to 44% of patients with IPAA; it presents with watery, bloody stools, urgency, frequency, abdominal pain, fever, malaise, and possible exacerbation of extra-intestinal manifestations of inflammatory bowel disease. The cause is uncertain, but the risk is greater in chronic ulcerative colitis than in familial polyposis. Pouch stasis, bacterial overgrowth, dysbiosis, ischemia, pelvic sepsis, oxygen-derived free radicals, altered immune status, and lack of mucosal trophic factors have been proposed as etiologic factors.

**12. How is pouchitis treated?**

Successful treatment regimens include metronidazole and other antianaerobic antibiotics as well as steroid or 5-aminosalicylate enemas. Topical volatile fatty acids and glutamine have been used with variable success. Maintenance with the probiotic VSL#3 has been reported to help prevent recurrences. Although half of patients with pouchitis at some time suffer a recurrence, very few develop intractable involvement requiring pouch excision.

**13. Does a defunctionalized colon develop colitis?**

Although controversial, some patients with a portion or the entire colon out of the fecal stream develop an inflammation difficult to distinguish from ulcerative colitis on biopsy. The *diagnosis of diversion colitis is suggested when bloody mucopus is passed from the separate colorectal segment*. The colon may be isolated by diverting ileostomy, end or loop colostomy, mucous fistula, or Hartmann procedure. It is believed that short-chain fatty acids normally produced by anaerobic bacteria serve as a trophic factor for the colonocytes. The diversion colitis quickly resolves on restoration of intestinal continuity; when restoration is not possible, the administration of short-chain fatty acid enemas is beneficial.

**14. What type of ileal pouches are used?**

Although higher-volume pouches are advocated (W = quadruple, S = triple, and J = two-limbed), the long-term functional results may not be all that different. The author prefers a long (15 cm) J pouch (when feasible in one stage) preserving the anal transition zone. The procedure has classically been two-staged, with construction of a temporary ileostomy followed at an interval by ileostomy takedown. Recent experience has shown that the morbidity of a one-stage IPAA may be less if the patient is taking no or low-dose steroids and the operation is performed without complication. Because there is really only *one shot* at getting it right (pelvic sepsis significantly diminishes ultimate pouch function), intraoperative judgment is at a premium.

## ANORECTAL DISEASE

**15. What are anal fissures?**

A generally painful rip or tear in the sensitive anoderm of the anal canal. Most anal fissures are located in the posterior (90%) or anterior (10%) midline of the anal canal.

**16. What disorders should be considered in patients with laterally situated anal fissures?**

Disorders to consider are Crohn's disease, ulcerative colitis, syphilis, tuberculosis, leukemia, carcinoma, and acquired immunodeficiency syndrome.

**17. How are acute fissures managed?**

Conservative treatment consists of stool softeners and bulk agents to avoid hard bowel movements, sitz baths to help decrease sphincter spasm, topical anesthetics, and topical steroids. Topical nitroglycerin or nifedipine ointment reduces anal spasm. Injection of botulinum toxin also has been used to relax the anal sphincter.

**18. What are the signs of a chronic anal fissure? What do they imply?**

A chronic anal fissure can be identified by the presence of a sentinel pile (skin tag or hemorrhoid), anal ulcer (with fibropurulent material or visible internal sphincter muscle in the base), and a hypertrophied anal papilla arising from the dentate line. A chronic anal fissure usually does not respond to conservative treatment, and surgical intervention is in order.

**19. Which surgical procedures are available for treatment of a chronic anal fissure?**

Open or closed lateral internal sphincterotomy, excision (ulcerectomy), excision and Y-V or other anoplasty, or anal dilation.

**20. Differentiate external from internal hemorrhoids.**

- External hemorrhoids originate distal to the dentate line of the anus and are covered by squamous epithelium. External hemorrhoids may thrombose or become filled with clotted blood. Typically these are painful, involving the anoderm.
- Internal hemorrhoids arise above (proximal to) the dentate line and are covered with transitional and columnar epithelium. **First-degree** hemorrhoids swell and bleed. **Second-degree** hemorrhoids prolapse and spontaneously reduce. **Third-degree** hemorrhoids prolapse and can be manually reduced, whereas **fourth-degree** hemorrhoids are irreducible. Typically these are not painful above the anoderm.

**21. How are acute hemorrhoids treated?**

- Topical medicines such as anesthetics, hydrocortisone preparations, and astringents (witch hazel, glycerin, magnesium sulfate) can be used.
- Emergency hemorrhoidectomy is performed to excise the inflamed hemorrhoid. Circular stapling devices have also been used to treat larger hemorrhoids.

**22. List several minimally invasive outpatient treatments of internal hemorrhoids.**

Outpatient treatments are rubber band ligation, bipolar cautery, direct current electrical therapy, infrared coagulation, sclerotherapy, and cryotherapy.

**23. How is an acute thrombosed external hemorrhoid best treated?**

Excision of the clot and involved hemorrhoidal complex (as opposed to incision alone) best prevent future recurrence at the same site.

**24. Explain the cause of anorectal abscesses and fistulas.**

A cryptoglandular origin seems to provide the best explanation. Four to 10 anal glands enter the anal canal at the level of the crypts in the dentate line. The glands extend back into the internal sphincter two thirds of the time and into the intersphincteric space half the time. Blockage of the gland leads to an overgrowth of bacteria with resultant pressure necrosis and abscess formation. An abscess or infection that causes an abnormal communication between two surfaces (such as the anal canal and perianal skin) creates a fistula.

**25. List the various types and locations of anorectal abscesses.**

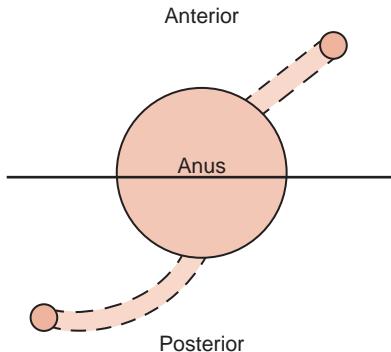
Types and locations are submucosal, intersphincteric, perianal (anal verge), ischiorectal (perirectal), and suprarectal.

**26. What is the best treatment for an anorectal abscess?**

Prompt incision and drainage. There is little or no role for antibiotics (exceptions are immunocompromised patients and patients with prosthetic heart valves or severe cellulitis) and no reason to wait for the abscess to point or become fluctuant before surgical treatment.

**27. What is the Goodsall rule?**

See Figure 76-1.



**Figure 76-1.** The Goodsall rule helps predict the location of the internal opening of an anal fistula based on the site of its external opening. Accurately determining the *criminal* crypt of fistula origin on the dentate line is important at the time of surgical treatment, generally fistulotomy. If the anus is divided into imaginary anterior and posterior halves in the coronal plane, posterior fistulas tend to curve into the posterior midline. Anterior fistulas shorter than 3 cm tend to proceed radially to the dentate line, whereas anterior fistulas longer than 3 cm may track back to the posterior midline.

**28. What is a seton?**

A seton is a drainage device used to control and treat an anal fistulous abscess. It is inserted through and through a fistula tract and secured to itself, thus making a circle about some portion of the anal sphincter muscle. It serves as a cutting device to exteriorize the fistula slowly. Typical setons are Penrose drains, Silastic vessel loops, or silk sutures.

**29. What are the common indications for inserting a seton?**

- High fistulous abscesses involving greater than one-half the length of the anal canal muscle
- Anterior fistulas in a woman
- Inflammatory bowel disease
- Older adult patients or patients with multiple previous anorectal surgeries

**30. List treatment options for anorectal fistulas.**

- Fibrin sealant glues
- Collagen plug
- Monoclonal anti-tumor necrosis factor antibodies for Crohn's fistulas
- Park fistulotomy procedure, with excision and debridement of the fistula tract, muscle repair, advancement flap coverage of the internal opening, and drainage of the external portion of the fistula tract

**31. When is anorectal suppurative disease especially dangerous?**

In the presence of neutropenia, as associated with chemotherapy. Unfortunately, surgery and even anorectal digital examination may be contraindicated. Often bacterial infection is widespread without formation of purulence or a classic abscess.

**32. What is Fournier gangrene?**

Fournier gangrene is a necrotizing soft tissue infection of the perineum. Although rare, it can present as a suspected perirectal abscess, so a high index of suspicion must be maintained. Treatment is prompt surgical debridement.

- Local signs—crepitance, bullae, cellulitis
- Systemic signs—altered mental status, hypotension, oliguria

**33. What is perianal Paget disease?**

Perianal (extramammary) Paget disease is characterized by a scaly, inflamed dermis resembling eczema. Biopsy reveals typical Paget cells with round, pale, vacuolated, mucin-positive cytoplasm with an eccentric reticular nucleus. It is often a chronic condition, but underlying carcinoma must be ruled out as invasive anorectal cancer may be associated with Paget disease.

**34. Which patient characteristics are associated with rectal prolapse?**

- Chronic constipation
- Deep pouch of Douglas
- Neurologic disease
- Patulous anus
- Female sex
- Diastasis of the levator ani muscles
- Nulliparity
- Lack of fixation of the rectum to the sacrum
- Redundant rectosigmoid colon
- Previous anorectal surgery

**35. What surgical options are available for rectal prolapse?**

Resection (standard or laparoscopic approach) of redundant colon and rectum with a rectal fixation (rectopexy) is generally associated with the best long-term results in patients who are fit for a major operation. For patients at higher risk for major surgery, other procedures have been described, including narrowing the anal orifice (Thiersch operation) or a perineal rectosigmoidectomy with levator placation (Altemeier procedure).

## **COLORECTAL MALIGNANCIES**

### **RECTAL CANCER**

**36. What is the best way to stage rectal cancer?**

It has been said that an educated finger is the best instrument; however, the overall accuracy of staging depends on the information desired and the modality chosen. Staging guidelines are outlined in Table 76-1; however, operator experience and judgment remain invaluable.

**37. When is endoscopic mucosal resection (EMR) indicated?**

EMR is indicated in the presence of large benign polyps and some T1 tumors. Those with adverse features such as lymphovascular invasion and positive margins need additional therapy such as full-thickness (surgical) excision or radiotherapy.

**Table 76-1.** Estimated Accuracy of Rectal Cancer Staging Modalities

	<b>ENDOSCOPIC ULTRASOUND (u)</b>	<b>MAGNETIC RESONANCE IMAGING</b>	<b>COMPUTED TOMOGRAPHY</b>
T stage	85%	80%	65%
N stage	75%	60%	55%
Overall	80%	70%	60%

**38. What are the indications for neoadjuvant (before surgery) and adjuvant (after surgery) therapy?**

Any N1 or T4 disease indicates the need for therapy. It is generally indicated for uT3 lesions and some uT2 lesions. Neoadjuvant therapy decreases local recurrence rates and improves chances for sphincter preservation.

**39. What is an abdominal perineal resection (APR), and when is it indicated?**

APR is the removal of the entire anus and rectum with an end colostomy. It is generally indicated for total anal incontinence or tumors that invade the anal sphincter. Low rectal cancers that do not directly invade the anal sphincter can, in certain situations, be managed with sphincter preservation and restorative coloanal anastomosis.

**COLON CANCER****40. What are the fundamental principles of colon resection for cancer?**

- A 5-cm margin on either side of the tumor
- Vascular supply taken at the origin of the closest named vessel (ileocolic, right colic, middle colic, left colic, inferior mesenteric artery)
- Adequate lymph node staging (generally aim for a minimum of 12 nodes evaluated)

**41. Does laparoscopic surgery compromise the chance for a cure?**

No. Several prospective randomized studies have demonstrated equivalent cancer survival from both open and laparoscopic approaches. The key to achieving this is to conduct the same extent of resection either way. Initial concerns for development of port site metastasis are unfounded.

**42. What are the pros and cons of laparoscopic versus open colectomy?****Pro**

- Smaller incisions
- Less pain medication
- Quicker recovery and return to work
- Possible earlier return of bowel function

**Con**

- Steep learning curve for technical proficiency
- Increased difficulty in reoperative setting or with acute inflammation (diverticulitis)

**BENIGN COLON AND SMALL BOWEL DISEASE****43. What are the findings of sigmoid volvulus on plain abdominal film and contrast enema?**

The plain film demonstrates a *bent inner tube* or *coffee-bean* sign of massively dilated, air-filled sigmoid colon arising out of the pelvis. The contrast enema shows a *bird's beak* appearance as the colon narrows at the twist at the rectosigmoid junction.

**44. How is a nonstrangulated sigmoid volvulus treated?**

Treatment is with a rigid or flexible sigmoidoscopic or colonoscopic decompression, followed by elective sigmoid resection.

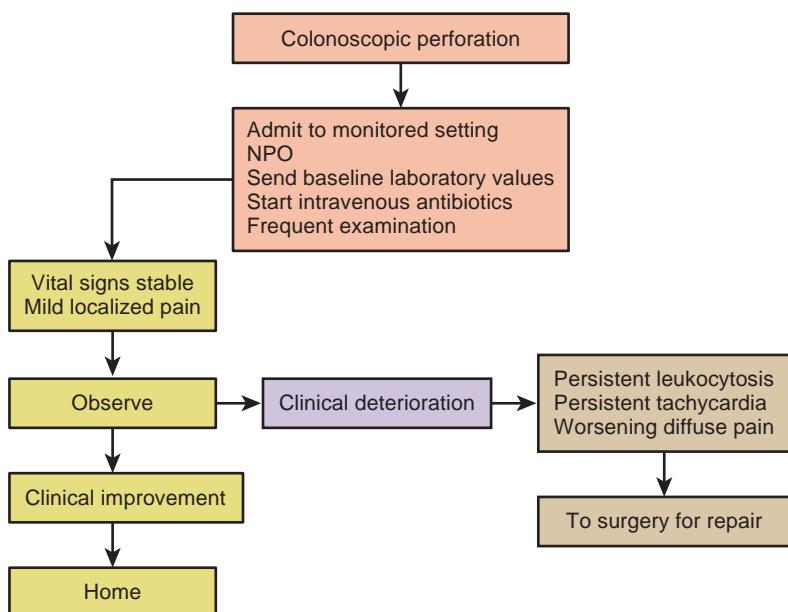
**45. Why should elective surgery be performed after a successful endoscopic detorsion and decompression of a sigmoid volvulus?**

Recurrence is the rule with sigmoid volvulus. Elective sigmoid resection of prepped and decompressed bowel generally can be accomplished with very low mortality. Emergency operation for a sigmoid volvulus involves a higher mortality rate.

**46. Do colon perforations from colonoscopy mandate surgical repair?**

Not all perforations require surgery. Sound clinical judgment is critical. Limited controlled perforations with minimal contamination generally seal spontaneously. Signs of systemic illness (tachycardia, fever, hypotension, increasing abdominal pain) generally require surgery (Figure 76-2).

**Figure 76-2.** Algorithm for managing colonoscopic perforation. NPO, Nothing by mouth.



#### 47. What is Ogilvie syndrome?

Colonic pseudoobstruction presents with signs, symptoms, and radiologic findings suggestive of obstruction without a mechanical source. It is most often seen in hospitalized patients with other underlying medical conditions found to have marked colonic air on abdominal radiograph. Treatments include managing the underlying medical issues, colonoscopic decompression, and neostigmine.

#### 48. What does plain radiographic study of the abdomen reveal in large bowel obstruction?

A large bowel obstruction demonstrates differential air-fluid levels (stair steps) of the small intestine or a massively dilated colon. The colon is identified by the presence of haustral folds, compared with the valvulae conniventes of the small intestine. The rectum is usually gasless, although gas distal with a colonic obstruction may not have completely cleared the distal colon. A picture resembling small bowel obstruction (SBO) alone may appear in a very proximal colon obstruction. Colonic pseudoobstruction also may give a roentgenographic picture similar to true obstruction.

#### 49. What radiologic findings are associated with gallstone ileus?

Air in gallbladder or biliary tree, SBO at the level of the ileocecal valve, large bowel obstruction at the sigmoid colon, and occasionally a calcified mass at the point of obstruction are associated with gallstone ileus.

#### 50. What does endometriosis have to do with the alimentary system?

Endometriosis is the presence of functioning endometrial tissue outside the uterus. When this hormonally active tissue implants on intestinal surfaces, it can cause pain, cyclical bleeding, and obstructive symptoms.

#### 51. What is a primary bowel obstruction?

*Primary bowel obstruction* refers to an intestinal obstruction without a known cause such as adhesions or a prior cancer diagnosis. Primary bowel obstructions generally require an operation at some point.

#### 52. How is postoperative ileus differentiated from postoperative SBO?

This distinction can be extremely difficult. Postoperative ileus generally occurs up to 1 week after operation, whereas postoperative SBO may last 7 to 30 days or longer. SBO is associated with nausea, vomiting, distention, and abdominal pain, whereas an ileus may be associated with painless failure to pass bowel movements. The radiographic picture may or may not include differential air-fluid levels in each disorder.

#### 53. Is treatment of postoperative SBO different from treatment of SBO remote from surgery?

Yes. Generally, one waits out an early postoperative obstruction for an indefinite period, as long as there is no evidence of strangulation or impending perforation. *Approximately 80% resolve without surgery.* Nasogastric suction is the mainstay of treatment for postoperative SBO, whereas “the sun never sets” on a suspected mechanical SBO remote from surgery; one generally operates as soon as the diagnosis of complete obstruction is made.

#### 54. What is the most common cause of SBO?

Adhesions are the most common cause of SBO.

**55. Can adhesions be prevented?**

Absorbable hyaluronate and carboxymethylcellulose membranes lead to a statistically significant reduction in the number and severity of intraabdominal adhesions, although it is unclear if this translates into a reduced future need for operative intervention.

**56. What are the pathologic findings of late radiation enteritis?**

Obliterative arteritis occurs in late radiation enteritis. Severe fibrosis commonly is accompanied by telangiectasia formation. The pelvis may be “frozen” because of incredibly dense adhesions and fibrosis.

**57. What are general principles of managing radiation enteritis?**

Medical management options are generally exhausted before surgery is contemplated or attempted. Cholestyramine, elemental diets, and total parenteral nutrition are commonly used. Although surgery is not withheld for urgent indications (complete obstruction, perforation, abscess not amenable to percutaneous drainage, bleeding, or unresponsive fistulas), it carries significant morbidity and mortality rates. Enterolysis, or separating of adhesions, in irradiated bowel is associated with a high rate of fistula formation. Anastomosis can be performed safely if at least one end of bowel to be connected has not been irradiated. Intestinal bypass procedures without resection may be necessary.

**58. What treatments are available for bleeding radiation proctitis?**

Treatments include topical antiinflammatory drugs (steroids, mesalamine enemas, or suppositories), targeted endoscopic application of thermal, bipolar, argon plasma coagulation or laser ablation of telangiectasias, and lastly application of 4% formaldehyde solutions (under controlled situations in the operating room).

Please access ExpertConsult to view a [Clinical Vignette](#) for this chapter.

**BIBLIOGRAPHY**

1. Beck DE. The ASCRS textbook of colon and rectal surgery. 2nd ed. New York: Springer Science and Business Media LLC; 2011.
2. Bordeianou L, Maguire L. State-of-the-art surgical approaches to the treatment of medically refractory ulcerative colitis. *J Gastrointest Surg* 2013 Nov;17(11):2013–9.
3. Danese S. New therapies for inflammatory bowel disease: from the bench to the bedside. *Gut* 2012;61(6):918–32.
4. Fazio VW, Kiran RP, Remzi FH, Coffey JC, Heneghan HM, Kirat HT, et al. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. *Ann Surg* 2013;257(4):679–85.
5. Fleshman J, Sargent DJ, Green E, et al. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. *Ann Surg* 2007;246:655–62.
6. Kumar S, Wong PF, Leaper DJ. Intra-peritoneal prophylactic agents for preventing adhesions and adhesive intestinal obstruction after non-gynaecological abdominal surgery. *Cochrane Database Syst Rev* 2009;1, CD005080.
7. Lacy BE, Weiser K. Gastrointestinal motility disorders: an update. *Dig Dis* 2006;24:228–42.
8. Patel SG, Ahnen DJ. Familial colon cancer syndromes: an update of a rapidly evolving field. *Curr Gastroenterol Rep* 2012;14 (5):428–38.
9. Shen B. Acute and chronic pouchitis—pathogenesis, diagnosis and treatment. *Nat Rev Gastroenterol Hepatol* 2012;9 (6):323–33.
10. Vasen HF, Mösllein G, Alonso A. Guidelines for the clinical management of familial adenomatous polyposis (FAP). *Gut* 2008;57:704–13.
11. Zaghiyan KN, Fleshner P. Anal fissure. *Clin Colon Rectal Surg* 2011;24(1):22–30.

**Websites**

American Society of Colon and Rectal Surgeons. <http://www.facsrs.org> [Accessed September 22, 2014].  
National Comprehensive Cancer Network. <http://www.nccn.org> [Accessed September 22, 2014].

# OBESITY AND SURGICAL WEIGHT LOSS

Jonathan A. Schoen, MD

## 1. What is the definition of obesity?

Obesity is excess body fat.

## 2. How is body fat relative to weight usually measured?

Body fat relative to weight is measured by calculating the body mass index (BMI). This is simply  $\text{kg}/\text{m}^2$ .

## 3. Describe the BMI classification system.

- underweight <18
- healthy weight 18-24
- overweight 24-29
- obese 30-39
- morbidly obese  $\geq 40$

## 4. What are the limitations of BMI?

BMI is limited in those with a higher proportion of fat relative to muscle (older adults) or in those with an unusually high proportion of muscle (bodybuilders).

## 5. In 2013, what proportion of the U.S. adult population is considered overweight?

In 2013, 69% or 155 million adults were considered by the CDC to be overweight.

## 6. In 2013, what proportion of the U.S. adult population is considered obese?

In 2013, 36% or 78 million adults were considered obese. Obesity is considered a national epidemic by the CDC.

## 7. How many U.S. adults are estimated to have a BMI of more than 40 (morbid or extreme obesity)?

More than 1 in 20 (6%) have a BMI of more than 40.

## 8. Are there health implications associated with a BMI of 30 or more?

Yes. Obesity is considered a major factor contributing to many health problems, including diabetes mellitus (DM), hypertension, sleep apnea and Pickwickian syndromes, asthma, coronary artery disease, cardiomyopathy including cardiac failure, gastroesophageal reflux disease (GERD), degenerative joint disease, hypercholesterolemia, fatty liver, gout, urinary incontinence, gallbladder disease, psychological disorders, menstrual irregularities, and certain cancers (endometrial, colon, postmenopausal breast, esophageal, hepatocellular, prostate, and kidney).

## 9. Can obesity lead to premature death?

Yes. Individuals who have a BMI of more than 30 have a 50% to 100% increased risk of premature death from all causes compared with individuals with a BMI 20 to 25.

This increased mortality is directly proportional to increasing BMI. Obesity causes 400,000 preventable deaths in the United States and is a close second to smoking as the leading cause of preventable death.

## 10. How successful is nonsurgical treatment of morbid obesity?

Evidence suggests that nonsurgical treatment (diet and behavior modification, exercise programs, and psychological support) for morbid obesity has a more than 90% failure rate. Similarly, pharmacologic therapy for morbid obesity has been hampered by serious side effects and, overall, has met with disappointing results.

## 11. Have there been any recent prospective randomized medical trials looking at efficacy of lifestyle intervention or pharmacotherapy?

Yes. The Look AHEAD (Action for Health in Diabetes) trial had an intensive lifestyle intervention arm with a significantly higher weight loss than the control group (6% vs. 3.5%). The trial was stopped early because the primary outcome of cardiovascular events was no different between groups.

Two pharmacotherapies have recently been approved by the Food and Drug Administration (FDA): phentermine plus topiramate (Qsymia) and Lorcaserin (Belviq). The CONQUER trial showed that Qsymia could lead to nearly 9% weight loss, which makes it currently the most effective nonsurgical therapy.

## 12. What is the most effective treatment of obesity?

The National Institutes of Health (NIH) consensus statement in 1991 concluded that medical therapy was ineffective for severe clinical obesity and that surgery was indicated for this population of patients.

**13. What was the NIH consensus conference statement?**

Those with severe clinical obesity defined as a BMI of 40 or more (morbid obesity) or a BMI of 35 to 39 with severe, debilitating comorbidities are best treated with a surgical weight loss procedure.

**14. Have there been any updates to the 1991 NIH surgical indication criteria?**

There have not been any NIH updates; however, there has been a trend in extending surgical criteria to those with BMIs less than 35. The International Diabetes Federation added to their position statement in 2011 that bariatric surgery should be considered for those with poorly controlled type 2 DM and BMI 30 or more. The FDA in 2011 added approval for gastric banding for individuals with a BMI of 30 or more provided a serious comorbidity exists.

**15. List the contraindications to bariatric operations.**

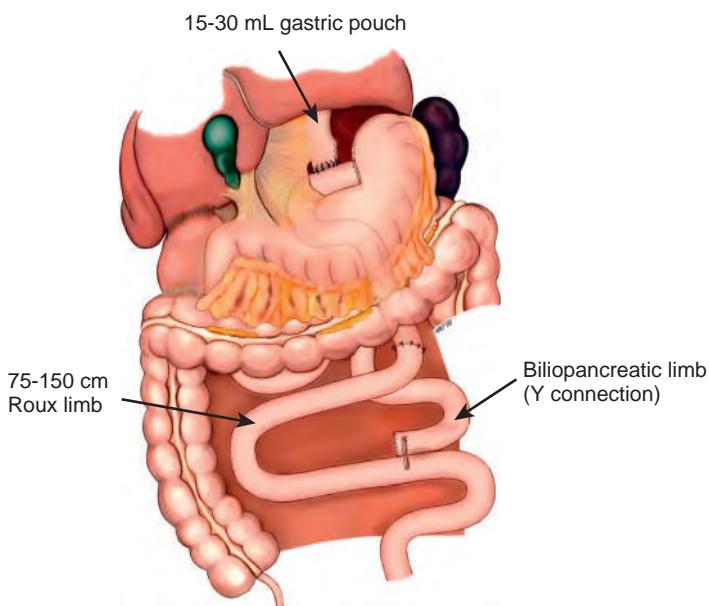
- Active endocrine disorders that contribute to obesity
- Psychological instability
- Alcohol or drug abuse
- End-stage organ disease or terminal cancer

**16. Categorize the surgical options for weight reduction.**

- Restrictive
- Combination restrictive and malabsorptive
- Malabsorptive
- Other

**17. List the options for restrictive surgery.**

- *Vertical-banded gastroplasty:* A stapling device is used to divide the stomach vertically along the lesser curve starting at the angle of His to create a small (20-mL) pouch. A prosthetic nonadjustable device is then wrapped around the outlet of the pouch to prevent it from dilating over time. This operation has fallen out of favor because of poor long-term weight loss and issues with GERD and pouch obstruction, and is no longer performed. This operation is frequently converted to a gastric bypass. The mistake often made is to dilate the outlet of the pouch, but with a fixed band this approach usually does not work.
- *Gastric banding:* This procedure is performed laparoscopically and involves placement of an adjustable silicone band around the top of the stomach to create a small (15-mL) pouch. The band is connected to a reservoir placed in the subcutaneous tissue that enables band adjustment.
- *Sleeve gastrectomy:* This procedure is gaining in popularity and involves stapling and removing a majority of the gastric body and fundus, leaving the lesser curvature and a small amount of antrum ([Figure 77-1](#)). The pylorus remains intact. The staple line is usually formed over a bougie sized between 32 and 40 French ([E-Figure 77-2](#)).



**Figure 77-1.** This anatomic drawing demonstrated the surgical changes seen with Roux-en-Y gastric bypass.



**E-Figure 77-2.** Postoperative upper gastrointestinal Gastrograffin radiograph demonstrates the sleeve gastrectomy (narrow gastric remnant arrows) and slow drainage of contrast into the antrum (\*) and duodenum (\*\*). (Courtesy Peter R. McNally, DO, MACG.)

**18. Describe the combined restrictive-malabsorptive surgical option.**

Known as the *Roux-en-Y gastric bypass*, the restrictive-malabsorptive option has been performed in the United States for nearly 50 years. It has been performed laparoscopically for the past 15 years and historically is the gold standard and most common operation for weight loss in this country.

The procedure is performed in the following way:

- A. A 15- to 30-mL gastric pouch is created by completely dividing the proximal stomach (the restrictive part).
- B. The proximal jejunum is divided 15 to 50 cm from the ligament of Treitz (length depends on surgeon preference).
- C. The distal end of this divided proximal jejunum is measured out between 75 and 150 cm and this Roux limb is anastomosed to the gastric pouch. The varying length of the Roux limb is thought to affect absorption of calories; however, this likely has a small role in weight loss unless the Roux limb is made very long (a distal gastric bypass).
- D. The proximal end of divided jejunum (biliopancreatic limb) is anastomosed to the Roux limb at the previously measured length, creating the Y configuration (see [Figure 77-1](#)).

**19. What is the option for malabsorptive surgery?**

Biliopancreatic diversion with and without a duodenal switch. A subtotal gastrectomy is performed, leaving a gastric remnant of 250 to 500 mL. The small bowel is divided 200 to 300 cm proximal to the ileocecal valve and the ileum is anastomosed to the stomach. The jejunum is connected to the side of the ileum approximately 50 to 100 cm from the ileocecal valve. This procedure results in malabsorption by creating a short common channel for digestion and absorption of food.

**20. What are some of the other weight-loss procedures?**

Alternative weight-loss procedures are the intragastric balloon, the gastric pacer, the intraluminal duodenal sleeve (EndoBarrier), and endoscopic or laparoscopic greater curve plication. These are being studied for efficacy and may have a limited role in the future.

**21. What are the weight-loss expectations after each procedure?**

Success following bariatric surgery is determined by both weight lost and improvement in obesity-related comorbidities. Most surgical studies report outcome as % excess weight loss (excess weight = preoperative weight – ideal weight). Gastric banding typically produces 40% to 50% excess weight loss over 2 to 3 years, but has at least a 20% failure rate. The gastric bypass has long-term data showing a 50% loss of excess body weight maintained over 14 years. Most current laparoscopic literature shows up to 5-year excess weight loss in the 60% to 80% range. There is typically some recidivism after 2 years and it has a 10% failure rate. The biliopancreatic diversion is the most effective weight loss procedure and results in the loss of 80% excess weight maintained over the long term. The sleeve gastrectomy is currently being studied for long-term success and 5-year data shows excess weight loss in the 50% to 60% range with a 20% failure rate.

**22. Are these weight loss procedures just cosmetic operations?**

No. Depending on the procedure, with the gastric band being the least effective but the safest and the biliopancreatic diversion carrying the greatest risks but the most efficacy, nearly all of the patient's obesity-induced comorbid conditions are improved or resolved within 1 year.

**23. Do surgical weight loss procedures translate to improved long-term survival?**

Yes. Recent studies have shown up to a 40% reduction in long-term mortality in a surgical group compared with a nonsurgical group.

**24. Which comorbidity can have the most dramatic improvement?**

Type 2 DM shows the most dramatic improvement. In fact, there is much discussion about the surgical treatment for type 2 DM given the very impressive results after the gastric bypass and biliopancreatic diversion.

Approximately 90% of diabetics are resolved of their hyperglycemia after these two operations even prior to weight loss. In fact, three recent prospective randomized studies comparing surgery to intensive medical therapy have confirmed that the biliopancreatic diversion is the most effective operation for type 2 diabetes followed by the Roux-en-Y gastric bypass and then the sleeve gastrectomy.

**24. How does the gastric bypass and biliopancreatic diversion "cure" diabetes prior to weight loss?**

This is more complex than calorie restriction and involves changes in gut hormones. Bypassing the duodenum and proximal jejunum (the proximal gut theory) changes gastric inhibitory polypeptide hormone levels and likely other as yet unknown hormonal levels that play a role in the incretin effect. The hindgut theory is based on the hypothesis that food now reaches the terminal ileum and colon faster, resulting in a greater activation and release of other hormones, namely glucagon-like peptide 1 and peptide YY 3-36, which result in greater insulin secretion and sensitivity.

**25. Can these changes in the gut hormonal milieu have a detrimental effect?**

Although these changes are only beginning to be understood, the rare hyperinsulinemic hypoglycemia and apparent beta cell hyperplasia seen years after a gastric bypass may be due to hormonal overstimulation of the pancreas.

**26. What are other complications can occur after a gastric bypass?**

Complications can be divided into early (<30 days) and late.

Early complications include mortality (0.3%), anastomotic leaks (2%), gastrointestinal bleeding (2%), pulmonary embolus (0.4%), and wound infection (3%).

Late complications include anastomotic stenosis (5%), small bowel obstruction from internal hernias (3%), marginal ulceration (10%), cholelithiasis (10%), and vitamin and mineral deficiencies.

**27. How are anastomotic leaks handled?**

These are usually at the gastrojejunostomy anastomosis and can be treated conservatively with total parenteral nutrition (TPN), maintaining nothing by mouth, percutaneous catheter drainage, and possibly covered stent if the patient is stable. For anastomotic leaks in an unstable patient or a nonhealing fistula, surgical repair necessary.

**28. What is a marginal ulcer and how is it treated?**

A marginal ulcer is usually found on the jejunal side of the gastrojejunostomy ([E-Figure 77-3](#)). It is often related to local ischemia, smoking, or nonsteroidal antiinflammatory drug use and usually heals with proton pump inhibitor or sucralfate therapy (Access ExpertConsult to see Video 77-1).

**29. How is an anastomotic stenosis treated?**

Many surgeons purposely make the gastrojejunostomy anastomosis small (approximately 0.8 cm) to enhance the restrictive aspect of the operation. If this anastomosis becomes too small for the patient to tolerate, endoscopic balloon dilatation is usually successful ([E-Figure 77-4](#) and Video 77-2; also see [E-Figure 77-3](#)).

**30. What are the vitamin and mineral deficiencies and potential long-term risks?**

Vitamin B<sub>12</sub>, folate, and iron deficiencies occur in up to 40% of patients without lifetime supplementation. Hypocalcaemia with or without vitamin D deficiency and resulting osteoporosis can also occur without lifelong supplementation. The deficiencies are a result of bypassing most of the stomach, all of the duodenum, and the proximal jejunum.

**31. Why would someone choose a gastric banding procedure over a Roux-en-Y gastric bypass?**

It is safer. It is simple to place and reversible as there is no anatomic reconfiguration. It also avoids vitamin and mineral deficiencies. It requires close follow-up for best results.

**32. What are the specific complications after gastric banding?**

Complications are erosion of the band through the pouch (1%), slippage or prolapse of the band around the pouch (5%), band migration and esophageal obstruction (5%-10%), port or tubing break or infection (<5%), and need for reoperation (at least 10%).

**33. What is the long-term failure rate for gastric banding?**

It may be as high as 50% because of weight loss failure or for complication, which is one of the reasons why its popularity and use has been decreasing worldwide.

**34. Why is the sleeve gastrectomy gaining in popularity?**

It has less long-term risk compared with the gastric bypass and biliopancreatic diversion (less marginal ulcers, small bowel obstruction, and vitamin and mineral deficiencies) and less maintenance than gastric banding, and the weight loss and comorbidity improvement results are good and lie between gastric banding and gastric bypass.

**35. What are the risks associated with the sleeve gastrectomy?**

Risks are mortality (0.3%), anastomotic leak (1%), obstruction (1%), new GERD (20%), and vitamin B<sub>12</sub> and calcium deficiency.

**36. Describe the location and treatment of leak and obstruction after sleeve?**

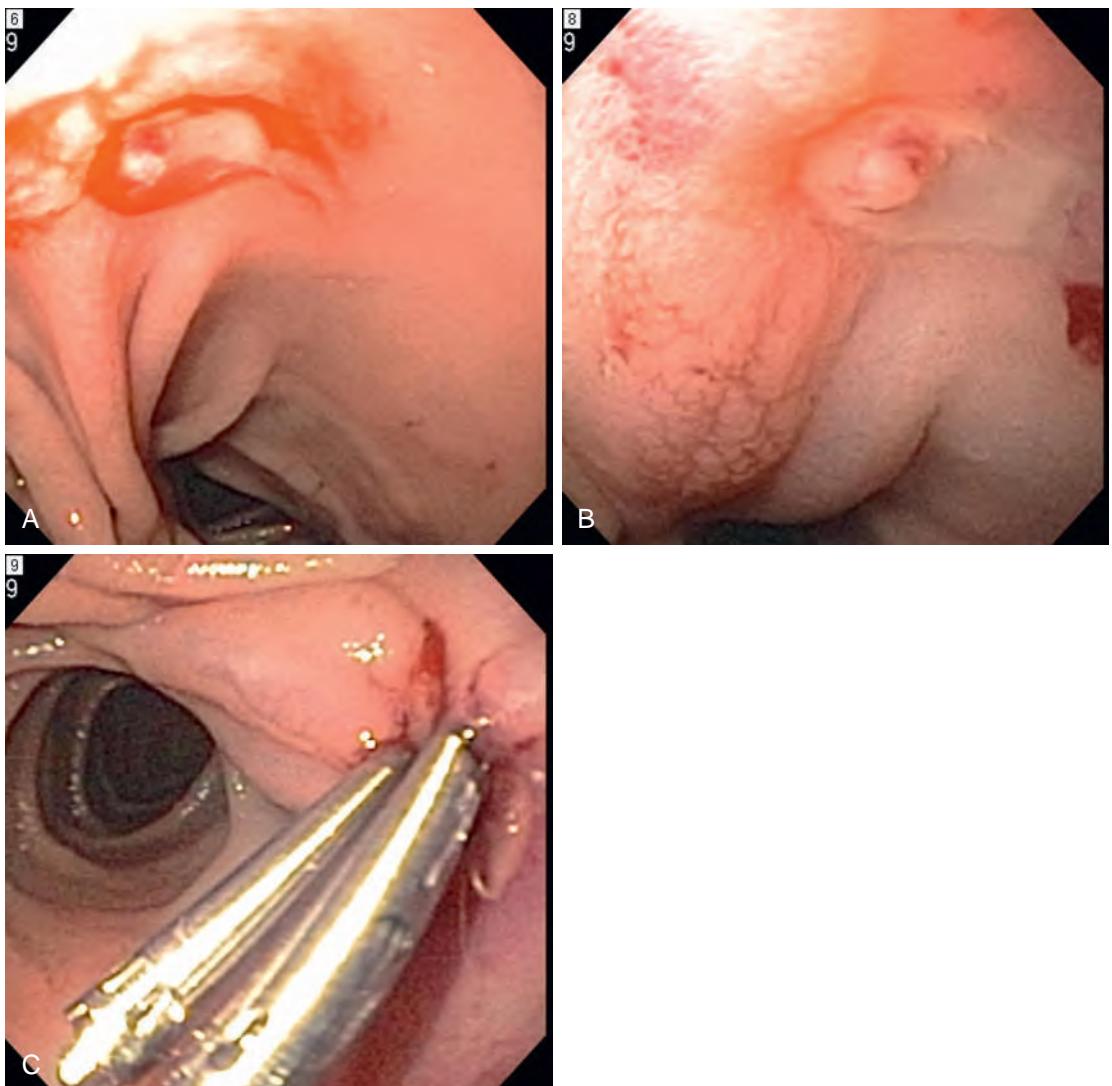
Leaks are most often near gastroesophageal junction at the angle of His, and are usually treated conservatively unless the patient is unstable. This includes percutaneous drainage and covered stent. Obstruction usually occurs at the incisura angularis and is treated with endoscopic dilation or laparoscopic myotomy. Rarely conversion to gastric bypass or esophagojejunostomy is needed for severe or non-healing complication.

**37. How does the biliopancreatic diversion work?**

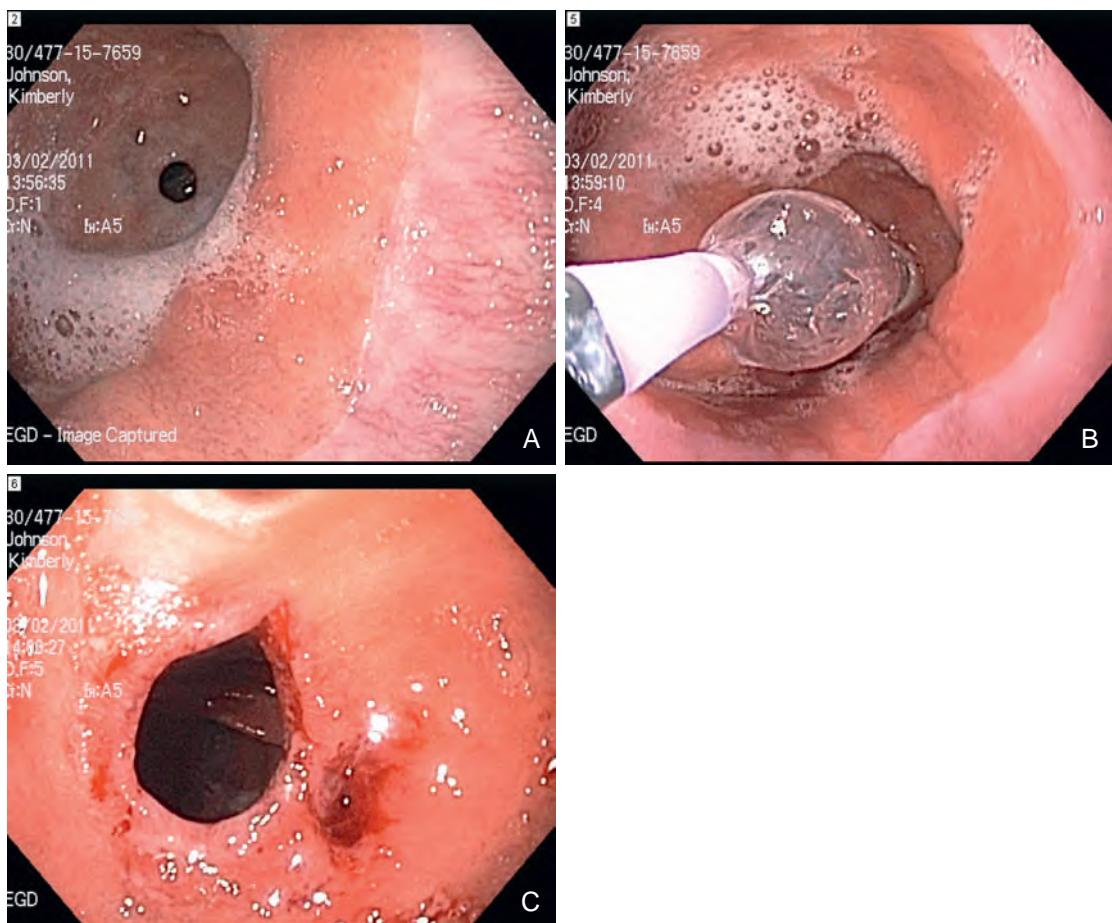
Biliopancreatic diversion creates a fixed amount of malabsorption whereby all fat and most starch can only be absorbed in 50 to 100 cm of terminal ileum.

**38. Is malnutrition seen with biliopancreatic diversion?**

Yes. Protein has only 200 to 300 cm of ileum to be absorbed. Up to 30% of patients end up with protein-calorie malnutrition requiring hospitalization and TPN or surgical revision. A high-protein, lower-carbohydrate diet is required to avoid inducing a state of starvation mimicking kwashiorkor disease.



**E-Figure 77-3.** Bleeding “jejunal side” anastomotic ulcer with visible vessel (A), treated with dilute (1:100,000) intramucosal epinephrine (B), and mucosal clips (C). (Courtesy Peter R. McNally, DO, MACG.)



**E-Figure 77-4.** Endoscopic photograph demonstrating an anastomotic stricture after Roux-en-Y gastric bypass treated by through-the-scope balloon dilation: A, predilation, B, intraprocedure dilation, and C, postdilation. (Courtesy Peter R. McNally, DO, MACG.)

### **39. Are there other health risks associated with biliopancreatic diversion?**

Yes. The risks are similar to gastric bypass except higher. Mortality is 1% to 2%. Leaks, obstructions, and ulcers can happen as well. Vitamin B<sub>12</sub>, folate, and iron deficiency anemia are common without lifelong supplementation. Hypocalcemia and bone demineralization are common, leading to bone pain and osteoporosis if calcium and vitamin D are not administered in high doses lifelong. Patients also complain of frequent diarrhea, foul-smelling stool and flatulence, and halitosis.

### **40. Why would one choose biliopancreatic diversion?**

Aside from being the most effective weight loss and metabolic improvement procedure, patients can eat as much as they want. This may be the best procedure for the binge-eater or compulsive snacker who classically fails the other weight loss procedures. The biliopancreatic diversion has also been proven to be effective for the so-called super morbid obese (BMI  $\geq 50$ ) who may not lose as much weight with the other procedures.

### **41. What does preoperative surgical counseling entail with any procedure?**

All patients undergo extensive preoperative education and counseling and must attend a required nutritional class and pass a psychological evaluation. Although this is practice dependent, all patients should be thoroughly educated that these procedures are just tools—the most effective tools for weight loss to date—and for long-term success they must combine the operation with diet compliance, daily exercise, support groups, and close follow-up.

Please access ExpertConsult to view the E-Figures and videos for this chapter.

### **BIBLIOGRAPHY**

1. Belachew M, et al. Laparoscopic adjustable gastric banding. *World J Surg* 1998;22:955–63.
2. Biertho L, et al. Laparoscopic gastric bypass versus laparoscopic adjustable gastric banding: a comparative study of 1,200 cases. *J Am Coll Surg* 2003;197:536–47.
3. Hess DS, Hess DW. Biliopancreatic diversion with a duodenal switch. *Obesity Surg* 1998;8:267–82.
4. Higa KD, et al. Laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Arch Surg* 2000;135:1029–34.
5. NIH Consensus Conference. Gastrointestinal surgery for severe obesity. *Ann Intern Med* 1991;115:956–61.
6. Podnos Y, et al. Complications after laparoscopic gastric bypass. *Arch Surg* 2003;138:957–61.
7. Pories W, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann Surg* 1995;222:339–51.
8. Schauer PR, et al. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Ann Surg* 2000;232:515–29.
9. Scopinaro N, et al. Biliopancreatic diversion. *World J Surg* 1998;22:936–46.
10. Wittgrove AC, et al. Laparoscopic gastric bypass, Roux-en-Y—500 patients: technique and results, with 3–60 month follow-up. *Obesity Surg* 2000;10:233–9.
11. Adams T, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007;357:753.
12. Buchwald H, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA* 2004;292:1724–37.
13. Buchwald H, et al. Trends in mortality in bariatric surgery: a systematic review and meta-analysis. *Surgery* 2007;142:621.
14. Demaria EJ, et al. High failure rate after laparoscopic adjustable silicone gastric banding for treatment of morbid obesity. *Ann Surg* 2001;233:809–18.
15. Gadde K, et al. CONQUER: a randomized, placebo-controlled, phase 3 trial. *Lancet* 2011;377.
16. Ikramuddin S, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia. *JAMA* 2013;309:21.
17. The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369:2.
18. Mingrone G, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012;366:17.
19. Sjöström L, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007;357:741.
20. Schauer P, et al. Bariatric surgery vs medical therapy in diabetes. *N Engl J Med* 2012;366:17.
21. Schauer P, et al. Effect of laparoscopic Roux-en-Y gastric bypass on type 2 diabetes mellitus. *Ann Surg* 2003;238:467.

# MINIMALLY INVASIVE SURGERY

*John J. Tiecklen, MD, and Anthony J. LaPorta, MD, FACS*

## 1. What does the field of minimally invasive surgery include?

Minimally invasive surgery encompasses laparoscopic surgery and endoscopic surgery. Almost any procedure that can be done in an open fashion can now be performed laparoscopically. Currently, natural orifice transluminal endoscopic surgery and robotic surgery are further expanding and refining the field of minimally invasive surgery.

## 2. When did laparoscopic surgery become an accepted surgical option?

Laparoscopic surgery has been explored since 1901, but did not fully develop until the late twentieth century. Dr. Kurt Semm, a German gynecologist, performed the first laparoscopic appendectomy in 1983. George Berci was one of the first general surgeons to champion laparoscopic surgery, but initially met resistance. In the late 1980s general surgeons in Germany, France, and the United States independently developed techniques for laparoscopic cholecystectomy. Barry McKenna and William Say are credited with performing the first laparoscopic cholecystectomy in the United States in 1988. At first denounced, this procedure quickly became the standard of care and by 1992 was considered the treatment of choice for symptomatic cholelithiasis (Table 78-1).

**Table 78-1.** Dates of Pioneering Laparoscopic Operations for Selected Procedures

YEAR	PROCEDURE	SURGEON
1983	Laparoscopic appendectomy	Kurt Semm (Germany)
1985	Laparoscopic cholecystectomy	Erich Muhe (Germany)
1991	Laparoscopic Nissen fundoplication	Dallemagne
1991	Laparoscopic inguinal hernia repair	Ger
1991	Laparoscopic splenectomy	Delaitre
1992	Laparoscopic adrenalectomy	Gagner
1992	Laparoscopic gastrojejunostomy	Brune and Mouiel
1993	Laparoscopic Roux-en-Y gastric bypass	Clark and Wittgrove

## 3. What are the advantages of laparoscopic surgery compared with open procedures?

Laparoscopic surgery is less invasive than open surgery, resulting in less trauma to tissue and organs. Respiratory function is less impaired and recovery is improved compared with open surgery. Animal and human studies have shown that laparoscopic surgery preserves immune function. Clinically, this translates into less postoperative discomfort, shorter postoperative hospital stays, and a more rapid return to baseline function. Recent studies also suggest that the lower incidence of adhesions may result in lower long-term risk of small bowel obstruction.

## 4. What are the contraindications to laparoscopic surgery?

Absolute contraindications include the patient's inability to tolerate general anesthesia or pneumoperitoneum, usually caused by advanced cardiopulmonary disease. Relative contraindications include coagulopathy and portal hypertension. The most important relative contraindication is lack of surgeon experience. The ability to safely create working space and the judgment to convert to an open procedure when necessary are paramount.

## 5. What are the respiratory effects of pneumoperitoneum (planned intraabdominal hypertension)?

Pneumoperitoneum alters respiratory mechanics. Intraabdominal hypertension results in elevation of the diaphragm, decreases in functional residual capacity and total lung volume, ventilation-perfusion inequalities, and atelectasis. Some patients may require increased peak inspiratory pressure to compensate for decreased respiratory compliance. No significant change occurs in arterial oxygenation in healthy patients under

pneumoperitoneum, but in patients with cardiopulmonary compromise, arterial oxygen desaturation has been reported, presumably secondary to mechanical pulmonary dysfunction (Table 78-2).

**Table 78-2.** Postoperative Pulmonary Function Tests: Open versus Laparoscopic Surgery

MEASUREMENT AT 24 HOURS AFTER SURGERY	PERCENTAGE OF PREOPERATIVE VALUE	
	Open Surgery	Laparoscopic Surgery
Forced vital capacity	54%	73%
Forced expiratory volume at 1 second	52%	72%
Forced expiratory flow at 25% to 75%	53%	81%

## 6. What are the hemodynamic effects?

Intraabdominal hypertension greater than 15 mm Hg can result in significant changes in central hemodynamics and even more pronounced changes in splanchnic circulation. Mean arterial blood pressure and systemic peripheral resistance are increased (up to 35% and 160%, respectively) at operative levels of pneumoperitoneum (12 to 15 mm Hg), presumably as a result of sympathetic vasoconstriction from hypercarbia. Cardiac index may increase 20%. As intraabdominal pressure increases more than 20 mm Hg, cardiac output falls and abdominal venous compliance decreases, reaching a point at which effective Trendelenburg position and higher pneumoperitoneum can combine in patients with preexisting cardiopulmonary disease to produce potential hemodynamic compromise.

## 7. Summarize the key strategies for safe laparoscopic cholecystectomy.

Dissection of the infundibulum down toward the cystic duct

Dissection from lateral to medial

Adequate inferolateral traction to open the triangle of Calot

Dissection to develop continuity both laterally and medially from the neck of the gallbladder onto the cystic duct

Achievement of the “critical view of safety” before dividing any structures

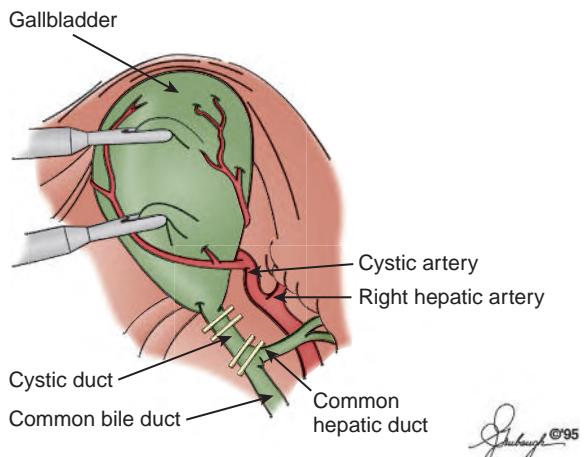
## 8. What is the critical view of safety?

When performing a laparoscopic cholecystectomy, it is imperative to achieve the critical view of safety before dividing any structures. Only two structures remain attached to the gallbladder when the critical view of safety is achieved: the cystic duct and the cystic artery. Additionally, the cystic plate of the liver is easily visible posteriorly.

## 9. When should an intraoperative cholangiogram (IOC) be performed?

Selective versus routine IOC remains controversial. A critical review of the literature demonstrates that routine IOC trends toward a decrease in the incidence of bile duct injury, but does not reach statistical significance. IOC may also identify unsuspected common bile duct stones that can then be removed via laparoscopic common bile duct exploration. An IOC does add time to the procedure, however, and surgeons often defer an IOC if the critical view of safety is achieved. SAGES recommends routine IOC (Figure 78-1).

**Figure 78-1.** The Calot triangle, formed by the cystic duct, cystic artery, and common hepatic duct, is essential for dissection in laparoscopic cholecystectomy. The hepatocystic triangle is defined as the area between the cystic duct, common hepatic duct, and border of the liver.



**10. What are the advantages of single-incision laparoscopic cholecystectomy (SILS) versus conventional four-port laparoscopic cholecystectomy?**

The principal advantage of SILS is satisfaction with the cosmetic result because of a reduced number of scars. Length of stay is not significantly decreased, nor is postoperative pain. Interestingly, a recent study concluded that although cosmetic result was preferred with SILS, there was no significant difference in patient overall satisfaction.

**11. What are the benefits and drawbacks of laparoscopic versus open inguinal hernia repair?**

Attempts at laparoscopic inguinal hernia repair immediately followed the success of laparoscopic cholecystectomy. Initial studies demonstrating increased recurrence rates dampened this enthusiasm. The learning curve for surgeons to become proficient at laparoscopic inguinal hernia repair is significant.

More recent studies have demonstrated equivalent recurrence rates. Furthermore, studies now suggest that the increased operative cost of laparoscopic inguinal hernia repair is offset by the decreased societal cost resulting from less pain, quicker recovery, and more rapid return to regular work duties. The laparoscopic approach also allows the surgeon to address the contralateral side simultaneously. Although the open repair remains an excellent option for de novo unilateral hernias, laparoscopic repair is certainly beneficial for recurrent or bilateral hernias.

**12. Which laparoscopic inguinal hernia repair is preferred: transabdominal preperitoneal (TAPP) hernia repair or totally extraperitoneal (TEP) patch plasty?**

There is no conclusive statistical evidence that one repair is superior to the other. TEP remains outside the abdominal cavity and can be converted to a TAPP easily. TAPP has a less stringent learning curve, however. Surgeon experience is one of the most important factors determining choice of procedure.

**13. Is there any clearly defined benefit to laparoscopic appendectomy?**

Laparoscopic appendectomy has been used with increased frequency compared with open appendectomy during the past decade. Multiple studies demonstrate a benefit in the pediatric, adult, older adult, and obese populations. Concerns remain about cost associated with laparoscopic appendectomy. One recent study demonstrated that the cost for nonperforated appendicitis was slightly higher. However, the cost for complicated appendicitis was lower. Overall there is a modest benefit of laparoscopic appendectomy in the uncomplicated case, which is more pronounced in the complicated cases.

**14. Is gangrenous or perforated appendicitis a contraindication to laparoscopic appendectomy?**

No. Although conversion rates vary between 6% and 50%, reportedly related to surgical experience, laparoscopic appendectomy is associated with a decreased wound infection rate, quicker return of bowel function, and no difference in intraabdominal abscess rate.

**15. Can laparoscopic cholecystectomy or laparoscopic appendectomy be done safely in the pregnant patient? What are some technical considerations specific to operating laparoscopically on the pregnant patient?**

Yes, both laparoscopic cholecystectomy and laparoscopic appendectomy can be safely performed in the pregnant patient during any trimester. The second trimester is the ideal trimester to perform a laparoscopic cholecystectomy. Gravid patients should be placed in a left lateral decubitus position, which will shift the uterus off the vena cava, improving venous return and cardiac output.

**16. What is the role of laparoscopic surgery for curable colon cancer?**

The role of laparoscopic surgery for curable colon cancer is now firmly established. The COST Study Group trial demonstrated that laparoscopic colectomy for curable cancer is not inferior to open surgery based on 5-year prospective outcome data. Several prospective studies have further shown that laparoscopic colon resection results in less use of narcotics and oral analgesics, quicker return of bowel function, and shorter length of stay.

Although most colon resections are still done in an open fashion in the United States today, laparoscopic colon resection will continue to become more common as the present generation acquires this operative skill set in residency and fellowship.

**17. How does laparoscopic gastric bypass compare to open gastric bypass?**

Roux-en-Y gastric bypass is the gold standard for bariatric surgery. Since 2004, laparoscopic gastric bypass has been more commonly used than open gastric bypass. Recent studies continue to document that laparoscopic gastric bypass is associated with shorter length of stay, lower morbidity and mortality, and lower cost compared with open gastric bypass.

**18. Does laparoscopy have a role in acute trauma care?**

Yes, laparoscopic surgery can be done safely and potentially decrease laparotomy rates in both blunt and abdominal trauma patients.

**19. What percentage of patients have free intraabdominal air on upright radiograph 24 hours after laparoscopic procedure?**

In the nonpostoperative state, the presence of subdiaphragmatic free air on upright chest radiograph is diagnostic of intraabdominal perforation. After an open abdominal or laparoscopic procedure, the significance of free

intraabdominal air is less clear. Nonpathologic subdiaphragmatic air may be seen in 24% to 39% of patients after laparoscopic surgery and in 60% of patients after open surgical procedures. The difference relates to the solubility of carbon dioxide used in laparoscopy versus the solubility of trapped room air within the abdominal cavity. Carbon dioxide is more soluble in serum than room air and is absorbed 32 times more quickly.

## **20. Will robotic technology revolutionize the field of surgery as laparoscopic surgery did in the 1990s?**

Robotic surgery has exponentially expanded over the past decade and is currently being explored in almost every surgical subspecialty. Distinct advantages to robotic surgery are three-dimensional imaging, increased optics, and improved ergonomics for the surgeon. Decreased haptics and increased operative times are some of the main drawbacks. Additionally, the expense may not justify the incremental improvement compared with laparoscopic surgery for many procedures that is readily observed when comparing laparoscopic surgery to open surgery. For select anatomic regions and select patients, robotic surgery will eventually occupy a niche, especially as robotic platforms improve and expense decreases.

Please access ExpertConsult to view a Clinical Vignette for this chapter.

## **BIBLIOGRAPHY**

1. Allendorf JD, Bessler M, Whelan RL, et al. Postoperative immune function varies inversely with the degree of surgical trauma in a murine model. *Surg Endosc* 1997;11:427–30.
2. Avgerinos C, Kelgiorgi D, Touloumis Z, et al. One thousand laparoscopic cholecystectomies in a single surgical unit using the “critical view of safety” technique. *J Gastrointest Surg* 2009;13:498–503.
3. Barone J, Bears S, et al. Outcome study of cholecystectomy during pregnancy. *Am J Surg* 1999;177:232–6.
4. Bittner R, Arregui ME, Bisgaard T, et al. Guidelines for laparoscopic (TAPP) and endoscopic (TEP) treatment of inguinal Hernia [International Endohernia Society (IEHS)]. *Surg Endosc* 2011;25:2773–843.
5. Boller AM, Nelson H. Colon and rectal cancer: laparoscopic or open? *Clin Canc Res* 2007;13:6894s–6s.
6. Cameron J. Current surgical therapy. 10th ed. Philadelphia: Elsevier; 2011.
7. DeVita V. Cancer: principles and practice of oncology. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2008.
8. Fitzgibbons Jr RJ, Giobbie-Hurder A, Gibbs JO, et al. Watchful waiting vs repair of inguinal hernia in minimally symptomatic men: a randomized clinical trial. *JAMA* 2006;295:285–92.
9. INCA Trialists Collaboration. Operation compared with watchful waiting in elderly male inguinal hernia patients: a review and data analysis. *J Am Coll Surg* 2011;212:251–259.e1–4.
10. Ishibashi S, Takechi H, et al. Length of laparotomy incision and surgical stress assessed by serum IL-6 lever. *Injury* 2006;37:247–51.
11. Masoomi H, Mills S, Dolich MO, et al. Comparison of outcomes of laparoscopic versus open appendectomy in adults: data from the Nationwide Inpatient Sample (NIS), 2006–2008. *J Gastrointest Surg* 2011;15:2226–31.
12. Masoomi H, Nguyen NT, Stamos MJ, Smith BR. Overview of outcomes of laparoscopic and open Roux-en-Y gastric bypass in the United States. *Surg Technol Int* 2012;30:22, doi:pii: sti22/15.
13. Nguyen N. The SAGES manual, volume 2—advanced laparoscopy and endoscopy. 3rd ed. New York: Springer; 2012.
14. NIH releases consensus statement on gallstones, bile duct stones and laparoscopic cholecystectomy. *Am Fam Physician* 1992;46:1571–4.
15. Reshef A, Hull TL, Kiran RP. Risk of adhesive obstruction after colorectal surgery: the benefits of the minimally invasive approach may extend well beyond the perioperative period. *Surg Endosc* 2013;27:1717–20.
16. Society of American Gastrointestinal and Endoscopic Surgeons. Guidelines for the clinical application of laparoscopic biliary tract surgery. <http://www.sages.org/publications/guidelines/guidelines-for-the-clinical-application-of-laparoscopic-biliary-tract-surgery> [Accessed September 22, 2014].
17. Soper N. Master of endoscopic and laparoscopic surgery. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2005.
18. Soper N. The SAGES manual volume 1—basic laparoscopy and endoscopy. 3rd ed. New York: Springer; 2012.
19. Zehetner J, Pelipad D, Darehzereshki A, et al. Single-access laparoscopic cholecystectomy versus classic laparoscopic cholecystectomy: a systematic review and meta-analysis of randomized controlled trials. *Surg Laparosc Endosc Percutan Tech* 2013;23:235–43.

# CLINICAL VIGNETTES

## CHAPTER 1—SWALLOWING DISORDERS AND DYSPHAGIA

A 28-year-old internal medicine resident presented to the emergency department with food impaction after eating a chicken sandwich at a noon conference. He was unable to swallow his own saliva and presented for medical attention after 2 hours. He reports no gastrointestinal symptoms until 5 years prior to this event, when he developed food impaction after eating a large piece of steak. At that time he underwent endoscopy and was treated with dilatation. He was started on a proton pump inhibitor at that time and was asymptomatic for approximately 1 year. Since that point, he has had mild dysphagia to solid food only, which has occurred approximately three times per week. His worst foods are meats and bread. He reports no heartburn or other gastrointestinal symptoms.

He was taken urgently to endoscopy where he underwent endoscopic disimpaction of the food bolus. A large piece of chicken was found in the distal esophagus with a superficial tear ([CV Figure 1-1](#)). This piece of chicken was macerated with biopsy forceps and pushed beyond the gastroesophageal junction into the stomach. Biopsies were taken at the time, which showed dense esophageal eosinophilia, with greater than 70 eosinophils per high-power field. He was given a diagnosis of eosinophilic esophagitis and started on swallowed fluticasone (440 mcg twice daily). A follow-up endoscopy showed absence of esophageal eosinophils. He was noted to have a stricture at the gastroesophageal junction and dilatation was performed with a through-the-scope balloon. He did well for several years and had no symptoms while on swallowed fluticasone and a proton pump inhibitor. After 2 years, fluticasone was discontinued and a follow-up biopsy 6 months later showed no eosinophilia. He completed residency training and moved to a different part of the country. Unfortunately, he developed recurrent food impaction after he moved and was restarted on swallowed fluticasone, which he has remained on since that time.

**CV Figure 1-1.** Endoscopic image demonstrating meat impaction in the esophagus. Multiple concentric rings are consistent with eosinophilic esophagitis.



## CHAPTER 2—GASTROESOPHAGEAL REFLUX DISEASE

A 25-year-old man was referred for evaluation of severe loss of dental enamel. The patient had experienced severe progression of dental carries for the last 2 years. His dentist referred the patient for evaluation of “high” gastroesophageal reflux disease (GERD).

Past medical and surgical history was unremarkable.

The patient is not taking any medications.

Review of systems remarkable for significant job stress and weight gain of 30 pounds during the preceding 18 months. No history of heart burn, dysphagia, nausea, or vomiting. His wife related no history of snoring or bruxism during sleep.

Laboratory testing was unremarkable.

Physical examination revealed an obese man 5'9" tall and 250 pounds. Pertinent physical findings were confined to the oral pharynx ([CV Figure 2-1A and B](#)). [CV Figure 2-1A](#) demonstrates loss of dental enamel on the lingual surface and an amalgam filling and [CV Figure 2-1B](#) demonstrates profound loss of enamel on the lingual surface of several teeth.

This patient is likely to have high acid reflux causing damage to the dental enamel. An esophagogastroduodenoscopy should be performed and if gastroesophageal reflux disease (GERD) is identified, then he should be started on aggressive antireflux therapy with proton pump inhibitor, weight reduction, and



**CV Figure 2-1.** Examination of the oral pharynx demonstrates loss of dental enamel on the lingual surface and an amalgam filling and CV Figure 2-1A demonstrates profound loss or enamel on the lingual surface of several teeth CV Figure 2-1B

dietary and lifestyle modification. If this patient continues to show signs of GERD and high acid reflux, surgical fundoplication should be considered.

### CHAPTER 3—ESOPHAGEAL CAUSES OF CHEST PAIN

A 28-year-old healthy man is referred by his primary care provider for the evaluation of chest pain. He has no cardiac risk factors and an electrocardiogram (ECG) was normal prior to referral. He describes a midsternal chest discomfort throughout the day, which is not exacerbated by strenuous activity. He also has intermittent heartburn, particularly after large meals. He denies dysphagia, odynophagia, weight loss, melena, early satiety, or constitutional symptoms. He reports only mild relief with a 8-week trial of high-dose omeprazole. He takes no other medications and has no significant family history. His examination is only notable for being slightly overweight. What is the next step in evaluating his chest pain?

An esophageal manometry and ambulatory pH/impedance study are the next steps. This patient has no personal or family risk factors for a cardiac cause. Following a normal ECG, his primary care provider proceeded with a proton pump inhibitor trial. Because this patient had only mild relief with acid suppression, further evaluation is warranted. The next best diagnostic study is esophageal manometry followed by transnasal pH/impedance testing. The manometry screens for a motility disorder as a potential source of chest discomfort and allows for proper placement of the transnasal pH/impedance catheter. Using a combined pH/impedance catheter can provide valuable diagnostic information such as ensuring adequate acid suppression and diagnosing nonacid reflux.

### CHAPTER 4—ACHALASIA

A 62-year-old woman presents with a 2-year history of progressive dysphagia. It was first noted with solids, but now has progressed to liquids. Hang up occurs primarily in the cervical esophagus, usually with every meal. The patient eats slowly and is the last to leave the dinner table. Regurgitation of undigested food occurs several times a week, usually after the evening meal. The patient has an intermittent nighttime cough, and her husband notes “gurgling” while she sleeps. She sometimes has white phlegm on her pillowcase in the morning. There is no chest pain. She is experiencing worsening heartburn unrelated to meals, and is not responding to twice-daily proton pump inhibitors. A 10-pound weight loss has occurred. Otherwise, she is in excellent health.

Initial endoscopy found minimally dilated esophagus with 50 ml of retained saliva. The lower esophageal sphincter seemed “spastic” but opened easily with pressure from the endoscope. The patient was dilated with an 18-mm bougie with no symptom relief. Barium esophagram suggests bird’s beak, a mildly dilated esophagus with to and fro movement. In the upright position, the patient maintained a column of barium 20 cm high (just below the clavicle) 5 minutes after drinking 8 oz of barium. High-resolution manometry identified pattern of Type II achalasia.

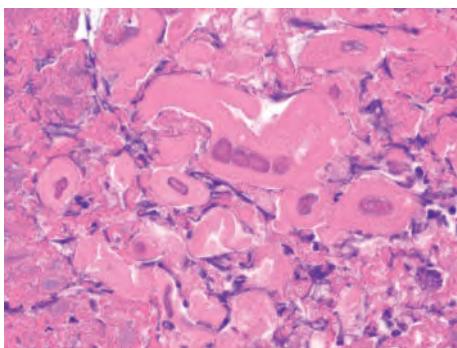
Treatment options of pneumatic dilation and laparoscopic myotomy with partial fundoplication was discussed with the patient with appropriate risks and benefits. She chose pneumatic dilation, which was performed with

a 30-mm Rigiflex balloon under fluoroscopic guidance at the time of endoscopy in the ambulatory surgery center. Follow up at 1 month found her free of symptoms. Timed barium swallow was repeated and now had a 3-cm column at 5 minutes. Follow-up 2 years later finds her doing well with excellent esophageal emptying. No dietary restrictions are necessary, and she has gained 20 pounds.

## CHAPTER 6—ESOPHAGEAL ANOMALIES, INFECTIONS, AND NONACID INJURIES

A 46-year-old man, status post–renal transplantation, presents with chest pain and odynophagia for 2 weeks. Symptoms have been so severe that he has had difficulty maintaining adequate oral intake. He also reports intermittent fevers and chills. Vital signs include temperature 38.2 °C, heart rate 110, blood pressure 115/90. On physical examination, he has oral ulcerations.

On upper endoscopy, there are multiple small ulcers with diffuse friability in the distal esophagus. Biopsies were obtained and histologic examination revealed Cowdry type A intranuclear inclusions and multinucleated cells, see [Figure 6-8](#). The diagnosis is Herpes simplex virus (HSV) esophagitis. He was treated with oral acyclovir 400 mg five times daily for 14 days with subsequent improvement in his symptoms.



**CV Figure 6-8.** Histology of HSV esophagitis with evidence of multinucleation, margination of chromatin, and molding of nuclei. Courtesy of Dora Lam-Himlin.

## CHAPTER 7—BARRETT'S ESOPHAGUS

See <http://www.youtube.com/watch?v=eLBSWIgGvxE>.

## CHAPTER 10—GASTRIC CANCER

A 37-year-old man presented to the emergency department with hematemesis. An emergent endoscopy revealed an ulcerated nodule in the proximal stomach. Biopsies revealed a carcinoid tumor.

Endoscopic ultrasound evaluation (CV Video 10-1) showed the tumor to be approximately 15 mm in cross-section. The tumor infiltrated through the gastric wall. Further evaluation revealed an abnormal lymph node. The node underwent endoscopic ultrasound–guided fine-needle aspiration, which demonstrated nodal involvement by carcinoid tumor.

The patient's gastrin level was normal. He was given the diagnosis of metastatic Type III carcinoid tumor and underwent partial gastrectomy with lymphadenectomy.

He continues to be without evidence of reoccurrence 3 years following surgery.

**CV Video 10-1.** Endoscopic ultrasound (EUS) evaluation of a patient with an ulcerated nodule in the proximal stomach. Previous biopsies revealed carcinoid tumor. EUS staging revealed a lesion that penetrated the gastric wall and had metastasized to a perigastric lymph node.

## CHAPTER 11—THICKENED GASTRIC FOLDS

A 54-year-old woman undergoes esophagogastroduodenoscopy to evaluate epigastric pain and has an incidental finding of a 2.5-cm subepithelial lesion in the gastric body. The overlying mucosa appears normal, and there is no “pillow sign.” Follow-up endoscopic ultrasound (EUS) reveals a hypoechoic, homogenous lesion in the fourth layer without calcifications or internal cystic spaces. What is the best option for diagnosis? What is in the differential diagnosis for this lesion? What additional testing can be done on the tissue to aid in diagnosis and determining its malignant potential?

Hypoechoic, fourth-layer gastric tumors smaller than 3 cm are best diagnosed with EUS and fine-needle aspiration with immunohistochemical analysis of the aspirated cells. The differential diagnosis for these lesions includes leiomyoma, leiomyosarcoma, neural origin tumors (schwannoma, neuroma, neurofibroma), gastrointestinal stromal tumor, lymphoma, and glomus tumors. Immunohistochemical stains including CD117, CD34, SMA, S100, and desmin can be used to distinguish these lesions.

## CHAPTER 12—GASTROPARESIS

A 31-year-old woman with a 15-year history of diabetes mellitus and gastroparesis since 2006 presents with persistent nausea and vomiting despite treatment with ondansetron, metoclopramide, and domperidone. Her gastric emptying scintigraphy test showed severe gastric retention of 65% 4 hours after ingestion of the test meal. She has already had a pyloroplasty and jejunostomy tube placement. What is the next available option for the patient?

The patient qualifies for a gastric electrical stimulator (GES) placement under the Food and Drug Administration's Humanitarian Device Exemption rule. She has failed medical therapy as well as pyloroplasty. The patient has very severely delayed gastric emptying time based on the preferred 4-hour gastric emptying study. She has tried the only available prokinetic in the United States, metoclopramide, which was stopped because of unacceptable side effects after 1 month. Additionally, she has failed the best antiemetic prokinetic in the world, domperidone. However, dosing could be reinvestigated because dosing must be 20 mg four times a day and can be increased to 30 mg four times a day before being considered a failure. Ondansetron is one of the preferred antiemetics for gastroparesis, and it is available in oral dissolvable tablets for patients with severe nausea and vomiting. It is a 5-HT<sub>3</sub> agonist that inhibits receptors in the area postrema of the brain. Granisetron is another 5-HT<sub>3</sub> agonist, and is also available as a 7-day patch for sustained blood levels. Pyloroplasty has been noted to lead to symptom improvement, acceleration in gastric emptying, and reduced need for prokinetics in one report of gastroparesis patients, particularly with short follow-up. GES offers a pathway to control nausea and vomiting at the central nervous system level and also increase vagal activity (e.g., fundic relaxation). Combining pyloroplasty with GES placement is a new development ensuring accelerated gastric emptying. Jejunostomy tubes can be combined with the GES surgery to provide additional nutrition for 3-6 months. See [Chapter 12, Figure 12-4](#), Algorithm for gastroparesis management.

Overall, the patient has not improved after multiple interventions and she is now a candidate for GES device placement.

## CHAPTER 13—EVALUATION OF ABNORMAL LIVER TESTS

A 30-year-old man with periodic midepigastric abdominal pain after eating was referred to a gastroenterologist for evaluation of possible gallbladder or liver disease. His primary care physician has obtained screening laboratory tests that showed the total bilirubin to be elevated to 3 (<1.5 mg/dL upper limit of normal [ULN]) with normal aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase values. His complete blood count (CBC) is normal and an ultrasound of the liver and gallbladder are normal. The patient was an avid runner and had frequently taken over-the-counter nonsteroidal antiinflammatory drugs (NSAIDs) for ankle and knee pains. He had not passed black stools or vomited blood or vomit with the appearance of coffee grounds. His physical examination was only remarkable for slight yellow tinge to the sclera.

The gastroenterologist obtained fractionated bilirubin, lactate dehydrogenase (LDH), CBC, and liver tests after a 24-hour fast. All tests were normal, except total bilirubin was now 3.8 mg/dL, all of which was unconjugated. The peripheral smear was normal and LDH enzyme was not elevated, making the diagnosis of hemolysis unlikely. The patient was given a prescription of omeprazole 20 mg, advised to substitute acetaminophen for NSAIDs, and try ice and topical analgesics for joint pain. His postprandial abdominal pain resolved completely.

This patient has indirect hyperbilirubinemia with normal liver enzyme tests, referred to as *Gilbert's syndrome*. It is found in 5% to 10% of the white population. Gilbert's syndrome is a congenital disorder, characterized by a 70% to 80% reduction in the glucuronidation activity of the enzyme, uridine 5'-diphosphate-glucuronosyltransferase. The principle differential diagnosis of indirect hyperbilirubinemia with normal liver enzyme tests and function is hemolysis, which can be excluded by a full blood count, haptoglobin, lactate dehydrogenase levels, and the absence of reticulocytosis. Gilbert's syndrome is a benign disorder that requires no therapy. When Gilbert's syndrome occurs in the background of elevated AST, ALT, or alkaline phosphatase, the clinical overlap can be confusing if the contributory diagnosis is not considered.

## CHAPTER 14—GENERAL CONCEPTS OF VIRAL HEPATITIS

A 30-year-old Nigerian woman who immigrated to the United States 10 years ago is now pregnant. She is G1, P1, and 14 weeks' pregnant. Prenatal blood tests showed normal complete blood count (CBC) and full chemistry panel, but the patient was hepatitis B surface antigen (HBsAg) positive. She has not previously been seen by a health care provider. She does not smoke tobacco or marijuana, or drink alcohol. She is a sales clerk at a department store, and is married and in a monogamous relationship. Physical examination is remarkable for a gravid uterus that is two to three fingerbreadths below the umbilicus. There are no stigmata of chronic liver disease on physical examination.

The patient is concerned about risk of transmitting the hepatitis B virus (HBV) to her baby. What are the new guidelines for managing HBV infection during pregnancy?

All women are checked for HBV infection at the initial prenatal visit. Those women identified to be HBsAg positive should undergo thorough serologic testing: hepatitis Be antigen, hepatitis Be antibody, HBV-DNA, complete liver panel, CBC, international normalized ratio, and liver ultrasound.

- If testing reveals inactive HBV infection, then HBV-DNA should be rechecked at 26 to 28 weeks of gestation.
- If testing reveals active HBV hepatitis or cirrhosis, then oral antiviral treatment should be considered.

For maternal HBV-DNA results at 26 to 28 weeks of gestation:

- For mothers with HBV DNA of more than  $10^6$  copies, oral antiviral therapy should be considered.
- For mothers with HBV DNA of less than  $10^6$  copies, close monitoring during the later stages of pregnancy is necessary.

Oral HBV antiviral therapy during pregnancy requires the caregiver to have extensive hepatology and obstetrical experience. Obtaining informed consent is advisable.

At birth neonates should receive:

- Passive immunization
- Hepatitis B immune globulin less than 12 hours after birth
- Active immunization:
  - The first dose at birth (within 12 hours if the mother has hepatitis B infection)
  - A second dose at 1 through 3 months
  - A third dose at 6 through 18 months of age

## REFERENCES

The antiretroviral pregnancy registry. Available from <http://www.apregistry.com>.

Munderi P, Wilkes H, Tumukunde D. Pregnancy and outcomes among women on triple-drug antiretroviral therapy (ART) in the DART trial. Curr Hepat Rep 2010;9:197–204.

## CHAPTER 15—ANTIVIRAL THERAPY FOR HEPATITIS C

A 53-year-old white man is found to have elevated alanine aminotransferase (ALT) levels on routine examination for a life insurance physical. The patient denied risk factors for viral hepatitis, was taking no medications, and denied use of alcohol. A hepatitis C virus (HCV) antibody test was positive, and HCV infection was confirmed with an HCV-RNA test by polymerase chain reaction revealing a viral load of 3,450,000 IU/mL. Liver function was normal with an albumin of 4.2 g/dL and a total bilirubin of 0.4 mg/dL. Infection with hepatitis B and human immunodeficiency viruses were excluded, and the patient was not immune to hepatitis A or B infection. Baseline hemoglobin was 14.8 g/dL, absolute neutrophil count was 4700/mm<sup>3</sup>, and the platelet count was 235,000/mm<sup>3</sup>.

A careful history uncovered no depression or history of psychiatric illness. The patient was counseled on the natural history of hepatitis C infection and the available therapies; immunizations against hepatitis A and B were initiated. The patient expressed interest in therapy and tested positive for genotype 1b HCV infection. A sustained virologic response rate of 70% to 75% was quoted to the patient and he agreed to therapy.

Four weeks after starting therapy with pegylated interferon alfa 2a 180 mcg/week, ribavirin 1200 mg/day and telaprevir 750 mg every 8 hours, the HCV was nondetectable. The patient complained of generalized pruritus and a macular rash was noted involving the trunk and proximal upper extremities. A topical steroid cream and systemic nonsedating antihistamines were prescribed and the patient was cautioned to avoid sun exposure.

At 6 weeks of therapy, the hemoglobin was 9.5 g/dL and the patient complained of fatigue. Ribavirin dose was reduced to 600 mg/day and therapy continued. By week 8 of therapy, the hemoglobin had stabilized at 10 g/dL and the rash had not progressed. Treatment with telaprevir was completed at week 12 and he continued pegylated interferon and ribavirin. The patient remained virus nondetectable at weeks 12 and 24 of therapy, and he stopped interferon and ribavirin at week 24. Twenty-four weeks after discontinuation of therapy, the patient continued to test negative for HCV and was declared cured of infection.

## CHAPTER 16—ANTIVIRAL THERAPY FOR HEPATITIS B

A 45-year-old man was diagnosed with hepatitis B infection while trying to donate blood. Six years later he underwent evaluation for possible therapy. At presentation, the patient was asymptomatic. The alanine aminotransferase (ALT) level was normal at 23 IU/mL, hepatitis B viral load was elevated at 25,000 IU/mL. The patient was hepatitis Be antigen-negative, hepatitis Be antibody-positive, and tested negative for human immunodeficiency virus (HIV) antibody. Liver synthetic function was normal. The patient declined a liver biopsy.

Because the liver enzyme levels were normal and the patient declined a liver biopsy, serial testing of liver enzymes was done. Three months later, ALT level was 98, hepatitis B virus (HBV)-DNA was 75,000 IU/mL, and the patient remained asymptomatic; renal function was normal.

With evidence of liver inflammation and viremia (ALT 98, HBV-DNA > 2000 IU/mL), the patient was started on tenofovir 300 mg once a day. Because the patient is e-antigen negative, lifelong therapy was recommended. He was asked to return in 3 months for reevaluation.

Three month later, the ALT was normal at 20 IU/mL, and the HBV-DNA was nondetectable, indicating a good response to therapy. Continued therapy with tenofovir 300 mg daily and follow-up every 6 months was recommended. The patient remained virus negative and with normal ALT for the next 1.5 years.

Three years later he presents for follow up. Repeat laboratory data shows an ALT of 210 IU/mL and a HBV-DNA level of 110,000 IU/mL. The patient was carefully questioned and he admitted to not being compliant with tenofovir because of cost. Tenofovir was restarted at the same dose and 6 months later the ALT had normalized and HBV-DNA was less than 40 IU/mL but detectable. Therapy was continued and the patient was again cautioned about the risks of discontinuation of therapy.

## CHAPTER 17—AUTOIMMUNE HEPATITIS: DIAGNOSIS

A 25-year-old woman presents with jaundice, fatigue, and arthralgia that developed during a 4-week period. Laboratory tests disclose serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels greater than tenfold the upper limit of normal (ULN) range; serum immunoglobulin G level greater than twofold ULN; antinuclear antibodies 1:640; smooth muscle antibodies 1:640; hepatitis A, B, and C markers negative; and ceruloplasmin level greater than ULN. Liver tissue examination discloses moderate to severe interface hepatitis with dense lymphoplasmacytic infiltrates and stage 2 fibrosis. Past history indicates that she took minocycline for 10 days for acne two weeks prior to the onset of symptoms and that she drinks two to three glasses of beer on weekends with friends. Treatment with prednisone and azathioprine induced clinical and laboratory resolution within 3 months and liver tissue examination at 6 months was normal. Gradual treatment withdrawal was followed by an increase in serum AST and ALT levels to fourfold ULN, and combination therapy was restarted.

Clinical clues to classical severe acute-onset autoimmune hepatitis are onset after discontinuation of minocycline, hepatic fibrosis, and relapse after corticosteroid withdrawal.

## CHAPTER 18—AUTOIMMUNE HEPATITIS: TREATMENT

A 32-year-old woman is discovered to have fourfold elevations of the serum aspartate and alanine aminotransferase levels above the upper limit of the normal (ULN) range during a routine medical examination. She is asymptomatic, taking no medication, has no other illnesses, has no alcohol or toxin exposures, maintains a body mass index of 24, and has a negative family history of liver disease. Antinuclear antibodies (1:320) and smooth muscle (1:160) are present; serum immunoglobulin G level is more than twofold the ULN. Liver tissue examination discloses mild to moderate interface hepatitis, lymphoplasmacytic infiltrate, and stage 1 fibrosis. Therapy was started with budesonide (3 mg thrice daily) and azathioprine (50 mg daily), and laboratory resolution was achieved in 3 months. Treatment was continued to ensure histologic resolution.

Justifications for treatment of asymptomatic mild autoimmune hepatitis the following: disease activity fluctuates unpredictably, indolent progression is possible, 26% to 70% of patients become symptomatic, mild hepatic fibrosis is already present, spontaneous resolution is uncertain, and budesonide has few side effects in noncirrhotic patients.

## CHAPTER 19—PRIMARY BILIARY CIRRHOSIS AND PRIMARY SCLEROSING CHOLANGITIS

A 46-year-old man is referred to a hepatologist after his primary care doctor incidentally noted elevated liver tests that have persisted during the preceding 6 months. He occasionally has three to four loose, nonbloody bowel movements, but otherwise has no complaints. He is otherwise healthy and does not have a family history of medical problems.

His physical examination is normal. His liver tests include an alkaline phosphatase 290 U/L, aspartate aminotransferase 45 U/L, alanine aminotransferase 75 U/L, total bilirubin 1.5 mg/dL, and direct bilirubin 1.0 mg/dL. The remainder of the laboratory tests, including albumin and international normalized ratio, are normal. Prior to the referral, the primary care doctor obtained a liver ultrasound, which was normal.

A magnetic resonance cholangiography is obtained (see Chapter 19, Figure 19-1) and shows stricturing and dilation of the intrahepatic bile ducts. A colonoscopy reveals pancolitis with a decreased vascular pattern and very mild friability. Surveillance biopsies demonstrated mild active chronic colitis without evidence of neoplasia.

This case is consistent with primary sclerosing cholangitis–chronic ulcerative colitis. Mesalamine is initiated and the patient is enrolled in a surveillance program that includes an annual ultrasound of the gallbladder and an annual colonoscopy with surveillance biopsies.

## CHAPTER 20—VACCINATIONS AND IMMUNOPROPHYLAXIS IN GASTROINTESTINAL AND LIVER DISORDERS

- 1. A 25-year-old female medical student comes to your clinic after a high-risk exposure to hepatitis A. What should be done? What vaccines should she have already received, and what other vaccines should be considered in this young woman?**

She should receive a single-dose antigen hepatitis A vaccine for postexposure prophylaxis.

She should have already received the measles-mumps-rubella, varicella, and tetanus-diphtheria-pertussis (Tdap) vaccines. If not, she should have these administered.

Furthermore, she should receive the hepatitis B virus (HBV) vaccine as well because she is a health care worker.

Because she is younger than 26, she should receive the human papillomavirus (HPV) vaccine as well.

She should also receive the influenza vaccine yearly.

- 2. A 67-year-old man with cirrhosis comes to your office for a checkup. What vaccinations should be considered?**

He's eligible for live vaccines unless he has received a liver transplantation. Given worsening immune system function with the progression of cirrhosis, he should be brought up to date and administered hepatitis A virus (HAV), HBV, Tdap, and varicella zoster vaccines.

Given this chronic illness as well as his age older than 65, he should also receive the pneumococcus vaccine and the influenza vaccine yearly.

**3. An 18-year-old woman with Crohn's disease, controlled on infliximab as monotherapy, lives in a college dormitory. What vaccinations should be considered?**

She's living in a college dormitory. She should undergo vaccination against influenza (killed injection formulation, not live intranasal), HAV, HBV, meningococcus, and pneumococcus.

She's on biologic therapy, so vaccination against varicella is generally contraindicated.

The HPV vaccine is indicated given her age.

## CHAPTER 21—PREGNANCY AND LIVER DISEASE

A 28-year-old woman, G4 P0 AB3, is now pregnant at 12 weeks of gestation. Her first prenatal checkup showed that she was hepatitis C virus (HCV) antibody-positive. The remainder of her prenatal blood tests were normal and she is hepatitis B surface antigen-negative and human immunodeficiency virus (HIV)-negative. She has not previously been seen by a health care provider. She does not smoke tobacco or marijuana or drink alcohol. She relates promiscuous sexual behavior and cocaine use in college, and now works as an accountant for a trucking firm. She is married in a monogamous relationship. Physical examination is remarkable for a gravid uterus that is two to three fingerbreadths below the umbilicus. There are no stigmata of chronic liver disease on physical examination. Additional blood tests showed alanine aminotransferase elevation to 68 (upper limit of normal < 40 IU/L) and HCV with polymerase chain reaction at 500,000 copies and HCV genotype 1. Ultrasound of the liver, serum total protein, albumin, international normalized ratio, and complete blood cell count were all normal.

**The patient is concerned about risk of transmitting HCV to her baby. What are the new guidelines for managing HCV infection during pregnancy?**

The risk for perinatal transmission of HCV is low when the viral load is less than 1 million copies, and not associated with HIV coinfection. Maternal-fetal HCV transmission rates are not decreased by elective cesarean section. Breast feeding does not appreciably increase the risk of transmitting HCV to the neonate.

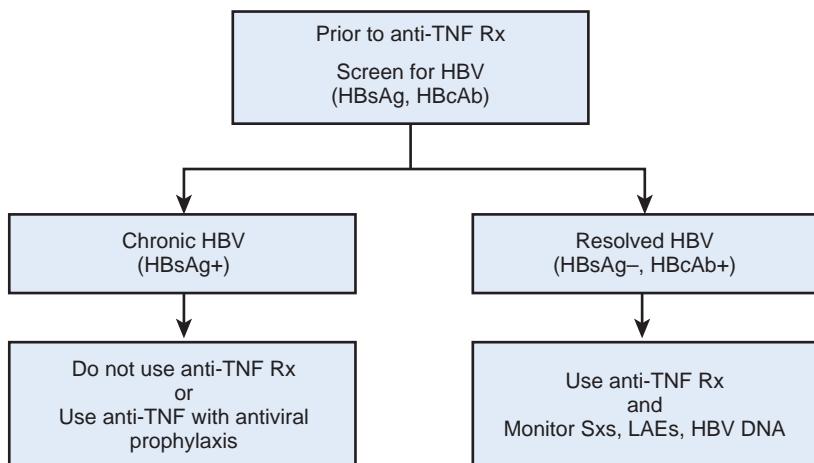
## CHAPTER 22—RHEUMATOLOGIC MANIFESTATIONS OF HEPATOBILIARY DISEASES

**A 35-year-old woman with Crohn's disease is referred to your office. She has failed mesalamine and azathioprine. She requires 20 mg of prednisone to control her symptoms and you decide to start infliximab. She has a normal chest radiograph and negative QuantiFERON gold test for tuberculosis. For what additional infectious disease should she be tested?**

She should be tested for hepatitis B. Guidelines recommend that all patients who will receive an anti-tumor necrosis factor (TNF) agent should be screened for hepatitis B and C infection. Although the use of TNF inhibitors have not been shown to exacerbate hepatitis C infection, several reports of hepatitis B virus (HBV) reactivation and fatalities have been reported particularly with infliximab therapy. Despite these recommendations, only 25% of patients are screened in clinical practice. At a minimum, patients should be tested for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb). Patients with chronic HBV or inactive HBV are both HBsAg+. These HBsAg+ patients are most at risk for developing liver inflammation and necrosis caused by HBV if treated with anti-TNF therapy. Therefore these patients should not receive biologic therapy. If biologic therapy is absolutely needed, they should receive antiviral prophylaxis while on therapy.

Patients with normal liver-associated enzymes, HBsAg-, and HBcAb+ have resolved HBV. Patients with resolved HBV will have undetectable HBV DNA viral loads and may or may not have antibodies to HBsAg. Patients with resolved hepatitis (HBsAg-, HBcAb+) can receive anti-TNF therapy without antiviral prophylaxis because the HBV reactivation rate in these patients is less than 2% to 3%. However, because HBV reactivation has occurred in these patients, they should be monitored prospectively for symptoms, increased hepatic enzymes, and viral DNA quantification. Prior to starting an anti-TNF agent, the algorithm can be followed (CV Figure 22-1).

**CV Figure 22-1.** Algorithm prior to starting an anti-tumor necrosis factor (TNF) agent.  
HBcAb, Hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LAE, liver-associated enzyme; Rx, prescription; Sx, symptom.



## CHAPTER 24—DRUG-INDUCED LIVER DISEASE

A 20-year-old man presents to his college dispensary with a complaint of yellow eyes, dark urine, and claylike stools. He is a college student athlete who competes in lacrosse. He does not drink alcohol, smoke marijuana or tobacco, or do illicit drugs. Medical and surgical history is remarkable for appendectomy at 5 years old. Physical examination shows a healthy but jaundiced man with scleral icterus. No cervical or axillary adenopathy is present. The liver is 11 cm to percussion in the mid clavicular line, and there is no splenomegaly or stigmata of chronic liver disease. Laboratory test results are as follows:

### LABORATORY

White blood cells: 10.2 (15% eosinophils)  
 Hematocrit: 42 (normal limit [NL])  
 Platelets: 250 (NL)  
 Aspartate aminotransferase: 210 ( $5 \times$  ↑ upper limit of normal [ULN])  
 Alanine aminotransferase: 245 ( $6 \times$  ↑ ULN)  
 Alkaline phosphatase: 250 ( $2 \times$  ↑ ULN)  
 Total bilirubin: 10/7 direct (<1.5 m/dL)  
 Total protein: 7 (NL)  
 Albumin: 4 (NL)  
 International normalized ratio: 1 (NL)

Hepatitis A, B, C and E serologic findings were negative.

The gastroenterologist noted that laboratory tests showed a mixed pattern of cholestatic-hepatitis and peripheral eosinophilia, suggestive for possible drug-induced liver disease.

Additional testing was performed, including an abdominal ultrasound and additional laboratory testing. Ultrasound showed a normal liver size, bile ducts, and gallbladder.

Serum copper and 24-hour urine copper were normal. Antinuclear antibody, antismooth muscle antibody, antineutrophil cytoplasmic antibody, antimitochondrial antibody, and mononucleosis spot tests were negative.

The peripheral eosinophilia in this case is a tip-off for a possible drug-induced liver injury (DILI). The patient had neglected to relate prescription of amoxicillin clavulanate (Augmentin) for strep tonsillitis that occurred on break while at home 6 weeks previous. He was observed for the next month and his test slowly and completely normalized.

### DRUG-INDUCED LIVER INJURY

More than 300 drugs in current use have been implicated to cause liver injury. DILI causes approximately 5% of community cases of acute hepatitis and 10% to 40% of hepatitis cases admitted to the hospital. Hepatic injury patterns defined by liver function test profiles and known risk factors for incidence and severity can be helpful in identifying DILI.

Hepatocellular	Cholestatic	“Mixed” Cholestatic Hepatitis
↑ ALT > 2-3 ×	↑ Alk Phos > 2-3 × Alk Phos ratio ALT ≤ 2	↑ ALT > 2-3 × and ↑ Alk Phos > 2 ×
INH, sulfonamides, phenytoin, disulfiram, ketoconazole, nitrofurantoin, minocycline, nicotinic acid	Estrogen, anabolic steroids, tamoxifen, azathioprine	Chlorpromazine, macrolide antibiotics, TCAs, amoxicillin clavulanate, ketoconazole, NSAIDs, captopril, enalapril

Alk Phos, Alkaline phosphatase; ALT, alanine aminotransferase; INH, isoniazid; NSAID, nonsteroidal antiinflammatory drug; TCA, tricyclic antidepressant.

Chronologic association between initiation of drug and the onset of liver injury is often helpful. The latent period can be hours to days (acetaminophen). Immunoallergic DILI reactions are usually delayed 2 to 10 weeks, and amoxicillin clavulanate-associated DILI may arise up to 6 weeks after discontinuation.

Consumer use of herbal remedies is common in the United States, with one in five adults taking at least one herbal agent. This industry is largely unregulated. Persons with preexisting liver disease should be cautious and consult their doctor and reputable websites, such as <http://nccam.nih.gov/>. Potentially hepatotoxic herbs are listed here with their condition that may result: autoimmune hepatitis may result from use of Syo-saiko-to, Ma-huang, and Germanander; cirrhosis may result from use of Syo-saiko-to, Chaparral, greater celandine, and Jin Bu Huan; cholestasis hepatitis may result from use of Cascara sagrada, chaparral, greater celandine, Kava, and Syo-saiko-to; fulminant hepatic failure may result from use of Atractylis gummifera, Chaparral, Cocaine, Germanander, and Kava; and venoocclusive disease may result from use of pyrrolizidine alkaloids (teas) and Skullcap.

## CHAPTER 25—ALCOHOL LIVER DISEASE, ALCOHOLISM, AND ALCOHOL WITHDRAWAL SYNDROME

You are asked to consult on a 20-year-old college student with abnormal liver tests. He was brought to the emergency department by friends when he injured his ankle playing rugby. He notes that his ankle “really hurts and swelled up

during the game." He also complains of some dull right upper quadrant (RUQ) pain and nausea. With more questioning, you learn that his team hosted a large party last night for the teams participating in their weekend tournament. He tells you he participated in several "keg stands and drank some shots." He says that he does not drink daily, only on some weekends. He says he is doing well in school, has had no legal problems, and seems to have good support from several friends with him who corroborate this. He denies any family history of liver disease, foreign travel, intravenous drug abuse, or unprotected sex. He has no allergies and takes ibuprofen for occasional headaches. Vital signs are unremarkable except for a heart rate of 108. Examination shows that he is alert and oriented, but has some tenderness to palpation in the RUQ and an edematous, bruised ankle. Ultrasound of the liver shows mild hepatomegaly with a smooth liver surface; increased echogenicity consistent with fatty liver; and no masses, biliary dilatation, or fluid collections. Aspartate aminotransferase (AST) level is 256 and alanine aminotransferase (ALT) level is 100 mg/dL; total bilirubin, alkaline phosphatase, creatinine, international normalized ratio, and cell counts are within normal limits. There is no ankle fracture on x-ray. You appropriately diagnose acute alcohol steatohepatitis and alcohol abuse in the form of binge drinking and mild withdrawal symptoms (tachycardia, nausea). He lacked tolerance, as well as substantial known negative legal, relationship, or occupational (school) consequences of alcohol use. You educate him that he is at risk for alcohol dependence if he continues to binge drink despite his now known health consequences (alcohol steatohepatitis). After 18 hours of observation, the patient is feeling better, tachycardia has subsided, liver tests are decreased, viral serologies are negative, and he is discharged. You give him a prescription for AST, ALT, alkaline phosphatase, and bilirubin testing in 1 month to check for persistent abnormalities indicative of chronic liver disease, and he agrees to review these with the college nurse. He also surprisingly consents to have you review this plan by phone with his parents, who are appreciative.

## CHAPTER 26—VASCULAR LIVER DISEASE

Ms. Reed is a 36-year-old white woman with a history of gastroesophageal reflux disease (GERD) and hypertension. She was referred to her local gastroenterologist with worsening bloating, anorexia, and dull abdominal pain not related to meals. She reported an unintentional 10-pound weight loss during the preceding 3 months. Her abdominal pain was generalized and not relieved with bowel movements or associated with nausea or vomiting. Her review of symptoms was otherwise unremarkable. Ms. Reed noted a weekly alcohol intake of one glass of wine and denied tobacco or illicit drug use. Her medications included a daily proton pump inhibitor for GERD and angiotensin-converting enzyme inhibitor for hypertension.

On examination, she was afebrile with a heart rate of 95, blood pressure of 132/84, respiratory rate of 12, and oxygen saturation of 99% on room air. In general, she was a thin woman (no jaundice) with normal active bowel sounds and tenderness to palpation in the right upper quadrant (RUQ) with a palpable liver edge 4 cm below the costal margin. Her abdomen was mildly distended, which she stated was new, along with trace bilateral pedal edema. Her cardiac examination demonstrated a regular rate and rhythm without murmurs, jugular venous distention, or hepatojugular reflux.

Her most recent laboratory results showed a normal basic metabolic and coagulation panel. Her complete blood count was significant for hemoglobin 17 g/dL and platelet count of 350,000 per microliter. She had elevated liver-associated enzymes in a mixed pattern: aspartate aminotransferase 85 U/L, alanine aminotransferase 97 U/L, alkaline phosphatase 207 IU/L, and total bilirubin 1.6 mg/dL. An acute viral hepatitis panel was negative. Her antinuclear antibody, antimitochondrial antibody, and smooth muscle actin were negative. Her RUQ ultrasound showed absent hepatic venous blood flow in the right hepatic vein. Follow-up three-phase contrast CT scan demonstrated caudate lobe hypertrophy and partial thrombus in the hepatic vein without hepatic or other masses.

She was diagnosed with Budd Chiari syndrome and placed on anticoagulation and diuretics, although she continued to have ascites and lower-extremity edema. A transjugular intrahepatic portosystemic shunt procedure was performed, which markedly improved her fluid status. Follow-up laboratory investigation was positive for JAK2 mutation but a hypercoagulable work up was otherwise negative. She was maintained on long-term anticoagulation with frequent follow-up.

## CHAPTER 27—NONALCOHOLIC FATTY LIVER DISEASE AND NONALCOHOLIC STEATOHEPATITIS

A 57-year-old Hispanic man presents to a gastroenterologist on referral from his primary care provider for elevated liver enzymes found when simvastatin was started for hyperlipidemia. The patient is asymptomatic, although he does endorse 25 pounds of weight gain in the last 10 years coincident with a knee injury that decreased his activity level. He was diagnosed with diabetes approximately 5 years ago and takes metformin 500 mg twice daily only along with lisinopril/hydrochlorothiazide for hypertension.

Physical examination is notable for an obese Hispanic male (body mass index 36) with a protuberant abdomen and a liver edge palpable 3 cm below the costal margin.

Complete blood count is notable only for a platelet count of 156,000, basic metabolic panel is normal, and international normalized ratio is 1. Liver enzymes are notable for alkaline phosphatase of 109, aspartate aminotransferase (AST) of 61, alanine aminotransferase (ALT) of 57, and total bilirubin 0.4. Serum ferritin is 225, iron is 68, and iron saturation is 39%. Serologic work-up is negative for other causes of chronic liver disease. Right upper quadrant ultrasound demonstrates increased echogenicity consistent with a fatty liver and mild hepatomegaly.

A liver biopsy is performed given the multiple risk factors for advanced disease, which include age older than 50, Hispanic ethnicity, diabetes, AST:ALT ratio or more than 0.8, ferritin more than 1.5 times normal. The biopsy reveals grade 2, stage 3 nonalcoholic steatohepatitis.

The patient is counseled that he has a significant risk of progression to cirrhosis as he already has stage 3 early bridging. He is started on pioglitazone 30 mg daily and enrolled in a supervised diet program with the goal of 8% to 10% body weight loss in 12 months. After clearance from his primary care physician to begin an exercise program, he begins a combined cardiovascular and weight training program, working up to a goal of 45 minutes four times per week of moderate-intensity exercise. His primary care provider is advised to restart the simvastatin, which was held for the elevated liver enzymes to modify his cardiovascular disease risk. He is counseled to avoid alcohol and consider moderate daily unsweetened caffeinated coffee intake. He will be seen in follow-up every 6 months with consideration of screening for hepatocellular carcinoma given his advanced fibrosis.

## CHAPTER 28—LIVER TRANSPLANTATION

### 1. A patient who underwent liver transplantation for cirrhosis caused by hepatitis C virus (HCV) returns with persistently elevated liver enzymes. Liver biopsy reveals chronic active hepatitis but no cirrhosis. Should antiviral therapy be initiated?

Virtually all patients who receive a liver transplant for hepatitis C will have recurrent infection, with 20% to 40% developing cirrhosis by the fifth postoperative year. Development of cirrhosis in this setting may result in an accelerated course, leading to clinical decompensation in more than 40% of patients within 1 year, followed by a decline in 1-year survival to as low as 40%. The diagnosis of HCV recurrence is primarily based on histologic examination. Most patients will have mild to moderate elevations in aminotransferases and evidence of fibrosis on liver biopsy. Surveillance liver biopsies are typically performed 6 to 12 months after surgery (or whenever liver function tests are elevated) to determine the extent of histologic injury. Antiviral therapy is generally considered in transplant recipients with histologic evidence of HCV recurrence and stage 2 fibrosis.

Treatment options include pegylated interferon alpha (PEG-IFN $\alpha$ ), ribavirin, and direct-acting antiviral (DAA) agents. Factors that must be considered prior to instituting therapy include the potential side effects of therapy, drug interactions, a recipient's psychological state, cytopenias, and physical recovery from transplantation. The use of PEG-IFN $\alpha$  and ribavirin in preemptive or recurrence-based approaches following liver transplantation is associated with low rates of sustained virologic response at 22% to 28%. A major challenge associated with posttransplant therapy involves a high discontinuation rate resulting from increased side effects associated with PEG-IFN $\alpha$  and ribavirin. The availability of DAA agents such as the protease inhibitors telaprevir and boceprevir has greatly improved treatment response rates; however, these agents can significantly alter the metabolism of immunosuppressive medications, making treatment more complex. Further advancements in hepatitis C therapy, including the addition of polymerase inhibitors and other DAA agents with greater efficacy and a lower potential for drug interactions will likely have a major effect on evolving treatment strategies for recurrent hepatitis C in liver transplant recipients.

### 2. A patient who had an uncomplicated transplant is noted to have rising liver enzymes on day 10 after transplantation. What is the differential diagnosis and which tests should be obtained?

Elevated liver enzymes within the first 7 to 14 days after transplantation may be the first indication of a significant problem with the hepatic allograft. One of the most common causes of elevated liver enzymes is acute cellular rejection. Approximately 10% to 30% of liver transplant recipients experience acute cellular rejection within the first 3 months after transplant. Early diagnosis is critical to ensure prompt initiation of immunosuppressive therapy (corticosteroid pulse) to prevent graft loss. Liver biopsy remains the gold standard for the diagnosis of rejection. The differential diagnosis includes thrombus of the hepatic artery or portal vein, biliary leak or stricture, cholangitis, drug toxicity, recurrent viral hepatitis, and opportunistic infection. In general, opportunistic infections and recurrent viral hepatitis appear later than day 10. Appropriate tests may include cyclosporine or tacrolimus level, hepatic Doppler ultrasound, cholangiogram, and liver biopsy. If these are unrevealing, infectious etiologic factors should be considered.

### 3. A patient with recurrent hepatitis C develops progressive jaundice within 6 months of transplant without evidence of biliary obstruction, vascular complications, infection, or rejection. What is the most likely cause?

Cholestatic hepatitis C occurs in fewer than 10% of liver transplant recipients with chronic hepatitis C. It is a rapidly progressive form of recurrent infection associated with severe cholestasis, high risk of allograft loss, and decreased survival. Characteristics of this syndrome include:

- a. Bilirubin greater than 6 mg/dL
- b. Elevated alkaline phosphatase or gamma glutamyltransferase levels more than five times the upper limit of normal
- c. High serum HCV RNA levels
- d. Histologic features: central hepatocyte ballooning without necrosis, cholangiolar proliferation without loss of bile ducts, and intrahepatic cholestasis without significant inflammation
- e. No biliary obstructive disease or vascular complications

Additional histologic features may include sinusoidal or pericellular fibrosis surrounding portal tracts. Onset typically occurs within the first 6 months of transplantation and rapid progression to allograft failure may occur

within 1 year with recently reported 3-year survival rates of less than 50% despite antiviral therapy use in the majority of patients.

## CHAPTER 29—ASCITES

A 45-year-old man with a history of hypertension, obesity, alcoholism, hepatitis B, and hepatitis C presented to the emergency department with a 2-day history of fever, abdominal pain and distention, and progressively worsening mental status. His home medications included metoprolol and lisinopril. His vital signs at presentation were significant for a temperature 38.5° Celsius, heart rate 120 beats/minute, blood pressure 80/40, respiratory rate 16 breaths/minute, and oxygen saturation 96% on room air. On examination, he was grossly disoriented, with jaundice and icterus. His abdominal examination was notable for diffuse tenderness, distention, a fluid wave, and guarding. A bedside ultrasound reveals ascites. Basic laboratories reveal a white blood cell count of 15,000/mL with 90% neutrophils, a platelet count of 70,000/mL, serum creatinine of 2.4 mg/dL, blood urea nitrogen of 55 mg/dL, and serum bilirubin of 5.4 mg/dL. A diagnostic paracentesis is performed and shows 1000 neutrophils/mm<sup>3</sup>.

This clinical vignette contains a number of key points demonstrated in this chapter. His medical history of obesity, alcoholism, and viral hepatitis places him at a high risk of developing cirrhosis. The constellation of fever, abdominal pain, and ascites in the context of vitals suggesting sepsis are highly concerning for spontaneous bacterial peritonitis (SBP). The finding of 1000 neutrophils/mm<sup>3</sup> on paracentesis is diagnostic for SBP. The case demonstrates a number of clinical considerations:

- A diagnostic abdominal paracentesis should be performed at the time of admission in all patients with new-onset ascites, and when there is evidence of clinical decompensation.
- The ascitic fluid neutrophil count is the single most important test for detecting bacterial infection of peritoneal fluid. An absolute neutrophil count of 250 cells/mm<sup>3</sup> or more warrants empiric antibiotic treatment.
- In patients with suspected SBP, antibiotics should be started as soon as possible. Cefotaxime should be given at a dose of 2 g intravenously every 8 hours.
- Albumin should be given at a dose of 1.5 g/kg at the time of diagnosis of SBP, and 1 g/kg on the third day of treatment.
- Antihypertensives such as beta-blockers and angiotensin-converting enzyme inhibitors should be held in the context of sepsis, hepatorenal syndrome, or cirrhosis with refractory ascites.
- Midodrine and octreotide should be considered, given the concern for renal dysfunction.

## CHAPTER 30—LIVER ABSCESS

**A 23-year-old Hispanic man presents to the emergency department with a 2-week history of fevers and abdominal pain localized to the right upper quadrant. On examination, the patient has hepatomegaly and point tenderness over the liver. Laboratory tests are pertinent for a leukocytosis of 17,000  $\mu$ L, hemoglobin 11 g/dL, hematocrit 33%, mean corpuscular volume 92 fL, platelets 170,000  $\mu$ L, normal basic metabolic panel, total protein 5.5 g/dL, albumin 2.6 g/dL, total bilirubin 0.5 mg/dL, alkaline phosphatase 100 units/L, aspartate aminotransferase 92 units/L, alanine aminotransferase 105 units/L, and indirect hemagglutination 1:889. Ultrasound shows an oval 2.5-cm hypoechoic mass with fine internal echoes with a thin wall in the right lobe of the liver near the diaphragm. What is the next step in the care of this patient?**

Based on this patient's clinical, laboratory, and imaging findings this is consistent with an amebic abscess.

Aspiration is not needed at this time because trophozoites are found less than 20% of the time, and there is a low likelihood that this is a pyogenic abscess. The next step should consist of metronidazole 750 mg three times per day for 10 days. This should then be followed by a course of an oral luminal amebicide (iodoquinol, diloxanide furoate, or paromomycin) because intestinal amebiasis can persist 40% to 60% of the time following a course of metronidazole.

## CHAPTER 31—INHERITABLE FORMS OF LIVER DISEASE

A 40-year-old man with persistent elevation of liver tests for more than 6 month is referred for gastroenterology consultation. The man has multiple medical problems, including arthritis, diabetes, hypertension, obesity, and hypercholesterolemia. He does not smoke tobacco or drink alcohol. Medications are metformin, lisinopril and hydrochlorothiazide, acetaminophen alternating with ibuprofen, and atorvastatin. His family history is remarkable for severe arthritis, cirrhosis, and heart failure in his paternal grandfather, father, and uncle (none drank alcohol). This patient has been debilitated by severe osteoarthritis since he was 20 years old. Physical examination is remarkable for an obese male, tan complexion, with osteoarthritic changes of the hand and fingers. Sclera are white. Liver is 13 cm in the midclavicular line. No spider angioma appears on the chest, but there is gynecomastia and palmar erythema.

## LABORATORY RESULTS

White blood cell count: 10.2 (normal limit [NL])

Hematocrit: 42 (NL)

Platelets: 100 (LOW)

Aspartate aminotransferase: 95 ( $3 \times \uparrow$  upper limit of normal [ULN])

Alanine aminotransferase 110 ( $3.5 \times \uparrow$  ULN)

Alkaline phosphatase: 120 (NL)

Total bilirubin: 2/1.5 direct (<1.5 m/dL)

Total protein: 6.8 (NL)

Albumin: 3.5 (NL)

International normalized ratio: 1 (NL)

Hepatitis A, B, C, and E serologies were negative.

The gastroenterologist noted there were a constellation of physical findings and clinical history that suggested possible hemochromatosis: bronze diabetes, arthritis, hepatomegaly, probable hypogonadism and family history for cirrhosis (not alcohol drinkers).

Additional testing was performed: An abdominal ultrasound and additional laboratory testing were performed. Ultrasound showed an enlarged liver 14 cm with prominent spleen. Antinuclear antibodies and anti-smooth muscle antibodies were negative. Ferritin was 1100 and iron saturation was 67%.

Key points about hemochromatosis are the following: Hereditary hemochromatosis (HHC) is a common genetic disorder. The frequency of heterozygotes is approximately 10% in white populations in the United States and western Europe, with a frequency of approximately 1 per 200 (0.5%) for the homozygous state.

Screening tests: Serum iron/total iron-binding capacity = % iron saturation (value >45 suggests need to screen for HHC with serum ferritin).

Serum ferritin: 400 ng/mL in men OR 300 ng/mL in women suggests HHC; should do liver biopsy and gene tests for HFE mutation.

Liver biopsy: A hepatic iron/age index (hepatic iron concentration in micromoles per gram dry weight divided by the patient's age) greater than 1.9 is consistent with homozygous HHC. A liver biopsy is not necessary for patients less than 40 years of age with genetically defined hemochromatosis (C282Y homozygous or C282Y/H63D mutations, so-called compound heterozygotes) with normal liver function tests.

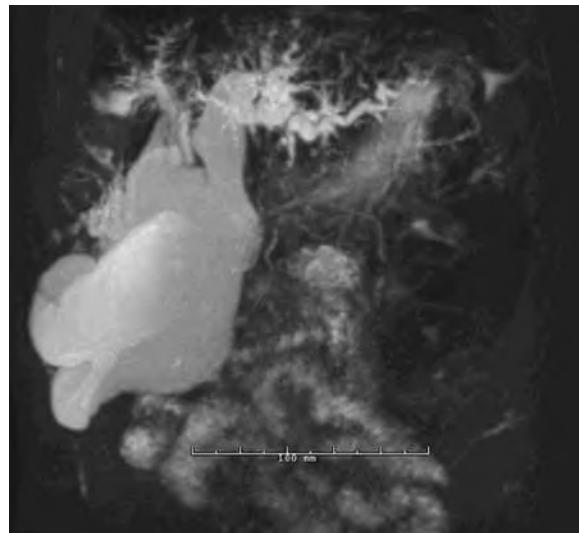
## CHAPTER 33—HEPATOBILIARY CYSTIC DISEASE

An 8-year-old girl presents to the emergency department with new-onset hematemesis at home. She was previously well. The family denies recent ingestions, infection, fever, pruritus, jaundice, bleeding, bruising, or fatigue. They deny medication use or herbal supplementation. There is no pertinent birth history or past medical history. She has had no prior surgeries. Family history is negative for bleeding disorders, gastrointestinal disease, and liver disease.

In the emergency department, nasogastric lavage reveals bright red blood and clots, and eventually clears. On physical examination, the patient is noted to be afebrile but pale and tachycardic. On abdominal examination, she is found to have hepatosplenomegaly. Examination is otherwise unremarkable.

On laboratory assessment, the white blood cell count is noted to be 3000/ $\mu$ L, hemoglobin measures 6 g/dL, and platelets are 85,000/ $\mu$ L. The international normalized ratio is elevated at 1.5. Liver enzymes are within normal limits.

She is admitted to the intensive care unit for resuscitation. An abdominal ultrasound with Doppler imaging shows a diffusely heterogeneous hepatic echotexture. The common bile duct is enlarged and cystic appearing. There is splenomegaly with a tortuous splenic vein but normal portal venous flow and patent vessels. Kidneys are normal. A magnetic resonance imaging scan of the abdomen shows intrahepatic and extrahepatic biliary dilatation involving a large portion of the common bile duct ([CV Figure 33-1](#)). An upper endoscopy is performed and multiple esophageal varices are noted.



**CV Figure 33-1.** Magnetic resonance image of the abdomen shows intrahepatic and extrahepatic biliary dilatation involving a large portion of the common bile duct.

A liver biopsy is obtained and is significant for cirrhosis with dilatation of the intrahepatic bile ducts without cholestasis or steatosis. Imaging and biopsy are consistent with Caroli disease.

In follow up, because of recurrent episodes of cholangitis, she underwent liver transplantation 7 years later.

## CHAPTER 34—GALLBLADDER DISEASE: STONES, CRYSTALS, AND SLUDGE

A 28-year-old woman at 30 weeks' gestation presents with abdominal pain, nausea, and vomiting. The pain is epigastric, severe, and radiates to her right shoulder. Physical examination is notable for right upper quadrant and epigastric tenderness. Laboratory findings include a normal complete blood count, transaminases, alkaline phosphatase, bilirubin, amylase, and lipase. Abdominal ultrasonography shows gallbladder stones and a normal common bile duct. She is ordered to take nothing by mouth and given intravenous fluids, and her pain gradually resolves. At 32 weeks' gestation, her abdominal pain recurs. Laboratory findings include amylase 350, lipase 270, alkaline phosphatase 150, but normal aspartate aminotransferase, alanine aminotransferase, and total bilirubin. Abdominal ultrasound again shows gallbladder stones and a normal common bile duct. The pancreas is not well visualized. She is diagnosed with mild pancreatitis and treated with supportive care. She is discharged from the hospital, but is readmitted with similar symptoms at 36 weeks' gestation. Her symptoms resolve, but given her recurrent biliary tract symptoms, she undergoes an elective induction of labor at 37 weeks with delivery of a normal, healthy infant. Plans are made for her to undergo cholecystectomy 2 to 3 weeks after delivery.

## CHAPTER 35—ERCP PLUS SPHINCTER OF ODDI DYSFUNCTION

- 1. A 35-year-old woman undergoes a laparoscopic cholecystectomy for symptomatic cholelithiasis. On postoperative day 1, she has increasing abdominal pain and fever. Ultrasound shows a fluid collection in the area of the gallbladder fossa. What is the diagnosis and how should this be treated?**

The clinical scenario fits a postoperative bile leak. This is a clinical “urgency” and can be treated with endoscopic retrograde cholangiopancreatography (ERCP) with or without biliary sphincterotomy and transpapillary biliary stent insertion to bridge the papilla. It is ideal to bridge the origin of the bile leak (e.g., cystic duct stump), but often biliary sphincterotomy alone with or without stent placement will be sufficient to divert bile flow and promote spontaneous closure of a “low-grade” bile leak. There is controversy as to what truly defines a “duct of Luschka” leak, but it is most likely related to technical factors of peeling the gallbladder off of the liver and potentially tearing accessory bile ducts that leak (called *supravesicular ducts*—the gastroenterologist's perspective) or disruption of an accessory duct that drains directly from the liver into the gallbladder or cystic duct (an aberrant cholecystohepatic duct entering Hartmann's pouch—the surgeon's perspective).

- 2. The patient in question 1 returns for medical evaluation 2 years after her cholecystectomy. Her pain is located in the right upper quadrant, radiates to the back, and on two occasions has been associated with elevation in hepatic enzymes, which then normalize when the pain is improved at time of follow-up with her primary care manager. Abdominal ultrasound shows a bile duct of 9 mm. What is your diagnosis?**

The diagnosis is most likely sphincter of Oddi dysfunction Type 2.

## CHAPTER 36—ACUTE PANCREATITIS

A 35-year-old woman with acute abdominal pain presents to the emergency department with acute onset midepigastic pain that radiated direct to the back. The pain began after a large meal and has not abated for the last 4 hours. She is diaphoretic, but has no fever. Medical and surgical history is remarkable for left knee reconstruction 10 years ago. She does not drink or smoke tobacco and takes no medications. Her family history is remarkable for grandmother, aunt, mother, and two sisters who had cholecystectomy for symptomatic gallstones. Physical examination shows normal blood pressure tachycardia (104 beats per minute [bpm]), afibrile, and 20 respirations per minute. She is in obvious pain laying on her side in a fetal position. Sclera are white, lungs exhibit rales, the abdomen is tender to palpation in the midepigastrium, and bowel sounds are absent.

### LAB

White blood cell (WBC) count: 15 ( $4\text{-}10.5 \times 10^3/\mu\text{L}$ )  
 Hemoglobin: 18 (12.6-17.7 g/dL)  
 Hematocrit: 55 (37.5-51%)  
 Platelets: 145 ( $140\text{-}415 \times 10^3/\mu\text{l}$ )  
 Glucose: 120 (65-99 mg/dL)  
 Blood urea nitrogen: 30 (6-24 mg/dL)  
 Creatinine: 1.3 (0.76-1.27 mg/dL)  
 Calcium: 8 (8.7-10.2 mg/dL)  
 Aspartate aminotransferase: 140 (0-40 IU/L)  
 Alanine aminotransferase: 160 (0-55 IU/L)

Alkaline phosphatase: 200 (5-150 IU/L)  
 Total bilirubin: 2/1.5 direct (0-1.2 mg/dL)  
 Amylase: 1254 (21-101U/L)  
 Lipase: 1035 (7-60U/L)

Ultrasound in the emergency department showed normal liver, gallbladder full of small stones, but normal gallbladder wall and common bile duct 9 mm (slightly enlarged) and possible 5 mm stone.

The diagnosis of acute pancreatitis (AP) requires the presence of two of the following three criteria:

- Abdominal pain strongly suggestive of AP (epigastric and radiating to back)
- Serum amylase or lipase higher than three times the upper limit of normal
- Characteristic findings of AP on imaging, with computed tomography the best and most universally available imaging modality.

The severity of acute pancreatitis can be estimated at the bedside using the bedside index of severity for acute pancreatitis (BISAP).

### FIRST 24 HOURS

1. Urea nitrogen more than 25 mg/dL
2. Impaired mental status (Glasgow coma score < 15)
3. Age older than 60 years
4. Pleural effusion
5. Presence of systemic inflammatory response syndrome (SIRS)

(A diagnosis of SIRS requires two or more of the following findings: pulse > 90 bpm, respirations > 20/min,  $\text{PaCO}_2 < 32$  mm Hg, temperature > 100.4 ° F, and WBC > 12,000 or < 4000 or > 10% bands.)

This patient has a BISAP score of 2, or a 4% estimated mortality from acute gallstone pancreatitis.

The first steps in the acute management of acute pancreatitis should be to control pain, provide supplemental oxygen, and provide aggressive intravenous fluids during the “Golden Hours” to maintain the pancreatic microcirculation with lactated Ringer’s solution. Prophylactic antibiotics should not be given for acute pancreatitis. A nasogastric tube should not be inserted unless there is symptomatic ileus. Control of pain with narcotics is essential, but one must monitor with pulse oximetry.

This patient’s laboratory tests and ultrasound suggest gallstone pancreatitis as the causal factor. Endoscopic retrograde cholangiopancreatography (ERCP) should not be performed routinely for biliary pancreatitis, including those with choledocholithiasis, within the first 24 hours. Emergent indications for ERCP in the first 24 hours include:

AP complicated by ascending cholangitis

Worsening clinical course with increasing liver function test levels

ERCP should be performed after resolution of AP to clear common bile duct of stones. Some favor the use of magnetic resonance cholangiopancreatography or endoscopic ultrasound to exclude the persistence of common bile duct stone preoperatively. Laparoscopic cholecystectomy should be performed during the same admission; otherwise recurrent pancreatitis is seen in 25% to 50% of cases.

### REFERENCES

- Banks PA, Bollen TL, Dervenis C, et al., Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis—2012: Revision of the Atlanta classification and definitions by international consensus. Gut 2012;62:102–111.
- Nebiker CA, et al. Early versus delayed cholecystectomy in patients with biliary acute pancreatitis. Surgery 2009;145:260–264.
- McCullough LK, et al. Gallstone pancreatitis: Does discharge and readmission for cholecystectomy affect outcome? HPB (Oxford) 2003;5:96–99.
- Bakker OJ, et al. Timing of cholecystectomy after mild biliary pancreatitis. Br J Surg 2011;98:1446–1454.

## CHAPTER 37—CHRONIC PANCREATITIS

A 45-year-old female recovered alcoholic with a history of recurrent chronic pancreatitis presented to your emergency room with a complaint of pain. The pain was characterized as acute-onset midpain that radiated direct to the back—identical to prior episodes. The pain began after a large meal and has not abated for the last 12 hours. She is diaphoretic, but has no fever. Medical and surgical history is remarkable for hepatitis C infection successfully treated 4 years ago, recurrent calcific pancreatitis for the last 3 years, and cesarean section. She has not consumed alcohol or tobacco in almost 2 years. Her family history is alcoholism and coronary heart disease. Physical examination shows normal blood pressure tachycardia (104 beats per minute), afebrile, and respirations of 20 per minute. She is in obvious pain laying on her side in a fetal position. Sclera are white, lungs exhibit rales, abdomen is tender to palpation in the midepigastrium, and bowel sounds are absent.

## LABORATORY RESULTS

White blood cell count: 12 ( $4\text{-}10.5 \times 10^3/\mu\text{L}$ )  
 Hemoglobin: 18 (12.6-17.7 g/dL)  
 Hematocrit: 50 (37.5-51%)  
 Platelets: 145 ( $140\text{-}415 \times 10^3/\mu\text{l}$ )  
 Glucose: 120 (65-99 mg/dL)  
 Blood urea nitrogen: 30 (6-24 mg/dL)  
 Creatinine: 1.1 (0.76-1.27 mg/dL)  
 Calcium: 8.7 (8.7-10.2 mg/dL)  
 Aspartate aminotransferase: 40 (0-40 IU/L)  
 Alanine aminotransferase: 60 (0-55 IU/L)  
 Alkaline phosphatase: 160 (5-150 IU/L)  
 Total bilirubin: 1.2 (0-1.2 mg/dL)  
 Amylase: 354 (21-101 U/L)  
 Lipase: 235 (7-60U/L)

Computed tomography (CT) scan in the emergency department shows normal liver, gallbladder, and common bile duct. Pancreas demonstrates diffuse stippled calcification of the gland and “chain of lakes” changes of the pancreatic duct.

A gastroenterology consult is requested. This patient has typical symptoms and CT changes of chronic pancreatitis. This episode should be treated with pain medication and intravenous fluids. Long-term management will include small meals, a low-fat diet, and abstention from all alcohol and tobacco. The utility of supplemental pancreatic enzymes is not clear for diminishing recurrent attacks, but is important for those with steatorrhea and fat malabsorption caused by exocrine insufficiency. Monitoring for development of diabetes, deficiencies of vitamin D and B<sub>12</sub>, and steatorrhea are important.

Although alcohol use is the cause of most cases of chronic pancreatitis, each case should be carefully examined for other causes, including:

- Hypercalcemia
- Hyperparathyroidism
- Hypertriglyceridemia
- Hereditary pancreatitis
- Tropical pancreatitis
- Autoimmune pancreatitis

## REFERENCES

- Conwell DL, Wu B. Chronic pancreatitis: Making diagnosis. Clin Gastroenterol Hepatol 2012;10:1088-1095.  
 Sah RP, Chari ST. Autoimmune pancreatitis: An update on classification, diagnosis, natural history and management. Curr Gastroenterol Rep 2012;14:95-105

## CHAPTER 40—CELIAC DISEASE

A 37-year-old white woman with no significant past medical history presents to her primary care physician’s office with 3 months of diarrhea, bloating, and fatigue. She is otherwise healthy. She is not on any medications, and denies any recent travel. No known drug allergies. Her sister has celiac disease. Initial evaluation revealed iron deficiency anemia and vitamin D deficiency. Stool studies were unremarkable. Patient underwent upper endoscopy and small bowel biopsy. Histologic examination revealed intraepithelial lymphocytosis (IELs) with preserved villous architecture. Based on this finding, the patient was referred to a gastroenterologist for further evaluation. The biopsies were reviewed by a gastrointestinal pathologist experienced in celiac disease who confirmed the presence of IELs. It was discovered that only two biopsies were taken and site not specified. Serum tissue transglutaminase immunoglobulin A was 40 units (normal 0-19 units). Given the minimal enteropathy findings and low positive serologic results, the patient underwent repeat endoscopy and multiple biopsies were taken from second portion of duodenum and duodenal bulb. The final histologic examination revealed Marsh 3 lesions, which confirmed celiac disease in the setting of positive serologic findings. The patient was placed on a gluten-free diet with resolution of her symptoms over the following months.

## CHAPTER 41—CROHN'S DISEASE

A 29-year-old Irish man with Crohn’s colitis since age 15 and in deep remission of disease, on weekly adalimumab 40 mg and 12.5-mg methotrexate injections, has developed diarrhea, but colonoscopy, ileoscopy and enterocomputed tomography do not show any relapse of disease. In fact, biopsies of the ileum and colon show only minimal microscopic activity. Stool tests show negative fecal leukocytes, stool culture and *Clostridium difficile* toxin. The patient has developed a very pruritic vesicular rash over the upper extremities.

What should the consulting gastroenterologist consider as a cause of symptoms in this patient? Certainly, supraimposed irritable bowel syndrome and giardia infection should be excluded from this diagnosis. The finding of

a pruritic vesicular rash should suggest dermatitis herpetiformis, a cutaneous manifestation often associated with gluten sensitivity. This patient should have celiac serologies obtained and small bowel biopsy performed to diagnosis the disorder. Celiac disease is seen in 1 in 120 Americans and is more common than Crohn's disease; it should be considered as a possible superimposed medical condition when inflammatory bowel disease is in deep remission.

#### REFERENCES

Tursi AL, Giorgetti GM, Brandimarte G, et al. High prevalence of celiac disease among patients affected by Crohn's disease. *Inflamm Bowel Dis* 2005;11(7):662–666.

### CHAPTER 42—ULCERATIVE COLITIS

An 18-year-old female high school student is about to go to college this fall. She has been diagnosed to have ulcerative colitis since the age of 14. Her treatment has included corticosteroids, mesalamine, and thiopurine drugs. She started adalimumab injections every other week 3 years ago, and has been in deep remission for 2 years. Her primary care doctor has called you for advice on immunizations.

You should advise that a college student residing in the dormitory should receive immunization for pneumococcus, meningococcus, and human papillomavirus. Annually she should receive the influenza shot vaccination. She should avoid all live vaccinations, including the flu mist.

#### REFERENCES

Dezfoli S, Melmed GY: Vaccination issues in patients with inflammatory bowel disease receiving immunosuppression. *Gastroenterol Hepatol (N Y)* 2012;8(8):504–512.

### CHAPTER 43—EOSINOPHILIC GASTROINTESTINAL DISEASE AND EOSINOPHILIC ESOPHAGITIS

A previously healthy 15-year-old girl initially presents with intermittent complaints of upper abdominal pain. Associated symptoms include intermittent nausea, heartburn, regurgitation, dysphagia, and occasional tingling in her throat with ingestion of particular foods such as watermelon. She has no extraintestinal manifestations or known history of atopy. Her family history is significant for both maternal grandparents with food impactions, and a sibling who had similar gastrointestinal (GI) symptoms that resolved over time. Her symptoms are significantly affecting her daily activities and she eventually stopped attending school. An initial upper endoscopy demonstrated increased eosinophils in her esophagus and colon, as well as a narrowed pyloric channel that was confirmed with ultrasonography and an upper GI contrast study. She was started on steroid therapy with budesonide (Entocort) capsules once daily, and a repeat upper endoscopy with dilation of the duodenum was performed 3 months later. Her symptoms initially decreased following the dilation, but have now returned. Laboratory studies include mildly elevated peripheral eosinophilia of 330 cells/mm<sup>3</sup> (normal <200 cells/mm<sup>3</sup>); an otherwise unremarkable complete blood count; normal erythrocyte sedimentation rate and C reactive protein inflammatory markers; negative celiac serology with normal tissue transglutaminase and immunoglobulin A; negative stool infectious studies including bacterial and parasitic pathogens; stool negative for occult blood; and radioallergosorbent test positive for egg whites, soy, cucumber, and peanuts. An abdominal computed tomography scan 3 months following her duodenal dilation revealed a short segment of narrowing in the second portion of the duodenum associated with localized bowel wall thickening. She received topical budesonide and was also started on a proton pump inhibitor. She improved symptomatically 2 months later and her obstruction resolved, but she continues to have mucosal inflammation that will likely require systemic steroids.

### CHAPTER 44—SMALL INTESTINAL BACTERIAL OVERGROWTH

A 75-year-old man with a long-standing history of gastroesophageal reflux disease, well controlled with proton pump inhibitor therapy, presents to his gastroenterologist with several months' history of diarrhea. Additionally, he reports a sensation of bloating, frequently accompanied by nausea. He is unsure if he's lost any weight or if bowel movements relieve his symptoms. Significant laboratory abnormalities include a macrocytic anemia.

Clinical clues to overgrowth are age, chronic diarrhea, proton pump inhibitor use, and anemia.

Vitamin B<sub>12</sub> level was low, folate high. Lactulose hydrogen breath test showed elevated baseline hydrogen (hydrogen plus two times methane value), an early rise of hydrogen 20 ppm above fasting baseline at the 20-minute sample, and a second hydrogen peak where the early rise value declined and then rose again at 120 minutes reflecting colonic fermentation.

Rifaximin 500 mg three times a day for 14 days was prescribed. Diarrhea and bloating resolved during treatment.

### CHAPTER 46—CONSTIPATION AND FECAL INCONTINENCE

A 20-year-old woman presents with long-standing constipation. Although she feels the urge to go and she attempts daily, she only produces a bowel movement approximately once per week. She strains regularly and often experiences a sensation of incomplete evacuation. She describes mostly Bristol type 1 stools, with some

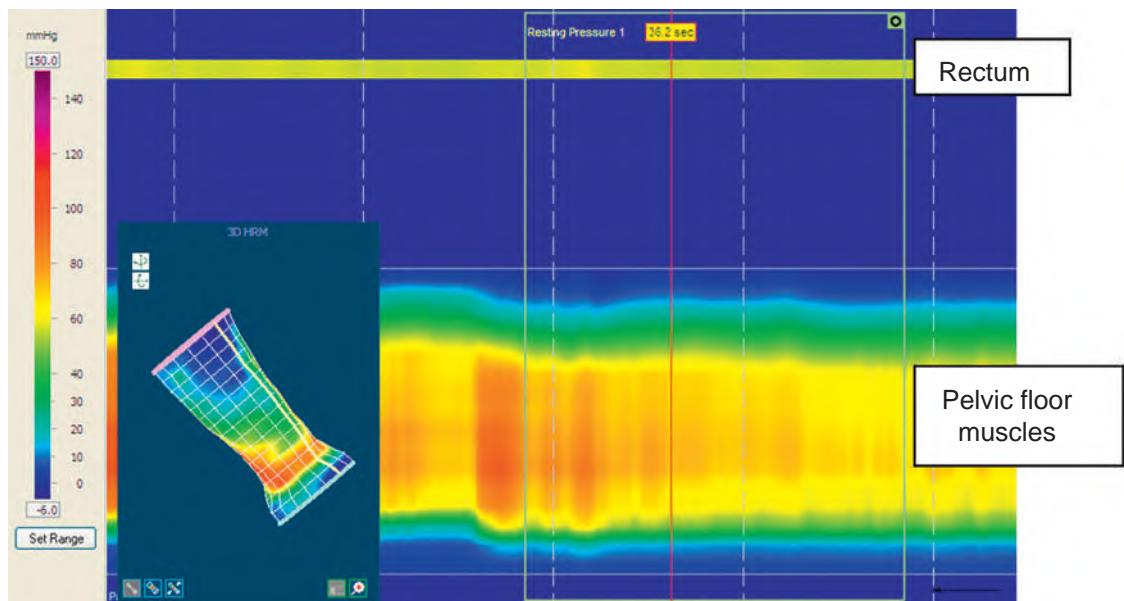
Bristol type 4. She has occasional abdominal discomfort but this is a less prominent symptom. She denies nausea, vomiting, blood in her stool, or weight loss. She has no significant medical history. Multiple laxatives have been prescribed in the past, and she is currently taking polyethylene glycol 3350 and lubiprostone twice daily.

Physical examination is unremarkable with the exception of her rectal examination. The perineum has no lesions and exhibits normal sensation. On digital examination, the patient demonstrates an aggressive squeeze, and when she is told to bear down to attempt defecation, the examiner notes contraction of the anorectal muscles.

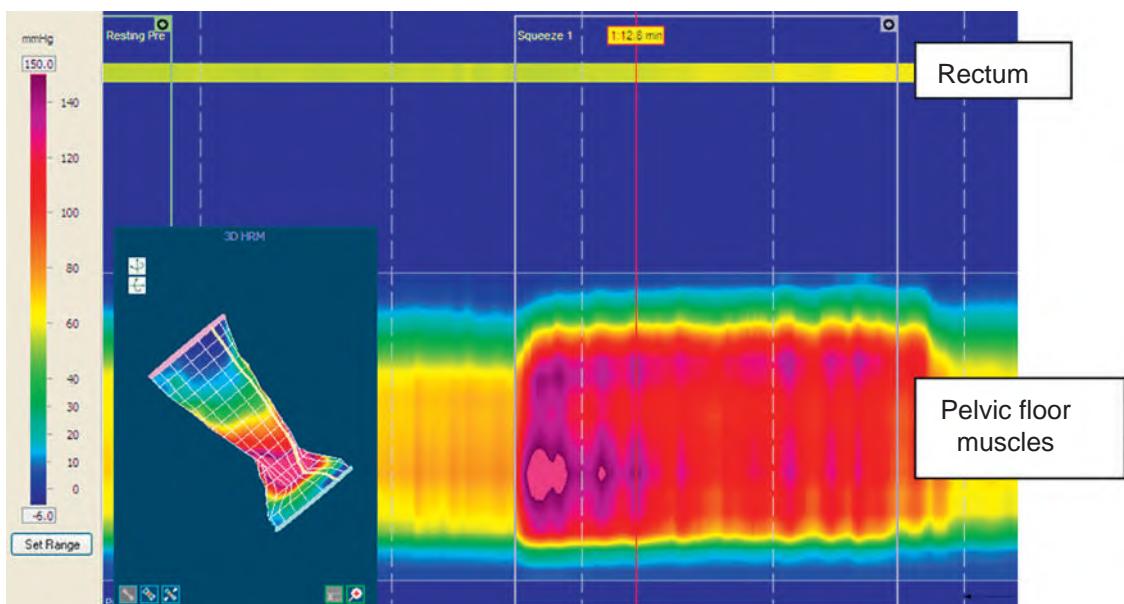
Laboratory testing was performed 1 month ago at her primary care office, including a complete blood count and basic chemistries that were within normal limits.

Three-dimensional (3D) high-resolution anorectal manometry is performed and the results are shown in Figures 46-1, 46-2, and 46-3.

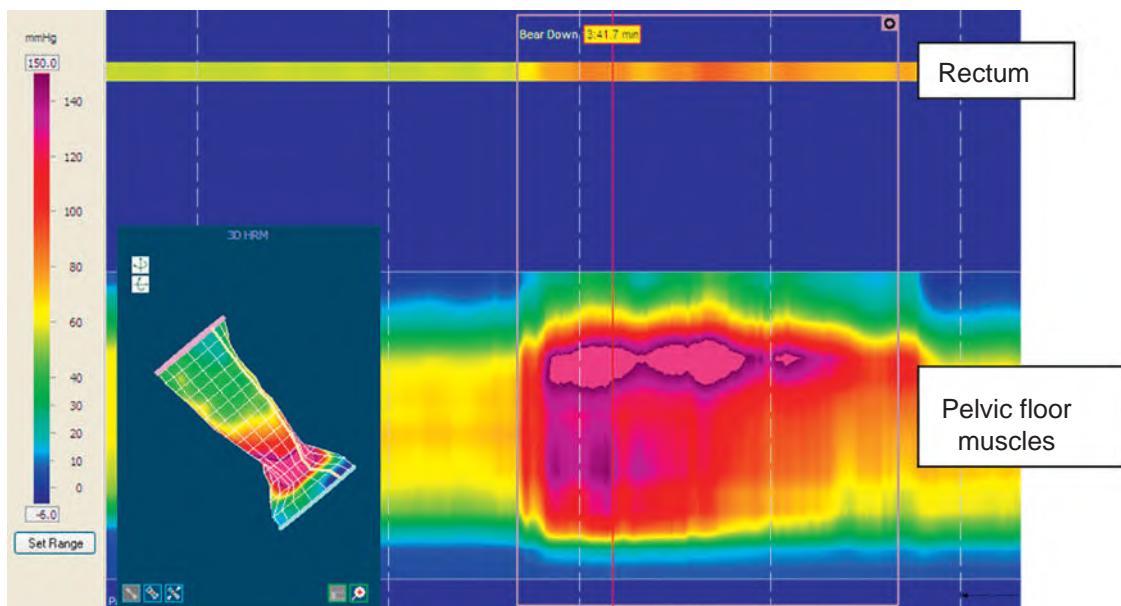
Finally, balloon expulsion testing reveals an inability to expel the balloon after 5 minutes.



**CV Figure 46-1.** Resting pressure.



**CV Figure 46-2.** Three-dimensional (3D) high resolution anorectal manometry demonstrating resting pressure.



CV Figure 46-3. Bear down.

#### DIAGNOSIS AND TREATMENT

This study shows evidence of pelvic floor dyssynergia, with paradoxical contraction of the anal muscles on attempted defecation. The 3D images help to visualize the sites of sphincter contraction, and the balloon expulsion results support the diagnosis. This patient will likely benefit from pelvic floor biofeedback.

### CHAPTER 50—UPPER GASTROINTESTINAL HEMORRHAGE

A 74-year-old man presents with 24 hours of melena and syncope. He denies abdominal pain. Past medical history includes hypertension, hyperlipidemia, and osteoarthritis. Medications include aspirin (81 mg daily by mouth), atenolol, hydrochlorothiazide, atorvastatin, and ibuprofen (200-400 mg every 6-8 hours as needed for joint pain). He does not smoke cigarettes or drink alcohol, and there is no personal or family history of gastrointestinal bleeding, esophageal, or gastric cancer.

Pertinent physical examination findings include blood pressure 94/68, heart rate 88, and oxygen saturation 95% on room air. There are no stigmata of chronic liver disease. Abdominal examination demonstrates a soft abdomen that is nontender, nondistended, with normal bowel sounds. Rectal examination shows melena.

Laboratory values include hematocrit 23%, platelet count of 246,000, international normalized ratio 1.1, mean corpuscular volume of 88, and blood urea nitrogen of 28 mg/dL.

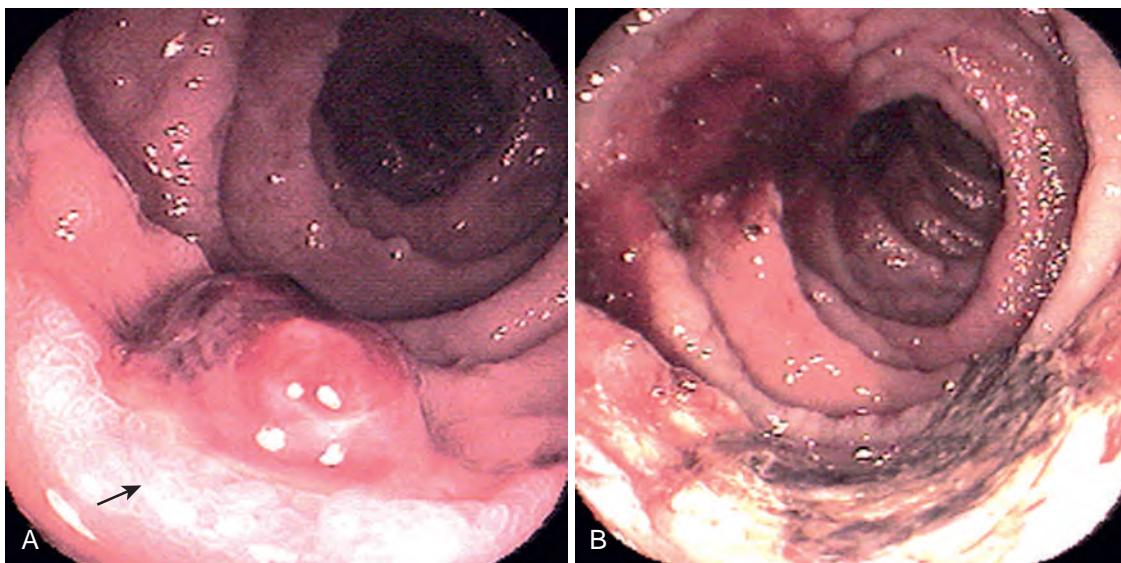
Based on a Blatchford score of 14, the patient is admitted to the intensive care unit (ICU). Initial resuscitation is performed, including intravenous (IV) access with two large-bore catheters, volume replacement (crystalloid), and type and cross of 6 units of packed red blood cells. IV pantoprazole is initiated with an 80 mg bolus and 8 mg/h continuous infusion thereafter.

Esophagogastroduodenoscopy is performed after resuscitation and a 1-cm duodenal ulcer is found in the duodenal sweep with a visible vessel. Endoscopic treatment is applied with 1 mL aliquots of 1:10,000 epinephrine injected four times at the base of the ulcer, and bipolar circumactive probe cautery is applied on the vessel and ulcer base ([CV Figure 50-1A and B](#)).

The patient remained in the ICU for 24 hours postendoscopy, and based on no further rebleeding, he was transferred to the general medical ward to complete 72 hours of IV proton pump inhibitor (PPI) therapy and was then discharged. Serology for *Helicobacter pylori* was obtained, which was negative. The patient's aspirin was discontinued as it was for primary cardiovascular protection, but, because of debilitating joint pain, he was switched from ibuprofen to celecoxib and thus continued indefinitely on oral PPI therapy.

### CHAPTER 51—LOWER GASTROINTESTINAL TRACT BLEEDING

A 72-year-old white man is admitted to the intensive care unit after the acute onset of large-volume painless hematochezia. On admission, his blood pressure is 92/60 and heart rate is 120 beats per minute (sinus rhythm).



**CV Figure 50-1.** Peptic ulcer with visible vessel before (A) and after (B) endoscopic treatment.

The patient has a syncopal event in the emergency department but there is no evidence of cardiac ischemia on his electrocardiogram. The patient has a history of high blood pressure and hyperlipidemia for which he takes lisinopril, simvastatin, and a daily aspirin. Polyp surveillance colonoscopy 5 years ago was devoid of polyps but did reveal severe sigmoid and mild ascending colon diverticulosis.

Two large-bore intravenous lines are placed, 1 liter of normal saline is administered, a nasogastric lavage is devoid of blood, and a rectal examination is remarkable for gross bright red blood with clots. The patient is typed and screened and a unit of platelets is thawed. The patient responds to initial resuscitation and undergoes a rapid polyethylene glycol bowel purge followed by a nondiagnostic upper endoscopy and ileocolonoscopy.

The patient remains stable for the next 2 days when he begins to produce multiple large bloody stools associated with marked symptomatic hypotension. After resuscitation the patient is sent for a computed tomography–angiogram that shows a swirl of intraluminal contrast in the sigmoid colon. Unfortunately, by the time the patient arrives for subselective angiography, the bleeding has stopped and coil embolization is not performed. Later that evening the patient bleeds again and responds to resuscitation, but the patient has now received a total of eight units of packed red blood cells and four units of platelets. After careful consultation with a general surgeon and the patient's family, the patient was taken for a sigmoidectomy with a Hartmann's procedure. There is no further bleeding.

## CHAPTER 53—EVALUATION OF ACUTE ABDOMINAL PAIN

The patient is a 32-year-old black G3, P2, SAB1 obese woman with Type II diabetes and reactive airway. Her last menstrual period was 8 weeks ago. She has had some dull recurrent epigastric and right upper quadrant (RUQ) pains over the past several months. Now she is having pain in the same area of increased intensity associated with nausea and vomiting for the past 6 hours. She has some dysuria and no recent bowel movement. She has had an appendectomy. She smokes daily and is a moderate to heavy drinker of alcohol, but does not use street drugs. There is a family history of gallstones.

Physical examination shows that the patient is uncomfortable, anxious, and mildly diaphoretic. There is RUQ tenderness with some guarding, but no rebound. No mass can be felt. The cervix is mildly tender on examination and there are some crackles at the lower lung bases. Her stool is negative for blood.

### What tests should be ordered next?

Complete blood count, comprehensive metabolic panel, amylase and lipase, beta-human chorionic gonadotropin (HCG), urinalysis, abdominal and chest X-rays

### What is your differential diagnosis?

Cholecystitis, pancreatitis, ectopic pregnancy, urinary tract infection, gastroenteritis, diabetic ketoacidosis (DKA), pneumonia, kidney stone, sickle cell crisis, volvulus or small bowel obstruction, or pelvic inflammatory disease

### Test results:

White blood count = 13,000, hematocrit = 30, beta-HCG positive, amylase ↑ 2 × upper limit of normal, lipase normal, liver enzymes normal, glucose = 400, and carbon dioxide (bicarb) = 18; chest X-ray normal, abdominal X-ray shows an ileus

**What is your revised differential diagnosis?**

Ectopic pregnancy, pancreatitis, DKA

**What tests would you now order?**

Pelvic ultrasound (US) or possibly a computed tomography scan, serum ketone levels

**Test results:**

Intrauterine material, no gallstones, noninflamed pancreas, and normal ovaries seen on US examination; blood positive for ketones

**Final diagnosis:**

Intrauterine pregnancy and DKA

## CHAPTER 54—EVALUATION OF ACUTE INFECTIOUS DIARRHEA

1. A patient presents with several days of diarrhea after returning from travel. Stool culture is performed and no pathogens are cultured; however, *Blastocystis hominis* is identified. How would you treat this patient?

*Blastocystis hominis* is the most common parasite isolated from stools of symptomatic and asymptomatic subjects. Prevalence is higher in developing countries and acquisition is associated with travel. However, a relationship between infection and a disease state has been controversial and remains unproven in humans despite some animal data available. Treatment often is not successful and the optimal therapy (metronidazole, tinidazole, and trimethoprim-sulfamethoxazole have been evaluated) for what is often transient and self-limited colonization remains undetermined. A comprehensive search for an alternate etiologic factor for persistent diarrhea should be pursued prior to attributing a clinical syndrome to this organism.

2. A 24-year-old healthy man develops crampy abdominal pain associated with multiple episodes of bloody stools. He has no history of prior gastrointestinal (GI) illnesses or chronic GI complaints. He has low-grade fevers, but no other symptoms. He has no sick contacts, and there have been no other cases of dysenteric illnesses in the local area recently. He presents to the emergency department where stool cultures are obtained. He is started empirically on ciprofloxacin. The stool cultures are negative 7 days later and the patient is still having five to six bloody bowel movements per day. His abdominal pain and low-grade fevers have resolved. What, if anything, should be done next?

Persistent bloody diarrhea in a young patient with negative stool cultures and minimal response to empiric antibiotics suggest a noninfectious source of diarrhea, such as inflammatory bowel disease. Flexible sigmoidoscopy should be performed to evaluate for the presence of ulcers and to assess extent and pattern of colitis.

3. A 27-year-old man who is otherwise healthy is traveling through Central America on vacation. A week into his trip, he develops the sudden onset of lower abdominal cramping, and watery bowel movements occurring four or five times per day. He has not had a fever, nor has he seen blood in his stool. He plans to take a 4-hour bus ride to the capital in 2 days. He is concerned because the buses here do not have bathrooms and do not like to make unscheduled stops. He has both 2 mg loperamide and 250 mg ciprofloxacin in his travel kit. Which, if either, of these should he take?

Unlike acute diarrhea in the developed world, travelers' diarrhea is often due to bacterial pathogens, particularly enterotoxigenic *Escherichia coli*. The combination of an appropriate antibiotic and an antimotility agent has been shown to decrease the duration of illness and improve quality of life. The patient described should take 750 mg of ciprofloxacin once and then take 4 mg of loperamide initially followed by 2 mg after every loose bowel movement (not to exceed eight tablets per day).

4. A Peace Corps volunteer to South America returns to the United States after a several-year tour of duty. While overseas he reports multiple episodes of diarrhea, some of which were bloody. He presents to his primary care manager with several weeks of fevers, right upper quadrant abdominal pain and a liver abscess on computed tomography scan. Which parasitic cause of diarrhea resulted in this presentation?

*Entamoeba histolytica* is a rare cause of traveler's diarrhea among routine travelers and is more commonly seen when individuals spend prolonged periods overseas and consume food and water contaminated with cysts. Acutely may present as watery diarrhea or dysentery. Repeated exposure may lead to progression and invasion with formation of *Entamoeba* liver abscess.

## CHAPTER 55—CHRONIC DIARRHEA

A 59-year-old woman presents with a 6-month history of diarrhea. She has six or seven loose, watery stools per day without bleeding or pain. The patient has not lost weight and blood counts and chemistry panel are unremarkable. Multiple stool tests for white blood cells, occult blood, and pathogens have been negative, and a flexible sigmoidoscopy by her internist was reported to be normal.

Additional tests were done and included:

Stool sodium concentration: 80 mmol/L

Stool potassium concentration: 55 mmol/L

Qualitative fecal fat (Sudan stain): Negative

Colonoscopy with biopsies from throughout the colon was done next. The mucosa of the terminal ileum and colon appeared to be normal. Histologic evaluation showed increased intraepithelial lymphocytes throughout the colon, an inflammatory infiltrate in the lamina propria, and thickening of the subepithelial collagen layer, suggesting a diagnosis of collagenous colitis.

The patient was treated with oral enteric-coated budesonide 9 mg daily for 4 weeks. Her diarrhea abated and she received additional courses of budesonide 6 mg daily for 4 weeks and 3 mg daily for a final 4 weeks. She has been off all medications for 8 months without clinical relapse.

This case demonstrates the value of stool analysis in directing the further evaluation of patients with chronic diarrhea. She produced electrolyte-rich stool with a small calculated osmotic gap ( $290 - 2 \times (80 + 55) = 20$  mosm/kg), consistent with secretory diarrhea. A prominent cause for secretory diarrhea in women of this age group is microscopic colitis. Diagnosis of this condition depends on obtaining colon biopsies when the colon mucosa is grossly normal, as in this case. Biopsies demonstrated the collagenous colitis variant of microscopic colitis and led to treatment with budesonide, a highly effective (but off-label) treatment for this condition.

## CHAPTER 56—AIDS AND THE GASTROINTESTINAL TRACT

A 38-year-old intravenous drug user presents with significant weight loss, diarrhea, and painful swallowing. He was previously diagnosed with human immunodeficiency virus infection approximately 3 years earlier, but because of lack of insurance, highly active antiretroviral therapy was never taken. During the preceding month he has noted the subacute onset of loose, watery stools of large volume up to 10 times per day. On one occasion he presented to an urgent care center where intravenous fluids were provided. During the preceding 10 days, he relates pain with swallowing such that he is now avoiding food altogether. During the preceding month, his weight has fallen approximately 30 pounds. Physical examination is pertinent for a male who appears older than his stated age, there is mild temporal wasting and minimal candidal plaques are seen in the oropharynx, his abdomen is soft and scaphoid, and there are no findings on skin or musculoskeletal examination.

Laboratory studies are pertinent for a CD4 count of 32 cells/mm<sup>3</sup>, hematocrit 38, white blood cells 2.9, and an albumin of 2.7. His liver tests are normal. Stool study shows no fecal white cells but numerous cryptosporidia. Upper endoscopy is performed showing mild oropharyngeal *Candidiasis* but significant ulceration of the distal esophagus (see Chapter 56, Figure 56-2). Multiple biopsies were obtained. These subsequently returned as herpes simplex virus esophagitis.

He was begun on highly active antiretroviral therapy and intravenous acyclovir. During the subsequent month, his diarrhea decreased significantly, his weight increased 15 pounds, and his esophageal complaints abated.

## CHAPTER 58—NUTRITION, MALNUTRITION, AND PROBIOTICS

A 55-year-old homeless, alcoholic man presents to your emergency room with coffee ground emesis. In the emergency room the blood pressure is 90/60, pulse 120, and afebrile. Medical and surgical history include recurrent admission for alcohol intoxication malnutrition, frostbite, hepatitis C infection, and depression. Physical examination identified a disheveled, unshaven, malnourished man. His height is 6 feet and weight 140 pounds. His sclera are white, spider angioma appear on the chest, and the liver is enlarged to 14 cm in the midclavicular line, but no ascites or splenomegaly are present. Palms are red, but no asterixis is present. Rectal examination is positive for melena.

### LABORATORY RESULTS

White blood cells: 3.9 ( $4\text{-}10.5 \times 10^3/\mu\text{L}$ )

Hemoglobin: 8 (12.6–17.7 g/dL)

Hematocrit: 24 (37.5–51%)

Mean corpuscular volume: 106 (779–97 fL)

Platelets: 125 ( $140\text{-}415 \times 10^3/\mu\text{L}$ )

Glucose: 120 (65–99 mg/dL)

Blood urea nitrogen: 30 (6–24 mg/dL)

Creatinine: 1.3 (0.76–1.27 mg/dL)

Calcium: 8 (8.7–10.2 mg/dL)

Aspartate aminotransferase: 100 (0–40 IU/L)

Alanine aminotransferase: 55 (0–55 IU/L)

Total protein: 5 (6–8.5 g/dL)

Albumin: 2.4 (3.5–5.5 g/dL)

Alkaline phosphatase: 155 (5–150 IU/L)

Total bilirubin: 1.5 (0–1.2 mg/dL)

The emergency department and gastroenterologist are concerned for portal hypertension and variceal bleeding.

The nutritional concerns in this patient are the following:

- Thiamine deficiency
- Folate deficiency
- Refeeding hypophosphatemia

- Protein calorie malnutrition
- Possible need for protein restriction 1 g/kg for cirrhosis and portal encephalopathy and salt restriction 2 g/day to avoid issues with ascites.

## CHAPTER 60—FOREIGN BODIES AND THE GASTROINTESTINAL TRACT

**A 3-year-old boy playing with his Christmas toy that contains a button battery suddenly begins grasping at his throat and hypersalivating. The parents call 911 and the child is brought to your emergency department.**

**Should you administer ipecac or glucagon, admit for observation, or obtain plan x-ray of neck and chest?**

Maintenance of the airway is the first priority. After that, determine the size and location of the foreign body with a plain x-ray. Identification of a button battery lodged in the esophagus is cause for an emergency removal. The lithium-containing button batteries can cause serious burns of the esophagus within hours and should be endoscopically removed as soon as possible.

### REFERENCES

- Ferrante J, O'Brien C, Osterhout C, Gilchrist J. Injuries from batteries among children aged <13 years—United States, 1995–2010. MMWR 2012;61(34):661–665. Accessed from <http://www.cdc.gov/mmwr/pdf/wk/mm6134.pdf>.  
Ruhl DSL, Cable BB, Rieth KK. Emergent treatment of button batteries in the esophagus: Evolution of management and need for close second-look esophagoscopy. Ann Otol Rhinol Laryngol 2014;123(3):206–213

## CHAPTER 64—Dermatologic Manifestations of Gastrointestinal Disease

- 1. A 39-year-old man with hepatitis C being treated with telaprevir presents with an asymptomatic morbilliform (measleslike) skin eruption 7 days after starting the new medication. Does the telaprevir need to be discontinued?**

Not necessarily. Approximately 56% of patients starting telaprevir will develop a measleslike (morbilliform) or less commonly an eczematoid drug eruption. In most cases these reactions are self-limited within 1 to 3 weeks, and can be treated with topical moisturizers or corticosteroids and oral antihistamines. However, if the eruption covers large areas of the body, has blisters, involves mucosal surfaces, or continues to progress, then the telaprevir should be discontinued and the patient evaluated for life-threatening reactions including drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens-Johnson syndrome, or toxic epidermal necrolysis. These mucocutaneous skin reactions occur in less than 1% of patients receiving the drug. The label for telaprevir now contains a black box warning from the Food and Drug Administration for these reactions.

- 2. A 25-year-old woman presents with painful, tender, red-to-violaceous subcutaneous nodules of the pretibial skin associated with diarrhea. What is the skin lesion?**

The patient most likely has erythema nodosum. The differential diagnosis also includes other types of panniculitis (e.g., erythema induratum, pancreatitis-associated panniculitis), infection, and deep vasculitis (e.g., periarteritis nodosum). Erythema nodosum is a form of hypersensitivity panniculitis that preferentially affects the fibrous septae between the fat lobules. Clinically, erythema nodosum most commonly presents on the anterior surface of the legs as painful red to violaceous subcutaneous nodules without overlying scale ([CV Figure 64-1](#)).



**CV Figure 64-1.** Typical lesions of erythema nodosum demonstrating bilateral, red, tender, subcutaneous nodules on the anterior lower legs.

Lesions are typically bilateral but unilateral and even annular variants exist. Typical lesions resolve during a period of 3 to 6 weeks, but atypical lesions may persist for months. The diagnosis is usually made clinically but occasional cases require biopsy. The pathogenesis is not understood. Ulcerative colitis, Crohn's disease, and infectious colitis (e.g., *Salmonella* and *Yersinia enterocolitidis*) are the most common gastrointestinal (GI) diseases associated with erythema nodosum. In patients with inflammatory bowel disease, erythema nodosum is most commonly associated with ulcerative colitis (up to 7% of patients) and less commonly with Crohn's disease. The disease activity of erythema nodosum often parallels the activity of the bowel disease.

**3. A 22-year-old woman presents with low-grade fever and an expanding, oozing ulcer of the hand that is rapidly increasing in size despite aggressive surgical debridement and intravenous antibiotics. What does this patient have?**

The patient most likely has pyoderma gangrenosum (PG). PG usually affects the lower legs but can involve any cutaneous surface and the mucosal surfaces of the eye and oral cavity. The lesion begins as a tender red papule or pustule that rapidly increases in size to form an ulcer with an undermined border ([CV Figure 64-2](#)). Lesions of PG may remain fixed or may rapidly expand at a rate of more than 1 cm per day. PG often demonstrates *pathergy*, which is the development of skin lesions at the site of trauma. PG mistaken for bacterial pyodermas may be treated with surgical debridement, which often makes the lesion worse. The pathogenesis of PG is controversial. Histologically, the predominant effector cells are neutrophils and some authorities have even considered it to be a form of vasculitis. More recent evidence suggests that it is probably lymphocyte mediated, which accounts for its marked response to cyclosporine.

**4. A 32-year-old man presents with a 2-year history of recurrent blisters that are intensely pruritic and have been recalcitrant to antihistamines and topical corticosteroids. They are primarily located on the elbows, knees, and buttocks. What does this patient most likely have?**

This patient most likely has dermatitis herpetiformis, an autoimmune vesiculobullous disease characterized by intensely pruritic blisters that are often grouped (herpetiform) or less commonly plaques studded with vesicles or bullae ([CV Figure 64-3](#)). Dermatitis herpetiformis has a classic symmetric distribution; the characteristic sites are the elbows, knees, buttocks, and scalp. Because of the intense pruritus, patients often present with excoriations only. The diagnosis is usually established by demonstrating the presence of immunoglobulin A autoantibodies along the dermoepidermal junction by direct immunofluorescence.

**5. A 30-year-old man presents with acute GI bleeding. He has yellowish, pebbly papules that coalesce into plaques of the neck, antecubital fossae, and axillae. Similar lesions are also present on his lower lip. What does he have?**

The patient has pseudoxanthoma elasticum (PXE), a disorder characterized by progressive calcification of elastic fibers. It is most commonly inherited in an autosomal dominant fashion but autosomal recessive variants have also been described. Mutations in the ABCC6 gene have been demonstrated in the majority



**CV Figure 64-2.** Typical lesion of pyoderma gangrenosum demonstrating tender, rapidly expanding ulcer with undermined edge.



**CV Figure 64-3.** Grouped vesicles and bullae on the elbows of a patient with dermatitis herpetiformis.



**CV Figure 64-4.** Confluent yellowish papules with appearance of “plucked chicken skin” in a patient with pseudoxanthoma elasticum.

of patients with PXE. Preliminary studies suggest that this mutation results in the reduced ability of vitamin K to prevent elastic tissue mineralization. The mucocutaneous manifestations are described as looking like *plucked chicken skin* (CV Figure 64-4). The histologic findings are diagnostic and demonstrate fragmentation of abnormal elastic fibers in the dermis associated with calcification. Identical yellowish papules are seen in the GI mucosa, including the mouth, esophagus, and stomach. Involvement of the elastic fibers in gastric arteries may result in acute and sometimes massive hemorrhage. Additional findings associated with PXE include angioid streaks of the retina, claudication, premature angina, and hypertension.

**6. A 24-year-old man presents with a history of unexplained melena, nose bleeds, and red macular lesions of his lips and fingers. What does he have?**

This patient most likely has hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease. This uncommon genetic disorder is inherited in an autosomal dominant fashion and is the result of mutations of two genes: *ENG* (HHT1) and *ALK1* (HHT2). The cutaneous lesions typically present at the time of puberty or later and manifest as linear, punctate, or macular lesions that most commonly affect the skin surfaces of the face, finger, and toes. Similar lesions are also found in many types of mucosal surfaces, including the nasal mucosa, lips, entire GI tract, and urinary tract. Arteriovenous malformations also may develop in



**CV Figure 64-5.** Hyperpigmented macules (lentigines) of the lips and perioral skin in a patient with Peutz-Jeghers syndrome. (Courtesy Fitzsimons Army Medical Center Teaching Collection.)

the central nervous system, eye, lungs, and liver. Patients continue to develop new lesions during their lifetime and may experience chronic iron-deficiency anemia caused by chronic low-grade blood loss from the GI tract.

**7. During evaluation for GI bleeding, a 25-year-old man is noted to have 2- to 4-mm pigmented macules of the lips and buccal mucosa. What does he most likely have?**

This patient most likely has Peutz-Jeghers syndrome, an autosomal-dominant disorder associated with germline mutations of the *STK39/LKB1* tumor suppressor gene. It is characterized by round to oval pigmented macules that vary from brown to blue-brown in color and small intestine hamartomatous polyps. The pigmented macules are usually present at birth or develop during infancy. The most commonly affected areas are the lips (CV Figure 64-5), buccal mucosa, hard palate, gingival, anus, palms, and soles. Because pigmented macular lesions may be seen in these areas in normal individuals and in association with other syndromes, clinical and historical correlation is necessary to make establish a diagnosis of Peutz-Jeghers syndrome. The lifetime risk of developing adenocarcinoma in the GI polyps seen in Peutz-Jeghers is calculated to be between 2% to 13%. Patients also demonstrate an increased incidence of other types of neoplasia, including breast carcinoma, cervical adenocarcinoma, and both benign and malignant tumors of the ovary and testes.

**8. During evaluation for numerous polyps of the colon, a 19-year-old man is noted to have multiple cysts of the skin and an osteoma. What does he most likely have?**

Gardner syndrome, which is inherited in an autosomal dominant fashion, is due to a mutation in the *APC* gene located at 5q21. This rare disorder occurs in 1 of every 14,000 births. The polyps resemble the polyps of familial adenomatous polyposis. Patients have colonic polyps and 10% have small intestine polyps. The cutaneous manifestations consist of epidermoid cysts (epidermal inclusion cysts), lipomas, fibromas, desmoid tumors, and rarely pilomatrixomas (uncommon hair follicle tumors). Patients often have bone tumors, most of which are osteomata; supernumerary teeth; and congenital hypertrophy of the retinal pigmented epithelium. The lifetime risk of colon cancer in Gardner syndrome approaches 100%. Proctocolectomy is recommended for all patients, followed by periodic monitoring of the rectal mucosal remnant and the upper GI tract. Patients with Gardner syndrome also have a higher incidence of extracolonic malignancies, including papillary thyroid carcinoma, adrenal carcinoma, hepatoblastoma, periampullary carcinoma, and duodenal carcinoma.

**9. A 64-year-old man presents with multiple hamartomatous polyps of the small and large bowel. Cutaneous examination reveals cobblestoning of the oral mucosa and multiple small papules and verrucous papules of this face. What does this patient most likely have?**

The patient most likely has Cowden disease, which is also known as *multiple hamartoma syndrome*. This rare syndrome is inherited in an autosomal fashion and is due to mutations in *PTEN*, a tumor suppressor gene located on chromosome 10q23. The mucocutaneous manifestations include small papules of the oral mucosa (CV Figure 64-6) that are usually most prominent on the gingival, are often numerous, and have been described as resembling cobblestones; papules and verrucous papules, usually located on the face that are trichilemmomas (benign follicular tumors), hyperkeratotic papules of the extremities, and firm nodules called *sclerotic fibromas*. Sclerotic fibromas are uncommon benign fibrous tumors that are typically solitary. Multiple sclerotic fibromas are considered to be a specific marker for Cowden disease; the incidence approaches 100% if two or more are present. Polyps are present in the GI tract in approximately 30% of patients and may be present at any site. The polyps associated with Cowden syndrome do not demonstrate an increased risk of malignancy. However, patients with Cowden syndrome demonstrate an increased incidence of thyroid disease; up to two-thirds have goiter and 10% develop thyroid carcinoma. Seventy-five percent of women with Cowden demonstrate breast neoplasia manifesting as fibrocystic breast disease, fibroadenomas, and breast carcinoma.



**CV Figure 64-6.** Characteristic papules of the gingiva of patient with Cowden syndrome. In some patients they become confluent and resemble cobblestones. (Courtesy Fitzsimons Army Medical Center Teaching Collection.)

**10. A 60-year-old man has had multiple keratoacanthomas removed from his skin and recently had a biopsy of a sebaceous adenoma of the cheek. For what syndrome should he be evaluated?**

This patient should be evaluated for Muir-Torre syndrome, which is characterized by multiple benign or malignant cutaneous sebaceous neoplasms, and an increased risk of gastrointestinal malignancies (colon adenocarcinoma, genitourinary tract carcinoma, and lymphoma). Patients may also demonstrate multiple keratoacanthomas (well-differentiated squamous cell carcinomas of the skin). Muir-Torre syndrome is inherited in an autosomal dominant manner and is caused by a defect in one or more of the DNA mismatch repair genes MLH1, MSH, MSH6, and PMS-2. Because the cutaneous neoplasms occur prior to the development of internal malignancy in these patients, appropriate workup and genetic counseling can be lifesaving.

**11. A 50-year-old woman presents with alopecia, unexplained 20-pound weight loss, and very superficial flaccid vesicles and erosions on an erythematous base that preferentially involves the perioral and perianal areas. What does she most likely have?**

The cutaneous lesions are consistent with necrolytic migratory erythema, a paraneoplastic cutaneous finding associated with alpha-2-glucagon-producing islet cell tumors of the pancreas. The cutaneous lesions characteristically start as broad areas of erythema that preferentially affect the face, intertriginous areas, ankles, and feet. The skin often appears to peel or demonstrate superficial vesicles. Patients also may demonstrate stomatitis, glossitis, alopecia, nail dystrophy, weight loss, diabetes mellitus, and anemia. Resection of the glucagon-producing tumor produces prompt resolution of the skin lesions.

## CHAPTER 65—ENDOCRINE ASPECTS OF GASTROINTESTINAL SYSTEM

A 38-year-old man presents with recurrent hypoglycemia, mostly after prolonged fasting. For several years now he has been having calcium oxalate kidney stones and lately he has noticed issues with erectile dysfunction.

Pertinent fasting laboratory results are calcium 11.2 mg/dL (nmol 8.5 to 10.5) and prolactin 400 ng/mL (normal < 18). Magnetic resonance imaging of the brain shows a 1.2-cm sellar mass. What pancreatic tumor could the patient have?

Multiple endocrine neoplasia type I is the potential pancreatic tumor.

What disorder does the patient have to explain the patient's constellation of clinical conditions?

- Hyperinsulinemia is caused by pancreatic neuroendocrine tumor.
- Elevated parathyroid hormone caused by parathyroid hyperplasia or adenoma increases serum calcium and likelihood of nephrolithiasis.
- Pituitary adenoma can cause hypersecretion of prolactin, erectile dysfunction, and nipple discharge.

## CHAPTER 66—PLAIN FILM, BARIUM, AND VIRTUAL RADIOGRAPHY

**1. Do guidelines exist for the appropriate management of computed tomographic colonography (CTC) findings?**

- If a mass is detected, surgical consultation is recommended.
- For a polyp 10 mm or greater in size, or if there are three or more polyps 6 mm or larger, endoscopic resection is recommended.
- If fewer than three polyps measuring 6 to 9 mm are detected, recommendations are less clear, with some advocating shorter-interval follow-up CTC, possibly in 3 years, whereas others suggest optical colonoscopy should be performed.
- For polyps 5 mm or smaller, continued routine screening with CTC is recommended in 5 years.

## 2. Can CTC be performed the same day in cases of failed optical colonoscopy?

Incomplete, or failed, optical colonoscopy is one of the proven indications for CTC. Anywhere from 5% to 35% of optical colonoscopies are incomplete, with a higher likelihood of occurrence in older patients, in female patients, and in patients with a history of abdominal surgery. In cases of an obstructing cancer causing the failed colonoscopy, CTC detects synchronous tumors and additional polyps in 7% and 41% of patients, respectively. However, if a polypectomy was performed at the time of optical colonoscopy, then CTC should be postponed for 4 weeks after the procedure as a precautionary measure because of the potential increased risk of perforation. This is in addition to the other generally accepted contraindications for CTC, including active inflammatory bowel disease and diverticulitis.

## CHAPTER 69—NONINVASIVE GI IMAGING: ULTRASOUND, COMPUTERIZED TOMOGRAPHY, AND MAGNETIC RESONANCE SCANNING

### 1. Outline the work-up for a suspected cavernous hemangioma initially discovered on ultrasound (US) or computed tomography (CT).

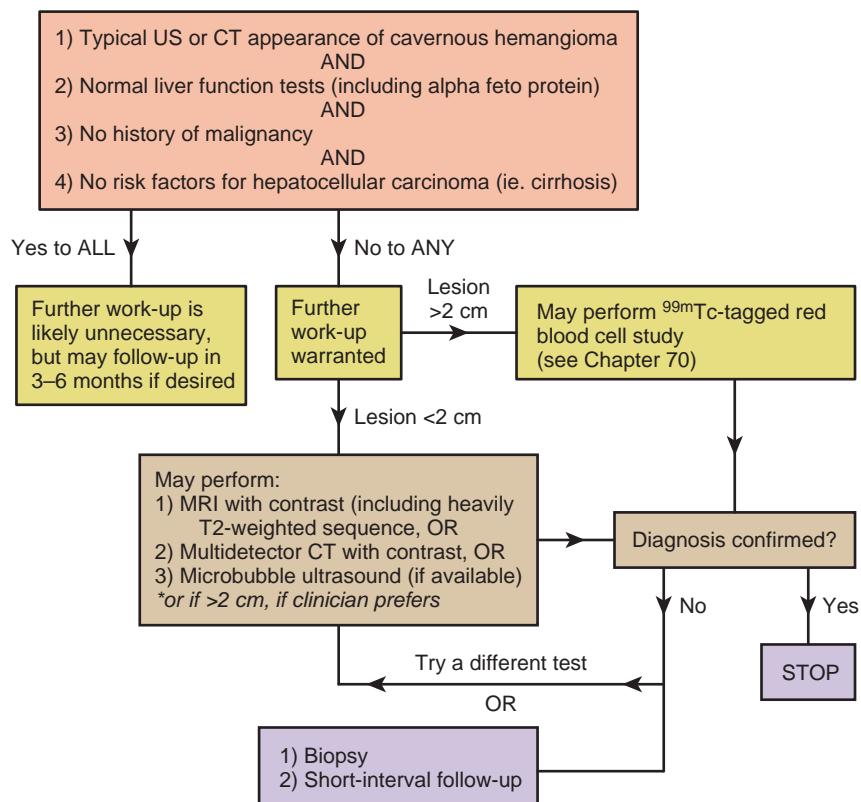
See CV Figure 69-1.

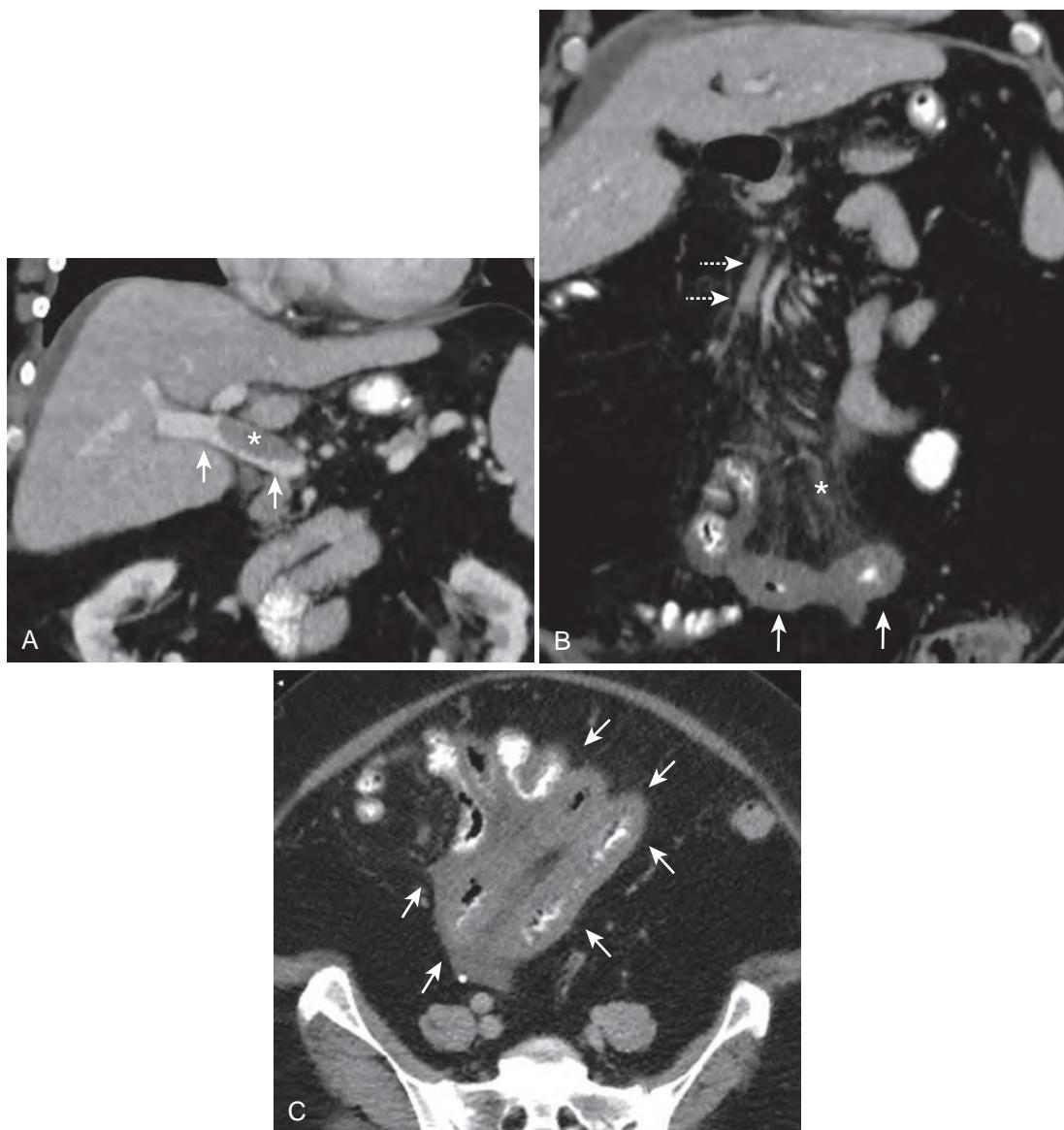
### 2. A 55-year-old woman presented with abdominal pain. The patient awoke with dull pain that became unbearable throughout the day. She described the pain as spreading across her midabdomen and into her back. She also experienced vomiting and a single episode of melena. She denied previous similar episodes.

Her past medical history was significant for bariatric surgery 20 days earlier, but she reports that she had been recovering well. She has a history of cirrhosis and reports confusion two to three times per week, but she has had only one episode of hepatic encephalopathy. She has gastroesophageal reflux and gastroparesis. She denied previous deep venous thrombosis (DVT), pulmonary embolus, bleeding disorder, ascites, paracentesis, jaundice or varices.

CT scan demonstrated near-complete occlusive thrombus within the portal vein (PV) (CV Figure 69-2A) and acute occlusive thrombus within the superior mesenteric vein (SMV) (CV Figure 69-2B). Mucosal edema, bowel wall thickening, and mesenteric stranding surrounding the distal jejunum and proximal ileum were identified, as was minimal wall thickening of the ascending colon (CV Figure 69-2C). These findings were

**CV Figure 69-1.** Work-up of suspected cavernous liver hemangioma detected incidentally on ultrasound (US) or computed tomography (CT). MRI, Magnetic resonance imaging.



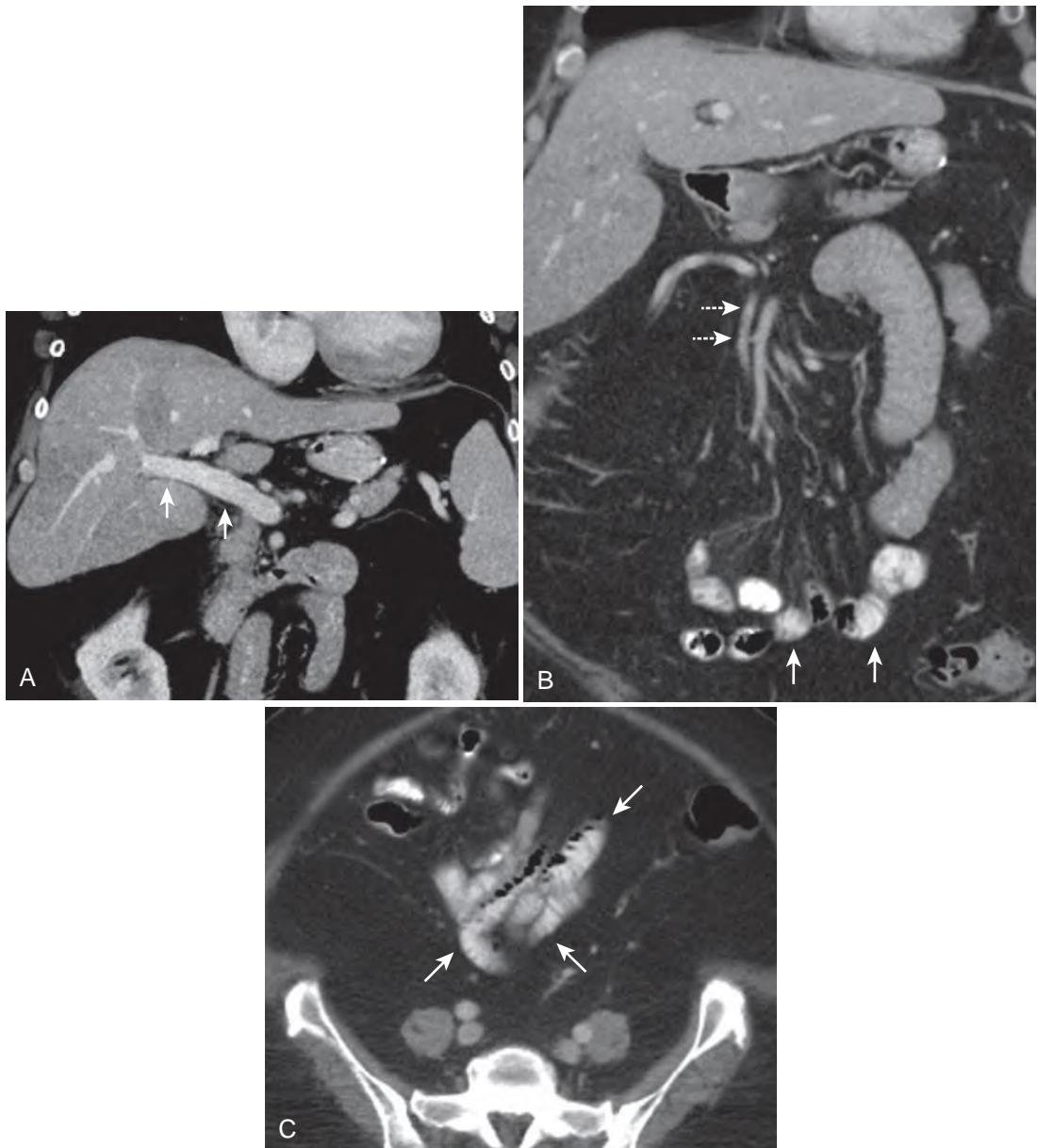


**CV Figure 69-2.** Presentation computed tomography (CT). **A**, Coronal CT multiplanar rendering (MPR) image demonstrates nearly occlusive thrombus (\*) in main portal vein (arrows). **B**, Coronal CT MPR image demonstrates enlarged superior mesenteric vein (dotted arrows) completely occluded with thrombus. More inferiorly, there is marked thickening of several small bowel loops (arrows) and stranding in the mesenteric fat (\*). **C**, Axial CT image demonstrates marked small bowel wall thickening (arrows) and interposed mesenteric edema.

consistent with ischemia secondary to venous congestion. No bowel obstruction, pneumatisis, or portal venous gas was present. Bilateral upper extremity Doppler US were negative for DVT and an esophagogastro-duodenoscopy was normal.

The patient's baseline international normalized ratio was normal. Anticoagulation therapy was initiated, including heparin and eventually enoxaparin and warfarin. During the admission, she had persistent nausea but no other episodes of emesis or melena. She tolerated a pureed diet. Hypercoagulable workup was positive for a heterozygous factor V Leiden mutation.

CT scan performed 82 days after presentation demonstrated complete resolution of previously seen PV and SMV thrombus, bowel wall thickening, mesenteric stranding and mesenteric fluid (CV Figure 69-3A-C).



**CV Figure 69-3.** Posttreatment CT. A, Coronal computed tomography (CT) multiplanar rendering (MPR) image demonstrates complete resolution of thrombus in main portal vein (arrows). B, Coronal CT MPR image demonstrates complete resolution of thrombus and return to normal size of the superior mesenteric vein (dotted arrows). More inferiorly, the small bowel loops (arrows) have returned to normal with resolution of the wall thickening and mesenteric edema. C, Axial CT image demonstrates resolution of the small bowel wall thickening and mesenteric edema (arrows).

### 3. What is CT or “virtual colonoscopy”?

Optimal performance of multiple detector computed tomography colonoscopy (CTC) requires thin-section (2- to 3-mm) images using a low-dose technique with additional dedicated CT colonography software.

Typical CT scan time is 5 to 7 seconds and both prone and supine images are obtained. Bowel preparation with magnesium citrate or sodium phosphate is required. The addition of dilute 2% CT barium to tag residual stool and diatrizoate (gastrograffin) to opacify luminal fluid helps differentiate stool from polyps. Distension is performed with either room air or automated carbon dioxide delivery via a small-caliber flexible catheter. Advantages over optical colonoscopy are that sedation is not required and other areas of the abdomen can be evaluated; however, CTC exposes the patient to radiation.

#### 4. How effective is CT or “virtual colonoscopy” in screening for polyps?

Most studies suggest that the accuracy of CTC is greater than barium enemas and approaches optical colonoscopy, especially for polyps larger than 10 mm if the colon is properly prepped and distended. However, interpretation of CTC examinations requires the review of both two- and three-dimensional images, and it is recommended that only radiologists with experience evaluating 50 or more CTC examinations should provide the interpretation.

### CHAPTER 71—ENDOSCOPIC ULTRASOUND

1. A 62-year-old man with hypertension, diabetes, and longstanding gastroesophageal reflux disease presents for esophagogastroduodenoscopy, which reveals a small, subtle mass in the distal esophagus; biopsies are consistent with esophageal adenocarcinoma. He is seen by a thoracic surgeon, with a positron emission tomography-computed tomography scan showing intense uptake in the distal esophagus, but not elsewhere. endoscopic ultrasound (EUS) demonstrates a T1sm lesion with two paraesophageal lymph nodes (LN). They are both round, hypoechoic, and well-defined, measuring 5 and 10 mm. Fine-needle aspiration of the larger LN shows cells consistent with adenocarcinoma. Therefore the patient undergoes chemotherapy and radiation before surgical resection.
2. A 49-year-old woman is admitted with severe epigastric pain with aspartate aminotransferase (AST) 62 U/L, alanine aminotransferase (ALT) 78 U/L, alkaline phosphatase 112 U/L, total bilirubin 2 mg/dL, amylase 1112 U/L, lipase 899 U/L, white blood count 11,000/uL, blood urea nitrogen (BUN) 15 mg/dL, and creatinine 0.8 mg/dL. Abdominal ultrasound shows sludge in the gallbladder and common bile duct 6 mm. She is treated with intravenous (IV) fluids and IV pain medications, and is ordered to take nothing by mouth. The next day she continues in pain with the following laboratory results: AST 65 U/L, ALT 66 U/L, alkaline phosphatase 120 U/L, total bilirubin 1.9 mg/dL, and BUN 10 mg/dL. Surgery requests endoscopic retrograde cholangiopancreatography (ERCP). On the third day of admission, EUS is performed that shows no stones or sludge in the CBD, which measures 5 mm with sludge seen in the gallbladder, and ERCP is not performed. Her pain resolves, and she undergoes cholecystectomy without incident before discharge.

### CHAPTER 76—COLORECTAL SURGERY: POLYPOSIS SYNDROMES AND INFLAMMATORY BOWEL DISEASE

A 28-year-old woman with a vague family history of intestinal surgery for her mother presents with a lower gastrointestinal bleed. Colonoscopy reveals polyps too numerous to count in the colon and rectum. Sampling biopsies reveal hamartomatous polyps without dysplasia. The terminal ileum has no polyps and an upper endoscopy reveals a stomach coated with fundic gland polyps. There are no polyps in the duodenum. APC gene testing in similarly affected family members is negative. Now what do you recommend?

You send the patient for formal genetic counseling and testing. More thorough testing might reveal mutations in the SMAD4 or BMPR1A genes, which are associated with juvenile polyposis syndrome. Generally the polyps are benign; however, there is a small lifetime risk of developing an intestinal malignancy (perhaps caused by chronic inflammation) and as a result, some type of surveillance endoscopy regimen would be appropriate.

### CHAPTER 78—MINIMALLY INVASIVE SURGERY

1. A 39-year-old woman presents with a 2-month history of right upper quadrant abdominal pain that most commonly occurs after eating fatty foods and usually resolves in 30 minutes. She is afebrile, and the physical examination is unremarkable. Laboratory values, including complete blood count and liver function tests, are normal. An abdominal ultrasound of the right upper quadrant demonstrates no evidence of cholelithiasis, gallbladder wall thickening, or pericholecystic fluid. What should be the next step in your evaluation?

The history is consistent with biliary colic. Typical symptoms of biliary colic include right upper quadrant pain or epigastric pain, which may radiate to the right scapula. The pain is often aggravated by eating, especially fatty foods. The cause of biliary dyskinesia is unknown. An initial diagnosis of cholelithiasis was not demonstrated by ultrasound. An upper gastrointestinal series or esophagogastroduodenoscopy would not evaluate the biliary system. A computed tomography scan is less sensitive than ultrasound for detection of gallstones and would not be helpful. Because the history points toward a biliary cause, a hepatobiliary iminodiacetic acid (HIDA) scan should be the next step in the evaluation.

2. The HIDA scan demonstrated rapid filling of the gallbladder and unobstructed flow into the duodenum. Cholecystokinin is administered, and the gallbladder ejection fraction (EF) is calculated at 30%. What is the most likely diagnosis? How should the patient be treated?

The most likely diagnosis is biliary dyskinesia, which is defined as the presence of symptoms of typical biliary colic without evidence of cholelithiasis and a gallbladder ejection fraction less than 35%. Cholecystectomy

resolves clinical symptoms in 85% of patients with typical symptoms of biliary colic and a gallbladder EF lower than 35%.

3. You begin a laparoscopic cholecystectomy on a 56-year-old woman with acute cholecystitis and a body mass index of  $38 \text{ kg/m}^2$ . The gallbladder is tense and difficult to grasp. You are able to aspirate 30 mL of thick, bilious fluid. During dissection toward the infundibulum, you note that the duodenum is adherent to the gallbladder. You are having difficulty retracting laterally and difficulty identifying the infundibular-cystic junction. What are your options?

As the specialty of laparoscopic surgery has matured, the threshold for conversion to open has increased. Basic laparoscopic principles still apply, however. To operate safely, one requires an adequate working space, sufficient optics, and instrumentation, and adequate visualization of anatomy. In this case, anatomy is suspect and unlikely to improve. Although dissection in an antegrade fashion (fundus first) or a laparoscopic subtotal cholecystectomy may be considered, conversion to an open procedure is justified in this circumstance.

4. A 37-year-old man presents with a 3-month history of an asymptomatic left inguinal bulge. He has no significant past medical history and takes no medications. You confirm a left inguinal hernia. There is no hernia in the right groin. The patient wants to know if he should have this hernia repaired.

A randomized study by Fitzgibbons in 2006 concluded watchful waiting is safe for minimally symptomatic inguinal hernias in select patients. Patients need to be educated and aware of the small but serious risk of strangulation. Over time, many patients will become symptomatic and request an operation. Surgical repair is recommended for older medically fit patients at the time of presentation.

5. A 67-year-old man presents with a 3-month history of an asymptomatic left inguinal bulge. He has a past medical history significant for hypertension and prostatism. You confirm a left inguinal hernia. There is no hernia in the right groin. The patient wants to know if he should have this hernia repaired.

In comparison with the patient in question 4, this patient is older and also has prostatism. Although watchful waiting remains an option, this patient should be advised that he is in a patient population more likely to fail watchful waiting. If he is medically fit, it is advisable to repair his hernia.

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