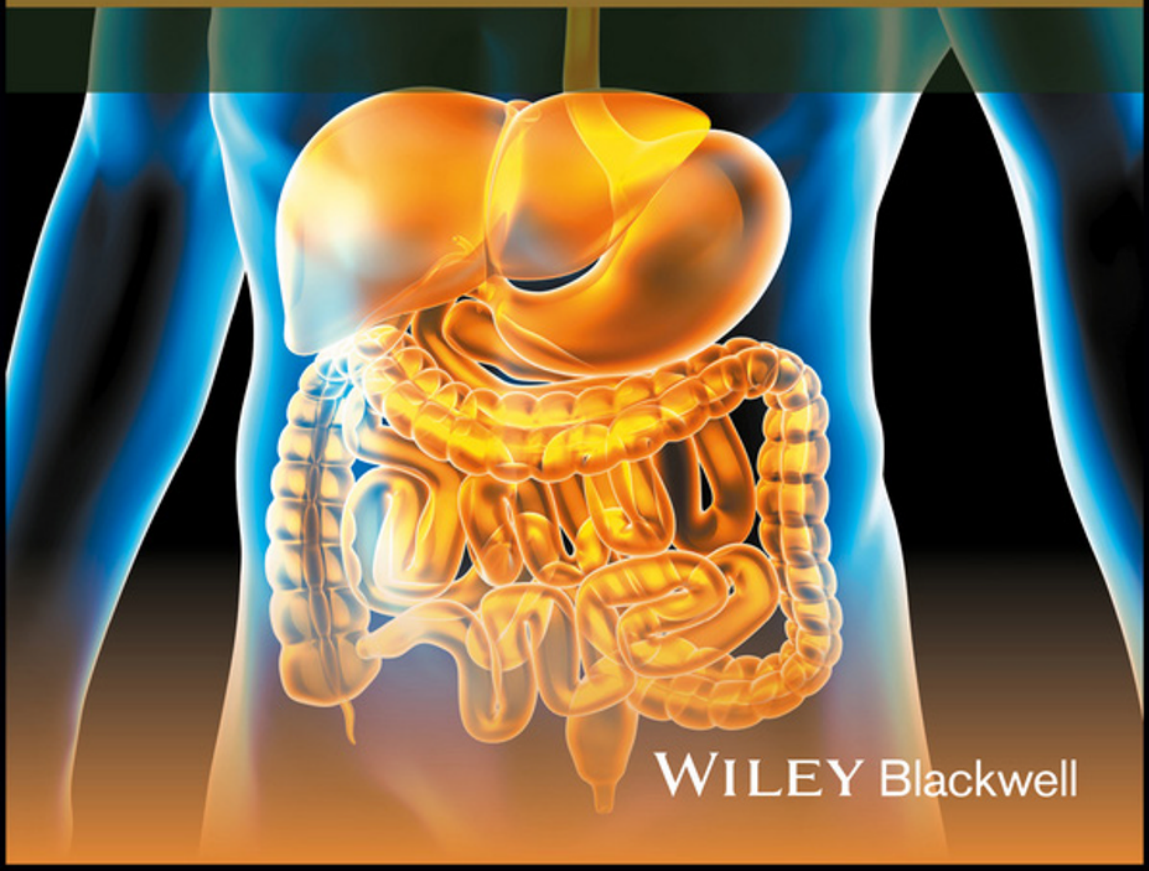
SITARAMAN AND FRIEDMAN'S

Essentials of Gastroenterology

Second Edition

Edited by
Shanthi Srinivasan
& Lawrence S. Friedman



WILEY Blackwell

Sitaraman and Friedman's
Essentials of Gastroenterology

Sitaraman and Friedman's Essentials of Gastroenterology

Edited by

Shanthi Srinivasan, MD

Professor of Medicine, Division of Digestive Diseases, Emory University School of Medicine;
Chief of Gastroenterology, Atlanta Veterans Affairs Medical Center, Atlanta, GA, USA

Lawrence S. Friedman, MD

Professor of Medicine, Harvard Medical School, Boston;
Professor of Medicine, Tufts University School of Medicine, Boston;
The Anton R. Fried, MD, Chair, Department of Medicine, Newton-Wellesley Hospital, Newton;
Assistant Chief of Medicine, Massachusetts General Hospital, Boston, MA, USA

Foreword by

Frank A. Anania, MD, FACP, AGAF, FAASLD

R. Bruce Logue Chair and Professor of Medicine, Director, Division of Digestive Diseases, Emory University Department of Medicine, Atlanta, GA, USA

Second Edition

WILEY Blackwell

This second edition first published 2018 © 2018 by John Wiley & Sons Ltd

Edition History
John Wiley & Sons Ltd (1e, 2012)

Registered Office(s)
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
9600 Garsington Road, Oxford, OX4 2DQ, UK
For details of our global editorial offices, customer services, and more information about Wiley products visit us at www.wiley.com.

Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

Library of Congress Cataloging-in-Publication Data

Names: Srinivasan, Shanthi, editor. | Friedman, Lawrence S. (Lawrence Samuel), 1953– editor.
Title: Sitaraman and Friedman's essentials of gastroenterology / edited by Shanthi Srinivasan, Lawrence S. Friedman.
Other titles: Essentials of gastroenterology. | Essentials of gastroenterology
Description: Second edition. | Hoboken, NJ : John Wiley & Sons, 2017. | Preceded by Essentials of gastroenterology / edited by Shanthi V. Sitaraman, Lawrence S. Friedman. 2012 | Includes bibliographical references and index. |
Identifiers: LCCN 2017034316 (print) | LCCN 2017035044 (ebook) | ISBN 9781119235194 (pdf) | ISBN 9781119235187 (epub) | ISBN 9781119235224 (pbk.)
Subjects: | MESH: Gastrointestinal Diseases | Handbooks | Case Reports
Classification: LCC RC801 (ebook) | LCC RC801 (print) | NLM WI 39 | DDC 616.3/3–dc23
LC record available at https://lccn.loc.gov/2017034316

Cover Design: Wiley
Cover Image: © Science Photo Library - PASIEKA/Gettyimages

Set in 10/12pt Warnock by SPi Global, Pondicherry, India

10 9 8 7 6 5 4 3 2 1

In Memory of Shanthi V. Sitaraman, MD, PhD

Contents

Contributor List

Frank A. Anania, MD, FACP, AGAF, FAASLD
R. Bruce Logue Chair and Professor of Medicine
Director, Division of Digestive Diseases, Department of Medicine
Emory University School of Medicine
Atlanta, GA, USA

Stephen H. Berger, MD
Physician
Huron Gastroenterology Associates
Ypsilanti, MI, USA

Qiang Cai, MD, PhD
Professor of Medicine
Director, Advanced Endoscopy Fellowship
Division of Digestive Diseases
Emory University School of Medicine
Atlanta, GA, USA

Lisa Cassani, MD
Assistant Professor of Medicine
Division of Digestive Diseases
Emory University School of Medicine
Atlanta Veterans Administration Medical Center
Atlanta, GA, USA

Saurabh Chawla, MD
Assistant Professor of Medicine
Division of Gastroenterology
Emory University School of Medicine
Grady Memorial Hospital
Atlanta, GA, USA

Jennifer Christie, MD, FASGE
Associate Professor of Medicine
Clinical Director
Division of Digestive Diseases
Emory University School of Medicine
Atlanta, GA, USA

Nader Dbouk, MD
Physician
Atlanta Gastroenterology Associates
Conyers, GA, USA

Tanvi Dhere, MD
Associate Professor
Division of Digestive Diseases
Emory University School of Medicine
Atlanta, GA, USA

Sujaata R. Dwadasi, MD
Gastroenterology Fellow
University of Chicago
Chicago, IL, USA

Mary M. Flynn, MD
Gastroenterology Fellow
Emory University School of Medicine
Atlanta, GA, USA

Ryan M. Ford, MD
Assistant Professor of Medicine
Division of Digestive Diseases
Emory University School of Medicine
Atlanta, GA, USA

Lawrence S. Friedman, MD
Professor of Medicine,
Harvard Medical School;
Professor of Medicine, Tufts University School of Medicine,
Boston, MA, USA

and

The Anton R. Fried, MD,
Chair, Department of Medicine
Newton-Wellesley Hospital
Newton;
Assistant Chief of Medicine
Massachusetts General Hospital
Boston MA, USA

Anthony M. Gamboa, MD
Assistant Professor of Medicine
Division of Gastroenterology
Vanderbilt University School of Medicine
Nashville, TN, USA

Stephan Goebel, MD
Assistant Professor of Medicine
Division of Digestive Diseases
Emory University School of Medicine;
Atlanta Veterans Administration Medical Center
Atlanta, GA, USA

Nicole M. Griglione, MD
GI Associates, LLC
Brookfield, WI, USA

Melanie S. Harrison, MD
Assistant Professor of Medicine
Division of Digestive Diseases
Emory University School of Medicine;
Atlanta Veterans Administration Medical Center
Atlanta, GA, USA

Steven Keilin, MD, FASGE
Associate Professor of Medicine
Director, Pancreaticobiliary Service
Associate Director, Advanced Endoscopy Fellowship
Division of Digestive Diseases
Emory University School of Medicine
Atlanta, GA, USA

Jan-Michael A. Klapproth, MD
Associate Professor of Medicine
Division of Gastroenterology
University of Pennsylvania
Philadelphia, PA, USA

Stephen K. Lau, MD
Assistant Professor
Department of Pathology
Emory University School of Medicine
Atlanta, GA, USA

Edward Lin, DO, MBA, FACS
Associate Professor of Surgery
Department of Surgery
Emory University School of Medicine
Atlanta, GA, USA

Rebecca G. Lopez, MD
Children's Healthcare of Atlanta at Egleston
Atlanta, GA, USA

Julia Massaad, MD
Assistant Professor of Medicine
Division of Digestive Diseases
Emory University School of Medicine
Atlanta, GA, USA

Pardeep K. Mittal, MD
Associate Professor
Department of Radiology and Imaging Sciences
Emory University School of Medicine
Atlanta, GA, USA

Courtney C. Moreno, MD
Associate Professor
of Radiology
Department of Abdominal Radiology
Emory University School
of Medicine
Atlanta, GA, USA

JP Norvell, MD
Assistant Professor of Medicine
Division of Digestive Diseases
Emory University School of Medicine
Atlanta, GA, USA

Kamil Obideen, MD
Atlanta Gastroenterology Associates
Northside Forsyth Hospital
Cumming, GA, USA

Samir Parekh, MD
Assistant Professor of Medicine
Division of Digestive Diseases
Emory University School of Medicine
Atlanta, GA, USA

Pruthvi Patel, MD, MPH
Assistant Professor of Medicine
Division of Gastroenterology
Stony Brook University School of Medicine
Stony Brook, NY, USA

Anjana A. Pillai, MD
Associate Professor of Medicine
University of Chicago Medical Center
Chicago, IL, USA

Meena A. Prasad, MD
Assistant Professor of Medicine
Division of Digestive Diseases
Emory University School
of Medicine;
Atlanta Veterans Administration Medical Center
Atlanta, GA, USA

Emad Qayed, MD, MPH
Assistant Professor of Medicine
Division of Gastroenterology
Emory University School of Medicine;
Grady Memorial Hospital
Atlanta, GA, USA

Shreya Raja, MD
Assistant Professor of Medicine
Division of Digestive Diseases
Emory University School of Medicine;
Atlanta Veterans Administration Medical Center
Atlanta, GA, USA

Preeti A. Reshamwala, MD
Assistant Professor of Medicine
Division of Digestive Diseases
Emory University School of Medicine
Atlanta, GA, USA

Zakiya P. Rice, MD
Assistant Professor
Department of Dermatology
Emory University School of Medicine
Atlanta, GA, USA

Robin E. Rutherford, MD
Emeritus Professor of Medicine
Emory University School of Medicine
Atlanta, GA, USA

Sonali S. Sakaria, MD
Assistant Professor of Medicine
Division of Gastroenterology
Emory University School of Medicine
Atlanta, GA, USA

Kavya M. Sebastian, MD
Assistant Professor of Medicine
Division of Digestive Diseases
Emory University School of Medicine
Atlanta, GA, USA

William C. Small, MD, PhD
Professor
Department of Abdominal Radiology
Emory University School of Medicine
Atlanta, GA, USA

Shanthi Srinivasan, MD
Professor of Medicine
Division of Digestive Diseases
Emory University School of Medicine;
Chief of Gastroenterology
Atlanta Veterans Affairs
Medical Center
Atlanta, GA, USA

Robert A. Swerlick, MD
Professor
Department of Dermatology
Emory University School of Medicine
Atlanta, GA, USA

Joel P. Wedd, MD
Assistant Professor of Medicine
Division of Digestive Diseases
Emory University School of Medicine
Atlanta, GA, USA

Field F. Willingham, MD, MPH
Associate Professor of Medicine
Director of Endoscopy
Division of Digestive Diseases
Emory University School of Medicine
Atlanta, GA, USA

Shani Woolard, MD
Gastroenterology Fellow
Emory University School of Medicine
Atlanta, GA, USA

Vincent W. Yang, MD, PhD
Professor and Chair
Department of Medicine
Stony Brook University School of Medicine
Stony Brook, NY, USA

Foreword

The practice of gastroenterology and hepatology continues to evolve at a seemingly revolutionary pace. Since the First Edition of *Essentials of Gastroenterology* was published in 2012, we have witnessed the advent of powerful new biologic agents for the treatment of inflammatory bowel disease. And who could have imagined then that we could cure over 90% of patients with chronic hepatitis C virus infection with direct-acting antiviral therapies? Despite these (and other) important advances, the clinical foundation of the field of gastroenterology that has been the basis of such important treatment strategies remains the same. Understanding the pathophysiology and clinical features of gastrointestinal and liver diseases is a critical aspect of every medical student's education in human diseases.

The First Edition of this textbook was developed and co-edited by the late Shanthi V. Sitaraman, MD, PhD, Professor of Medicine and Pathology at Emory University School of Medicine who, sadly, did not live to see her work published. Shanthi was an exceptional teacher, physician and scientist who died far too young in April 2011. Lawrence S. Friedman, MD, Professor of Medicine at Harvard Medical School and Tufts University School of Medicine, co-edited the first edition with Shanthi and suggested to me that we update the text as a Second Edition, and I am truly grateful that Shanthi Srinivasan, MD, Professor of Medicine and Chief of Gastroenterology at the Atlanta Veterans' Affairs Medical Center and a colleague and close friend of Shanthi Sitaraman, agreed to serve as co-editor with Dr Friedman of this Second Edition.

As in the First Edition of *Essentials of Gastroenterology*, each chapter of the Second Edition begins with a clinical vignette after which the fundamental aspects of pathophysiology, clinical features, and approach to treatment are presented. This technique in education is used in many medical schools, including Emory University School of Medicine, in which first-year medical students are immersed in patient-related case histories when studying each organ system. The chapters are written concisely to give the trainee the ability to take away key points ('Pearls') that are critical to the development of skills in differential diagnosis, assessment, and treatment planning. Furthermore,

easy-to-understand diagrams and tables, as well as exceptionally clear illustrations, endoscopic photographs, and radiologic images, make this book particularly useful not only as a guidebook for medical students, but also as a quick reference for medical house officers who are confronted with patients with gastrointestinal and liver disease.

The success of the First Edition of this textbook and its design is not fortuitous. Dr Friedman, one of the foremost master clinicians of gastroenterology and hepatology in Boston – and a former mentor of the late Dr Sitaraman – has once again, along with Dr Srinivasan, devoted a great amount of time to carefully editing each chapter. The result is a brilliantly crafted, concise, and enjoyable book to read. The questions and answers presented at the end of each chapter are timely and integrative in design, giving trainees the ability to sharpen the depth of their conceptual knowledge about the approach to the natural history of diseases seen in the practice of gastroenterology. Impressively, Drs Srinivasan, Friedman, and the contributing authors of the updated text provide new information on treatment approaches for the major diseases covered in this book.

Finally, the editors and authors owe a tremendous debt of gratitude to Carla Fairclough and Alison Sholock, who incorporated the numerous editorial changes made by Drs Srinivasan and Friedman. They meticulously transformed handwritten edits sent to them on the original and revised manuscripts into polished final versions. Their organization has made the work of the editors immensely easier. I am also deeply grateful to our faculty (including some former faculty) in the Division of Digestive Diseases at Emory University School of Medicine who wrote and revised all of the chapters in this text. Many of them are teachers in the first-year medical student curriculum 'Foundations of Medicine' course, which was initially organized by Dr Sitaraman. To paraphrase a sentiment expressed by Dr Daniel K. Podolsky in the Foreword to the First Edition of *Essentials of Gastroenterology*, "…though we have been deprived of Shanthi Sitaraman's distinguished career as a teacher, mentor, physician, and investigator," the Second Edition of this textbook "…once again serves as an important hallmark of Shanthi's enduring legacy" to our discipline.

Frank A. Anania, MD, FACP, AGAF, FAASLD
Emory University School of Medicine

Preface

This Second Edition of *Essentials of Gastroenterology* is the first for which Shanthi V. Sitaraman has not served as a co-editor, because of her untimely death as the First Edition was published in 2012. A tribute to Shanthi Sitaraman follows this Preface and the Acknowledgments. Succeeding Shanthi Sitaraman as co-editor is her colleague and friend, Shanthi Srinivasan, an accomplished editor, gastroenterologist, and professor at the Emory University School of Medicine with an interest in basic enteric neuroscience and gastrointestinal motility. The title of the book has been revised to include Shanthi Sitaraman's name to reflect her enduring contribution.

The field of gastroenterology and hepatology has progressed at a rapid pace, and *Sitaraman and Friedman's Essentials of Gastroenterology, Second Edition*, reflects this progress with an updated content five years after the First Edition of the book was published. In editing this book, we have kept the format similar to that of the First Edition, which was well received, but have updated the content. Throughout the book, we have continued to emphasize fundamental clinical points in a clear, organized, and concise manner. Our goal remains for the book to provide up-to-date, foundational knowledge of gastrointestinal medicine and of the most important and common clinical problems encountered in the field. Among the areas in which remarkable changes have occurred since publication of the First Edition are new treatment regimens for hepatitis C, improved management of portal hypertension, and expanded drug therapy for inflammatory bowel disease. Primary biliary cirrhosis is now called primary biliary cholangitis. In the chapter on peptic ulcer disease, treatment protocols for *Helicobacter pylori* and the indications for confirming the eradication of *H. pylori* have been updated. Other major changes include updated methodology for the diagnosis of motility disorders, including the wireless motility capsule and three-dimensional high-resolution manometry, a new section on eosinophilic esophagitis, and updated criteria for the diagnosis of irritable bowel syndrome.

The book represents contributions from faculty and fellows in the Division of Digestive Diseases and the Departments of Pathology, Radiology, and Surgery

at the Emory University School of Medicine, and is geared toward medical students studying gastroenterology in an introductory course on clinical medicine or on a clinical rotation in medicine or gastroenterology. Many of the contributors have been recipients of awards for outstanding contributions to medical education. New authors include faculty who have recently come to Emory. Each has helped to revitalize and refresh the book.

The format of the Second Edition remains unchanged. The book has 28 chapters that are organized into five sections. Each chapter covers a key clinical issue in the practice of gastroenterology, and the Picture Gallery provides the proverbial 'textbook' examples of dermatology, radiology, and pathology findings in gastroenterology. The chapters are written in an easy-to-read outline format that covers the basics of pathophysiology, clinical features, diagnosis, natural history, prognosis, and treatment of the common disorders seen in the practice of gastroenterology. Figures and tables illustrate and highlight key information. Shaded boxes draw attention to important practice points, and a concluding segment in each chapter in the first four sections provides a list of 'pearls' useful in clinical practice. Illustrative cases begin each chapter in the first four sections, and multiple-choice questions pertaining to these clinical vignettes and to the content of the chapter provide an opportunity for the reader to test his or her knowledge of the subject matter after reading a chapter. A few key references and web links are provided. The aim is to make the information as clear, concise, and 'digestible' as possible. Medical students will find the information relevant and readily understandable, while more senior trainees can use the book to obtain a quick and practical review of the field in a short amount of time. Readers should find the book useful and focused, without being overwhelming.

We are excited to present this Second Edition and hope that it will continue to be an enduring tribute to Shanthi Sitaraman's dream of fostering excellence in medical education.

Shanthi Srinivasan, MD
and Lawrence S. Friedman, MD

Acknowledgments

We are grateful for the invaluable assistance and support of the faculty and fellows at the Emory University School of Medicine, and particularly of members of the Division of Digestive Diseases. Their adherence to deadlines, attention to detail, and commitment to excellence were essential to the successful completion of this book. We are particularly grateful to Dr. Frank A. Anania, Chief of the Division of Digestive Diseases at Emory, for his extraordinary support of this project and for his gracious preparation of the Foreword to this book. Each contributor to this book deserves acknowledgment for his or her effort. We are also grateful for the support of our families, including parents Anbukili and V.K. Chetty, husband Muthayyah, and children Karthik, Arjun, and Anand (S.S) and wife Mary Jo Cappuccilli, son Matthew Friedman, and grandson Christopher Friedman (L.S.F.).

The support of the staff of our publisher, Wiley, including Oliver Walter and Priyanka Gibbons (Publishers, Clinical Medicine), Alice Wheeler (Editorial assistant), Thaatcher Missier-Glen (Project Editor), Arabella Talbot (Editorial assistant), Yogalakshmi Mohanakrishnan (Project Editor), William Down (Copyeditor), and Sandeep Kumar (Production Editor) was phenomenal, and we cannot thank them enough. We also acknowledge the remarkable efforts of our Assistants, Carla Fairclough (S.S.) and Alison Sholock (L.S.F), who served as surrogate editors for the book.

Shanthi Srinivasan, MD
and Lawrence S. Friedman, MD

Tribute to Shanthi V. Sitaraman

Essentials of Gastroenterology, First Edition, was conceived, developed, and co-edited by Shanthi V. Sitaraman, MD, PhD, who tragically passed away after a long illness as the book was nearing completion. The book reflects Shanthi's dream and vision to create a textbook of gastroenterology targeted specifically to medical students but useful as well to residents rotating on a gastroenterology service and fellows and practitioners preparing for certification examinations and desiring a quick, focused review of the state-of-the-art of the field.

The opportunity to work with Shanthi Sitaraman on the First Edition of this book was a once-in-a-lifetime experience that we will always treasure. We have both had the privilege and honor of working with Shanthi. To Shanthi Srinivasan, Shanthi was a best friend, mentor, colleague, and confidante. To Lawrence Friedman, Shanthi was a star trainee, superb clinician, and accomplished researcher. As we edited each chapter, we remember the discussions we had with Shanthi about the book and the passion she infused in us to make it as perfect as possible. She loved students, and the book was her long-lasting gift to them and an enduring legacy to the field of gastroenterology. Her love of gastroenterology and passion for teaching were evident throughout the entire project, and shine in this book.

Shanthi was a brilliant and dedicated physician-scientist who, as a faculty member at Emory, made numerous contributions to education, research, and clinical practice. Her work in inflammatory bowel diseases resulted in over 200 publications that advanced our understanding of basic mechanisms of inflammation and led to novel approaches to therapy. Her devotion to patients was legendary, and in 2011 she received the Crohn's and Colitis Foundation of America Premier Physician Award in Georgia. She mentored and taught countless medical students, residents, fellows, and junior faculty, and her humanitarian service to the greater Atlanta community was inspiring.

Essentials of Gastroenterology is both a fitting tribute to, and a wonderful legacy of, an exceptional educator, colleague, and friend. Shanthi herself was an award-winning teacher who was beloved by the students, residents, fellows, and faculty at Emory. She was a recipient of the Silver Pear Mentoring Award

from the Department of Medicine, the Student Association Teaching Award and Dean's Teaching Award from the School of Medicine, and the Attending of the Year designation and the Mentor Award from the Division of Digestive Diseases at Emory, among numerous other honors. She is sorely missed, and we are proud to dedicate the Second Edition of the retitled *Sitaraman and Friedman's Essentials of Gastroenterology* to her.

Shanthi Srinivasan, MD
and Lawrence S. Friedman, MD

Luminal Gastrointestinal Tract

Shreya Raja and Melanie S. Harrison

1

Gastroesophageal Reflux Disease

Shani Woolard and Jennifer Christie

Clinical Vignette

A 50-year-old man with a history of hypertension and hyperlipidemia presents with a 4-month history of chest discomfort. He describes the discomfort as a burning and occasionally a pressure sensation in the mid-sternal area. The discomfort often occurs 45 minutes after eating a meal and lasts for about 3 hours, gradually improving thereafter. He occasionally awakens in the morning with a sore throat, cough, and bitter taste in his mouth. He has tried over-the-counter ranitidine, with only minimal relief. He was recently seen in the emergency department for an episode of severe chest pain. A cardiac work-up, including an electrocardiogram, cardiac enzymes, and a stress echocardiogram, was negative. Physical examination reveals a well-built, well-nourished man in no apparent distress. The blood pressure is 137/84 mmHg, pulse rate 72 per minute, respiratory rate 14 per minute, and body mass index 30. The physical examination is otherwise unremarkable.

General

- Gastroesophageal reflux disease (GERD) is defined as symptoms or tissue damage caused by the reflux of gastric contents into the esophagus.
- GERD is a common disorder, affecting almost half of the US population, with varying severity. Some 40% of the US population experiences reflux symptoms about once per month, 20% complain of symptoms once per week, and 7–10% report daily symptoms.
- GERD affects 10–20% of western populations. It is less common in Asian and African countries.
- It is estimated that GERD costs the US nearly $2 billion each week in lost productivity.

Sitaraman and Friedman's Essentials of Gastroenterology, Second Edition.
Edited by Shanthi Srinivasan and Lawrence S. Friedman.

The most common symptoms of GERD are heartburn and regurgitation. GERD is the most common cause of noncardiac chest pain.

Risk Factors

- Advancing age (>65 years)
- Obesity
- Genetic factors
- Alcohol use
- Pregnancy
- Smoking

Spectrum of GERD

- The clinical spectrum of GERD ranges from nonerosive reflux disease (NERD) to erosive esophagitis (Figure 1.1). NERD is defined as symptoms of acid reflux without evidence of esophageal damage, such as mucosal erosions or breaks on esophagogastroduodenoscopy (EGD) in patients who are not on acid-suppressive therapy.
- A small proportion of patients will develop metaplasia of the squamous esophageal epithelium to columnar epithelium (Barrett's esophagus). Barrett's esophagus is a risk factor for adenocarcinoma.
- Some patients who present with heartburn have 'functional' heartburn. This is defined as a burning retrosternal discomfort in the absence of

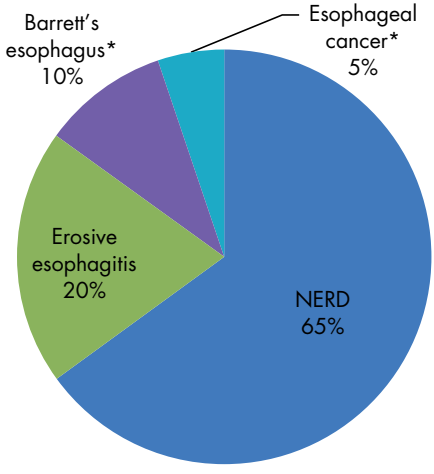


Figure 1.1 Clinical spectrum of GERD. (*May be associated with erosive esophagitis; NERD, nonerosive esophageal reflux disease.)

gastroesophageal reflux or an esophageal motor disorder. Ambulatory pH testing may be useful to differentiate NERD from functional heartburn.

Pathophysiology

- Transient lower esophageal sphincter relaxations (TLESRs):
  - The etiology of GERD is multifactorial; however, 'aberrant' TLESRs are the major pathophysiologic factors in many patients with GERD.
  - A TLESR is defined as relaxation of the lower esophageal sphincter in response to gastric distension. In healthy persons, TLESRs occur in the absence of a swallow, last 10–30 seconds, and result in physiologic gastroesophageal reflux.
  - TLESRs are regulated by the neurotransmitter γ-aminobutyric acid (GABA) acting on GABA type B receptors located in the peripheral nervous system, as well as in the brainstem.
  - In many cases, GERD is thought to be caused by an increased number or a prolonged duration of TLESRs.
- Gastric factors:
  - Increased gastric acid production as well as delayed gastric emptying with distention may trigger TLESRs.
- Diminished esophageal clearance:
  - Poor esophageal clearance due to defects in primary or secondary esophageal peristalsis allows prolonged exposure of the esophageal mucosa to acid.
- Diet and medications:
  - Dietary factors such as acidic foods, caffeine, alcohol, peppermint, and chocolate may reduce lower esophageal sphincter (LES) tone or increase gastric acid production.
  - Medications such as calcium channel blockers, hormones (e.g., progesterone, cholecystokinins, secretin), beta-adrenergic agonists (albuterol), nitrates, and barbiturates can decrease LES tone, thereby predisposing to gastroesophageal reflux.
  - Smoking has also been associated with a predisposition to gastroesophageal reflux.
- Hiatal hernia:
  - A hiatal hernia usually occurs when there is a defect in the diaphragmatic hiatus that allows the proximal stomach to herniate above the diaphragm and into the thorax. It is unclear how this predisposes to gastroesophageal reflux. The barrier function of the LES to prevent the reflux of gastric contents into the esophagus is thought to be disrupted. Large hiatal hernias also lead to increased acid dwell times in the distal esophagus.

Clinical Features

- Thorough history-taking detailing the onset and duration of symptoms and the association of symptoms with meals and diet should be conducted. 'Alarm symptoms' such as vomiting, gastrointestinal bleeding, weight loss, dysphagia, early satiety, and symptoms of cardiac disease should be elicited.
- Patients may present with typical (classic) or atypical symptoms.
- Typical symptoms:
  - **Heartburn** is described as a burning sensation in the substernal area that may radiate to the neck and/or back.
  - **Regurgitation** is the feeling of stomach contents traveling retrograde from the stomach up to the chest and often into the mouth.
  - **Dysphagia** (difficulty swallowing) is reported in about 30% of patients with GERD, even in the absence of esophageal inflammation or a stricture.
  - Less common symptoms associated with GERD include water brash, burping, hiccups, nausea, and vomiting. Water brash is the sudden appearance of a sour or salty fluid in the mouth, and represents secretions from the salivary glands in response to acid reflux. Odynophagia (painful swallowing) occurs when there is severe esophagitis.
  - The sensitivity of typical symptoms for detecting GERD is poor.
- Atypical symptoms:
  - Patients may present with chest pain, chronic cough, difficult-to-treat asthma, and laryngeal symptoms such as hoarseness, throat clearing, or throat pain.
  - Patients with atypical symptoms are less likely than patients with typical symptoms to have endoscopic evidence of esophagitis or Barrett's esophagus. They also have a less predictable response to therapy. Ambulatory esophageal pH testing (see later) is not as sensitive for diagnosing GERD in patients with atypical symptoms as it is in patients with typical symptoms.
- In uncomplicated GERD, physical findings are minimal or absent.

GERD as the etiology of chest pain should be pursued only after potentially life-threatening cardiac etiologies have been excluded.

Diagnosis

Trial of Proton Pump Inhibitor (PPI) Therapy

- A PPI trial is the simplest approach for diagnosing GERD and evaluating symptom response to treatment.

- A 30-day trial of a PPI (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, dexlansoprazole) once daily (taken 1 hour before breakfast) is recommended. If the patient has GERD, symptoms will usually improve within 1–2 weeks.
- The pooled sensitivity of a PPI trial for diagnosing GERD is 78% with a specificity of 54% when compared with 24-hour pH testing.

A PPI trial is recommended as the initial diagnostic and therapeutic intervention in patients with uncomplicated GERD. In patients who fail a PPI trial, additional testing is recommended.

Barium Swallow

- This is a radiographic test that can detect reflux of barium contrast into the esophagus after the patient drinks the contrast solution (see Chapter 27).
- A barium swallow can evaluate other potential mechanical causes for the symptoms (e.g., stricture, neoplasm); however, the test lacks sensitivity (20–30%) to assess mucosal damage. Therefore, barium swallow studies should not be used to diagnose GERD.

Upper Endoscopy

- Upper endoscopy (esophagogastroduodenoscopy, EGD) allows direct visualization of the esophageal mucosa.
- The test has a high sensitivity (90–95%) for diagnosing GERD, but the specificity is only 50%.
- The spectrum of findings on upper endoscopy in persons with GERD includes normal mucosa and esophageal inflammation characterized by erythema, erosions, mucosal breaks, bleeding, and ulceration of the esophageal mucosa.
- Upper endoscopy is recommended for all patients with alarm symptoms such as weight loss, dysphagia, hematemesis, and bleeding.
- Upper endoscopy is used to detect complications of GERD such as stricture or Barrett's esophagus and other upper gastrointestinal disorders (e.g., peptic ulcer).
- Los Angeles classification of erosive esophagitis:
  - grade A: greater than 1 mucosal break, ≤5 mm long;
  - grade B: greater than 1 mucosal break, >5 mm long;
  - grade C: greater than 1 mucosal break, bridging tops of folds but <75% of the circumference of the esophagus;
  - grade D: greater than 1 mucosal break, bridging tops of folds ≥75% of the circumference of the esophagus;
  - Most patients have mild (LA grade A–B) esophagitis.

Endoscopic mucosal biopsies should be obtained in all patients with dysphagia to exclude eosinophilic esophagitis (see Chapter 2).

Ambulatory Esophageal pH Testing

- If an upper endoscopy is normal in a patient with GERD symptoms, esophageal pH testing should be performed next.
- pH monitoring is the 'gold standard' for detecting acid reflux and correlation of reflux with the patient's symptoms.
- A pressure catheter is inserted transnasally and advanced to 5 cm above the manometrically determined LES. The catheter is attached to a data logger that records pH values of the distal esophagus for 24 hours. The patient records his/her meals, position (upright/supine), and symptoms. The patient returns the data logger, and the pH data are downloaded onto a computer that transforms the data into a 24-hour tracing.
- The sensitivity of pH monitoring ranges from 79–96%, with a specificity of 85–100%, in patients with typical symptoms of gastroesophageal reflux.
- A wireless ambulatory pH capsule (Bravo) placed endoscopically allows for 48 hours of pH data recording. The sensitivity of this technique is greater than that of conventional pH monitoring.
- Ambulatory esophageal reflux monitoring should be performed before consideration of endoscopic or surgical therapy in patients with NERD. It is also part of the evaluation of patients refractory to PPI therapy, and should additionally be used in situations when the diagnosis of GERD is questionable.
- Many patients (25–60%) with noncardiac chest pain will have an abnormal ambulatory pH study result.
- Clinical indications for pH monitoring include:
  - refractory gastroesophageal reflux symptoms;
  - atypical symptoms;
  - typical symptoms and a normal upper endoscopy;
  - preoperatively before a fundoplication;
  - follow up of antireflux therapy (see later).
- The most sensitive parameter used to determine pathologic acid reflux includes the percentage of time the pH remains <4 and the correlation with symptoms. A pH <4 suggests that active pepsin may be a part of the refluxate, leading to erosion of the esophageal mucosa and symptoms.
- Some patients continue to have reflux symptoms despite documentation of a negative 24-hour pH test. Weakly acidic (pH = 4–7) as well as nonacidic (pH >7) reflux can produce reflux symptoms. **Multichannel impedance testing** combined with pH testing can be used to assess acidic, weakly acidic, and nonacidic reflux and the relationship of reflux events to symptom events.

Complications

Esophageal Stricture

- The frequency of esophageal strictures (also called peptic strictures) in patients with GERD is 0.1%.
- Esophageal strictures are generally smooth, scarred, circumferential narrowings usually in the distal esophagus (see Chapter 2).
- Patients typically present with progressive dysphagia for solids that usually is not associated with weight loss, as occurs with malignant strictures (see Chapter 2).
- Esophageal peptic strictures are treated with per-endoscopic dilation. Dysphagia improves once the esophageal luminal diameter reaches 15 mm or above.

Barrett's Esophagus

- Prolonged esophageal acid exposure can result in damage to the esophageal mucosa, leading to metaplasia of the squamous epithelium of the distal mucosa to specialized columnar mucosa with goblet cells; this is referred to as **intestinal metaplasia**.
- The diagnosis of GERD is associated with a 10–15% risk of Barrett's esophagus.
- In some persons, intestinal metaplasia may progress to dysplasia and esophageal adenocarcinoma. The risk of progression to adenocarcinoma is estimated to be 0.5–1.0% per year.
- The frequency of Barrett's esophagus is highest in Caucasian men over 50 years of age.
- The diagnosis of Barrett's esophagus is suspected on upper endoscopy by the detection of salmon-colored mucosa extending above the gastroesophageal junction (Z-line) (Figure 1.2). The diagnosis is confirmed by histologic examination (see Chapter 28).
- Endoscopic surveillance should utilize high-resolution/high-definition white-light endoscopy.
- Virtually all patients with Barrett's esophagus are treated with a PPI once daily, indefinitely.
- For Barrett's esophagus patients without dysplasia, endoscopic surveillance should take place at intervals of 3–5 years.
- Endoscopic ablative therapies should not be performed routinely in patients with nondysplastic Barrett's esophagus because of their low risk of progression to esophageal adenocarcinoma.
- In patients with dysplasia, radiofrequency ablation (RFA) is currently the preferred endoscopic ablative therapy, with the goal of removing all neoplasia and Barrett's mucosa. RFA is used to perform circumferential and then focal ablation of dysplasia.

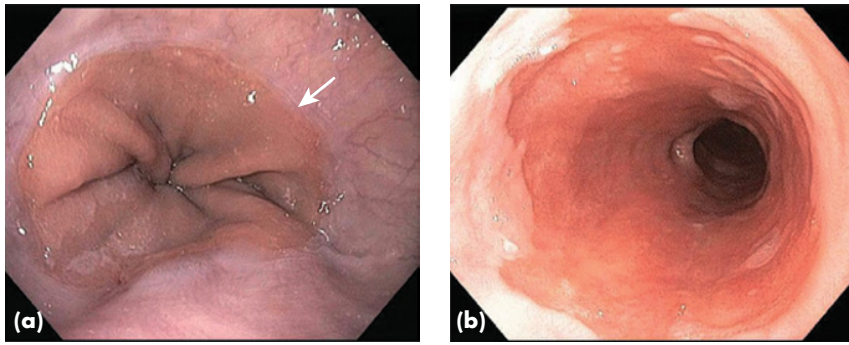


Figure 1.2 Endoscopic images of the normal esophagus and complications of GERD. (a) Normal esophagus showing the squamocolumnar junction (arrow); (b) Barrett's esophagus: intestinal metaplasia is seen as salmon-colored mucosa that extends above the gastroesophageal junction.

- Cryotherapy is a newer method of treating dysplasia, in which liquid nitrogen or carbon dioxide is applied under endoscopic visualization. Studies suggest it eradicates dysplasia in 85–90% of patients.
- Photodynamic therapy uses a photosensitizing agent and laser light to cause cytotoxicity in Barrett's mucosa. It is not used as often as RFA and cryotherapy.
- Endoscopic resection is a technique in which the excision of a large segment of mucosa down to the submucosa is performed. It can be combined with other ablative therapies to eradicate Barrett's esophagus
- After complete elimination of intestinal metaplasia, endoscopic surveillance should be continued to detect recurrent metaplasia or dysplasia.

Treatment

Treatment of GERD depends on the severity of symptoms. Therapy includes lifestyle modification, medication, surgery, or a combination of these.

Lifestyle Modifications

- In patients with mild and infrequent symptoms, lifestyle modifications can decrease the frequency and severity of symptoms, and are considered first-line therapy.
- Recommended changes include weight loss, avoidance of late-night meals, elevation of the head of the bed to at least a 30° angle in an attempt to minimize acid reflux, the avoidance of spicy and greasy foods, acidic foods (such as tomato-based products, and citrus juices), cessation of smoking, and a reduction in alcohol consumption and caffeinated products such as chocolate and carbonated beverages.

- Weight loss and elevation of the head of the bed seem to be the most beneficial lifestyle interventions.

Antacids

- Antacids neutralize gastric acid, thereby raising the pH above 4 and decreasing reflux symptoms.
- The onset of action is approximately 5 minutes after ingestion, and the effect lasts for 90 minutes.
- Over-the-counter antacids and alginates have been found to be helpful in patients with mild, infrequent symptoms of GERD.
- Side effects include diarrhea with magnesium-containing products, and constipation with aluminum-containing formulations.

Histamine H2 Receptor Antagonists (H2RAs)

- H2RAs block histamine H2 receptors on parietal cells of the stomach, thereby inhibiting histamine binding to the cell and decreasing gastric acid production.
- They have a rapid onset of action with a duration of effect from 6–10 hours.
- The healing rate for esophagitis is 50% compared with 24% for placebo.
- These drugs are effective in patients with mild, infrequent symptoms of GERD.

PPIs

- PPIs bind covalently and irreversibly with the hydrogen/potassium adenosine triphosphatase (H+/K + -ATPase) pump on the apical surface of parietal cells in the stomach.
- PPI therapy is the mainstay of treatment for moderate to severe GERD and is used as maintenance therapy.
- Usually, once-a-day dosing is effective. PPIs have been shown to maintain intragastric pH above 4 for 15–21 hours. Occasionally, twice-daily dosing is necessary for patients with severe symptoms or those with erosive esophagitis.
- PPIs have been shown to be superior to H2RAs in healing esophagitis at 8 weeks (83–96% for PPIs versus 50% for H2RAs).
- Reasons for a failure to respond to a PPI include poor adherence, inadequate acid suppression with breakthrough acid secretion, weakly acidic reflux as the cause of symptoms, duodenogastroesophageal reflux, delayed gastric emptying, and functional heartburn.
- The most common side effects of PPIs include diarrhea, headache, and abdominal pain. Chronic PPI use has been associated with a slightly increased susceptibility to enteric infections, including *Clostridium difficile* colitis, small intestinal bacterial overgrowth, electrolyte abnormalities, hip fractures, chronic kidney disease, and dementia, although conclusive evidence for most of these complications is lacking.

- Although there may be slight differences among the various PPIs with respect to potency, the choice of PPI is best made on the basis of prescription plan coverage and a history of adverse side effects.

Additional Medications

- Prokinetic agents such as metoclopramide, a dopamine antagonist, may be effective as an adjunct to PPIs in persons with delayed gastric emptying. Prokinetic agents have no effect in improving esophageal clearance. Side effects include tremors, Parkinson-like symptoms, and tardive dyskinesia. The US Food and Drug Administration (FDA) has not approved metoclopramide for GERD.
- Two GABA-B agonists, baclofen and lesogaberan, have been studied in the treatment of GERD in patients who have not responded to PPIs. They act by inhibiting TLESRs and reflux episodes. Side effects include drowsiness, nausea, and an increased risk of seizures. Neither drug is approved by the FDA for the treatment of GERD.

Endoscopic Therapy

- Endoscopic approaches to the treatment of GERD are considered experimental and are not recommended for its routine treatment.
- The goals of endoscopic therapy are to reduce reflux, alter neural response to acid, and improve symptoms.
- Endoscopic approaches include the delivery of radiofrequency energy to the gastroesophageal junction, the injection of bulking agents in the LES, and the implantation of a prosthetic device into the LES.
- Following such therapy, patients often must continue acid-suppression therapy because of persistent, although often less severe, symptoms.
- Endoscopic gastroplication is a technique in which sutures are placed immediately below the LES to strengthen the LES and reduce reflux. This method has been shown to improve symptoms and quality of life.

Surgical Therapy

- Antireflux surgery corrects the mechanical factors that contribute to GERD. The most common surgical procedure performed is the Nissen fundoplication. The technique involves a 360° wrap of the upper portion of the stomach (fundus) around the distal esophagus to enhance the integrity of the LES (see Chapter 4). This prevents gastric contents from flowing in a retrograde manner into the esophagus, thereby reducing GERD symptoms and allowing the esophageal mucosa to heal. In a patient with a hiatal hernia, the hernia is reduced back into the abdomen during surgery.
- A partial wrap (Toupet fundoplication) is performed in patients who have poor esophageal motility.

- These procedures are most often done laparoscopically to reduce the length of hospital stay and operative morbidity.
- Surgery does not appear to reduce the rate of progression of Barrett's esophagus to adenocarcinoma.
- Surgery is as effective as PPIs in controlling symptoms in the short term (5 years).
- Common adverse effects of a fundoplication include dysphagia (20%) due to too tight a wrap at the LES, and so-called 'gas–bloat syndrome' due to difficulty in expelling air from the stomach. Half of all patients who undergo fundoplication still require acid-suppression medication.
- Surgical fundoplication is a good alternative to PPI treatment in patients who:
  - respond to PPI therapy but want a more permanent treatment or do not tolerate PPIs;
  - respond to PPIs in terms of a decrease in heartburn but continue to have regurgitation;
  - develop recurrent complications of GERD such as a stricture or respiratory complications.

An algorithm for the management of GERD is shown in Figure 1.3.

Pearls

- GERD is a common chronic gastrointestinal disorder. Most patients have mild or moderate symptoms that respond to lifestyle modifications and antacid therapy. However, some patients have severe daily, as well as night-time, symptoms that can significantly reduce their quality of life.
- In patients with typical symptoms (heartburn and regurgitation), a PPI is the mainstay of therapy.
- In patients with atypical or refractory symptoms, ambulatory pH testing and, in some cases, impedance testing are helpful in determining whether the symptoms are truly related to gastroesophageal reflux.
- Early recognition of GERD can result in a reduction in both symptoms and complications of GERD and an improved quality of life.
- GERD can lead to Barrett's esophagus, which can occasionally progress to esophageal adenocarcinoma. Therefore, early diagnosis and treatment of GERD are key.
- There are various methods of treating GERD and its complications.
- Surgical treatment is appropriate in patients who do not wish to be on long-term medical therapy or who continue to have complications of GERD.

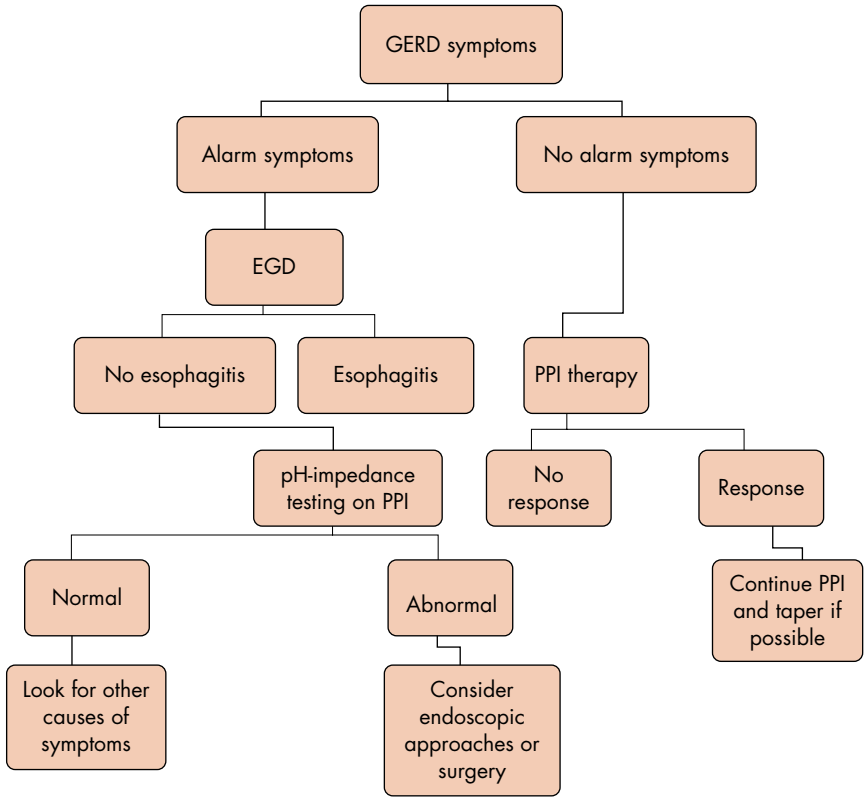


Figure 1.3 Algorithm for the management of GERD. EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

Questions

Questions 1 and 2 relate to the clinical vignette discussed at the beginning of this chapter.

1 Which of the following management strategies would you recommend for this patient?
- **A** Schedule an EGD.
- **B** Continue ranitidine as needed.
- **C** Start a PPI.
- **D** Order a barium swallow.
- **E** Order a 24-hour pH study.

2 Six months later, the patient reports intermittent difficulty swallowing solid food such as bread or rice. He denies odynophagia, weight loss, vomiting, or other symptoms. Which of the following is the most likely cause of dysphagia?

A Achalasia.
B Benign esophageal stricture.
C Esophageal cancer.
D Barrett's esophagus.
E Hiatal hernia.

3 Which of the following is considered to be the major pathophysiologic factor in GERD?

A Hiatal hernia.
B Smoking.
C Poor esophageal motility.
D TLESRs.
E Obesity.

4 Long-standing GERD is a risk factor for which of the following?

A Squamous cell cancer of the esophagus.
B Adenocarcinoma of the esophagus.
C Peptic ulcer disease.
D Gastric adenocarcinoma.
E Achalasia.

5 Surgical fundoplication for GERD has been shown to result in which of the following?

A Greater improvement in symptoms of GERD compared with therapy with a PPI.
B Greater improvement in symptoms of GERD in patients with persistent regurgitation despite therapy with a PPI.
C Improvement in esophageal clearance.
D Reduction in the frequency of adenocarcinoma in patients with Barrett's esophagus.
E Reduction in gastric acid production.

6 Which of the following does NOT reduce the symptoms of GERD?

A Weight loss.
B Avoidance of caffeine.
C Alcohol cessation.
D Gluten-free diet.
E Tobacco cessation.

7 Which of the following medications does NOT provide symptomatic improvement in GERD?
A GABA-B agonists.
B PPIs.
C Benzodiazepines.
D H2RAs.
E Antacids.

Answers

1 C
The patient presents with symptoms of GERD, including heartburn, chest discomfort, a sore throat, and a bitter taste in the mouth. GERD may cause chest pain that can be indistinguishable from ischemic cardiac pain, and the first priority often is to rule out heart disease as the etiology. In this patient, a cardiac work-up was negative. An upper endoscopy may be a reasonable choice if the patient is >50 years of age (the risks of Barrett's esophagus and adenocarcinoma increase with age), has alarm symptoms such as unintentional weight loss, gastrointestinal bleeding, vomiting, or dysphagia, or does not respond to a trial of a PPI. The most cost-effective diagnostic test for GERD in a younger person is a trial of a PPI. A barium swallow is not sensitive to diagnose GERD. A 24-hour pH study may be obtained if the patient does not respond to a trial of a PPI.

2 B
The most common complication of GERD is a benign esophageal stricture, which occurs in 0.1% of patients with GERD. Esophageal cancer (adenocarcinoma) is a possibility in a patient with long-standing GERD, but is less likely in the absence of alarm symptoms. Patients with Barrett's esophagus are often asymptomatic or have typical symptoms of GERD. A hiatal hernia contributes to GERD but generally does not cause dysphagia. Achalasia is a motility disorder of the esophagus that presents with progressive dysphagia for both solids and liquids.

3 D
The etiology of GERD is multifactorial; smoking, poor esophageal motility, obesity, and hiatal hernia may contribute to GERD. TLESRs are the major etiologic factors in most patients with GERD.

4 B

5 B
Surgical fundoplication (wrapping or plicating of the stomach around the esophagus) is as effective as PPI therapy in controlling symptoms in the short

term (5 years). It is a good alternative to PPI treatment in patients who have persistent regurgitation or develop complications of GERD, such as a benign stricture or respiratory complications. Surgical fundoplication does not decrease the rate of progression of Barrett's esophagus to adenocarcinoma and does not affect gastric acid secretion.

6 D

All of the approaches listed have been shown to improve GERD symptoms except for a gluten-free diet. Gluten intake has not been shown to have any effect on GERD.

7 C

Benzodiazepines have not been shown to alleviate GERD symptoms. GABA-B agonists, PPIs, H2RAs, and antacids have all been shown to provide symptomatic improvement in GERD.

Further Reading

Katz, P., Gerson, L., and Vela, M. (2013) ACG Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. *American Journal of Gastroenterology*, **108**, 308–328.

Ness-Jensen, E., Lindam, A., Lagergren, J., and Hveem, K. (2013) Weight loss and reduction in gastroesophageal reflux. A prospective population-based cohort study: the HUNT study. *American Journal of Gastroenterology*, **108**, 376–382.

Richter, J.E. and Friedenberg, F.K. (2016) Gastroesophageal reflux disease, in Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management, 10th edition, (eds M. Feldman, L.S. Friedman, and L.J. Brandt), Saunders Elsevier, Philadelphia, pp. 733–754.

Shaheen, N., Falk, G., Gerson, L., *et al.* (2016) ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. *American Journal of Gastroenterology*, **111**, 30–50.

Singh, S., Garg, S.K., and Singh, P. (2014) Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. *Gut*, **63**, 1229–1237.

Weblinks

http://www.nlm.nih.gov/medlineplus/gerd.html
http://www.acg.gi.org/physicians/guidelines/GERDTreatment.pdf
http://www.gastrojournal.org/article/S0016-5085(08)01605-3/fulltext

2

Dysphagia

Emad Qayed and Shanthi Srinivasan

Clinical Vignette

A 55-year-old man is seen in the office for difficulty swallowing for the past 6 months. He says that food 'sticks' in the middle of his chest in the mid-sternal area. This sensation has been worsening over the past several months. For the past 5 years he has had occasional heartburn. He has no difficulty swallowing liquids, and denies odynophagia, choking, cough, or shortness of breath. He denies nausea, vomiting, or abdominal pain. His weight has been stable. His past medical and surgical history is unremarkable. He takes ranitidine as needed for his heartburn, but no other medications. His family history is unremarkable. He works as a consultant in a computer software company. He is married and has three children, all of whom are healthy. He drinks a few beers on the weekends and does not smoke cigarettes. He has no history of illicit drug use. A colonoscopy done 4 years ago was unremarkable. Physical examination reveals a well-nourished, middle-aged man with a blood pressure of 128/88 mmHg, pulse rate 72 per minute, temperature 98.5 °F (37 °C), and body mass index 29. Examination of the oral cavity reveals no lesions, and there are no palpable lymph nodes or swelling in his neck. The chest, cardiac, and abdominal examinations are unremarkable. The neurologic examination is normal. When asked to swallow a sip of water, he swallows normally without choking or coughing. Routine laboratory tests show a normal complete blood count and comprehensive metabolic panel.

Sitaraman and Friedman's Essentials of Gastroenterology, Second Edition.
Edited by Shanthi Srinivasan and Lawrence S. Friedman.

General

- **Dysphagia** refers to difficulty swallowing. The condition results from impeded transport of liquids, solids, or both, from the pharynx to the stomach.
- **Odynophagia** refers to pain during swallowing and is frequently associated with dysphagia.
- Swallowing disorders can occur in all age groups, but the frequency of dysphagia is higher in the elderly. From 7–10% of adults older than 50 years of age, up to 25% of hospitalized patients, and 30–40% of nursing home residents experience problems with swallowing.
- Although dysphagia is more common in the elderly, it is not a normal consequence of aging and should be investigated
- Dysphagia is classified as oropharyngeal and esophageal dysphagia. **Oropharyngeal** dysphagia, or transfer dysphagia, refers to difficulty transferring food (solids, liquids, or both) from the oropharynx to the esophagus. **Esophageal** dysphagia refers to difficulty passing food through the esophagus into the stomach.

Physiology of Swallowing

- Normal swallowing is a smooth, coordinated process that involves a complex series of voluntary and involuntary neuromuscular contractions (Figure 2.1). The process of swallowing typically is divided into three distinct phases: oral; pharyngeal; and esophageal. Impairment of any of these phases results in dysphagia.
- The **oral** phase involves preparing and propelling the food from the anterior oral cavity into the oropharynx, where an involuntary swallowing reflex is initiated.

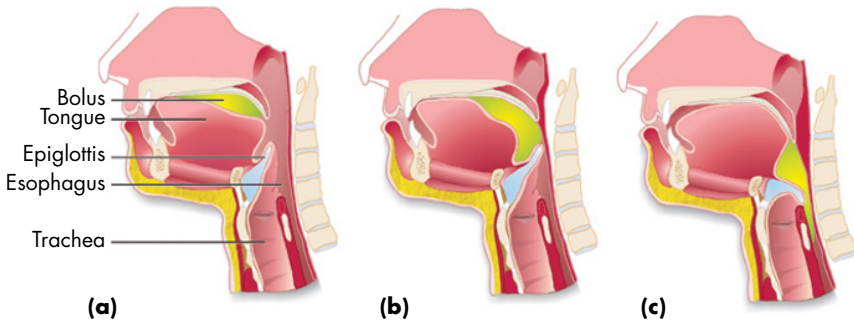


Figure 2.1 Oral and pharyngeal phases of swallowing. The diagram shows the transfer of a bolus of food from the mouth (a) to the oropharynx (b) to the upper esophagus (c).

The oral phase is the only voluntary phase of swallowing and requires coordinated contractions of the tongue and striated muscles of mastication.

- The **pharyngeal** phase involves overlapping events that are critical to protect the airway while allowing the bolus to transfer to the esophagus. The food bolus is propelled into the pharyngeal cavity, while the soft palate elevates and closes the nasal aperture and the larynx begins to elevate. The food bolus is then propelled into the hypopharynx by pharyngeal contractions. The larynx closes and the soft palate and the posterior pharyngeal wall oppose the posterior aspect of the tongue to prevent reflux of food into the oral cavity. The last step involves opening of the upper esophageal sphincter to allow the passage of food to the esophageal lumen.
  - Alteration of any step of the oral or pharyngeal phases of swallowing, due to mechanical obstruction or a neuromuscular condition, results in oropharyngeal dysphagia.
- In the **esophageal** phase, the food bolus is propelled down the esophagus by peristaltic contractions.
  - Once the food reaches the esophageal lumen, primary peristaltic contractions propel the food bolus down the length of the esophagus to the distal esophagus. This is accompanied by a relaxation of the lower esophageal sphincter and emptying of the esophageal contents into the gastric lumen.
  - Residual food in the esophagus causes local distension and triggers secondary peristaltic contractions that clear the esophagus of remaining food in the lumen.
  - Altered esophageal peristaltic contractions or failure of the lower esophageal sphincter to relax can result in esophageal dysphagia.
  - Another important mechanism of esophageal dysphagia is mechanical obstruction of the esophagus. This can be secondary to intraluminal obstruction or extrinsic compression.

Etiology

Oropharyngeal Dysphagia

Oropharyngeal dysphagia can be caused by mechanical obstruction or neuromuscular disease (Table 2.1). Stroke is the most common cause of oropharyngeal dysphagia in the inpatient setting.

Esophageal Dysphagia

Esophageal dysphagia can be caused by mechanical obstruction of the esophageal lumen, or can be secondary to dysmotility of the esophagus or lower esophageal sphincter (Figure 2.2).

Table 2.1 Causes of oropharyngeal dysphagia.

Category	Etiologies
Structural lesions	Benign or malignant tumors Candidal infection (thrush) Caustic ingestion Cervical spondylosis Peritonsillar abscess Radiation Retropharyngeal abscess or mass Thyromegaly Zenker's diverticulum
Neuromuscular causes	Diseases of the cerebral cortex and cranial nerves: • Alzheimer's disease • Bulbar and pseudobulbar palsy • Cerebral palsy • CNS tumors (benign or malignant) • Multiple sclerosis • Metabolic encephalopathy • Parkinson's disease • Stroke • Vascular dementias Neuromuscular disorders: • Botulism • Myositis (polymyositis, dermatomyositis) • Myasthenia gravis • Primary myopathies (myotonic dystrophy, oculopharyngeal myopathy)

CNS, central nervous system.

Mechanical Obstruction

The most common cause of esophageal dysphagia is mechanical obstruction of the esophageal lumen (Table 2.2) due to intraluminal (intrinsic) lesions or extrinsic compression. Dysphagia usually occurs when the diameter of the esophageal lumen is 13 mm or less. The symptoms depend on the degree of obstruction. For example, mild narrowing of the esophageal lumen causes symptoms only with large boluses of food, whereas more complete obstruction

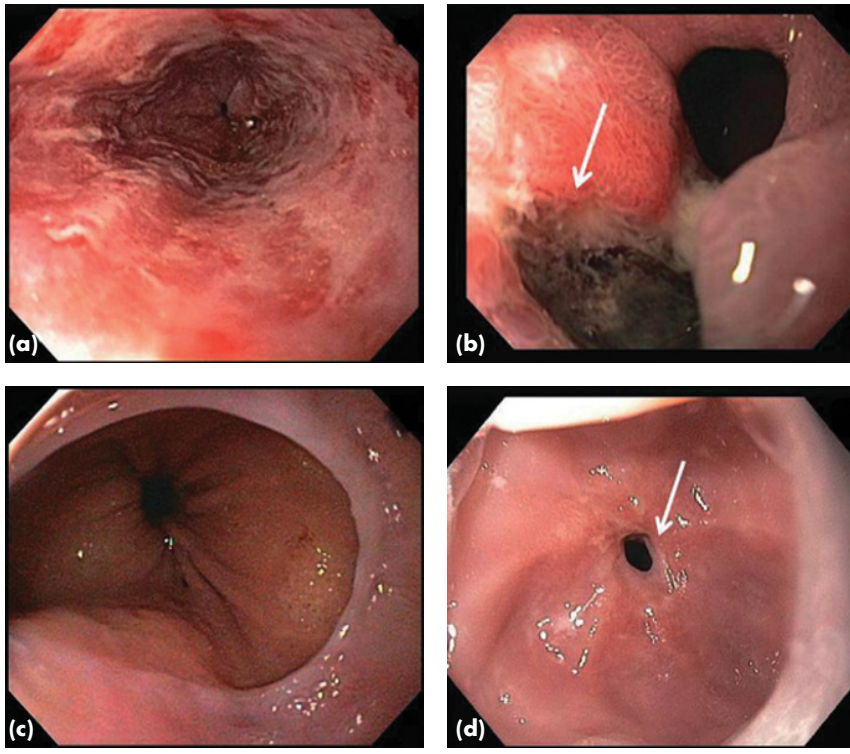


Figure 2.2 Endoscopic images of various disorders that cause esophageal dysphagia. (a) Reflux esophagitis: superficial ulcerations, edema, and erythema are seen in a continuous fashion from the gastroesophageal junction to proximal esophagus in a patient with chronic gastroesophageal reflux; (b) Pill-induced esophagitis: a discrete deep ulcer with sharply demarcated edges and necrotic center (arrow) is seen in a patient with a history of tetracycline use; (c) Esophageal ring: a fibrotic circumferential ring is seen in the lower esophagus; (d) Esophageal stricture: severe narrowing of the esophageal lumen (arrow) with dilatation of the proximal esophagus is seen in a patient with history of lye ingestion.

results in dysphagia for both solids and liquids. Intraluminal causes of dysphagia include the following:

- **Esophageal cancer**: patients with esophageal cancer present with dysphagia that is progressive, from solids to liquids, and associated with constitutional symptoms such as weight loss and anorexia. Patients may have risk factors such as smoking and alcohol use in the case of squamous cell carcinoma, or longstanding gastroesophageal reflux disease in the case of adenocarcimona.

Table 2.2 Causes of esophageal dysphagia.

Mechanical obstruction
Intrinsic narrowing:
• Benign strictures: gastroesophageal reflux disease, caustic substances, medications, postsurgical, radiation therapy
• Cricopharyngeal hyperplasia/bar
• Esophagitis: infectious, eosinophilic, pill-induced; gastroesophageal reflux disease
• Esophageal rings and webs
• Esophageal diverticula
• Tumors: benign or malignant
Extrinsic compression:
• Anterior mediastinal mass
• Vascular lesions:
– Congenital: aberrant right subclavian artery (dysphagia lusoria), right-sided aorta
– Acquired: aortic aneurysm, left atrial enlargement, right-sided aorta
Esophageal motility disorders
• Achalasia
• Distal esophageal spasm
• Hypertensive peristalsis (jackhammer esophagus)
• Hypotensive peristalsis (scleroderma)

- **Esophageal stricture**: esophageal strictures can be caused by caustic ingestion, certain medications, gastroesophageal reflux disease, and radiation therapy.
- **Esophageal rings and webs**: rings or webs typically cause intermittent nonprogressive dysphagia.
- **Esophagitis**: dysphagia caused by esophagitis is usually accompanied by odynophagia. Medications known to cause esophagitis include aspirin and other nonsteroidal anti-inflammatory drugs, doxycycline or tetracycline, bisphosphonates, and potassium preparations.
- **Eosinophilic esophagitis** is an increasingly recognized cause of dysphagia.

Eosinophilic esophagitis is a condition in which the esophageal mucosa is abnormally infiltrated with eosinophils. It usually affects males aged younger than 45 years. It is important to rule out eosinophilic esophagitis in patients with dysphagia and a normal upper endoscopy; therefore, an esophageal biopsy is always recommended in such patients, and typically results in intermittent dysphagia and food bolus impactions. Although eosinophilic esophagitis can present without endoscopic changes, most patients will have one or more of the following endoscopic findings: esophageal strictures; rings; longitudinal mucosal furrows; or white specks that mimic the appearance of candidal esophagitis. Some cases respond to treatment with acid suppression using a

proton pump inhibitor (PPI) and are referred to as PPI-responsive esophageal eosinophilia. The diagnosis is confirmed by esophageal mucosal biopsies showing eosinophils (>15 per high-power field). For patients who do not respond to a PPI, the dietary elimination of common allergens, including milk, egg, soy, wheat, nuts and shellfish, or treatment with swallowed topical steroids is considered.

Motility Disorders

Esophageal motility disorders are a less common cause of dysphagia than are mechanical causes. Dysphagia due to esophageal dysmotility typically results in difficulty swallowing both solids and liquids. The diagnosis of esophageal motility disorders is frequently made using esophageal manometry, which assesses motor function of the upper and lower esophageal sphincters and the presence or absence of peristalsis of the esophageal body.

- **Achalasia**: characteristic manometric features of achalasia include an absence of esophageal peristalsis and failure of the lower esophageal sphincter to relax with swallowing. The etiology of achalasia is unknown. A selective loss of postganglionic inhibitory neurons innervating the smooth muscle of the esophagus is typically seen, and is thought to result in a hypertensive lower esophageal sphincter that fails to relax with swallowing and leads to a functional obstruction.
- Certain diseases mimic clinical, radiologic, and manometric features of achalasia. Such conditions are termed **pseudoachalasia**. An example of pseudoachalasia is gastric adenocarcinoma of the cardia. Paraneoplastic syndromes can also cause pseudoachalasia.
- Spastic motility disorders have been termed distal (or diffuse) **esophageal spasm** and **jackhammer esophagus**. Patients with these disorders usually present with chest pain in addition to dysphagia
- Systemic diseases such as **scleroderma** can present with dysphagia. Scleroderma causes hypomotility of the esophagus along with a hypotensive lower esophageal sphincter and aperistalsis. Patients often present with gastroesophageal reflux in addition to dysphagia.

Clinical Features

- The clinical history is extremely important in evaluating the cause of dysphagia. In addition to dysphagia, a history of odynophagia should be elicited. Dysphagia should be distinguished from **globus sensation**, which refers to the constant feeling of a lump or tightness in the throat without any demonstrable abnormality in swallowing. Important questions to ask the patient with dysphagia include the time of onset of symptoms, progression, severity,

and pattern (intermittent or constant) of symptoms, presence of heartburn, type of food that induces symptoms (liquids or solids, or both), history of head and neck malignancy or surgery, and associated neurologic disorders. A medication history should be obtained.

- Typical symptoms of oropharyngeal dysphagia include choking, cough, or shortness of breath with swallowing. Patients often have difficulty initiating a swallow, and point to the throat as the location where the food is stuck. In some patients, liquids are regurgitated through the nose. Other associated symptoms include dysarthria, nasal speech, hoarseness, weight loss, and recurrent pulmonary infections.
- Symptoms of esophageal dysphagia include a sensation that food is stuck in the chest or throat. Most patients will point to the lower or mid sternum as the location of their symptoms; however, this localization often does not correlate with the anatomic level of the abnormality. Other associated symptoms include heartburn, odynophagia, hematemesis, chest pain, sensitivity to hot or cold liquids, and weight loss.
- Esophageal dysphagia to both solids and liquids initially suggests a motility disorder of the esophagus, whereas dysphagia to solids that progresses over time to involve liquids suggests a mechanical obstruction. Odynophagia suggests esophagitis.
- Physical examination:
  - Important elements of the physical examination include the patient's general appearance and nutritional status, and an assessment of the patient's respiratory distress as well as a mental status examination.
  - Examination of the cranial nerves (especially V and VII–XII) should be performed.
  - Systemic examination should focus on skin and nail, respiratory, and abdominal findings. **Tylosis** is a genetic syndrome characterized by hyperkeratosis of the palm and soles associated with a high frequency of squamous cell carcinoma of the esophagus.
  - It is often helpful to ask the patient to take a sip of water while being observed for symptoms of oropharyngeal dysphagia.

Diagnosis

- In most patients the distinction between oropharyngeal and esophageal dysphagia, as well as among mechanical, motility and neuromuscular causes, can be made by careful history-taking and physical examination. An approach to the diagnosis of esophageal dysphagia is shown in Figure 2.3.
- **Video-radiographic studies (video fluoroscopy)**. If the clinical history and physical examination suggest oropharyngeal dysphagia, especially with a risk of aspiration (e.g., neurologic impairment), video-radiographic studies

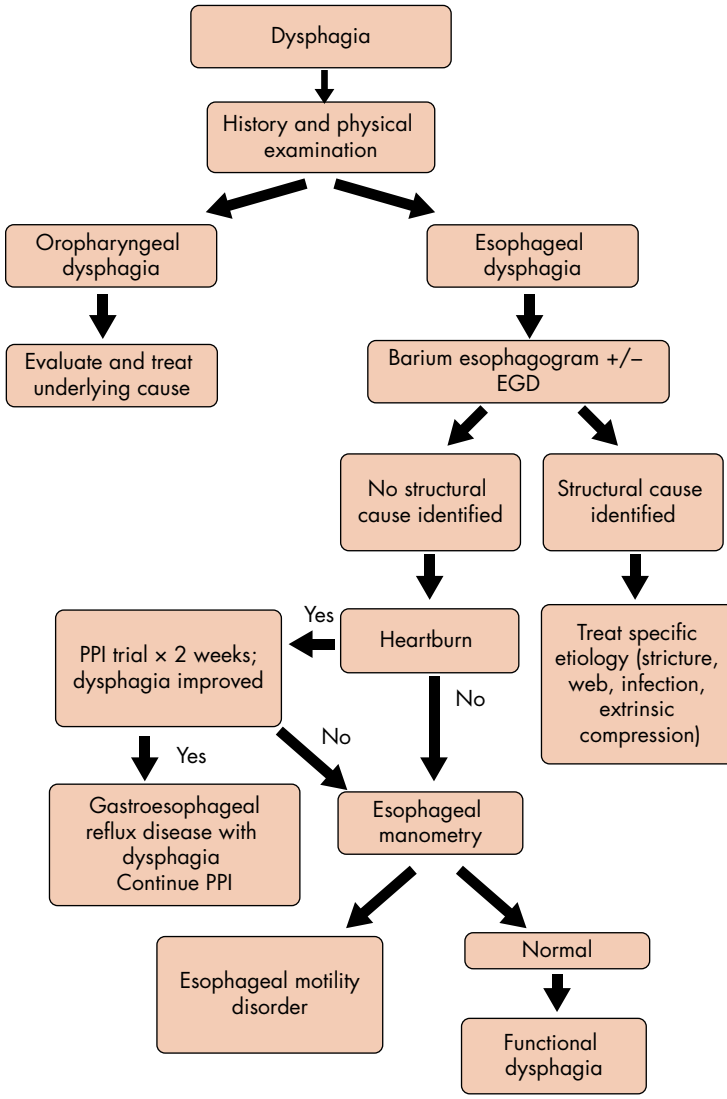


Figure 2.3 Algorithm for the diagnostic evaluation of esophageal dysphagia. EGD, esophagogastroduodenoscopy; PPI, proton pump inhibitor.

are performed to identify the presence, nature and severity of oropharyngeal swallowing dysfunction. This test is performed by a team composed of a radiologist, otolaryngologist, and speech pathologist.

- **Barium studies**. A barium swallow (barium esophagogram) is often recommended as the initial test for esophageal dysphagia. It can help to identify a

structural or obstructive lesion of the esophagus, such as Zenker's diverticulum, caustic injury, benign or malignant stricture, or tumor. A barium swallow can show the location of a lesion and the complexity of a stricture, and is a safer initial test than esophagogastroduodenoscopy (upper endoscopy) in this setting. A barium swallow with a solid bolus (barium tablet or marshmallow) is useful in detecting extrinsic compression or a subtle esophageal ring that can be missed by endoscopy. A double-contrast barium study provides better visualization of the esophageal mucosa than a single-contrast study (see Chapter 27).

- **Upper endoscopy**. This provides the best assessment of the esophageal mucosa and allows diagnostic (e.g., biopsy of lesions) and therapeutic (e.g., dilation of a stricture, removal of impacted food bolus) intervention. Upper endoscopy should be the initial test in patients with dysphagia due to a food impaction. If the mucosa appears normal, esophageal biopsies should be obtained to evaluate for the presence of eosinophilic esophagitis.
- **Manometry**. Esophageal manometry assesses the motor function of the esophagus. A nasogastric catheter with electronic probes is used to measure pressure during esophageal contractions and upper and lower esophageal body and sphincter responses to swallowing. Manometry is indicated in patients with dysphagia in whom a barium esophagogram or upper endoscopy reveals no abnormality. High-resolution manometry is the 'gold standard' for diagnosing achalasia.
- **pH measurements**. Although cumbersome, esophageal pH monitoring remains the 'gold standard' for confirming suspected gastroesophageal reflux disease. A pH probe is placed in the patient's esophagus via a nasogastric catheter or endoscopically and detects acid reflux. (pH testing can be combined with impedance testing to assess both acidic and nonacidic gastroesophageal reflux.) The patient is asked to record the occurrence of symptoms over a 24-hour period, and their symptoms are compared with the recorded pH measurements to determine if gastric acid reflux correlates with the symptoms. Combined recordings of esophageal pH levels and intraluminal esophageal pressure may aid in diagnosing patients with reflux-induced esophageal spasm. pH monitoring and manometry are usually available through referral to gastroenterologists.

A barium swallow is the first step in evaluating patients with symptoms of esophageal dysphagia especially if an obstructive lesion is suspected. Upper endoscopy is the recommended initial study with acute obstruction such as an impacted food bolus.