YAMADA'S

HANDBOOK OF Gastroenterology

THIRD EDITION

EDITOR

Tadataka Yamada

ASSOCIATE EDITOR

John M. Inadomi

CONTRIBUTING AUTHORS

Renuka Bhattacharya
Jason A. Dominitz
Joo Ha Hwang

- Key practice points
- Essentials of diagnosis
- Potential pitfalls
- Case studies

WILEY-BLACKWELL

Yamada's Handbook of Gastroenterology

Foreword

From its inception, the *Textbook of Gastroenterology* was intended to provide an encyclopedic reference to the rapidly evolving science and practice of gastroenterology to practitioners who encountered patients with digestive and liver diseases and to researchers in the field. Recognizing the need to provide access to the essential elements of the *Textbook* in a more concise format that was optimized to provide information of particular usefulness to medical students, house officers and fellows, we undertook the editing of *Yamada's Handbook of Gastroenterology*. The success of the first two editions of the *Handbook* has provided evidence of its utility not only as a guide to those in training but also as a resource for practicing physicians.

Dr. John Inadomi, the Associate Editor, has carried forward the best elements of past editions and improved on them in the third edition of *Yamada's Handbook of Gastroenterology*, with important additions such as key practice points, case studies, management algorithms and questions and answers, all within fewer pages. Moreover, this edition is available in electronic format to make it more compatible with the needs of practicing physicians.

I am indebted to Dr. Inadomi and his contributing authors Drs. Renuka Bhattacharya, Jason Dominitz and Joo Ha Hwang for the enormous time and effort they put into making this edition so clear and complete and hope that these qualities provided to the reader will help them to deliver the best possible care to their patients.

Tadataka Yamada
2013

Preface

On behalf of my co-authors, Drs. Bhattacharya, Dominitz and Hwang, I am pleased to introduce the third edition of *Yamada's Handbook of Gastroenterology*. *Yamada's Handbook* is based on the *Textbook of Gastroenterology* and *Principles of Clinical Gastroenterology* by Tadataka Yamada, and is divided into two major sections: symptom-based evaluation chapters and disease-based management chapters. In addition to updating the content for this version of *Yamada's Handbook*, Dr. Yamada challenged us to change the format for this version by incorporating pedagogical features that would enhance the learning experience for the reader. For this reason this version differs from previous editions of *Yamada's Handbook* by providing Key Practice Points, easily identified in "call-out boxes" in each chapter, which highlight the most important factors that guide clinical care. The case scenarios created for each chapter in Part 1: "Approach to Patients with Gastrointestinal Symptoms" are accompanied by discussions that we hope will provide the context necessary to translate medical knowledge to clinical practice. Finally, we have written a series of questions, with detailed answers located in the back of *Yamada's Handbook*, that should provide a means to test and solidify the reader's knowledge base.

We hope *Yamada's Handbook of Gastroenterology* is a useful companion to the Yamada *Textbook of Gastroenterology* and *Principles of Clinical Gastroenterology*, especially for readers interested in a condensed reference guiding the care of patients with gastrointestinal and liver diseases. In addition, we expect that trainees of all levels will benefit from *Yamada's Handbook* by providing a solid foundation upon which they may build a comprehensive understanding of this exciting and rapidly evolving field of medicine.

John M. Inadomi
2013

List of Abbreviations

5-ASA 5-aminosalicylate
6-MMP 6-methylmercaptopurine
6-MP 6-mercaptopurine
6-TG 6-thioguanine
ACCR amylase-to-creatinine clearance ratio
ACE angiotensin-converting enzyme
ADH alcohol dehydrogenase
AFP α-fetoprotein (AFP
AIDS acquired immunodeficiency syndrome
AIH autoimmune hepatitis
ALD alcoholic liver disease
ALDH acetaldehyde dehydrogenase
ALT alanine aminotransferase
AMA antimitochondrial antibody
ANA antinuclear antibody
APC adenomatous polyposis coli; argon plasma coagulation
ASCA anti-*Saccharomyces cerevisiae* antibody
ASMA anti-smooth muscle antibody
AST aspartate aminotransferase
BRIC benign recurrent intrahepatic cholestasis
BUN blood urea nitrogen
CBC complete blood count
CC chronic constipation
CCK cholecystokinin
CDC Centers for Disease Control and Prevention
CEA carcinoembryonic antigen
CHRPE congenital hypertrophy of the retinal pigment epithelium
CREST calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia
CRP C-reactive protein
CT computed tomography
CTC computed tomography colonography
DES diffuse esophageal spasm
DS double strength

EAC esophageal adenocarcinoma
ECG electrocardiogram
EGD esophagogastroduodenoscopy
EGG electrogastrography
EHEC enterohemorrhagic *Escherichia coli*
EIEC enteroinvasive *Escherichia coli*
ELISA enzyme-linked immunosorbent assay
EMR endoscopic mucosal resection
EPEC enteropathogenic *Escherichia coli*
ERCP endoscopic retrograde cholangiopancreatography
ERP endoscopic retrograde pancreatography
ESD endoscopic submucosal dissection
ESR erythrocyte sedimentation rate
ETEC enterotoxigenic *Escherichia coli*
EUS endoscopic ultrasound
FAP familial adenomatous polyposis
FIT fecal immunochemical test
FNA fine needle aspiration
FOBT fecal occult blood test
GABA γ-aminobutyric acid
GAVE gastric arteriovenous ectasia, gastric antral vascular ectasia
GERD gastroesophageal reflux disease
GGT γ-glutamyl-transferase
GI gastrointestinal
GIST gastrointestinal stromal tumor
HAART highly active antiretroviral therapy
HAV hepatitis A virus
HBIG hepatitis B immune globulin
HBV hepatitis B virus
HCC hepatocellular carcinoma
HCT hematocrit
HCV hepatitis C virus
HDV hepatitis D virus
HE hepatic encephalopathy
HEV hepatitis E virus
HGD high-grade dysplasia
HHC hereditary hemochromatosis
HIAA hydroxyindoleacetic acid
HII hepatic iron index
HIV human immunodeficiency virus
HNPCC hereditary nonpolyposis colorectal cancer
HPF high-power field
HVPG hepatic venous pressure gradient

IBD inflammatory bowel disease
IBS irritable bowel syndrome
IBS-C irritable bowel syndrome – constipation predominant
ICU intensive care unit
Ig immunoglobulin
IGF insulin-like growth factor
IHC immunohistochemistry
IL interleukin
IM intramuscular
I-MIBG I-labeled metaiodobenzylguanidine
INR international normalized ratio
IPMN intraductal papillary mucinous neoplasm
IPSID immunoproliferative small intestinal disease
IU international unit
IV intravenous
LAP leucine aminopeptidase
LDH lactate dehydrogenase
LES lower esophageal sphincter
MALT mucosa-associated lymphoid tissue
MCV mean corpuscular volume
MELD Model for End-Stage Liver Disease
MEN multiple endocrine neoplasia
MRCP magnetic resonance cholangiopancreatography
MRI magnetic resonance imaging
NADH nicotinamide adenine dinucleotide
NAFLD nonalcoholic fatty liver disease
NASH nonalcoholic steatohepatitis
NCCN National Comprehensive Cancer Network
NG nasogastric
NSAID nonsteroidal anti-inflammatory drug
OLT orthotopic liver transplantation
pANCA perinuclear antineutrophil cytoplasmic antibody
PAS periodic acid-Schiff
PBC primary biliary cirrhosis
PCNA proliferating cell nuclear antigen
PCR polymerase chain reaction
PDGFR platelet-derived growth factor receptor
PEG polyethylene glycol
PEI percutaneous ethanol injection
PET positron emission tomography
PFIC progressive familial intrahepatic cholestasis
PICC peripherally inserted central catheter
PJS Peutz–Jeghers syndrome

po *per os*
PPI proton pump inhibitor
PPN peripheral parenteral nutrition
PSBL primary small bowel lymphoma
PSC primary sclerosing cholangitis
PTC percutaneous transhepatic cholangiography
PUD peptic ulcer disease
qid *quater in die*
RFA radiofrequency ablation
RUQ right upper quadrant
SAAG serum-ascites albumin gradient
SBP spontaneous bacterial peritonitis
SCC squamous cell carcinoma
SGOT serum glutamic oxaloacetic transaminase
SGPT serum glutamic pyruvic transaminase
SLA soluble liver antigen
SO sphincter of Oddi
SOD sphincter of Oddi dysfunction
SVR sustained virological response
TACE transarterial chemoembolization
TARE transaterial radioembolization
TCA tricyclic antidepressant
TGF transforming growth factor
TIBC total iron-binding capacity
TIPS transjugular intrahepatic portosystemic shunt
TLESR transient lower esophageal sphincter relaxation
TNF tumor necrosis factor
TPMT thiopurine methyltransferase
TPN total parenteral nutrition
TSH thyroid-stimulating hormone
tTG tissue transglutaminase
TTS through-the-scope
UES upper esophageal sphincter
UGT uridine diphosphate glucuronosyltransferase
VCE video capsule endoscopy
VEGF vascular endothelial growth factor
VIP vasoactive intestinal peptide
WBC white blood count
WDHA watery diarrhea, hypokalemia, and achlorhydria
ZES Zollinger–Ellison syndrome

Contents

PART 1
Approach to Patients with Gastrointestinal Symptoms

CHAPTER 1
Approach to the Patient with Dysphagia or Odynophagia

Dysphagia is the sensation of food hindered in its passage from the mouth to the stomach. Dysphagia is differentiated from odynophagia (pain on swallowing) and from globus sensation (perception of a lump, tightness, or fullness in the throat that is temporarily relieved by swallowing). The act of swallowing has four phases: the oral preparation phase, the oral transfer phase, the pharyngeal phase, and the esophageal phase. An abnormality of any of the phases can produce dysphagia. Dysphagia is usually divided into two categories: (1) oropharyngeal: disorders of the oral preparation, oral transfer, or pharyngeal phases of swallowing; and (2) esophageal: dysfunction of the esophageal phase of swallowing (Table 1.1).

Clinical presentation

History

The patient's symptoms help define whether dysphagia or odynophagia is oropharyngeal or esophageal in location and structural or neuromuscular in origin. If dysphagia occurs within 1 sec of swallowing or is associated with drooling, choking, coughing, aspiration, or nasal regurgitation, an oropharyngeal process is likely. Conversely, an esophageal cause is probable if dysphagia occurs more than 1 sec after swallowing, if there is retrosternal pain or if there is regurgitation of unchanged food. Dysphagia perceived in the retrosternal or subxiphoid area is nearly always diagnostic of an esophageal source. Dysphagia perceived in the cervical area may result from either oropharyngeal or esophageal disease. Structural esophageal disorders generally produce solid food dysphagia with progression to liquid dysphagia only if lumenal narrowing becomes severe. Patients with neuromuscular disorders of the esophagus usually report both liquid and solid dysphagia from the onset of symptoms. Both structural and neuromuscular oropharyngeal disorders produce early liquid dysphagia.

Yamada's Handbook of Gastroenterology, Third Edition. Edited by Tadataka Yamada and John M. Inadomi.

Table 1.1 Differential diagnosis of dysphagia and odynophagia

Oropharyngeal dysphagia
Neuromuscular diseases
Cerebrovascular accident
Parkinson disease
Amyotrophic lateral sclerosis
Brainstem tumors
Bulbar poliomyelitis
Myasthenia gravis
Muscular dystrophies
Polymyositis
Metabolic myopathy
Amyloidosis
Systemic lupus erythematosus
Local mechanical lesions
Inflammation (pharyngitis, abscess, tuberculosis, radiation, syphilis)
Neoplasm
Congenital webs
Extrinsic compression (thyromegaly, cervical spine hyperostosis, adenopathy)
Radiation or caustic damage
Upper esophageal sphincter disorders
Primary cricopharyngeal dysfunction
Cricopharyngeal bar
Zenker diverticulum
Esophageal dysphagia
Motor disorders
Achalasia
Scleroderma
Diffuse esophageal spasm
Other spastic motor disorders
Other rheumatic conditions
Chagas disease
Intrinsic mechanical lesions
Benign stricture (peptic, lye, radiation)
Schatzki ring
Carcinoma
Eosinophilic esophagitis
Esophageal webs
Esophageal diverticula
Benign tumors
Foreign bodies
Extrinsic mechanical lesions
Vascular compression
Mediastinal abnormalities
Cervical osteoarthritis

Table 1.1 (*cont'd*)

Odynophagia
Mechanical
Trauma
Inflammatory
Pill-associated ulceration
Infectious
CMV, HSV, HIV

CMV, cytomegalovirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus.

In patients with odynophagia, risk factors for opportunistic infection should be assessed and a careful medication history is warranted if pill esophagitis is a consideration.

Physical examination

The head and neck must be examined for sensory and motor function of the cranial nerves, masses, adenopathy, or spinal deformity. The patient should be observed swallowing water to visualize the co-ordinated symmetrical action of the neck and facial musculature. Evidence of systemic disease, including sclerodactyly, telangiectasias, and calcinosis in scleroderma, neuropathies or muscle weakness from generalized neuromuscular disease, and hepatomegaly or adenopathy due to esophageal malignancy should be sought. The presence of thrush suggests candidal infection as a cause of odynophagia.

Additional testing

If dysphagia is believed to be oropharyngeal, barium swallow radiography or endoscopy of the pharynx and esophagus may show occlusive lumenal lesions. Transnasal or peroral endoscopy also may reveal vocal cord paralysis, indicating neural dysfunction. Videofluoroscopy of mastication and swallowing of three different preparations (thin liquid, thick liquid, solid) is helpful in examining the co-ordination of the swallowing process in patients with suspected neuromuscular disease. In some instances, specialized manometry can reveal abnormal upper esophageal sphincter (UES) relaxations.

Endoscopy has become the preferred mode for assessing suspected esophageal dysphagia; however, contrast esophageal radiographic testing remains more sensitive for subtle structural lesions. Endoscopy is also optimal for identifying the etiology of odynophagia.

Differential diagnosis

Esophageal dysphagia

Obstructive esophageal lesions

Esophageal dysphagia is most commonly caused by structural lesions that physically impede bolus transit. Patients with esophageal strictures secondary to acid peptic damage may present with progressive dysphagia after a long history of heartburn. These strictures usually are located in the distal esophagus. More proximal strictures develop above the transition point to columnar mucosa in patients with Barrett esophagus. A Schatzki ring, a thin, circumferential mucosal structure at the gastroesophageal junction, causes episodic and nonprogressive dysphagia that often occurs during rushed ingestion of poorly chewed meat. Eosinophilic esophagitis should be considered in younger patients who present with intermittent solid food dysphagia or food impaction. Patients with squamous cell carcinoma also report progressive dysphagia, similar to peptic disease, but affected patients often are older and have had long-standing exposure to tobacco or alcohol and no prior pyrosis. Esophageal adenocarcinoma develops in areas of Barrett metaplasia resulting from prolonged gastroesophageal reflux. Other mechanical lesions (e.g. abnormal great vessel anatomy, mediastinal lymphadenopathy, and cervical vertebral spurs) can cause dysphagia.

Motor disorders of the esophagus

Primary and secondary disorders of esophageal motor activity represent the other main etiology of esophageal dysphagia. Primary achalasia is an idiopathic disorder characterized by esophageal body aperistalsis and failure of lower esophageal sphincter (LES) relaxation on swallowing with or without associated LES hypertension. Conditions that mimic primary achalasia include secondary achalasia, a disorder with identical radiographic and manometric characteristics caused by malignancy at the gastroesophageal junction or by paraneoplastic effects of a distant tumor, and Chagas disease, which results from infection with *Trypanosoma cruzi*. Other spastic esophageal dysmotilities, such as diffuse esophageal spasm, have also been associated with dysphagia. Systemic diseases (e.g. scleroderma and other rheumatic diseases) also cause dysphagia because of reduced rather than spastic esophageal motor function.

Odynophagia

Oropharyngeal odynophagia most commonly results from malignancy, foreign body ingestion, or mucosal ulceration. Esophageal odynophagia usually is a consequence of caustic ingestion, infection (e.g. *Candida albicans*, herpes simplex virus, cytomegalovirus), radiation damage, pill esophagitis, or ulcer disease induced by acid reflux (see Table 1.1).

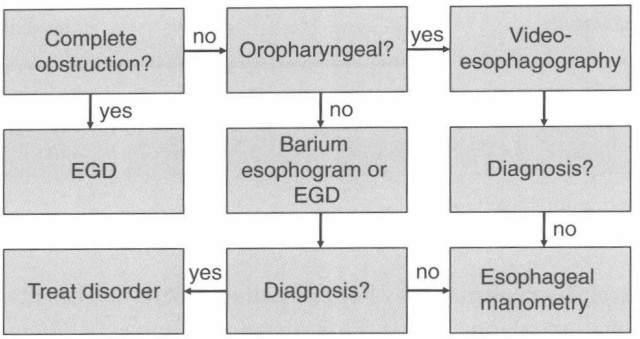

Figure 1.1 Evaluation of dysphagia or odynophagia. EGD, esophagogastroduodenosocpy.

Diagnostic investigation

Patients who present with complete obstruction should undergo upper endoscopy (Figure 1.1). Contrast radiography is not only associated with an aspiration risk but lesions found on radiography may be obscured by the contast media. Airway protection is mandatory so there should be a low threshold for endotracheal intubation.

In the absence of complete obstruction, the history further dictates the next step in investigation. For dysphagia of presumed esophageal origin, barium swallow radiography or endoscopy may reveal occlusive lesions such as carcinomas, strictures, rings, or webs. Barium swallow testing also can show the characteristic bird's beak deformity of achalasia. The addition of a solid bolus (e.g. a marshmallow or barium pill) can increase the detection of subtle abnormalities during contrast radiography. Upper endoscopy affords the additional capability to perform a biopsy of any suspicious areas, including evaluation for eosinophilic esophagitis. If structural testing is nondiagnostic, manometry of the esophageal body and LES may detect the characteristic findings of achalasia, systemic diseases such as scleroderma, and other primary and secondary esophageal motor disorders.

Oropharyngeal dysphagia is best evaluated by video-esophagography. Endoscopy is rarely diagnostic so further evaluation of oropharyngeal symptoms should be directed towards manometric testing.

Since mucosal lesions are common, endoscopy is the procedure of choice for odynophagia. In addition, plain radiography of the neck may detect pharyngeal foreign bodies.

Management

Dysphagia

Selected causes of oropharyngeal dysphagia, including Parkinson disease, hypothyroidism, polymyositis, and myasthenia gravis, may have specific