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Clinical manifestations and diagnosis of gastroesophageal reflux in adults

AUTHOR: Peter J Kahrilas, MD

SECTION EDITOR: Nicholas J Talley, MD, PhD **DEPUTY EDITOR:** Shilpa Grover, MD, MPH, AGAF

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Literature review current through: **Sep 2023.**

This topic last updated: Jul 15, 2022.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is notable for its high prevalence, variety of clinical presentations, under-recognized morbidity, and substantial economic consequences.

This topic will review the clinical manifestations and diagnosis of GERD. The pathophysiology and management of GERD are discussed in detail separately. (See "Pathophysiology of reflux esophagitis" and "Medical management of gastroesophageal reflux disease in adults" and "Surgical treatment of gastroesophageal reflux in adults".)

TERMINOLOGY

Some degree of reflux is physiologic [1]. Physiologic reflux episodes typically occur postprandially, are short-lived, asymptomatic, and rarely occur during sleep.

Pathologic reflux is associated with symptoms or mucosal injury and often occurs nocturnally.

• Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications [2].

GERD is classified based on the appearance of the esophageal mucosa on upper endoscopy into the following:

- **Erosive esophagitis** Erosive esophagitis is characterized by endoscopically visible breaks in the distal esophageal mucosa with or without troublesome symptoms of GERD. (See 'Endoscopic findings' below.)
- Nonerosive reflux disease Nonerosive reflux disease or endoscopy negative reflux disease is characterized by the presence of troublesome symptoms of GERD without visible esophageal mucosal injury.

EPIDEMIOLOGY

In a systematic review of 15 epidemiological studies, the prevalence of gastroesophageal reflux disease (GERD) was found to be 10 to 20 percent in the Western world and less than 5 percent in Asia [3]. The incidence in the Western world was approximately five per 1000 person-years or 0.5 percent per year. In a subsequent population-based survey in the United States, 22 percent of respondents reported that they had heartburn or regurgitation within the last month while 16 percent reported regurgitation [4]. Heartburn or regurgitation was clinically significant (≥twice weekly) in 6 and 3 percent, respectively.

There are limitations in the epidemiologic estimates of the prevalence of GERD, as they are based upon the assumption that heartburn and/or regurgitation are the only indicators of the disease [3,4]. However, patients with objective evidence of GERD (eg, esophagitis or Barrett's esophagus) do not always have heartburn and heartburn is not always sufficiently severe to be indicative of GERD [5].

CLINICAL FEATURES

Clinical manifestations — Classic symptoms of gastroesophageal reflux disease (GERD) are heartburn (pyrosis) and regurgitation.

- Heartburn is typically described as a burning sensation in the retrosternal area, most commonly experienced in the postprandial period [2]. Heartburn is considered troublesome if symptoms occur two or more days a week [2].
- Regurgitation is defined as the perception of flow of refluxed gastric content into the mouth or hypopharynx [2]. Patients typically regurgitate acidic material mixed with small

amounts of undigested food.

Other symptoms of GERD include dysphagia, chest pain, water brash, globus sensation, odynophagia, extraesophageal symptoms (eg, chronic cough, hoarseness, wheezing), and, infrequently, nausea.

- Dysphagia is common in the setting of longstanding heartburn and is often attributable to reflux esophagitis but can be indicative of an esophageal stricture [6]. Odynophagia is an unusual symptom of GERD but, when present, usually indicates an esophageal ulcer. (See "Approach to the evaluation of dysphagia in adults".)
- GERD-related chest pain can mimic angina pectoris, and is typically described as squeezing or burning, located substernally and radiating to the back, neck, jaw, or arms. The pain can last anywhere from minutes to hours and resolve either spontaneously or with antacids. It usually occurs after meals, awakens patients from sleep, and may be exacerbated by emotional stress [1]. Patients with reflux-induced chest pain may also have typical reflux symptoms. However, heartburn is a poor predictor of whether patients with chest pain have evidence of GERD by objective reflux testing (eg, esophageal pH monitoring) [7].
- Water brash or hypersalivation is a relatively unusual symptom in which patients can foam at the mouth, secreting as much as 10 mL of saliva per minute in response to reflux.
- Globus sensation is the almost constant perception of a lump in the throat (irrespective of swallowing), which has been related to GERD in some studies. However, the role of esophageal reflux in globus is uncertain [8]. (See "Globus sensation".)
- Nausea is infrequently reported with GERD, but a diagnosis of GERD should be considered in patients with otherwise unexplained nausea [9]. (See "Approach to the adult with nausea and vomiting", section on 'Gastroesophageal reflux'.)

Radiographic findings — Double contrast barium swallow examination is of limited diagnostic utility in patients with GERD. The demonstration of reflux of barium during the study is of dubious significance since it can be provoked in 25 to 71 percent of symptomatic patients and 20 percent of normal controls [10]. In one study, the diagnostic accuracy of barium radiography in patients with mild, moderate, and severe esophagitis on upper endoscopy is 25, 82 percent, and 99 percent, respectively [11].

Mucosal changes associated with esophagitis and peptic strictures seen on double contrast barium radiography include the following:

- In early stages of reflux esophagitis, the mucosa of the distal third of the esophagus appears granular or nodular with numerous ill-defined, 1 to 3 mm lucencies [12].
- In patients with erosive esophagitis, shallow ulcers and erosions may be visualized as tiny collections of barium in the distal esophagus near the gastroesophageal junction, sometimes surrounded by a radiolucent halo of edematous mucosa.
- A benign peptic stricture due to GERD has the appearance of a smooth, tapered area of concentric narrowing in the distal esophagus that is usually 1 to 4 cm in length and 0.2 to 2.0 cm in diameter (image 1). However, many peptic strictures have an asymmetric appearance with puckering of one wall of the stricture due to eccentric scarring.

Complications — Complications from GERD can arise even in patients who lack typical esophageal symptoms. These complications may be esophageal (eg, Barrett's esophagus, esophageal stricture, esophageal adenocarcinoma) or extra-esophageal (eg, chronic laryngitis, exacerbation of asthma). (See "Complications of gastroesophageal reflux in adults".)

DIAGNOSIS

Patients with classic symptoms — The diagnosis of gastroesophageal reflux disease (GERD) can often be based on clinical symptoms alone in patients with classic symptoms such as heartburn and/or regurgitation [2,13]. However, patients may require additional evaluation if they have alarm features, risk factors for Barrett's esophagus, or abnormal gastrointestinal imaging performed for evaluation of their symptoms. (See 'Evaluation in selected patients' below.)

Although 40 to 90 percent of patients with symptoms suggestive of GERD have a symptomatic response to proton pump inhibitors (PPIs), a response to antisecretory therapy is not a diagnostic criterion for GERD [14,15]. A meta-analysis of diagnostic test characteristics found that a response to PPIs did not correlate well with objective measures of GERD such as ambulatory pH monitoring [15]. Pooled sensitivity and specificity were 78 and 54 percent, respectively. Thus, a response to PPIs does not correspond to a GERD diagnosis based on reflux testing.

Patients without classic symptoms — Other symptoms (eg, chest pain, globus sensation, chronic cough, hoarseness, wheezing, and nausea) may be seen in the setting of GERD, but are not sufficient to make a clinical diagnosis of GERD in the absence of classic symptoms of heartburn and regurgitation. Other disorders need to be excluded before attributing the

symptoms to GERD. As an example, unexplained chest pain should be evaluated with an electrocardiogram and exercise stress test prior to a gastrointestinal evaluation.

EVALUATION IN SELECTED PATIENTS

Additional evaluation is required in selected patients with suspected gastroesophageal reflux disease (GERD) to rule out alternative etiologies, confirm the diagnosis of GERD, and assess for complications (eg, Barrett's esophagus). (See "Complications of gastroesophageal reflux in adults".)

Upper gastrointestinal endoscopy

Indications — Upper endoscopy is indicated in patients with suspected GERD to evaluate alarm features or abnormal imaging if not performed within the last three months. Upper endoscopy should also be performed to screen for Barrett's esophagus in patients with risk factors. On upper endoscopy, biopsies should target any areas of suspected metaplasia, dysplasia, or, in the absence of visual abnormalities, normal mucosa to evaluate for eosinophilic esophagitis [16]. (See 'Alarm features' below and 'Risk factors for Barrett's esophagus' below and 'Abnormal upper gastrointestinal tract imaging' below.)

Upper endoscopy is not required to make a diagnosis of GERD. However, upper endoscopy can detect esophageal manifestations of GERD (eg, Barrett's metaplasia, erosive esophagitis) and can rule out an upper gastrointestinal tract malignancy. Upper endoscopy can also rule out other etiologies in patients with GERD symptoms that are refractory to a trial of proton pump inhibitor (PPI) therapy. (See "Approach to refractory gastroesophageal reflux disease in adults", section on 'Diagnostic strategies and initial management' and "Medical management of gastroesophageal reflux disease in adults", section on 'Pretreatment evaluation'.)

Alarm features — Alarm features that are suggestive of a gastrointestinal malignancy include:

- New onset of dyspepsia in patient ≥60 years
- Evidence of gastrointestinal bleeding (hematemesis, melena, hematochezia, occult blood in stool)
- Iron deficiency anemia
- Anorexia
- Unexplained weight loss
- Dysphagia
- Odynophagia

- Persistent vomiting
- Gastrointestinal cancer in a first-degree relative

Risk factors for Barrett's esophagus — Screening for Barrett's esophagus is typically recommended for patients with multiple risk factors (one of which must be duration of GERD of at least 5 to 10 years).

Risk factors for Barrett's esophagus include:

- Duration of GERD of at least 5 to 10 years
- Age 50 years or older
- Male sex
- White individuals
- Hiatal hernia
- Obesity
- Nocturnal reflux
- Tobacco use (past or current)
- First-degree relative with Barrett's esophagus and/or adenocarcinoma

Multiple societies have issued guidelines regarding screening patients for Barrett's esophagus with varying recommendations. These are discussed in detail separately. (See "Barrett's esophagus: Epidemiology, clinical manifestations, and diagnosis", section on 'Screening patients for Barrett's esophagus'.)

Abnormal upper gastrointestinal tract imaging — Abdominal imaging is not required to establish the diagnosis of GERD but may have been performed for evaluation of concurrent symptoms. In such cases, luminal imaging abnormalities in the upper gastrointestinal tract may warrant diagnostic evaluation with upper endoscopy.

Endoscopic findings — Upper endoscopy may be normal in patients with GERD, or there may be evidence of esophagitis of varying degrees [17]. Among untreated GERD patients, approximately 30 percent will have endoscopic esophagitis. The severity and duration of symptoms correlate poorly with the severity of esophagitis.

In contrast to infectious and medication-induced esophagitis, which tend to be in the midesophagus, the ulcerations seen in peptic esophagitis are usually irregularly shaped or linear, multiple, and are in the very distal esophagus. (See "Pill esophagitis", section on 'Upper endoscopy and biopsy in selected patients' and "Approach to the evaluation of dysphagia in adults", section on 'Infectious esophagitis'.)

Other endoscopic findings in patients with longstanding GERD include peptic strictures, Barrett's metaplasia, and esophageal adenocarcinoma. (See "Complications of gastroesophageal reflux in adults".)

- **Grading the severity of esophagitis** Erosive esophagitis is graded according to its severity to guide management. Several endoscopic grading schemes have been devised to decrease inter-operator variability of endoscopy in assessing the severity of peptic esophagitis. Of these, the Los Angeles classification is the most thoroughly evaluated classification for esophagitis and is the most widely used [18]. (See "Medical management of gastroesophageal reflux disease in adults", section on 'Recurrent symptoms'.)
 - Los Angeles classification The Los Angeles classification grades esophagitis severity by the extent of mucosal abnormality, with complications recorded separately. In this grading scheme, a mucosal break refers to an area of slough adjacent to more normal mucosa in the squamous epithelium with or without overlying exudate.
 - Grade A One or more mucosal breaks each ≤5 mm in length (picture 1)
 - Grade B At least one mucosal break >5 mm long, but not continuous between the tops of adjacent mucosal folds (picture 2)
 - Grade C At least one mucosal break that is continuous between the tops of adjacent mucosal folds, but which is not circumferential (picture 3)
 - Grade D Mucosal break that involves at least three-fourths of the luminal circumference (picture 4)

Cytokine triggered inflammation stimulates histopathological events in the development of esophagitis. Lymphocytic inflammation and dilated intercellular spaces occur deep in the epithelium, not at the luminal surface, and regenerative changes (basal cell hyperplasia, papillary elongation) are initiated prior to the development of surface necrosis. (See

"Pathophysiology of reflux esophagitis", section on 'Mechanisms of gastroesophageal reflux disease'.)

Esophageal manometry — In patients with suspected GERD with chest pain and/or dysphagia and a normal upper endoscopy, an esophageal manometry should be performed to exclude an esophageal motility disorder. Manometry is useful in ensuring that ambulatory pH probes are placed correctly but cannot diagnose GERD. It is also used to evaluate peristaltic function before antireflux surgery for GERD [20]. (See "Surgical treatment of gastroesophageal reflux in adults" and "Approach to refractory gastroesophageal reflux disease in adults", section on 'Residual acid reflux'.)

Ambulatory esophageal pH monitoring — Ambulatory pH monitoring is also used to confirm the diagnosis of GERD in those with persistent symptoms (whether typical or atypical, particularly if a trial of twice-daily PPI has failed) or to monitor the adequacy of treatment in those with continued symptoms [21,22]. The approach to management of patients with refractory GERD is discussed in detail separately. (See "Approach to refractory gastroesophageal reflux disease in adults", section on 'Esophageal impedance pH testing'.)

Ambulatory pH monitoring can be performed with either a transnasally placed catheter or a wireless, capsule-shaped device that is affixed to the distal esophageal mucosa [23,24]. Esophageal pH monitoring with impedance is an alternative to wired or wireless pH studies with the advantage of detecting weakly acid reflux in addition to acid reflux, making it more useful in ascertaining symptom-reflux correlation.

In each case, the pH sensor is coupled with compact, portable data recorders, and computerized data analysis. The catheter type pH electrode is positioned 5 cm above the manometrically defined upper limit of the lower esophageal sphincter. In the case of the wireless device, the pH capsule is attached 6 cm proximal to the endoscopically defined squamocolumnar junction. Tests are traditionally conducted for a 24-hour period with patients advised to consume an unrestricted diet. Studies with the wireless device are conducted for two to four days, potentially varying the dietary and/or therapeutic circumstances among days [25]. Increasing the monitoring period in patients undergoing evaluation using a wireless device increases the yield of the study for detecting reflux episodes and correlating those events with symptoms [24,26]. (See "Esophageal multichannel intraluminal impedance testing".)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of gastroesophageal reflux disease (GERD) includes infectious esophagitis, pill esophagitis, and eosinophilic esophagitis. Other causes of dysphagia include esophageal rings/webs, and impaired peristalsis due to an esophageal motility disorder. Slowly progressive dysphagia for solids with episodic esophageal obstruction is suggestive of a stricture or an esophageal cancer. Odynophagia may be due to infectious or medication-induced esophagitis. GERD can be distinguished from these conditions by esophageal manometry and upper endoscopy with biopsies of the esophagus. The differential diagnosis and evaluation of patients with dysphagia is discussed in detail separately. (See "Approach to the evaluation of dysphagia in adults", section on 'Symptom-based differential diagnosis'.)

Frequent heartburn may also be due to reflux hypersensitivity or functional heartburn. GERD can be distinguished from these conditions by pH or pH-impedance testing. Patients with reflux hypersensitivity have normal acid exposure but a positive symptom association with acid or weakly acid reflux. Patients with functional heartburn have normal acid exposure and a negative symptom reflux association. Patients with functional dyspepsia have heartburn in one third of cases, but early satiety and postprandial fullness are the predominant symptoms. (See "Approach to refractory gastroesophageal reflux disease in adults", section on 'Functional heartburn' and "Functional dyspepsia in adults", section on 'Clinical manifestations'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Gastroesophageal reflux in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Acid reflux and GERD in adults (The Basics)" and "Patient education: Upper endoscopy (The Basics)" and "Patient education: Esophagitis (The Basics)")
- Beyond the Basics topics (see "Patient education: Gastroesophageal reflux disease in adults (Beyond the Basics)" and "Patient education: Upper endoscopy (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Terminology Physiologic reflux episodes typically occur postprandially, are short-lived, asymptomatic, and rarely occur during sleep. Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. (See 'Terminology' above.)
- **Epidemiology** The estimated prevalence of GERD is approximately 10 to 20 percent of individuals in the Western world and less than 5 percent in Asia. However, prevalence estimates are limited by the assumption that heartburn and/or regurgitation are the only indicators of the disease. (See 'Epidemiology' above.)
- Clinical features Classic symptoms of GERD are heartburn (pyrosis) and regurgitation. Other symptoms of GERD include dysphagia, chest pain, water brash, globus sensation, odynophagia, extraesophageal symptoms (eg, chronic cough, hoarseness, wheezing), and infrequently, nausea. (See 'Clinical manifestations' above.)
- **Diagnosis** The diagnosis of GERD can be based upon clinical symptoms alone in patients with classic symptoms. In patients without classic symptoms of GERD, other disorders need to be excluded before attributing the symptoms to GERD. (See 'Patients with classic symptoms' above and 'Patients without classic symptoms' above.)
- Additional evaluation in selected patients Additional evaluation is required in selected patients with suspected GERD to rule out alternative etiologies, confirm the diagnosis of GERD, and assess for complications (eq., Barrett's esophagus).
 - **Indications for upper endoscopy** Upper endoscopy with biopsy should be performed at presentation for patients with an esophageal GERD syndrome with any of the following:

- Alarm features suggestive of a gastrointestinal malignancy
- Abnormal upper GI tract imaging
- Risk factors for Barrett's esophagus
 Patients with suspected GERD who have not responded to an empirical trial of twice-daily proton pump inhibitor (PPI) therapy. (See 'Evaluation in selected patients' above.)

Alarm features that are suggestive of a gastrointestinal malignancy include:

- New onset of dyspepsia in patient ≥60 years
- Evidence of gastrointestinal bleeding (hematemesis, melena, hematochezia, occult blood in stool)
- Iron deficiency anemia
- Anorexia
- Unexplained weight loss
- Dysphagia
- Odynophagia
- Persistent vomiting
- Gastrointestinal cancer in a first-degree relative
- Ambulatory pH monitoring for persistent symptoms despite PPI therapy Ambulatory pH monitoring is also used to confirm the diagnosis of GERD in those with persistent symptoms (whether typical or atypical, particularly if a trial of twice-daily PPI has failed) or to monitor the adequacy of treatment in those with continued symptoms. (See 'Ambulatory esophageal pH monitoring' above.)
- Esophageal manometry in patients with chest pain and/or dysphagia We perform an esophageal manometry to exclude an esophageal motility disorder in patients with chest pain and a normal upper endoscopy. Manometry is also performed to evaluate esophageal peristaltic function prior to antireflux surgery. (See 'Esophageal manometry' above.)

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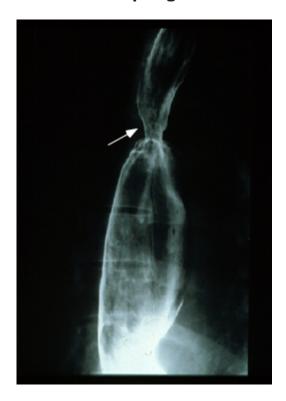
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GRAPHICS

Proximal esophageal stricture



Barium swallow shows proximal esophageal stricture (arrow) due to reflux esophagitis.

Courtesy of Peter J Kahrilas, MD.

Graphic 66161 Version 2.0

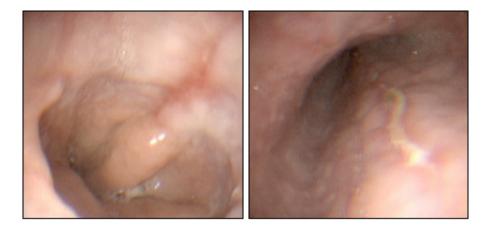
Los Angeles grade A esophagitis



Los Angeles grade A esophagitis: One or more mucosal breaks no longer than 5 mm, not bridging the tops of mucosal folds. Mucosal breaks are defined as an area of slough or erythema with a discrete line of demarcation from the adjacent, more normal looking mucosa.

Graphic 60311 Version 4.0

Los Angeles grade B esophagitis



Los Angeles grade B esophagitis: One or more mucosal breaks longer than 5 mm, but not bridging the tops of mucosal folds.

Graphic 74162 Version 3.0

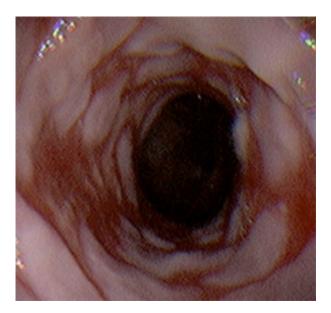
Los Angeles grade C esophagitis



Los Angeles grade C esophagitis: One or more mucosal breaks bridging the tops of mucosal folds involving less than 75 percent of the circumference of the lumen.

Graphic 53483 Version 3.0

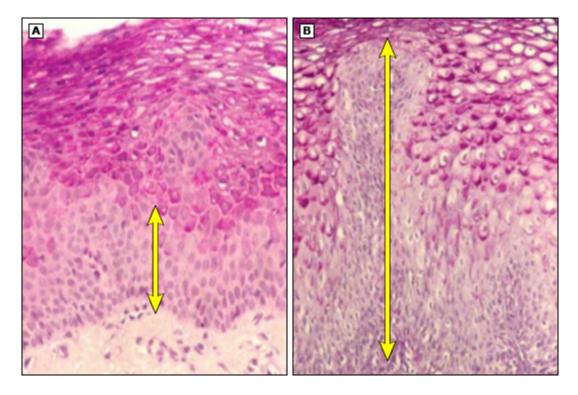
Los Angeles grade D esophagitis



Los Angeles grade D esophagitis: One or more mucosal breaks bridging the tops of mucosal folds involving more than 75 percent of the circumference of the lumen.

Graphic 63178 Version 3.0

Histologic findings in GERD



- (A) Increased basal layer thickness (noncornified stratified squamous).
- (B) Papillary elongation (noncornified stratified squamous).

GERD: gastrointestinal reflux disease.

Graphic 56086 Version 1.0

Contributor Disclosures

Peter | Kahrilas, MD Patent Holder: Medtronic [FLIP panometry methods and technology]. Consultant/Advisory Boards: Ironwood [Irritable bowel]; Johnson & Johnson [Anti-reflux surgery]; Reckitt [Reflux disease]. Speaker's Bureau: Phathom [Reflux disease, H. pylori]. All of the relevant financial relationships listed have been mitigated. Nicholas J Talley, MD, PhD Patent Holder: Australian Provisional Patent [Diagnostic marker for functional gastrointestinal disorders]; Biomarkers of irritable bowel syndrome [Irritable bowel syndrome]; Mayo Clinic [Dysphagia questionnaire]; Mayo Clinic [Bowel Disease questionnaire]; Nepean Dyspepsia Index [Dyspepsia]; Nestec [Irritable bowel syndrome]; Singapore Provisional Patent [BDNF Tissue Repair Pathway]. Grant/Research/Clinical Trial Support: Alimetry [Gastric mapping device research collaboration]; Allakos [Gastric eosinophilic disease]; AstraZeneca [Eosinophilic gastritis, eosinophilic gastroenteritis]; Intrinsic Medicine [Bowel syndrome with constipation]; NHMRC Centre for Research Excellence in Digestive Health [NHMRC Investigator grant]. Consultant/Advisory Boards: Adelphi Values [Functional dyspepsia]; Allakos [Gastric eosinophilic disease, AK002]; AstraZeneca [Eosinophilic gastritis, eosinophilic gastroenteritis]; AusEE [Eosinophilic gut diseases]; Bayer [Inflammatory bowel syndrome]; BluMaiden [Microbiome Ad Board]; Comvita Mānuka Honey [Digestive health]; Dr Falk Pharma [Eosinophilia]; GlaxoSmithKline Australia [Educational speaker eosinophilic gut disease]; Glutagen [Celiac disease]; International Foundation for Functional Gastrointestinal Disorders [Advisory board, functional GI disorders]; Intrinsic Medicine [Human milk oligosaccharide]; IsoThrive [Esophageal microbiome]; Planet Innovation [Gas capsule, inflammatory bowel syndrome]; Progenity Inc [Intestinal capsule]; Rose Pharma [IBS]; Viscera Labs [Inflammatory bowel syndrome, diarrhea]. Other Financial Interest: Elsevier textbook royalties [Medical education]. All of the relevant financial relationships listed have been mitigated. Shilpa Grover, MD, MPH, AGAF No relevant financial relationship(s) with ineligible companies to disclose.

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