Gastroenterology 2026;170:1224–1239

Functional Esophageal Disorders

C. Prakash Gyawali,[1] Sabine Roman,[2] Frank Zerbib,[3] Edoardo V. Savarino,[4] Shobna Bhatia,[5] Ronnie Fass,[6] and John E. Pandolfino[7]

[1]Division of Gastroenterology, Washington University School of Medicine, St Louis, Missouri; [2]CHU de Lyon, Hospices Civils de Lyon, Lyon I University, Digestive Physiology, INSERM 1032 LabTAU, Lyon, France; [3]CHU de Bordeaux, Centre Médico-Chirurgical Magellan, Hôpital Haut-Lévêque, Department of Gastroenterology, Université de Bordeaux, INSERM CIC 1401, Bordeaux, France; [4]Gastroenterology Unit, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy; [5]HBT Medical College and Dr RN Cooper Municipal General Hospital, Mumbai, India; [6]Esophageal and Swallowing Center, MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio; and [7]Division of Gastroenterology and Hepatology, Department of Medicine, Northwestern University and Kenneth C. Griffin Esophageal Center, Digestive Health Institute, Northwestern Medicine, Chicago, Illinois

Functional esophageal disorders manifest a complex interplay between subtle physiomechanical perturbations and altered peripheral and central neuropsychological processing. These disorders present with heartburn, chest pain, globus and/or dysphagia, in the absence of structural abnormalities, esophageal motility disorders, or overt gastroesophageal reflux disease. Visceral hypersensitivity from peripheral or central neural dysfunction is thought to contribute significantly to symptom generation, potentially triggered by low-grade inflammation or compensatory responses to repetitive noxious stimuli. Hypervigilance impairs interpretation and regulation of internal sensory signals, modulated by cognitive and affective processes and by psychosocial stressors. Therapeutic approaches targeting minimal motor abnormalities or further reducing physiologic reflux have limited benefit. In contrast, modulation of peripheral sensory inputs and central perception pathways are conceptually and clinically promising, although outcome data remain sparse. Future research should prioritize elucidating the neurobiological mechanisms underlying esophageal hypersensitivity and hypervigilance to inform the development of targeted and effective treatments.

Keywords: Heartburn; Chest Pain; Dysphagia; Rome V.

Functional esophageal disorders, now classified as esophageal disorders of gut–brain interaction (E-DGBI), are defined by esophageal symptoms of heartburn, chest pain, globus, and/or dysphagia in the absence of identifiable structural, inflammatory, or major motor abnormalities[1] (Table 1). A key evolution in Rome V from Rome IV is the formal integration of updated diagnostic frameworks, specifically the Chicago Classification version 4.0 (CCv4.0) and the Lyon Consensus 2.0, which now serve as foundational components in defining and excluding relevant organic and motility-based esophageal diseases[2,3] (Table 1).

The evaluation of esophageal symptoms follows a pathway that focuses on endoscopic assessment with complementary physiologic testing (Figure 1). Patients with E-DGBI typically manifest normal findings on upper endoscopy, without evidence of advanced grade esophagitis (Los Angeles [LA] grades B, C, or D) or mechanical obstruction. High-resolution manometry (HRM), interpreted using CCv4.0 criteria, confirms the absence of motility disorders, including achalasia, esophagogastric junction outflow obstruction (EGJOO), absent contractility, distal esophageal spasm (DES), and hypercontractile esophagus.[3] Concurrently, esophageal reflux monitoring based on Lyon 2.0 standards demonstrates no pathologic reflux burden, thereby excluding gastroesophageal reflux disease (GERD) as the primary driver of symptoms.[2]

Rome V also reflects a more refined role of eosinophilic esophagitis (EoE), not only as a distinct clinicopathologic entity but also as a potential diagnostic confounder. Endoscopic biopsies are therefore essential to exclude EoE, particularly in patients presenting with dysphagia, chest pain with eating, or food impaction.[4] Only after exclusion of EoE, using histologic confirmation (<15 eosinophils/high power field) in the appropriate clinical context, can a diagnosis of an E-DGBI be appropriately considered.

In the absence of structural, inflammatory, and motor abnormalities, pathophysiological emphasis shifts to the altered interaction between peripheral sensory signaling and central neural perception. In this context, the integrity of the esophageal mucosal barrier is normal. Further, functional esophageal disorders do not progress along a structurally measurable natural history but instead reflect chronic dysregulation of gut–brain communication. To

Abbreviations used in this paper: **AET, acid exposure time; CBT, cognitive behavioral therapy; DES, distal esophageal spasm; DGBI, disorders of gut–brain interaction; E-DGBI, esophageal disorders of gut–brain interaction; EGJ, esophagogastric junction; EGJOO, esophagogastric junction outflow obstruction; EoE, eosinophilic esophagitis; FLIP, functional lumen imaging probe; GERD, gastroesophageal reflux disease; GI-CBT, gastrointestinal cognitive behavioral therapy; HRM, high-resolution manometry; IEM, ineffective esophageal motility; LA grade, Los Angeles grade; MNBI, mean nocturnal baseline impedance; NCCP, noncardiac chest pain; NERD, nonerosive reflux disease; PCAB, potassium competitive acid blocker; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; UES, upper esophageal sphincter.**

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2026.02.005

Table 1. Major Definition Changes in Rome V to Improve Diagnosis of Esophageal Disorders of Gut–Brain Interaction

Esophageal disorders	Main changes in Rome V classification
All disorders	The thresholds to rule out GERD are in accordance with the Lyon Consensus 2.0 criteria. Previous version used Lyon 1.0 criteria.
All disorders	The thresholds to rule out esophageal motility disorders are in accordance with the Chicago Classification version 4.0 criteria. Previous version used Chicago Classification version 3.0 criteria.
Functional chest pain	Esophageal biopsies are required only if chest pain is meal related (while biopsies were required for all patients in Rome IV). Previous version suggested esophageal biopsy for all patients with chest pain.
Globus	The clinical impact on gastric inlet patch is decreased. Previous version was more supportive of ablation therapy.

capture this chronicity, diagnostic criteria require symptoms to be present for at least 3 months, with onset at least 6 months before diagnosis. This criterion underscores the enduring and nonprogressive nature of these disorders, in alignment with the gut–brain interaction model that forms the cornerstone of the Rome V classification (Figure 2).

The pathogenesis of E-DGBI centers on disrupted communication between the peripheral esophageal

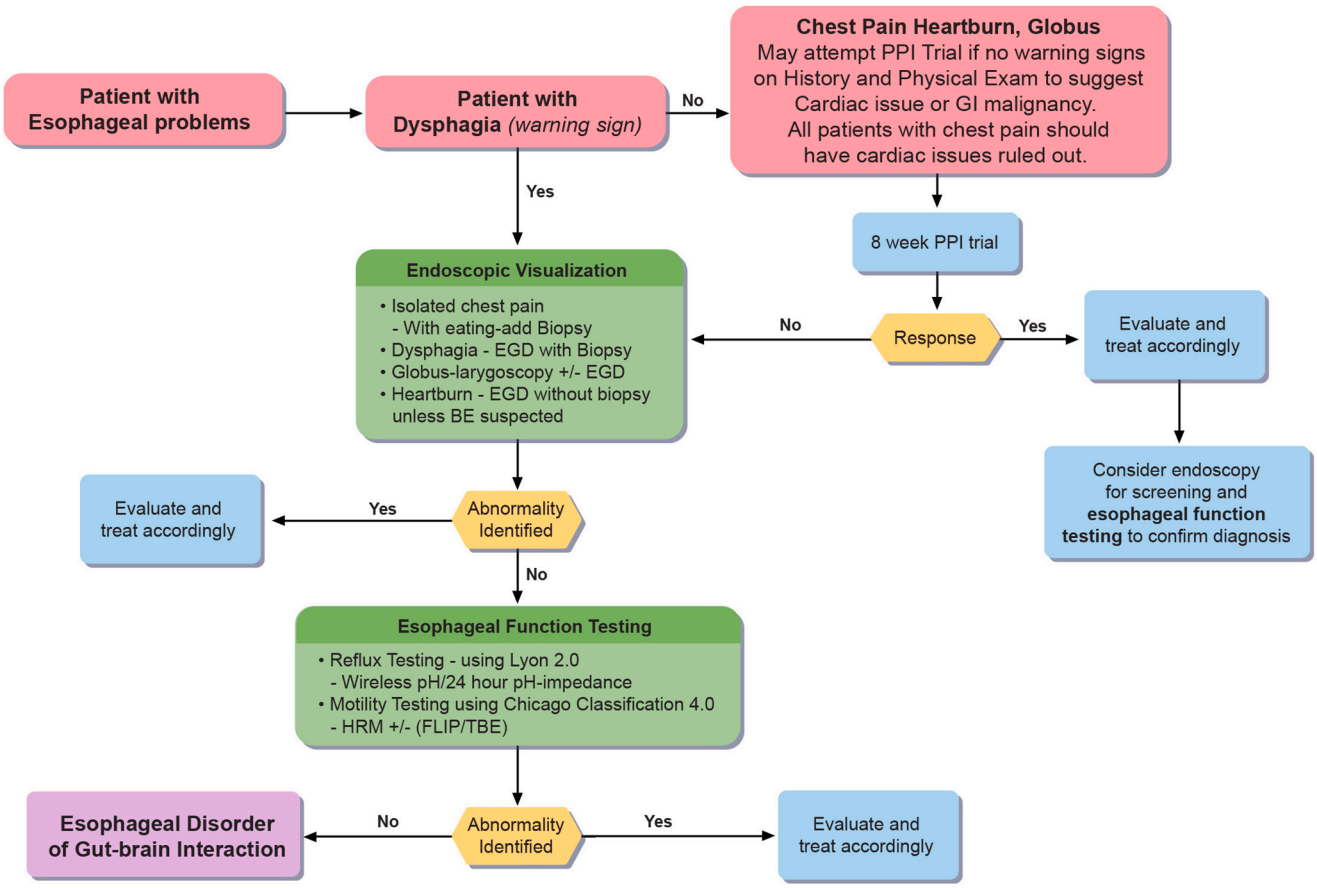

Figure 1. Global algorithm for evaluation and classification of E-DGBI. The general approach to E-DGBI focuses on upfront assessment with PPI unless patients present with a warning sign (dysphagia with or without weight loss, chest pain with eating). In addition, cardiac causes should be ruled out before an esophageal cause is investigated. Eventually, all patients diagnosed with an E-DGBI will undergo endoscopy and esophageal function testing to rule out clinically significant mucosal abnormalities, mechanical obstruction, pathologic gastroesophageal reflux, and/or a major motility disorder. New criteria have been applied to reflect Lyon Consensus 2.0 and Chicago Classification version 4.0. This algorithm is a global view; the individual disease states will be presented later in this chapter and will have minor differences to reflect the underlying pathogenesis and testing applied. EGD, esophagogastroduodenoscopy; GI, gastrointestinal; TBE, timed barium esophagram.

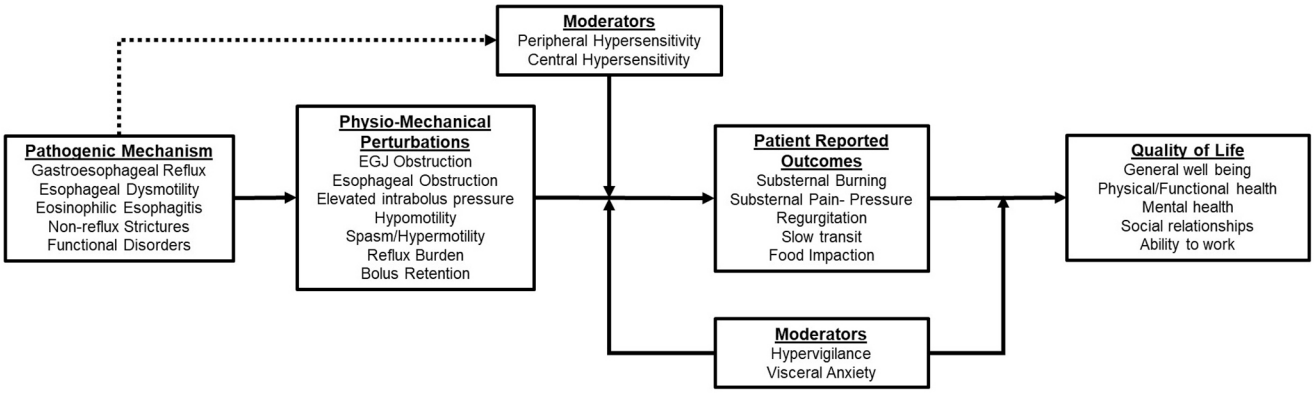

Figure 2. Concept model. The clinico-pathogenic model of symptom generation and the effect on quality of life (QoL). Esophageal disorders generate symptoms from physiomechanical perturbations through complex gut–brain interactions that are moderated by visceral sensitivity, which in turn may be influenced by inflammation from the underlying disease. Patient-reported outcome (PRO) instruments developed for the specific disease state are well suited to assess patient experience and can complement global and disease-specific QoL tools. Behavioral factors including hypervigilance and visceral anxiety may further augment symptom severity perception, assessment of which will improve outcome assessments, as these measures are both a PRO and an important moderator of symptom severity and QoL.

environment and central neural processing. Unlike structural or inflammatory diseases, E-DGBI arise from altered sensory signaling, aberrant neural integration, and maladaptive cognitive-affective responses to esophageal stimuli. A core feature is esophageal hypersensitivity—where normal or minimally provocative stimuli are perceived as painful or distressing—mediated through mechanisms such as allodynia (pain from nonpainful stimuli) and hyperalgesia (exaggerated pain response).[5] These perceptual abnormalities are often amplified by psychological factors, including hypervigilance (excessive attention to bodily sensations) and symptom-specific anxiety.

Functional chest pain and functional heartburn exemplify conditions in which symptoms do not correlate with gastroesophageal reflux or structural pathology. In contrast, reflux hypersensitivity involves similar neuropsychological profiles, but symptoms are temporally associated with physiologic reflux events. In all these disorders, peripheral sensitization—via mucosal or neural mechanisms—triggers exaggerated central processing. For instance, acid exposure, even in the absence of erosive injury, may provoke esophageal epithelial cells to release cytokines such as interleukin-8, contributing to local immune activation and nociceptor sensitization.[6] Notably, in functional heartburn, mucosal innervation is deep and resembles that seen in healthy individuals, suggesting central factors predominate in symptom generation.[7] Conversely, nonerosive reflux disease (NERD) demonstrates more superficial mucosal nerve endings, possibly explaining increased chemosensitivity and supporting the potential utility of protective topical agents.[8]

The origins of the esophageal hypersensitivity were first established in patients with noncardiac chest pain (NCCP), where esophageal balloon distension produced pain at lower thresholds compared with healthy controls.[9] Subsequent studies reported that up to 75% of patients with NCCP exhibit hypersensitivity to balloon distension.[10] Similarly, patients with functional heartburn—defined by normal pH monitoring, negative symptom-reflux association, and lack of proton pump inhibitor (PPI) response—demonstrate increased sensitivity to mechanical and chemical stimulation compared with patients with NERD, erosive esophagitis, and healthy individuals.[11] However, findings are not universal. Shapiro et al[12] found increased chest pain, somatization, and altered autonomic tone in patients with functional heartburn but not increased chemoreceptor sensitivity, further emphasizing the role of central perception.

Esophageal hypersensitivity is increasingly accepted as the core mechanism in many E-DGBI, likely driven by a combination of physiological triggers and psychosocial factors.[5] Elements of hypersensitivity are also believed to contribute to symptom expression in globus and functional dysphagia, even though most mechanistic data come from studies of perceptive symptoms such as chest pain and heartburn. In addition, hypervigilance and symptom-specific anxiety are emerging as critical cognitive-affective traits that influence patient experience and outcomes across esophageal and other disorders of gut–brain interaction (DGBI).[13] Together, these findings support a model in which E-DGBI arise from dynamic and reciprocal interactions between peripheral sensory input and central emotional and cognitive processes.

A1. Functional Chest Pain

Definition

Functional chest pain is defined as recurring retrosternal chest pain of presumed esophageal origin, different from heartburn, not explained on the basis of GERD, other mucosal disorders, or motor processes. Functional chest pain is a subset within the broad umbrella of NCCP. History and physical examination do not reliably segregate esophageal from cardiac chest pain, stressing the need for initial cardiac evaluation in appropriate clinical settings.

Epidemiology

The pooled prevalence of functional chest pain is 1.4% (95% confidence interval, 1.3%–1.5%) based on a global survey of 54,127 individuals over the internet across 26 countries and 18,949 through personal interviews in 9 countries using household surveys.[14] Functional chest pain is slightly more common in women (1.5%) than men (1.3%), and more prevalent in adults younger than 65 years (1.4%–1.5%) compared with those older than 65 (1.0%). Among patients with NCCP, approximately 50% to 60% have GERD, 15% to 18% have esophageal motility disorders, and 32% to 35% meet criteria for functional chest pain.[15]

Clinical Evaluation

Exclusion of cardiac disease is an initial key step, and esophageal workup should only proceed after confirmation (typically from the patient's cardiologist or primary care physician) that symptoms are unrelated to either concurrent or new coronary artery disease. Further workup is guided by the prevalence of the underlying causes of NCCP and potential clues from clinical evaluation that may support one of these causes. Given the high prevalence of GERD within NCCP, an 8-week course of optimized antisecretory therapy using PPIs or potassium competitive acid blockers (PCABs) is simple and cost-effective in determining whether GERD may be triggering underlying chest pain.[16] The role of upper endoscopy is unclear based on limited data available, but this has exclusionary value. Therefore, endoscopy is performed using indications similar to traditional GERD with the caveat that mucosal biopsies are considered to rule out EoE if chest pain is meal-triggered.[4]

A1. Diagnostic Criteria[a] for Functional Chest Pain

Must include *all* of the following:

1. Retrosternal chest pain or discomfort[b]
2. Absence of associated esophageal symptoms, such as heartburn or dysphagia
3. Absence of evidence that gastroesophageal reflux disease[c] or nonreflux esophagitis are the cause of the symptoms[d]
4. Absence of disorders of esophagogastric junction (EGJ) outflow and/or disorders of esophageal peristalsis[e]

[a]Criteria fulfilled for the past 3 months, with symptom onset at least 6 months before diagnosis with a frequency of at least once a week despite optimized antisecretory therapy for at least 8 weeks.
[b]Cardiac causes should be ruled out.
[c]Abnormal endoscopy (≥LA B esophagitis) or reflux burden based on reflux testing guided by Lyon 2.0 criteria.
[d]Consider mucosal biopsies if chest pain occurs with meals as this could be a surrogate for dysphagia.
[e]Disorders of EGJ function (achalasia, conclusive EGJOO) and/or disorders of peristalsis (absent contractility, hypercontractile esophagus, and distal esophageal spasm) except ineffective esophageal motility (IEM), guided by Chicago Classification version 4.0.

Patients not responding to the PPI trial may be referred for ambulatory reflux testing if clinical suspicion for GERD remains high; in this context, this test should be performed off acid suppression.[2] There are insufficient data assessing superiority of one reflux monitoring method over the others in the evaluation of NCCP; therefore, pH monitoring, combined pH-impedance monitoring, or prolonged wireless pH monitoring beyond 24 hours can be used, reflecting availability and expertise of the interpreting physician. Most patients with NCCP have normal motor function; esophageal HRM should be considered once GERD has been comfortably ruled out, as the diagnosis of esophageal motor disorders represents another important exclusion in functional chest pain.

Justification for Criteria Change

The updated Rome V criteria for functional chest pain clarify that this diagnosis is made after exclusion of structural, motor, mucosal, and reflux-related causes, thereby implying an E-DGBI. Symptoms must be bothersome, occur at least once weekly, and persist for at least 3 months with onset at least 6 months before diagnosis, despite optimized antisecretory therapy with a PPI or PCAB for at least 8 weeks. Diagnostic refinement incorporates current standards to exclude GERD (using Lyon Consensus 2.0),[2] major motor disorders (via Chicago Classification version 4.0),[3] and mucosal diseases such as EoE, especially when chest pain occurs during eating, which may serve as a surrogate for dysphagia.[17] Inconclusive EGJOO may coexist with functional chest pain, while conclusive EGJOO remains exclusionary; IEM is not an exclusion. There is no definitive clinical test to confirm esophageal origin of chest pain, making functional chest pain a diagnosis of exclusion following thorough negative evaluation.

Psychophysiologic Mechanisms

Functional chest pain is primarily driven by esophageal hypersensitivity resulting from peripheral and/or central sensitization, altered visceral signal processing, and autonomic dysregulation. Studies consistently show heightened esophageal sensitivity and altered pain perception in these patients.[18] Peripheral sensitization may result from tissue injury, inflammation, or repetitive mechanical stimuli, with hypersensitivity often persisting beyond the original insult. The determinants of such persistence remain unclear. Enhanced central processing is supported by cerebral evoked potential studies showing distinct latency patterns in patients with NCCP.[19] However, these findings are variable, suggesting possible mechanistic heterogeneity within the functional chest pain spectrum. Autonomic dysfunction may represent a distinct subset. The presence of minor motility abnormalities is unlikely to play a causal role in patients with functional chest pain; however, sustained longitudinal contractions have been linked to chest pain, possibly through an ischemic mechanism, although this remains unproven.[20]

Abelchia (also termed retrograde cricopharyngeal dysfunction or inability to belch) is an underrecognized

Table 2. Summary of Data From Randomized Controlled Trials of Neuromodulators in the Management of Esophageal Disorders of Gut–Brain Interaction

Class of drug	Author, journal, year	Dose	Number of patients	Disorder	Side effects[a]	Response
TCAs						
Imipramine	Cannon RO et al, N Engl J Med 1994	50 mg/d	20	NCCP	±	Symptoms – 52%
Imipramine	Cox ID et al, Eur Heart J 1998	50 mg/d	18	NCCP	++	Symptoms – Significant
Imipramine	Limsrivilai J et al, Am J Gastroenterol 2016	25 mg/d	43	FH, RH	±	Patients – 37.2%
Amitriptyline	You LQ et al, World J Gastroenterol 2013	25 mg/d	30	Globus	±	Symptoms – 75%
Amitriptyline	Park SW, World J Gastroenterol 2013	10 mg/d	20	FCP	±	Patients – 70.6%
SSRIs						
Sertraline	Varia I et al, Am Heart J 2000	50–200 mg/d	30	NCCP	–	Symptoms – 48%
Sertraline	Keefe FJ et al, Pain 2011	50–200 mg/d	115	NCCP	±	Symptoms – 50%
Paroxetine	Doraiswamy PM et al, Psychopharmacol Bull 2006	50–75 mg/d	50	NCCP	±	Symptoms - Modest
Paroxetine	Spinhoven P et al, J Psychosom Res 2010	10–40 mg/d	69	NCCP	±	Symptoms – 21.7%
Citalopram	Broekaert, Aliment Pharmacol Ther 2006	20 mg IV	10	ES	±	Symptoms – Significant
Trazodone						
Trazodone	Clouse RE et al, Gastroenterology 1987	100–150 mg/d	29	Esophageal dysmotility	±	Symptoms – 59%
SNRIs						
Venlafaxine	Lee H et al, Am J Gastroenterol 2010	75 mg/d	43	FCP	±	Symptoms – 59%
Other						
Theophylline	Rao SS et al, Am J Gastroenterol 2007	200 mg bid	24	NCCP	++	Symptoms – 58%
Gabapentin	Kirch S et al, Ann Otol Rhinol Laryngol 2013	300 mg tid	87	globus	±	Patients – 66%

bid, twice a day; ES, esophageal sensitivity; FCP, functional chest pain; FH, functional heartburn; IV, intravenous; RH, reflux hypersensitivity; SNRIs, serotonin norepinephrine reuptake inhibitors; tid, 3 times a day.
[a]Side effects are graded as none (–), mild (±), and significant (++).

motility disorder that may lead to esophageal symptoms including chest pain and audible gurgling noises in the chest.[21] The disorder consists of a failure of the belch reflex resulting in air entrapment in the esophagus. HRM may show absence of upper esophageal sphincter (UES) relaxation during gastroesophageal reflux events, and pH-impedance monitoring reveals periods of continuously high impedance levels corresponding to esophageal air entrapment.

Psychiatric comorbidities—especially anxiety, depression, and somatization—are present in up to 75% of patients with NCCP.[22] Chest pain is a common feature of panic attacks, and patients often exhibit higher levels of neuroticism. These psychological factors are associated with poorer quality of life, more frequent pain episodes, and reduced treatment response.[23] Whether causal or consequential, addressing psychological comorbidities is essential for effective management.

Treatment

The treatment of functional chest pain primarily targets neuromodulation of pain using medications (Table 2) such as tricyclic antidepressants (TCAs), serotonin norepinephrine reuptake inhibitors, and trazodone, with randomized trials

showing up to 50% effectiveness above placebo,[24] whereas selective serotonin reuptake inhibitors (SSRIs) show inconsistent results.[25] Side effects or stigma may limit use of neuromodulators. Alternative agents like gabapentin, pregabalin, dronabinol, and theophylline have been explored, but require cautious use because of potential side effects. Behavioral interventions—including gastrointestinal cognitive behavioral therapy (GI-CBT), gut-directed hypnotherapy, and biofeedback—have emerged as important complementary therapies with minimal adverse effects.[26,27] A Cochrane review showed GI-CBT reduced symptom frequency (relative risk, 0.70; 95% confidence interval, 0.53–0.92),[28] and controlled trials confirm reductions in severity and psychological comorbidities.[29] Gut-directed hypnotherapy and biofeedback, including diaphragmatic breathing, also offer symptomatic benefit,[30] whereas energy healing using Johrei has shown promise in a small study.[31]

A2. Functional Heartburn

Definition

Functional heartburn is defined as retrosternal burning discomfort or sensation that persists despite optimized antisecretory therapy in the absence of esophagitis, EGJ dysfunction, or major motility disorders (Figure 1). Rome III included functional heartburn under the NERD spectrum, but Rome IV excluded patients with abnormal esophageal acid exposure or positive reflux-symptom association in the diagnosis. Rome V maintains this approach but aligns with updated criteria from Lyon Consensus 2.0 and Chicago Classification version 4.0, clearly distinguishing functional heartburn from reflux hypersensitivity.[2,3]

Wireless pH monitoring is preferred for assessing day-to-day variability in acid exposure and for ruling out NERD when acid exposure is within physiologic range.[2,32] In addition, normal baseline impedance (>2500 Ω) on pH-impedance monitoring supports a diagnosis of functional heartburn as an E-DGBI when other causes are excluded.[2] The term "functional" reflects the absence of an identifiable structural or reflux-based cause.

Rome IV first introduced the concept of overlap between GERD and E-DGBI in patients with persistent symptoms on PPI therapy.[1] In 2 small cohort studies of patients with proven GERD, only 28% to 40% had proven ongoing GERD and the remainder had overlap between GERD and E-DGBI.[33,34] Further, patients with overlapping E-DGBI and GERD have clinical, psychological, and functional profiles similar to those of patients with conventional E-DGBI without concomitant GERD.[35]

Epidemiology

The true incidence and prevalence of functional heartburn are difficult to define because of its reliance on reflux testing and response to PPI therapy, both of which have limitations in accurately excluding GERD. In a global population-based internet survey (54,127 individuals in 26 countries) and household survey (18,949 individuals in 9 countries), the investigators reported functional heartburn prevalence rates of 1.1% and 0.4%, respectively.[14] However, the diagnosis of functional heartburn is difficult to obtain without confirmation of endoscopy and reflux testing.

Among patients referred to gastrointestinal visits, functional heartburn may affect 20% to 30% of patients with heartburn. Thus, up to 70% of patients with heartburn have normal endoscopy, and are further phenotyped based on reflux monitoring.[2] A Department of Veterans Affairs trial found that of 366 patients with refractory reflux symptoms, 99 (27%) had normal acid exposure and no symptom correlation, meeting criteria for functional heartburn.[36] In another study using 96-hour wireless pH monitoring, 18% (24 of 132) had normal acid exposure across all days.[32] These data suggest that 18% to 30% of patients with reflux-like symptoms refractory to PPIs may fall within the E-DGBI spectrum using Rome V definitions.

Long-term outcomes are limited, but a French follow-up study reported that two-thirds of patients remained symptomatic at 2 years, whereas about 20% experienced reduced symptom intensity and frequency.[37] This suggests that functional heartburn is generally persistent, with modest improvement in a subset of patients.

Clinical Evaluation

Functional heartburn is diagnosed when burning retrosternal discomfort persists despite optimal PPI or PCAB therapy for ≥8 weeks, and alternative causes such as GERD and major motility disorders are excluded. The symptom must be bothersome, occur ≥2 days/week for at least 3 months, and have started ≥6 months before diagnosis.

PPI nonresponse is central to the diagnosis. Only 20% to 30% of patients achieve relief with high-dose PPIs.[38] PCABs may offer better outcomes.[39] Patients often mislabel throat symptoms or epigastric burning as heartburn; careful history taking improves diagnostic accuracy. Patients with functional heartburn and those with GERD are otherwise clinically similar.[35]

Endoscopy is the first-line test in PPI-refractory heartburn but has limited yield when performed on PPI therapy because of high mucosal healing rates.[40] To detect baseline GERD (LA grade B/C/D), endoscopy should ideally be done after 2 to 4 weeks off PPIs. LA grade B is now accepted as conclusive GERD based on comparable acid exposure time (AET) and reflux episodes to grade C esophagitis.[41] Routine esophageal biopsies for EoE are not recommended in the absence of dysphagia, chest pain with eating, or suggestive endoscopic features.[4]

Esophageal manometry is used to locate the lower esophageal sphincter and rule out major motor disorders like achalasia, EGJOO, DES, and hypercontractile esophagus per Chicago Classification version 4.0.[3] IEM is not exclusionary. Ambulatory reflux monitoring is essential. Wireless 96-hour pH monitoring off PPIs is preferred to assess AET variability and exclude GERD. Two expert consensus statements define GERD as AET >6% on ≥2 days and exclude GERD if AET <4% on all days with negative symptom association.[2,42] If unavailable, 24-hour pH-

impedance off therapy provides similar diagnostic accuracy and enhances reflux-symptom correlation.[43] Normative pH-impedance values vary: AET <4% and <40 reflux episodes rule out GERD, whereas AET >6% and >80 episodes suggest GERD.[2,44] Mean nocturnal baseline impedance (MNBI) <1500 Ω supports GERD, whereas MNBI >2500 Ω supports functional heartburn.[2,44]

Refractory GERD is defined by AET >4% and >80 reflux episodes on pH-impedance monitoring on double dose PPI, supported by outcomes in surgical and endoscopic therapies.[45] Functional heartburn on double dose PPI is defined by AET <1%, <40 reflux episodes, and MNBI >2500 Ω.[2,45] Overlap between GERD and E-DGBI has been recognized. Patients with overlap phenotypes share clinical, psychological, and functional features with patients with conventional DGBI, suggesting shared mechanisms and implications for therapy.[33–35]

Justification for Criteria Change

The Rome V criteria for functional heartburn build on Rome IV, incorporating updated physiologic thresholds from Lyon Consensus 2.0 and Chicago Classification version 4.0.[1–3] Diagnosis requires retrosternal burning symptoms at least once weekly for ≥3 months, with symptom onset ≥6 months prior, persisting despite 8 weeks of optimized PPI or PCAB therapy.

Lyon 2.0 defines conclusive GERD based on LA grade B/C/D esophagitis, biopsy-proven Barrett's esophagus, peptic strictures, or AET >6%. LA grade B is now also considered conclusive based on evidence of pathologic reflux metrics on reflux monitoring in most patients in this category.[2,41] A normal endoscopy does not exclude GERD, but when combined with AET <4% and <40 reflux episodes on pH-impedance monitoring off PPI, it supports a non-GERD diagnosis.[44]

A2. Rome V Diagnostic Criteria[a] for Functional Heartburn

Must include *all* of the following:

1. Burning retrosternal discomfort
2. No symptom relief despite optimized antisecretory therapy for at least 8 weeks
3. Absence of evidence that GERD[b] or nonreflux esophagitis are the cause of symptoms[b]
4. Absence of disorders of EGJ obstruction and/or disorders of esophageal peristalsis[c]

[a]Criteria fulfilled for the past 3 months, with symptom onset at least 6 months before diagnosis with a frequency of at least once a week despite optimized antisecretory therapy for at least 8 weeks.
[b]Abnormal endoscopy (≥LA B esophagitis) or reflux burden based on reflux testing guided by Lyon 2.0 criteria (normal MNBI is supportive of functional heartburn).
[c]Disorders of EGJ function (achalasia, conclusive EGJ outflow obstruction) and/or disorders of peristalsis (absent contractility, hypercontractile esophagus, and distal esophageal spasm) except IEM, guided by Chicago Classification version 4.0.

AET values between 4% and 6% are classified as inconclusive. In such cases, low mean nocturnal baseline impedance (MNBI <1500 Ω) may support GERD, whereas MNBI >2500 Ω can reasonably exclude it.[2,44,46] Reflux-symptom association analysis remains important for differentiating reflux hypersensitivity from functional heartburn but is limited by patient reporting accuracy.[2] A poor PPI response carries high negative predictive value for GERD and supports an E-DGBI diagnosis.[47]

Routine esophageal biopsies to exclude EoE are not mandatory unless dysphagia, chest pain with eating, or endoscopic signs are present, based on recent findings.[4]

Psychophysiological Mechanisms

The pathogenesis of functional heartburn involves complex interactions between altered peripheral sensitivity and central processing of esophageal stimuli. Although reflux is excluded as a symptom trigger, increased mucosal permeability may still allow noxious luminal substances to activate deeper chemoreceptors and inflammatory pathways without a temporally linked reflux event.[1] Although superficial mucosal innervation has been implicated in NERD,[8] patients with functional heartburn show mucosal biopsies and esophageal innervation similar to healthy controls, suggesting different underlying mechanisms.[7] Visceral hypersensitivity, stress and emotion-induced amplification of esophageal signals, and altered brain–gut interactions resulting in abnormal central processing of esophageal signals are likely contributors. Psychological comorbidities including anxiety, depression, symptom-specific anxiety, and esophageal hypervigilance are more prevalent in functional heartburn and correlate with symptom severity.[35,48] Stress and poor sleep further exacerbate symptom perception by enhancing pain sensitivity and altering esophageal responsiveness.[49] Hypervigilance, in particular, has been shown to predict symptom severity independent of anxiety, reinforcing its central role in symptom generation.[13] In addition, patients with functional heartburn report greater somatization, lower social support, and impaired quality of life compared with those with GERD,[48] further highlighting the influence of psychophysiological factors.

Treatment

Treatment for functional heartburn remains empirical and should be tailored to underlying pathophysiology, potential medication mechanisms, and psychosocial contributors. Clinicians should provide reassurance, discourage repeated invasive testing, and watch for excessive or disproportionate food avoidance. Antireflux surgery should be avoided. Given the proposed role of peripheral and central sensitization, neuromodulators such as low-dose TCAs, SSRIs, and others used in functional chest pain are considered appropriate (Table 2). A sham-controlled trial did not demonstrate any benefit of esophageal endoscopic radiofrequency energy delivery in patients with refractory heartburn, including those with functional heartburn,

although the number of participants was small and duration of follow-up was short (24 weeks).[50]

Psychogastroenterological interventions have shown growing value. GI-CBT has been effective in reducing symptoms, visceral anxiety, and improving quality of life, and is appropriate in cases with esophageal hypervigilance, symptom-specific anxiety, or maladaptive beliefs.[27] A study found esophageal disorders had greater symptom response to multimodal therapy involving psychogastroenterology compared with conventional treatment.[26] Biofeedback techniques, including diaphragmatic breathing focused on heart rate variability, have reduced symptoms in GERD and are considered safe for functional heartburn.[26,27] Although studies specific to functional heartburn are limited, behavioral interventions—such as cognitive behavioral therapy (CBT), hypnotherapy, diaphragmatic breathing, and relaxation therapy—are low-risk options and can aid with both symptom management and PPI withdrawal in this population.

A3. Reflux Hypersensitivity

Definition

Reflux hypersensitivity is defined by the presence of heartburn or chest pain in patients with normal endoscopy and physiologic acid exposure, but with a positive reflux-symptom association on reflux monitoring. The diagnosis excludes regurgitation and belching, which are typically related to mechanical (eg, hiatal hernia, hypotensive lower esophageal sphincter) or behavioral causes like supragastric belching and rumination.[51] Although some patients may respond to antireflux therapy, the pathogenesis aligns more closely with esophageal hypersensitivity. Overlap with GERD can occur when physiologic reflux elicits symptoms on PPI therapy, supported by reflux-symptom correlation (Figure 1). Patients with proven GERD off PPIs may still experience persistent symptoms due to overlapping E-DGBI, including reflux hypersensitivity. Data suggest reflux hypersensitivity is less common than functional heartburn in this overlap context, affecting 25% to 37% of patients.[34,35] The presence of GERD off PPI does not exclude reflux hypersensitivity on therapy. However, its overall prevalence in this setting appears to be low.

Epidemiology

The precise epidemiology of reflux hypersensitivity remains unclear. In a global Rome Foundation survey, prevalence was reported as 0.8% (internet based) and 0.6% (household based).[14] Among patients without esophagitis, 37% to 60% have normal pH monitoring off therapy.[52] One study of 329 patients found 36% had reflux hypersensitivity, 40% had NERD, and 24% had functional heartburn,[53] whereas a larger study of 573 patients reported a 42% prevalence of reflux hypersensitivity in those with refractory symptoms.[54] In contrast, the Spechler et al[36] trial found only 10% of such patients met criteria, suggesting an overall prevalence range of 10% to 42% in the refractory population.

Clinical Evaluation

The diagnosis of reflux hypersensitivity relies on detecting a positive reflux-symptom association despite physiologic acid exposure, whether tested on or off PPI therapy (Figure 1).[51] Consensus guidelines indicate physiologic reflux when AET $<4\%$ on all days of a prolonged wireless pH study, or AET $<4\%$ with <40 reflux episodes and MNBI $>2500\ \Omega$ on pH-impedance monitoring.[2] The key distinction from functional heartburn is the presence of a positive symptom association with reflux events using symptom index $\geq 50\%$ and/or symptom association probability $\geq 95\%$.[2] If belching and/or regurgitation are the only symptoms associated with reflux events, alternative diagnosis such as rumination or supragastric belching should be considered.[51] As with functional heartburn, the workup includes endoscopy, reflux monitoring, and exclusion of esophageal motility disorders using HRM.

Justification for Change in Criteria

The diagnostic criteria for reflux hypersensitivity remain largely consistent with Rome IV but now incorporate Lyon Consensus 2.0 to exclude GERD[2] and CCv4.0 to exclude esophageal motility disorders, with IEM not considered exclusionary.[3] Diagnosis requires bothersome heartburn or chest pain occurring at least once weekly for ≥ 3 months, with symptom onset ≥ 6 months prior, despite 8 weeks of optimized PPI or PCAB therapy. The definition now clearly excludes regurgitation, belching, rumination, supragastric belching, and abelchia as qualifying symptoms or diagnoses.[51] Normative reflux monitoring thresholds—both off and on PPIs—follow updated Lyon 2.0 criteria and recent population-based data.[2,44]

Psychophysiological Mechanisms

Reflux hypersensitivity shares similar pathophysiologic mechanisms with functional heartburn and functional chest

A3. Rome V Diagnostic Criteria[a] for Reflux Hypersensitivity

Must include *all* of the following:

1. Retrosternal burning and/or chest pain
2. Regurgitation and belching are not considered in this definition if they occur by themselves or together
3. Evidence of triggering of symptoms by reflux events
4. Absence of evidence that GERD[b] or nonreflux esophagitis are the cause of the symptoms
5. Absence of disorders of EGJ obstruction and/or disorders of esophageal peristalsis[c]

[a]Criteria fulfilled for the past 3 months, with symptom onset at least 6 months before diagnosis with a frequency of at least once a week despite optimized antisecretory therapy for at least 8 weeks.
[b]Abnormal acid exposure based on technology and approach, and/or LA grades B or higher esophagitis.
[c]Disorders of EGJ function (achalasia, conclusive EGJOO) and/or disorders of peristalsis (absent contractility, hypercontractile esophagus, and distal esophageal spasm) except IEM, guided by Chicago Classification version 4.0.

pain, including peripheral and central sensitization, altered visceral signal processing, autonomic dysregulation, and psychological comorbidities. The key distinction is that symptoms in reflux hypersensitivity are triggered by reflux events detectable on monitoring. Impaired mucosal integrity may contribute to symptom generation, as shown by lower MNBI in reflux hypersensitivity compared with functional heartburn,[55] although MNBI thresholds are not yet diagnostic. Upregulation of acid-sensitive receptors such as TRPV1 and increased expression of neurogenic inflammation markers like substance P and NK1R further support a sensitization model.[56] Anxiety, depression, and hypervigilance are common and contribute to altered perception, stress-induced autonomic changes, and mucosal barrier dysfunction.[13] These features reinforce that reflux hypersensitivity, like other E-DGBIs, results from a complex interaction between physiological triggers and brain–gut axis dysregulation.

Treatment

Management of reflux hypersensitivity parallels that of functional heartburn, starting with reassurance and education that no serious underlying disease is present. Although empirical, response to antisecretory therapy may be better than in other functional esophageal disorders. Patients with an acid-sensitive esophagus may improve with standard or high-dose PPIs[57] or potentially PCABs, but those with weakly acid or nonacid reflux triggers often remain refractory.[58] Limited data suggest that antireflux surgery may help select patients, particularly with concurrent hiatal hernia.[59,60] In contrast, a sham-controlled trial of endoscopic radiofrequency therapy showed no benefit.[50] In a randomized trial, Spechler et al[36] found antireflux surgery superior to medical therapy (PPI, baclofen, desipramine) in patients with refractory heartburn, including those with reflux hypersensitivity, although response did not differ by acid burden. Pain modulators such as TCAs, SSRIs, serotonin norepinephrine reuptake inhibitors, and gabapentenoids remain the cornerstone of treatment, although direct evidence is limited (Table 2). A placebo-controlled trial showed citalopram reduced symptoms in patients with reflux hypersensitivity (38.5% symptomatic vs 66.7% on placebo; $P = .021$).[61] Psychological therapies—including gut-directed CBT, hypnosis, and biofeedback—also may be beneficial and should be integrated into management when appropriate.

A4. Globus

Definition

Globus sensation is a persistent or intermittent nonpainful sensation of a lump or foreign body in the throat.[1] The symptom is commonly episodic, located in the midline between the thyroid cartilage and sternal notch, unassociated with dysphagia or odynophagia and frequently improves with eating and swallowing. The diagnosis of globus requires the absence of structural lesions, mucosal abnormalities like a gastric inlet patch, GERD, or major motor disorders.

Epidemiology

Globus is a common symptom, with up to 46% of otherwise healthy individuals reporting the sensation at some point, typically peaking in middle age and occurring equally in both sexes, although women seek care more frequently.[62] A survey in China reported a lifetime prevalence of 21.5%, with peak onset between ages 35 and 54 and similar gender distribution.[63] Using Rome IV criteria, a population-based study across the United States, United Kingdom, and Canada found an 8.1% prevalence.[64] Global data from the Rome Foundation showed that 7.5% of more than 54,000 participants reported a sensation of something sticking in the throat more than twice weekly, with the highest rate in China (18.9%).[65] The prevalence of feeling a lump between meals was 7.0%, and among those, 9.9% also reported dysphagia. The overall prevalence of globus sensation was 0.8%.[14] Globus accounts for about 4% of new ear, nose, and throat referrals, and although benign, it is often chronic, persisting in 75% of patients at 3 years and in 50% at 7 years.[1,62]

Clinical Evaluation

The diagnosis is primarily made by eliciting a compatible clinical history and ruling out an identifiable cause, such as a structural lesion, GERD, or a major motor disorder. As with other E-DGBI, there must be no dysphagia and

A4. Diagnostic Criteria[a] for Globus

Must include *all* of the following:

1. Persistent or intermittent, nonpainful, sensation of a lump or foreign body in the throat with no structural lesion identified on physical examination and laryngoscopy
   a. Occurrence of the sensation between meals
   b. Absence of dysphagia or odynophagia
   c. Absence of a gastric inlet patch in the proximal esophagus[b]
2. Absence of evidence that GERD[c] or nonreflux esophagitis are the cause of the symptom
3. Absence of disorders of EGJ obstruction and/or disorders of esophageal peristalsis[d]

[a]Criteria fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis with a frequency of at least once a week following optimized antisecretory therapy for at least 8 weeks.
[b]Because DGBI requires lack of a mucosal abnormality, gastric inlet patch precludes a diagnosis of DGBI.
[c]Abnormal endoscopy (≥LA B esophagitis) or reflux burden based on reflux testing guided by Lyon 2.0 criteria.
[d]Disorders of EGJ function (achalasia, conclusive EGJOO) and/or disorders of peristalsis (absent contractility, hypercontractile esophagus, and distal esophageal spasm) except IEM, guided by Chicago Classification version 4.0.

no alarm features (eg, odynophagia, weight loss). Physical examination of the neck followed by examination of the pharynx via laryngoscopy are advised as initial evaluation. Once localized structural or inflammatory causes are excluded, the workup may proceed with an empiric trial of antisecretory therapy (PPI or PCAB) for 4 to 8 weeks. If the patient responds, the management shifts to GERD. If the patient does not respond, endoscopy to assess for a gastric inlet patch or other esophageal mucosal processes can be considered to identify an alternative cause. HRM may be helpful to rule out a major motor disorder; however, there are limited data to support a distinct motor pattern associated with globus. Patients not responding to PPI and without an identifiable cause in the oropharynx, larynx, and esophagus are diagnosed with globus.

Justification for Criteria Change

The Rome V criteria for globus remain largely unchanged from Rome IV, requiring no identifiable structural, motor, or mucosal cause for the sensation.[1] Although limited data suggest that ablation of a gastric inlet patch may improve globus symptoms,[66] the presence of an inlet patch precludes an E-DGBI diagnosis, although this recommendation is based on low-quality evidence. Chronicity is defined as bothersome symptoms occurring at least once weekly for $\geq$3 months, with onset $\geq$6 months prior, despite 8 weeks of optimized PPI or PCAB therapy. GERD must be excluded per Lyon Consensus 2.0,[2] and major motility disorders ruled out using Chicago Classification version 4.0.[3]

Psychophysiologic Mechanisms

The pathogenesis of globus involves both potential peripheral triggers and central perceptual responses, resembling mechanisms seen in other E-DGBI. Globus may arise in the presence of identifiable abnormalities—such as GERD, esophageal motor disorders, or gastric inlet patches—but in idiopathic cases, neither a clear stimulus nor a mechanistic pathway is evident.[62] Visceral hypersensitivity is considered a key mechanism, particularly in idiopathic globus, in which altered peripheral sensitivity or central processing amplifies normal sensory input.[62] UES pressure abnormalities have been inconsistently reported. Although some patients with globus show elevated UES tone or exaggerated respiratory variation, these findings are not universally observed and can be influenced by emotional stress.[67] Esophageal distention and impaired bolus transit may trigger reflex UES contraction via vagal pathways, and some studies suggest achalasia and other major motility disorders may rarely present as globus,[68] although borderline motility issues like IEM are unlikely to explain symptoms.

Balloon distention studies show that patients with globus often experience symptoms at lower thresholds than controls, despite similar motor responses, suggesting an esophageal hypersensitivity mechanism.[69] This may involve peripheral triggers with central viscerosomatic referral to the neck. Psychological factors are often implicated, with some studies reporting higher levels of anxiety and depression in patients with globus, although others show no significant psychiatric differences from controls.[1,62] Although baseline psychopathology is not required for diagnosis, emotional stress and recent life events appear to play a modulatory role, with up to 96% of patients reporting symptom worsening during strong emotional experiences.[70] Ultimately, globus likely reflects a multifactorial interplay among sensory dysfunction, altered brain–gut communication, and psychosocial stress, underscoring the importance of a holistic diagnostic and therapeutic approach.

Treatment

Treatment of globus should follow a systematic approach, beginning with ruling out structural lesions and assessing for GERD, as some patients may respond to an 8-week empiric PPI trial, particularly when typical reflux symptoms coexist, although response rates are modest and PPI therapy should be discontinued if ineffective.[71] PCABs have not been studied in this context, and data do not support antireflux surgery for globus alone. In a trial of patients with proven GERD and atypical symptoms (including globus), both Nissen and Toupet fundoplication reduced reflux-symptom index scores, but more than half of the cohort also had typical GERD symptoms and there was no control group, limiting interpretation.[72] Gastric inlet patch ablation (eg, with argon plasma coagulation or radiofrequency) has shown symptomatic benefit in small studies, but supporting evidence remains low-quality and not definitive.[66] Once GERD and other structural or motor abnormalities are excluded, the primary treatment centers on explanation, reassurance, and psychobehavioral approaches. CBT-based psychoeducation, speech therapy with pharyngolaryngeal relaxation exercises, and hypnosis have shown symptom improvement in small studies.[73] Neuromodulators such as amitriptyline, paroxetine, and flupenthixol/melitracen combinations have demonstrated greater efficacy than PPIs in randomized controlled trials (Table 2),[62] supporting their use in selected patients. Given the benign course of idiopathic globus, behavioral interventions—with their low side-effect profile—should be prioritized over medications or invasive procedures.

A5. Functional Dysphagia

Definition

Functional dysphagia is characterized by the sensation of food sticking or abnormal bolus transit through the esophagus in the absence of structural, mucosal, or major motor abnormalities that could explain the symptom. With Chicago Classification version 4.0, the diagnostic framework has evolved to emphasize exclusion of EGJ outflow obstruction and major disorders of peristalsis using HRM.[3] However, HRM has limitations, particularly in detecting subtle or borderline mechanical resistance or contractile abnormalities. This can be addressed with the use of the functional lumen imaging probe (FLIP), which can identify

mechanical or functional outflow resistance not seen on manometry alone.[74] FLIP findings have shown that a subset of patients previously classified as having functional dysphagia under Rome IV actually had EGJ abnormalities or borderline achalasia-like patterns that would have been missed without this additional evaluation.[75] Therefore, establishing a diagnosis of functional dysphagia now requires a comprehensive assessment that includes not only structural and mucosal evaluation, but also motor testing with HRM complemented by FLIP or timed barium esophagogram, to ensure more accurate phenotyping and avoid misclassification.

Epidemiology

The true prevalence of functional dysphagia remains uncertain. Early surveys estimated that 7% to 8% of dysphagia was unexplained by structural or motor causes.[76] A global Rome IV–based survey of nearly 55,000 individuals reported a 3.2% prevalence of functional dysphagia, slightly higher in female (3.5%) than male individuals (2.9%).[14] However, many of these cases likely included oropharyngeal or structural causes not systematically excluded. In a large tertiary referral series, only 2.4% of 694 patients had persistent dysphagia despite negative testing, although FLIP was not used in that cohort.[77] Because FLIP can identify subtle EGJ or contractile abnormalities missed by standard testing,[74] the true prevalence of functional dysphagia is likely even lower, making it the least common E-DGBI.

Clinical Evaluation

A thorough clinical history is essential to exclude oropharyngeal dysphagia and evaluate for symptom mimics such as globus, xerostomia, or odynophagia. Opioid use has emerged as a significant factor contributing to esophageal dysmotility, including esophageal outflow obstruction and heightened symptom reporting, and should be routinely queried during clinical evaluation.[78] GERD and EoE are key exclusions, and are typically ruled out via a combination of antisecretory therapy and upper endoscopy with biopsy.[4] Barium studies, particularly with solid boluses (tablet, cookie, marshmallow), are useful to detect subtle strictures or obstructive lesions, including paraesophageal hernias, that may be missed on endoscopy.[79] Videofluoroscopy remains the test of choice when oropharyngeal dysphagia is suspected.

In the absence of structural pathology, HRM is used to exclude esophageal motility disorders using the updated Chicago Classification version 4.0, which has improved specificity by requiring adjunctive evidence for diagnosing EGJ outflow obstruction or peristaltic abnormalities.[3] Provocative maneuvers such as multiple rapid swallows, test meals, and rapid drink challenge can enhance detection of subtle motor dysfunction but are complementary rather than required.[3]

FLIP panometry now plays a key complementary role in dysphagia evaluation. FLIP provides real-time assessment of EGJ opening, esophageal wall distensibility, secondary peristalsis, and contractile responses to distension. In one study of 164 symptomatic patients with normal HRM, FLIP identified previously undetected EGJ obstruction or abnormal esophageal contractility in nearly one-third.[80] This highlights its ability to uncover subtle physiological abnormalities that traditional manometry may miss. Importantly, the Dallas Classification recommends that in patients with negative endoscopy and normal FLIP metrics, a diagnosis of functional dysphagia is likely and can be made earlier in the workup.[74] As FLIP becomes integrated earlier in the diagnostic pathway, it is anticipated that the prevalence of truly idiopathic functional dysphagia will continue to decline.

Justification for Criteria Change

The updated diagnostic criteria for functional dysphagia reflect improved understanding that organic causes of dysphagia (structural, mucosal, or motor) inherently result in abnormal bolus transit. Advances in diagnostic frameworks for GERD and esophageal motility, including the Lyon Consensus 2.0 and Chicago Classification version 4.0, have increased specificity in identifying these disorders.[2,3] To establish chronicity, criteria must be met for at least 3 months, with symptom onset at least 6 months before diagnosis. Dysphagia from GERD, EoE, and other mucosal diseases (eg, lichen planus, pemphigus, pemphigoid, lymphocytic esophagitis) can occur even in the absence of visible endoscopic findings, making esophageal biopsies essential.[81] These biopsies may miss EoE if performed while on PPI therapy or in fibro-stenotic EoE phenotypes. Moreover, deeper muscular inflammation can contribute to symptoms, often in association with spastic motor patterns or EGJ outflow obstruction.[82]

Reflux monitoring off PPI therapy may be needed to rule out GERD, which can occasionally present solely with

A5. Rome V Diagnostic Criteria[a] for Functional Dysphagia

Must include *all* of the following:

1. Sense of solid and/or liquid foods sticking to, lodging in, or passing abnormally through the esophagus
2. Absence of evidence that esophageal mucosal or structural abnormality is the cause of the symptom[b]
3. Absence of evidence that gastroesophageal reflux[c] or nonreflux esophagitis are the cause of the symptoms
4. Absence of disorders of EGJ obstruction and/or disorders of esophageal peristalsis[d]

[a]Criteria fulfilled for the past 3 months, with symptom onset at least 6 months before diagnosis with a frequency of at least once a week.
[b]Normal esophagram with a tablet/marshmallow, or normal FLIP may be supportive of functional dysphagia.
[c]Abnormal endoscopy (≥LA B esophagitis) or reflux burden based on reflux testing guided by Lyon 2.0 criteria.
[d]Disorders of EGJ function (achalasia, conclusive EGJOO), and/or disorders of peristalsis (absent contractility, hypercontractile esophagus, distal esophageal spasm) except IEM, guided by Chicago Classification version 4.0 (normal solid test meal during HRM may be supportive of functional dysphagia).

dysphagia or cause subtle strictures. Barium studies, including upright timed esophagograms and solid bolus testing, help identify subtle strictures and EGJ obstruction.[79] FLIP has improved diagnostic accuracy by detecting abnormal EGJ opening in patients with otherwise normal testing. In one study, 17 of 34 symptomatic patients with normal HRM had abnormal FLIP responses,[83] and another showed that up to 32% of 164 patients with normal HRM had abnormal FLIP patterns.[80] Despite its utility, FLIP is not a mandatory component for diagnosis as it is not available everywhere.

Mild bolus stasis and ineffective swallows occur even in asymptomatic individuals, complicating the definition of physiologic vs pathologic transit.[84] CCv4.0 has improved classification of EGJ obstruction, distinguishing clinically meaningful patterns using adjunctive measures like test meals and intrabolus pressure, as well as supportive tests like FLIP and barium studies.[3] Although disorders like achalasia exclude functional dysphagia, IEM, despite more stringent CCv4.0 criteria, is not consistently associated with symptom generation or bolus stasis and does not exclude functional dysphagia.[85] Thus, a diagnosis of functional dysphagia can be made only after comprehensive exclusion of mucosal, structural, and major motor abnormalities, using HRM, endoscopy with biopsy, barium studies, and potentially FLIP.

Psychophysiologic Mechanisms

Bolus transit is influenced by consistency and posture, and even in healthy individuals, dry solid boluses may require multiple swallows for clearance.[84] In patients without organic disease, heightened esophageal perception may increase the likelihood of reporting dysphagia with minimal esophageal stasis, whereas true mechanical or motor abnormalities more consistently correlate with abnormal transit.[86] Major motor disorders such as hypercontractility, absent contractility, or premature contractions are strongly associated with impaired bolus transit, whereas minor disorders like IEM or even normal motility may be seen in patients with significant dysphagia symptoms and normal objective findings. For example, upright high-resolution impedance manometry with 200 mL water in symptomatic patients showed that dysphagia was reported in 23% to 25% of those with normal motility or IEM, despite no evidence of stasis or pressurization,[87] underscoring the role of heightened sensory perception.

Esophageal hypersensitivity plays a key role in functional dysphagia. Balloon distension and esophageal acidification can provoke sensations of food sticking and induce peristaltic responses, now quantifiable via FLIP panometry.[80] A normal FLIP—defined by adequate EGJ opening, distensibility, and peristaltic response—effectively rules out mechanical causes and supports a perceptual origin for symptoms.[74] Sensory nerve endings in both the mucosa and deeper muscle layers detect mechanical and tension-related stimuli,[88,89] with heightened sensitivity in the proximal esophagus.[90] Recent findings show superficially located nociceptive fibers in patients with reflux hypersensitivity and dysphagia phenotypes, suggesting a potential mechanistic overlap with other DGBI.[8,91]

Mittal and colleagues[92] have shown that in a subset of patients with functional dysphagia, esophageal distensibility is impaired despite normal bolus transit metrics. Nadir impedance values during provocative swallows correlate with narrow luminal areas, indicating less esophageal stretch may underlie perceived bolus arrest.[92] These findings, along with earlier observations linking decreased distention with symptom perception, especially in patients with esophageal hypersensitivity,[93] highlight an esophageal phenotype characterized by perceptual rather than structural abnormalities.

Psychological factors further modulate symptom experience. Hypervigilance, anxiety, and fear of swallowing or choking are common in functional dysphagia and contribute to symptom severity, regardless of whether organic abnormalities are present.[94] In addition, patients with functional dysphagia demonstrate higher rates of depression and somatization, and there is an association with emotional distress and anxiety. Acute stress can transiently disrupt esophageal motility,[95] and dysregulated brain–gut signaling has been implicated in symptom perception and chronicity in DGBI.[96] The dynamic interplay between impaired sensory processing, abnormal distension, and psychological comorbidities is central to understanding and managing functional dysphagia.

Treatment

Functional dysphagia often follows a benign, self-limited course, with reassurance and simple strategies—such as upright eating, thorough chewing, and liquid chasers—sufficing in mild cases.[97] A short course of acid suppression may be helpful, particularly if reflux is suspected. Although not definitively proven, TCAs and other neuromodulators may relieve symptoms in selected patients (Table 2). Empiric bougie dilation to 50 to 54 Fr has shown benefit in 68% to 85% of patients with unexplained food dysphagia, likely addressing subtle proximal esophageal abnormalities missed on routine testing,[98,99] unlike balloon dilation at the EGJ, which has shown limited utility.[100] However, with the integration of FLIP panometry, dilation can now be more precisely targeted to areas of subtle obstruction or wall stiffness—such as reduced EGJ distensibility or abnormal esophageal compliance—enhancing both diagnostic accuracy in ruling out functional dysphagia and therapeutic outcomes. In patients with maladaptive beliefs, symptom-specific anxiety or other psychological comorbidities, GI-CBT techniques—such as psychoeducation, diaphragmatic breathing, and fear-exposure—may be effective,[26] and gut-directed hypnotherapy may offer additional benefit by reducing visceral hypersensitivity and hypervigilance.

Recommendations for Future Research

Despite their high prevalence and increasing recognition, E-DGBI remain understudied, largely because of the lack of standardized algorithms for symptom assessment and esophageal physiologic testing. This has limited the

development of evidence-based management approaches. Several key areas for future research include the following:

1. **Validation of Diagnostic Criteria:** Prospective studies are needed to validate Rome V diagnostic criteria for E-DGBI. Improved symptom-based criteria with greater sensitivity and specificity are essential, especially in distinguishing between perceptive and obstructive dysphagia.
2. **Mechanistic Insights:** The underlying mechanisms of symptom generation remain incompletely understood. Advances in physiologic assessment tools—such as HRM, FLIP, mucosal integrity testing, high-frequency ultrasound, and central nervous system imaging—should be leveraged. Notably, FLIP studies and distention plots using high-resolution impedance manometry have revealed impaired esophageal wall distensibility and reduced cross-sectional area in a subset of patients with functional dysphagia, even when other modalities are normal, suggesting a role for wall stiffness in symptom generation.[92]
3. **New Motility Patterns:** Standard diagnostic schemas like the Chicago Classification do not account for all symptomatic motor abnormalities. For example, repetitive simultaneous contractions observed during FLIP, HRM, or solid bolus swallows may represent clinically relevant, yet currently unclassified, esophageal motor dysfunction.[80] Future iterations of motility classifications should incorporate such findings to better characterize patients who fall outside conventional categories.
4. **Therapeutic Trials:** Randomized controlled trials targeting E-DGBI subtypes are lacking. Controlled studies are necessary to assess pharmacologic, endoscopic, surgical, and behavioral interventions, including neuromodulators, behavioral therapy (eg, GI-CBT), and hypnotherapy.
5. **Patient-Centered Outcomes:** In addition to symptom reduction, treatment studies should assess health-related quality of life, functional capacity, and health care utilization to determine meaningful clinical benefit.
6. **Abelchia and Other Emerging Syndromes:** Abelchia, characterized by absent esophageal bolus transit without anatomic or major motor findings, has been recognized in small case series but remains poorly defined. Studies will be needed in abelchia as well as other emerging syndromes to establish their prevalence, pathophysiology, and relationship to E-DGBI.

References

1. Aziz Q, Fass R, Gyawali CP, et al. Functional esophageal disorders. Gastroenterology 2016;150:1368–1379.
2. Gyawali CP, Yadlapati R, Fass R, et al. Updates to the modern diagnosis of GERD: Lyon consensus 2.0. Gut 2024;73:361–371.
3. Yadlapati R, Kahrilas PJ, Fox MR, et al. Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0((c)). Neurogastroenterol Motil 2021;33:e14058.
4. Oude Nijhuis RAB, Curvers WL, van der Ende M, et al. Utility of routine esophageal biopsies in patients with refractory reflux symptoms. Am J Gastroenterol 2021; 116:816–820.
5. Knowles CH, Aziz Q. Basic and clinical aspects of gastrointestinal pain. Pain 2009;141:191–209.
6. Ustaoglu A, Nguyen A, Spechler S, et al. Mucosal pathogenesis in gastro-esophageal reflux disease. Neurogastroenterol Motil 2020;32:e14022.
7. Nikaki K, Woodland P, Lee C, et al. Esophageal mucosal innervation in functional heartburn: closer to healthy asymptomatic subjects than to non-erosive reflux disease patients. Neurogastroenterol Motil 2019;31:e13667.
8. Woodland P, Shen Ooi JL, Grassi F, et al. Superficial esophageal mucosal afferent nerves may contribute to reflux hypersensitivity in nonerosive reflux disease. Gastroenterology 2017;153:1230–1239.
9. Richter JE, Barish CF, Castell DO. Abnormal sensory perception in patients with esophageal chest pain. Gastroenterology 1986;91:845–852.
10. Nasr I, Attaluri A, Hashmi S, et al. Investigation of esophageal sensation and biomechanical properties in functional chest pain. Neurogastroenterol Motil 2010; 22:520–526, e116.
11. Yang M, Li ZS, Chen DF, et al. Quantitative assessment and characterization of visceral hyperalgesia evoked by esophageal balloon distention and acid perfusion in patients with functional heartburn, nonerosive reflux disease, and erosive esophagitis. Clin J Pain 2010; 26:326–331.
12. Shapiro M, Green C, Bautista JM, et al. Functional heartburn patients demonstrate traits of functional bowel disorder but lack a uniform increase of chemoreceptor sensitivity to acid. Am J Gastroenterol 2006; 101:1084–1091.
13. Guadagnoli L, Yadlapati R, Taft T, et al. Esophageal hypervigilance is prevalent across gastroesophageal reflux disease presentations. Neurogastroenterol Motil 2021;33:e14081.
14. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation Global Study. Gastroenterology 2021;160:99–114.e3.
15. Fass R, Dickman R. Non-cardiac chest pain: an update. Neurogastroenterol Motil 2006;18:408–417.
16. Fass R, Fennerty MB, Ofman JJ, et al. The clinical and economic value of a short course of omeprazole in patients with noncardiac chest pain. Gastroenterology 1998;115:42–49.
17. Achem SR, Almansa C, Krishna M, et al. Oesophageal eosinophilic infiltration in patients with noncardiac chest pain. Aliment Pharmacol Ther 2011; 33:1194–1201.
18. Fass R, Tougas G. Functional heartburn: the stimulus, the pain, and the brain. Gut 2002;51:885–892.

19. Sarkar S, Aziz Q, Woolf CJ, et al. Contribution of central sensitisation to the development of non-cardiac chest pain. Lancet 2000;356:1154–1159.
20. Jiang Y, Mittal RK. Low esophageal mucosal blood flow in patients with nutcracker esophagus. Am J Physiol Gastrointest Liver Physiol 2016; 310:G410–G416.
21. Oude Nijhuis RAB, Snelleman JA, Oors JM, et al. The inability to belch syndrome: a study using concurrent high-resolution manometry and impedance monitoring. Neurogastroenterol Motil 2022;34:e14250.
22. Clouse RE, Carney RM. The psychological profile of non-cardiac chest pain patients. Eur J Gastroenterol Hepatol 1995;7:1160–1165.
23. Beitman BD, Kushner MG, Basha I, et al. Follow-up status of patients with angiographically normal coronary arteries and panic disorder. JAMA 1991; 265:1545–1549.
24. Weijenborg PW, de Schepper HS, Smout AJ, et al. Effects of antidepressants in patients with functional esophageal disorders or gastroesophageal reflux disease: a systematic review. Clin Gastroenterol Hepatol 2015;13:251–259.e1.
25. Atluri DK, Chandar AK, Fass R, et al. Systematic review with meta-analysis: selective serotonin reuptake inhibitors for noncardiac chest pain. Aliment Pharmacol Ther 2015;41:167–176.
26. Hurtte E, Rogers BD, Richards C, et al. The clinical value of psycho-gastroenterological interventions for functional esophageal symptoms. Neurogastroenterol Motil 2022;34:e14315.
27. Luo Y, Keefer L. The clinical value of brain-gut behavioral therapies for functional esophageal disorders and symptoms. Neurogastroenterol Motil 2022;34:e14373.
28. Kisely SR, Campbell LA, Yelland MJ, et al. Psychological interventions for symptomatic management of non-specific chest pain in patients with normal coronary anatomy. Cochrane Database Syst Rev 2015; 2015:CD004101.
29. Coss-Adame E, Erdogan A, Rao SS. Treatment of esophageal (noncardiac) chest pain: an expert review. Clin Gastroenterol Hepatol 2014;12:1224–1245.
30. Jones H, Cooper P, Miller V, et al. Treatment of non-cardiac chest pain: a controlled trial of hypnotherapy. Gut 2006;55:1403–1408.
31. Gasiorowska A, Navarro-Rodriguez T, Dickman R, et al. Clinical trial: the effect of Johrei on symptoms of patients with functional chest pain. Aliment Pharmacol Ther 2009;29:126–134.
32. Yadlapati R, Gyawali CP, Masihi M, et al. Optimal wireless reflux monitoring metrics to predict discontinuation of proton pump inhibitor therapy. Am J Gastroenterol 2022;117:1573–1582.
33. Caldart F, Gabriel C, Vauquelin B, et al. Overlap of esophageal disorders of gut-brain interactions and gastroesophageal reflux disease is highly prevalent in patients with refractory reflux symptoms. Am J Gastroenterol 2025;120:1770–1778.
34. Abdallah J, George N, Yamasaki T, et al. Most patients with gastroesophageal reflux disease who failed proton pump inhibitor therapy also have functional esophageal disorders. Clin Gastroenterol Hepatol 2019; 17:1073–1080.e1.
35. Rengarajan A, Pomarat M, Zerbib F, et al. Overlap of functional heartburn and reflux hypersensitivity with proven gastroesophageal reflux disease. Neurogastroenterol Motil 2021;33:e14056.
36. Spechler SJ, Hunter JG, Jones KM, et al. Randomized trial of medical versus surgical treatment for refractory heartburn. N Engl J Med 2019;381:1513–1523.
37. Surdea Blaga T, Dumitrascu D, Galmiche JP, et al. Functional heartburn: clinical characteristics and outcome. Eur J Gastroenterol Hepatol 2013; 25:282–290.
38. Fass R, Sontag SJ, Traxler B, et al. Treatment of patients with persistent heartburn symptoms: a double-blind, randomized trial. Clin Gastroenterol Hepatol 2006;4:50–56.
39. Jung HK, Tae CH, Song KH, et al. 2020 Seoul Consensus on the diagnosis and management of gastroesophageal reflux disease. J Neurogastroenterol Motil 2021;27:453–481.
40. Poh CH, Gasiorowska A, Navarro-Rodriguez T, et al. Upper GI tract findings in patients with heartburn in whom proton pump inhibitor treatment failed versus those not receiving antireflux treatment. Gastrointest Endosc 2010;71:28–34.
41. Visaggi P, Del Corso G, Gyawali CP, et al. Ambulatory pH-Impedance findings confirm that grade B esophagitis provides objective diagnosis of gastroesophageal reflux disease. Am J Gastroenterol 2023;118:794–801.
42. Yadlapati R, Gawron AJ, Gyawali CP, et al. Clinical role of ambulatory reflux monitoring in PPI non-responders: recommendation statements. Aliment Pharmacol Ther 2022;56:1274–1283.
43. Patel A, Sayuk GS, Gyawali CP. Parameters on esophageal pH-impedance monitoring that predict outcomes of patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2015;13:884–891.
44. Sifrim D, Roman S, Savarino E, et al. Normal values and regional differences in oesophageal impedance-pH metrics: a consensus analysis of impedance-pH studies from around the world. Gut 2021;70:1441–1449.
45. Gyawali CP, Tutuian R, Zerbib F, et al. Value of pH impedance monitoring while on twice-daily proton pump inhibitor therapy to identify need for escalation of reflux management. Gastroenterology 2021;161:1412–1422.
46. Frazzoni M, Frazzoni L, Ribolsi M, et al. Applying Lyon Consensus criteria in the work-up of patients with proton pump inhibitory-refractory heartburn. Aliment Pharmacol Ther 2022;55:1423–1430.
47. de Bortoli N, Martinucci I, Savarino E, et al. Proton pump inhibitor responders who are not confirmed as GERD patients with impedance and pH monitoring: who are they? Neurogastroenterol Motil 2014;26:28–35.
48. Guadagnoli L, Geeraerts A, Geysen H, et al. Psychological processes, not physiological parameters, are most important contributors to symptom severity in patients with refractory heartburn/regurgitation symptoms. Gastroenterology 2023;165:848–860.

49. Fass R, Zerbib F, Gyawali CP. AGA clinical practice update on functional heartburn: expert review. Gastroenterology 2020;158:2286–2293.
50. Zerbib F, Sacher-Huvelin S, Coron E, et al. Randomised clinical trial: oesophageal radiofrequency energy delivery versus sham for PPI-refractory heartburn. Aliment Pharmacol Ther 2020;52:637–645.
51. Sawada A, Guzman M, Nikaki K, et al. Identification of different phenotypes of esophageal reflux hypersensitivity and implications for treatment. Clin Gastroenterol Hepatol 2021;19:690–698.e2.
52. Martinez SD, Malagon IB, Garewal HS, et al. Non-erosive reflux disease (NERD)–acid reflux and symptom patterns. Aliment Pharmacol Ther 2003;17:537–545.
53. Savarino E, Zentilin P, Tutuian R, et al. Impedance-pH reflux patterns can differentiate non-erosive reflux disease from functional heartburn patients. J Gastroenterol 2012;47:159–168.
54. Ribolsi M, Cicala M, Zentilin P, et al. Prevalence and clinical characteristics of refractoriness to optimal proton pump inhibitor therapy in non-erosive reflux disease. Aliment Pharmacol Ther 2018;48:1074–1081.
55. de Bortoli N, Martinucci I, Savarino E, et al. Association between baseline impedance values and response proton pump inhibitors in patients with heartburn. Clin Gastroenterol Hepatol 2015;13:1082–1088.e1.
56. Yoshida N, Kuroda M, Suzuki T, et al. Role of nociceptors/neuropeptides in the pathogenesis of visceral hypersensitivity of nonerosive reflux disease. Dig Dis Sci 2013;58:2237–2243.
57. Savarino E, Zentilin P, Savarino V. NERD: an umbrella term including heterogeneous subpopulations. Nat Rev Gastroenterol Hepatol 2013;10:371–380.
58. Weijenborg PW, Cremonini F, Smout AJ, et al. PPI therapy is equally effective in well-defined non-erosive reflux disease and in reflux esophagitis: a meta-analysis. Neurogastroenterol Motil 2012; 24:747; 757, e350.
59. Broeders JA, Bredenoord AJ, Hazebroek EJ, et al. Effects of anti-reflux surgery on weakly acidic reflux and belching. Gut 2011;60:435–441.
60. Patel A, Sayuk GS, Gyawali CP. Prevalence, characteristics, and treatment outcomes of reflux hypersensitivity detected on pH-impedance monitoring. Neurogastroenterol Motil 2016;28:1382–1390.
61. Viazis N, Keyoglou A, Kanellopoulos AK, et al. Selective serotonin reuptake inhibitors for the treatment of hypersensitive esophagus: a randomized, double-blind, placebo-controlled study. Am J Gastroenterol 2012; 107:1662–1667.
62. Zerbib F, Rommel N, Pandolfino J, et al. ESNM/ANMS Review. Diagnosis and management of globus sensation: a clinical challenge. Neurogastroenterol Motil 2020;32:e13850.
63. Tang B, Cai HD, Xie HL, et al. Epidemiology of globus symptoms and associated psychological factors in China. J Dig Dis 2016;17:319–324.
64. Josefsson A, Palsson O, Simren M, et al. Oesophageal symptoms are common and associated with other functional gastrointestinal disorders (FGIDs) in an English-speaking Western population. United European Gastroenterol J 2018;6:1461–1469.
65. Palsson OS, Sperber AD, Bangdiwala S, et al. Prevalence and associated factors of disorders of gut-brain interaction in the United States: comparison of two nationwide internet surveys. Neurogastroenterol Motil 2023;35:e14564.
66. Bajbouj M, Becker V, Eckel F, et al. Argon plasma coagulation of cervical heterotopic gastric mucosa as an alternative treatment for globus sensations. Gastroenterology 2009;137:440–444.
67. Kwiatek MA, Mirza F, Kahrilas PJ, et al. Hyperdynamic upper esophageal sphincter pressure: a manometric observation in patients reporting globus sensation. Am J Gastroenterol 2009;104:289–298.
68. Shaker R, Hogan WJ. Reflex-mediated enhancement of airway protective mechanisms. Am J Med 2000;108-(Suppl 4a):8S–14S.
69. Chen CL, Szczesniak MM, Cook IJ. Evidence for oesophageal visceral hypersensitivity and aberrant symptom referral in patients with globus. Neurogastroenterol Motil 2009;21:1142-e96.
70. Harris MB, Deary IJ, Wilson JA. Life events and difficulties in relation to the onset of globus pharyngis. J Psychosom Res 1996;40:603–615.
71. Timon C, O'Dwyer T, Cagney D, et al. Globus pharyngeus: long-term follow-up and prognostic factors. Ann Otol Rhinol Laryngol 1991;100:351–354.
72. Paranyak M, Patel R. A prospective randomized trial on laparoscopic total vs partial fundoplication in patients with atypical symptoms of gastroesophageal reflux disease. Langenbecks Arch Surg 2023;408:269.
73. Poovipirom N, Ratta-Apha W, Maneerattanaporn M, et al. Treatment outcomes in patients with globus: a randomized control trial of psychoeducation, neuromodulators, and proton pump inhibitors. Neurogastroenterol Motil 2023;35:e14500.
74. Carlson DA, Pandolfino JE, Yadlapati R, et al. A standardized approach to performing and interpreting functional lumen imaging probe panometry for esophageal motility disorders: the Dallas Consensus. Gastroenterology 2025;168:1114–1127.e5.
75. Carlson DA, Baumann AJ, Donnan EN, et al. Evaluating esophageal motility beyond primary peristalsis: assessing esophagogastric junction opening mechanics and secondary peristalsis in patients with normal manometry. Neurogastroenterol Motil 2021;33:e14116.
76. Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Dig Dis Sci 1993;38:1569–1580.
77. Bill J, Rajagopal S, Kushnir V, et al. Diagnostic yield in the evaluation of dysphagia: experience at a single tertiary care center. Dis Esophagus 2018;31(6).
78. Ratuapli SK, Crowell MD, DiBaise JK, et al. Opioid-induced esophageal dysfunction (OIED) in patients on chronic opioids. Am J Gastroenterol 2015;110:979–984.
79. Gyawali CP, Carlson DA, Chen JW, et al. ACG clinical guidelines: clinical use of esophageal physiologic testing. Am J Gastroenterol 2020;115:1412–1428.

80. Carlson DA, Baumann AJ, Prescott JE, et al. Prediction of esophageal retention: a study comparing high-resolution manometry and functional luminal imaging probe panometry. Am J Gastroenterol 2021;116:2032–2041.
81. Aby ES, Eckmann JD, Abimansour J, et al. Esophageal lichen planus: a descriptive multicenter report. J Clin Gastroenterol 2024;58:427–431.
82. Ghisa M, Laserra G, Marabotto E, et al. Achalasia and obstructive motor disorders are not uncommon in patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2021;19:1554–1563.
83. Carlson DA, Gyawali CP, Kahrilas PJ, et al. Esophageal motility classification can be established at the time of endoscopy: a study evaluating real-time functional luminal imaging probe panometry. Gastrointest Endosc 2019;90:915–923.e1.
84. Pouderoux P, Shi G, Tatum RP, et al. Esophageal solid bolus transit: studies using concurrent videofluoroscopy and manometry. Am J Gastroenterol 1999;94:1457–1463.
85. Chugh P, Collazo T, Dworkin B, et al. Ineffective esophageal motility is associated with impaired bolus clearance but does not correlate with severity of dysphagia. Dig Dis Sci 2019;64:811–814.
86. Bogte A, Bredenoord AJ, Oors J, et al. Sensation of stasis is poorly correlated with impaired esophageal bolus transport. Neurogastroenterol Motil 2013;26:538–545.
87. Zerbib F, Luna D, Marin I, et al. The added value of symptom analysis during a rapid drink challenge in high-resolution esophageal manometry. Neurogastroenterol Motil 2021;33:e14008.
88. Berthoud HR, Blackshaw LA, Brookes SJ, et al. Neuroanatomy of extrinsic afferents supplying the gastrointestinal tract. Neurogastroenterol Motil 2004;16(Suppl 1):28–33.
89. Wang YB, de Lartigue G, Page AJ. Dissecting the role of subtypes of gastrointestinal vagal afferents. Front Physiol 2020;11:643.
90. Bredenoord AJ, Weusten BL, Curvers WL, et al. Determinants of perception of heartburn and regurgitation. Gut 2006;55:313–318.
91. Sawada A, Zhang M, Ustaoglu A, et al. Superficial oesophageal mucosal innervation may contribute to severity of symptoms in oesophageal motility disorders. Aliment Pharmacol Ther 2024;59:100–112.
92. Mittal RK, Muta K, Ledgerwood-Lee M, et al. Abnormal esophageal distension profiles in patients with functional dysphagia: a possible mechanism of dysphagia. Gastroenterology 2021;160:1847–1849.e2.
93. Nguyen NQ, Holloway RH, Smout AJ, et al. Automated impedance-manometry analysis detects esophageal motor dysfunction in patients who have non-obstructive dysphagia with normal manometry. Neurogastroenterol Motil 2013;25:238–245, e164.
94. Carlson DA, Gyawali CP, Roman S, et al. Esophageal hypervigilance and visceral anxiety are contributors to symptom severity among patients evaluated with high-resolution esophageal manometry. Am J Gastroenterol 2020;115:367–375.
95. Galmiche JP, Clouse RE, Balint A, et al. Functional esophageal disorders. Gastroenterology 2006;130:1459–1465.
96. Farmer AD, Ruffle JK, Aziz Q. The role of esophageal hypersensitivity in functional esophageal disorders. J Clin Gastroenterol 2017;51:91–99.
97. Smout A, Fox M. Weak and absent peristalsis. Neurogastroenterol Motil 2012;24(Suppl 1):40–47.
98. Colon VJ, Young MA, Ramirez FC. The short- and long-term efficacy of empirical esophageal dilation in patients with nonobstructive dysphagia: a prospective, randomized study. Am J Gastroenterol 2000;95:910–913.
99. Jacob R, Danta M, Feller R, et al. Empiric esophageal dilatation for solid-food dysphagia: presence of mucosal tear on relook endoscopy predicts symptomatic response. Am J Gastroenterol 2023;118:1888–1890.
100. Scolapio JS, Gostout CJ, Schroeder KW, et al. Dysphagia without endoscopically evident disease: to dilate or not? Am J Gastroenterol 2001;96:327–330.

Received December 16, 2025. Accepted February 6, 2026.

Correspondence
Address correspondence to: Sabine Roman, MD, PhD, Digestive Physiology, Hôpital Edouard Herriot, 5, place d'Arsonval, 69437 Lyon cedex 03, France. e-mail: sabine.roman@chu-lyon.fr.

Conflicts of interest
These authors disclose the following: C. Prakash Gyawali is a consultant for Medtronic, Phathom, Braintree, Alimentiv, and Anaptys bio; and a speaker for Carnot. Sabine Roman is a consultant for Dr Falk Pharma, Sanofi, and AstraZeneca, and has received research support from Medtronic. Frank Zerbib is a consultant for Medtronic, Dr Falk Pharma, Coloplast, AstraZeneca, Sanofi, and Bioprojet. Edoardo V. Savarino is a speaker for AbbVie, Aboca, Abivax, Agave, AGPharma, Alfasigma, Apoteca, Biosline, CaDiGroup, Celltrion, Dr Falk, EG Stada Group, Eli Lilly, Fenix Pharma, Galapagos, Giuliani, Johnson&Johnson, JB Pharmaceuticals, Innovamedica/Adacyte, Lionhealth, Malesci, Mayoly Biohealth, Montefarco, Novartis, Omega Pharma, Pfizer, Rafa, Reckitt Benckiser, Recordati, Sandoz, Sanofi/Regeneron, SILA, Takeda, Tillots, and Unifarco; has served as a consultant for AbbVie, Alfasigma, Apogee, AstraZeneca, Biogen, Bristol Myers Squibb, Celltrion, Dr. Falk, Eli Lilly, Fenix Pharma, Ferring, Giuliani, Grunenthal, Johnson&Johnson, JB Pharmaceuticals, Merck & Co, Nestlé, Pfizer, PRO.MED.CS Praha a.s., Reckitt Benckiser, Recordati, Sanofi/Regeneron, SILA, Takeda, and Unifarco; and has received research support from Bonollo, Difass, Pfizer, Reckitt Benckiser, Sanofi/Regeneron, SILA, Unifarco, and Zeta Farmaceutici. Ronnie Fass has served as an advisor/consultant for Medtronic, Phathom Pharmaceuticals, Evoke Pharma, Dexcal, Syneos, GIE Medical, Braintree Labs/Sebela, Daewoong, and Castle Bioscience; as a speaker for Takeda, Eisai Pharmaceuticals, Carnot, Intra-Sana Laboratories, Daewoong, Megalab, Abbott Pharmaceuticals; and received research support from Diversatek. John E. Pandolfino has performed patent, licensing, consulting, and speaking for Medtronic; IP, licensing, and consulting for Laborie; consulting and speaking for Phathom; and consulting for Braintree. The remaining author discloses no conflicts.

Funding
The Rome Foundation provided organizational and editorial support.