

## SECTION II: FGIDs: DIAGNOSTIC GROUPS

### Esophageal Disorders



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**Functional esophageal disorders consist of a disease category that presents with esophageal symptoms (heartburn, chest pain, dysphagia, globus) that are not explained by mechanical obstruction (stricture, tumor, eosinophilic esophagitis), major motor disorders (achalasia, esophagogastric junction outflow obstruction, absent contractility, distal esophageal spasm, jackhammer esophagus), or gastroesophageal reflux disease. Although mechanisms responsible are unclear, it is theorized that visceral hypersensitivity and hypervigilance play an important role in symptom generation, in the context of normal or borderline function. Treatments directed at improving borderline motor dysfunction or reducing reflux burden to subnormal levels have limited success in symptom improvement. In contrast, strategies focused on modulating peripheral triggering and central perception are mechanistically viable and clinically meaningful. However, outcome data from these treatment options are limited. Future research needs to focus on understanding mechanisms underlying visceral hypersensitivity and hypervigilance so that appropriate targets and therapies can be developed.**

**Keywords:** Heartburn; Chest Pain; Dysphagia; Globus; Esophageal Motility Disorders; Gastroesophageal Reflux Disease; Rome IV.

**F**unctional esophageal disorders present with typical esophageal symptoms that are not associated with structural, inflammatory, or a major motor abnormality<sup>1</sup> (Table 1). Thus, these patients typically present in the context of a normal endoscopy, and no evidence of mechanical obstruction or biopsy-confirmed eosinophilic esophagitis (EoE). In addition, there is no evidence of a major motor disorder (achalasia, esophagogastric junction [EGJ] outflow obstruction, absent contractility, distal esophageal spasm, jackhammer esophagus) and no pathologic esophageal acid exposure. The pathophysiology of these disorders focuses on alterations in neural processing between peripheral triggering and central perception of esophageal symptoms. These disorders do not progress along a tangible organic natural history, and, accordingly, a chronicity exists that reflects the underlying pathogenesis and disease burden. Thus, an arbitrary requirement of at

least 3 months of symptoms with an onset at least 6 months before diagnosis is applied to each diagnosis to establish chronicity.

Recent advances in our understanding of esophageal motor disorders,<sup>2</sup> and the appreciation that EoE may be associated with diverse esophageal symptoms<sup>3</sup> (Figure 1) have led to more specific revisions of exclusionary criteria for functional esophageal disorders. Similar to ROME III, achalasia and absent contractility remain exclusion criteria.<sup>1</sup> However, the term *histopathology-based esophageal motor disorder* used in previous definitions (Rome III) is no longer accurate because these motor disorders are not diagnosed based on histology, but instead are defined by motor patterns. Furthermore, recent descriptions of spastic and hypercontractile motor phenotypes have expanded the exclusion criteria.<sup>4</sup> In contrast, borderline motor abnormalities, such as ineffective esophageal motility and fragmented peristalsis, are not exclusionary because these motor patterns can be seen in asymptomatic controls, and likely generate symptoms in the context of a secondary process, such as gastroesophageal reflux disease (GERD), visceral hypersensitivity, and hypervigilance.<sup>2</sup>

The current ROME IV criteria place a strong emphasis on ruling out mechanical obstruction as a mechanism of symptom generation. For instance, evidence of EGJ outflow obstruction would rule out a functional diagnosis because this can represent achalasia in evolution or a subtle mechanical obstruction. Further evaluation targeting structural EGJ processes (eg, endoscopic ultrasound, contrast radiography) should be considered once an EGJ outflow obstruction pattern is recognized.<sup>2</sup> Similarly, evidence of EoE on endoscopy or on mucosal biopsy also excludes a functional diagnosis because esophageal symptoms (heartburn, chest pain, dysphagia) can be related to the underlying inflammation and mechanical effects on the esophageal wall.<sup>3</sup>

**Abbreviations used in this paper:** EGJ, esophagogastric junction; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; NCCP, noncardiac chest pain; NERD, nonerosive reflux disease; PPI, proton pump inhibitor; SSRI, serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

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**Table 1.** Functional Esophageal Disorders

Functional chest pain
Functional heartburn
Reflux hypersensitivity
Globus
Functional dysphagia

Another major change in the ROME IV classification is the more restrictive definition of GERD, accepting that sensitivity to a physiologic reflux burden may sit more firmly within the functional realm than true GERD, albeit within a spectrum allowing for overlap with GERD (Figure 2). The previous exclusion of patients with symptom–reflux correlation (based on response to proton pump inhibitor [PPI] therapy and symptom–reflux association with physiologic esophageal acid exposure) from functional esophageal disorders places undue emphasis on the strength of the PPI trial, and negates the underlying pathogenesis of visceral sensitivity in the reflux-hypersensitive esophagus. Thus, response to PPI as a criterion for defining GERD has been tempered by the high placebo response, low specificity, and limited predictive value.<sup>5</sup> Although patients with symptom–reflux correlation to physiologic reflux events may respond to PPI therapy, the most logical pathophysiologic explanation is consistent with the current understanding of visceral hypersensitivity and mechanisms of peripheral or central sensitization; thus, these should be included within the functional paradigm. However, care should be exercised in interpreting these designations because heavy emphasis is placed on the accuracy of ambulatory reflux monitoring, which can be falsely negative and subject to day-to-day variation in reflux burden.<sup>6</sup> The role of weakly acidic reflux events (reflux events with pH values between 4 and 7) in generating symptoms and end-organ damage remains controversial; one could argue that this, too, would be more consistent with hypersensitivity and abnormal

perception in the context of heartburn and chest pain (Figure 2).

## A1. Functional Chest Pain

### Definition

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

### Epidemiology

The prevalence of functional chest pain is unknown and is based largely on inferential data from studies assessing NCCP. Population-based surveys assess the prevalence of NCCP at 19%–33%.<sup>7,8</sup> However, this includes chest pain from other esophageal processes including GERD, EoE, and esophageal motor disorders, and therefore likely overestimates the prevalence of true functional chest pain. For instance, Fass et al<sup>9</sup> estimated that within NCCP cohorts, 50%–60% have GERD, 15%–18% have esophageal dysmotility, and approximately 32%–35% have true functional chest pain. Within these limitations, the prevalence appears to be gender-equal, higher in patients younger than 45–55 years of age and lower in less-developed countries.

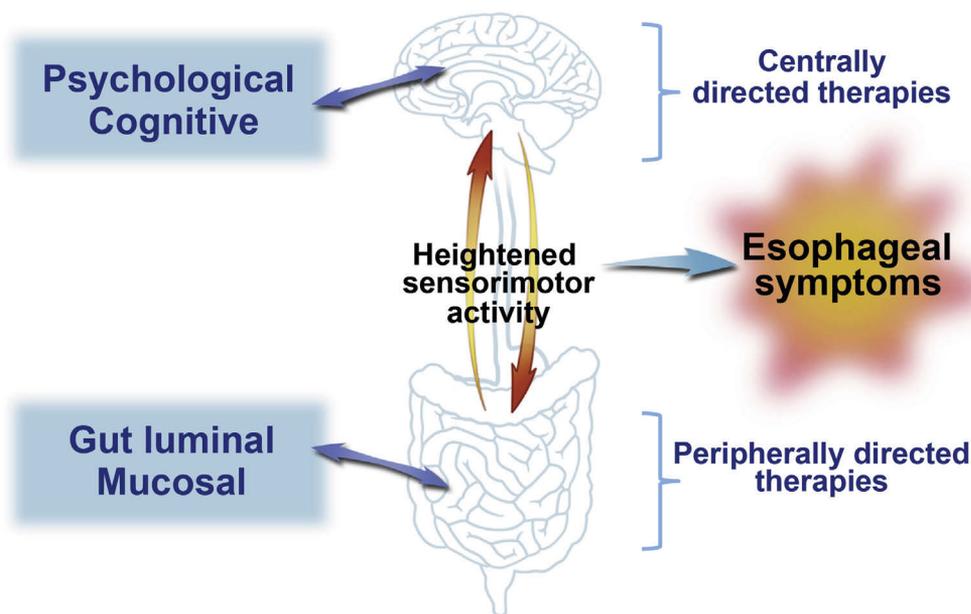
### Clinical Evaluation

Initial exclusion of cardiac disease is a key step, and esophageal work-up should proceed only after confirmation (typically from the patient's cardiologist or primary care physician) that symptoms are unrelated to concurrent coronary artery disease. After exclusion of a cardiac cause, further work-up is guided by the prevalence of the underlying causes of NCCP, and potential clues from clinical

**Table 2.** Pain Modulators for the Treatment of Functional Esophageal Disorders

Class of drug	Dose	Disorder	RCT	Side effects	Response
<b>TCAs</b>					
Imipramine	50 mg/day	NCCP	+	+/-	57%
Amitriptyline	10–20 mg/day	NCCP, globus	+	+/-	52%
<b>SSRIs</b>					
Sertraline	50–200 mg/day	NCCP	+	+	57%
Paroxetine	50–75 mg/day	NCCP	+	+/-	Modest
Citalopram	20 mg/day	ES	+	+/-	Significant
<b>Trazodone</b>					
Vs clomipramine	50/25 mg/day	NCCP	-	+	Modest
Trazodone alone	100–150 mg/day	dysmotility	+	+/-	29%–41%
<b>SNRIs</b>					
Venlafaxine	75 mg/day	NCCP	+	++	52%
<b>Other</b>					
Theophylline	200 mg twice/day	NCCP	+	+/-	58%
Gabapentin	300 mg 3 times/day	globus	+	+/-	66%

ES, esophageal hypersensitivity; RCT, randomized control trial; SNRI, serotonin norepinephrine reuptake inhibitor.



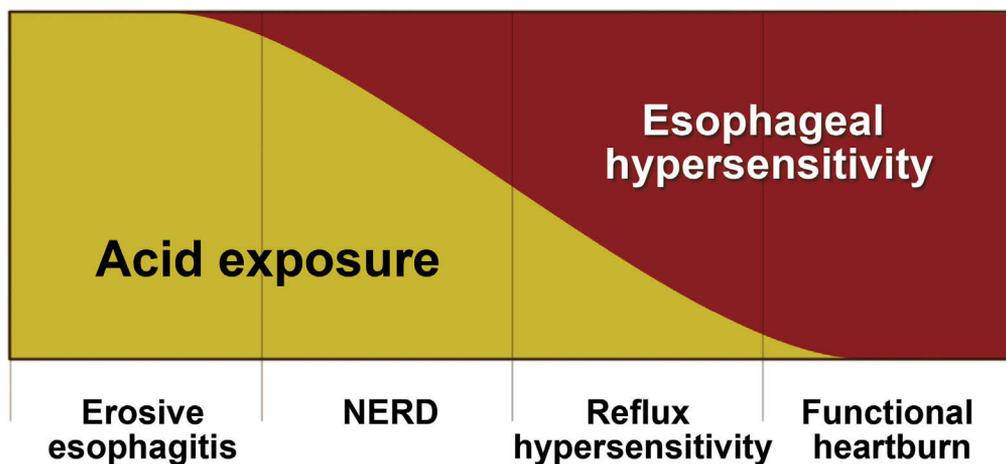
**Figure 1.** The role of the brain–gut axis in mediating esophageal symptoms. Gut luminal and mucosal injury can sensitize visceral afferents causing allodynia or hyperalgesia. Psychological and cognitive factors such as hypervigilance participate in heightened pain perception. Both centrally and peripherally directed treatments can be helpful in management.

evaluation that may support one of these causes. Given the high prevalence of GERD within NCCP, a short course of high-dose PPI therapy is simple and cost effective in determining whether GERD may be triggering chest pain.<sup>10</sup> 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. 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.<sup>11</sup> There are insufficient data assessing the superiority of one reflux monitoring method over the others; therefore, either pH monitoring, combined [pH-impedance monitoring](#), or extended [pH monitoring beyond 24 hours](#) can be used,

reflecting availability and expertise of the center. Most patients with NCCP have normal motor function; esophageal manometry should be considered once GERD has been comfortably ruled out because the diagnosis of major motor disorders represents another important exclusion criteria.

**Diagnostic criteria for functional chest pain.** Criteria must be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis with a frequency of at least once a week. The criteria must include all of the following.

1. Retrosternal chest pain or discomfort; cardiac causes should be ruled out.
2. Absence of associated esophageal symptoms, such as heartburn and dysphagia.



**Figure 2.** The interplay between esophageal hypersensitivity and acid exposure in the reflux symptom spectrum. Symptoms in erosive esophagitis are dominated by abnormal acid exposure whereas symptoms in functional heartburn are dominated by hypersensitivity. Symptoms in NERD and reflux hypersensitivity are related to a combination of both acid exposure and hypersensitivity, with a shift reflecting a more pronounced effect of acid exposure along the NERD diagnostic spectrum and a more pronounced effect of esophageal hypersensitivity along the reflux hypersensitivity diagnostic spectrum.

3. Absence of evidence that gastroesophageal reflux or eosinophilic esophagitis are the cause of the symptom.
4. Absence of major esophageal motor disorders (achalasia/EGJ outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis).

### Justification for Criteria Change

The criteria have been revised to ensure that the definition is consistent with the clinical description of NCCP. Overt GERD and EoE overlaps are addressed with the requirement that concurrent heartburn and dysphagia are not present. The current recognition that EoE can present with chest pain, and the new categorization of spastic and hypercontractile disorders within the Chicago Classification, warrant a more detailed description of exclusion criteria.

### Physiological Features

The major physiologic mechanisms that underlie functional chest pain focus on hypersensitivity from peripheral and/or central sensitization, altered central processing of visceral stimuli, and altered autonomic activity. Studies consistently have shown altered pain perception and heightened visceral sensitivity in functional chest pain.<sup>12</sup> Esophageal tissue injury, inflammation, or repetitive mechanical stimuli all can sensitize peripheral afferent nerves, and esophageal hypersensitivity can be shown long after the original stimulus has resolved. However, it remains unclear as to what factors determine persistence of such hypersensitivity. In addition, a role for enhanced central processing of visceral sensory input also has been suggested, based on studies using cerebral evoked potentials, which show unique latency patterns in NCCP patients.<sup>13</sup> These mechanisms are neither completely understood nor consistently reported, and it is possible that variations in mechanisms may exist within the functional chest pain spectrum. Autonomic dysregulation could reflect another subcategory within functional chest pain. The understanding of the role of motor abnormalities remains incomplete despite the association of spasm, hypercontractile disorders, and achalasia with chest pain. However, there is little evidence to support a causal relationship between minor motor abnormalities and chest pain. Recent evidence suggests that sustained longitudinal muscle contraction can be associated with chest pain,<sup>14</sup> and hypotheses regarding pathogenesis focus on an ischemic model; however, further research is needed to prove that this is causal and not an epiphenomenon.

### Psychological Features

Psychiatric diagnoses, particularly anxiety disorders, depression, and somatization disorder, have been shown in up to 75% of NCCP patients.<sup>15</sup> Chest pain is an important component of panic attacks; furthermore, there are higher levels of neuroticism in patients with NCCP. These associations are important because NCCP patients with psychological comorbidity show diminished quality of life, more

frequent chest pain, and refractoriness to treatment when compared with patients without psychological comorbidity.<sup>16</sup> Regardless of cause or effect, treatment of underlying psychological issues is paramount to successful therapy.

### Treatment

The treatment of functional chest pain has focused predominantly on medications that target neuromodulation of pain (Table 2).<sup>17</sup> However, benefits of complementary behavioral treatments, such as cognitive behavioral therapy and hypnosis, increasingly are recognized, and these modalities are being used often as acceptance of these approaches in gastroenterology widens.<sup>18</sup>

Antidepressants modulate both peripheral and central hyperalgesia independent of mood, and these agents should be considered as first-line medical treatment. Different categories of antidepressants have been used, including tricyclic antidepressants (TCAs), serotonin reuptake inhibitors (SSRIs), serotonin noradrenergic reuptake inhibitors, and trazodone; effectiveness can be as high as 50% greater than placebo in randomized trials (Table 1).<sup>17</sup> However, their side-effect profile and social stigma limit their utilization, prompting study of alternate agents, such as gabapentin, pregabalin, and theophylline. In all instances, clinical use of these neuromodulators should be weighed against potential side effects.

Behavioral therapies are an important alternative and sometimes complementary approach to neuromodulators because these therapies can offer symptom improvement with minimal side effects.<sup>18</sup> Psychological intervention, using cognitive behavioral therapy, coping skills, and hypnosis, has been shown to be effective and durable in both patients with and without psychological comorbidity.

## A2. Functional Heartburn

### Definition

Functional heartburn is defined as retrosternal burning discomfort or pain refractory to optimal antisecretory therapy in the absence of GERD, histopathologic mucosal abnormalities, major motor disorders, or structural explanations. The definition of functional heartburn has evolved over the years. The so-called acid sensitive esophagus initially included in the functional heartburn group in ROME II, was revised further by ROME III as a part of the non-erosive reflux disease (NERD) spectrum.<sup>1</sup> However, the acid-sensitive esophagus in ROME IV has been defined as a stand-alone functional esophageal diagnosis. The current diagnosis of functional heartburn remains focused on a lack of conclusive evidence for GERD, no evidence of a symptom reflux correlation, and a negative response to acid-suppressive therapy because this should alert the physician to the potential of a functional disorder.

### Epidemiology

The incidence and prevalence are difficult to define because this diagnosis is linked inherently to ambulatory reflux testing and response to PPI, both of which are limited

in their discriminative ability to define GERD. As many as 70% of patients with heartburn who undergo endoscopic evaluation will have a normal endoscopy<sup>19</sup>; these patients are defined further into categories based on the presence or absence of abnormal acid exposure and symptom-reflux association. The breakdown of these groups is influenced further by response to PPI therapy. Functional heartburn is found in approximately 50% of PPI nonresponders and in 25% of PPI responders.<sup>5,6,11</sup> This variation in PPI response could be explained by day-to-day variation in reflux burden influencing diagnostic designations.

The long-term natural history of functional heartburn is incompletely known. As many as two thirds of patients with functional heartburn remain symptomatic over 2 years of follow-up evaluation, and symptom intensity and frequency decrease in approximately 20%.<sup>20</sup> This limited evidence suggests that the diagnosis of functional heartburn is durable over follow-up evaluation in the majority of patients.

### Clinical Evaluation

The diagnosis of functional heartburn is made after a careful history identifies the dominant symptom as burning retrosternal discomfort, and stepwise evaluation supports the absence of GERD, EoE, and a major esophageal motor disorder. Most patients are identified when heartburn fails to respond to optimal antisecretory therapy, and, thus, this is a crucial component of our current diagnostic criteria. Endoscopy typically is used in PPI nonresponders as the initial test to evaluate for macroscopic evidence of reflux, esophagitis, long-segment Barrett's esophagus, or an alternative diagnosis, such as EoE or a nonpeptic inflammatory process.

The next step in the evaluation determines whether pathologic gastroesophageal reflux is present using ambulatory reflux testing, but data are insufficient to recommend the optimal technique. However, patients with unproven GERD (ie, no prior documented evidence of reflux-related pathology on endoscopy or ambulatory reflux monitoring) will have the best yield if they are studied off antisecretory therapy.<sup>11,21</sup> The use of pH-impedance in this setting may increase the yield of defining a positive symptom reflux correlation, while extended pH monitoring will identify patients with day-to-day variation in reflux burden.<sup>6,11</sup> Patients are categorized with NERD if esophageal acid exposure is increased, with reflux hypersensitivity if acid exposure is normal but a positive association with acid and/or weakly acidic reflux is present, and with functional heartburn if none of these conditions is present (Figure 3).

Patients not responding to PPI in the context of proven GERD (based on endoscopy and ambulatory reflux testing) represent an interesting subgroup with several possible pathophysiologic scenarios: truly refractory reflux (if acid exposure is abnormal during pH impedance testing on PPI), overlap between functional heartburn and GERD (if acid exposure is normal with no symptom reflux association on pH-impedance testing on PPI), or overlap between reflux hypersensitivity and GERD (if acid exposure is normal with positive symptom reflux association on pH impedance testing on PPI). Definition of these phenotypes could be

important, and functional overlap situations may prompt therapeutic approaches different from true refractory GERD.

**Diagnostic criteria for functional heartburn.** Criteria must be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis with a frequency of at least twice a week. Must include all of the following.

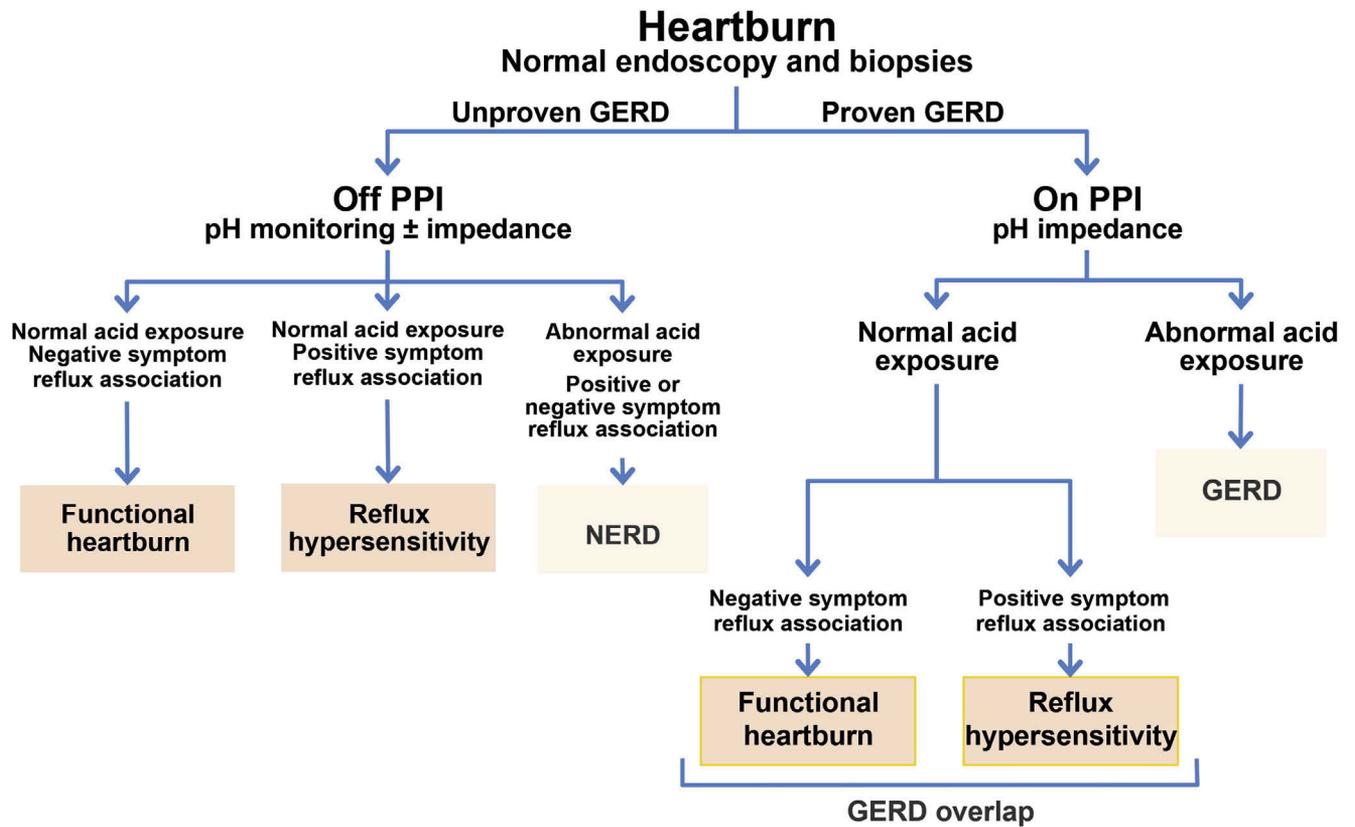
1. Burning retrosternal discomfort or pain.
2. No symptom relief despite optimal antisecretory therapy.
3. Absence of evidence that gastroesophageal reflux (abnormal acid exposure and symptom reflux association) or EoE is the cause of symptoms.
4. Absence of major esophageal motor disorders (achalasia/EGJ outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis).

### Justification for Criteria Change

The most significant points discussed in ROME IV are the definition and implication of PPI refractoriness, the inclusion of findings on pH-impedance monitoring in some of the designations, the implications of reflux testing on and off PPI therapy, and the exclusion of EoE before a functional diagnosis.

Ambulatory reflux monitoring can be associated with variable sensitivity of acid burden assessments when borderline, particularly with day-to-day variation in acid exposure, which can shift functional heartburn diagnoses to NERD.<sup>6</sup> Symptom-reflux association analyses, integral to the definition of functional heartburn and reflux hypersensitivity, have their own pitfalls, and represent the weakest link because they rely on patients promptly reporting symptoms when they occur.<sup>22</sup> Taking these limitations into account, lack of response to PPI therapy should be considered as an important diagnostic criterion to establish that symptoms are not related to gastroesophageal reflux. Clinical experience suggests that lack of response to PPI probably has a high negative predictive value for the diagnosis of GERD.<sup>5</sup> Whether incomplete (partial) response to PPI therapy should be differentiated from complete absence of response remains to be determined. Although not accepted universally, physicians often increase PPI dosing, but only 20%–30% will achieve adequate symptom control after 6–8 weeks of double-dose therapy.<sup>23</sup> Finally, mild heartburn occurring 2 or more days/week negatively impacts quality of life in GERD, and the same threshold could be applied in functional heartburn. Therefore, functional heartburn should be considered in patients who continue to report troublesome symptoms at least 2 times a week for the previous 3 months despite double-dose PPI taken appropriately before meals.

Esophageal biopsies are important in the definition of functional heartburn, regardless of the gross appearance of the esophageal mucosa, to rule out EoE despite its relatively low prevalence (0.9%–4%) in this clinical setting.<sup>3</sup> Although the importance of mucosal integrity and histologic correlates cannot be denied, additional data are needed before



**Figure 3.** Further classification of patients with heartburn and no evidence of esophagitis at endoscopy using ambulatory pH monitoring and response to a therapeutic trial of PPIs. The subset of patients with functional heartburn had no findings that would support a presumptive diagnosis of endoscopy-negative reflux disease. The precise thresholds for separation of subjects at each step remain uncertain. The figure shows classification categories by findings and is not meant to suggest a diagnostic management algorithm for use in clinical practice.

these histopathologic parameters can be included in the definition of functional heartburn.

**Physiological Features**

The mechanism of symptom generation in functional heartburn is unclear, with the prevailing view focused on altered esophageal perception as a major factor.<sup>24</sup> The trigger for provoking heartburn rules out reflux in the current definition and thus, hypotheses revolving around impaired mucosal integrity and increased permeability must be resolved with a lack of reflux correlation that is now inherent in the definition. This has led to a focus on increased sensitization of acid chemoreceptors; it is possible that increased permeability may allow noxious sensitizing luminal substances access to the deeper layers of the esophagus where they may induce various inflammatory cytokines without a temporally associated reflux trigger.<sup>25</sup> In addition, a role for abnormal central processing of esophageal signals also could support symptom generation without a reflux event trigger.

**Psychological Features**

Psychological factors likely have a similar permissive role in functional heartburn as in other functional disorders;

however, studies specifically focusing on functional heartburn are scarce. Several models of acute experimental stress (eg, auditory stress or sleep deprivation) indicate that stress enhances perception of esophageal acid in GERD patients. In addition, patients with functional heartburn show greater anxiety and somatization scores, and poor social support compared with patients with reflux-associated symptoms,<sup>26</sup> further supporting co-existing psychological factors within functional heartburn.

**Treatment**

Therapies for functional heartburn remain largely empiric and may be tailored to the proposed pathophysiology of the condition, presumed mechanism of action of medications, and underlying psychosocial issues. The clinician should provide reassurance and avoid repetitive invasive testing. In addition, an escalation of antireflux therapy, particularly to antireflux surgery, should be avoided because a lack of symptom response to PPI and normal acid burden are predictors of poor outcome.

Given that abnormal peripheral sensitization and central processing are considered relevant in the pathogenesis of functional heartburn, it is reasonable to consider esophageal pain modulators, such as low-dose TCAs and SSRIs similar to that described in Table 1 (functional chest pain).<sup>17</sup> One

small pilot study supported the role of hypnosis in a subset of patients.<sup>27</sup> Psychological approaches such as behavioral modification, acupuncture, or relaxation therapy may be beneficial, despite the paucity of literature for use in functional heartburn.

### A3. Reflux Hypersensitivity

#### Definition

Reflux hypersensitivity identifies patients with esophageal symptoms (heartburn or chest pain) who lack evidence of reflux on endoscopy or abnormal acid burden on reflux monitoring, but show triggering of symptoms by physiologic reflux. Some patients fulfilling criteria potentially could respond to antireflux measures, however, the underlying pathogenesis is more consistent with esophageal hypersensitivity from a functional basis. Furthermore, overlap could exist between true GERD and reflux hypersensitivity, manifest as physiologic acid burden when monitored on PPI therapy, but as symptom reflux correlation between identified reflux events and symptom episodes.

#### Epidemiology

The epidemiology and prevalence rates of reflux hypersensitivity are not known, but inferences can be made from the NERD population. It is estimated that 37%–60% of NERD patients have normal ambulatory pH monitoring studies off medication,<sup>28</sup> and that less than 10% of patients undergoing ambulatory pH monitoring show acid sensitivity.<sup>29</sup> In a study of 329 NERD patients, 36% showed symptom–reflux correlation in the absence of abnormal reflux parameters (reflux hypersensitivity), whereas 40% had abnormal acid exposure (true NERD) and 24% had normal pH–impedance monitoring (functional heartburn).<sup>30</sup> An increased number of weakly acidic reflux events and a higher rate of proximal reflux discriminated reflux hypersensitivity from functional heartburn, with lesser degrees of overlap between reflux hypersensitivity and healthy volunteers, compared with high overlap between functional heartburn and healthy volunteers.<sup>30</sup>

#### Clinical Evaluation

The clinical presentation of patients with reflux hypersensitivity is indistinguishable from those with functional heartburn and NERD. As with functional chest pain and functional heartburn, evaluation starts with an empiric PPI trial, the performance characteristics of which are described in detail under the previous section on functional chest pain.<sup>10</sup> Some level of refractoriness to PPIs represents the starting point for consideration of both functional heartburn and reflux hypersensitivity<sup>23</sup> and endoscopy is performed to rule out esophagitis, Barrett's esophagus, and EoE.<sup>3,31</sup>

The diagnosis of reflux hypersensitivity hinges on identifying sensitivity to acid-reflux events on reflux testing (Figure 2).<sup>32</sup> To make a diagnosis of reflux hypersensitivity, acid parameters need to be within the physiologic range, whether tested on or off PPI therapy. It generally is accepted that acid exposure time thresholds of approximately

3.9%–4.2% have discriminative value in assigning a GERD etiology to symptoms when catheter-based pH studies are performed off antisecretory therapy<sup>33</sup>; thresholds used are slightly higher, approximately 5.3%, when wireless pH testing is used. The distinction of reflux hypersensitivity from functional heartburn lies in the presence of significant symptom–reflux association in the former. Although controversy exists as to the true clinical value of symptom–reflux association,<sup>22</sup> the identification of reflux events triggering symptoms in the setting of physiologic reflux parameters is key to the diagnosis of reflux hypersensitivity.<sup>29</sup>

As with other functional esophageal disorders, major motor disorders (achalasia/EGJ outflow obstruction, diffuse esophageal spasm, aperistalsis, and jackhammer esophagus) need to be excluded.<sup>2</sup>

**Diagnostic criteria for reflux hypersensitivity.** Criteria must be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis with a frequency of at least twice a week. Must include all of the following.

1. Retrosternal symptoms including heartburn and chest pain.
2. Normal endoscopy and absence of evidence that EoE is the cause for symptoms.
3. Absence of major esophageal motor disorders (achalasia/EGJ outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis).
4. Evidence of triggering of symptoms by reflux events despite normal acid exposure on pH or pH–impedance monitoring (response to antisecretory therapy does not exclude the diagnosis).

#### Justification for Change in Criteria

The ROME III classification of esophageal functional disorders generated controversy by expanding the definition of NERD to include patients with normal esophageal acid exposure but positive symptom association (acid-hypersensitive group).<sup>1</sup> Because mechanisms of symptom generation in the acid-sensitive esophagus focus on enhanced sensitivity, and patients clinically behave akin to functional heartburn in terms of PPI response, the reflux hypersensitivity category was introduced to highlight this specific subgroup. Patients with acid hypersensitivity respond suboptimally to PPIs; similarly, the expected response in patients with weakly acidic and non-acid reflux also is poor. However, there is variability within this subgroup; patients with sensitivity to acid-reflux events but responding to PPIs may represent overlap with NERD, wherein abnormal reflux burden fluctuates day-to-day.<sup>6</sup>

Further justification for separating patients with symptoms triggered by physiological acid and non-acid reflux events from functional heartburn is that the former cohort shows a greater likelihood of esophageal mucosal changes (including dilated intercellular spaces, basal cell thickness, and papillary elongation) compared with the functional heartburn cohort.<sup>34</sup>

## Pathophysiology

Pathophysiologic mechanisms underlying reflux hypersensitivity are believed to be similar to those underlying functional chest pain and functional heartburn with the caveat that symptoms are triggered by reflux events on ambulatory reflux monitoring. The same mechanisms driving symptom perception, including peripheral and/or central sensitization, altered central processing of visceral stimuli, altered autonomic activity, and psychological abnormalities, are hypothesized to drive reflux hypersensitivity, the only difference is that the actual reflux trigger, chemical or mechanical, is identified on reflux monitoring. There also is evidence of up-regulation of acid-sensitive receptors (eg, TRPV1 receptor) in response to acid exposure, and neurogenic inflammation is suggested by an increase in both substance P release and its receptor, neurokinin 1-receptor expression.<sup>35</sup>

## Psychological Features

In the setting of psychological stress, centrally mediated processes can alter autonomic nervous system activity and modulate spinal transmission of nociceptive signals, while peripherally, permeability of gut mucosa can be altered by mast cell degranulation.<sup>36</sup> These mechanisms support the concept of exaggerated perception of physiologic stimuli, such as reflux events, in settings of psychological stress. Therefore, psychological features are an important component of reflux hypersensitivity, similar to other functional esophageal disorders.

## Treatment

Similar to management of functional heartburn, reassurance is provided, and patients are counseled that no ominous diagnosis exists. Treatment remains empiric, but response to antisecretory therapy may be better than in other functional esophageal disorders. For instance, some patients with acid-sensitive esophagus may respond to standard or double-dose PPIs.<sup>37</sup> However, patients with weakly acid- and non-acid reflux-triggered symptoms generally are refractory to PPIs.<sup>38</sup> There is very limited evidence suggesting that acid- or weakly acid reflux-triggered symptoms refractory to PPI can respond to antireflux procedures.<sup>39</sup> Further large-scale controlled clinical trials are necessary to confirm these preliminary findings before this approach can be recommended uniformly.

The mainstay of treatment of esophageal hypersensitivity is with pain modulators including TCAs, SSRIs, serotonin noradrenergic reuptake inhibitors, and gabapentinoids, as described in [Table 1](#). However, therapeutic trials with these agents remain empiric because clinical trials specifically showing efficacy of these treatments in functional reflux sensitivity are scarce.<sup>40</sup>

## A4. Globus

### Definition

Globus sensation is a persistent or intermittent non-painful sensation of a lump or foreign body in the throat.<sup>1</sup>

The symptom is nonpainful, 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 such as a gastric inlet patch, GERD, or major motor disorders.

### Epidemiology

Globus sensation is a common symptom and is reported by up to 46% of apparently healthy individuals.<sup>41</sup> However, similar to other functional disorders that require a systematic exclusion of identifiable causes, the actual prevalence is unknown. The symptom has a peak onset in middle age and is prevalent equally in both sexes, but women are more likely to seek health care for this complaint. The condition is durable, and symptoms typically persist for more than 3 years in 75% of patients, although as many as 50% have persistent symptoms after 7 years.<sup>42</sup>

### Clinical Evaluation

The diagnosis is made primarily 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 functional esophageal disorders; there must be no dysphagia and no alarm features (eg, sore throat, odynophagia, weight loss). Physical examination of the neck followed by laryngoscopic examination of the pharynx are advised as the initial evaluation. Once localized structural or inflammatory causes are excluded, the work-up may proceed with an empiric trial of PPI therapy for 4–8 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 mucosal processes can be considered to identify an alternative cause. Manometry 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 and esophagus are diagnosed with globus.

**Diagnostic criteria for globus.** Criteria must be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis with a frequency of at least once a week. 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, laryngoscopy, or endoscopy.
  - a. Occurrence of the sensation between meals.
  - b. Absence of dysphagia or odynophagia.
  - c. Absence of a gastric inlet patch in the proximal esophagus.
2. Absence of evidence that gastroesophageal reflux or EoE is the cause of the symptom.

3. Absence of major esophageal motor disorders (achalasia/EGJ outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis).

### Justification for Criteria Change

The diagnostic criteria have been modified relative to the recent insights into the gastric inlet patch in globus symptom generation, and a concerted effort to support endoscopic evaluation of the oropharynx. Similar to other functional disorders, separating out major motor disorders not encountered in health from the borderline motor disorders found in asymptomatic controls also was included in the definition of globus.

### Physiological Features

Globus sensation may be a function of the perception of a space occupying lesion, a manifestation of GERD, associated with a gastric inlet patch and potentially related to a major motor disorder. When no identifiable cause is found, globus likely is related mechanistically to the same pathophysiologic processes associated with abnormal visceral hypersensitivity and central processing of peripheral stimuli seen with other functional esophageal disorders.

Consistent evidence is lacking to attribute globus to any specific anatomic abnormality, including the cricopharyngeal bar. Upper esophageal sphincter mechanics do not seem relevant, and the pharyngeal swallow mechanism is normal. Esophageal balloon distention can reproduce globus sensation at low distending thresholds, suggesting some degree of esophageal hypersensitivity.<sup>43</sup> Globus is reportedly more common in conjunction with reflux symptoms, although a strong relationship between GERD and globus has not been established.<sup>44</sup> However, the symptom does not respond well to antireflux therapy. Although gastroesophageal reflux and distal esophageal motor disorders can include globus in their presentations, these mechanisms are thought to play a minimal role in the pathophysiology of globus.

### Psychological Features

Psychiatric diagnoses are prevalent in globus patients seeking health care, but an explanation distinct from ascertainment bias has not been established, and no specific psychological characteristic has been identified in globus subjects. Increased reporting of stressful life events preceding symptom onset has been observed in several studies, suggesting that life stress might be a cofactor in symptom genesis or exacerbation.<sup>45</sup> Up to 96% of sufferers report symptom exacerbation during periods of high emotional intensity.

### Treatment

Given the benign nature of the condition, the likelihood of long-term symptom persistence, and absence of highly effective pharmacotherapy, the mainstay of treatment rests with explanation and reassurance. Expectations for prompt symptom resolution are low because symptoms persist in up to 75% of patients at 3 years.<sup>42</sup> Controlled trials of

antidepressants and behavioral therapy for globus are unavailable, but there is anecdotal evidence for their utility.<sup>46,47</sup>

## A5. Functional Dysphagia

### Definition

Functional dysphagia is defined as a sensation of abnormal bolus transit through the esophageal body in the absence of structural, mucosal, or motor abnormalities to explain the symptom. The diagnosis of functional dysphagia requires thorough exclusion of oropharyngeal mechanisms of dysphagia, structural lesions in the tubular esophagus, GERD, EoE, and major motor disorders.

### Epidemiology

The true prevalence of functional dysphagia is unknown. A population survey of functional disorders estimated that 7%–8% of dysphagia was unaccounted for by exclusionary criteria,<sup>48</sup> and a validation study of Rome II criteria estimated 0.6% of functional gastrointestinal disease patients complained of frequent dysphagia.<sup>49</sup> Functional dysphagia is estimated to be the least prevalent of functional esophageal disorders.

### Clinical Evaluation

A careful history is taken to exclude oropharyngeal dysphagia, and to evaluate for conditions mimicking or contributing to dysphagia (globus, xerostomia, odynophagia). GERD and EoE are important conditions to exclude, typically with a combination of a trial of PPI therapy and upper endoscopy with biopsy. Barium contrast studies, especially using solid boluses (tablet, cookie, marshmallow), can evaluate for subtle strictures often overlooked on endoscopy or other obstructive processes such as paraesophageal or axial hiatus hernias.<sup>50</sup> In the absence of structural lesions, esophageal manometry is performed to exclude major motor disorders. Borderline or minor motor disorders remain compatible with a diagnosis of functional dysphagia because these disorders can be seen in asymptomatic controls and patients without dysphagia,<sup>2</sup> even though these disorders may be identified more often in nonobstructive dysphagia. Provocative testing with multiple rapid swallows, free water drinking, or food ingestion during manometry may enhance detection of obstructive motor mechanisms to explain dysphagia.<sup>51,52</sup>

New investigative modalities such as endoscopic functional luminal imaging probe and high-frequency ultrasound may show abnormal esophageal distensibility and lack of coordination between circular and longitudinal muscle contraction, respectively.<sup>53,54</sup> However, these findings have not been correlated consistently with dysphagia. As newer investigative modalities identify additional structural or motor mechanisms for nonobstructive dysphagia overlooked on routine evaluation, the prevalence of functional dysphagia is anticipated to decrease further.

**Diagnostic criteria for functional dysphagia.** Criteria must be fulfilled for the past 3 months with symptom

onset at least 6 months before diagnosis with a frequency of at least once a week. Must include all of the following.

1. Sense of solid and/or liquid foods sticking, lodging, or passing abnormally through the esophagus.
2. Absence of evidence that esophageal mucosal or structural abnormality is the cause of the symptom.
3. Absence of evidence that gastroesophageal reflux or EoE is the cause of the symptom.
4. Absence of major esophageal motor disorders (achalasia/EGJ outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis).

### Justification for Criteria Change

The diagnostic criteria for functional dysphagia have been revised to ensure exclusion of subtle mucosal or structural processes, including those encountered in GERD and EoE. Dysphagia can occur even without overt structural lesions in EoE, necessitating histopathology for exclusion of this condition. Finally, major motor disorders can be associated with abnormal bolus transit leading to dysphagia, and therefore need to be excluded with manometry.

### Physiological Features

The relationship between esophageal bolus stasis and the sensation of dysphagia is not perfect. Bolus transit is highly dependent on bolus consistency and patient posture, and it can take several swallows to clear dry solid boluses even in normal individuals.<sup>55</sup> Therefore, despite reports of simultaneous contractions, spastic contractions, or ineffective esophageal motility in nonobstructive dysphagia, it is difficult to attribute dysphagia consistently to these motor abnormalities.<sup>56,57</sup> In contrast, premature peristalsis, hypercontractility, or absent contractility seen as part of major motor disorders are associated consistently with abnormal bolus transit, and therefore can explain dysphagia.

Similar to other functional esophageal disorders, abnormal esophageal sensory perception is theorized to participate in symptom generation in functional dysphagia. For instance, a feeling of food sticking can be induced with balloon distension or acidification of the esophagus, both of which also can induce peristaltic dysfunction<sup>58</sup>; correlation with provoked dysphagia is high but imperfect.<sup>59</sup> In this context, minor peristaltic disorders may represent epiphenomena associated with abnormal sensitivity to the distending stimulus. Therefore, although both peristaltic dysfunction and abnormal visceral sensitivity are potential contributory mechanisms, the latter is more in keeping with common pathophysiologic themes in functional disorders.

### Psychological Features

There are limited data supporting a higher likelihood of psychological distress, anxiety, depression, and somatization disorders in patients with unexplained dysphagia, similar to observations in functional chest pain.<sup>60</sup> Acute stress experiments can provoke peristaltic dysfunction and abnormal

bolus transit in the esophagus,<sup>1</sup> but these results cannot be extrapolated directly to chronic symptoms seen with functional dysphagia.

### Treatment

Functional dysphagia may regress over time, and aggressive management approaches may not be necessary. Reassurance and simple nonpharmacologic measures such as eating in the upright position, avoiding precipitating food items, careful chewing of food, and chasing food with liquids may suffice in mild cases.<sup>61</sup> A short trial of PPI may be useful because dysphagia can be part of the reflux spectrum. Despite a lack of proven efficacy, antidepressants, particularly TCAs, can be tried. Empiric bougie dilation has been reported to benefit 68%–85% of patients with intermittent food dysphagia without an identifiable source,<sup>62,63</sup> a benefit not observed with through-the-scope balloon dilators targeting the EGJ.<sup>64</sup> Thus, bougie dilation to 50–54F can be considered because this may impact subtle rings or strictures that may be overlooked on routine testing.

## Recommendations For Future Research

Despite their high prevalence rates and increasing awareness, functional esophageal disorders have not been well studied. Therefore, effective management approaches have been difficult to establish. Several areas requiring additional research are identified.

1. Studies validating the diagnostic criteria are needed and methods for improving the accuracy of symptom-based criteria are encouraged.
2. The fundamental mechanisms of symptom production remain poorly defined. Further application of new technologies for measuring reflux events, motor physiology, and esophageal sensation, as well as central signal modulation, is recommended (eg, multichannel intraluminal impedance monitoring, high-resolution manometry, functional lumen imaging, high-frequency ultrasound, brain imaging).
3. Well-designed, controlled treatment trials would be welcomed in any of these disorders.
4. Treatment trials should include measures of quality of life and functional outcome. The impact of interventions on health care resource use should be a focus in measuring treatment success.

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#### Conflicts of interest

The authors disclose no conflicts.

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