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Review article

Esophageal disorders of gut-brain interaction: An update based on Rome V

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Abstract

Introduction: Esophageal disorders of gut-brain interaction are characterized by symptoms such as heartburn, chest pain, globus sensation, and dysphagia in the absence of structural, inflammatory, motor, or reflux-related abnormalities that adequately account for their occurrence. The Rome V criteria incorporate recent advances in the physiological assessment of the esophagus and should be interpreted in conjunction with the Chicago Classification v4.0 and Lyon Consensus 2.0. **Results:** This update reviews the five esophageal disorders of gut-brain interaction recognized by Rome V: functional chest pain, functional heartburn, reflux hypersensitivity, globus, and functional dysphagia. Their principal clinical features, diagnostic criteria, pathophysiological mechanisms, and therapeutic strategies are analyzed. Particular emphasis is placed on the central role of esophageal hypersensitivity and central sensory processing mechanisms, as well as on the influence of hypervigilance and cognitive, affective, and psychosocial factors on symptom perception. **Conclusions:** Rome V proposes an integrated diagnostic approach that allows esophageal symptoms to be interpreted in conjunction with endoscopic and physiological findings, thereby avoiding overinterpretation of minor abnormalities and unnecessary repetition of diagnostic testing. Once relevant structural, inflammatory, motor, and reflux-related diseases have been excluded, management should target the mechanisms perpetuating symptoms, including hypersensitivity and hypervigilance. Patient education, neuromodulation, and psychobehavioral interventions constitute relevant therapeutic tools, although the available evidence supporting many of these interventions remains limited.

Keywords

Gut-brain axis, hypervigilance, dysphagia, Rome V.

INTRODUCTION

Functional esophageal disorders, currently classified as esophageal disorders of gut-brain interaction (DGBIs), are characterized by symptoms such as heartburn, chest pain, globus sensation, or dysphagia in the absence of structural or inflammatory abnormalities or major motility disorders that adequately account for their presence[1]. Rome V retains this concept but places it within the context of recent advances in the physiological assessment of the esophagus, more explicitly incorporating the Chicago Classification version 4.0 (CCv4.0) and Lyon Consensus 2.0 as complementary frameworks for identifying and excluding esophageal motility disorders and gastroesophageal reflux disease (GERD), respectively[2,3].

In clinical practice, the evaluation of patients with esophageal symptoms begins with a thorough medical record and endoscopic assessment, supplemented, when appropriate, by physiologic testing. Upper endoscopy with esophageal biopsies allows structural lesions and mucosal diseases to

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be excluded, whereas high-resolution manometry (HRM), interpreted according to CCv4.0, allows major motility disorders such as achalasia, esophagogastric junction outflow obstruction, absent contractility, distal esophageal spasm, and hypercontractile esophagus to be excluded[3]. Complementarily, reflux monitoring, interpreted according to the Lyon Consensus 2.0, allows GERD to be established or excluded as an explanation for symptoms[2]. Thus, Rome V proposes an integrated diagnostic approach in which symptoms are interpreted in conjunction with endoscopic and physiologic findings rather than in isolation. Another relevant consideration is the need to exclude mucosal diseases that may mimic an esophageal DGBI, such as eosinophilic esophagitis. Esophageal biopsies are particularly important in patients with dysphagia, meal-related chest pain, or a history of food impaction[4,5]. Only after these conditions have been adequately excluded should a diagnosis of an esophageal DGBI be considered (**Figure 1**).

Once relevant structural, inflammatory, and motility abnormalities have been excluded, the diagnostic focus shifts from identifying a lesion to understanding how signals originating in the esophagus are generated, transmitted, and processed. Reflecting the chronic nature of these disorders, Rome V specifies that symptoms must have been present for at least 3 months, with symptom onset occurring at least 6 months before diagnosis. From a pathophysiologic perspective, esophageal DGBIs can be understood as resulting from impaired bidirectional communication between the esophagus and the central nervous system. Esophageal hypersensitivity is central to this model and refers to an exaggerated perception of stimuli that would normally be innocuous or cause only minimal discomfort. It may manifest as allodynia, in which nonpainful stimuli are perceived as painful, or hyperalgesia, in which an exaggerated response occurs to stimuli that are potentially painful[6]. The symptomatic experience is not determined solely by signals originating in the esophagus. Peripheral sensory information may be modulated by central mechanisms as well as cognitive and affective factors. Among these, hypervigilance, defined as heightened attention to bodily sensations, and symptom-related anxiety may alter the interpretation of esophageal signals and contribute to greater symptom

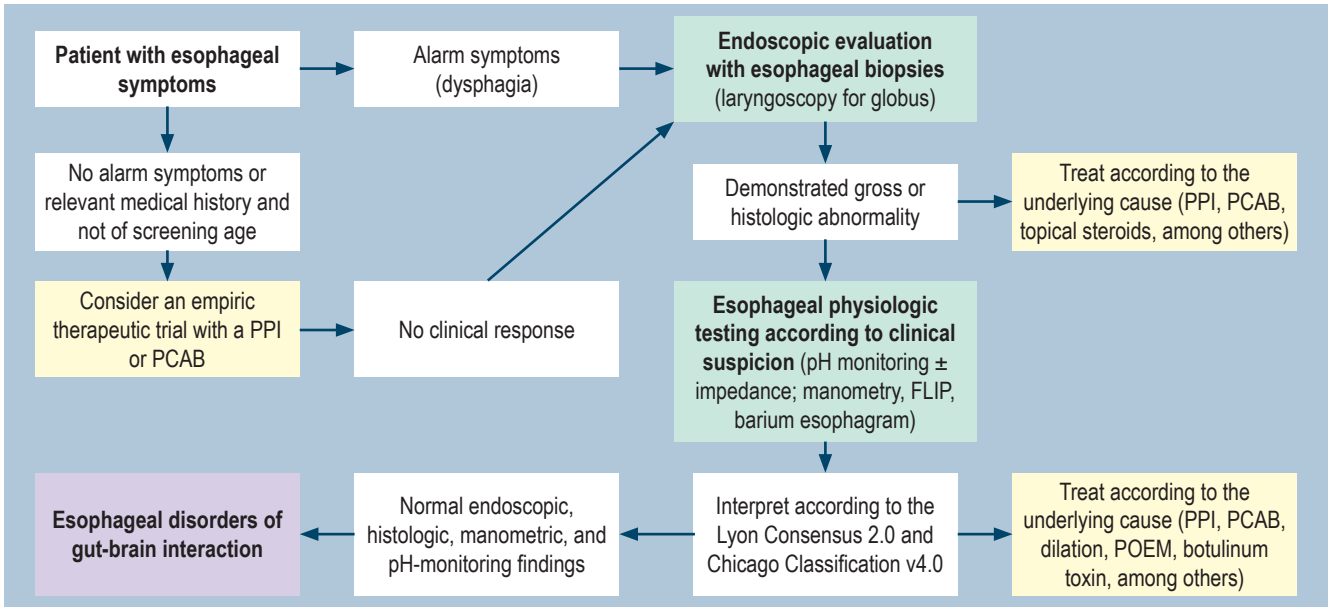


Figure 1. Diagnostic algorithm for esophageal symptoms and disorders of gut-brain interaction. In the absence of alarm symptoms, a relevant medical record, or indications for screening, an initial therapeutic trial with proton pump inhibitors (PPIs) or potassium-competitive acid blockers (PCABs) may be considered. In the presence of alarm symptoms, such as dysphagia, upper endoscopy with esophageal biopsies is recommended, including targeted biopsies to exclude eosinophilic esophagitis when appropriate. When gross or histologic abnormalities are identified, treatment should be directed toward the underlying etiology. In the absence of explanatory structural or histologic findings, physiologic testing should be guided by the clinical suspicion and may include pH monitoring with or without impedance monitoring, high-resolution esophageal manometry, functional lumen imaging probe (FLIP) testing, or barium esophagography. Results should be interpreted according to the Lyon Consensus 2.0 and Chicago Classification 4.0. When endoscopic, histologic, manometric, and pH-monitoring findings are normal, an esophageal disorder of gut-brain interaction should be considered according to the Rome V diagnostic criteria. FLIP: functional lumen imaging probe; PPI: proton pump inhibitor; PCAB: potassium-competitive acid blocker; POEM: peroral endoscopic myotomy. Image courtesy of the authors.

burden[6]. This model helps explain why symptom severity does not always correlate directly with objective findings on diagnostic testing.

Repeated exposure to noxious stimuli, even in the absence of overt mucosal injury, may promote activation of inflammatory pathways and sensitization of nociceptors. For example, acid exposure may induce esophageal epithelial cells to release cytokines such as interleukin-8, thereby contributing to a local immune response and potentially to peripheral sensitization[7]. However, these mechanisms do not fully account for all cases. In patients with functional heartburn, the distribution of nerve endings within the esophageal mucosa may be similar to that observed in healthy individuals. This finding supports an important role for central mechanisms in symptom generation in these patients[8]. By contrast, more superficial nerve endings have been described in GERD. This finding may contribute to increased chemosensitivity and may, at least in part, explain the interest in mucosal protective strategies[9].

Initial evidence of esophageal hypersensitivity came from patients with noncardiac chest pain, in whom esophageal balloon distension elicited pain at lower thresholds than those observed in healthy individuals[10]. Subsequent studies demonstrated that up to 75% of patients with this condition may exhibit hypersensitivity to esophageal distension[11]. Similarly, patients with functional heartburn exhibit greater sensitivity to mechanical and chemical stimuli than patients with GERD and healthy controls[12]. However, these findings are not consistent across studies. Shapiro et al.[13] reported greater chest pain, somatization, and abnormalities in autonomic tone among patients with functional heartburn. However, they did not find increased sensitivity to chemosensory stimuli, further supporting the importance of central mechanisms in symptom perception. Likewise, hypervigilance and symptom-specific anxiety have gained increasing recognition as cognitive-affective factors capable of influencing the symptomatic experience and clinical outcomes in these patients[14].

Overall, Rome V conceptualizes esophageal DGBIs not simply as diagnoses of exclusion, but as disorders in which the manner in which the esophagus generates, transmits, and processes sensory signals plays a central role. This shift in perspective has practical implications: once relevant structural, inflammatory, motility, and reflux-related diseases have been excluded, the goal is no longer to identify an additional abnormality that might explain the symptoms, but rather to understand the mechanisms that determine their perception. The following sections review the five esophageal entities recognized in Rome V: functional chest pain (A1), functional heartburn (A2), reflux hypersensitivity (A3), globus (A4), and functional dysphagia (A5), highlighting for each the main changes from Rome IV, the diagnostic approach, the proposed pathophysiologic mechanisms, and the implications for clinical management (**Figure 2**).

RESULTS

Functional chest pain

Functional chest pain is characterized by recurrent episodes of retrosternal pain of presumed esophageal origin that are not attributable to heartburn and cannot be explained by gastroesophageal reflux disease (GERD), mucosal abnormalities, or major esophageal motility disorders. It is part of the spectrum of noncardiac chest pain and, by definition, represents a diagnosis of exclusion. Medical record alone cannot reliably distinguish cardiac from esophageal chest pain; therefore, when clinically suspected, cardiovascular evaluation should precede gastrointestinal investigation. In an international survey conducted by the Rome Foundation that included more than 54,000 participants, the prevalence of functional chest pain was approximately 1.4%, with a slightly higher frequency among women[15]. Among patients with noncardiac chest pain, approximately half have GERD, whereas approximately one-third meet criteria for functional chest pain[16].

Once a cardiac cause has been excluded, the initial evaluation should focus on GERD, given its high prevalence among patients with noncardiac chest pain. Endoscopy allows structural and mucosal disease to be excluded when clinically indicated. Proximal and distal esophageal biopsies should be considered to exclude eosinophilic esophagitis[5]. In the absence of alarm features, an empiric therapeutic trial of a double-dose proton pump inhibitor (PPI) or a once-daily potassium-competitive acid blocker (PCAB) for 8 weeks may be considered[17]. If there is no response to antisecretory therapy and suspicion of GERD persists, ambulatory reflux monitoring may be performed, with the choice of pH monitoring, pH-impedance monitoring, or prolonged wireless pH monitoring guided by the clinical context and local availability[2]. High-resolution manometry should subsequently be considered when suspicion of a motility disorder persists, primarily to exclude major motility disorders according to the Chicago Classification v4.0[3], including hypercontractile esophagus, achalasia, esophagogastric junction outflow obstruction, and esophageal spasm, the latter being the least common but most widely recognized. Most patients with functional chest pain have normal esophageal motility.

Once the diagnosis has been established, it is important to explain to the patient that structural diseases have been excluded and that the symptoms are consistent with altered perception and processing of esophageal signals. Treatment is based primarily on visceral pain neuromodulation.

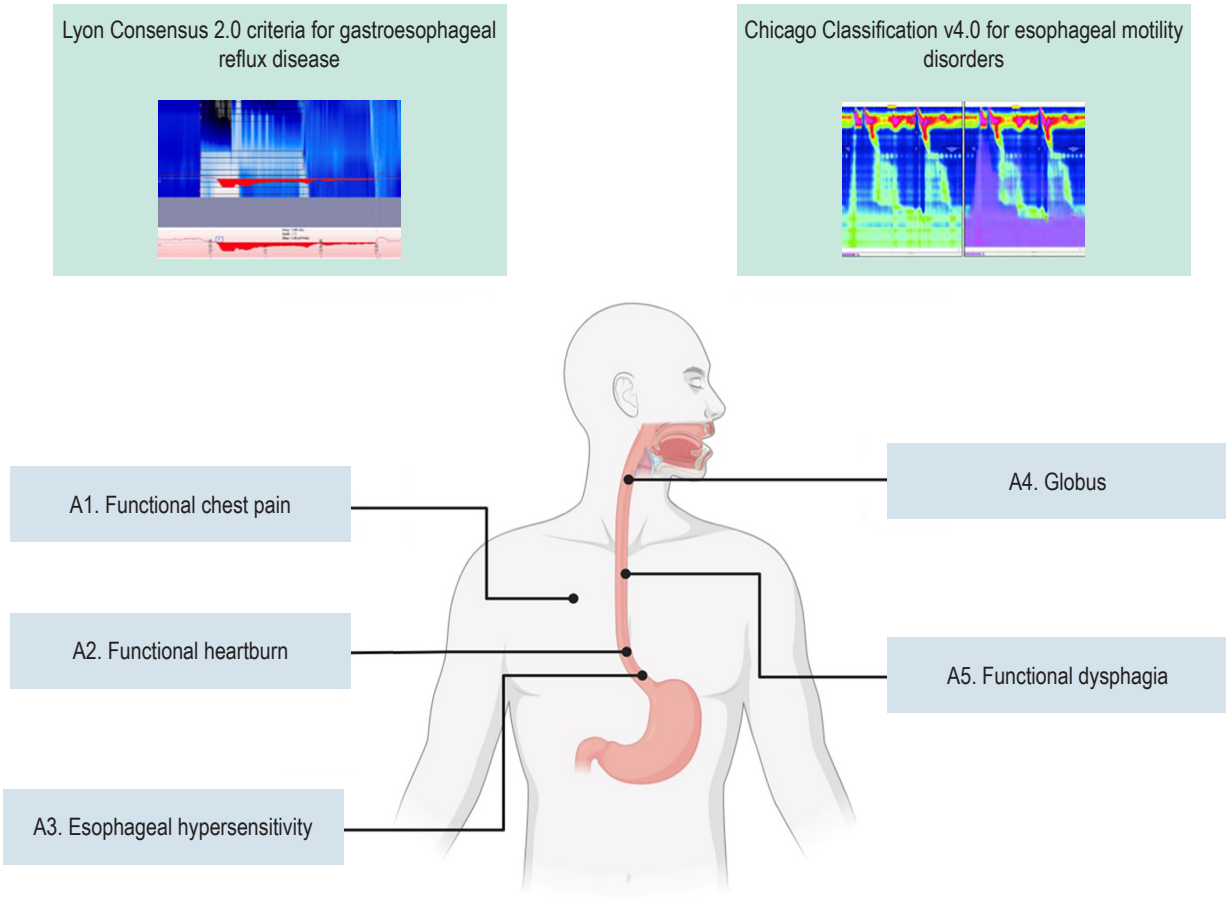


Figura 2. Classification of esophageal disorders of gut-brain interaction according to the Rome V criteria. Five clinical entities are included: A1: functional chest pain; A2: functional heartburn; A3: esophageal hypersensitivity; A4: globus sensation; and A5: functional dysphagia. These disorders are characterized by persistent esophageal symptoms in the absence of a structural, mucosal, or motility abnormality that adequately explains the symptoms, in accordance with the Rome V diagnostic criteria. Image courtesy of the authors.

Tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and trazodone have demonstrated benefit, whereas the evidence for selective serotonin reuptake inhibitors is less consistent[18,19]. Psychological interventions, particularly gastrointestinal symptom–directed cognitive behavioral therapy and gut-directed hypnotherapy, may be used as adjunctive treatments, especially in the presence of hypervigilance or symptom-related anxiety[20-22].

Functional heartburn

Functional heartburn is characterized by a retrosternal burning sensation that persists despite optimized antisecretory therapy with a PPI or PCAB and cannot be explained by GERD, mucosal abnormalities, or major motility disorders. Unlike reflux hypersensitivity (*vide infra*), functional heartburn is not characterized by a temporal association between symptoms and physiologic reflux episodes[2,3]. Rome V, in conjunction with the Lyon Consensus 2.0, helps distinguish these phenotypes and guides treatment toward their respective underlying mechanisms. Rome V requires bothersome symptoms at least once per week during the preceding 3 months, with symptom onset at least 6 months before diagnosis, and persistence despite optimized PPI or PCAB therapy for at least 8 weeks. The estimated population prevalence of functional heartburn is approximately 1%, although it is likely underestimated because diagnosis requires objective assessment of reflux exposure by pH monitoring[15]. Among patients presenting with heartburn or reflux-like symptoms, approximately 20%–30% may have a phenotype consistent with functional heartburn[2]. In patients with PPI-refractory symptoms, prolonged pH-monitoring studies suggest that approximately 18%–30% have normal acid exposure and no symptom association[23,24].

Upper endoscopy allows erosive esophagitis, strictures, and other mucosal diseases to be excluded. In patients

with refractory symptoms, endoscopy should ideally be performed after discontinuation of PPIs and PCABs for 2–4 weeks when the objective is to determine whether previously undiagnosed GERD is present. Although biopsies to exclude eosinophilic esophagitis are desirable, they are not routinely required in the absence of dysphagia, chest pain, or other suggestive findings[5,25]. The key test for differentiating functional heartburn from GERD or reflux hypersensitivity is ambulatory reflux monitoring. When available, prolonged wireless pH monitoring may be particularly useful because it allows assessment of day-to-day variability in acid exposure[2,23]. According to the Lyon Consensus 2.0, an acid exposure time (AET) <4% and fewer than 40 reflux episodes support the exclusion of GERD, whereas an AET >6% supports its diagnosis. Intermediate values are inconclusive and require integration with other parameters[2,26]. pH-impedance monitoring may provide additional information, particularly when assessment of the association between symptoms and nonacid reflux episodes is required. Mean nocturnal baseline impedance (MNBI) may also contribute to interpretation: values >2,500 Ω support a functional heartburn phenotype, whereas values <1,500 Ω favor GERD[2,26]. High-resolution manometry does not diagnose functional heartburn but should be performed when necessary to exclude major motility disorders according to Chicago Classification v4.0[3].

Treatment is directed primarily toward neuromodulation of esophageal symptom perception. Low-dose neuromodulators, such as tricyclic antidepressants, may be considered, following principles similar to those used in other esophageal DGBIs. Specific evidence for functional heartburn remains limited, and treatment should be individualized. The first step is to explain the diagnosis. Once clinically relevant GERD has been excluded, further escalation of acid suppression or repetition of invasive testing generally provides little additional benefit. Antireflux surgery should be avoided in patients with functional heartburn. Psychogastroenterology interventions are particularly relevant in the presence of hypervigilance, symptom-specific anxiety, or maladaptive beliefs. Gastrointestinal symptom–directed cognitive behavioral therapy may improve symptoms and quality of life, while techniques such as hypnotherapy, relaxation, and diaphragmatic breathing represent low-risk alternatives[20,21].

Reflux hypersensitivity

Reflux hypersensitivity is characterized by heartburn or chest pain in patients with normal endoscopy and physiologic reflux exposure who nevertheless demonstrate a positive temporal association between symptoms and reflux episodes detected during monitoring. This represents the principal distinction from functional heartburn, in which no such association is present[2,3]. Thus, both diagnoses may be associated with normal acid exposure, but the key question is whether reflux episodes, despite being physiologic, temporally coincide with symptoms. A symptom index (SI) ≥50% and symptom association probability (SAP) ≥95% support a temporal relationship between symptoms and reflux episodes[2]. pH-impedance monitoring is particularly useful because it allows both acid and nonacid reflux episodes to be identified and determines whether they coincide with symptom onset. The decision to perform testing on or off acid suppression depends on whether GERD has previously been objectively established[2]. Regurgitation, belching, and symptoms attributable to rumination or supragastric belching are not included in this diagnosis and should prompt consideration of other mechanisms, which will be addressed in other reviews[27].

The estimated population prevalence is approximately 0.6%–0.8%, although studies of patients with refractory symptoms have reported substantially higher rates[15]. Depending on the population studied and the criteria applied, reflux hypersensitivity has been reported in approximately 10%–42% of patients with persistent symptoms despite treatment, reflecting the heterogeneity of this population[24,28–31]. In clinical practice, rather than focusing on a single prevalence estimate, it is important to recognize that reflux hypersensitivity represents a common phenotype among patients with persistent symptoms and inconclusive or normal reflux studies.

As with the other entities, treatment should begin with a clear explanation of the diagnosis. It is important to convey that the patient has physiologic reflux exposure and that the underlying problem is not necessarily excessive acid production, but rather an exaggerated response to stimuli that would be tolerated by others. Unlike functional heartburn, some patients with reflux hypersensitivity may benefit from acid suppression, particularly when symptomatic episodes are associated with acid reflux. However, the response is generally less predictable when weakly acidic or nonacid reflux episodes predominate[32,33]. Neuromodulators represent an important therapeutic strategy, particularly when symptoms persist despite adequate acid suppression. Tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids have been studied, although specific evidence remains limited. One clinical trial also demonstrated a benefit of citalopram compared with placebo in patients with reflux hypersensitivity[34]. Antireflux surgery should be reserved for carefully selected patients with objectively demonstrated GERD and should not be performed solely on the basis of a positive association between reflux and symptoms[24,35,36]. Psychogastroenterology interventions,

including cognitive behavioral therapy, hypnotherapy, and other behavioral strategies, may complement treatment, particularly in the presence of hypervigilance or symptom-related anxiety.

Globus

Globus is defined as a persistent or intermittent, typically nonpainful sensation of a lump, foreign body, or "something stuck" in the throat, usually localized along the midline between the thyroid cartilage and the sternal notch[1]. A characteristic feature is the absence of dysphagia or odynophagia, with symptoms improving in many patients while eating or swallowing. The diagnosis requires exclusion of a structural or inflammatory cause, GERD, or a major motility disorder that could account for the symptoms. Accordingly, globus should be distinguished from true dysphagia from the outset, as the latter warrants a different diagnostic evaluation. Rome V specifies that symptoms must be bothersome, occur at least once per week during the preceding 3 months, have begun at least 6 months before diagnosis, and persist despite optimized antisecretory therapy for at least 8 weeks. The diagnosis also requires exclusion of GERD and major motility disorders[1-3]. Globus is a common symptom in the general population. Population-based studies have reported widely varying prevalence estimates depending on the definition used, ranging from approximately 0.8% to more than 20%[15]. It may occur at any age but is more common during middle age. Although it affects both sexes, women seek medical attention more frequently. Its chronic course is an important consideration. Although globus is a benign condition, symptoms may persist for years; therefore, repeated investigations should be avoided once relevant causes have been adequately excluded[1].

The pathophysiology of globus is multifactorial. In some patients, peripheral triggers such as reflux or local abnormalities may be present; however, in the absence of an identifiable cause, altered perception and processing of esophagopharyngeal signals appears to play a particularly important role. Esophageal distension studies suggest that some patients with globus exhibit increased sensitivity to stimuli that do not elicit symptoms in healthy individuals, supporting a mechanism of visceral hypersensitivity[37]. Although abnormalities in upper esophageal sphincter function have been described, these findings have not been consistent and should not be considered a universal explanation for the symptom[38]. Emotional factors may also modulate symptom severity. Anxiety, stress, and life events may exacerbate globus, although the presence of anxiety or a psychiatric disorder is not required to establish the diagnosis[39].

Once relevant causes have been excluded, the first step is to provide an explanation of the diagnosis and reassurance. It is important to convey that idiopathic globus is benign and that persistence of the symptom does not necessarily indicate progressive disease. PPIs or PCABs may initially be used when concomitant GERD is suspected; however, if there is no response, acid suppression should not be continued or intensified indefinitely. Ablation of a gastric heterotopia patch has been associated with symptomatic improvement in small studies, but the available evidence is insufficient to recommend this procedure routinely[40]. In patients with persistent globus without an identifiable cause, treatment should be directed primarily toward behavioral and psychogastroenterology-based strategies. Cognitive behavioral therapy, speech-language therapy incorporating pharyngolaryngeal relaxation techniques, and hypnotherapy have shown favorable results in small studies[41]. Given their low risk and the benign nature of the disorder, these interventions are particularly attractive before pharmacologic treatment or invasive procedures are considered.

Functional dysphagia

Functional dysphagia is characterized by a sensation of impaired passage of food in the absence of a structural, mucosal, or major motility abnormality that adequately explains the symptoms. The diagnosis therefore requires a more comprehensive evaluation than simply demonstrating normal endoscopy with biopsies and normal manometry. In line with Chicago Classification v4.0, Rome V emphasizes the need to exclude major motility disorders and esophagogastric junction outflow obstruction. However, high-resolution manometry may not detect subtle mechanical abnormalities or impaired esophageal distensibility. In selected patients, functional lumen imaging probe (FLIP) testing or a timed barium esophagram may provide additional information before a diagnosis of functional dysphagia is established[3,42,43]. The exact prevalence remains uncertain. Population-based studies using Rome IV criteria have estimated a prevalence of approximately 3%, although this figure likely overestimates the true prevalence because patients in whom structural or motility disorders were not systematically excluded may have been included[15,44]. The availability of FLIP has also enabled the identification of abnormalities that may previously have been misclassified as functional dysphagia, suggesting that this may be the least common entity among esophageal DGBIs[43,45].

From a practical standpoint, functional dysphagia should be considered only after a sufficiently comprehensive structural, mucosal, and motility evaluation has been completed, rather than simply on the basis of normal manometry. Esophageal hypersensitivity may amplify sensations generated by esophageal distension or bolus passage, causing minor physiologic variations to be perceived as food

sticking. In addition, some FLIP studies suggest that a subset of patients may have reduced esophageal wall distensibility even when conventional tests are normal[46,47]. As with other esophageal DGBIs, hypervigilance, anxiety, and fear of swallowing or choking may increase symptom severity and perpetuate the disorder[48]. This does not imply that dysphagia is "psychological"; rather, the perception of esophageal transit results from an interaction between peripheral stimuli and their central processing.

As previously discussed, treatment should begin with an explanation of the diagnosis and reassurance once an appropriate evaluation has been completed. In mild cases, simple measures such as eating slowly, chewing thoroughly, maintaining an upright position, and using liquids to facilitate bolus passage may be helpful[49]. When concomitant GERD is suspected, a limited course of antisecretory therapy may be considered. However, in the absence of evidence of reflux, acid suppression should not be continued indefinitely. Evidence supporting the use of neuromodulators remains limited, but they may be considered in selected patients, particularly when hypersensitivity, hypervigilance, or food-related anxiety predominates. Empiric dilation may benefit some patients with unexplained esophageal dysphagia, but its role should be interpreted cautiously. The incorporation of FLIP into the diagnostic evaluation may help identify patients with subtle abnormalities in distensibility or outflow obstruction in whom targeted intervention would be more appropriate[50–52]. When fear of swallowing, maladaptive beliefs, or hypervigilance is present, psychogastroenterology interventions, including cognitive behavioral therapy, psychoeducation, and breathing techniques, may be useful as part of comprehensive management[20].

CONCLUSIONS

The Rome V criteria consolidate a conceptual framework for esophageal disorders of gut-brain interaction (DGBIs) in which symptoms are interpreted in conjunction with endoscopic and physiologic findings. Integration with Chicago Classification v4.0 and Lyon Consensus 2.0 provides a more structured approach to excluding major motility disorders and GERD, thereby reducing the risk of overinterpreting minor physiologic abnormalities. Once relevant structural, inflammatory, motility, and reflux-related diseases have been excluded, the focus should shift toward the mechanisms that determine symptom perception, including esophageal hypersensitivity, hypervigilance, and cognitive-affective factors. This has an important practical implication: persistent symptoms do not necessarily warrant additional testing or further escalation of acid suppression. Management should be individualized and, when appropriate, incorporate education, neuromodulation, and behavioral interventions. For the general gastroenterologist, the principal contribution of Rome V is to provide a framework for determining when further investigation is warranted and when the therapeutic objective should shift from searching for an abnormality to addressing the mechanisms that perpetuate symptoms.

Conflicts of interest

None.

Use of artificial intelligence

Artificial intelligence was used solely as an auxiliary tool for the grammatical and stylistic review and correction of the manuscript. The content, analysis, and interpretation remain the responsibility of the authors.

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Author contributions

- Study design and conception: Christian von Muhlenbrock.
- Data acquisition: Christian von Muhlenbrock and Javier Venegas.
- Data analysis and interpretation: Christian von Muhlenbrock.
- Manuscript drafting: Christian von Muhlenbrock and Javier Venegas.
- Critical revision of the manuscript: Christian von Muhlenbrock and Federico Aronsohn.

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