Management of reflux hypersensitivity

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Purpose of review
The challenges in distinguishing reflux hypersensitivity (RH) from other functional esophageal disorders demand a comprehensive understanding of RH. This review aims to discuss the latest practices in diagnosis and management of RH, examining the pathophysiology, diagnostic criteria, and evolving treatment strategies for RH, with an emphasis on the role of effective patient-physician communication.

Recent findings
Esophageal hypersensitivity appears to play a significant role in symptoms generation for RH patients. Diagnostic algorithms have improved with updates from the Lyon consensus. Management strategies including treatments with neuromodulators, proton-pump inhibitors, behavioral interventions, and antireflux surgery are potential therapeutic options for patients with RH.

Summary
Effective RH management requires a patient-centered approach that considers possible pharmacologic, behavioral, and surgical strategies. Effective patient-physician communication is essential to educate patients and address their concerns about neuromodulators, and to reframe treatment strategies to target esophageal hypersensitivity rather than a psychiatric disorder.

Keywords
effective patient-physician communication, reflux hypersensitivity

INTRODUCTION

Reflux hypersensitivity (RH) has been considered a functional esophageal disorder characterized by reflux symptoms in the setting of normal acid exposure and positive symptom association documented by esophageal reflux monitoring. RH accounts for 14% of all patients presenting with heartburn [1]. Despite the setting of normal acid exposure, patients with RH can experience genuine reflux symptoms due to esophageal hypersensitivity. Esophageal hypersensitivity refers to when the esophagus exhibits an exaggerated response to stimuli, leading to pain or discomfort despite the absence of visible pathology (i.e., erosive esophagitis). Although proton pump inhibitor (PPI) acid-suppressant therapy achieves mucosal healing in 90% of erosive esophagitis (EE) cases, only 48% of reflux cases experience symptomatic resolution after 2 months of PPI therapy. This disparity is thought to be due to esophageal hypersensitivity, with a gap between symptoms and mucosal healing [2▪▪]. Therefore, esophageal hypersensitivity plays a significant role in RH, and it is regarded as the cornerstone of functional esophageal disorders.

Functional esophageal disorders account for more than 90% of reflux patients who lack adequate response to twice daily PPI therapy, and RH accounts for 35% of these patients who fail twice daily PPI therapy [3]. According to ROME IV criteria, RH [4] is defined as: presence of retrosternal symptoms including heartburn and chest pain, absence of eosinophilic esophagitis on esophageal biopsies, absence of esophageal motor disorders (i.e. achalasia, ineffective esophageal motility, absent contractility), and presence of reflux events (including nonacid events) in the setting of normal esophageal acid exposure. Criteria must be fulfilled for 3 months with symptom onset at least 6 months prior to diagnosis, with a frequency of symptoms occurring at least twice weekly. ROME IV criteria for RH share high overlap with diagnostic criteria for functional heartburn (FH), and this along with potential GERD overlap can make management of RH challenging.

This challenge in management is further compounded by use of neuromodulator therapy in RH.

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KEY POINTS

- Reflux hypersensitivity (RH) is a functional esophageal disorder characterized by esophageal hypersensitivity and a positive symptom association in the setting of normal acid exposure.
- Esophageal hypersensitivity is the primary driving factor behind symptom generation in RH, with contributing factors including weakly acidic reflux, impaired mucosal integrity, and psychological comorbidities.
- Diagnosing RH requires pH-impedance testing to confirm normal acid exposure with positive symptom association, and complementary impedance metrics can aid diagnostic confidence.
- Treatment of RH includes neuromodulators, behavioral therapies, and surgical options tailored to individual patient needs.
- Effective patient-physician communication is essential in RH management to quell patient concerns regarding their symptom burden despite normal acid exposure and enhance understanding of neuromodulator therapy

When used for a functional condition like RH that is not inherently psychiatric, this can lead to patient reluctance and concerns about stigma. Effective patient-physician communication can enhance patient understanding and alleviate anxiety [5] about neuromodulator therapy by reframing treatment as targeting brain-gut interaction rather than a psychiatric condition. Given the complex management and increased prevalence of anxiety among RH patients [6], there is a need to understand the pathophysiology, clinical presentation/diagnosis, and treatment of RH, in order to provide effective patient-physician communication in the clinical setting. This review aims to reach this objective.

PATHOPHYSIOLOGY

The pathophysiology of RH is multifactorial, with esophageal hypersensitivity due to central/peripheral sensitization being the primary driving factor behind symptom generation. Esophageal hypersensitivity refers to the perception of pain when there should be no pain (allodynia), or increased pain when there should be less pain (hyperalgesia). Potential factors contributing to esophageal hypersensitivity include weakly acidic reflux events, impaired mucosal integrity, TRPV1 receptors or acid sensing ion channels, psychological comorbidity, stress, anxiety, and sleep deprivation [4]. RH patients can have lower tolerance for pain as noted with increased chemo- and mechano-receptor sensitivity to balloon distention and acid perfusion when RH patients are compared to healthy controls, FH patients, and nonerosive reflux disease (NERD) patients [4]. This lower threshold for pain (esophageal hypersensitivity) introduces symptomatic burden for patients with RH.

Even in the setting of normal acid exposure, RH patients can experience symptoms from weakly acidic reflux events due to esophageal hypersensitivity. Savarino *et al.* found significantly higher numbers of weakly acidic reflux events and higher rates of proximal reflux in RH patients than in those with FH [7]. It is thought that weakly acidic reflux events may induce microscopic injury to the esophageal mucosa, resulting in heightened perception of symptoms and increased sensitization. Another factor in esophageal hypersensitivity is the mucosal integrity of the esophagus. Mucosal integrity (MI) refers to esophageal barrier function, and impaired MI can contribute to symptom burden associated with RH. Impaired MI enables passage of noxious substances through the mucosa, and the degree of MI impairment correlates directly with levels of hypersensitivity in NERD [4]. Esophageal mucosal dilated intercellular space (DIS) is a pathologic finding holding a causal link with MI [6], and DIS may also be a contributing factor in esophageal hypersensitivity.

Esophageal hypersensitivity can also be affected by sensory nerve channels including transient receptor potential vanilloid reptor-1 (TRPV1) and acid-sensing ion channels (i.e. ASIC3) that can increase visceral hypersensitivity and inflammation from epithelial response [6]. Lastly, patient psychological comorbidities, stress, anxiety, and sleep deprivation can play a role in visceral hypersensitivity and potentiation of stimuli within the esophagus [6]. These psychosocial and behavioral factors may be implicated in the altered processing of afferent signals from the esophagus, thereby subjecting patients to increased symptom burden. Anxiety and RH create a vicious cycle in which heightened anxiety amplifies visceral perception [6] and lowers the pain threshold, while persistent esophageal discomfort reinforces stress and anxiety, further exacerbating symptoms.

CLINICAL PRESENTATION AND DIAGNOSIS

Without esophageal reflux monitoring, the diagnosis of RH can be challenging given its symptom similarities to FH. Like LH, one cannot distinguish between the severity, duration, and frequency of symptoms in RH compared to other phenotypes of GERD [8]. RH and FH share symptom overlap with other functional gastroduodenal disorders

including supragastric belching and rumination syndrome, and studies show that about 40% and 10% of patients with RH have supragastric belching and rumination syndrome, respectively [9]. One study showed the following profile characterizing a cohort of RH patients: 66.5% women, 47.7% with hiatal hernia, 48.2% with irritable bowel syndrome, 15% with functional dyspepsia, and 35.8% with anxiety [10]. Though a recent study did demonstrate a higher rate of anxiety among patients with FH [11] when compared to patients with RH, the overall increased prevalence of functional gastrointestinal disorders among both RH and FH suggests a common underlying mechanism of visceral hypersensitivity.

The notion of a common underlying mechanism of visceral hypersensitivity in FH and RH is consistent with the similar diagnostic algorithm used to diagnose those disorders. Per ROME IV criteria [4], patients with typical reflux symptoms refractory to high-dose proton pump inhibitor (PPI) or potassium-competitive acid blocker (P-CAB) therapy for 8 weeks should have esophagogastroduodenoscopy (EGD) with multiple biopsies taken to assess for structural and mucosal abnormalities (e.g., eosinophilic esophagitis). High-resolution manometry should be performed to rule out motor processes, as reflux-like symptoms can be noted in patients with disorders of esophageal motility (up to 75% of achalasia patients [12] and 35% of patients with hypercontractile esophagus [13]). When EGD and pathology findings are negative, formally establishing esophageal acid exposure with pH testing should be performed with either 24-h catheter-based or wireless capsule testing. Formal reflux testing should be completed ON acid suppression therapy if GERD has previously been documented (by endoscopy or prior pH monitoring), and testing should be done OFF therapy if there is no prior documentation of reflux disease. Patients without reflux esophagitis on endoscopy who have abnormal acid exposure OFF therapy are considered to have NERD. In the setting of normal esophageal acid exposure, reflux symptom association (by symptom index or symptom association probability) is negative in FH and positive in RH. ROME IV criteria also establish that patients with documented GERD who have normal acid exposure while they are ON PPI therapy are considered to have FH with GERD overlap if there is a negative symptom reflux association, or RH with GERD overlap if there is positive reflux symptom association. 96-h wireless pH monitoring is considered the preferred diagnostic tool for establishing whether or not patients have GERD, and wireless monitoring can establish a diagnosis of RH when it shows normal acid exposure time and a positive correlation between the "normal" acid reflux episodes and heartburn episodes. However, wireless pH monitoring does not detect nonacidic reflux episodes. Detection of RH to nonacidic reflux episodes requires impedance-pH monitoring, which presently is only available as a 24-h catheter-based test.

While ROME IV provides guidelines for diagnosis, the Lyon consensus 2.0[2] adds a necessary complement by confirming cutoff criteria for abnormal acid exposure and positive reflux symptom association. Lyon 2.0 consensus established the following criteria as conclusive evidence of abnormal acid exposure: Los Angeles grade B-D esophagitis, peptic esophageal stricture, biopsy-confirmed Barrett's esophagus, acid exposure time $>6\%$. Regarding reflux symptom association, the most common indices are the symptom index (SI) and symptom association probability (SAP). SI is determined by dividing the number of reflux-related symptom episodes by the total number of symptom episodes, where symptoms marked within 2 min of a reflux episode are considered reflux-related. SI is considered positive when $\geq 50\%$. An alternative index is the SAP, which divides the day into 2-min increments, evaluates those increments for reflux-symptom correlations, and uses a Fisher's exact test to determine the probability that reflux and symptom events are randomly distributed. An SAP $\geq 95\%$ is considered positive, where the SAP refers to the statistical association between reflux episodes and symptoms. Overall, the Lyon 2.0 consensus established that having acid exposure time $<4\%$ on all days of testing and positive symptom association with SI and/or SAP, increases confidence for a diagnosis of RH.

When acid exposure time is 4–6% and/or only SI or SAP is positive, the diagnosis of RH can be inconclusive. The mean nocturnal baseline impedance (MNBI), postreflux swallow peristaltic wave (PSPW) index, and number of reflux events (including weakly acidic) are complementary impedance metrics that can be used to aid confidence in RH diagnosis. The MNBI is a metric that provides long-term evidence of reflux-induced mucosal injury, and it is a surrogate marker for mucosal integrity. Some studies have shown MNBI can help differentiate between FH and RH, with NERD patients having significantly lower baseline impedance values [4]. The Lyon consensus 2.0 revised prior MNBI cutoff criteria from >2292 Ohm to >2500 Ohm as evidence against GERD, pointing towards functional heartburn. It is recognized that additional studies are needed to define specific MNBI cutoff criteria to discriminate between RH and FH, though one has shown that the combined use of MNBI and PSPW index

discriminates well between FH and RH (AUROC >0.85) [14]. PSPW can be a useful tool for phenotyping refractory GERD, as a low PSPW index suggests that there is impaired clearance of refluxed material. Some studies show RH patients have a lower PSPW index than FH patients, which likely reflects poor reflux clearance in the RH population. When acid exposure time is inconclusive, the number of reflux events can aid as adjunctive evidence for GERD, with >80 reflux episodes in a day thought to be abnormal [4]. Lastly, Savarino *et al.* [7] suggest that RH patients have a higher number of weakly acidic events and higher rate of proximal reflux than FH patients, and that this can be considered when differentiating between these two disorders in the absence of other evidence. Though these impedance metrics are not diagnostic for GERD or RH, use of these complementary markers may aid in phenotyping the type of reflux disease.

TREATMENT

As the definition of FH has evolved through successive Rome criteria updates, the concept of RH has similarly shifted, prompting changes in therapeutic strategies. There is growing emphasis on an integrative approach that combines mind-body, pharmacological, and surgical interventions with multidisciplinary framework. Given RH is a functional esophageal disease heavily affected by the brain-gut axis, mind-body interventions may be effective for symptom control such as diaphragmatic breathing. Diaphragmatic breathing has been shown to have equal or greater efficacy than other therapies for supragastric belching and rumination syndrome [15▪], and with low adverse risk profile, diaphragmatic breathing is an excellent option for RH patients to trial first. Given the high overlap with other behavioral disorders, cognitive behavioral therapy to curtail symptoms and lifestyle modifications for anxiety/stress reduction should be considered [4], and RH patients may benefit from referral to GI psychology for specialized management.

Pharmacologically, patients are often trialed on antisecretory agents (PPIs/P-CABs) to maximize acid suppression. When RH is confirmed, PPIs/P-CABs are recommended to be stopped given the pathophysiology often lies within esophageal hypersensitivity. Histamine-2 receptor antagonists have been shown to reduce esophageal sensitivity to acid exposure. This suggests that ranitidine may help RH symptoms by both modulating visceral hypersensitivity and suppressing acid production [16]. Further, neuromodulators can aid visceral hypersensitivity among patients with functional esophageal disorders. However, there are few studies assessing the efficacy of neuromodulators in the RH patient population. Neuromodulators, such as antidepressants and anticonvulsants, act on the brain-gut axis and both central and peripheral neurons to alter visceral pain perception in patients with RH [17]. Tricyclic antidepressants (TCAs) have been shown to be effective in managing esophageal pain for individuals with functional esophageal disorders, including functional chest pain, globus sensation, and noncardiac chest pain. However, these medications generally do not influence esophageal sensitivity thresholds in humans, and their effectiveness in treating RH remains unclear [18]. Selective serotonin reuptake inhibitors (SSRIs) have proven effective in treating various functional esophageal disorders. Notably, SSRIs are the only class of neuromodulators that have been tested in patients with RH. In a randomized, double-blind, placebo-controlled trial, citalopram effectively reduced heartburn symptoms in individuals with RH, resulting in nearly twice the symptom reduction compared with placebo [19]. Treatment should be tailored using effective patient-physician communication to understand patient's response to therapy, side effects, availability, and patient preference [6].

If RH patients remain refractory to pharmacologic therapy, surgical intervention can be considered but with caution. Spechler *et al.* recently validated the effectiveness of surgery in a prospective, randomized, controlled trial [20]. This study utilized preoperative pH-impedance monitoring to identify different GERD phenotypes. Laparoscopic Nissen fundoplication demonstrated significantly superior reflux symptom control (67%) compared to active medical treatment (28%) and control medical treatment (12%) in patients with a confirmed reflux-symptom association. These findings reinforce the success of antireflux surgery in patients with RH and highlight the importance of accurately distinguishing RH from FH, as FH patients are unlikely to benefit from surgical intervention.

CONCLUSION

RH is a functional esophageal disorder largely driven by esophageal hypersensitivity due to central/peripheral sensitization. Esophageal hypersensitivity can be influenced by stress, anxiety, and other psychological factors, making it difficult to distinguish RH from other functional esophageal conditions that are also modulated by the mind-gut axis including FH. Formal testing with pH-impedance monitoring plays a crucial role in confirming RH by identifying a positive symptom association in the setting of normal acid exposure. Other diagnostic tools, such as high-resolution manometry, can help

rule out structural or motor abnormalities. Overall diagnosis requires a holistic approach that integrates not only endoscopic data but the recognition of RH pathophysiology to discern for behavioral disorders that may increase suspicion for RH.

Treating RH also requires a holistic approach that integrates both physiological and psychological aspects of care. Given the significant overlap between RH and other functional and behavioral disorders, effective patient-physician communication should be a cornerstone of management. Effective patient-physician communication is a collaborative exchange of clear, compassionate, and honest information that fosters mutual understanding, trust, and informed decision-making [21]. Educating patients about the nature of RH – particularly the disconnect between positive symptom association in the setting of negative acid exposure – helps validate their experiences and reduce anxiety surrounding their condition. Another challenge in RH management is patients' concerns about using medications such as PPIs [22], SSRIs [23], or TCAs [24]. Effective patient-physician communication about the role of neuromodulators in modulating esophageal hypersensitivity, rather than treating a psychiatric disorder, can quell anxiety and improve symptoms [22,25▪▪]. Effective patient-patient communication can also aid in the discussion of mind-body and surgical interventions, and this has the potential to provide patients with an increased sense of control over their symptoms [21]. Ultimately, a patient-centered approach that emphasizes reassurance, education, and collaborative decision-making can enhance patient confidence, improve symptom management, and optimize overall quality of life for patients with RH.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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In an era of neuropsychopharmacology, effective patient-physician communication has been shown to enhance the patient-physician relationship and improve outcomes. This is imperative in the management of RH where neuromodulation is often a cornerstone of management. Effective patient-physician communication is essential to address patient questions about requirements for neuromodulation or etiology of their reflux symptoms in the setting of normal acid exposure.