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REVIEW ARTICLE

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A perspective on the clinical relevance of weak or nonacid reflux

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Abstract

Background: Advances in ambulatory esophageal reflux monitoring that incorporated impedance electrodes to pH catheters have resulted in better characterization of retrograde bolus flow in the esophagus. With pH-impedance monitoring, in addition to acid reflux episodes identified by pH drops below 4.0, weakly acid reflux (WAR, pH 4–7) and nonacid reflux (NAR, pH >7.0) are also recognized, although both may be included under the umbrella term NAR. However, despite identification of ambulatory pH-impedance monitoring, data on clinical relevance and prognostic value of NAR are limited. The Lyon Consensus, an international expert review that defines conclusive metrics for gastroesophageal reflux disease (GERD), identifies NAR as "supportive" but not conclusive for GERD.

Purpose: This review provides perspectives on whether NAR fulfills three criteria for clinical relevance: whether NAR sufficiently explains pathogenesis of symptoms, whether it is associated with meaningful manifestations of GERD, and whether it can predict treatment efficacy.

KEYWORDS
gastroesophageal reflux disease, nonacid reflux, reflux monitoring, weakly-acid reflux

1 | INTRODUCTION

Up to 13% of the global population suffer from gastroesophageal reflux disease (GERD) symptoms on at least a weekly basis, with a rising prevalence in the US population.[1,2] The Montreal consensus introduced a practical definition for GERD: "symptoms or complications arising from the reflux of gastric contents into the esophagus".[3] Based on original studies where acid instilled into the esophagus directly triggered pain, with shorter lag time to symptoms at lower pH levels,[4] the Montreal definition supported the reflux of *acidic* gastric contents in triggering symptoms. In fact, a long-touted axiom was "no acid, no heartburn." It has since become evident that pathophysiologic mechanisms of symptoms attributed to reflux of gastric content are not that simple. Symptoms may be generated by chemical irritants in gastric juice other than acid, such as bile acids, trypsin, and pepsin.[5] Additional mechanisms include esophageal stretch receptor activation from esophageal distension, such as that from refluxed nonacidic content, and motor responses to various stimuli, often in exaggerated fashion. Esophageal hypersensitivity from alterations in esophageal sensory perception as well as enhanced esophageal afferent neuron location and sensitivity through specific acid sensing channel receptors and central sensitization mechanisms[6–9] can also initiate and propagate symptoms. Finally, esophageal hypervigilance and catastrophization can modify the patient's perception and response to esophageal triggering of symptoms.[10] Therefore, it has become evident since the introduction of the Montreal definition that not all troublesome symptoms attributed to GERD have demonstrable abnormalities on ambulatory reflux monitoring.

Objective evidence of abnormal gastroesophageal reflux focuses on acid burden in the distal esophagus, primarily quantified as the cumulative percentage time pH is <4.0 in the distal esophagus over the course of a day, termed acid exposure time (AET).[11] Pathologic AET associated with reflux symptoms, erosive changes in esophageal mucosa, and symptom improvement from acid suppressive

therapy and/or antireflux interventions.[12,13] One mechanism challenging the "no acid, no heartburn" axiom is the ability of nonacid (NAR) or "weakly acid" reflux (WAR) to cause symptoms. Despite persistence of WAR or NAR in a proportion of patients with "refractory GERD," their clinical relevance remains in flux. Outcomes studies for either medical or surgical therapy find that while metrics of acid burden are predictive of favorable treatment response, outcomes from treating nonacid reflux remain inconsistent. To establish the relevance of NAR to reflux syndromes, three criteria need to be fulfilled: Can the pathogenesis of patient symptoms be explained? Can harm or complications be demonstrated in objective terms? Does detection on diagnostic testing effectively help guide management or predict treatment efficacy? The goal of this review is to determine whether NAR or WAR fulfills these criteria.

Key Points

- The clinical relevance of non-acid or weakly acid reflux, defined as episodes in which pH is above 4, is questioned.
- Current evidence does support its role in symptom pathogenesis for regurgitation, reflux hypersensitivity, pulmonary conditions, and to a lesser extent heartburn and extra-esophageal symptoms.
- Excess weakly acid reflux determined by quantitative testing may predict treatment response, however it is often combined with total reflux exposure metrics in outcome studies, tempering strength of prediction.

2 | TERMINOLOGY AND DEFINITIONS

While pH-metry utilizes distinct acid-based parameters such as AET, pH-impedance monitoring provides a means for detecting both antegrade and retrograde liquid bolus flow regardless of pH. By combining a pH sensor with multiple impedance electrodes, a reflux event can be characterized by duration, extent of proximal flow, and degree of acidification.[14,15] An event during which pH is <4 is considered acidic, between 4 and 7 weakly acidic, and above 7 nonacidic.[16] Terminology is somewhat inconsistent throughout the literature; some studies differentiate weakly acid events from "nonacidic" or alkaline events, while others simplify the terminology by defining any event with pH above 4 as "nonacidic." For simplification in this review, the term "nonacid reflux" will be used to encompass both terms except where specified.

Physiologically, true NAR is rare and would require the lack of gastric acid production, either suppressed by antisecretory medications, or because of hypochlorhydria. A few normative studies have recorded WAR and NAR (Figure 1). In a study of 60 asymptomatic controls undergoing 24-hour pH-impedance testing, the 95th percentile value for WAR was 26, compared with 1 for NAR.[14] In a French cohort of 46 healthy volunteers, the 95th percentile value for WAR was 21, and no patient had true NAR[17]; in an Italian cohort of 48 healthy volunteers, the 95th percentile NAR value (which was not differentiated from WAR) was 45.[18] In 390 international asymptomatic controls, the 95th percentile value for NAR was 27 using the Sandhill/Diversatek system, and 37 using the Laborie system.[19] Defining thresholds for NAR in patient populations has been challenging due to the uncertainty of direct clinical relevance, and total reflux episode counts that include both acidic and NAR episodes are more frequently reported.

In the original normative pH-impedance study of 60 healthy volunteers, the 95th percentile value for total number of reflux events was 73 (Figure 2), and this threshold has been used variably as a singular cutoff below which reflux episode counts were designated physiologic.[14] However, this is problematic, as other studies have reported lower 95th percentile values: 53 in the French healthy volunteer cohort of 46 patients,[17] and 54 in the Italian healthy volunteer cohort of 48 patients.[18] Because of these inconsistencies, a large international multicenter study of 390 healthy volunteers was undertaken to conclusively define normative thresholds. This study revealed that normative values vary by proprietary software and catheter systems. The 95th percentile for total reflux events was significantly different between the two systems used for analysis, 55 for Diversatek (Boulder CO, USA) and 78 for Laborie (Enschede, Netherlands), $p < 0.02$. Additionally, normative values were associated with regional differences, which should be taken into account when interpreting the literature.[19]

The Lyon Consensus proposed thresholds of >80 total events as supportive of GERD, and between 40 and 80 as equivocal based on expert consensus and on available normative data (Figure 2), with the caveat that this measure is considered an adjunctive metric supporting AET rather than a stand-alone metric.[11,20] Post hoc analysis from a randomized trial evaluating MSA and twice-daily PPI therapy[21] indicates that treatment satisfaction and improvement of GERD-health-related quality of life scores associated with reflux counts below 40, and counts >80 predicted symptom improvement in patients crossing over from bid PPI to MSA arms.[22] These cutoffs include both acidic and nonacidic episodes in the count, and available data indicate a higher sensitivity for detection of reflux-symptom association when such total reflux episode counts are incorporated into the symptom association analyses.

3 | THE ROLE OF NONACID REFLUX IN GERD POPULATIONS

The pathogenesis of GERD symptoms stems from the direct exposure of the esophageal epithelium to gastric refluxate. Acid is detected by acid sensing ion channels in the esophageal epithelium[23] while both acid and nonacid are detected by transient receptor potential cation channel subfamily V member 1 (TRPV1) receptors.[24] However, other mechanisms such as luminal distention, decreased clearance, superficial location of sensory afferents,

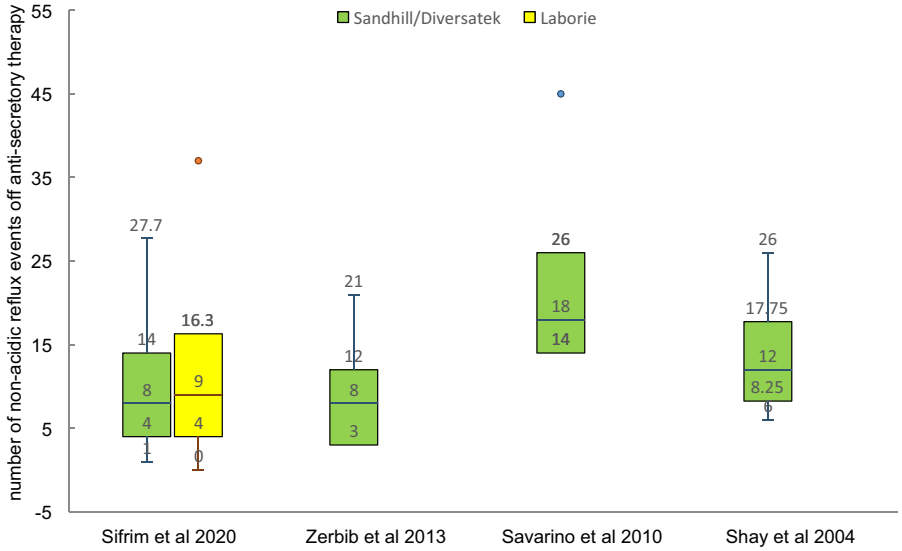

FIGURE 1 Normative values for nonacidic reflux (NAR) or weakly acidic reflux (WAR) on pH-impedance studies performed off antisecretory therapy in healthy volunteers. The boxes represent 25th–75th percentile values, with a median line. The whiskers represent 95th percentile, and when available, 5th percentile values. Ninety-fifth percentile values appear variable between the studies, compromising the establishment of a normative threshold; besides, direct clinical relevance of NAR/WAR has been difficult to demonstrate.

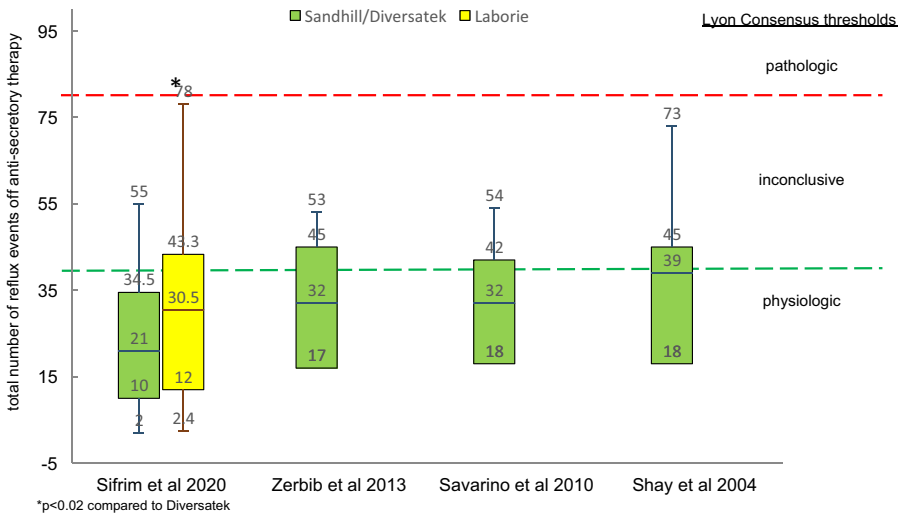

FIGURE 2 Normative values for total numbers of reflux episodes, including acidic reflux, nonacidic reflux (NAR), and weakly acidic reflux (WAR) on pH-impedance studies performed off antisecretory therapy in healthy volunteers. The boxes represent 25th–75th percentile values, with a median line. The whiskers represent 95th percentile values, and when available, 5th percentile values. While median values and 75th percentile values are generally at or below 40 reflux episodes, 95th percentile values are higher, but less than 80 reflux episodes. On the basis of these normative values, expert opinion, and limited available outcome studies, the Lyon Consensus has suggested >80 episodes as pathologic, <40 episodes as physiologic, and 40–80 episodes as inconclusive. Reflux episode counts have been designated adjunctive rather than primary criteria for establishing presence of GERD.

visceral hypersensitivity, and hypervigilance can play a role.[8,9] Nevertheless, acid suppression with proton pump inhibitor (PPI) therapy is the mainstay of medical treatment for GERD and has proven effective for symptom control and healing of esophagitis in many high-quality studies.[25] Therefore, reflux of gastric acid is believed to be the dominant mechanism for symptom generation across GERD phenotypes. Nevertheless, nonacid reflux may play a role in unique populations.

3.1 | Refractory regurgitation

While PPIs reduce the number of acid reflux events, the overall number of reflux events remains the same, since selective inhibition of gastric acid secretion shifts reflux events from acid to nonacid. On 2-hour postprandial pH-impedance monitoring in 12 patients, Vela et al. recorded 98 acidic reflux events and 119 NAR, which shifted to 254 NAR and 7 acidic reflux events when testing

was repeated on PPI. Heartburn and acid taste were more commonly linked to acid events whereas regurgitation was reported equally with acid and NAR.[26] On pH-impedance testing in 168 patients with persistent GERD symptoms on twice-daily PPI, Maine et al. demonstrated that 37% had a positive symptom index (SI) with NAR compared with only 11% with acid reflux events. Regurgitation was the symptom most often associated with a positive SI with NAR.[27] These data support the use of reflux episode counts that include both acidic events and NAR when analyzing studies performed on antisecretory medications (Figure 3). Relevant to the evaluation of reflux-symptom association is that when regurgitation is the dominant symptom, the volume of refluxate that leads to the perception of regurgitation remains unknown, and likely varies from patient to patient since the lowest threshold for sensing gastric content in the esophagus is difficult to measure with pH-impedance monitoring.

Even though regurgitation is considered a typical GERD symptom, improvement in regurgitation is often relegated to a secondary outcome measure in GERD treatment studies, since this symptom does not respond well to antisecretory therapy.[28] Indeed, the original GERD quality of life questionnaire (GERD-HRQL) used in many GERD outcome studies does not query regurgitation severity.[29] Paradoxically, regurgitation is the GERD symptom that responds best to antireflux surgery (ARS), magnetic sphincter augmentation (MSA), and transoral endoscopic fundoplication (TIF).[30] A randomized control trial comparing MSA to twice-daily PPI in patients with regurgitation found that MSA performed better than PPI for symptom control (96% vs. 19%, $p < 0.001$).[31] While abnormal acid exposure was an inclusion criterion, a post hoc analysis of the pH-impedance testing parameters found that acid exposure variables decreased equally in both arms. Rather than pre-operative AET, reduction in reflux episodes to <35 had optimal performance characteristics in predicting treatment success, though acid reflux episodes and WAR were combined into a single metric.[22] WAR or NAR comprised 60% of the episodes when testing was performed on PPI. A randomized study of TIF vs. sham procedure with PPI therapy showed that TIF eliminated regurgitation in significantly more subjects (67%) compared with the PPI arm (45%, $p = 0.028$). As PPI therapy would have improved acid exposure but not total number of reflux events, the greater improvement in regurgitation in the TIF arm was likely due to improvement in total reflux events, including NAR.[32]

3.1.1 | Perspective

The presence of NAR is highly relevant to regurgitation associated with GERD, especially when pH-impedance monitoring is performed on PPI therapy. Consequently, abnormally high NAR can be used as a decision point in planning invasive GERD management (Figure 3). However, it is difficult to separate NAR from total reflux episodes, since GERD outcomes have been tested against total reflux episodes rather than NAR (Figure 2).

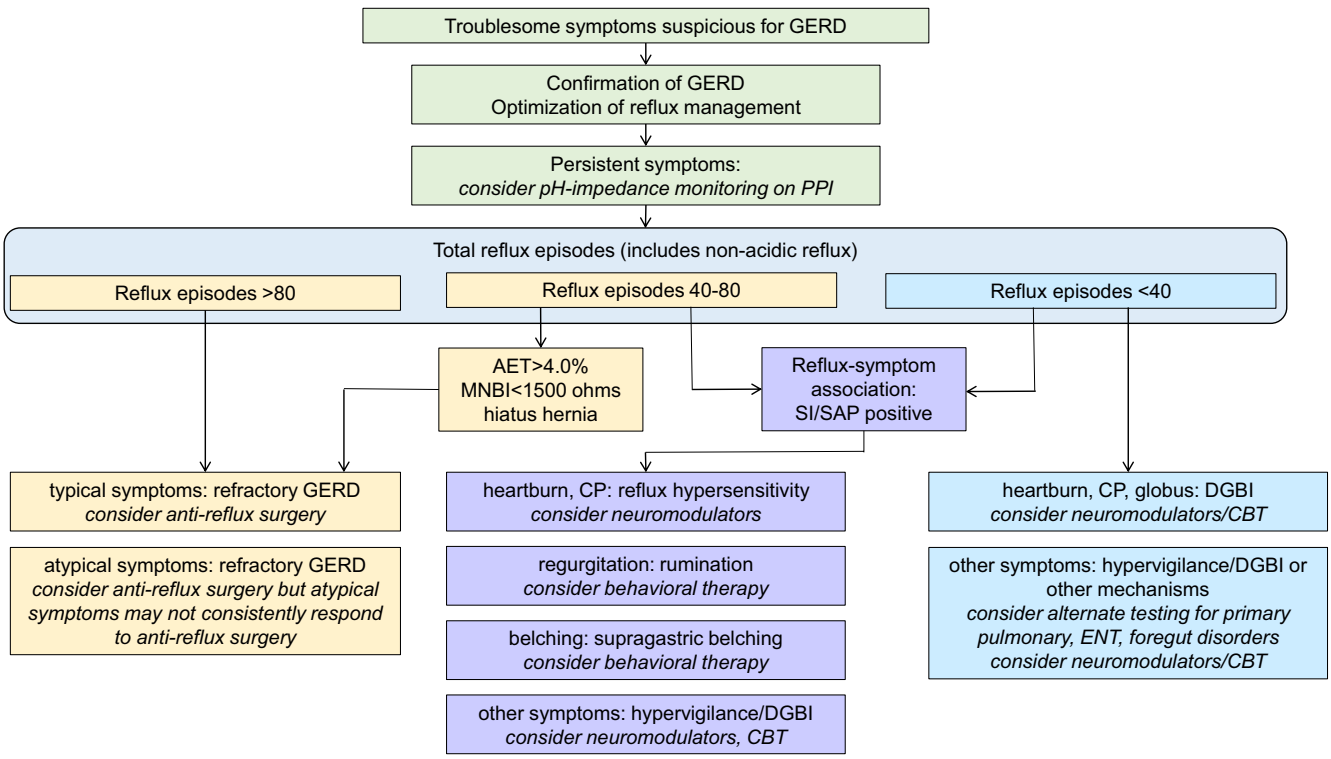

FIGURE 3 Proposed treatment algorithm based on symptom phenotype and results of ambulatory reflux monitoring. Correction added after online publication 29th September 2023. Figure 3 has been replaced with the revised version figure.

3.2 | Refractory heartburn

Whether patients with proven GERD and normalized AET with PPIs can have persistent heartburn from abnormal NAR is an important clinical question. In a study of 317 patients with PPI-refractory heartburn, where 23% had pathologic AET (>6%) and 17% had inconclusive AET (4%–6%), 73% with pathologic AET but only 56% with inconclusive AET had evidence of WAR (>40 total reflux events on impedance). Using elevated WAR as an adjunctive GERD metric yielded a diagnostic gain of 14%.[33] While regurgitation was the symptom most associated with NAR in Mainie et al's study of 168 patients on twice-daily PPI, 23% of patients reporting heartburn had a positive SI to nonacid events.[27] In a similar study of 74 patients, 13% of those reporting heartburn had a positive SI with NAR off PPI, which fell to 9.8% when tested on PPI.[34] Therefore, only limited evidence exists to implicate NAR in persistent heartburn.

Other mediators of heartburn likely exist. A study of 42 patients with abnormal AET but persistent heartburn on twice-daily PPI found that bile acid exposure stratified symptom severity. Despite having similar heartburn severity off PPI at baseline, patients with elevated bile exposure using spectrophotometry (Bilitec) had higher heartburn scores despite similar AET on PPI compared to patients without abnormal bile exposure. The total number of events and WAR on 24-hour pH-impedance monitoring was similar between the two groups, showing that number of reflux events on pH-impedance testing does not capture degree of bile reflux as spectrophotometry does.[35] Thus, "bile reflux" is not equivalent to NAR, and refractory symptoms could have just as well been triggered by activation of sensory receptors by WAR because of overlap reflux hypersensitivity (RH).[36,37]

The success of ARS in improving heartburn in patients with NAR would more firmly solidify this association. In a cohort of refractory heartburn patients, 96 with previously proven GERD (defined as erosive esophagitis or increased AET) underwent pH-impedance monitoring on twice-daily PPI prior to ARS. Only 20% had breakthrough elevated AET whereas the larger majority had increased total reflux events (>40) with normal AET, suggesting ongoing WAR. On 3-year follow-up, increased total reflux events on pre-operative monitoring were associated more often with surgical success (71%) compared with patients with persistent symptoms (33%, $p = 0.018$).[33] Abnormal AET did not discriminate whether ARS would be successful (20% of surgical success group vs. 25% failure group, $p = 0.7$).[38] Gyawali et al. further confirmed the importance of demonstrating an elevated number of total events on pH-impedance testing on twice-daily PPI. In a prospective study of 85 patients from US and European cohorts, ARS was successful in 79% if the total acid exposure was >0.5% and total number of events >40. This suggests ARS could still be successful if acid exposure was normal (<4%) but the number of WAR is elevated while on bid PPI therapy. However, the improvement rates for heartburn (60%) were lower than improvement rates for regurgitation (83%) in this cohort. Overall success further improved to 85% if AET >4% and total reflux events >80, solidifying the importance of persistent acid exposure metrics while on PPI in predicting surgical success.[39]

3.2.1 | Perspective

Persistent NAR in the presence of controlled acid reflux may be a cause of refractory heartburn, but may be difficult to differentiate from NAR hypersensitivity.[37] Therefore, ARS, MSA, or TIF should only be considered with caution, and patients counseled carefully about the risk of failure to control symptoms and new symptoms related to intervention (Figure 3).

3.3 | Reflux hypersensitivity

RH is defined by the presence of esophageal symptoms in response to reflux events despite normal total AET, with positive reflux-symptom correlation using SI and/or SAP. Mechanistically, this can be explained by esophageal hypersensitivity, with lowered threshold for chemo- and mechanosensitivity, abnormal central processing of sensation, and hypervigilance.[40–42] However, Savarino et al. found that the prevalence of dilated intracellular spaces in RH patients was increased similar to nonerosive reflux when compared to functional heartburn or healthy controls, indicating that some RH patients have characteristics within the GERD realm rather than a pure disorder of brain–gut interaction.[43] This raises the likelihood of even WAR having epithelial access in activating chemosensitive receptors, thereby contributing to damage to esophageal mucosal integrity. In a cohort of 77 patients with RH, Patel et al. found that 94% had a positive SAP to either WAR or both acid and WAR, with only 6% sensitive to acid events only.[44] Therefore, over 50% of RH patients would have been undiagnosed if only acid events were analyzed. In 53 RH patients offered medical management with PPI and neuromodulators, 57% of patients had a >50% improvement in global symptom severity, indicating that treating WAR correlated with symptom response. The few "acid-sensitive only" patients did worse, while 30% who underwent ARS reported significant symptom improvement.[44] In another study, RH constituted half of 78 refractory heartburn patients randomized to ARS versus medical therapy after pH-impedance monitoring on therapy, and ARS was similarly superior to medical management in patients with RH and abnormal AET.[45] These data further support ARS for subsets of RH related to WAR who may have GERD-like pathophysiology.

Symptoms within the spectrum of RH also matter—the original ROME description intended for this diagnosis only with symptoms of heartburn and chest pain.[46] In fact, reflux-symptom association with regurgitation without abnormal reflux burden might implicate rumination if symptoms are in the postprandial period, especially in the context of prompt symptom reporting.[47,48] Similarly, reflux-symptom association with belching might implicate supragastric

belching, which can be associated with reflux episodes, either preceding or following belching.[49] Finally, reflux-symptom association with cough or throat clearing might implicate a hypersensitivity or hyperresponsive state.

3.3.1 | Perspective

NAR may be an important contributor to symptoms in patients with RH. Nevertheless, treatment should be aimed primarily at the reduction of esophageal sensory dysfunction rather than the reduction in NAR. The exception is when dominant postprandial regurgitation or belching episodes are associated with reflux events, in which instance rumination and supragastric belching need to be considered and managed with behavioral approaches (Figure 3).

3.4 | Extraesophageal reflux

Two mechanisms by which GERD can induce extraesophageal symptoms are proximal extent of refluxate migration, and a neural reflex triggered by reflux events. High proximal flow of refluxate can lead to microaspiration and direct irritation of the larynx or pulmonary system. In the reflex theory, distal reflux triggers a vagally mediated reflex derived from the common embryologic origin of the esophagus and bronchial tree.[50] There is no reason why these two mechanisms need to be limited to acid reflux events, and thus could include WAR.

In patients with laryngeal and throat symptoms, mechanistic studies have focused mainly on the direct effect of gastric contents on laryngeal tissue. Due to a lack of epithelial and mechanical protective barriers, it has been proposed that laryngeal tissue is especially sensitive to injury from both acidic and nonacidic mediators including pepsin, bile acids, and trypsinogen.[51] Pepsin causes proteolysis and damage and is most active between pH 2 and 5.[52] Johnston et al. used posterior cricoid biopsy specimens to culture hypopharyngeal epithelial cells. Inactivated pepsin at pH 7 was taken intracellularly via endocytosis and reactivated at pH 5, causing mitochondrial damage. Therefore, pepsin has the potential to induce injury in the presence of WAR.[53] Similarly, at weakly acidic pH levels between 5 and 6, bile acids can still promote DNA damage, RNA damage, and activation of NF-Kappa Beta, which is a mediator of cell proliferation and inhibits apoptosis.[52]

Proving that GERD (and specifically NAR) is the cause of laryngeal symptoms in a clinical population is fraught with difficulty as there is neither a gold standard for the diagnosis of reflux-induced laryngeal symptoms nor the amount of refluxate exposure that leads to injury and/or symptoms in vivo. Furthermore, most outcomes studies have used symptom scores and laryngoscopy findings, which are known to have low specificity for true injury.[54] Even when using reflux testing, there is no gold standard for which type of reflux test to use (wireless pH monitoring, pH-impedance monitoring, dual pH testing, pharyngeal pH-impedance monitoring, or combined hypopharyngeal and esophageal impedance testing) or definition of normative values in patients with laryngeal symptoms.[55–57] Reflux monitoring studies may yield conflicting results, such as increased hypopharyngeal acid without elevated distal esophageal AET.[58] Even, elevated AET on esophageal reflux monitoring only demonstrates association and not causation of laryngeal symptoms.[59] Hoppo T et al. defined a cohort of 24 patients with predominantly laryngeal symptoms with positive reflux testing *and* positive symptom response to either PPI or surgical intervention. Using a specialized bifurcated combined hypopharyngeal and esophageal pH-impedance catheter, they compared this cohort with 40 healthy asymptomatic volunteers. A "laryngopharyngeal reflux event" was defined as a hypopharyngeal reflux event following full-column reflux in the esophagus. The total number of reflux events did not differ between symptomatic patients and controls (23.5 vs. 22, $p = 0.3$), but patients had more hypopharyngeal reflux events (1 vs. 0, $p < 0.001$) and full-column reflux events (9.5 vs. 1, $p < 0.001$), with majority acidic events (62%; only 9.1% were NAR).[60] Establishing a "true reflux" cohort is thus difficult in patients with chronic laryngeal symptoms. Thus, the origin of laryngeal symptoms can be multifactorial, with other contributing factors such as allergies, post-nasal drip, mucosal irritation from throat clearing, and neurogenic sensitivity obfuscating the picture and increasing the difficulty of proving NAR as a causative factor. Consequently, definitive evidence confirming a reflux mechanism or NAR thresholds for chronic laryngeal symptoms remains elusive.

WAR has also been linked to the pathogenesis of chronic cough. Using simultaneous high-resolution esophageal manometry and pH-impedance monitoring, Sifrim et al. demonstrated that of 647 "cough bursts" detected by manometry, 98 were preceded by a reflux event within a 2-minute window. Of these reflux-cough events, 65% were acidic, 29% were WAR, and 6% NAR.[61] The strength of this study in implicating WAR in chronic cough is the delineation of a temporal order of cough-reflux versus reflux-cough sequence and the use of objective detection of cough using manometry rather than using patient-reported symptom events, known to be subject to under-reporting.[62] However, 69% of all cough events in this study were neither preceded or followed by any reflux event and thus causality remains unproven. In contrast to speculation of direct mucosal irritation in the majority of studies evaluating laryngeal symptoms, the reflex theory has been confirmed in chronic cough, where instillation of acid in the distal esophagus triggers more cough episodes compared with normal saline, and blunting the afferent signal with topical lidocaine in the esophagus reduces the number of cough events.[63] Qiu et al. measured capsaicin cough threshold in 19 patients with GERD-related cough, 10 patients with GERD without cough, and 12 controls, and used pH-impedance monitoring to determine symptom correlation with acid events versus NAR. The capsaicin threshold was equally low with both acid and NAR in GERD-related cough, compared with GERD without cough and controls.[64] This suggests that cough in this context may be a hypersensitivity phenomenon, triggered partly by stimulation of the esophagus.

Nevertheless, clinical studies demonstrating the efficacy of sphincter augmenting maneuvers such as fundoplication in patients with chronic cough are limited. A systematic review of surgical outcomes in extraesophageal reflux symptoms found efficacy ranges between 37% and 81% for chronic cough.[65] Sample sizes were small and methodology only included uncontrolled or retrospective studies. The largest prospectively collected cohort study by Park et al. included 232 patients undergoing Nissen fundoplication, of whom 77% had complete resolution of cough at follow-up.[66] The authors of this study stressed the importance of objective evidence of GERD and a multidisciplinary approach to optimize outcomes. Nevertheless, pre-operative pH testing did not predict treatment response. There are fewer investigations focused on fundoplication efficacy in NAR-related chronic cough and small sample sizes again limit strong recommendations. Tutuian et al. examined patients on twice-daily PPI with a positive SI for cough and NAR on pH-impedance testing, of which six were offered Nissen fundoplication and all had complete symptomatic response.[67]

3.4.1 | Perspective

There are both association and mechanistic data linking reflux events to cough. However, the lack of clinical therapeutic outcome data for NAR as a cause of cough and laryngeal dysfunction should lead the clinician to assess for other causes first, and provide a tempered recommendation for especially irreversible options for NAR management that mechanically augment the LES barrier.

3.5 | Pulmonary disease

While not as closely linked as esophageal disease, NAR may be associated with complications in patients with pulmonary disease. In idiopathic pulmonary fibrosis (IPF) for example, reflux events may play a role in the progression of fibrosis due to microaspiration. Conversely, IPF may in turn induce reflux via changes in abdomino-thoracic pressure gradients, proving direction of causality can be challenging. A retrospective cohort of 84 IPF patients undergoing baseline pH-impedance testing were reassessed at 1 year for outcomes of hospitalization for pulmonary exacerbation or death. Even after adjusting for baseline lung function with diffusing capacity of carbon monoxide (DLCO), age, and smoking status, only abnormal bolus exposure (OR of 4.18, $p = 0.03$) was an independent predictor for poor outcomes, and not AET (OR 0.55, $p = 0.43$), implicating NAR and esophageal stasis independent of AET as contributors to poor IPF outcomes.[68] Further support that poor outcomes are tied to NAR and perhaps volume regurgitates is a lack of improvement with PPI therapy. Kilduff et al performed simultaneous 24-hour pH-impedance monitoring using an acoustic cough detection system before and after high-dose PPI in 14 patients with IPF. Despite clear improvement in AET, total reflux was unchanged and instead replaced by NAR, while cough counts were not diminished.[69]

NAR may also play a role in the development of interstitial lung disease (ILD) in patients with systemic sclerosis (SSc). Both GERD and ILD are present in a significant proportions of patients with SSc, thus establishing causation can be difficult. Savarino et al evaluated 40 SSc patients with and without ILD, and found that even though age, tobacco use, and esophageal hypomotility were similar, acid exposure, total reflux events and especially NAR events were significantly higher in the ILD group.[70] The number of nonacid reflux events in ILD patients was significant higher than non-ILD patients. However, the effect of targeting acid reflux alone vs. NAR on ILD progression has not been well elucidated.[71]

NAR with resulting microaspiration is also implicated in complications in the lung transplant population. Both bile and pepsin can be found in bronchioalveolar lavage fluid (BALF) and have cytotoxic effects on type II pneumocytes, suggesting that acid is not the sole noxious aspirated substance.[72,73] One mechanism of chronic lung allograft dysfunction (CLAD) is bronchiolitis obliterans syndrome (BOS) to which GERD and aspiration may contribute.[74,75] Patients with BOS show higher concentrations of bile acids on BALF compared to those without BOS, and elevated bile acid levels are an independent predictor for chronic allograft dysfunction.[72,76,77] Using reflux monitoring instead of BALF, further evidence for NAR injury was shown in a study of 30 patients with pre-operative pH-impedance testing; total reflux exposure and abnormal bolus clearance increased the risk of early graft injury (HR 4.11, $p = 0.01$).[78] In a similar cohort of 32 lung transplant recipients, pre-operative total reflux exposure (which includes WAR) predicted early graft failure (HR 1.88) whereas acid parameters did not (HR 1.03).[79] These studies highlight not only the potential for harm from NAR but also the importance of early testing, preferably with pH-impedance monitoring to assess NAR. Outcomes studies using fundoplication that show the reduction in CLAD or pulmonary outcomes further implicate the injurious effect of NAR, since fundoplication improves both acid and NAR while medical management with PPI would not improve NAR. Additionally, fundoplication would not improve intraesophageal stasis if that is the dominant mechanism for microaspiration and lung injury. Early fundoplication within 3 months of transplant has been shown to extend survival time without BOS.[80] Using abnormal pH-impedance monitoring as the indication for fundoplication in the setting of declining forced expiratory volume (FEV1), Abbassi-Ghadi et al found significant improvement in FEV1 in patients who underwent fundoplication. Of note, pooling all reflux episodes on pre-operative testing revealed that about half the reflux events were NAR.[81] A systematic review and meta-analysis of 6 studies found that in 197 patients, fundoplication reversed the trend of decline in FEV1.[82] Finally, a retrospective review of 129 patients who had fundoplication prior to CLAD found a significant mortality benefit, independent of acid exposure on pre-operative testing.[83]

3.5.1 | Perspective

NAR may play an important role for the progression of pulmonary fibrosis and lung transplant failure. Although proving causation is difficult, in the absence of other identifiable causes and progression of lung disease, interventions to augment the LES including fundoplication can be considered.

4 | ESOPHAGEAL CANCER

NAR has been implicated as a contributor to squamous cell carcinoma of the esophagus. In vivo studies found that squamous cells that are exposed to chenodeoxycholic acid produce more reactive oxygen species (ROS) in a neutral environment compared with an acidic environment, leading to increases in inflammatory mediators and cell proliferation.[84] A small clinical study in South Africa of 32 esophageal squamous cell cancer patients and 49 controls found the odds of cancer was 8.8 with NAR on pH-impedance monitoring (73% in cancer group vs. 22% in controls), but not with acid reflux (6% in cancer group vs. 63% in controls, OR 0.04).[85]

Surprisingly, few studies have used pH-impedance monitoring to assess the role of NAR in Barrett's esophagus or adenocarcinoma. A prospective study of 92 patients with GERD symptoms yielded 12 with BE on diagnostic workup. The patients with BE had significantly higher rates of nocturnal NAR and nonacid bolus reflux time on pH-impedance monitoring compared with patients with nonerosive reflux or with esophagitis.[86] A study comparing reflux metrics in patients with endoscopically treated Barrett's-related adenocarcinoma with non-dysplastic BE found that the total number of reflux events was greater in the adenocarcinoma group (67) compared with the BE group (45, $p=0.046$). The number of acidic events (19 vs. 16) was similar, but the adenocarcinoma group had greater number of weakly acidic events (34 vs. 21, $p=0.09$) and alkaline events (2 vs. 0, $p=0.042$).[87]

In addition, bile acids are implicated in carcinogenesis in multiple organs including the esophagus.[88] Conjugated bile acids are found in higher concentration in aspirates of patients with Barrett's esophagus (BE) and adenocarcinoma compared to patients

TABLE 1 Summary of evidence supporting relevance of non-acid reflux in specific GERD populations.

GERD phenotype	Pathogenesis of symptoms	Excess harm	Treatment efficacy
Regurgitation on PPI	• Medical therapy reduces acidity but not total reflux burden • Regurgitation associated with positive symptom indices for NAR	N/A	Elevated reflux event count on testing while on PPI adequately predicts treatment response to fundoplication
Persistent heartburn	Symptom association has been demonstrated, difficult to prove whether related to reflux hypersensitivity or excessive exposure	N/A	Reflux exposure with >40 events (combined acid and nonacid) may predict fundoplication response, however outcomes less robust for heartburn than for regurgitation.
Reflux hypersensitivity	Patients with reflux hypersensitivity have positive symptom association probability with both acid and weakly acid reflux events	N/A	Treating the underlying mechanism of sensory dysfunction in patients sensitive to WAR is efficacious.
Extraesophageal reflux	• Lack of normative values and gold standard testing makes link between NAR and laryngeal symptoms associative but not causative • NAR can trigger chronic cough through reflex theory/neural hypersensitivity	• In vitro studies suggest pepsin causes laryngeal tissue injury in weakly acidic environments	Limited data
Pulmonary conditions	Microaspiration of pepsin and bile suggested by bronchioalveolar lavage studies in pulmonary fibrosis and lung transplant recipients	• Progression of fibrosis and increased hospitalizations in IPF • Chronic allograft lung dysfunction in patients with GERD, independent of acid exposure	• Early fundoplication extends survival time from bronchiolitis obliterans • Fundoplication mortality benefit was not dependent on acid exposure
Esophageal cancer	N/A	• In one small study, odds of ESCC higher in those with NAR on testing • Bile acids mediate DNA damage, proliferation, and carcinogenesis in BE and Adenocarcinoma	Limited data

Abbreviations: BE, Barrett's esophagus; DNA, deoxyribonucleic acid; ESCC, esophageal squamous cell cancer; GERD, gastroesophageal reflux disease; IPF, idiopathic pulmonary fibrosis; NAR, nonacid reflux; PPI, proton pump inhibitor.

with nonerosive reflux, but damage is triggered by an acidic environment rather than NAR, and bile reflux is not equivalent to NAR.[89] Conjugated bile acids are also implicated in the progression of adenocarcinoma given their effects on pathways leading to cell proliferation, invasion, and expansion.[90] Whether these findings represent causation or merely association through increased volumetric reflux is unclear. Unfortunately, fundoplication has not been proven to be superior to PPIs in reducing incident cancer in Barrett's patients implying a lesser role for control of NAR in the progression of metaplasia to dysplasia.

4.1 | Perspective

Evidence for NAR in esophageal squamous cell carcinoma is limited, but NAR could play a role in adenocarcinoma. However, sphincter augmentation therapy to control NAR has not been shown to offer a distinct advantage over medical therapy in this context unless there are symptoms clearly related to uncontrolled NAR.

5 | CONCLUSION

WAR/NAR can play a pathophysiologic role in multiple phenotypes of GERD. These include patients with regurgitation-predominant GERD, reflux hypersensitivity, and extraesophageal GERD, particularly cough. Unfortunately, there are few data fulfilling all three proposed criteria for proving NAR is the cause (Table 1). As a result, the association of NAR to each of these symptoms and syndromes is variable and recommendation for sphincter augmenting therapy such as fundoplication can at best be conditional (Figure 3). In the presence of progression of pulmonary fibrosis or rejection of lung transplant, the threshold to perform fundoplication should be low even in the absence of proof of causality. For conditions that reflect volume reflux such as regurgitation, fundoplication has been proven to be more effective than PPI therapy. For less severe conditions such as cough and hoarseness, NAR may be a measurable co-factor where causation cannot be proven, and invasive sphincter augmentation should be recommended with caution since the probability of success cannot be defined.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the manuscript.

CONFLICT OF INTEREST STATEMENT

DJ reports consulting for Atmo Biosciences. DK reports consulting for Sanofi/Regeneron and research funding for Medtronic. CPG reports consulting for Medtronic and Diversatek and served as a speaker in Carnot.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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