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Management of Patients With Refractory Reflux-Like Symptoms Despite Proton Pump Inhibitor Therapy: Evidence-Based Consensus Statements

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Keywords: endoscopy | gastro-oesophageal reflux disease (GERD) | GRADE | manometry | pH-impedance | refractory

ABSTRACT

Background: Many patients diagnosed with gastro-oesophageal reflux disease (GERD) have persistent symptoms despite proton pump inhibitor (PPI) therapy.

Aims: The aim of this consensus is to provide evidence-based statements to guide clinicians caring for patients with refractory reflux-like symptoms (rRLS) or refractory GERD.

Methods: This consensus was developed by the International Working Group for the Classification of Oesophagitis. The steering committee developed specific PICO questions pertaining to the management of PPI rRLS. Methodologists conducted systematic reviews of the literature. The quality of evidence and strength of recommendations were rated using the GRADE approach.
Results: Consensus was reached on 13 of 17 statements on diagnosis and management. For rRLS, suggested diagnostic strategies included endoscopy, ambulatory reflux testing and oesophageal manometry. The group did not reach consensus on the role of oesophageal biopsies or the use of reflux-symptom association in patients undergoing reflux testing. The group suggested against increasing the PPI dose in patients who had received 8 weeks of a twice-daily PPI. Adjunctive alginate or antacid therapy was suggested. There was no consensus on the role of adjunctive prokinetics. There was little role for adjunctive transient lower oesophageal sphincter relaxation (TLESR) inhibitors or bile acid sequestrants. Endoscopic or surgical anti-reflux procedures should not be performed in patients with rRLS in the absence of objectively confirmed GERD.
Conclusions: The management of rRLS should be personalised, based on shared decision-making regarding the role of diagnostic testing to confirm or rule out GERD as a basis for treatment optimisation. Anti-reflux procedures should not be performed without objective confirmation of GERD.

1 | Introduction

Gastro-oesophageal reflux disease (GERD) is one of the most common diagnoses in clinical practice. Globally, GERD is estimated to affect 4%–14% of the population [1]. Whilst proton pump inhibitors (PPIs) are the mainstay of treatment for GERD, an estimated 45%–55% of patients in observational studies have persistent symptoms despite therapy [2, 3]. Heartburn and regurgitation have been defined as the characteristic symptoms of the typical reflux syndrome [4], and the consensus group was convened to address the management of refractory reflux-like symptoms (rRLS); that is, characteristic symptoms that persist despite treatment. Patients with rRLS despite therapy may or may not have an objective diagnosis of GERD, and it has been suggested that the specific term refractory GERD (rGERD) is used only for patients with persisting symptoms in whom GERD features have been demonstrated by endoscopy or oesophageal reflux testing [5]. However, it should be recognised that when the term rGERD is applied to patients in the published literature, there is marked variability in the definitions of rGERD. In practice, endoscopic features of GERD may not be present in patients who have refractory symptoms after a course of PPI therapy; conversely, endoscopic features of GERD may occur in the absence of typical symptoms. Furthermore, oesophageal reflux testing is not widely available and has not been an inclusion criterion for many rGERD studies. For the purposes of this consensus process, rGERD and rRLS will refer to patients whose condition is refractory to PPI therapy, regardless of whether or not they have received other treatments, including lifestyle changes, antacids, H_2 receptor antagonists (H_2RAs), potassium-competitive acid blockers (PCABs), motility agents or surgery.

In patients without objective evidence of GERD, it is important to exclude other potential causes when symptoms have not resolved with PPI therapy. Even in patients who have reflux-related abnormalities at endoscopy or oesophageal reflux testing, the symptoms may not be reflux-related [5]. Other diagnoses such as eosinophilic oesophagitis (EoE) and disorders of gut–brain interaction (DGBI), including functional heartburn, functional dyspepsia, rumination syndrome, supragastric belching and motility disorders, should be considered [5–8], as should cardiac or pulmonary conditions.

Patients should not be considered to have rRLS unless they have undergone an adequate trial of PPI therapy, defined as 8 weeks of treatment with a twice-daily PPI [6, 9]. In addition, it is important to ensure that the PPI therapy has been optimised with respect to both dosing and time of administration. Currently available PPIs vary markedly in potency as characterised by the duration of acid suppression (hours per day with gastric pH above 4) [10]. Thus, although meta-analyses suggest that overall GERD symptom relief and healing rates are similar for the available PPIs [11–13], pharmacodynamic studies show marked differences in acid suppression potencies (Table 1), and it may therefore be reasonable to consider switching PPIs if the patient has rRLS [10, 14].

Lifestyle modifications are important in the management of GERD [5]. Smoking, intake of coffee or certain foods, sedentary lifestyle and obesity have been shown to increase the risk of GERD symptoms [5, 6, 15], whilst elevating the head of the bed or sleeping in the left lateral position to address nocturnal symptoms and adjusting meal times may be helpful for some patients [5, 6, 16]. However, there is little evidence from randomised controlled trials (RCTs) that these lifestyle modifications are beneficial in patients with rGERD [5].

TABLE 1 | Potency of proton pump inhibitors according to omeprazole equivalents.

Drug and dose (mg)	Relative potency	Omeprazole equivalent (mg)
Pantoprazole, 20	0.23	4.5
Lansoprazole, 15	0.90	13.5
Omeprazole, 20	1.00	20
Esomeprazole, 20	1.60	32
Rabeprazole, 20	1.82	36

Note: From references [10, 14].

The current statements were developed using a GRADE approach, beginning with PICO questions (Patients, Intervention, Comparator, Outcomes). The patient group includes patients with persistent reflux-like symptoms despite adequate PPI therapy, both those with and those without previous objective evidence of GERD unless otherwise specified. Because persistent symptoms are associated with significantly reduced physical and mental health-related quality of life (HRQoL) [17], the chosen outcome was generally the impact of an intervention on patient symptoms (particularly heartburn and regurgitation). For the statements on diagnostic strategies, the outcome was to identify rGERD or other causes for the symptoms and help guide therapy. In the majority of statements, the comparator intervention was presumed to be 'continuation of usual care' unless otherwise specified.

Evidence suggests that there continues to be uncertainty among practising clinicians around the definition, diagnosis and treatment of patients with PPI rRLS and the distinction between rRLS and rGERD [18]. The goal of this consensus was to review the literature and provide evidence-based statements to guide clinicians who care for these patients. The statements were developed by the IWGCO (International Working Group for the Classification of Oesophagitis) (https://iwgco.net), an independent, not-for-profit organisation with a multinational membership.

2 | Methods

2.1 | Scope and Purpose

The consensus meeting and resulting statements focussed on specific PICO questions, pertaining to the management of PPI rRLS that were identified by the steering committee (D.A., A.P.H., P.J.K., P.S., D.S., P.M. and M.V.). The development of these consensus statements, which began in August 2020, was substantially disrupted by the COVID-19 pandemic but continued online and via teleconferences, before a final in-person meeting of the consensus group in May 2023.

2.2 | Sources and Searches

A systematic literature of MEDLINE (from 1946), EMBASE (from 1974) and CENTRAL (Cochrane Central Register of Controlled Trials from inception) for studies published through August 2021 was conducted by the Cochrane Gut Group at McMaster University. Key search terms related to GERD and specific keywords from individual PICO questions with only human studies published in English were considered. Further details of the search strategies are shown in Appendix S1. Additional searches (focussed but non-systematic) were performed prior to the consensus meeting. Subsequently, a full update of the initial search, using the same terms, was conducted to identify any relevant publications for the 3-year period from August 2021 to August 2024. Three reviewers (D.A., S.A. and Y.Y.) reviewed the titles and abstracts to identify any new studies relevant to the specific PICO questions. Although the searches identified some new original studies, notably related to the use of PCABs, none specifically addressed the investigation or treatment of rRLS and rGERD (Appendix S1).

2.3 | Review and Grading of Evidence

A non-voting methodologist (P.M.) determined the overall quality of evidence using the GRADE process that included, among other considerations, a risk assessment for bias, indirectness, inconsistency and imprecision [19, 20]. Evidence quality, classified as very low, low, moderate or high as described by GRADE [19] was presented to the group during online meetings and at the consensus meeting for selected statements.

Product labelling approved by governmental regulators varies from country to country; therefore, some recommendations in this consensus document may not reflect specific product labelling for each particular country. However, all recommendations are based on available evidence found in the literature and the ensuing discussions among the consensus group.

2.4 | Consensus Process

The international consensus group comprised 19 voting members during the online iterations. Only 15 members participated and voted during the face-to-face meeting. The group included gastroenterologists, endoscopists, gastrointestinal tract physiologists, a general surgeon, a general practitioner with interest in gastroenterology, a patient representative and a specialist in medical informatics. Consensus group members were invited based on their acknowledged expertise in the field with a goal of ensuring diversity in geography, sex and clinical practice. Non-voting participants included the co-chairs (D.A. and P.S.) and a methodologist (P.M.).

The steering committee developed the PICO questions, and the literature searches were conducted by the GRADE methodologists (P.M., Y.Y.). Based on the summary of the evidence presented by the GRADE methodologists, the steering committee withdrew nine PICO questions from further development due to the absence of any relevant evidence, lack of clinical relevance or overlap with other PICO questions or because they were deemed outside the scope of the initiative (Appendix S2).

The voting members used a web-based platform administered by the IWGCO (https://iwgco.net) to indicate their level of agreement and provide comments. A summary report of the search results was provided to the participants before the first online vote and uploaded to the voting platform. The recommendation statements were developed in an iterative process through three rounds of online voting. The first round entailed voting on agreement with the subject of each PICO question, the second entailed voting on the questions transformed into recommendation statements based on the feedback and the third entailed voting only on statements for which agreement had not been reached in round 2. A statement achieved consensus and was accepted if $\geq 80\%$ of participants voted 'strongly agree' or 'agree' on a five-item scale, which also included 'uncertain', 'disagree' and 'strongly disagree'.

In most cases, the 'strength' of the recommendation was determined by the steering committee and GRADE methodologists based on the evidence. In line with GRADE methods, statements

were designated as 'strong' with the phrase 'we recommend' or 'conditional' with the phrase 'we suggest' (Table 2) [21].

Written disclosures were provided by all participants for any potential conflicts of interest during the 24 months before the start of the process and these were updated before the consensus meeting.

2.5 | Role of the Funding Sources

The consensus process was supported by independent educational grants to the IWGCO from Cinclus Pharma, Ironwood Pharmaceuticals and Phathom Pharmaceuticals. All aspects of the process were managed by the IWGCO. The funding sources were neither involved in nor aware of any part of the process from the development of the initial search strings to the submission of the final manuscript.

3 | Guidance Statements and Evidence

Each statement is followed by a summary of the strength of evidence based on GRADE analyses and the voting result. This is followed by a discussion of the evidence considered for the specific statement. A summary of the recommendation statements is provided in Table 3. See Appendix S3 for a summary of GRADE assessments.

TABLE 2 | Implications of strong (recommend) and conditional (suggest) statements.

Strong statement for (we recommend)	Most patients would want the course of action and only a small proportion would not • Clinicians should recommend the course of action to most patients
Conditional statement for (we suggest)	Many patients would want the course of action, but MANY would not • Clinicians should recognise that different choices will be appropriate for different patients, and they must help each patient to determine the course of action consistent with their values and preferences
Strong statement against (we recommend against)	Most patients would not want the course of action and only a small proportion would • Clinicians should not recommend the course of action to most patients
Conditional statement against (we suggest against)	Many patients would not want the course of action, but SOME would • Clinicians should recognise that different choices will be appropriate for different patients, and they must help each patient to determine the course of action consistent with their values and preferences

Note: Based on reference [21].

Statements that did not achieve consensus after three iterations of online voting were discussed and revised at the in-person consensus meeting with the goal of achieving consensus on all statements. Despite this, the group did not achieve consensus on four statements; however, the evidence and reasons for and against the statement are included.

The majority of statements were classified as 'conditional', based on low- or very low-quality evidence. One statement warranted a 'strong' classification based on moderate quality evidence (Statement 3). One additional statement was determined by the group to warrant a strong recommendation based on other factors described in the text (Statement 13). These statements do not mandate a course of action; rather, they provide guidance for the discussion between the patient and the physician as to whether most (recommend; strong for), many (suggest; conditional for), few (suggest; conditional against) or very few (recommend; strong against) patients will proceed with the course of action presented in a statement [21].

3.1 | Diagnostic Strategies

1. In patients with refractory reflux-like symptoms, we suggest that upper gastrointestinal endoscopy should not be performed routinely in conjunction with a consultation solely for the purpose of providing patient reassurance.

GRADE: Conditional, very low that consultation and NO evidence that endoscopy adds reassurance.

Endoscopy may be considered for rRLS to confirm a diagnosis of GERD, to identify GERD complications or to reassure the patient that there is no serious disease. However, endoscopy has low sensitivity for the diagnosis of GERD in patients receiving PPI therapy, and the overall prevalence of complications in GERD patients is low. From the few studies that have assessed this, there is no evidence (Appendix S3) that endoscopy will decrease patient anxiety. Conversely, studies in other conditions do suggest that a patient-centred consultation approach may improve patient symptoms and satisfaction. Thus, endoscopy should not be done with the sole aim of reassuring patients with rRLS despite the fact that it may be indicated for other reasons in patients with GERD or rGERD (see Statement 2).

2. In patients with refractory reflux-like symptoms, we suggest performing endoscopy to identify patients with erosive oesophagitis or other reflux-related injury.

GRADE: Conditional, low.

Consistent with other published guidelines [5, 6], the consensus group agreed that endoscopy was warranted in patients with suspected GERD or rGERD who continue to have persistent symptoms on PPI therapy and no previously documented GERD. Other indications are noted in Table 4 [6].

Overall, the yield of endoscopy was low in the evaluated studies (Appendix S3) [22]; 14% of patients had evidence of oesophagitis,

TABLE 3 | Summary of statements, with and without consensus, and related recommendations for the management of patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy.

STATEMENTS WITH CONSENSUS
Diagnostic strategies
1. In patients with refractory reflux-like symptoms, we suggest that upper gastrointestinal endoscopy should not be performed routinely in conjunction with a consultation solely for the purpose of providing patient reassurance. *GRADE*: Conditional recommendation, very low quality of evidence (i.e., very low-quality evidence that consultation is reassuring [and improves health outcomes] but NO evidence that upper gastrointestinal endoscopy adds reassurance) *VOTE* ($N=19$): strongly agree 16%; agree 74%; uncertain 0%; disagree 10%; strongly disagree 0%
2. In patients with refractory reflux-like symptoms, we suggest performing endoscopy to identify patients with erosive esophagitis or other reflux-related injury *GRADE*: Conditional recommendation, low quality of evidence *VOTE* ($N=19$): strongly agree 21%; agree 68%; uncertain 10%; disagree 0%; strongly disagree 0%
3. In patients with refractory reflux-like symptoms, we recommend *against* treatment of confirmed *Helicobacter pylori* infection solely for the purpose of improving reflux symptoms *GRADE*: Strong recommendation, moderate quality of evidence *VOTE* ($N=19$): strongly agree 37%; agree 57%; uncertain 0%; disagree 5%; strongly disagree 0%
4. In patients with refractory reflux-like symptoms, we suggest oesophageal manometry to identify other causes for the symptoms. GRADE: Conditional recommendation, very low quality of evidence VOTE ($N=19$): strongly agree 32%; agree 63%; uncertain 0%; disagree 5%; strongly disagree 0%
5. In patients with refractory reflux-like symptoms, we suggest that oesophageal pH testing should be performed *off* PPI therapy to determine whether the patient has excess acid gastroesophageal reflux as a cause for symptoms *GRADE*: Conditional recommendation, very low quality of evidence *VOTE* ($N=19$): strongly agree 37%; agree 47%; uncertain 10%; disagree 0%; strongly disagree 5%
6. In patients with refractory reflux-like symptoms, we suggest oesophageal pH-impedance testing *off* PPI therapy compared to oesophageal pH-impedance testing *on* PPI therapy to determine whether the patient has excess GER as a cause for symptoms *GRADE*: Conditional recommendation, very low quality of evidence *VOTE* ($N=19$): strongly agree 32%; agree 53%; uncertain 10%; disagree 5%; strongly disagree 0%
7. In patients with refractory reflux-like symptoms for whom testing is performed on PPI therapy, we suggest oesophageal *pH-impedance* rather than oesophageal *pH testing* to identify reflux as a cause for the symptoms *GRADE*: Conditional recommendation, very low quality of evidence *VOTE* ($N=19$): strongly agree 42%; agree 53%; uncertain 0%; disagree 5%; strongly disagree 0%
Management strategies
Pharmacological management strategies
8. In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy, we suggest *against* using higher dose PPI therapy compared to continuing twice-daily PPI therapy to improve symptoms *GRADE*: Conditional recommendation. Very low quality of evidence *VOTE* ($N=19$): strongly agree 37%; agree 53%; uncertain 5%; disagree 0%; strongly disagree 5%
9. In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy without objective evidence of GERD, we suggest *against* adding a TLESR inhibitor to twice-daily PPI therapy to improve symptoms *GRADE*: Conditional recommendation, low quality of evidence *VOTE* ($N=13$): strongly agree 31%; agree 69%; uncertain 0%; disagree 0%; strongly disagree 0%
10. In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy, we suggest adding an alginate and/or antacid to twice-daily PPI therapy to improve symptoms *GRADE*: Conditional recommendation, low quality of evidence *VOTE* ($N=19$): strongly agree 21%; agree 74%; uncertain 0%; disagree 5%; strongly disagree 0%
11. In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy, we suggest *against* adding a bile acid sequestrant to twice-daily PPI therapy to improve symptoms *GRADE*: Conditional recommendation, very low quality of evidence *VOTE* ($N=15$): strongly agree 20%; agree 73%; uncertain 7%; disagree 0%; strongly disagree 0%
Endoscopic or surgical management strategies
12. In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy without objective evidence of GERD, we suggest *against* performing an endoscopic anti-reflux procedure to improve symptoms *GRADE*: Conditional recommendation, low quality of evidence *VOTE* ($N=15$): strongly agree 60%; agree 40%; uncertain 0%; disagree 0%; strongly disagree 0%

(Continues)

TABLE 3 | (Continued)

STATEMENTS WITH CONSENSUS
13. In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy without objective evidence of GERD, we recommend *against* performing surgical fundoplication to improve symptoms *GRADE*: Strong recommendation, very low quality of evidence *VOTE* ($N=15$): strongly agree 60%; agree 40%; uncertain 0%; disagree 0%; strongly disagree 0%
STATEMENTS WITHOUT CONSENSUS
Diagnostic strategies
A. In patients with refractory reflux-like symptoms undergoing endoscopy, the consensus group does not make a recommendation (for or against) addition of oesophageal biopsy compared to endoscopy alone to identify patients with non-reflux-related pathology. *VOTE* ($N=14$): strongly agree 0%; agree 57%; uncertain 21%; disagree 21%; strongly disagree 0%
B. In patients with refractory reflux-like symptoms undergoing pH-impedance testing on PPI therapy, the consensus group does not make a recommendation (for or against) adding reflux-symptom association compared to pH-impedance testing alone to identify reflux-related symptoms *VOTE* ($N=15$): strongly agree 27%; agree 33%; uncertain 13%; disagree 13%; strongly disagree 13%
C. In patients with refractory reflux-like symptoms undergoing pH-testing on PPI therapy, the consensus group does not make a recommendation (for or against) adding reflux-symptom association compared to pH-testing alone to identify reflux-related symptoms *VOTE* ($N=15$): strongly agree 0%; agree 7%; uncertain 7%; disagree 33%; strongly disagree 53%
Management strategies
D. In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy, the consensus group does not make a recommendation (for or against) adding a prokinetic to twice-daily PPI therapy to improve symptoms VOTE ($N=15$): strongly agree 0%; agree 27%; uncertain 13%; disagree 47%; strongly disagree 13%

Abbreviations: PPI, proton pump inhibitor; TLESR, transient lower oesophageal sphincter relaxation.

and 5% had Barrett's oesophagus but few patients had oesophagitis that would warrant escalation of management, with only 10% of cases being LA grades C or D [5]. Endoscopy is often done whilst patients are still taking or have recently stopped PPI therapy, and this can impact the yield. Thus, the persistence of LA grade B, C or D oesophagitis when endoscopy is performed on PPI therapy would indicate rGERD [5, 6, 23, 24]. Endoscopy can be a useful diagnostic aid under appropriate circumstances (Table 4), and it also plays a role for capsule placement if wireless pH reflux testing is contemplated, as described in Statements 5, 6 and 7.

TABLE 4 | Potential utility of endoscopy [6].

Clinical contexts where endoscopy may be warranted	Endoscopy can aid diagnosis of
• Suspected GERD or rGERD + persistent symptoms despite PPI + no previously documented GERD	• Hiatal hernia
• Chest pain without heartburn if heart disease has been excluded	• Eosinophilic oesophagitis
• Initial evaluation of patients with dysphagia or other alarm symptoms (e.g., weight loss, GI bleeding)	• Barrett's oesophagus
• Initial evaluation of patients with multiple risk factors for Barrett's oesophagus	• Pre-neoplastic oesophageal lesions
• Patients at high risk for upper GI cancer	• Oesophageal neoplasia

No consensus A. In patients with refractory reflux-like symptoms undergoing endoscopy, we do not make a recommendation (for or against) addition of oesophageal biopsy compared to endoscopy alone to identify patients with non-reflux-related pathology.

GRADE: NO recommendation, low

Although biopsy is warranted in some patients, the consensus group was divided about whether qualifiers describing the patient type should be included in the statement, and what those qualifiers should be. Studies (Appendix S3) have shown an increased likelihood of EoE associated with dysphagia, history of atopy and endoscopic features of EoE, and in the absence of these, the diagnostic yield of biopsy is negligible [25–27].

Some participants argued that since the prevalence of dysphagia in patients with GERD/rGERD is high at around 50% [28, 29], routine biopsy may be warranted in PPI refractory cases. However, although dysphagia increases the likelihood of diagnosing EoE, the prevalence of EoE in population-based studies remains low at 3.4/10,000 individuals [30]. In addition, obtaining biopsies only from patients with endoscopic features of EoE may miss as many as 30% of cases who have a normal-appearing mucosa [31]. Biopsy may also be useful in the diagnosis of functional heartburn and non-erosive reflux disease (NERD) [32]. The patient representative on the panel stated that from a patient's perspective, there would be a preference for having a biopsy at the time of the index endoscopy rather than perhaps needing to undergo a second procedure.

Other participants argued that in the absence of dysphagia, there is little role for biopsy, and obtaining them in all patients

would lead to a high volume of biopsies, increased costs, increased risks of complications and longer procedure times [25, 33]. A modelling analysis determined that biopsy would be cost-effective only when the prevalence of EoE in patients with rGERD undergoing endoscopy was greater than 8% [33].

3. In patients with refractory reflux-like symptoms, we recommend *against* treatment of confirmed *H. pylori* infection *solely* for the purpose of improving reflux symptoms.

GRADE: Strong, moderate.

Testing patients with rRLS for *H. pylori* is not warranted, since eradication of *H. pylori* is unlikely to improve reflux symptoms and should not be done solely for this purpose. However, *H. pylori* is a World Health Organisation (WHO)-designated carcinogen and the strongest known risk factor for gastric cancer [34]. Patients with confirmed *H. pylori* infection should be treated to reduce long-term gastric or duodenal complications irrespective of whether reflux symptoms might improve [35, 36]. Eradication should be performed following test and treat guidelines according to regional circumstances (i.e., prevalence and antibiotic resistance rates) (Appendix S3) [34, 35, 37].

4. In patients with refractory reflux-like symptoms, we suggest oesophageal manometry to identify other causes for the symptoms.

GRADE: Conditional, very low.

The rates of achalasia in patients with rRLS are low (Appendix S3), but oesophageal manometry can reveal this and other diagnoses that may be causing refractory symptoms. Oesophageal manometry would be warranted in patients with suspected achalasia or rumination syndrome and in those being evaluated for anti-reflux surgery [38]. Manometry can be performed with concurrent transnasal reflux testing. An analysis of rGERD patients undergoing both tests found that 68% had definite GERD and 32% had other conditions such as motility disorders, functional heartburn and hypersensitive oesophagus [39]. Manometry has both positive and negative aspects, which should be thoroughly discussed with the patient (Table 5).

5. In patients with refractory reflux-like symptoms, we suggest that oesophageal pH testing should be performed *off* PPI therapy to determine whether the patient has excess acid gastro-oesophageal reflux as a cause for symptoms.

GRADE: Conditional, very low.

Oesophageal pH testing can be performed off PPI therapy to document pathological acid reflux and confirm GERD or on PPI therapy to determine whether there is persistent acid reflux that might warrant dose escalation. In patients who have not had a prior objective diagnosis of GERD, oesophageal pH testing off PPI therapy can document abnormal acid reflux, which can be invoked as a cause for the symptoms. Conducting the test off PPI therapy increases the likelihood of detecting acid reflux (Appendix S3) which, if present, would justify escalation of therapy [40]. In deciding whether to offer oesophageal pH testing

TABLE 5 | Pros and cons of manometry.

Pros	Cons
• Assist in excluding other diagnoses (e.g., rumination)[a]	• Invasive
• Assist in quantifying magnitude of hiatal hernia or oesophageal body hypomotility[a]	• Uncomfortable
	• Some findings unlikely to alter symptom management ◦ e.g., normal motility, ineffective oesophageal motility, oesophageal spasm or hypercontractility in context of GERD

[a]With concomitant impedance testing.

to patients with rRLS, the clinician should recognise that cessation of PPI therapy may be associated with worsening symptoms, possibly attributable to rebound acid hypersecretion, that the optimal interval between PPI cessation and testing has not been determined and that the patient should be aware that their symptoms may worsen, that the treatment options in this period may be limited and that interpretation of the test results may not be definitive.

Other testing modalities, including wireless pH capsule testing for up to 96 hours and 24 h combined impedance-pH testing, may be considered. Some participants noted a preference for impedance-pH testing, since it provides additional information on non-acid reflux compared with pH testing alone, but there were no relevant comparative studies in rRLS patients off therapy. The role of wireless pH testing for rRLS was not considered in detail, as the literature search did not identify any relevant data specific to its use for rGERD or rRLS that would support the relevant PICO question.

6. In patients with refractory reflux-like symptoms, we suggest oesophageal pH-impedance testing *off* PPI therapy rather than oesophageal pH-impedance testing *on* PPI therapy to determine whether the patient has excess acid gastrooesophageal reflux as a cause for symptoms.

GRADE: Conditional, very low.

Oesophageal pH-impedance testing can be performed off PPI therapy to document pathological reflux and confirm GERD or on PPI therapy to determine whether there is persistent acid or non-acid reflux that might warrant a change in therapy. In patients who have not had a prior objective diagnosis of GERD (by endoscopy or pH testing), pH-impedance testing off PPI therapy can document abnormal reflux and confirm a diagnosis of GERD [5] warranting increased antisecretory therapy for rRLS; conversely, the absence of abnormal reflux would support discontinuation of anti-reflux therapy [41–45].

However, it should be noted that another study in patients with reflux symptoms did not identify any reflux pattern on pH-impedance testing that was associated with a response to PPIs (Appendix S3) [46].

7. In patients with refractory reflux-like symptoms for whom testing is performed on PPI therapy, we suggest oesophageal *pH-impedance* rather than oesophageal *pH testing* to identify reflux as a cause for symptoms.

GRADE: Conditional, very low.

If reflux testing is performed on PPI therapy with the aim of detecting persistent reflux as a cause of rRLS, pH-impedance testing is preferred to pH testing alone because the latter detects only acid reflux. Because PPIs reduce both the acidity and volume of gastric secretions [47], abnormal oesophageal acid exposure is uncommon in patients on PPI therapy (18%–28%); the more common finding of normal acid exposure (45%–63%) suggests that symptoms are not reflux-related (Appendix S3). However, non-acid reflux, detected by pH-impedance studies, may still cause symptoms related to oesophageal distension or the presence of non-acid gastroduodenal contents in the oesophagus [48–50]. Oesophageal pH-impedance studies can help distinguish hypersensitive oesophagus from functional heartburn [45, 51–53]. Detecting regurgitation-predominant GERD may help identify patients who require an escalation of therapy or who may respond to anti-reflux surgery [54, 55].

No consensus B. In patients with refractory reflux-like symptoms undergoing pH-impedance testing on PPI therapy, we do not make a recommendation (for or against) adding reflux-symptom association assessment compared to pH-impedance testing alone to identify reflux-related symptoms.

No consensus C. In patients with refractory reflux-like symptoms undergoing pH-testing on PPI therapy, we do not make a recommendation (for or against) adding reflux-symptom association assessment compared to pH-testing alone to identify reflux-related symptoms.

GRADE for both statements: NO recommendation, NO evidence.

The consensus group was divided regarding the value of symptom index correlation. The Lyon consensus concluded that 'reflux-symptom association on ambulatory reflux testing provides supportive evidence for reflux-triggered symptoms, and may predict a better treatment outcome when present.' [56] However, in the current process, the group considered the evidence (Appendix S3) for a positive or negative correlation between symptom indices and acid reflux episodes in pH studies to be insufficient to support evidence-based recommendations.

Consensus members in favour of the use of symptom indices cited the data suggesting that a positive reflux-symptom association has been shown to predict response to both pharmacologic and surgical therapy [5, 41, 57, 58]. Thus, they may help define the range of treatment options for a patient, especially whether there is a need to intensify therapy. The Rome IV consensus defines NERD, reflux hypersensitivity and functional heartburn based in part on symptom association [8]. Symptom association may be particularly helpful in diagnosing non-acid related symptoms.

Other participants argued that symptom association correlates poorly with the diagnosis of GERD, having low positive and negative predictive values [59]. Only about 1/3 of patients with PPI refractory symptoms demonstrate a positive symptom association [60]. The danger is that in clinical practice, symptom indices may be improperly implemented, and the results misinterpreted [56]. Thus, a negative symptom correlation may lead to ruling out GERD as a cause of the patient's symptoms, despite lack of evidence for that conclusion. Although symptom indices are inaccurate, the data from pH-impedance testing are accurate, with acid exposure time correlating well with the severity of reflux and diagnosis of GERD and response to therapy [5, 56].

In the case of the 'No consensus C' statement, almost no participants were in favour of the statement. One of the major issues, in addition to those put forth for the 'No consensus B' statement on reflux-symptom association, was an objection to performing pH-testing on PPI therapy. The group agreed that there is little or no value to performing pH-testing alone on PPI therapy (with or without reflux-symptom association), since this will show very few real acid reflux episodes.

3.2 | Pharmacological Management Strategies

8. In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy, we suggest *against* using higher dose PPI therapy compared to continuing twice-daily PPI therapy to improve symptoms.

GRADE: Conditional, very low.

There was no direct evidence (Appendix S3) to inform this statement, but available data suggest that there is no substantial effect of increasing PPI therapy beyond twice-daily dosing (see Table 1 for PPI dose equivalencies). A meta-analysis of studies assessing time with intragastric pH >4 over 24 h found that thrice-daily PPIs performed similarly to twice-daily PPIs [10]. Another consideration is that the potencies of the available PPIs used in pH studies vary [10, 14]. PCABs, including linaprazan (AZD065), vonoprazan, fexuprazan, tegoprazan, keverprazan and linaprazan glurate (X842), have become available or are in development with the intent of offering more rapid and greater inhibition of gastric acid than PPIs [61]. In RCTs, PCABs have shown similar healing rates and heartburn relief rates compared to PPI therapy, and although PCABs may provide superior results in patients with more severe oesophagitis [62–70], there are no RCTs in patients with rRLS or rGERD.

TABLE 6 | Concerns regarding prokinetic agents.

- Lack of pathophysiologic rationale for effect in GERD
- Uncertain mechanisms of action
- Safety profile (e.g., tachyphylaxis with long-term domperidone)
- Potential availability issues
- Questionable cost-effectiveness
- Cost

No consensus D. In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy, we do not make a recommendation (for or against) adding a prokinetic to twice-daily PPI therapy to improve symptoms.

GRADE: NO recommendation, low.

The majority of the consensus group was uncertain or disagreed with adding a prokinetic to acid suppression therapy. The data (Appendix S3) suggest that benefits are weak and most studies do not specify the PPI dose or the definition of rGERD. It is likely that the prokinetic was being added to once-daily PPI therapy in many cases. In fact, the trial that compared prokinetic added to high-dose PPI found no symptomatic improvement versus PPI therapy alone [71]. Participants opposing the statement noted several issues (Table 6).

Conversely, some participants were in favour of adding a prokinetic to PPI therapy because there is some evidence to suggest symptomatic benefit without an increase in adverse events. A lack of mechanistic rationale should not preclude their use if efficacy data suggest that some patients may benefit. Prokinetics may play a role in patients with concomitant symptoms suggesting gastroparesis.

9. In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy without objective evidence of GERD, we suggest *against* adding a TLESR inhibitor to twice-daily PPI therapy to improve symptoms.

GRADE: Conditional, low.

TLESR inhibitors do not appear to have a role in patients with rRLS despite PPI therapy if they do not have objective evidence of GERD (Appendix S3). Meta-analysis of four RCTs ($N=1425$) in patients with rGERD showed a marginally statistically significant ($p=0.05$) increase in the symptom response rate when a TLESR inhibitor was added to PPI therapy compared to PPI therapy alone (RR, 0.93; 95% CI, 0.86–1.00) [72–75]. However, numerous concerns were noted regarding the use of TLESR inhibitors for rRLS patients (Table 7), and the participants did not reach consensus on the use of TLESR inhibitors for patients who had objective evidence of GERD.

TABLE 7 | Concerns regarding TLESR inhibitors.

- Inability to clinically identify appropriate patients
- Lack of symptom-specific data
- Potential availability issues (baclofen is, currently, the only TLESR inhibitor available)
- Cost
- Adverse effects

Abbreviation: TLESR, transient lower oesophageal sphincter relaxation.

10. In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy, we suggest adding an alginate and/or antacid to twice-daily PPI therapy to improve symptoms.

GRADE: Conditional, low.

There is evidence (Appendix S3) suggesting that some patients with GERD or rGERD may have symptomatic benefit when an alginate and/or antacid is added to PPI therapy. In a meta-analysis of six RCTs ($N=659$) in patients with GERD [76–79] or rGERD [80], the addition of antacid/alginate to PPI therapy did improve reflux symptoms over PPI alone (RR, 0.81; 95% CI, 0.67, 0.97; $p=0.02$) [77–80]. In addition, the treatment is associated with few adverse events and is widely available at low cost.

11. In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy, we suggest *against* adding a bile acid sequestrant to twice-daily PPI therapy to improve symptoms.

GRADE: Conditional, very low.

There does not appear to be a role for adding a bile acid sequestrant to PPI therapy in patients with rRLS. Evidence (Appendix S3) of benefit is very low quality. It is possible that a subpopulation of patients who have undergone gastric surgery may benefit, but evidence for this was not reviewed. A bile acid sequestrant (IW-3718) developed for use in rGERD [81] is no longer in development, and although there are other bile acid sequestrant agents, they have not been studied in the rRLS or rGERD populations.

3.3 | Endoscopic or Surgical Management Strategies

12. In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy, without objective evidence of GERD, we suggest *against* performing an endoscopic anti-reflux procedure to improve symptoms.

GRADE: Conditional, low.

13. In patients with refractory reflux-like symptoms after 8 weeks of twice-daily PPI therapy without objective evidence of GERD, we recommend *against* performing surgical fundoplication to improve symptoms.

GRADE: Strong, very low.

There was no evidence (Appendix S3) to support radiofrequency energy delivery, but endoscopic fundoplication can be effective for rRLS. Similarly, there was little evidence (Appendix S3) to suggest that surgical interventions would effectively improve rRLS, although they may play a role in patients with objectively confirmed rGERD.

The consensus group concluded that neither an endoscopic nor a surgical anti-reflux procedure should be performed in

patients with rRLS who do not have objectively confirmed GERD because such patients are more likely to have an alternative, non-acid-related condition that would not be expected to respond to anti-reflux procedures. This is consistent with the recent recommendation of a multi-society consensus conference that endoscopy, manometry and pH testing should be performed in all patients with oesophageal symptoms of medically refractory reflux who are undergoing pre-operative evaluation [82].

Conversely, for selected patients with rRLS and objective evidence of GERD, surgical fundoplication, endoscopic fundoplication or magnetic sphincter augmentation (MSA) may be effective (Appendix S3). Surgical fundoplication may be particularly effective for patients with an anatomical defect such as a large hiatus hernia, whereas studies of endoscopic fundoplication or MSA have typically excluded patients with a large hiatus hernia or severe oesophagitis (LA Grade C or D). In practice, the choice of anti-reflux procedure requires consideration of access, costs, complications, choice of procedures and skill of operators. In addition, there are few studies in patients with rRLS or rGERD and few long-term outcome data. For endoscopic treatments, the statement was classed as 'suggest against', meaning that appropriate candidates should be carefully selected and the pros and cons thoroughly discussed with the patient. However, the consensus group took a stronger stance against performing surgical therapy in patients without objective evidence of GERD due to the potential for complications, as well as the high costs and invasive nature of surgery.

4 | Discussion

The current consensus process on rRLS did not consider atypical symptoms [23] but, even if these atypical symptoms are excluded, the management of rRLS remains a challenge. Empiric acid suppression therapy is, generally, recommended for individuals who present with typical or characteristic symptoms of heartburn, regurgitation [6] and, in some guidelines, chest pain [23]. However, RLS that respond to acid suppression therapy are not, necessarily, diagnostic of GERD and, conversely, RLS that persist despite adequate acid suppression therapy do not, necessarily, rule out rGERD. rRLS caused by reflux (i.e., rGERD) must be distinguished from symptoms attributable, for example, to reflux hypersensitivity, functional heartburn, achalasia or oesophageal dysmotility [6]. In principle, therefore, the treatment of rRLS should be predicated on a confirmed diagnosis of GERD to maximise treatment efficacy, avoid inappropriate or unnecessary therapy and minimise potential treatment harms. Recent clinical guidance has emphasised the importance of confirming GERD objectively [6, 23] with specific criteria that provide 'conclusive', 'borderline or inconclusive' and 'adjunctive or supportive' evidence for pathologic reflux or evidence against pathologic reflux [23]. In practice, therefore, there are some patients who will have inconclusive evidence of GERD, even if they are tested off therapy. Furthermore, the sensitivity of endoscopy for the diagnosis of GERD is limited, partly because a high proportion of patients has NERD and partly because, even if PPIs are discontinued for 2–4 weeks as recommended, 6-month remission rates for patients whose reflux oesophagitis was healed with a PPI are as high as 29.1% [83, 84]. Reflux testing, off therapy, to confirm pathological reflux is probably more sensitive than endoscopy but 72- to 96-h wireless pH capsule testing, which is considered to be more sensitive and accurate than catheter-based testing, is expensive and is not widely available [23]. The use of endoscopy and reflux testing studies to confirm GERD in all patients with rRLS is not practicable, as it would require significant increases in resources and incur considerable direct and indirect costs. This is an important issue given that only about half of the patients with rRLS will have GERD [1–3], and the fact that additional diagnostic testing often does little or nothing to reassure patients or alleviate their symptoms [85–87]. The consensus statements do, however, acknowledge the need to confirm GERD objectively before endoscopic or surgical anti-reflux procedures because of the greater risk associated with these therapeutic approaches and their essentially irreversible nature compared with medical therapy; the need for objective confirmation of GERD was considered separately for each statement, as the balance of risks, costs and benefits differed for each medical intervention.

4.1 | Unmet needs and future directions

The current consensus process has highlighted a number of challenges in the management of rRLS, a major unmet need being an inability to distinguish rRLS patients who have rGERD from those who do not, without resorting to costly and burdensome investigation strategies. For many individuals, rRLS are likely to be a disorder of gut–brain interaction (DGBI) [88] and, as for other DGBI, management should be guided by making a positive diagnosis of the disorder rather than by extensive investigations to confirm GERD or exclude other extra-oesophageal conditions [7, 8, 89]. Such an approach should be accompanied by greater awareness among all healthcare providers and patients of the role played by psychological factors, including anxiety and depression, in generating somatic symptoms [90] as well as the roles of dietary and other life-style and non-pharmacological factors [91]. Patient-centred consultation is increasingly recognised to be beneficial in many areas of clinical practice including primary care [92], and the enhancement of communication skills to improve the patient–provider relationship and healthcare outcomes has been endorsed for gastroenterology practice by a Rome Foundation Working Team with respect to the care of individuals with DGBI [93]. Advances in the management of rRLS will benefit from a system-wide approach that addresses patients' symptoms and expectations and enables all healthcare providers to adopt a common, evidence-based framework to determine the aetiology and most appropriate, personalised treatment strategies for each patient [94].

New evidence-based management strategies will need to be supported by research into the epidemiology, aetiology, and treatment of rRLS that addresses patient-relevant outcomes such as symptom improvement, treatment satisfaction and quality of life rather than physiologic outcomes such as acid exposure time or number of acid reflux episodes.

Table 8 summarises some of the most important areas of research that are needed to advance the management of rRLS and rGERD.

TABLE 8 | Unmet needs and future areas of research that may help advance the management of refractory reflux-like symptoms and rGERD.

Unmet needs

1. A standard definition of refractory GERD
2. Standard definitions of reflux-like symptoms
3. A standard definition of refractory reflux-like symptoms
4. An understanding of the various oesophageal and extra-oesophageal mechanisms underlying the generation and perception of reflux-like symptoms
5. More accurate and less invasive tools to identify individuals whose reflux-like symptoms are caused by gastro-oesophageal reflux
6. Tools to identify individuals whose reflux-like symptoms are manifestations of disordered gut–brain interactions
7. An understanding of the extent to which current treatments achieve the effects required to alleviate reflux-like symptoms
8. Treatments for reflux-like symptoms (including refractory symptoms) attributable to reflux-related and reflux-unrelated mechanisms, including disorders of gut–brain interaction

Future research

1. Epidemiological studies, using standard definitions, to determine the spectrum of reflux-like and other symptoms including dysphagia, pain, belching, rumination, heartburn and regurgitation in patients with and without GERD
2. Outcome studies to correlate patient-reported symptoms, quality of life and other outcomes with findings from a structured history and investigations (including endoscopy, manometry, pH/pH-impedance, etc.) and their responses to therapies
3. The role of oesophageal hypersensitivity in the pathogenesis of reflux-like symptoms
    a. How to diagnose oesophageal hypersensitivity, on and off therapy
    b. How to manage refractory reflux-like symptoms and rGERD in patients with oesophageal hypersensitivity
4. The role of oesophageal hypervigilance and psychological factors in the pathogenesis of reflux-like symptoms
    a. How to use the EHAS and 'reflux-symptom association' measures in the diagnosis of oesophageal DGBIs, on and off therapy
    b. How to manage refractory reflux-like symptoms and rGERD in patients with hypervigilance
5. The role of oesophageal biopsy and histology in the diagnosis and management of refractory reflux-like symptoms and rGERD
6. Development of new and improved algorithms for reflux symptom association analysis to identify individuals whose symptoms are reflux-related
7. Development of new and improved algorithms for oesophageal pH/pH-impedance testing performed on or off PPI therapy, including parameters, such as MNBI or PSPW index, to identify individuals whose symptoms are reflux-related
8. The role of hiatus hernia in the pathogenesis of refractory reflux-like symptoms and rGERD, including regurgitation
9. The effect of new treatment strategies, including sensory modulators and topical oesophageal mucosal protection, in alleviating reflux-like symptoms and rGERD

Abbreviations: DGBI, disorders of gut–brain interaction; EHAS, esophageal hypervigilance and anxiety scale; MNBI, mean nocturnal baseline impedance; PSPW, post-swallow reflux-induced peristaltic wave.

International Working Group for the Classification of the Oesophagitis (IWGCO) Statement

These consensus statements were developed under the direction of Dr. David Armstrong and Dr. Prateek Sharma, in accordance with the policies and procedures of the IWGCO. The guidance was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of an international panel of experts on this topic. The guidance aims to provide a reasonable and practical approach to care for specialists and allied health professionals charged with the duty of providing optimal care to patients and families and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The guidance is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

Author Contributions

David Armstrong: conceptualization, funding acquisition, supervision, writing – original draft, writing – review and editing. **A. Pali Hungin:** writing – review and editing. **Peter J. Kahrilas:** writing – review and editing. **Daniel Sifrim:** writing – review and editing. **Paul Moayyedi:** formal analysis, investigation, writing – review and editing. **Michael F. Vaezi:** writing – review and editing. **Sameer Al-Awadhi:** writing – review and editing. **Sama Anvari:** investigation, writing - review and editing. **Reginald Bell:** writing – review and editing. **Brendan Delaney:** writing – review and editing. **Fabian Emura:** writing – review and editing. **C. Prakash Gyawali:** writing – review and editing. **Peter Katelaris:** writing – review and editing. **Adriana Lazarescu:** writing – review and editing. **Yeong Yeh Lee:** writing – review and editing. **Alessandro Repici:** writing – review and editing. **Sabine Roman:** writing – review and editing. **Ceciel T. Rooker:** writing - review and editing. **Edoardo Vincenzo Savarino:** writing – review and editing. **Paul Sinclair:** funding acquisition, project administration, writing – review and editing. **Kentaro Sugano:** writing – review and editing. **Rena Yadlapati:** writing – review and editing. **Yuhong Yuan:** investigation, writing - review and editing. **Frank Zerbib:** writing – review and editing. **Prateek Sharma:** conceptualization, funding acquisition, supervision, writing – review and editing.

Conflicts of Interest

Armstrong: Support from Nestlé Health Sciences and the Weston Family Foundation for research unrelated to the submitted work; honorarium from Sanofi for advisory board participation (non-voting); unpaid advisory board participation for Cinclus Pharma (non-voting) and Phathom Pharmaceuticals (non-voting); honorarium from Fresenius Kabi for speakership unrelated to the submitted work; is the co-founder of AI VALI Inc., an unpaid position unrelated to the submitted work. Hungin: Honoraria from Reckitt Benckiser for advisory board and speaker's bureau participation; research support from Reckitt Benckiser. Kahrilas: Honoraria from Ironwood Pharmaceuticals and Reckitt Benckiser for consulting work. Sifrim: Research funding from Reckitt Benckiser UK and Alfasigma Italy; an honorarium for speaking from Jinshan Technology China. Vaezi: Honoraria from Phathom Pharmaceuticals, Ironwood Pharmaceuticals and Cinclus Pharma for consulting work; an honorarium from Diversatek Healthcare for an advisory role. Bell:

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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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Supporting Information

Additional supporting information can be found online in the Supporting Information section.