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Knowledge gaps in the management of refractory reflux-like symptoms: Healthcare provider survey

David Armstrong[1] | Amrit Pali Hungin[2] | Peter J. Kahrilas[3] | Daniel Sifrim[4] | Paul Sinclair[5] | Michael F. Vaezi[6] | Prateek Sharma[7]

[1]Division of Gastroenterology & Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada

[2]Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK

[3]Division of Gastroenterology, Northwestern University, Chicago, Illinois, USA

[4]Barts and The London School of Medicine and Dentistry, Queen Mary, University of London, London, UK

[5]INSINC Consulting Inc., Guelph, Ontario, Canada

[6]Division of Gastroenterology, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[7]Division of Gastroenterology and Hepatology, Veterans Affairs Medical Center, University of Kansas School of Medicine, Kansas City, Missouri, USA

Correspondence
David Armstrong, Division of Gastroenterology, McMaster University Medical Centre, 1280 Main Street West, HSC-3V68, Hamilton, ON L8S 4K1, Canada.
Email: armstro@mcmaster.ca

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Abstract

Background: Refractory reflux-like symptoms have a substantial impact on patients and healthcare providers. The aim of the survey was to qualitatively assess the needs and attitudes of practicing clinicians around the management of refractory reflux symptoms and refractory gastroesophageal reflux disease (rGERD).

Methods: An International Working Group for the Classification of Oesophagitis (IWGCO) steering committee invited clinicians to complete an online survey including 17 questions.

Key results: Of the 113 clinicians who completed the survey, 70% were GIs, 20% were primary care physicians, and 10% were other specialties. Functional heartburn was considered the most common reason for an incomplete response to proton pump inhibitor (PPI) therapy (82%), followed by stress/anxiety (69%). More GIs identified esophageal hypersensitivity as a cause, while more non-GIs identified esophageal dysmotility and non-reflux-related esophageal conditions. As the first step, most clinicians would order investigations (70–88%). Overall, 72% would add supplemental therapy for patients with partial response, but only 58% for those with non-response. Antacid/alginate was the most common choice overall, while non-GIs were more likely to add a prokinetic than were GIs (47.8 vs. 24.1%). Approximately 40% of clinicians would switch PPIs in patients with partial response, but only 29% would do so in non-responders. Preferences for long-term therapy were highly variable. The most common initial investigation was upper endoscopy. Choice of esophageal manometry and pH monitoring was more variable, with no clear preference for whether pH monitoring should be conducted on, or off, PPI therapy.

Conclusions and Inferences: The survey identified a number of challenges for clinicians, especially non-GI physicians, treating patients with refractory reflux-like symptoms or rGERD on a daily basis.

KEYWORDS
gastroesophageal reflux disease, proton pump inhibitors, refractory, resistant, supplemental therapy

1 | INTRODUCTION

Proton pump inhibitors (PPIs) are the mainstay of treatment for gastroesophageal reflux disease (GERD), but many patients continue to be symptomatic despite therapy. The Global Burden of Disease study, estimated the age-standardized prevalence of GERD in North America to be 10–12%.[1] In a large US population-based study, persistent symptoms were reported by 54% of respondents who were taking a daily PPI.[2]

There is no standardized definition of refractory GERD (rGERD), in terms of symptom frequency and severity, or the proportion of patients who have persistent symptoms despite treatment with once- or twice-daily PPI therapy.[3,4] However, persistent reflux symptoms have a substantial impact on patient quality of life.[5]

In addition to the lack of a standardized definition, there are other challenges around the diagnosis and management of rGERD. Reflux-like symptoms have limited specificity for the diagnosis of GERD.[6] Persistent symptoms may not be attributable to a failure to treat reflux, and escalation of reflux therapy may not necessarily improve symptoms. There is uncertainty as to how to diagnose patients with continuing reflux, including how to rule out rGERD, or make a positive diagnosis of functional heartburn, esophageal hypersensitivity, and esophageal dysmotility.[7] There is also uncertainty as to the options for the treatment of symptoms of rGERD if (a) there is evidence of persistent reflux, (b) if there is no evidence of persistent reflux, or (c) if there is evidence of non-acid reflux.

Although several recent guidelines for the management of GERD have been published, these would have had little time for uptake in the community,[3] at the time of this survey, or post-date it.[4] Other consensus documents have focused on diagnosis alone.[8] The International Working Group for the Classification of Oesophagitis (IWGCO) was formed as an independent, not-for-profit organization with a multinational membership. IWGCO conducted a survey to evaluate the knowledge and attitudes of practicing clinicians with the goal of determining the need for consensus recommendations. In light of the recent publication of newer guidelines, this survey can serve as a baseline, which if repeated may provide some insight into the uptake of recommendations in clinical practice.

Recognizing the wide variations in practice internationally, the purpose of this survey was to qualitatively assess the needs and challenges of healthcare providers' managing refractory reflux symptoms or rGERD. It was intended to identify relevant topics that should be addressed in a consensus guideline, rather than being a quantitative survey of current practice.

Key Points

- Refractory reflux-like symptoms have a substantial impact on patients and healthcare providers.
- A survey was conducted by the International Working Group for the Classification of Oesophagitis (IWGCO) to qualitatively assess the needs and attitudes of practicing clinicians around the management of refractory reflux-like symptoms and refractory gastroesophageal reflux disease (rGERD).
- Among the 113 clinicians who completed the survey (70% GIs), challenges that were identified included: defining PPI non-response, potential causes of the symptoms, most appropriate diagnostic approaches, and optimal treatment strategies for refractory reflux-like symptoms and rGERD.

2 | METHODS

A group of 25 IWGCO members from around the world invited other clinicians from their home countries to complete an online survey on the topic of refractory reflux symptoms, which was hosted on the IWGCO website (iwgco.net). Personalized email requests to complete the survey were sent to a convenience sample of colleagues involved in the management of patients with GERD from a variety of specialties.

The initial survey questions were developed by DA, PSi, and PSh, then revised by the steering committee for the rGERD consensus project (APH, PJK, DS, and MFV). There were a total of 17 multiple choice questions, with four questions collecting basic demographic data, and two asking about the patient composition of the respondent's practice (See Appendix S1). The remaining 11 questions evaluated clinicians' current practice strategies. The questionnaire was designed to assess all aspects of the journey of a patient with persistent reflux-like symptoms despite therapy, including potential causes, clinical features that support a diagnosis of rGERD, initial management options, and appropriate investigations.

The completed online surveys were assessed for completeness, and duplicate entries were removed from the data set. The numbers and percentages of participants who responded affirmatively to each question or sub-question were tabulated for descriptive analyses. Results are presented for the overall group, and for subgroups of respondents who indicated their specialty as gastroenterologists (GIs) and those who chose other specialties (non-GIs). No formal statistical analysis was performed as this was a descriptive study to identify potential knowledge gaps but not to determine the prevalence of any differences.

3 | RESULTS

Overall, 113 clinicians completed the survey, between February and May 2021. The majority were from North America or Europe, and had been in practice for over 10 years (Table 1). Most were gastroenterologists (GIs) (69.9%) and over half were from academic medical centers (56.6%), with primary care physicians and surgeons accounting for the majority of non-GI clinicians.

More than 50% of clinicians estimated the proportion of their patients with troublesome refractory reflux symptoms despite PPI therapy to be between 6 and 40% for once-daily, and <6–20% for

TABLE 1 Demographic characteristics of respondents ($n = 113$)

Characteristic	*n* (%)		
Location			
North America	48 (42.5)		
Europe	27 (23.9)		
South America	21 (18.6)		
Asia/Oceania	17 (15.0)		
Years in practice			
<6	10 (8.8)		
6–10	14 (12.4)		
11–20	25 (22.1)		
21–30	29 (25.7)		
>30	35 (31.0)		
Practice type			
Academic medical center-based practice	64 (56.6)		
Out-of-hospital community practice	23 (20.4)		
Community hospital-based practice	21 (18.6)		
Other	5 (4.4)		
Specialty			
Gastroenterology	79 (69.9)		
Primary care	23 (20.4)		
Surgery	5 (4.4)		
Other[a]	6 (5.3)		
Proportion of patients in respondent's practice with refractory symptoms and incomplete response to PPI, *n* (%)			
Once-daily		**Twice-daily**	
<6%	6 (5.3)	<6%	28 (24.8)
6–10%	23 (20.4)	6–10%	31 (27.4)
11–20%	28 (24.8)	11–20%	25 (22.1)
21–30%	20 (17.7)	21–30%	12 (10.6)
31–40%	16 (14.2)	31–40%	8 (7.1)
41–50%	10 (8.8)	41–50%	2 (1.8)
>50%	10 (8.8)	>50%	7 (6.2)

[a]Includes internal medicine (2), obstetrics/gynecology (1), pediatric hospital medicine (1), neurology (1), psychiatry (1).

twice-daily (Table 1). An incomplete response to once-daily PPI therapy in more than 20% of patients was reported for once-daily therapy by 64.6% (51/79) of GIs and by 14.7% (5/24) of non-GIs; for twice-daily therapy, an incomplete response in more than 20% of patients was reported by 31.6% (25/79) of GIs and by 11.8% (4/24) of non-GIs.

3.1 | Potential causes of persistent reflux-like symptoms despite therapy

When asked to select the five most common reasons for incomplete response to PPI therapy despite adherence to dosing recommendations, functional heartburn was chosen by the greatest proportion overall (82.3%). However, 79.7% of GIs placed esophageal hypersensitivity in their top five compared with only 35.3% of non-GIs, conversely, a greater proportion of non-GIs chose esophageal dysmotility (47.1 vs. 27.8%) and non-reflux-related esophageal conditions (44.1 vs. 27.8%) to be among the top five reasons for PPI failure (Figure 1). Stress/anxiety was the second most common choice overall (69.0%), but more often by non-GIs (82.4%) compared with GIs (63.3%).

3.2 | Diagnosis of rGERD

Approximately two-thirds of surveyed clinicians agreed that "heartburn or regurgitation that persists unchanged after ≥8 weeks of a once-daily, standard-dose PPI, followed by ≥8 weeks of a twice-daily, standard-dose PPI" (8 weeks qd + 8 weeks bid PPI) would be consistent with a diagnosis of rGERD (Table 2). A much greater proportion of non-GIs (47.1 vs. 29.1%) agreed that "non-cardiac chest pain that persists unchanged after 8 weeks qd + 8 weeks bid PPI" would be consistent with a diagnosis of rGERD. Almost 1 in 4 non-GIs included in their choices the scenario of "heartburn, regurgitation, or chest pain that has resolved after 8 weeks qd + 8 weeks bid PPI but with Barrett's esophagus," as consistent with rGERD, whereas no GIs did (data not shown).

3.3 | Management options for persistent reflux-like symptoms despite therapy

For the initial management, the majority (69.9%) of clinicians indicated they would initially order one or more investigations for a fully compliant patient with persistent, but less frequent and less severe, heartburn, or regurgitation despite 8 weeks qd + 8 weeks bid PPI (partial response) (Table 3). This rose to 87.6% for patients with no symptom improvement (non-response). For non-responders, almost all GIs (92.4%) would order investigations but nearly one-quarter of non-GIs would not (23.8%), being more likely to add supplemental therapies or consider surgery.

The second most common strategy was to add supplemental therapies, being chosen by 72% of clinicians in cases of partial response, and 58% for non-response. Approximately 40% of clinicians would switch PPIs in patients with a partial response, but only 27–35% would consider this strategy in patients with a non-response after 8 weeks qd + 8 weeks bid PPI. Few clinicians would further increase the PPI dose beyond twice-daily.

When the strategy was to add supplemental therapy, antacid/alginate was the most common choice for patients with unresolved heartburn or regurgitation despite 8 weeks qd + 8 weeks bid PPI (Figure 2). While the first choice among GIs was to add an antacid/alginate (34.2%), it was less common among non-GIs (29.4%), which was mainly driven by primary care physicians (PCPs). Among PCPs, only 26.1% chose an antacid/alginate, while nearly half (47.8%) opted for a prokinetic. Only 24.1% of GIs would add a prokinetic (data not shown).

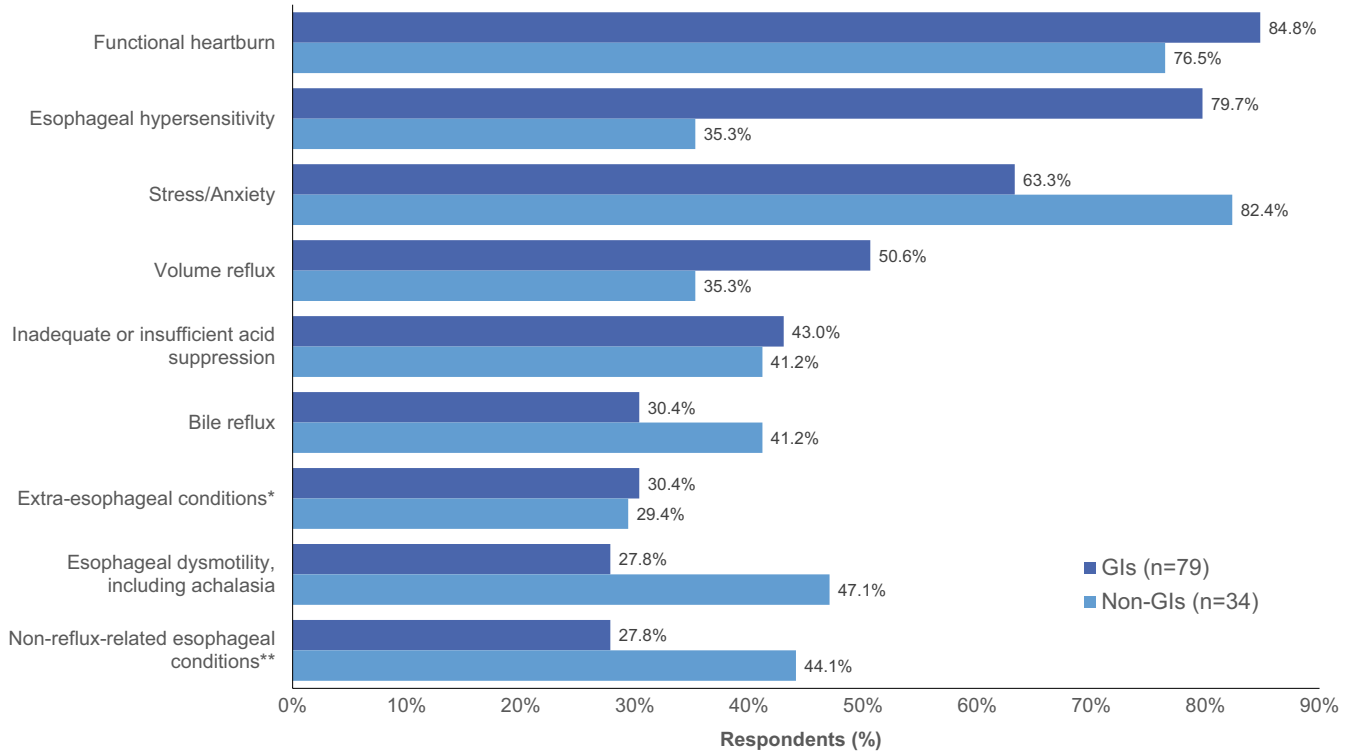

FIGURE 1 Most common reasons for incomplete response to qd or bid PPI therapy in patients with reflux-like symptoms (choose 5). *e.g., eosinophilic esophagitis; **e.g., musculoskeletal, cardiac, and respiratory conditions

TABLE 2 Patient scenarios considered consistent with a diagnosis of refractory GERD (select all that apply)

Response	*n* (%)
Heartburn or regurgitation that persists unchanged after 8 weeks or more of a once-daily, standard-dose PPI, followed by 8 weeks or more of a twice-daily, standard-dose PPI	75 (66.4)
Heartburn or regurgitation that is less frequent or severe but is still troublesome after 8 weeks or more of a once-daily, standard-dose PPI, followed by 8 weeks or more of a twice-daily, standard-dose PPI	67 (59.3)
Heartburn, regurgitation, or chest pain that have resolved after 8 weeks or more of a once-daily, standard-dose PPI, followed by 8 weeks or more of a twice-daily, standard-dose PPI but with persistent erosive reflux esophagitis	52 (46.0)
Non-cardiac chest pain that persists unchanged after 8 weeks or more of a once-daily, standard-dose PPI, followed by 8 weeks or more of a twice-daily, standard-dose PPI	39 (34.5)
Non-cardiac chest pain that is less frequent or severe but is still troublesome after 8 weeks or more of a once-daily, standard-dose PPI, followed by 8 weeks or more of a twice-daily, standard-dose PPI	37 (32.7)
Heartburn, regurgitation, or chest pain that have resolved after 8 weeks or more of a once-daily, standard-dose PPI, followed by 8 weeks or more of a twice-daily, standard-dose PPI but with Barrett's esophagus	8 (7.1)

3.4 | Longer-term management options

The long-term therapy options that clinicians would consider varied depending on the patient's response after adding supplemental therapy after a less than complete response to 8 weeks qd + 8 weeks bid PPI (Figure 3). For full responders, the most common option was to "reduce to once-daily PPI therapy and continue the original supplemental therapy" (65.5%). For patients with partial response, there was a lot of variability among GIs, and especially among non-GIs. This was also true for patients with no response, with the exception of "refer for anti-reflux surgery" (39.8%). Overall, there was no clear preference for continuing PPI therapy at twice-daily vs. reducing to once-daily, and continuing, switching or adding another supplemental therapy.

3.5 | Potential investigations in patients with persistent reflux-like symptoms despite therapy

As indicated above, almost 70% of clinicians indicated they would initially order one or more investigations. In the overall group, most clinicians would include upper endoscopy among any

initial investigations for patients with a partial or non-response after 8 weeks qd + 8 weeks bid PPI (86.7% and 81.4%, respectively) (Table 4). High-resolution esophageal manometry, and esophageal pH-impedance monitoring were chosen by GIs more often, while gastric emptying study, and upper GI contrast study (barium swallow) were more common among non-GI respondents.

Among GIs, 83.5% believed that "excessive acid exposure on pH monitoring (on PPI therapy)" was the most common finding supportive of a diagnosis of rGERD over functional heartburn or non-reflux related symptoms, compared with only 58.8% of non-GIs (Figure 4). Conversely, more non-GIs chose "a positive symptom-reflux event correlation on pH monitoring" as the most common finding supportive of a diagnosis of rGERD (85.3% vs. 60.8% of GIs). Compared with GIs, non-GIs were much more likely to believe "an irregular squamocolumnar junction (SCJ) at endoscopy" (47.1 vs. 10.1%) or "biopsy results consistent with GERD just proximal to the SCJ" (35.3 vs. 8.9%) to be supportive of rGERD diagnosis. Overall, few clinicians chose "abnormal esophageal impedance planimetry (EndoFLIP)" or "a hiatus hernia less than 2 cm" for this question (data not shown).

4 | DISCUSSION

Incomplete or non-response to an adequate trial of PPI therapy may be under-recognized in real-world practice. In RCTs, about one-third of patients have an inadequate response to 8 weeks of bid PPI therapy,[3] whereas approximately 50% of clinicians in this survey estimated the proportion of such patients in their practice was less than 20%. This illustrates the need for guidance to assist clinicians in assessing response to PPI therapy in a timely manner and determining when and how PPI therapy should continue.

Heartburn and regurgitation can persist despite PPI therapy for a variety of reasons, most commonly residual acid reflux, nonacidic or weakly acidic reflux, acid pocket, esophageal hypersensitivity, or functional heartburn.[9] Stress and anxiety have also been linked to refractory GERD symptoms, however, such as psychological comorbidities are not the most common etiology. Yet in this survey of the reasons for an incomplete response to PPI therapy, "stress/anxiety" was the second most common choice among GIs, and the most common among non-GIs. A better understanding of the potential etiologies would be helpful, especially for non-GI clinicians, to make more informed decisions should PPI response be unsatisfactory.

There is substantial heterogeneity in the literature regarding definitions of "refractory GERD symptoms" and "refractory GERD," both in terms of the severity of symptoms, and the dose and duration of optimal PPI therapy.[3,4] For the purposes of this survey, "optimal" PPI therapy included at least 8 weeks of once-daily followed by at least 8 weeks of twice-daily PPI therapy. A standardized definition continues to be an issue that impacts the choice of the most appropriate diagnostic and therapeutic strategies for managing rGERD.

In this survey, with the exception patients with Barrett's esophagus, the other 5 out of the 6 patient scenarios were considered to be consistent with a diagnosis of rGERD by about 35–65% of clinicians. These scenarios differed in the degree of response to PPI therapy, the presence of erosive reflux esophagitis, and the qualifier "non-cardiac chest pain," but the results suggest that clinicians, both GIs and non-GIs have a very "loose" definition of rGERD.

TABLE 3 Initial actions to be taken when symptoms persist after treatment with PPI qd for ≥8 weeks followed by PPI bid for ≥8 weeks[a] (select all that apply)

	Overall ($N = 113$)	GIs ($n = 79$)	Non-GIs ($n = 34$)
Partial response			
Arrange one or more investigations	69.9%	69.6%	70.6%
Add a supplemental therapy[b]	71.7%	69.6%	76.5%
Switch PPI therapy	40.7%	40.5%	41.2%
Consider surgical fundoplication	12.4%	10.1%	17.6%
Increase PPI therapy to 3 or 4 times daily	3.5%	3.8%	2.9%
Reduce PPI therapy to once-daily	2.7%	1.3%	5.9%
Non-response			
Arrange one or more investigations	87.6%	92.4%	76.5%
Add a supplemental therapy[b]	57.5%	51.9%	70.6%
Switch PPI therapy	29.2%	26.6%	35.3%
Consider surgical fundoplication	14.2%	8.9%	26.5%
Increase PPI therapy to 3 or 4 times daily	0.9%	1.3%	0.0%
Stop PPI therapy	17.7%	20.3%	11.8%

[a]Assuming compliance with lifestyle changes, timing, and dose of medications.

[b]One or more of prokinetic, sensory modulator or antidepressant, mucosal protectant, histamine H2-receptor antagonist, and or bile acid sequestrant.

As an initial strategy for patients with inadequate response to PPI therapy, most clinicians would arrange investigations, but perspectives on pharmacological treatment varied. For example, approximately 30%-40% of clinicians in this survey stated that they would consider switching PPIs if the heartburn or regurgitation in patients with a partial on non-response after 8 weeks qd + 8 weeks bid PPI. There is limited randomized controlled trial evidence in support of this strategy, although open-label and cohort studies have suggested switching can result in greater symptom relief.[10,11]

Adding supplemental therapy was a common initial strategy for patients with persistent heartburn or regurgitation. The type of adjunctive agent chosen varied among clinicians in the present survey. Although adding an antacid/alginate or prokinetic were the most common choices, these were selected by only about 1/3 of clinicians. There is some evidence suggesting that adding an alginate[12] or a prokinetic[13] to PPI therapy may be superior to PPI monotherapy in patients with rGERD. However, data are likely to have been influenced by the fact that prokinetics are not available in many locations.

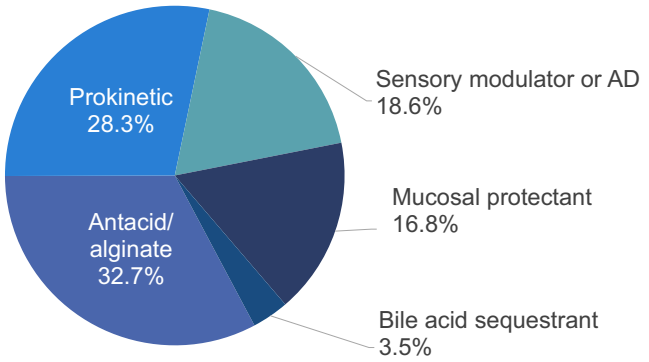

FIGURE 2 Initial supplemental therapy choice if incomplete response after treatment with PPI qd for ≥8 weeks followed by PPI bid for ≥8 weeks (select one). AD, antidepressant

One of the most challenging management questions is how to help patients in the long-term. For patients with a full response, most GIs would lower the PPI dose and continue the supplement; however, for non-GIs, the choice was less clear. In patients with partial or non-response to optimal PPI therapy, referral for anti-reflux surgery was the most common strategy; however, this was selected by only 30–40% of clinicians. For the remaining responses, there was a lot of variability with no clear preference for continuing PPI therapy at twice-daily vs. reducing to once-daily dosing, and continuing, switching, or adding another supplemental therapy.

The choice of continuing bid PPI in patients with no response might reflect uncertainty regarding the optimal duration of PPI therapy. Concerns around patient adherence may also account for inadequate response,[14] thus, continuing a PPI may be useful if patient adherence can be enhanced through education and other tools.

The confusion around the appropriateness of continuing or discontinuing PPI therapy is underscored by a prior survey conducted among Canadian primary and specialty care fellows.[15] While 98% of clinicians stated they would adhere to PPI prescribing guidelines,

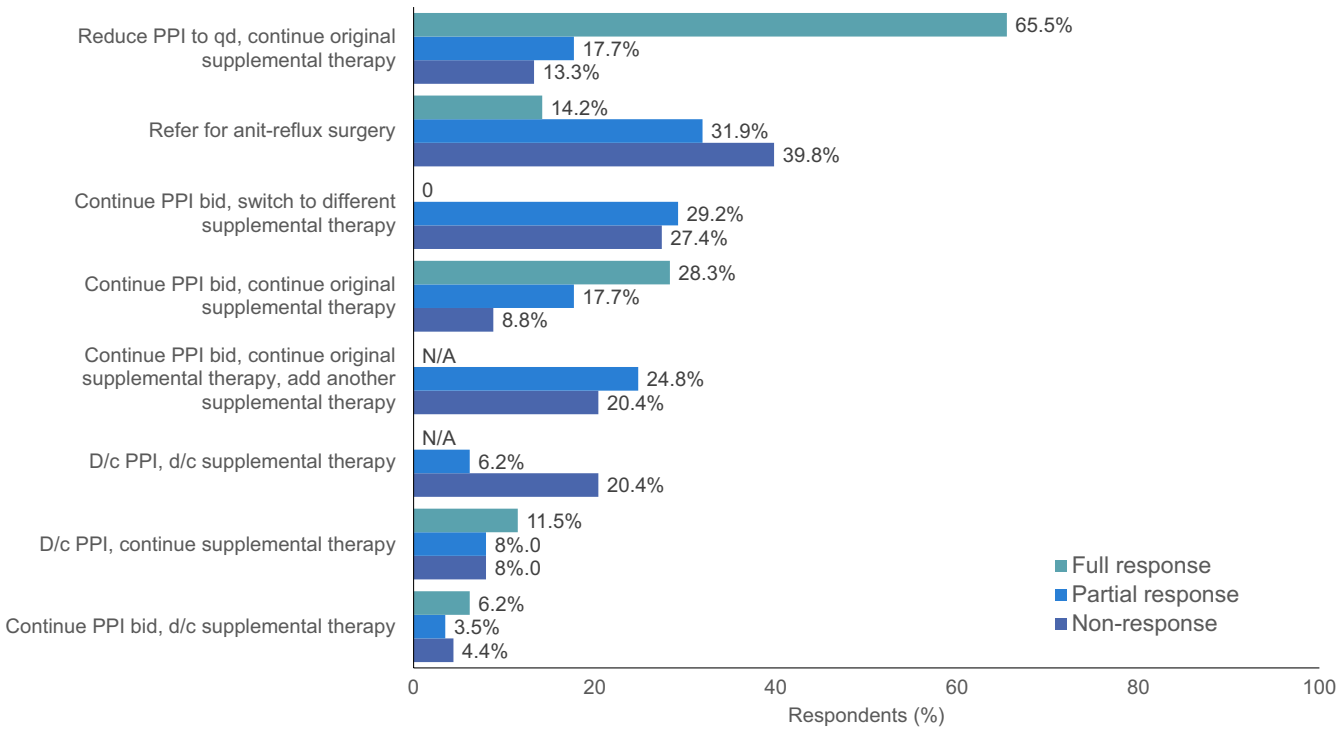

FIGURE 3 Long-term therapy selections after addition of supplemental therapy† to PPI therapy according to treatment response (select all that apply). †Supplemental therapy (e.g., antacid/alginate, mucosal protectant, prokinetic, bile acid sequestrant, sensory modulator, or antidepressant) added due to persistence of symptoms after treatment with PPI qd for ≥8 weeks followed by PPI bid for ≥8 weeks. d/c = discontinue; N/A = answer choice not available for survey question

TABLE 4 Initial investigations when symptoms persist after treatment with PPI qd for ≥8 weeks followed by PPI bid for ≥8 weeks (select all that apply)

	Overall (*N* = 113)	GIs (*n* = 79)	Non-GIs (*n* = 34)
Partial response			
Upper endoscopy	86.7%	83.5%	94.1%
High-resolution esophageal manometry	41.6%	49.4%	23.5%
Esophageal pH-impedance monitoring during twice-daily PPI therapy	35.4%	45.6%	11.8%
Esophageal pH-impedance monitoring after discontinuation of twice-daily PPI therapy	25.7%	27.8%	20.6%
Esophageal pH monitoring after discontinuation of twice-daily PPI therapy	17.7%	16.5%	20.6%
Gastric emptying study	15.0%	13.9%	17.6%
Esophageal pH monitoring during twice-daily PPI therapy	13.3%	13.9%	11.8%
Upper GI contrast study (barium swallow)	8.0%	3.8%	17.6%
Esophageal impedance planimetry (EndoFLIP)	0.0%	0.0%	0.0%
Non-response			
Upper endoscopy	81.4%	81.0%	82.4%
High-resolution esophageal manometry	46.9%	54.4%	29.4%
Esophageal pH monitoring after discontinuation of twice-daily PPI therapy	31.0%	36.7%	17.6%
Esophageal pH-impedance monitoring after discontinuation of twice-daily PPI therapy	29.2%	32.9%	20.6%
Esophageal pH-impedance monitoring during twice-daily PPI therapy	21.2%	25.3%	11.8%
Gastric emptying study	17.7%	11.4%	32.4%
Esophageal pH monitoring during twice-daily PPI therapy	10.6%	8.9%	14.7%
Upper GI contrast study (barium swallow)	8.0%	5.1%	14.7%
Esophageal impedance planimetry (EndoFLIP)	3.5%	1.3%	8.8%

only 42% had been educated on prescribing long-term PPIs. When presented with case scenarios, 26–76% opted to inappropriately discontinue PPI therapy when long-term PPI was warranted; conversely, 15–44% opted to inappropriately continue PPI therapy where its use was poorly supported. There are possible risks with the long-term use of PPIs,[16] and these should also be considered in management decisions when a patient is not benefiting from PPI therapy.

When the initial strategy was to arrange investigations, the vast majority of clinicians chose upper endoscopy for patients with a partial or non-response to PPI therapy. As would be expected, there were differences between GIs and non-GIs around the indications for and the usefulness of tests beyond an upper GI endoscopy. However, non-GIs often do not have access to specialized investigations, which should be considered when interpreting the survey findings. High-resolution esophageal manometry was chosen by GIs almost twice as often as by non-GIs. Esophageal pH monitoring was also a frequent choice; however, there was no clear preference for whether this should be conducted on or off PPI therapy, and whether pH-impedance should be used. This may have been impacted by the fact that the survey did not specify whether a diagnosis of GERD had previously been confirmed. While more non-GIs would consider surgery, this may reflect the fact that "refer to a GI specialist" was not an answer choice, and that this was interpreted as encompassing referral to a gastroenterologist.

Clinicians are unsure of the investigative findings that support a diagnosis of rGERD. Excessive acid exposure on pH monitoring (on PPI therapy) predominated among GIs, while non-GIs were more likely to look for positive symptom-reflux event correlation on pH monitoring. The wide variability among the other choices again reinforces the uncertainty about the diagnosis of rGERD, both in terms of symptoms and with regard to objective findings.

This survey suggests that there is a need, not only for a clear evidenced-based approach to the diagnosis and management of patients with persistent symptoms despite optimal PPI therapy but also at the very least wider dissemination of available guidance to clinicians. Specifically, the wide variability of responses illustrates gaps in defining PPI non-response, most appropriate diagnostic criteria and approaches, and appropriate optimal treatment strategies for refractory reflux-like symptoms and rGERD.

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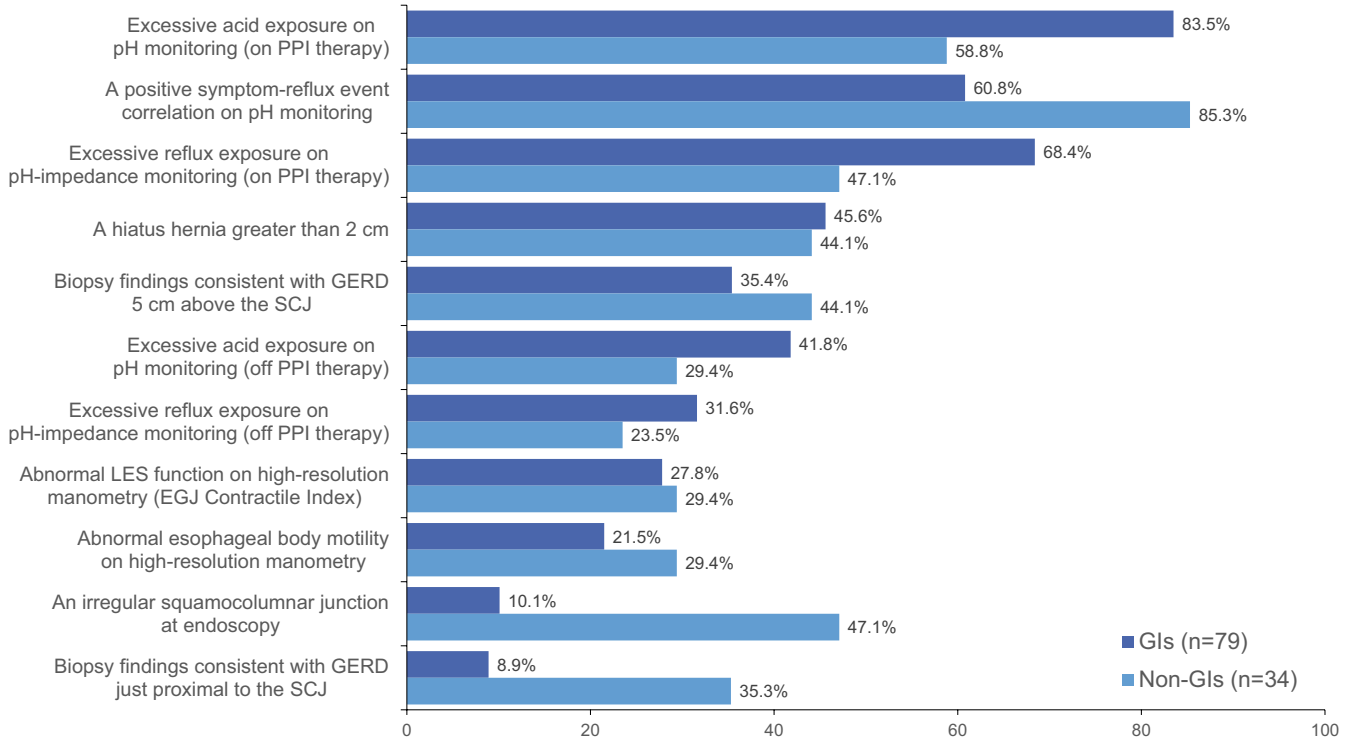

FIGURE 4 Findings considered to be supportive of rGERD diagnosis vs. functional heartburn or non-reflux related symptoms (select all that apply). EGJ, esophagogastric junction; LES, lower esophageal sphincter; SCJ, squamocolumnar junction

DISCLOSURE

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AUTHOR CONTRIBUTIONS

All authors contributed to the development of the survey questions and invited participants to respond. DA and PSh, with the assistance of the medical writers, co-wrote the initial draft of the manuscript, which was then critically revised and approved by all authors.

ORCID

Peter J. Kahrilas https://orcid.org/0000-0002-8260-1250
Daniel Sifrim https://orcid.org/0000-0002-4894-0523

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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