CHEST

Original Research

SIGNS AND SYMPTOMS OF CHEST DISEASES

Response of Chronic Cough to Acid-Suppressive Therapy in Patients With Gastroesophageal Reflux Disease

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Background: **Epidemiologic and physiologic studies suggest an association between gastroesophageal reflux disease (GERD) and chronic cough. However, the benefit of antireflux therapy for chronic cough remains unclear, with most relevant trials reporting negative findings. This systematic review aimed to reevaluate the response of chronic cough to antireflux therapy in trials that allowed us to distinguish patients with or without objective evidence of GERD.**

Methods: **PubMed and Embase systematic searches identified clinical trials reporting cough response to antireflux therapy. Datasets were derived from trials that used pH-metry to characterize patients with chronic cough.**

Results: **Nine randomized controlled trials of varied design that treated patients with acid suppression were identified (eight used proton pump inhibitors [PPIs], one used ranitidine). Datasets from two crossover studies showed that PPIs significantly improved cough relative to placebo, albeit only in the arm receiving placebo first. Therapeutic gain in seven datasets was greater in patients with pathologic esophageal acid exposure (range, 12.5%-35.8%) than in those without (range, 0.0%-8.6%), with no overlap between groups.**

Conclusions: **A therapeutic benefit for acid-suppressive therapy in patients with chronic cough cannot be dismissed. However, evidence suggests that rigorous patient selection is necessary to identify patient populations likely to be responsive, using physiologically timed cough events during reflux testing, minimal patient exclusion because of presumptive alternative diagnoses, and appropriate power to detect a modest therapeutic gain. Only then can we hope to resolve this vexing clinical management problem.** ***CHEST 2013; 143(3):605–612***

Abbreviations: GERD = gastroesophageal reflux disease; LPR = laryngopharyngeal reflux; PPI = proton pump inhibitor

Chronic cough, defined as cough that persists for > 8 weeks, affects 11% to 20% of the adult population[1] and significantly impairs health-related quality of life,[2] leading to substantial socioeconomic burden. Epidemiologic studies suggest an association between gastroesophageal reflux and chronic cough,[3] and this relationship is supported by convincing physiologic data. First, in patients with chronic cough, acid infusion into the distal esophagus increases the frequency of coughing[4] and cough reflex sensitivity.[5] Second, approximately one-half of unselected patients with chronic cough show a positive symptom association between cough and reflux during reflux monitoring.[6] However, unlike heartburn, which is usually caused by acid reflux,[7] chronic cough has a diverse range of potential causes. Estimates of the proportion of patients with chronic cough in whom reflux is the underlying cause vary greatly among specialists, ranging from 0% to 41%.[8] Given the implicit variation in approaches used to identify patients with reflux-related cough, it is perhaps not surprising that a Cochrane review found insufficient evidence to conclude that proton pump inhibitor (PPI) treatment is beneficial in treating nonspecific chronic cough.[9]

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The relationship between gastroesophageal reflux and reflux symptoms is complex in general, but it is particularly complex in the case of chronic cough, in which other disease processes, issues of cause and

effect, and hypersensitivity all come into play. Hence, a more thoughtful exploration of the literature may be required to elucidate any treatment benefit for acid-suppressive therapy in this patient group and/or to identify factors that may have prevented studies from detecting benefit with acid-suppressive treatments. For example, with another potential gastroesophageal reflux disease (GERD) syndrome, unexplained chest pain, a recent analysis showed that PPI therapy was effective in patients with objective evidence of GERD (pathologic esophageal acid exposure and/or reflux esophagitis) but not in those without.[10] To our knowledge, the impact of this and other variations in study design on therapeutic outcomes for acid-suppressive therapy in patients with chronic cough has not been explored. Thus, the aim of this systematic review was to evaluate the response of chronic cough to acid-suppressive therapy in relation to variations in study design, with a particular focus on distinguishing between studies that included patients with and without objective measures of GERD.

Materials and Methods

Systematic Searches

A systematic search of PubMed and Embase (for all years until August 20, 2011) was conducted (Fig 1) as well as a search of recent review articles and abstracts from recent congresses (Digestive Diseases Week, 2008-2011; United European Gastroenterology Week, 2008-2011). Included studies were placebo-controlled clinical trials reporting data on the impact of antireflux therapy on cough in patients selected based on the presence of chronic cough or laryngopharyngeal reflux (LPR), of which cough was a component symptom, and diagnosed with GERD or LPR by objective measures and/or reflux symptoms.

Reviews, studies not conducted in adult humans, and studies not published in English were excluded using search engine filters. Studies were also excluded if they did not specify the type of acid-suppressive therapy used or if they used a crossover study design without presenting data separately for the first period. The latter exclusion criterion was based on likely period effects for cough (ie, that it tends to improve with time) and the bias associated with carryover effects when an adequate washout period is not used.[1] The remaining studies were screened based on titles and abstracts and on the full article when the relevancy of the study was not clear from the abstract.

Analysis of Therapeutic Gain

Where possible, the therapeutic gain associated with acid-suppressive treatment of chronic cough was calculated. This approach was used in recent systematic reviews to compare the therapeutic response of heartburn, regurgitation,[11] and unexplained chest pain[10] to PPIs across different studies. Therapeutic gain was calculated by subtracting the percentage change from baseline in cough (symptom score or proportion of responders) in the placebo group from that in the treatment group. Second-arm data from crossover studies were not included in the analysis, as discussed previously. Attempts were made to contact study authors for additional information needed for full analysis of their data.[12-16]

Results

Systematic Searches and Study Selection

The systematic searches are summarized in Figure 1. Seven studies were excluded for the following reasons: Four were epidemiologic studies,[17-20] one was not published in English,[21] and two did not select patients based on the presence of chronic cough or LPR reflux.[12,22] A citation list search of the remaining 24 studies identified four additional studies for potential inclusion (28 in total). A placebo control group was not included in 10 of these, and they were excluded.[23-32] Another study was excluded because it did not specify the definition of GERD used.[33]

Study Characteristics

Characteristics of the nine included studies are summarized in Table 1.[13-16,34-38] All assessed pharmacologic interventions for cough (no placebo-controlled studies assessing surgery were found); eight assessed PPIs (once daily or bid for 8-16 weeks)[13-16,34-37]; and one assessed the histamine type 2-receptor antagonist ranitidine, 150 mg daily for 8 weeks.[38] No unpublished data were used in this review because no additional information that aided the analysis was obtained from authors.

Methods for assessing cough varied substantially across studies. Five used patient diaries consisting of visual analog scales to assess cough severity and/or frequency (Table 1),[13,16,34,36,38] questionnaires were used in two studies (Table 1),[14,35] and two studies did not specify the method of data acquisition (Table 1).[15,37] Two studies assessed efficacy in terms of the proportion of patients who met prespecified criteria for response (Table 1)[16,36]; the remainder measured change in mean cough scores relative to baseline for treatment vs placebo. Sample sizes across the studies were 15 to 40, and the sample sizes for placebo and active

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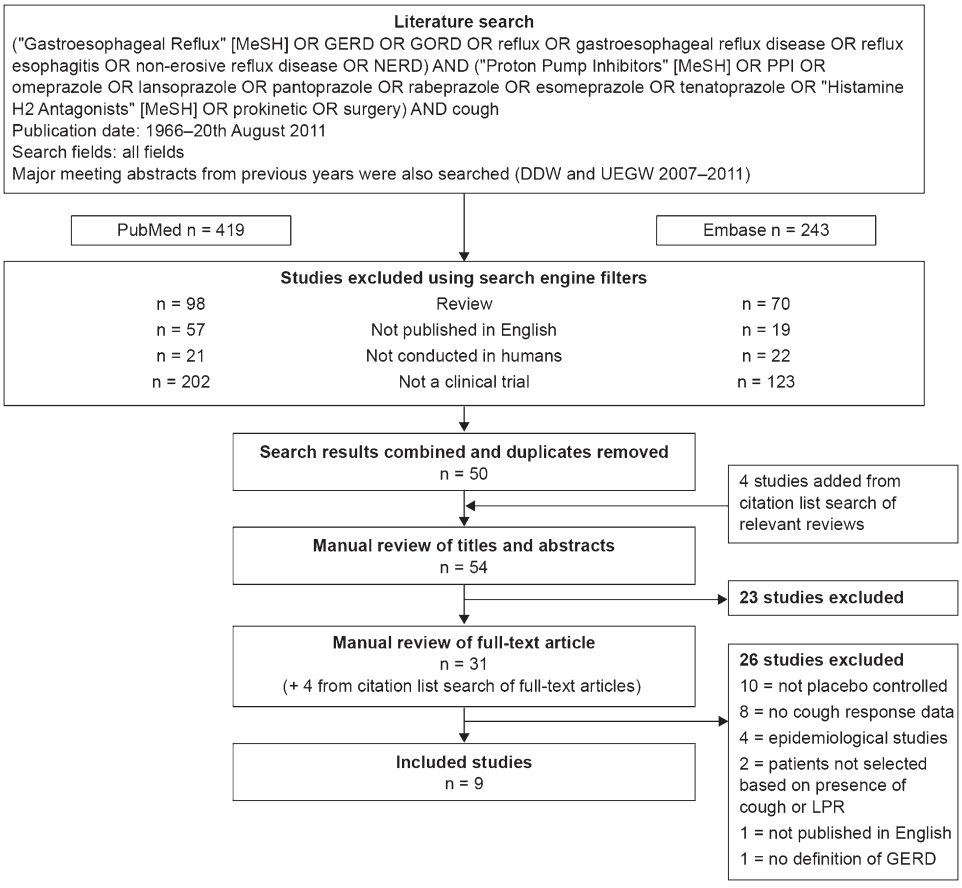

FIGURE 1. Summary of the systematic search strategy and study selection process. DDW = Digestive Diseases Week; GERD = gastroesophageal reflux disease; GORD = gastrooesophageal reflux disease; LPR = laryngopharyngeal reflux; NERD = non-erosive reflux disease; PPI = proton pump inhibitor; UEGW = United European Gastroenterology Week.

treatment groups were seven to 19 and eight to 22, respectively.

Reported Analyses for the Response of Chronic Cough to Acid-Suppressive Therapy

Chronic cough was reported to respond significantly to acid-suppressive therapy in two of the nine included trials (Table 1)[34,38]; both used a crossover design to assess the impact of 8 weeks of acid-suppressive therapy on cough scores in patients with pathologic esophageal acid exposure. In each case, the statistically significant response was only detected for the first period of the crossover study. Another study, which also assessed the impact of 8 weeks of acid-suppressive therapy on cough scores in patients with pathologic esophageal acid exposure but was not a crossover design, reported a trend toward improved cough scores (Table 1).[35] Of the six studies that did not report significantly improved cough scores, five used a treatment period of ≥ 12 weeks (Table 1),[13,15,16,36,37] three included patients who did not have pathologic esophageal acid exposure (Table 1),[15,16,37] and two excluded patients with heartburn (Table 1).[16,37]

Therapeutic Response of Chronic Cough to Acid-Suppressive Therapy

Sufficient data for calculating the therapeutic gain of acid-suppressive therapy were available in six studies (Table 1).[16,34-38] Shaheen et al[37] (Table 1) reported data separately for patients with and without pathologic esophageal acid exposure and, thus, contributed two datasets, resulting in a total of seven datasets for further analysis. One dataset showed no therapeutic gain (Table 1).[16] Therapeutic gains across the six remaining datasets were 8.6% to 35.8% (nonweighted mean, 21.5%).

Patients With Pathologic Esophageal Acid Exposure: The five datasets with the greatest therapeutic gain were those that included only patients with pathologic esophageal acid exposure. The range was 12.5% to 35.8% (nonweighted mean, 24.1%) (Fig 2). The three with the greatest therapeutic gain in this group all assessed treatment efficacy in terms of the change in cough score from baseline after 8 weeks of therapy. The lowest therapeutic gain was observed for ranitidine.[38] The two datasets with the lowest therapeutic

Table 1—*Description of Included Studies*

Study/Year	Study Inclusion: Chronic Cough and…	Study Exclusion	Treatment Arms	Method of Cough Assessment
Ing et al[38]/1992	Abnormal pH-metry	Not specified	Ranitidine 150 mg bid (n = 11) Placebo (n = 13)	Diaries: mean change in cough score
Havas et al[15]/1999	(a) LPR with abnormal pH-metry; (b) LPR with normal pH-metry	Chronic airflow limitation, severe reflux esophagitis	(a) Lansoprazole 30 mg bid (n = 5); placebo (n = 3); (b) Lansoprazole 30 mg bid (n = 3); placebo (n = 4)	Mean change in cough score (frequency × severity)
Kiljander et al[34]/2000	Abnormal pH-metry	Postnasal drip, asthma, abnormal chest radiograph, smokers	Omeprazole 40 mg (n = 9) Placebo (n = 12)	Mean change in cough score over final 3 wk
Noordzij et al[35]/2001	LPR with abnormal pH-metry	Infectious laryngitis, laryngeal cancer, allergies	Omeprazole 40 mg bid (n = 15) Placebo (n = 15)	Questionnaire: mean change in cough score (frequency × severity)
Ours et al[36]/1999	Abnormal pH-metry	Asthma, abnormal chest radiograph, smokers	Omeprazole 40 mg bid (n = 8) Placebo (n = 15)	Diaries: cough score (frequency × severity, day/night) prespecified criteria
Shaheen et al[37]/2011	(a) Abnormal pH-metry; (b) Normal pH-metry	Postnasal drip, heartburn, abnormal chest radiograph, smokers	(a) Esomeprazole 40 mg bid (n = 10); placebo (n = 7); (b) Esomeprazole 40 mg bid (n = 12); placebo (n = 11)	Fisman cough severity and frequency score; mean change
Steward et al[14]/2004	LPR symptoms	GI surgery, malignancy	Rabeprazole 20 mg bid (n = 18) Placebo (n = 19)	Mean change in cough score (frequency × severity)
Wo et al[13]/2006	LPR with abnormal pH-metry	Prior LPR, GERD, or gastric surgery	Pantoprazole 40 mg (n = 20) Placebo (n = 19)	Mean change in cough score
Vaezi et al[16]/2006	LPR with normal pH-metry	Infectious laryngitis, malignancy, sinusitis	Esomeprazole 40 mg bid (n = 11) Placebo (n = 8)	Diaries: cough severity, prespecified criteria

GERD = gastroesophageal reflux disease; LPR = laryngopharyngeal reflux.

gain both used a treatment period of 12 weeks. In addition, one assessed efficacy in terms of the proportion of patients meeting prespecified response criteria (Table 1),[36] and one excluded patients with heartburn (Table 1).[37]

Patients Without Pathologic Esophageal Acid Exposure: The two lowest therapeutic gains were 0.0% and 8.6% and were observed in the only two datasets (Table 1)[16,37] that selected patients with normal esophageal acid exposure (Fig 2). Both also excluded

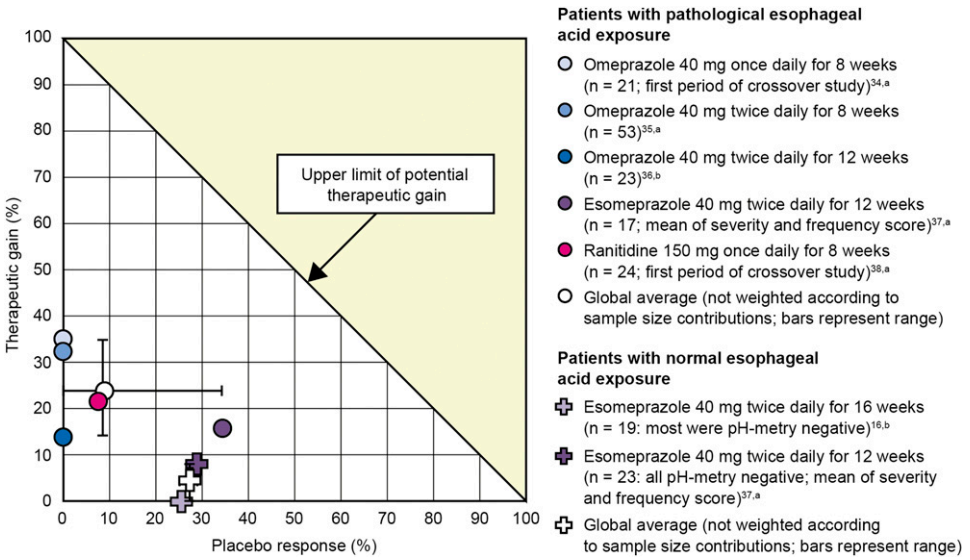

FIGURE 2. Calculated therapeutic gain for datasets derived from patients with pathologic esophageal acid exposure and populations including patients with normal esophageal acid exposure. [a]Percentage change in symptom score; [b]Percentage change in proportion of responders.

patients with heartburn. In addition, the dataset exhibiting no therapeutic gain was after 16 weeks of treatment (the longest treatment period across all studies) and was calculated based on the proportion of responders meeting prespecified response criteria.

Placebo Response of Chronic Cough to Therapy

The mean placebo response rate across all seven datasets was 13.8%. The greatest placebo response rate was 33.5% and was from the Shaheen et al[37] study that included only patients with pathologic esophageal acid exposure. This was similar to the placebo response rate of 29.5% observed in patients without pathologic esophageal acid exposure from the same study. However, the mean placebo response rate across the five datasets that included only patients with pathologic esophageal acid exposure was less than the mean placebo response rate across the two datasets that included patients with normal esophageal acid exposure (8.4% vs 24.1%) (Fig 2).

Discussion

Reflux-cough syndrome is something of an enigma, in that despite substantial uncontrolled data, well summarized in the American College of Chest Physicians 2006 Practice Guidelines, suggesting efficacy of diet, antacids, histamine-2 receptor antagonists, prokinetics, PPIs, and antireflux surgery in improving or curing reflux cough syndrome,[39] controlled trials have consistently failed to demonstrate this.[39] Hence, we aimed to systematically review studies assessing the response of chronic cough to acid-suppressive therapy, with a focus on relating study outcomes to differences in study design and whether the patients studied had objective evidence of GERD. Of the nine placebo-controlled, randomized clinical trials identified, only two reported a statistically significant reduction in cough frequency and/or severity after pharmacologic acid-suppressive therapy. However, in six[34-38] of the seven datasets in which therapeutic gain could be calculated, acid-suppressive treatment had a greater effect than placebo. The only dataset demonstrating no therapeutic gain[16] was from a study that enrolled patients with normal esophageal pH-metry. When therapeutic gains were classified according to pH-metry characteristics, they were greater in patients with pathologic esophageal acid exposure (range, 12.5%-35.8%)[34-38] than in those without (range, 0.0%-8.6%).[16,37]

The suggestion that acid suppression may be beneficial in treating chronic cough in patients with GERD begs the question of why so few studies were able to detect a statistically significant effect. Clearly, small sample sizes may be an issue. Indeed, most studies appear to be powered to detect a therapeutic benefit for acid suppression of the magnitude that might be expected for heartburn, regurgitation,[11] or unexplained chest pain.[10] However, for reasons discussed later, a therapeutic benefit of that magnitude is unlikely for chronic cough, even in patients with pathologic esophageal acid exposure. And, of course, even though our findings hint at a relatively consistent effect for acid-suppressive therapy relative to placebo on cough in patients with pathologic esophageal acid exposure, they should be viewed with caution given the absence of sufficient data for meta-analysis.

If acid-suppressive treatment does have a therapeutic benefit in some patients with chronic cough, it is clear that the effect is substantially less than that observed in patients with GERD for heartburn, regurgitation, or unexplained chest pain,[10,11] despite the use of pH-metry to enrich the study population with patients with reflux. The elegant study by Smith et al[6] provides insight into why patients with chronic cough are relatively refractory to GERD therapy. That study combined sound recordings with acoustic analysis and pH-impedance recordings to accurately define the temporal relationship between cough and reflux events. Of the unselected patients with chronic cough assessed, 48% had a positive symptom association probability for cough preceded by reflux. Even more importantly, 56% of patients had a positive symptom association probability for reflux preceded by cough, and 32% had a positive symptom association probability in both directions. The authors concluded that in addition to reflux potentially inducing cough, cough could also induce reflux, possibly by increasing transient lower esophageal sphincter relaxations (considered a major mechanism for generating reflux events[40,41]) via a CNS mechanism. Furthermore, it was shown that many patients had cough associated with both acid and weakly acidic reflux. Finally, building upon earlier experimental observations of increased sensitivity of the cough reflex with esophagitis[42] and an acute lowering of the tussigenic threshold to inhaled capsaicin by esophageal acid perfusion in patients with GERD irrespective of whether they had chronic cough,[5] Smith and colleagues observed increased sensitivity to a tussigenic challenge in the subset of patients with cough preceded by reflux. Together, these observations strongly implicate increased cough sensitivity as an important operant mechanism in patients with reflux cough.

The implications of the findings of Smith et al[6] for the current study are twofold. First, many patients with chronic cough may have pathologic esophageal acid exposure because of acid reflux induced by coughing. Hence, although they have both conditions, the chronic cough may still be caused by other factors and, consequently, be unresponsive to acid suppression. Second, even in patients whose cough is caused by reflux, weakly acidic reflux resulting from acid-suppressive

therapy may still be sufficient to perpetuate cough. The apparent success of antireflux surgery in treating patients with chronic cough refractory to PPI therapy, albeit in uncontrolled trials, supports the concept that weakly acidic reflux may be sufficient to perpetuate chronic cough in some patients.[39,43] Both of these factors and the observed hypersensitivity of the cough reflex would lead to a diminution of the therapeutic response observed in clinical trials of acid suppression in patients with chronic cough if pathologic esophageal acid exposure was the only coselection criterion. Conversely, the therapeutic response rate for acid-suppressive therapy for patients with chronic cough may be improved by adopting the methodology of Smith et al[6] to select only patients with a significant symptom association pattern for cough preceded by acid reflux. Obviously, no such trial has yet been conducted. However, an indication that more stringent patient selection criteria might improve response rates was provided in the observational study by Hersh et al.[44] Despite less precise methodology than that used by Smith et al,[6] Hersh et al[44] reported that patients with a positive symptom association pattern for cough and reflux (60% of the series) had a better response to antireflux therapy compared with patients with pathologic esophageal acid exposure but negative symptom association (44% of the series). Surgery was also included among antireflux therapies in the Hersh et al[44] study. Antireflux surgery may be more effective than acid-suppressive therapy in patients with chronic cough, as both acid and weakly acidic reflux should be reduced. Consistent with our findings, a recent retrospective analysis concluded that this was particularly true in patients with concomitant heartburn or > 12% esophageal acid exposure on pH-metry.[45] However, among the many studies reporting benefit in reduced chronic cough after antireflux surgery,[23,24,27,32] none were placebo controlled, which is essential for a condition that tends to resolve naturally over time.

Apart from verifying objective evidence of reflux disease, our findings suggest other design aspects to consider in future trials. Clearly, a crossover design should be avoided both because of a potential spontaneous recovery and because of carryover effect. With respect to trial duration, 8 weeks seemed optimal, as the best responses were observed in trials of that duration, with longer trials actually exhibiting less treatment effect. The cough outcome measure is also a key aspect of study design. Complete resolution of cough, although desirable, was rarely achieved, and studies stipulating arbitrary, strict cutoff values to define patient response had few, if any, responders.[16,36] More reasonable would be to use a validated cough assessment instrument linking the definition of a response to a patient-defined meaningful improvement in quality of life. Finally, the two studies with the lowest therapeutic gain for acid-suppressive therapy were also the only two studies to exclude patients with heartburn.[16,37] Including patients with pathologic esophageal acid exposure who do not have heartburn likely selects for patients with low esophageal sensitivity, as suggested in a recent comprehensive review of reflux perception.[7] Given that esophageal sensitivity may play a role in reflux-induced cough, these criteria may inadvertently select against likely responders.

In conclusion, a therapeutic benefit for acid-suppressive therapy in patients with chronic cough could not be dismissed. However, evidence reviewed suggests that rigorous patient selection is likely necessary to identify responsive patient populations. Future trials of GERD therapy for chronic cough should include patients irrespective of concomitant conditions such as asthma or post-nasal drip who have a positive reflux-cough association determined by physiologically timed cough events during reflux testing. Clinical efficacy should be assessed after 8 weeks' treatment and should be based on a clinically meaningful, but not necessarily complete, improvement in symptom score relative to baseline. Finally, studies need to be sufficiently powered to detect a therapeutic gain in the range of 20% to 30%. Only then can we hope to resolve this vexing clinical management problem.

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Dr Kahrilas: contributed to conceiving and writing the manuscript, data analysis and clinical interpretation of the data, and independently screening the search results and approving the final draft of the manuscript.

Dr Howden: contributed to conceiving and writing the manuscript, data analysis and clinical interpretation of the data, and independently screening the search results and approving the final draft of the manuscript.

Dr Hughes: contributed to conceiving and writing the manuscript, data analysis, and independently screening the search results and approving the final draft of the manuscript.

Dr Molloy-Bland: contributed to conceiving and writing the manuscript, data analysis, and independently screening the search results and approving the final draft of the manuscript.

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