Approach to refractory gastroesophageal reflux disease in adults

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INTRODUCTION

Despite treatment with proton pump inhibitors (PPIs), some patients with gastroesophageal reflux disease (GERD) continue to have reflux symptoms or endoscopic evidence of esophagitis. This topic will review an approach to patients with refractory GERD. The clinical manifestations, diagnosis, and initial medical management of GERD are discussed in detail separately. (See "Medical management of gastroesophageal reflux disease in adults".)

TERMINOLOGY

The definition of refractory gastroesophageal reflux disease (GERD) is controversial [1]. According to most experts, patients with GERD who exhibit partial or lack of response to proton pump inhibitor (PPI) twice daily are considered to have failed PPI therapy [2]. GERD in these patients is termed refractory GERD. However, we suggest that lack of satisfactory symptomatic response to PPI once a day should be considered a failure of PPI therapy.

EPIDEMIOLOGY

Approximately 10 and 40 percent of patients with gastroesophageal reflux disease (GERD) fail to respond symptomatically, either partially or completely, to proton pump inhibitors (PPIs) [3-6]. Most patients with GERD who do not respond to a PPI have either nonerosive reflux (NERD) or functional heartburn. In patients with NERD, the pooled symptomatic response rate to PPI once daily at four weeks is 37 percent [7,8]. In contrast, in patients with erosive esophagitis, which accounts for 30 to 40 percent of the GERD population, the pooled symptomatic response rate is 56 percent [7].

ETIOLOGY

Insufficient acid suppression — A range of mechanisms can result in insufficient suppression of gastric acid.

Medication related factors

Medication timing and adherence — Poor compliance with proton pump inhibitor (PPI) timing and adherence is an important cause for inadequate acid suppression and refractory GERD [9-11]. PPIs should be administered 30 to 60 minutes before breakfast for maximal inhibition of proton pumps. In one study that included 100 patients with GERD, only 46 percent of patients prescribed a PPI for GERD were taking it as advised [12,13]. Administration of PPIs before a meal provides better control of intragastric pH as compared with administration during or after a meal [14]. (See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders", section on 'Dose and timing of administration'.)

Differences in PPI metabolism — PPIs are metabolized through the hepatic cytochrome system, with CYP2C19 having the dominant role. The activity of CYP2C19 is determined to some extent by a genetic polymorphism. Approximately 5 percent of White patients and >10 percent of Asian patients are homozygous for a *CYP2C19* mutation (ie, slow metabolizers), potentially leading to greater suppression of gastric acidity. However, in wild type homozygotes (rapid metabolizers) the effect of PPIs on gastric acidity is diminished and may contribute to PPI failure. (See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders".)

Residual acid reflux — Residual acid reflux has been documented in patients despite PPI therapy, however, the incidence in patients on twice daily therapy is low [15-19]. As an example, in one retrospective review of pH testing results in 135 GERD subjects with refractory symptoms on once or twice daily PPI therapy, results were abnormal in 31 and 4 percent, respectively [20].

The presence of concentrated, highly acidic gastric juice postprandially at the gastroesophageal junction, termed the acid pocket, likely has a limited role in refractory GERD by causing re-reflux of gastric acid. A study that included 18 patients with GERD, of whom nine had a partial response to PPIs, demonstrated no difference in the pH or position of the acid pocket between PPI responders and nonresponders [21]. (See "Pathophysiology of reflux esophagitis", section on 'Impaired esophageal acid clearance'.)

Weakly acidic or alkaline reflux (non-acid reflux) — Non-acid reflux episodes primarily occur in the postprandial period as transient lower esophageal sphincter relaxation occurs more frequently following meal-induced gastric fundus distension. In patients on PPIs, treatment changes the acidity of the refluxate but does not decrease the volume of reflux or affect structural and motility abnormalities at the gastroesophageal junction responsible for GERD. In patients not on acid suppressive therapy, non-acid reflux results when gastric acid is buffered by the ingested food in the postprandial period. The clinical manifestations, diagnosis, and management of non-acid reflux is discussed in detail separately. (See "Pathophysiology of reflux esophagitis", section on 'Anatomic disruption of the gastroesophageal junction' and "Non-acid reflux: Clinical manifestations, diagnosis, and management", section on 'Pathogenesis'.)

Reflux hypersensitivity — Reflux hypersensitivity is characterized by retrosternal symptoms, including heartburn and chest pain associated with non-pathologic acid exposure [22]. In patients with esophageal hypersensitivity, proximal migration of weakly acidic reflux and the presence of gas in the refluxate are pivotal for symptom generation [21,23].

There are limited data on the prevalence of reflux hypersensitivity [24,25]. In a study of 329 patients with non-erosive reflux disease who underwent pH–impedance monitoring, 40 percent had abnormal acid exposure. The prevalence of reflux hypersensitivity and functional heartburn were 36 and 24 percent, respectively [24].

According to the Rome IV criteria, a diagnosis of reflux hypersensitivity requires all of the following criteria be fulfilled for the last three months with symptom onset at least six months prior to the diagnosis [26]:

- Retrosternal symptoms including heartburn or chest pain
- Normal endoscopy and absence of evidence that eosinophilic esophagitis is the cause for symptoms
- Absence of major esophageal motor disorders (achalasia/esophagogastric junction outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis)

- Evidence of triggering of symptoms by reflux events despite normal acid exposure on pH or pH–impedance monitoring (response to antisecretory therapy does not exclude the diagnosis)

Esophageal hypersensitivity is analogous to the visceral hyperalgesia described in other functional gastrointestinal disorders (eg, functional chest pain, functional dyspepsia) and is driven by similar mechanisms of altered central processing of visceral stimuli, altered autonomic activity, and psychological abnormalities. (See "Evaluation of the adult with chest pain of esophageal origin" and "Functional dyspepsia in adults".)

Functional heartburn — Functional heartburn is among the most common cause for failure of PPI treatment. It is estimated that up to 58 percent of patients with persistent heartburn despite PPI therapy have functional heartburn [15,16].

According to the Rome IV criteria, a diagnosis of functional heartburn requires all of the following criteria be fulfilled for the last three months with symptom onset at least six months prior to the diagnosis [26]:

- Burning retrosternal discomfort or pain
- Absence of symptom relief despite optimal antisecretory therapy
- Absence of evidence that gastroesophageal reflux (abnormal acid exposure and symptom reflux association) or eosinophilic esophagitis are the cause of symptoms
- Absence of major esophageal motor disorders (achalasia/esophagogastric junction outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis)

Most patients with functional heartburn have chronic symptoms that vary in severity over time. In one study that included 40 patients with functional heartburn, 22 months after initial testing, 66 percent of patients remained symptomatic [27]. The underlying mechanisms responsible for symptoms in functional heartburn remain to be elucidated. Increased esophageal sensitivity to chemical, mechanical, and electrical stimuli in this patient population has not been consistently demonstrated [28-31]. Psychological co-morbidities may provide an explanation for functional heartburn [32]. Patients with poor correlation of symptoms with acid reflux events display a high level of anxiety as compared with patients who demonstrate a close correlation between symptoms and acid reflux events [33]. In population-based studies, anxiety and depression have been also been demonstrated to increase GERD-related symptoms [34].

Alternative diagnoses — Other diseases that can mimic symptoms of GERD include achalasia, eosinophilic esophagitis, infectious esophagitis, pill esophagitis, gastroparesis, and rarely esophageal stricture or cancer. Rumination syndrome may also be misdiagnosed as GERD.

Refractory GERD can be distinguished from these conditions by diagnostic testing. Patients with functional dyspepsia commonly also complain of heartburn which may be misdiagnosed as refractory GERD [35]. (See 'Diagnostic testing' below and "Approach to the adult with nausea and vomiting", section on 'Rumination syndrome'.)

Bile reflux may have a role in a subset of patients with difficult to manage symptomatic reflux. In a study that included 65 patients with persistent heartburn and regurgitation while on single-dose PPI therapy, seven patients (11 percent) had only pathological acid exposure, 25 (38 percent) had only pathological bile exposure, and 17 (26 percent) had pathological exposure to both acid and bile [36]. Furthermore, in a carefully selected group of patients with symptoms refractory to PPI therapy, baclofen significantly reduced bile reflux exposure and heartburn. Although these studies suggest a role for measurement of bile reflux in patients with persistent reflux symptoms despite PPI therapy, bile reflux monitoring is not widely available. (See "Pathophysiology of reflux esophagitis" and "Non-acid reflux: Clinical manifestations, diagnosis, and management".)

INITIAL ASSESSMENT

Compliance with proton pump inhibitors (PPI) therapy and specifically, timing in relation to meals, should be sought. Patients with continued symptoms should be carefully reassessed, paying specific attention to the type of ongoing symptoms, and the degree to which symptoms have improved or worsened. It is important to recognize that complete relief of heartburn with PPIs occurs at a rate of approximately 11.5 percent per week [37]. Thus, endoscopic healing and symptom relief are achieved within eight weeks in the majority of patients. However, patients with severe esophagitis (eg, Los Angeles C or D esophagitis) may take longer to heal. (See 'Medication timing and adherence' above.)

In addition, we perform blood count to identify patients with iron deficiency anemia, if not recently performed. (See 'Alarm features' below.)

DIAGNOSTIC STRATEGIES AND INITIAL MANAGEMENT

The timing and extent of diagnostic evaluation in a patient with refractory gastroesophageal reflux disease (GERD) is based on the type of ongoing symptoms and the presence of alarm features. A suggested approach to the management of patients who have failed once daily proton pump inhibitors (PPI) therapy is outlined in the algorithm (algorithm 1).

Alarm features — Alarm features that may be suggestive of a gastrointestinal malignancy include:

- New onset dyspepsia in patient ≥60 years
- Evidence of gastrointestinal bleeding (hematemesis, melena, hematochezia, occult blood in stool)
- Iron deficiency anemia
- Anorexia
- Unexplained weight loss
- Dysphagia
- Odynophagia
- Persistent vomiting
- Gastrointestinal cancer in a first-degree relative

Patients with alarm features

Early upper endoscopy — An early upper endoscopy (within two weeks) should be performed for the evaluation of new alarm features to determine the underlying etiology. Upper endoscopy should not be delayed pending a trial of empiric therapy in patients with alarm symptoms. In patients who have previously undergone an upper endoscopy, we perform a repeat upper endoscopy if new alarm features developed since the last upper endoscopy was performed. Biopsies of the esophagus should be obtained to rule out eosinophilic esophagitis. (See "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)", section on 'Diagnosis'.)

In patients with a normal upper endoscopy, additional evaluation may be required based on symptoms (eg, abdominal imaging in patients with concurrent weight loss). If this evaluation is normal and symptoms of GERD persist, patients should be managed similarly to patients without alarm features. (See 'Patients without alarm features' below.)

Patients without alarm features

General measures — Lifestyle and dietary modification, and compliance with PPI therapy should be reinforced. Patients should be instructed to take a PPI 30 minutes before a meal. Lifestyle and dietary modification include avoidance of identified dietary triggers, weight loss for patients who are overweight or have had recent weight gain, elevation of the head of the bed in individuals with nocturnal symptoms, refraining from assuming a supine position after meals and avoidance of meals two to three hours before bedtime. (See "Medical management of gastroesophageal reflux disease in adults", section on 'Lifestyle and dietary modification'.)

Optimize PPI therapy — In patients with reflux symptoms despite standard dose once daily PPI (eg, omeprazole 40 mg once daily), options include splitting the dose (eg, omeprazole 20 mg twice daily), doubling the PPI dose (eg, omeprazole 40 mg twice daily), or switching to another PPI (eg, lansoprazole 30 mg once daily). When splitting or doubling the PPI dose, PPIs should be administered before breakfast and before dinner. Physiologic studies have also demonstrated improved nocturnal acid breakthrough with split dosing as compared with once daily dosing [38].

We usually double the PPI dose for eight weeks before considering an alternative PPI. In one study, doubling the PPI dose in patients with symptomatic GERD, despite once daily PPI therapy, increased the rate of overall symptom improvement by 22 to 26 percent [39,40].

However, both options appear to be effective in controlling heartburn [39,41]. In a randomized trial, 328 patients with persistent GERD symptoms on treatment with single dose lansoprazole were assigned to twice daily lansoprazole or single dose esomeprazole for eight weeks. At the end of treatment, there was no significant difference in the number of heartburn-free days between the two groups. Some experts have suggested splitting the doses to provide double dose PPI four times daily (eg, rabeprazole 10 mg four times daily). However, evidence to support this strategy is limited to a physiologic study which demonstrated greater reduction in intragastric pH over 24 hours as compared with once or twice daily dosing [42]. Data to support a further escalation in PPI dose are lacking.

Diagnostic testing — Diagnostic testing in patients with GERD usually consists of an upper endoscopy and esophageal impedance pH testing. Additional evaluation should be pursued based on the type of ongoing symptoms (eg, esophageal manometry in patients with regurgitation, gastric emptying study in patients with vomiting).

Upper endoscopy — In all patients who fail PPI therapy, we perform an upper endoscopy with biopsies of the esophagus, if not performed in the last one year. Upper endoscopy can rule out alternative diagnoses (eg, eosinophilic esophagitis, infection and pill injury, achalasia). However, adequate biopsies of the esophagus are needed to rule out eosinophilic esophagitis (two to four biopsies from the distal esophagus and two to four from the mid or proximal esophagus). (See "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)", section on 'Histology'.)

Esophageal impedance pH testing — Patients who fail twice daily PPI therapy should also undergo esophageal pH monitoring. Esophageal pH monitoring with impedance is preferred to wireless pH capsule and the traditional pH probe, as it has the advantage of detection of non-

acid in addition to acid reflux [43,44]. (See "Esophageal multichannel intraluminal impedance testing".)

Impedance pH testing can be performed while off PPI therapy in patients without typical GERD symptoms to determine if gastroesophageal reflux is the cause of their symptoms. Testing should be performed while on PPI treatment in patients with a partial response to PPIs to determine if there is continued pathological acid or non-acid exposure despite acid suppressive therapy [45]. It can also help predict which patients have acid reflux off PPI therapy [46]. (See "Esophageal multichannel intraluminal impedance testing", section on 'Testing on or off proton pump inhibitors'.)

Esophageal manometry — We perform esophageal manometry in patients with dysphagia and regurgitation and prior to invasive antireflux therapies to exclude an esophageal motility disorder [45,47,48]. GERD can be distinguished from rumination syndrome by impedance pH manometry by detecting gastric straining preceding or during reflux events that extend to the proximal esophagus. (See "Achalasia: Pathogenesis, clinical manifestations, and diagnosis", section on 'Esophageal manometry' and "Overview of gastrointestinal motility testing", section on 'Esophageal manometry' and "High resolution manometry".)

SUBSEQUENT MANAGEMENT

Subsequent management in patients who have undergone esophageal pH testing are based on the pH of the refluxate. If pH testing cannot be performed, empiric management is based on the type of ongoing symptoms. (See 'Patients with impedance-pH results' below and 'Patients without impedance pH testing' below.)

Patients with impedance-pH results

Residual acid reflux

- **Alginates** – In patients with refractory heartburn, who demonstrate acid reflux on esophageal pH testing while on a twice daily PPI, we use concurrent sodium alginate, if available. Alginates can potentially buffer the acid pocket in the most proximal gastric cardia and form a viscous raft at the gastroesophageal junction. However, the efficacy of sodium alginate in patients with refractory GERD has not been demonstrated and its availability is limited. (See "Pathophysiology of reflux esophagitis", section on 'Impaired esophageal emptying'.)

- **H2 receptor antagonists** – In patients with persistent acid reflux symptoms despite PPI therapy (with or without alginates), we add a bedtime histamine 2 receptor antagonist (H2RA) [49]. Tolerance develops rapidly in patients on H2RAs and can develop after one week of therapy [50-53]. If clinical tolerance develops, H2RA can be used intermittently or on demand [54]. (See "Medical management of gastroesophageal reflux disease in adults", section on 'Surface agents and alginates'.)

- **Reflux inhibitors** – We use baclofen as adjunctive treatment in patients with persistent symptoms despite a PPI with a H2RA. We initiate baclofen at a low dose (5 to 10 mg twice a day before meals). In patients who fail to respond, we make incremental changes and increase the dose by 5 mg every four days to 20 mg three times a day while carefully monitoring for side effects. Because baclofen crosses the blood-brain barrier, a variety of central nervous system-related side effects may occur. These include somnolence, confusion, dizziness, lightheadedness, drowsiness, weakness, and trembling. We usually continue baclofen for four to eight weeks before stopping if it is ineffective.

  Data to support the use of baclofen in patients with refractory GERD have several limitations. In a meta-analysis of nine randomized trials that included 283 patients with GERD and healthy volunteers who were assigned to baclofen or placebo, baclofen resulted in a reduction in the number of reflux episodes per patient, the average length of reflux episodes, and the incidence of transient lower esophageal sphincter relaxation [55]. However, only one trial included in the meta-analysis evaluated baclofen as an add-on therapy to PPIs. Other limitations included short duration of follow-up (range 12 hours to four weeks) and the inclusion of patients with ongoing non-acid reflux. (See "Non-acid reflux: Clinical manifestations, diagnosis, and management", section on 'Reflux inhibitors'.)

- **Anti-reflux procedures**

  - **Anti-reflux surgery** – Antireflux surgery is reserved for patients who require high doses of PPIs to control symptoms, for persistent proven GERD symptoms or esophageal mucosal damage despite maximal medical therapy, and when there is significant structural disruption at the esophagogastric junction (eg, hiatus hernia). Surgery is not recommended in patients who demonstrate a complete lack of response to PPI therapy [45]. (See "Surgical treatment of gastroesophageal reflux in adults".)

  - **Endoscopic procedures** – The two main endoscopic approaches for treating GERD include application of controlled radiofrequency energy to the lower esophageal sphincter region (Stretta procedure) and transoral incisionless fundoplication [56]. Both techniques have demonstrated a decrease in PPI requirement in patients with GERD.

However, their long-term efficacy has not been established. (See "Radiofrequency treatment for gastroesophageal reflux disease".)

Reflux hypersensitivity or functional heartburn — Patients should be reassured regarding the benign nature of these conditions. In patients with functional heartburn or reflux hypersensitivity, we suggest a trial of pain modulators (eg, tricyclic antidepressant, selective serotonin uptake inhibitor, serotonin-norepinephrine reuptake inhibitors, or trazodone). We usually begin with nortriptyline 25 mg, citalopram 20 mg, or fluoxetine 20 mg. The initial dose should be adjusted based upon tolerance and response. Due to the delayed onset of action of antidepressants, two to four weeks of therapy should be attempted before increasing the dose. We usually continue treatment for 12 weeks before stopping if it is ineffective.

The decision to continue PPI therapy in patients with reflux hypersensitivity or functional heartburn is based on the patients response to PPI therapy (partial response or no response), and whether pH testing was performed on PPI therapy.

- In patients with reflux hypersensitivity or functional heartburn who have had a partial response to PPI therapy (or in whom pH testing was performed on PPI therapy), pain modulators are used in addition to PPI therapy.
- In patients reflux hypersensitivity or functional heartburn without a symptomatic response to PPI therapy (or in whom pH testing was performed off PPI therapy), we discontinue PPI therapy and use pain modulators alone.

Pain modulators have been shown to improve esophageal pain in patients with other functional esophageal disorders such as functional chest pain of esophageal origin. However, evidence of their efficacy in patients with reflux hypersensitivity and functional heartburn are limited given the lack of randomized trials [57-60]. In a randomized trial that included 252 patients who underwent pH impedance testing, 75 patients with reflux hypersensitivity were assigned to receive citalopram or placebo [60]. At six months, patients treated with citalopram were significantly less likely to report reflux symptoms (39 versus 67 percent).

Non-acid reflux — In patients with refractory GERD who demonstrate symptoms associated with non-acid reflux, we suggest a trial of baclofen. The diagnosis and management of patients with non-acid reflux is discussed in detail separately. (See "Non-acid reflux: Clinical manifestations, diagnosis, and management", section on 'Management'.)

Patients without impedance pH testing

- In patients whose symptoms are primarily regurgitation, we use an empiric trial of baclofen. (See 'Residual acid reflux' above and 'Non-acid reflux' above.)

- In patients who primarily report heartburn, we generally begin with a trial of an H2 receptor antagonist (H2RA) at bedtime but advise that it be used intermittently to avoid tachyphylaxis. We reserve a trial of pain modulators (eg, nortriptyline, citalopram) for patients who fail to respond to the addition of H2RAs. (See 'Reflux hypersensitivity or functional heartburn' above.)

Other therapies

- **Prokinetics in patients with delayed gastric emptying** – Prokinetic agents (eg, metoclopramide) are reserved for patients with refractory GERD and objective evidence of delayed gastric emptying on diagnostic testing. (See "Gastroparesis: Etiology, clinical manifestations, and diagnosis", section on 'Assess gastric motility'.)

  A meta-analysis of 12 randomized trials that included 2403 patients with GERD demonstrated modest reductions in symptom scores when prokinetics were added to PPI therapy [61]. The combination did not increase healing of erosive esophagitis or improve esophageal motor performance, but patients treated with prokinetics were significantly more likely to experience adverse effects. (See "Gastroparesis: Etiology, clinical manifestations, and diagnosis", section on 'Assess gastric motility' and "Treatment of gastroparesis", section on 'Prokinetics'.)

- **Bile acid binders** – Bile acid binders may have a role in the treatment of refractory GERD when used in combination with PPI therapy or as stand-alone therapy, however, further studies are needed [11,62]. In a randomized trial in which 280 patients with refractory GERD symptoms despite once-daily PPI therapy were assigned to receive an investigational gastric retentive, extended release colesevelam formulation (IW-3718; 500 mg, 1000 mg, or 1500 mg twice daily) or placebo, IW-3718 (1500 mg twice daily) significantly reduced heartburn (53 versus 37 percent) and regurgitation (46 versus 34 percent) [11]. Constipation was the most frequent adverse effect. (See 'Alternative diagnoses' above.)

- **Acupuncture** – Acupuncture has been evaluated in patients with GERD who failed PPI once daily [63]. In a small randomized trial 30 patients with classic heartburn refractory to once daily PPI were assigned to doubling the PPI dose (standard of care) or adding acupuncture to their PPI for four weeks. As compared with baseline, the acupuncture group had significant improvement in regurgitation and heartburn. While the potential

benefit may be related to treatment of visceral pain, additional studies are needed to define the role of acupuncture in patients with refractory GERD.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Gastroesophageal reflux in adults" and "Society guideline links: Esophageal manometry and pH testing".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Acid reflux and GERD in adults (The Basics)")
- Beyond the Basics topics (see "Patient education: Gastroesophageal reflux disease in adults (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Approximately 10 and 40 percent of patients with gastroesophageal reflux disease (GERD) fail to respond symptomatically, either partially or completely, to a standard dose of proton pump inhibitors (PPIs). Continued symptoms of GERD despite PPI therapy may be due to insufficient acid suppression, reflux hypersensitivity, functional heartburn, or an alternative etiology. (See 'Epidemiology' above and 'Etiology' above.)

- **Initial assessment and alarm features** – Patients with continued symptoms should be carefully reassessed, paying specific attention to the compliance and timing of PPI therapy, type of ongoing symptoms and the presence of alarm features that may be suggestive of a gastrointestinal malignancy. Alarm features include:

  - New onset dyspepsia in patient ≥60 years
  - Evidence of gastrointestinal bleeding (hematemesis, melena, hematochezia, occult blood in stool)
  - Iron deficiency anemia
  - Anorexia
  - Unexplained weight loss
  - Dysphagia
  - Odynophagia
  - Persistent vomiting
  - Gastrointestinal cancer in a first-degree relative

  Diagnostic evaluation and initial management – The timing and extent of diagnostic evaluation in a patient with refractory GERD is based on the type of ongoing symptoms and the presence of alarm features (algorithm 1).

  - **Patients with alarm features** – We perform early upper endoscopy. Patients with alarm features in whom the early upper endoscopy is negative are subsequently managed similarly to patients without alarm features (algorithm 1). (See 'Patients with alarm features' above.)

  - **Patients without alarm features** – Initial management consists of reinforcement of lifestyle modification and compliance with PPI therapy. In patients with persistent symptoms despite once daily PPI therapy, we suggest twice daily PPI therapy (**Grade 2B**). Switching to a different PPI may be an equally effective alternative. In all patients who fail twice daily PPI therapy, we perform an upper endoscopy with biopsies of the esophagus, if not performed in the last one year. (See 'Residual acid reflux' above.)

- **Additional measures based on esophageal pH testing/symptoms** – Subsequent management in patients who have undergone esophageal pH testing are based on the pH of the refluxate. If pH testing cannot be performed, empiric management is based on the type of ongoing symptoms.

  - In patients with persistent acid reflux on esophageal impedance pH testing or when testing is unavailable and patients primarily report heartburn, we suggest adding a

bedtime H2RA (**Grade 2C**). If clinical tolerance develops, H2RA can be used intermittently or on demand. (See 'Residual acid reflux' above.)

- In patients with symptoms associated with non-acidic reflux on an esophageal impedance pH study or when testing is unavailable and patients primarily report regurgitation, we suggest a trial of baclofen (**Grade 2C**). (See 'Non-acid reflux' above and "Non-acid reflux: Clinical manifestations, diagnosis, and management".)

- In patients with refractory GERD who have a normal esophageal impedance and pH study (esophageal hypersensitivity or functional heartburn), we suggest a trial of visceral analgesics (pain modulators), such as a tricyclic antidepressant, serotonin-norepinephrine reuptake inhibitor, selective serotonin uptake inhibitor, or trazodone (**Grade 2C**). (See 'Reflux hypersensitivity or functional heartburn' above.)

- In patients with persistent GERD symptoms despite PPI therapy and delayed gastric emptying, we suggest treatment with prokinetics (**Grade 2C**). (See 'Other therapies' above.)

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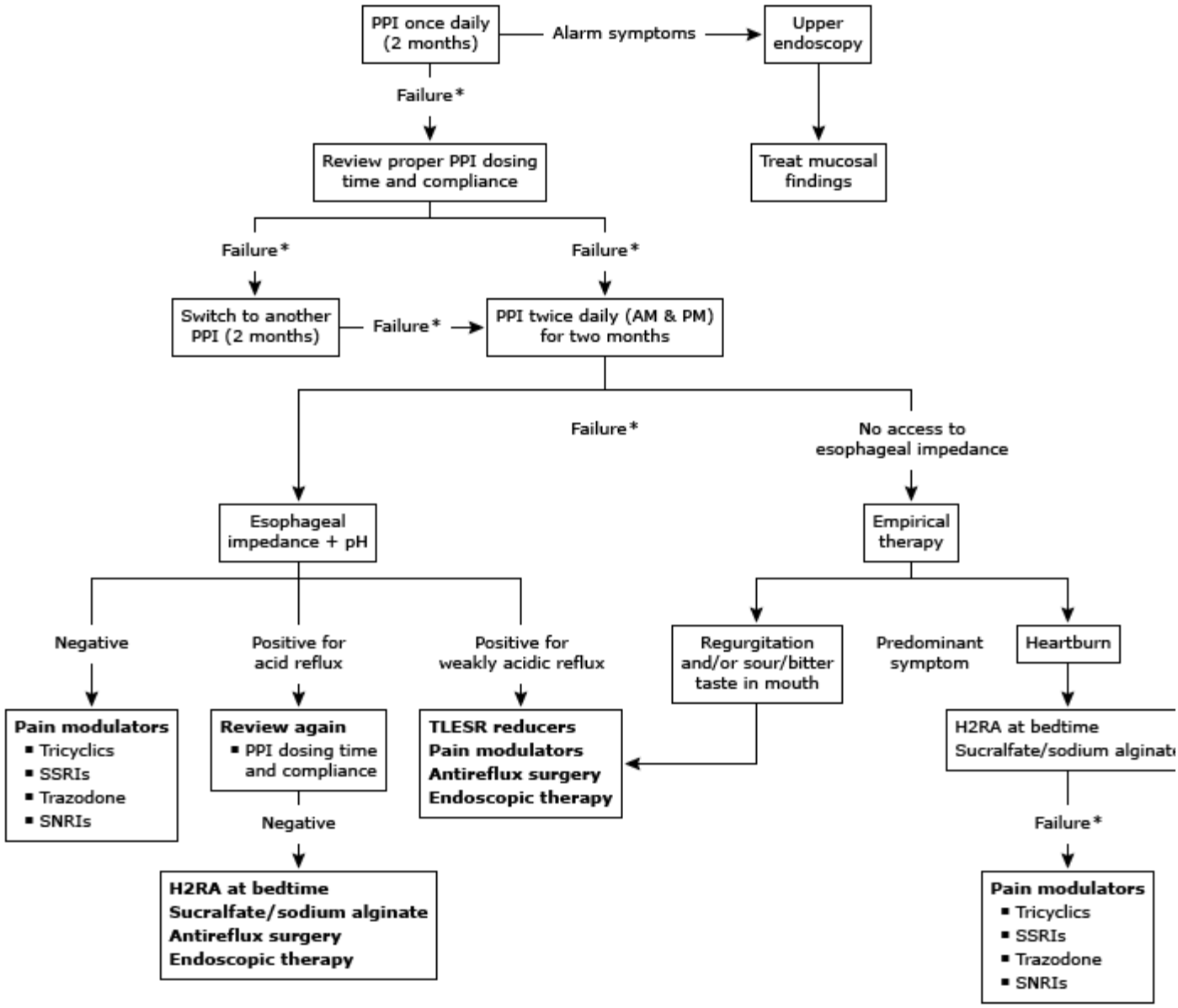
GRAPHICS

Management algorithm of GERD patient who failed PPI once daily



Management algorithm of gastroesophageal reflux disease (GERD) patient who failed PPI once daily (complete or partial*).

PPI: proton pump inhibitor; SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin-norepinephrine reuptake inhibitors; TLESR: transient lower esophageal sphincter relaxation; H2RA: histamine 2 receptor antagonist.

* Partial or incomplete relief of symptoms.

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Contributor Disclosures

Ronnie Fass, MD Equity Ownership/Stock Options: Ginger-Health [GERD]. Consultant/Advisory Boards: Celexio [GERD]; Dexcal [GERD]; Evoke [Gastroparesis]; GERDCare [GERD]; Medtronics [Esophageal manometry]; Phantom [GERD]; Takeda [GERD]; Veritas [GERD]. Speaker's Bureau: Adcock-Ingram [GERD]; AstraZeneca [GERD]; Carnot [GERD]; Eisai [GERD]; Johnson & Johnson [GERD]; Laborie [Esophageal manometry]; Medicamenta [GERD]; Takeda [GERD]. All of the relevant financial relationships listed have been mitigated. **Nicholas J Talley, MD, PhD** Patent Holder: Australian Provisional Patent [Diagnostic marker for functional gastrointestinal disorders]; Biomarkers of irritable bowel syndrome [Irritable bowel syndrome]; Mayo Clinic [Dysphagia questionnaire]; Mayo Clinic [Bowel Disease questionnaire]; Nepean Dyspepsia Index [Dyspepsia]; Nestec [Irritable bowel syndrome]; Singapore Provisional Patent [BDNF Tissue Repair Pathway]. Grant/Research/Clinical Trial Support: Alimetry [Gastric mapping device research collaboration]; Allakos [Gastric eosinophilic disease]; AstraZeneca [Eosinophilic gastritis, eosinophilic gastroenteritis]; Intrinsic Medicine [Bowel syndrome with constipation]; NHMRC Centre for Research Excellence in Digestive Health [NHMRC Investigator grant]. Consultant/Advisory Boards: Adelphi Values [Functional dyspepsia]; Allakos [Gastric eosinophilic disease, AK002]; AstraZeneca [Eosinophilic gastritis, eosinophilic gastroenteritis]; AusEE [Eosinophilic gut diseases]; Bayer [Inflammatory bowel syndrome]; BluMaiden [Microbiome Ad Board]; Comvita Mānuka Honey [Digestive health]; Dr Falk Pharma [Eosinophilia]; GlaxoSmithKline Australia [Educational speaker eosinophilic gut disease]; Glutagen [Celiac disease]; International Foundation for Functional Gastrointestinal Disorders [Advisory board, functional GI disorders]; Intrinsic Medicine [Human milk oligosaccharide]; IsoThrive [Esophageal microbiome]; Planet Innovation [Gas capsule, inflammatory bowel syndrome]; Progenity Inc [Intestinal capsule]; Rose Pharma [IBS]; Viscera Labs [Inflammatory bowel syndrome, diarrhea]. Other Financial Interest: Elsevier textbook royalties [Medical education]. All of the relevant financial relationships listed have been mitigated. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

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