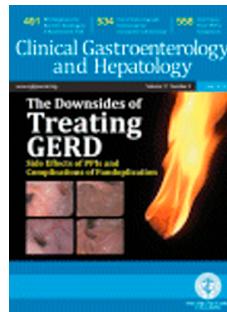


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Personalized Approach to the Evaluation and Management of Gastroesophageal Reflux Disease

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Personalized Approach to the Evaluation and Management of Gastroesophageal Reflux

Disease

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ABSTRACT:

Description: As many as half of all patients with suspected gastroesophageal reflux disease (GERD) do not derive benefit from acid suppression. This review outlines a personalized diagnostic and therapeutic approach to GERD symptoms.

Methods: The Best Practice Advice statements presented here were developed from expert review of existing literature combined with extensive discussion and expert opinion to provide practical advice. Formal rating of the quality of evidence or strength of recommendations was not the intent of this clinical practice update.

Best Practice Advice:

1. Clinicians should develop a care plan for investigation of symptoms suggestive of gastroesophageal reflux disease (GERD), selection of therapy (with explanation of potential risks and benefits), and long-term management, including possible de-escalation, in a shared-decision making model with the patient.
2. Clinicians should provide standardized educational material on GERD mechanisms, weight management, lifestyle and dietary behaviors, relaxation strategies, and awareness about the brain-gut axis relationship to patients with reflux symptoms.
3. Clinicians should emphasize safety of proton pump inhibitors (PPIs) for the treatment of GERD.
4. Clinicians should provide patients presenting with troublesome heartburn, regurgitation and/or non-cardiac chest pain without alarm symptoms a 4 to 8 week trial of single dose PPI therapy. With inadequate response, dosing can be increased to twice a day or switched to a more effective acid suppressive agent once a day. When there is adequate response, PPI should be tapered to the lowest effective dose.
5. If PPI therapy is continued in a patient with unproven GERD, clinicians should evaluate the appropriateness and dosing within 12 months after initiation, and offer endoscopy

with prolonged wireless reflux monitoring off PPI therapy to establish appropriateness of long-term PPI therapy.

6. If troublesome heartburn, regurgitation and/or non-cardiac chest pain do not respond adequately to a PPI trial or when alarm symptoms exist, clinicians should investigate with endoscopy and, in the absence of erosive reflux disease (Los Angeles B or greater) or long-segment ($\geq 3\text{cm}$) Barrett's esophagus, perform prolonged wireless pH monitoring off medication (96 hour preferred if available) to confirm and phenotype GERD or to rule out GERD.
7. Complete endoscopic evaluation of GERD symptoms includes inspection for erosive esophagitis (graded according to the Los Angeles classification when present), diaphragmatic hiatus (Hill grade of flap valve), axial hiatus hernia length, and inspection for Barrett's esophagus (graded according to the Prague classification and biopsied when present).
8. Clinicians should perform upfront objective reflux testing off medication (rather than an empiric PPI trial) in patients with isolated extra-esophageal symptoms and suspicion for reflux etiology.
9. In symptomatic patients with proven GERD, clinicians should consider ambulatory 24 hour pH-impedance monitoring on PPI as an option to determine the mechanism of persisting esophageal symptoms despite therapy (if adequate expertise exists for interpretation).
10. Clinicians should personalize adjunctive pharmacotherapy to the GERD phenotype, in contrast to empiric use of these agents. Adjunctive agents include alginate antacids for breakthrough symptoms, nighttime H₂ receptor antagonists for nocturnal symptoms, baclofen for regurgitation or belch predominant symptoms, and prokinetics for coexistent gastroparesis.

11. Clinicians should provide pharmacologic neuromodulation, and/or referral to a behavioral therapist for hypnotherapy, cognitive behavioral therapy (CBT), diaphragmatic breathing and relaxation strategies in patients with functional heartburn or reflux disease associated with esophageal hypervigilance reflux hypersensitivity and/or behavioral disorders.
12. In patients with proven GERD, laparoscopic fundoplication and magnetic sphincter augmentation are effective surgical options, and transoral incisionless fundoplication is an effective endoscopic option in carefully selected patients.
13. In patients with proven GERD, Roux-en-Y gastric bypass is an effective primary anti-reflux intervention in obese patients, and a salvage option in non-obese patients, while sleeve gastrectomy has potential to worsen GERD.
14. Candidacy for invasive anti-reflux procedures includes confirmatory evidence of pathologic GERD, exclusion of achalasia, and assessment of esophageal peristaltic function.

Keywords

Gastroesophageal reflux disease; ambulatory reflux monitoring; proton pump inhibitors

Background

The prevalence of symptomatic gastro-esophageal reflux disease (GERD) is rising, with more than 30% of US adults reporting at least weekly symptoms^{1,2}. Symptoms of GERD encompass heartburn or regurgitation (typical esophageal symptoms), non-cardiac chest pain (atypical esophageal symptom), and a myriad of extra-esophageal symptoms which include cough, dysphonia, sore throat, and globus³. Further, symptoms can arise from coexisting or confounding pathophysiology such as mechanical defects, physiologic abnormalities, heightened nociception, and hypervigilance. Despite heterogeneous presentations and pathogeneses, GERD patients have historically been managed in a similar catch-all fashion, often in the absence of objective abnormalities. Up to 50% of patients, however, do not derive adequate relief with empirical proton pump inhibitor (PPI) therapy.⁴⁻⁶ Drivers of inadequate response include absence of pathologic GERD to begin with or symptom pathophysiology that is insufficiently targeted with acid suppression⁷. In recognition of this problem, the current care paradigm has shifted towards a personalized approach to the evaluation and management of GERD symptoms⁸. This Clinical Practice Update provides best practice advice for a personalized diagnostic and therapeutic approach to GERD.

Methods

This expert review was commissioned jointly by the AGA Institute Clinical Practice Updates Committee (CPUC), the AGA Center for GI Innovation and Technology (CGIT) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership. The AGA CGIT Consensus Conferences bring together content experts, stakeholders (Industry, regulatory, and payor), along with a patient advocate to discuss current needs and gaps in innovation relevant to the topic. This is an exhaustive, comprehensive didactic and discussion session created to provide a novel interactive environment to foster the

AGA CGIT mission. The topic of this CPU was thoroughly discussed by expert faculty contributors selected by AGA CGIT, industry representatives and patient advocates at the conference organized and hosted by AGA CGIT. The content of this expert review was generated, discussed and voted upon by the expert faculty contributors at a closed-door meeting during the AGA CGIT conference. All faculty contributors provided up to date declaration of conflicts of interest to ensure credibility of this document, and signed off on the final manuscript, which underwent internal peer review by the CPUC as well as external peer review through standard procedures of *Clinical Gastroenterology and Hepatology*.

Approaching GERD Symptoms in the Clinic

Care Plan

Patients with GERD symptoms seek care from a spectrum of health care providers including primary care physicians, gastroenterologists, otolaryngologists, pulmonologists, and surgeons. Health care providers and patients alike have questions and concerns regarding treatment of choice, need for objective testing, concerns about GERD complications over time and risks of long-term treatments. Consistent, standardized approaches across health care teams are essential to streamline GERD evaluation and management. *Clinicians should develop a care plan for investigation of symptoms suggestive of gastroesophageal reflux disease (GERD), selection of therapy (with explanation of potential risks and benefits), and long-term management, including possible de-escalation, in a shared decision making model with the patient (BPA 1).*

To develop a care plan, providers need to ascertain the likelihood of pathologic GERD and discern which mechanisms may be driving symptoms. Symptom characterization is an essential first step. Typical esophageal symptoms of heartburn and regurgitation are approximately 70% sensitive and specific for objective GERD, providing the rationale for first-line PPI trials with high

therapeutic gain for symptom relief despite lack of prior objective testing.⁶ Conversely, an empiric PPI trial is not optimal for isolated extra-esophageal symptoms since mechanisms other than GERD frequently contribute to symptom generation, making likelihood of PPI non-response high.^{9,10} Additional clinical factors that can explain symptom generation include central obesity and/or a known hiatal hernia pointing to a mechanical etiology of gastro-esophageal reflux, anxiety or stress-induced symptoms suggesting visceral hypersensitivity and/or hypervigilance, behavioral disorders including rumination and supragastric belching, or mixed connective tissue disorder raising suspicion for esophageal dysmotility and reduced refluxate clearance^{11,12,13}.

Patient Education

During the initial clinic visit, it is essential that *clinicians provide standardized educational material on GERD mechanisms, weight management, lifestyle and dietary behaviors, relaxation strategies, and awareness about the brain-gut axis relationship to patients with reflux symptoms (BPA 2)*. Patient education should emphasize that gastro-esophageal reflux is a physiologic process, commonly mediated through transient lower esophageal sphincter relaxations and controlled by protective factors such as the anti-reflux barrier, effective esophageal peristalsis and salivation, and downstream gastric motility.¹⁴ This discussion frames patient expectations in terms of response to acid suppression and potential need for adjunctive strategies. For instance, appreciating the role of the crural diaphragm may facilitate adherence to diaphragmatic breathing.¹⁵ Further, understanding the intra-abdominal to intra-thoracic pressure gradient may improve acceptance of weight management and modified dietary/nighttime routines.¹⁶⁻¹⁹ For patients with a known hiatal hernia and/or symptom burden following meals or during sleep, reduction of supine GERD by elevating the head of the bed and avoiding meals within 3 hours of bedtime are useful.²⁰ An introductory discussion about the brain-gut axis can also empower and encourage the patient to integrate stress-reducing activities such as mindfulness into their daily lives, and can open the door for future psychological interventions.²¹

The supplemental document available with this update is a handout that can be provided to patients with suspected GERD (Supplemental Figure).

PPI Trial (Figure 1)

Clinicians should provide patients presenting with troublesome heartburn, regurgitation and/or non-cardiac chest pain without alarm symptoms a 4-8 week trial of single dose PPI therapy (BPA 4). Any commercially available PPI can be used for the trial, the choice of which may be guided by payor coverage, out of pocket costs, and prior experiences with a particular PPI. Patients should be counseled to take the PPI 30 to 60 minutes prior to a meal. Education and literature emphasizing safety of PPIs for the treatment of GERD should be provided (BPA 3).²² Patient symptoms should be reassessed after a 4-8 week trial (Figure 1). With inadequate response, dosing can be increased to twice a day or switched to a more effective acid suppressive agent once a day (BPA 4). These can include PPIs that are more potent²³, less metabolized through the CYP2C19 pathway (e.g., rabeprazole, esomeprazole), or available in an extended release formulation (e.g., dexlansoprazole),²⁴ as well as potassium competitive acid blockers (PCABs) when available. Routine re-evaluation of treatment should be performed, and the PPI should be tapered to the lowest effective dose when there is adequate response (BPA 4) (Figure 1). Best practices surrounding PPI de-prescribing are further elaborated in a separate AGA Clinical Practice Update.

Personalized Diagnostic Approach to GERD Symptoms

Indications for Objective Testing

Particular clinical scenarios warrant objective evaluation. *If troublesome heartburn, regurgitation and/or non-cardiac chest pain do not respond adequately to a PPI trial or if alarm symptoms exist, clinicians should investigate with endoscopy and, in the absence of erosive reflux disease*

(Los Angeles B or greater) or long-segment ($\geq 3\text{cm}$) Barrett's esophagus, perform prolonged wireless pH monitoring off medication (96 hour preferred if available) to confirm and phenotype or to rule out GERD (BPA 6). In addition, clinicians should perform upfront objective reflux testing (rather than an empiric PPI trial) in patients with isolated extra-esophageal symptoms and suspicion of reflux etiology (BPA 8).

Another indication for objective testing may include patients with unproven GERD that have a symptom response to empiric PPI therapy, in order to establish the appropriateness of long-term PPI therapy (Figure 1). Thus, if proton pump inhibitor (PPI) therapy is continued in a patient with unproven GERD, clinicians should evaluate the appropriateness and dosing within 12 months after initiation, and offer endoscopy with prolonged wireless reflux monitoring off PPI therapy to establish appropriate use of long-term PPI therapy (BPA 5). In this context, endoscopy with prolonged reflux monitoring is optimally performed after withholding PPI for 2-4 weeks whenever possible²⁵. This is an important consideration in terms of shared decision making as many patients want to understand why they may need chronic lifelong maintenance therapy.

Upper Endoscopy

Complete endoscopic evaluation of GERD symptoms includes inspection for erosive esophagitis (graded according to the Los Angeles classification when present), diaphragmatic hiatus (Hill grade of flap valve), axial hiatus hernia length, and inspection for Barrett's esophagus (with grading according to the Prague classification and biopsy when present) (BPA 7).^{26 27} Confirmatory evidence of erosive reflux on endoscopy is found in a minority of patients. These findings include esophagitis (Los Angeles B or greater) and/or the presence of long-segment ($\geq 3\text{cm}$) Barrett's esophagus, with Los Angeles C or D esophagitis constituting severe erosive disease. However, up to 80% of symptomatic patients will not have objective reflux

evidence on endoscopy.²⁸ Of note, Los Angeles A esophagitis can be seen in healthy asymptomatic volunteers and is not considered evidence of erosive reflux disease (Figure 2).

Ambulatory Reflux Monitoring

Ambulatory reflux monitoring is available in two configurations. Wireless pH monitoring (Bravo) uses a pH capsule introduced via a trans-oral catheter during sedated EGD that adheres to the distal esophagus (6cm proximal to the endoscopically identified squamocolumnar junction) using a vacuum suction mechanism²⁹. Wireless pH monitoring measures acid exposure in the distal esophagus for up to 96 hours (based on recorder battery life) and assesses the relationship between patient reported symptoms and acid reflux episodes³⁰. Catheter based pH monitoring uses a trans-nasal catheter placed without sedation, which measures acid exposure in the distal esophagus as well as reflux-symptom association for up to 24 hours. Ideally, catheter-based pH monitoring is combined with multiple pairs of intraluminal impedance electrodes to assess air and liquid movement along the esophagus irrespective of pH²⁹. Based on advantages in assessing acid exposure over a prolonged period of time to account for day to day variability, ease of placement during sedated upper endoscopy, and patient tolerance, wireless pH monitoring is the preferred ambulatory reflux monitoring method to objectively assess for GERD in a symptomatic patient.^{31 32} Outcome data from a recent prospective study demonstrated that normal acid exposure time (<4.0%) on all 4 days of a 96 hour wireless study had an odds ratio of 10.0 (95% confidence interval 2.70-43.32) in predicting successful PPI withdrawal, and abnormal acid exposure time on ≥2 days had an odds ratio of 5.3 (95% confidence interval 2.91-13.44) in predicting need for continuing PPI treatment²⁵. If wireless pH monitoring is not available, 24 hour impedance-pH monitoring off PPI therapy can be utilized when expertise in frame by frame interpretation is available.^{9, 33} In particular, 24-hour impedance-pH monitoring off PPI may be preferred in the evaluation of extra-esophageal

symptoms³⁴, and is the optimal reflux monitoring system in symptomatic patients with previously proven GERD with the test performed on twice a day PPI therapy.³⁵

Precision Management Approach Based on Ambulatory Reflux Monitoring and Upper GI Endoscopy (Figure 2 and 3)

Esophageal acid exposure time (AET), the percent time spent at pH of 4.0 or less, is a key physiомarker for phenotyping patients with GERD.^{25, 28, 30} Reflux symptom association on ambulatory reflux monitoring (symptom association probability >95% and symptom index >50%) increase confidence that symptoms are truly associated with reflux when AET is increased, and indicate reflux hypersensitivity (a functional esophageal disorder) when AET is physiologic²¹. In addition to acid exposure, other key determinants that need to be considered in planning GERD management include reflux-symptom association (RSA) on ambulatory reflux monitoring, integrity of the anti-reflux barrier, central obesity, esophageal physiology, visceral sensitivity, hypervigilance, and downstream gastrointestinal motility.

Absence of Erosive Findings on Upper GI Endoscopy & Physiologic Acid Exposure

In general, absence of erosive reflux disease on upper GI endoscopy and findings of a physiologic AET of less than 4.0% across all days of wireless pH monitoring reflects normal gastro-esophageal reflux physiology^{25, 28}. Patients with normal acid exposure are not considered to have GERD and have a high likelihood of a functional esophageal disorder²¹. PPI therapy should be weaned off in these patients unless symptoms demonstrate a clear escalation off therapy and improve with PPI, a pattern seen in some patients with reflux hypersensitivity. Strong consideration should be given to referral to a GI psychologist for cognitive behavioral therapy (CBT), esophageal directed hypnotherapy, and/or pharmacologic neuromodulation, as detailed below. High-resolution manometry may be considered to evaluate patients with suspected rumination syndrome or an esophageal motor disorder²⁸.

Erosive Findings on Upper GI Endoscopy and/or Elevated Acid Exposure

The presence of erosive reflux disease and/or an AET of greater than 4.0% across at least one day of wireless pH monitoring performed off PPI reflects elevated acid burden. The presence of Los Angeles B or greater esophagitis and/or ≥2 days with AET >6% support a GERD diagnosis.

²⁸ Specifically, the presence of Los Angeles C or D esophagitis, bi-positional reflux, extreme levels of acid exposure (such as AET >12% or DeMeester score >50) and/or a large hiatal hernia represents a more severe manifestation of GERD.³⁶ At the other end of the spectrum, Los Angeles A esophagitis and/or elevated AET not meeting GERD criteria defined above identifies a borderline GERD group.

Lifestyle Optimization

Most patients with non-severe GERD typically improve with optimization of lifestyle, PPI therapy and adjunctive pharmacotherapy when appropriate. Aggressive lifestyle modifications and weight management, as outlined in the supplemental material, should be utilized.

PPI Optimization

Optimization of PPI includes ensuring adequate timing of dose, considering escalation to double dose, and/or switching to a different PPI³⁴. When symptoms are adequately controlled, acid suppression should be weaned down to the lowest effective dose, or switched to H2 receptor antagonists or other antacids for most patients. Exceptions to weaning acid suppression include patients with erosive esophagitis (Los Angeles B or greater), biopsy proven Barrett's esophagus and/or peptic stricture, who will require at least single dose long-term PPI therapy³⁴. Patients with severe GERD require indefinite long-term PPI therapy and/or an invasive anti-reflux procedure.

Adjunctive Pharmacotherapy

Clinicians should personalize adjunctive pharmacotherapy to the GERD phenotype, in contrast to empiric use of these agents. Adjunctive agents include alginate antacids for breakthrough

symptoms, nighttime H2 receptor antagonists for nocturnal symptoms, baclofen for regurgitation or belch predominant symptoms, and prokinetics for coexistent gastroparesis (BPA 10).

Alginates are useful in neutralizing the post-prandial acid pocket, and may be particularly useful for patients with post-prandial and/or nighttime symptoms, and in those with a known hiatal hernia^{34, 37}. Histamine-2 receptor antagonists (H2RAs) may be helpful for breakthrough and/or night-time symptoms, however use is limited by tachyphylaxis³⁸⁻⁴⁰. Transient lower esophageal sphincter relaxation inhibition with baclofen, a GABA-B agonist, may be effective for belch predominant symptoms and mild regurgitation, although often limited by central nervous system and GI side effects.^{28, 41} Prokinetics have not been shown to be useful in GERD, but may have a role in patients with concomitant gastroparesis.^{28, 34}

As highlighted by the Rome IV update, esophageal hypervigilance and visceral hypersensitivity can augment symptom burden across the entire spectrum of acid exposure, from normal to severe.²¹ Adjunctive pharmacotherapy can include neuromodulation with low dose anti-depressants, which requires familiarity and comfort with prescribing and following patients treated with these agents.⁴² With the recognition of the role of esophageal hypersensitivity, hypervigilance, behavioral disorders including supragastric belching and rumination, and other psychosocial factors in esophageal symptomatology, behavioral interventions to target these underlying mechanisms are becoming increasingly utilized.^{34, 43} The most researched behavioral interventions for esophageal disorders include cognitive behavioral therapy (CBT), esophageal-directed hypnotherapy and diaphragmatic breathing.⁴⁴⁻⁴⁷ Treatments are typically administered by clinical health psychologists or other mental health professionals that have specialized training in treating a variety of chronic GI disorders. Thus, *clinicians should provide pharmacologic neuromodulation, and/or referral to a behavioral therapist for hypnotherapy, cognitive behavioral therapy (CBT), diaphragmatic breathing and relaxation strategies in*

patients with functional heartburn or reflux disease associated with esophageal hypervigilance, reflux hypersensitivity and/or behavioral disorders (BPA 11).

Inadequate Symptom Response Despite Optimization

If symptoms are inadequately controlled following lifestyle and pharmacotherapy optimization, additional testing can be useful, including assessment of esophageal peristaltic function and exclusion of achalasia (with high-resolution manometry, for instance) and gastric emptying testing if delayed gastric emptying is suspected⁴⁸. *Clinicians should consider ambulatory 24 hour pH-impedance monitoring on PPI as an option to determine the mechanism of persisting esophageal symptoms despite therapy (BPA 9)*, particularly in patients without a known major abnormality in the anti-reflux barrier, to confirm PPI refractory GERD and exclude other etiologies of ongoing symptoms such as an overlap with reflux hypersensitivity, rumination syndrome or a belching disorder³⁵. Clinicians should then escalate therapy via a precision approach based on the pattern of reflux on impedance-pH monitoring, integrity of the anti-reflux barrier, presence of obesity, and/or psychological considerations (Figure 3). ^{34, 35}

Endoscopic & Surgical Anti-Reflux Procedures

Laparoscopic fundoplication is often utilized in the non-obese patient. Type of fundoplication may be tailored, with partial fundoplication preferred in patients with known esophageal hypomotility or impaired peristaltic reserve when there is concern of post-operative dysphagia⁴⁹⁻⁵¹. Magnetic sphincter augmentation is another option, often combined with a crural repair in the setting of known hiatal hernia⁵². Transoral incisionless fundoplication is an endoscopic anti-reflux procedure that is increasingly performed for carefully selected patients with GERD in the absence of a hiatal hernia⁵³. These approaches have demonstrable value in patients with regurgitation-predominant GERD^{53, 54}. Recent data suggest efficacy of transoral incisionless fundoplication with a combined laparoscopic hiatal hernia and crural repair in patients with a

minor crural defect.⁵⁵ Further research into risks/benefits, durability, effectiveness and treatment outcomes will enhance optimal utilization of these newer endoscopic and surgical options. *In patients with proven GERD, laparoscopic fundoplication and magnetic sphincter augmentation are effective surgical options, and transoral incisionless fundoplication (TIF) is an effective endoscopic option in carefully selected patients (BPA 12). In patients with proven GERD, Roux-en-Y gastric bypass is an effective primary anti-reflux intervention in obese patients, and a salvage option in non-obese patients, while sleeve gastrectomy has potential to worsen GERD (BPA 13). Candidacy for invasive anti-reflux procedures includes confirmatory evidence of pathologic GERD, exclusion of achalasia, and assessment of esophageal peristaltic function (BPA 14).*

CONCLUSION

For patients presenting with GERD symptoms, a stepwise diagnostic approach will identify mechanisms driving symptoms for a precision management approach. Patients should receive education on GERD pathophysiology and lifestyle modifications, and be involved in a shared decision making model. A 4 to 8 week trial of single dose PPI is considered safe and appropriate for patients with typical reflux symptoms and no alarm symptoms, with escalation to twice a day dosing or switch to a more potent acid suppressive agent if symptoms persist. Symptom response should prompt PPI titration to the lowest effective dose. When long-term PPI therapy is planned, objective reflux testing should be offered to establish a diagnosis of GERD and a long-term management plan. Objective testing with upper GI endoscopy is warranted in PPI non-response, presence of alarm signs/symptoms, isolated extra-esophageal symptoms or in patients who meet criteria to undergo screening for Barrett's esophagus. In the absence of confirmed erosive disease or Barrett's esophagus on endoscopy, prolonged wireless pH monitoring off PPI therapy is utilized to assess esophageal acid exposure. Patients without

erosive disease on endoscopy and with physiologic acid exposure often have a functional esophageal disorder. In these patients, neuromodulation or behavioral interventions can be utilized and PPI therapy can be titrated off as tolerated. Patients with non-severe GERD often respond well to optimization of lifestyle and pharmacotherapy, and may ultimately be able to wean pharmacotherapy down to the lowest effective dose (unless erosive reflux disease or Barrett's esophagus exists). On the other hand, patients with severe GERD will generally require long-term anti-reflux management. A precision approach to escalation of management is suggested for patients with ongoing symptoms despite these measures, which should be driven by integrity of the anti-reflux barrier, presence of visceral hypersensitivity and hypervigilance, confirmation of PPI refractory-GERD, symptom profile, body mass index, and esophageal (as well as gastric) motor function.

BEST PRACTICE ADVICE STATEMENTS**Approaching GERD Symptoms in Clinic**

BPA #1. Clinicians should develop a care plan for investigation of symptoms suggestive of gastroesophageal reflux disease (GERD), selection of therapy (with explanation of potential risks and benefits), and long term management, including possible de-escalation, in a shared-decision making model with the patient.

BPA #2. Clinicians should provide standardized educational material on GERD mechanisms, weight management, lifestyle and dietary behaviors, relaxation strategies, and awareness about the brain-gut axis relationship to patients with reflux symptoms.

BPA #3. Clinicians should emphasize safety of proton pump inhibitors (PPIs) for the treatment of GERD.

BPA #4. Clinicians should provide patients presenting with troublesome heartburn, regurgitation and/or non-cardiac chest pain without alarm symptoms a 4 to 8 week trial of single dose PPI therapy. With inadequate response, dosing can be increased to twice a day or switched to a more effective acid suppressive agent once a day. When there is adequate response, PPI should be tapered to the lowest effective dose.

Personalized Diagnostic Approach to GERD Symptoms

BPA #5. If proton pump inhibitor (PPI) therapy is continued in a patient with unproven GERD, clinicians should evaluate the appropriateness and dosing within 12 months after initiation, and offer endoscopy with prolonged wireless reflux monitoring off PPI therapy to establish appropriate use of long-term PPI therapy.

BPA #6. If troublesome heartburn, regurgitation and/or non-cardiac chest pain do not respond adequately to a PPI trial or when alarm symptoms exist, clinicians should investigate with endoscopy and, in the absence of erosive reflux disease (Los Angeles B or greater) or long-

segment (≥ 3 cm) Barrett's esophagus, perform prolonged wireless pH monitoring off medication (96 hour preferred if available) to confirm and phenotype or to rule out GERD.

BPA #7. Complete endoscopic evaluation of GERD symptoms includes inspection for erosive esophagitis (graded according to the Los Angeles classification when present), diaphragmatic hiatus (Hill grade of flap valve), axial hiatus hernia length, and inspection for Barrett's esophagus (with grading according to the Prague classification and biopsy when present).

BPA #8. Clinicians should perform upfront objective reflux testing off medication (rather than an empiric PPI trial) in patients with isolated extra-esophageal symptoms and suspicion of reflux etiology.

BPA #9. In symptomatic patients with proven GERD, clinicians should consider ambulatory 24 hour pH-impedance monitoring on PPI as an option to determine the mechanism of persisting esophageal symptoms despite therapy (if adequate expertise exists for interpretation).

Precision Management Approach to GERD

BPA# 10 Clinicians should personalize adjunctive pharmacotherapy to the GERD phenotype, in contrast to empiric use of these agents. Adjunctive agents include alginate antacids for breakthrough symptoms, nighttime H₂ receptor antagonists for nocturnal symptoms, baclofen for regurgitation or belch predominant symptoms, and prokinetics for coexistent gastroparesis.

BPA #11 Clinicians should provide pharmacologic neuromodulation, and/or referral to a behavioral therapist for hypnotherapy, cognitive behavioral therapy (CBT), diaphragmatic breathing and relaxation strategies in patients with functional heartburn or reflux disease associated with esophageal hypervigilance, reflux hypersensitivity and/or behavioral disorders.

BPA #12 In patients with proven GERD, laparoscopic fundoplication and magnetic sphincter augmentation are effective surgical options, and transoral incisionless fundoplication (TIF) is an effective endoscopic option in carefully selected patients.

BPA #13 In patients with proven GERD, Roux-en-Y gastric bypass is an effective primary anti-reflux intervention in obese patients, and a salvage option in non-obese patients, while sleeve gastrectomy has potential to worsen GERD.

BPA #14 Candidacy for invasive anti-reflux procedures includes confirmatory evidence of pathologic GERD, exclusion of achalasia, and assessment of esophageal peristaltic function.

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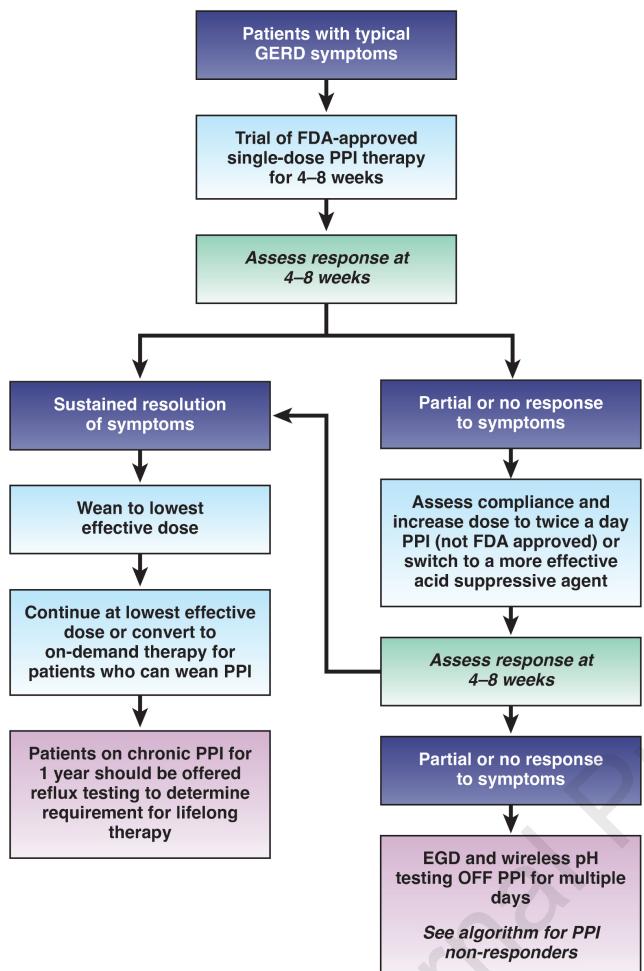
FIGURE LEGEND

Figure 1. Utilization of empiric proton pump inhibitor (PPI) therapy in suspected gastroesophageal reflux disease. Patients with typical reflux symptoms (heartburn, acid regurgitation) without alarm symptoms can be offered a trial of single dose PPI therapy, and response assessed in 4-8 weeks. Responders can be weaned down to the lowest effective dose, and if symptoms remain controlled, titrated further to on demand therapy if possible. Patients who need to remain on chronic PPI therapy can be offered reflux testing at the 1 year time point to determine appropriateness of long term therapy. Dose increase to twice a day or a switch to a more efficacious PPI can be offered to non- or partial responders to single dose PPI trial. If response remains suboptimal, esophageal testing is suggested (see Figure 3). Patients with isolated extra-esophageal GERD symptoms benefit most from up-front esophageal testing rather than an empiric PPI trial.

Figure 2. Utilization of prolonged reflux monitoring off proton pump inhibitor (PPI) therapy to characterize severity of GERD. Reflux monitoring is offered in patients without higher grades of reflux esophagitis on endoscopy. Absence of pathologic acid exposure on ambulatory reflux monitoring (acid exposure time, AET<4.0% on all 4 days of the prolonged wireless pH study) with a normal endoscopy rules out GERD. Erosive esophagitis of Los Angeles Grade B or higher, and/or AET \geq 6.0% on two or more days constitutes conclusive GERD evidence. Patients with LA grade A esophagitis, and/or AET \geq 4.0% but otherwise not meeting criteria for conclusive GERD are considered to have borderline GERD.

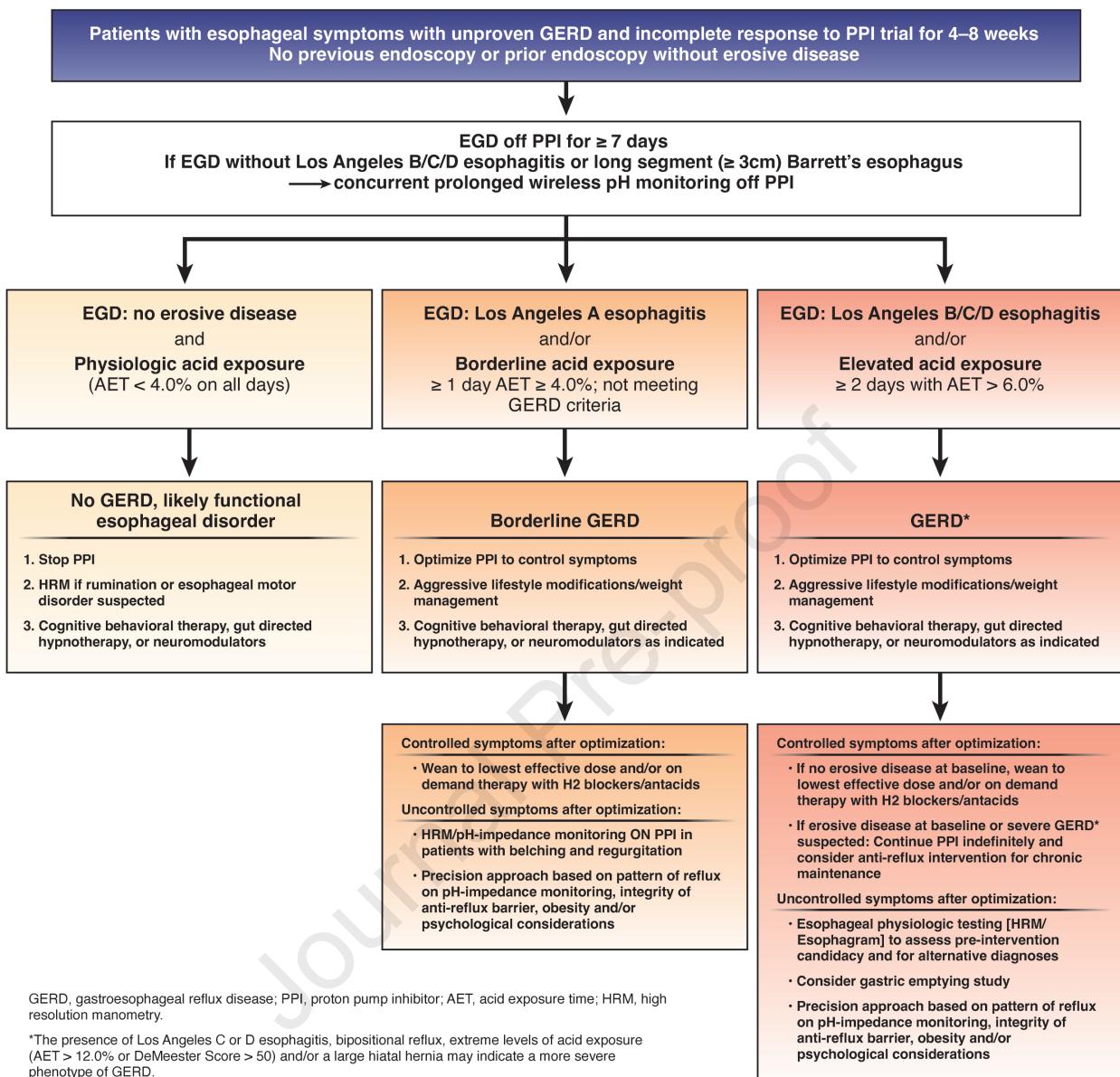
Figure 3. Personalized approach to diagnosis and GERD based on findings on endoscopy and prolonged ambulatory wireless pH monitoring. Patients with no GERD likely have an alternate explanation for symptoms, which can be a functional disorder; hence PPIs can be discontinued, and other management options explored. Patients with borderline GERD may need PPIs but these are titrated to the lowest dose or frequency that controls symptoms, or replaced with H2

receptor antagonists. Adjunctive approaches include life-style and behavior modification. Patients with GERD have Los Angeles grade B esophagitis or higher, and/or acid exposure time (AET) $\geq 6.0\%$ on 2 or more days on prolonged wireless pH monitoring performed off PPI therapy. Within patients with GERD, a severe GERD phenotype exists characterized by advanced grade esophagitis (Los Angeles grade C or D), and/or AET $>12.0\%$, bipositional reflux or Demeester score >50 , which requires either continuous long-term PPI therapy or invasive anti-reflux procedures, in addition to optimization of life-style measures. Medical management may be adequate for patients with GERD patients who respond to therapy, while escalation to anti-reflux procedures can be considered after appropriate esophageal physiologic testing for non-responders despite optimization of therapy.



		Prolonged ambulatory reflux monitoring off PPI			
		All days AET < 4.0%	≥ 1 day AET ≥ 4.0%; not meeting criteria for GERD	≥ 2 days with AET > 6%	
Upper GI endoscopy	No erosive reflux disease	No GERD	Borderline	GERD*	
	Los Angeles A esophagitis	Borderline			
	Los Angeles B/C/D esophagitis	GERD*; ambulatory reflux monitoring off PPI not recommended			

*In a patient with GERD, the presence of Los Angeles C or D esophagitis, AET > 12.0%, DeMeester score > 50, bipositional reflux, and/or a large hiatal hernia indicates a more severe GERD phenotype



GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; AET, acid exposure time; HRM, high resolution manometry.

*The presence of Los Angeles C or D esophagitis, bipositional reflux, extreme levels of acid exposure (AET $> 12.0\%$ or DeMeester Score > 50) and/or a large hiatal hernia may indicate a more severe phenotype of GERD.

Supplemental Table: Dosing of proton pump inhibitors

Proton Pump Inhibitor	Starting Dose*	Maximal Dose
Pantoprazole	40mg qd	40 mg bid
Lansoprazole	15mg qd	30 mg bid
Omeprazole	20mg qd	40 mg bid
Esomeprazole	20mg qd	40 mg bid
Dexlansoprazole	30mg qd	60 mg qd
Rabeprazole	20mg qd	20 mg bid

* in order of potency based on omeprazole equivalents

once daily dose optimally taken 30-60 min before breakfast; twice daily dose taken 30-60 min before breakfast and dinner;

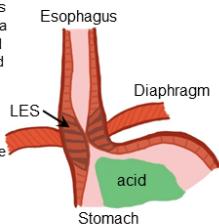
adapted from reference 22. Maximal doses reported based on doses used in clinically published studies

What is GERD?

Gastroesophageal reflux occurs when stomach contents back up into the esophagus. Occasional reflux is normal and commonly occurs after eating a meal.

What is the Esophagus? When you eat, food moves from your mouth to your stomach through the esophagus, a tube-like structure that is approximately 10 inches long and 1 inch wide in adults. The esophagus is made of tissue and muscle layers that expand and contract to propel food to your stomach through a series of wave-like movements called peristalsis.

At the lower end of the esophagus, where it connects to the stomach, there is a circular ring of muscle called the lower esophageal sphincter (LES). After you swallow, the LES relaxes to allow food to enter your stomach, where food mixes with acids that help with digestion. The LES then contracts to prevent the food and acid from backing up into your esophagus.



What is gastroesophageal reflux disease (GERD)?

However, sometimes the LES relaxes inappropriately; this allows stomach contents to wash back into the esophagus. This happens occasionally to everyone. Most of these episodes occur shortly after meals, are brief, and do not cause symptoms. Normally, reflux should rarely occur during sleep.

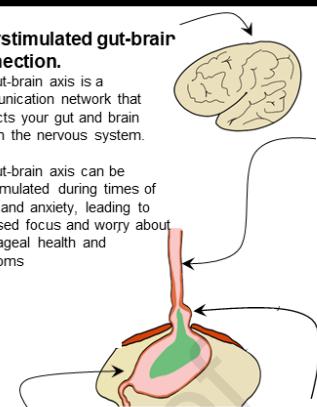
In some people, acid reflux causes bothersome symptoms or injury to the esophagus over time; when this happens, GERD is a consideration. The most common symptoms of GERD are heartburn (a burning sensation in the center of the chest) or regurgitation (when stomach contents flow back into your mouth or throat). Other symptoms of GERD may include chest pain, sore throat, voice hoarseness, cough, or a sense of a lump in the throat.

What are risk factors for GERD?

Overstimulated gut-brain connection.

The gut-brain axis is a communication network that connects your gut and brain through the nervous system.

The gut-brain axis can be overstimulated during times of stress and anxiety, leading to increased focus and worry about esophageal health and symptoms



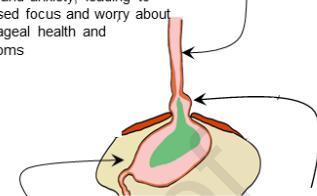
Nerve sensitivity.

There are multiple nerve endings in the esophagus, and the sensitivity of these nerve endings differs among individuals. In some people even normal amounts of reflux can stimulate symptoms.

Weak esophageal muscles can impair the ability to push refluxed contents back into the stomach

Increased abdominal pressure.

such as with obesity or in pregnancy, can reverse the flow gradient from stomach to esophagus



Hiatus hernia

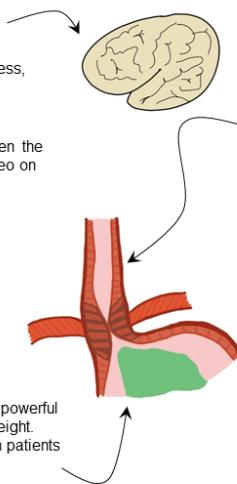
is a condition where part of the upper stomach pushes up through the diaphragm. The barrier between the esophagus and stomach is weakened in the presence of a hiatus hernia, which can allow reflux to occur

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Routine modifications to improve esophageal health if you have symptoms:

Stress Reduction.

Integrate methods to reduce stress in your life to disrupt the overstimulated gut-brain connection. These include mindfulness, meditation, and massage therapy.



Belly Breathing.

Belly breathing or diaphragmatic breathing can help strengthen the diaphragm and reduce esophageal disease and reflux. A video on diaphragmatic breathing can be found here: <https://www.youtube.com/watch?v=UB3tSaiEbNY>

Weight Management.

Losing weight, particularly weight around the abdomen, is a powerful tool to improve GERD symptoms for patients that are overweight. Maintaining a healthy weight is important to control GERD in patients with a normal weight.

Avoid tight fitting clothing.

Tight-fitting clothing can increase discomfort, and may also increase pressure in the abdomen, forcing stomach contents into the esophagus.

Avoid Trigger Foods.

If you have noticed that certain food items trigger your symptoms, it will be useful to avoid these items, as some foods may relax the lower esophageal sphincter and promote acid reflux. However, not all patients have the same trigger foods.

Quit smoking.

Saliva helps to neutralize refluxed acid, and smoking reduces the amount of saliva in the mouth and throat. Smoking also lowers the pressure in the lower esophageal sphincter and provokes coughing, causing frequent episodes of acid reflux in the esophagus. Quitting smoking can reduce or eliminate symptoms of mild reflux.

Chew gum or use oral lozenges.

Chewing gum or using lozenges can increase saliva production, which may help to neutralize and clear stomach acid that has entered the esophagus.

Avoid late meals.

Lying down with a full stomach may increase the risk of acid reflux. By avoiding eating within three hours before bedtime and avoiding late night snacks, nighttime reflux may be reduced.

If you have nighttime symptoms, raise the head of your bed.

Raising the head of your bed by 6 to 8 inches raises the head and shoulders higher than the stomach, allowing gravity to prevent acid from refluxing. Raising the head of the bed can be done with blocks of wood/bricks under the legs of the bed or a foam wedge under the mattress. Several manufacturers have developed commercial products for this purpose. However, it is not helpful to use additional pillows; this can cause an unnatural bend in the body that increases pressure on the stomach, which can worsen acid reflux.

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