Advances in the diagnosis and management of gastroesophageal reflux disease

David A Katzka,1 Peter J Kahrilas2

Introduction
Gastroesophageal reflux disease (GERD) has been defined from varied perspectives. According to the Montreal definition,1 “GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications.” The elegance of this definition is in its simplicity, uniting a large, seemingly unrelated set of symptoms and potential complications. However, the Montreal definition does not consider cofactors that interact with reflux, leading to atypical phenotypes captured under that umbrella. The Lyon Consensus definition2 is physiomorphologic, defining GERD by the presence of excess gastroesophageal reflux, esophageal motor perturbations, and increased epithelial permeability that can be associated with reflux. However, most of these features are non-specific for GERD. The Rome IV Conference definition3 is symptom based, focused on defining functional syndromes with GERD characteristics. However, functional syndromes can mimic GERD without reflux causality. Merging these documents is challenging. In this review, GERD is defined as a family of syndromes attributable to, or exacerbated by, gastroesophageal reflux, evident symptomatically, endoscopically, or by physiological testing, which impart morbidity through troublesome symptoms and/or risk.

Being a common disease with diverse manifestations, GERD is managed by many clinicians across many specialties: general practitioners, internists, gastroenterologists, surgeons, emergency department physicians, hospitalists, otolaryngologists, pulmonologists, obstetricians, and pediatricians. This has spawned a variety of perspectives. Several management topics—including the usage and safety of proton pump inhibitors (PPIs), the indications for endoscopy, recommended dietary interventions, and the roles of surgical and endoscopic interventions—have evolved in recent years, resulting in a somewhat overwhelming volume of publications. This narrative review is intended to simplify this often contradictory literature on GERD in the adult population for clinicians, academicians, and clinical researchers.

Sources and selection criteria
We searched PubMed, Medline, and the Cochrane databases from 2010 to May of 2020 using the search...
terms gastroesophageal reflux, gastroesophageal reflux disease, esophagitis, Barrett’s esophagus, esophageal hypersensitivity, hypersensitive esophagus, non-erosive gastroesophageal reflux, and functional heartburn. Sifting through the results, we prioritized studies by design, likely interest to the readership, and publication date, and we included older studies of continued relevance. Our initial search returned more than 13,000 unique citations making it especially difficult to limit this narrative review. No patient input was solicited.

Prevalence and geographic distribution
GERD is a worldwide disease with reported prevalence values ranging from 2.5% in China to 51.2% in Greece. This range is likely reflective of both true differences and methodological factors, with some surveys equating GERD with weekly heartburn and/or regurgitation and others stipulating erosive esophagitis. Interestingly, although the prevalence of GERD symptoms is similar among racial groups, complications of GERD such as erosive esophagitis and esophageal adenocarcinoma (EAC) are more common in white people, particularly with central obesity. Reflux is also increasingly common in young adults with the greatest increase seen in people aged 30-39 and EAC increasing in patients under 50.

Morbidity and mortality
Although GERD itself is not a fatal condition, potentially morbid complications include EAC, bleeding, esophageal rupture, aspiration, lung transplant rejection, aspiration pneumonia, and iatrogenic causes including surgery and dilations. The Canadian annual death rate directly related to GERD was estimated as 65 patients. In a Swedish population study, the annual death rate was 0.20/100,000 caused by hemorrhagic esophagitis (51.9%), aspiration pneumonia (34.6%), perforated esophageal ulcer (9.6%), and spontaneous esophageal rupture (3.9%).

On the other hand, the societal cost of GERD is substantial. In 2004-05, the annual direct cost for GERD care in Canada was C$52,235,910 (£30.2 million, €33.4 million). In the US, GERD accounted for 8,863,568 physician visits, 65,634 hospitalizations, and an estimated $12.3 billion spent on upper endoscopies in a year. In Japan, the mean medical cost for GERD patients aged 20-59 was $266 per patient per month in 2014, about 2.4 times the mean national healthcare cost.

Pathogenesis
Obesity and the Western lifestyle
Several studies have shown a correlation between obesity and GERD and a stronger correlation between central adiposity and GERD complications including EAC. A meta-analysis of 107 international studies demonstrated a 1.73 relative risk of at least weekly GERD symptoms in obese patients, albeit in a pooled analysis with a large amount of heterogeneity among studies. In a separate meta-analysis of 40 studies, patients with central adiposity had a 1.87 relative risk of erosive esophagitis (95% confidence interval, 1.51 to 2.31) and a 1.98-fold risk of Barrett’s esophagus that persisted after adjusting for body mass index. Mechanistically, central adiposity leads to increased intra-abdominal and intragastric pressure challenging the anti-reflux barrier and promoting the development of hiatus hernia. Obesity is also associated with overeating, causing gastric distension and eliciting transient lower esophageal sphincter (LES) relaxations. Metabolic sequelae of central obesity may also play a role: even without pathologic reflux, the distal esophageal epithelium of obese patients exhibits increased permeability, indicative of a perturbed epithelial barrier.

Helicobacter pylori
Although discovered relatively recently, H pylori is known to have infected humans for at least 50,000 years. Its strongest disease associations are in promoting peptic ulcers and gastric cancer. However, the infection may also provide protective effects with respect to GERD. Epidemiologic data demonstrate that erosive esophagitis, Barrett’s esophagus, and EAC are inversely related to H pylori infection. The proposed protective mechanism is that chronic H pylori gastritis leads to atrophic gastritis and relative hypochlorhydria, which in turn diminishes the acidity of gastroesophageal reflux. Supporting this concept, PPIs are more effective in the presence of H pylori, owing to the already diminished gastric acid secretion. However, two large randomized controlled trials of H pylori eradication versus placebo did not show an increase in reflux symptoms two years after eradication, leaving open the possibility that the observed inverse association between H pylori infection and GERD is not a causal one.

Physiology: the Lyon Consensus
The Lyon Consensus analyzed the role of physiological testing in GERD diagnosis. This consensus agreed that the cornerstone of GERD pathophysiology is incompetence of the esophagogastric junction (EGJ) evident both by separation between the crural diaphragm and LES as occurs with hiatus hernia, and a low EGJ contractile index, an integral of sphincter pressure over time derived from high resolution manometry. Whereas historically, investigators have focused solely on low LES pressure as indicative of an impaired reflux barrier, the EGJ contractile index broadens the concept to include both the crural diaphragm and the LES. A low EGJ

ABBREVIATIONS
EAC: esophageal adenocarcinoma; EGJ: esophagogastric junction; GERD: gastroesophageal reflux disease; H2 RA: histamine-2 receptor antagonist; LES: lower esophageal sphincter; MSA: magnetic sphincter augmentation; NERD: non-erosive reflux disease; PCAB: potassium competitive acid blocker; PPIs: proton pump inhibitors; TIF: transoral incisionless fundoplication
contractile index is common with erosive esophagitis and Barrett’s esophagus.

Many GERD patients have an EGJ contractility index within the normal range yet still exhibit excessive acid reflux by the mechanism of transient LES relaxation,24 the physiologic mechanism of belching. Transient LES relaxations occur through a vago-vagal reflex triggered by distension of the proximal stomach.25 What appears to differentiate GERD patients from normal controls is the frequency with which transient LES relaxations are associated with acid (liquid) reflux as opposed to only venting gas.26 Mechanistically, this is facilitated by increased compliance of the EGJ, leading to wider opening (and larger volumes of reflux) during relaxation.27

Hiatus hernia: the co-conspirator
Axial or sliding hiatal hernia is strongly associated with GERD, particularly with peptic esophagitis and its complications, to the point that some patients and physicians view hiatal hernia and GERD as being synonymous. While that is clearly erroneous, the contribution of a hiatal hernia to GERD pathophysiology is profound and multifaceted. The most obvious effect is of separating the two functional components of the EGJ, the LES and the crural diaphragm, thereby diminishing their ability to work in concert as a barrier to reflux events and in promoting esophageal acid clearance following reflux. Another mechanistic role of hiatal hernia in GERD has been proposed: the repositioning of the acid pocket.27 The acid pocket forms postprandially as newly secreted acid layers on top of ingested food, becoming the reservoir for postprandial reflux. With a hiatal hernia, the acid pocket migrates into the hernia compartment and facilitates exposure of the distal esophageal epithelium to gastric acid during any period of LES relaxation, even that associated with swallowing or secondary peristalsis.28 A postulated mechanism of action of alginate compounds in treating GERD is of capping the acid pocket with a protective gelatinous raft and displacing it away from the LES.29 The Lyon Consensus endorsed the significance of hiatal hernia in GERD pathophysiology, particularly when >3 cm in size.

The inflammation hypothesis
The conventional model of reflux esophagitis has been the “burn hypothesis” proposing that the caustic effects of hydrochloric acid combined with enzymatic digestion by pepsin erodes the esophageal epithelium from the lumen inward. However, recent experiments have challenged this concept, instead proposing that much of the injury is chronic and chemokine mediated.30 In rats, acutely induced reflux esophagitis was associated with lymphocyte infiltration, initially at the submucosa, progressing to the epithelial surface. The lymphocytic inflammation was associated with secretion of IL-8 and IL-1β and an injury pattern that persisted for weeks. An analogous process was subsequently demonstrated in high grade esophagitis patients, first healed with PPIs, and then observed to develop recurrent esophagitis with cessation of PPI therapy.11 These findings suggest that alternative pharmacologic approaches independent of acid suppression may be feasible to treat esophagitis.

Diagnostic testing: endoscopy, reflux monitoring, motility testing
Endoscopy is the primary test for suspected GERD syndromes because of its availability, relative safety, biopsy capability, therapeutic potential, and specificity of potential findings. Using the Los Angeles Classification, four severity grades of esophagitis (A-D) are defined, based on the extent of erosions (mucosal breaks) in the distal esophagus. The Lyon Consensus considered only Los Angeles C and D esophagitis to be hard evidence of GERD, but we extend that to include Los Angeles B esophagitis with the caveat that it must be accurately graded. Los Angeles A esophagitis, on the other hand, is found in 5-7% of normal individuals and is not hard evidence of GERD.32 33 Other potentially relevant findings are peptic strictures, Barrett’s metaplasia, and hiatus hernia.

Prolonged ambulatory esophageal reflux monitoring (pH or combined pH impedance) has three potential uses in managing GERD: 1) quantifying abnormal esophageal acid exposure in the absence of esophagitis; 2) determining if a patient’s symptoms correlate with reflux events; and 3) determining if gastroesophageal reflux (acid or weakly acidic in the case of pH impedance studies) is controlled by therapy. This becomes relevant in evaluating atypical symptoms or refractory symptoms despite ostensibly adequate pharmacologic and/or surgical therapy. Verifying physiologically defined disease is also essential when considering procedural therapies for GERD.

High resolution manometry can detect physiological abnormalities associated with GERD such as a low EGJ contractility index, hiatus hernia, or weak/absent peristalsis, but is not useful in defining treatment. The exception is when procedural treatments are contemplated, in which case manometry is mandated to detect unsuspected achalasia and to ascertain that peristaltic function is sufficiently preserved for the contemplated intervention.34 35

GERD phenotypes
Implicit in the Montreal definition is that GERD can be defined either by endoscopic features or by a symptom complex caused by gastroesophageal reflux. This creates management challenges because the determinants of mucosal injury differ from the determinants of symptoms and it would be unreasonable to think that treatment strategies should not differ as well. The evolving concept is that rather than being a continuum of disease with esophagitis simply exemplifying more severe non-erosive reflux disease (NERD), GERD has distinct phenotypes, each
with unique and shared features. Table 1 itemizes the major GERD phenotypes along with important distinguishing features.

Supporting the concept of GERD as a family of phenotypes are 20 year longitudinal data showing that progression from NERD to high grade esophagitis, stricture, or Barrett’s esophagus is uncommon. Additionally, patients with severe esophagitis or Barrett’s esophagus have important predispositions, typically being white, male, having central obesity, and family history. This is in contrast to NERD where there is neither racial nor gender predilection. The degree to which esophageal hypersensitivity plays into pathophysiology also varies widely among phenotypes. The Rome IV classification conceptualized this within the NERD population by subdividing it into “true NERD,” reflux hypersensitivity, and functional heartburn with reflux as the dominant symptom determinant at one end and hypersensitivity as the dominant determinant at the other end (functional heartburn). In summary, although gastroesophageal reflux is a contributing element to all of these syndromes (with the possible exception of functional heartburn), its dominance as a pathophysiological determinant ranges widely.

Barrett’s esophagus and esophageal adenocarcinoma

The most severe potential consequence of GERD is EAC, a cancer whose incidence has risen precipitously in the West for the past three decades, paralleling that of GERD. A now classic epidemiological study links these trends, and shows a dose dependent relation such that patients with severe reflux symptoms (>3 times per week for >5 years) have a 16-fold increased risk of EAC. Furthermore, most EAC presents at an advanced stage with poor prognosis and poor 5 year survival. This led to screening endoscopy protocols to detect either early EAC that has much better survival or, more commonly, the precursor lesion, Barrett’s metaplasia. Hence, societal guidelines (with considerable variability, table 2) have proposed using symptom burden as criteria for endoscopic screening and subsequent surveillance of Barrett’s esophagus. Although controversial, a systematic analysis of retrospective case-control studies suggested that such Barrett’s surveillance programs lead to earlier EAC diagnosis and improved mortality. Up to 40% of EAC patients present without a preceding history of significant reflux symptoms, however. Furthermore, 80%-95% of EAC patients present de novo. In other words, only a small minority of EAC patients have a symptom burden of sufficient severity to warrant endoscopic screening for a Barrett’s surveillance program.

Atypical and extraesophageal manifestations

Reflux has been implicated in causing myriad atypical and extraesophageal syndromes—laryngitis, pharyngitis, chronic cough, postnasal drip, non-cardiac chest pain, bronchiectasis, poorly controlled asthma, globus, cardiac arrhythmias, laryngeal cancer, subglottic stenosis, vocal fold granulomata, halitosis, dental erosions, hiccups, aspiration pneumonia, pulmonary fibrosis, lung transplant rejection, sleep apnea, burning tongue, dysgeusia, and chronic sinusitis—with the strength of supportive evidence for each entity ranging from sheer conjecture to supportive treatment trials. Reliable attribution of these syndromes to GERD is confounded by proposed pathogenesis models distinct from those of esophageal syndromes, promoting the hypothesis that physiologic (or “silent”) reflux may be injurious. Symptoms such as cough or arrhythmias may result from shared neural pathways stimulated by reflux, but not to the threshold required to elicit esophageal symptoms. It

<table>
<thead>
<tr>
<th>GERD phenotype</th>
<th>Major GERD phenotypes with key distinguishing features</th>
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| Non-erosive reflux disease (NERD) | Heterogeneous population

When defined by pH-metry, very similar to low grade esophagitis, but when defined by symptoms, overlaps with GERD hypersensitivity and functional heartburn |

| Functional heartburn | Esophageal hypersensitivity

Conceptually differentiated by pH-metry or pH impedance findings, but in practice, these entities can be clinically indistinguishable |

| Low grade erosive esophagitis, (Los Angeles grade A or B) | Poor EG barrier function with excess acid reflux and typical reflux symptoms (heartburn and regurgitation)

LA A esophagitis found in about 6% of asymptomatic controls making it a non-specific finding |

| High grade erosive esophagitis, (LA grade C or D) | Prolonged esophageal acid clearance with grossly abnormal EG function and prominent recumbent (nocturnal) reflux

Usually associated with hiatus hernia and impaired esophageal motility |

| Barrett’s esophagus | Greatest risk for esophageal adenocarcinoma

Endoscopic spectrum from intestinal metaplasia at the EG to short segment Barrett’s to long segment Barrett’s (>3 cm)

Biological spectrum from non-dysplastic metaplasia to low grade dysplasia to high grade dysplasia

Indicative of both acid and bile reflux

Independent risk factors: central obesity, male gender, white ethnicity, smoking, genetics |

| Reflux chest pain syndrome | Chest pain that can be indistinguishable from angina

Reflux is the most common cause of esophageal chest pain

Much more amenable to GERD therapy when associated with +pH-metry, esophagitis, or typical reflux symptoms

Partial rather than complete symptom resolution with treatment is common |

| Regurgitation dominant reflux disease | Grossly incompetent EG barrier with frequent large volume reflux often elicited by postural changes or abdominal straining

Much less responsive than heartburn to medical therapy

Need to differentiate from rumination and achalasia |

| Laryngopharyngeal reflux (LPR) | Usually multifactorial with dominant non-esophageal cofactors exacerbated by reflux

Strongly driven by neuronal hypersensitivity

More amenable to GERD therapy when associated with abnormal pH-metry, esophagitis, or typical reflux symptoms |
is further proposed that when structures such as the vocal folds are exposed to gastric content, the lack of a robust mucosal defense mechanism causes injury with parameters of reflux deemed normal in the esophagus. Consequently, testing for these atypical syndromes is problematic as esophageal reflux testing may lack sensitivity, and coexisting endoscopic findings are uncommon.13 Furthermore, proposed technologies to measure pepsin or acid reflux in a supraesophageal distribution are unvalidated.12 53

Given these shortcomings, most pertinent data are in the form of uncontrolled medical or surgical treatment trials. The few randomized controlled PPI trials that have been conducted in patients with poorly controlled asthma, reflux laryngitis, and postnasal drip have been either completely negative or, in the case of postnasal drip, only slightly positive in a highly selected population.14-56

Evident from the above discussion, the management of putative atypical GERD syndromes is plagued by uncertainties regarding diagnosis, causality, and treatment efficacy. Certain general principles emerge, however. First, although it can cause atypical syndromes, it is uncommon for reflux to be the dominant cause in patients not also experiencing typical esophageal symptoms. For example, in the randomized controlled trial of esomeprazole for posterior laryngitis that purposely excluded patients with frequent heartburn, the placebo response to treatment numerically exceeded the esomeprazole treatment response.51

Undoubtedly, reflux can be an important etiologic factor in laryngitis, but multiple potential cofactors (or alternative explanations) exist, including heavy voice use, visceral hypersensitivity, environmental irritants, postnasal drip, and so on. Consequently, if not responsive to PPI, effective management generally involves a multidisciplinary approach aimed at identifying causal cofactors and adjunctive treatments and these syndromes should not mandate a gastroenterology referral. A second theme is that reflux testing (pH-metry or pH impedance monitoring) is more useful when negative, excluding reflux as a cause, rather than when equivocal or positive, leaving the door open to (but not proving) a reflux cause. A third observation is that although fundoplication effectively eliminates reflux, no high quality data exist supporting its efficacy in atypical syndromes that are unresponsive to high dose PPI therapy. Again going to the example of reflux laryngitis, in a controlled trial of patients unresponsive to PPIs, no improvement was seen in laryngeal symptoms in the subgroup subsequently treated with surgical fundoplication.57

In summary, atypical and extraesophageal GERD is a management conundrum guided by expert opinion with experts of varied disciplines disagreeing with each other. From a gastroenterology viewpoint, the Clinical Practice Updates Committee of the American Gastroenterological Association endorses a therapeutic trial of aggressive acid suppression for 6-8 weeks focusing on the response of the extraesophageal symptoms and using reflux testing primarily to exclude rather than prove a reflux cause. In the same document, they discourage the use of unvalidated tests to implicate GERD and the surgical treatment of atypical syndromes not responsive to PPI therapy.50

Management

The principles of managing suspected GERD syndrome are to provide symptomatic relief and to minimize health risks through some combination

Table 2 | Societal guidelines for Barrett’s/EAC screening and surveillance endoscopy

<table>
<thead>
<tr>
<th>Society</th>
<th>Screening endoscopy recommendations</th>
<th>Surveillance endoscopy recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSG16</td>
<td>• Not feasible or justified for an unscreened population with reflux symptoms</td>
<td>• Suspected Barrett’s &lt;3 cm without intestinal metaplasia or dysplasia, repeat endoscopy is recommended to confirm diagnosis</td>
</tr>
<tr>
<td>2014</td>
<td>• Can be considered in patients with chronic reflux symptoms and at least three risk factors (age ≥50 years, white, male, obesity)</td>
<td>• Barrett’s with intestinal metaplasia &lt;3 cm, every 3-5 years</td>
</tr>
<tr>
<td></td>
<td>• Lower threshold with family history (first degree relative with Barrett’s or EAC)</td>
<td>• Barrett’s ≥3 cm, every 2-3 years</td>
</tr>
<tr>
<td>ESGE17</td>
<td>• Screening for BE not recommended</td>
<td>• Suspected Barrett’s &lt;1 cm, no biopsies or surveillance advised</td>
</tr>
<tr>
<td>2017</td>
<td>• Screening considered with reflux symptoms ≥5 years and multiple risk factors (age ≥50 years, white, male, obesity, first degree relative with BE or EAC)</td>
<td>• 1-3 cm, every 5 years.</td>
</tr>
<tr>
<td></td>
<td>• Barrett’s with intestinal metaplasia &lt;3 cm or dysplasia</td>
<td>• 3-10 cm Barrett’s, every 3 years</td>
</tr>
<tr>
<td>AGA18</td>
<td>• Screening is not recommended</td>
<td>• Barrett’s with no dysplasia, surveillance at unspecified interval</td>
</tr>
<tr>
<td>2011</td>
<td>• Consider with ≥5 years reflux symptoms and multiple risk factors (age ≥5 years, white, male, obesity, first degree relative with Barrett’s or EAC)</td>
<td>• Barrett’s with no dysplasia, 3-5 years</td>
</tr>
<tr>
<td>ASGE19</td>
<td>• Insufficient evidence of effectiveness</td>
<td>• Barrett’s with no dysplasia, surveillance at unspecified interval</td>
</tr>
<tr>
<td>2019</td>
<td>• If done, restrict to at risk population</td>
<td>• Barrett’s with no dysplasia, surveillance at unspecified interval</td>
</tr>
<tr>
<td></td>
<td>• High risk: family history of Barrett’s or EAC</td>
<td>• Barrett’s with no dysplasia, surveillance at unspecified interval</td>
</tr>
<tr>
<td></td>
<td>• Moderate risk: reflux and at least one other risk factor</td>
<td>• Barrett’s with no dysplasia, surveillance at unspecified interval</td>
</tr>
<tr>
<td>ACG20</td>
<td>• Consider in men with chronic (≥5 years) and/or frequent reflux symptoms and ≥2 risk factors (age ≥50 years, white, central obesity, smoking, first degree relative with Barrett’s or EAC)</td>
<td>• Barrett’s with no dysplasia, 3-5 years</td>
</tr>
<tr>
<td>2015</td>
<td>• Not recommended in females</td>
<td>• After initial examination, no repeat endoscopy in 1 year</td>
</tr>
<tr>
<td></td>
<td>• Consider with multiple risk factors (age ≥50 years, white, chronic and/or frequent reflux symptoms, central obesity, smoking, first degree relative with Barrett’s or EAC).</td>
<td>• Barrett’s with no dysplasia, 3-5 years</td>
</tr>
<tr>
<td>CCA21</td>
<td>• Consider based on age, sex, reflux history, central adiposity, smoking, and family history of EAC and/or Barrett’s</td>
<td>• Barrett’s with intestinal metaplasia &lt;3 cm, every 3-5 years</td>
</tr>
<tr>
<td>2015</td>
<td>• Barrett’s ≥3 cm, every 2-3 years</td>
<td>• Barrett’s ≥3 cm, every 2-3 years</td>
</tr>
</tbody>
</table>

BSG=British Society of Gastroenterology; ESGE=European Society of Gastroenterology; AGA=American Gastroenterological Association; ASGE=American Society of Gastrointestinal Endoscopy; ACG=American College of Gastroenterology; CCA=Cancer Council Australia; NDBE=non-dysplastic Barrett’s esophagus.
of lifestyle modifications, diagnostic testing, pharmaceuticals, and surgery. The decision of whether or not to perform diagnostic testing is based on the management history, risk assessment, and symptom assessment. Generally speaking, empiric therapy is appropriate for typical GERD symptoms, whereas atypical symptoms, a history of failed treatments, or alarm symptoms (dysphagia, bleeding, vomiting, or unintentional weight loss) prompt endoscopic evaluation. The objective of endoscopy is both diagnostic and to control the risk of EAC by detecting early cancers or identifying Barrett’s metaplasia as a marker of a high risk group suitable for subsequent endoscopic surveillance. Performing endoscopy on patients with typical reflux symptoms, but without alarm symptoms, is unlikely to alter management, however. Illustrative of this are data from a US database of 543,103 endoscopies performed from 2003 through 2014 which identified 73,535 (13.5% of the total) done for uncomplicated GERD symptoms.58 Expressed as a percentage of positive findings, the yield of these procedures was 0.1% for esophageal tumors, 0.1% for gastric tumors, 2.8% for esophageal strictures, 2% for high grade esophagitis, and 1.4% for suspected long segment Barrett’s. The authors concluded that additional risk factors should also be considered in deciding who should get screening endoscopy.

Lifestyle modifications
Lifestyle modifications aimed at controlling GERD symptoms utilize three general strategies: 1) avoid foods that may precipitate reflux (coffee, alcohol, chocolate, fatty food); 2) avoid foods that may elicit heartburn as direct irritants (citrus, carbonated drinks, spicy foods); and 3) adopt therapeutic behaviors (weight loss, smoking cessation, raising the head end of the bed, avoiding late meals, and postprandial recumbency). However, evidence supporting these recommendations is generally weak, so they should be advised selectively.59 For example, someone who consistently experiences heartburn after ingestion of alcohol, coffee, or any specific food will benefit from avoiding these, but an individual without such problems need not be restricted. Cigarette smoking, however, should be uniformly discouraged, both for general health and for its association with many cancers, including EAC.

Obesity and weight control warrant emphasis as a therapeutic intervention because evidence points to the obesity epidemic as a root cause of the GERD epidemic. Epidemiological data reveal a dose dependent relation between increasing body mass index and frequent reflux symptoms.60 The benefit of weight loss for controlling GERD symptoms has not been demonstrated in clinical trials, however, and instead rests on observational epidemiology.51-63 Nonetheless, if weight gain paralleled the development of reflux symptoms, even without the individual being overweight, it is reasonable to propose weight loss as a treatment strategy.

Antacids, alginates, and surface acting compounds
Antacids neutralize gastric acid without reducing acid secretion, thereby briefly relieving GERD symptoms. However, their efficacy may be enhanced when combined with alginates, natural polysaccharide polymers that precipitate into a low density viscous gel on contact with acid. The ac also releases CO₂ from the bicarbonate. With the CO₂ trapped in the alginate gel, this mixture floats to the top of the gastric content.64 Newly secreted acid also layers on top of an ingested meal forming the “acid pocket” evident within 20 minutes of eating and serving as the reservoir for post-cibal acid reflux.65-66 The alginate-antacid gel displaces the acid pocket distally, positioning it away from the EGJ causing the gel to reflux in lieu of acid.67-69 Analogous to this, a hyaluronic acid-chondroitin sulfate based bioadhesive formulation has been developed to create a barrier on the esophageal mucosa to reduce contact with refluxate. A randomized, double blind trial of 154 patients with NERD showed that the combination of the mucosal protectant and acid suppression improved symptom relief in NERD patients compared with acid suppression alone (53% vs 32%, P<0.01).70

Acid suppression: H₂ receptor antagonists, PPIs, potassium competitive acid blockers
Although gastric acid secretion is rarely abnormal in GERD patients, pharmacologically reducing acid secretion compensates for the fundamental problems of excessive acid reflux and/or impaired acid clearance, making this the dominant pharmacological strategy. Three drug classes achieve this: H₂ receptor antagonists (H₂RAs), PPIs, and potassium competitive acid blockers (PCABs). The most potent drugs inhibit the gastric H⁺/K⁺ ATPase to block the final common pathway for acid secretion either by covalently binding to it in the case of the PPIs or by reversible inhibition in the case of the PCABs. The PPIs are by far the dominant class, having been available since 1990; PCABs have only recently been approved in select countries, specifically South Korea and Japan. H₂RAs competitively block histamine stimulated acid secretion making them fundamentally less potent because acid secretion is also stimulated by gastrin and acetylcholine.

Although H₂RAs revolutionized the treatment of peptic ulcers, they proved inadequate to heal esophagitis. PPIs and PCABs are substantially more effective, particularly in healing high grade esophagitis. Studies comparing the relative effectiveness of PPIs conclude that the fraction of the day that they maintain intragastric pH >4 is a reliable physiokinetic marker of effectiveness in high grade esophagitis,117,118 with the target being 50-70% of a 24 hour period.73 This value varies from 35-68% of the day at 5 day steady state among different PPIs (with substantial inter-individual variability) and is up to 93% of the day on the first day of administration for the PCAB, vonoprazan (fig 1). However, translating the data in figure 1 to the clinical endpoint of healing
esophagitis is challenging. This is exemplified in figure 2, which illustrates the results of a randomized, double blind, parallel group, dose ranging study, in 732 subjects comparing vonoprazan with a mid-potency PPI, lansoprazole 30 mg. Although trends toward greater efficacy are evident in the two week time point for LA C/D esophagitis with the higher doses of vonoprazan, none of the differences are clinically or statistically significant. It should also be emphasized that a drug’s efficacy in healing high grade esophagitis does not necessarily parallel its efficacy for symptomatic clinical endpoints wherein reflux acidity is but one of multiple symptom determinants. Figure 3 compares the randomized controlled trial data on the efficacy of PPIs for healing esophagitis with that of resolving key symptomatic endpoints: resolving heartburn and regurgitation. Not only is the efficacy substantially lower for the symptomatic endpoints, but within the individual PPI trials that tested multiple doses, no dose-response relation was seen for either heartburn or regurgitation relief.75-77 Furthermore, a 13% difference in therapeutic gain is evident for heartburn dependent on whether or not it occurs in the context of erosive esophagitis or NERD, suggesting that its specificity as an acid induced symptom is less in the absence of esophagitis.

Whatever the presentation of GERD, the likelihood of spontaneous, sustained remission is low and maintenance therapy is usually required. Although even the most severe esophagitis can be healed with PPIs, recurrence is in approximately 80% of patients within six months of discontinuation78 and the likelihood of recurrence is directly related to the initial severity of esophagitis. Symptoms also usually relapse after PPI discontinuation. Maintenance therapy should be adjusted to the minimal level of acid suppression necessary to maintain symptom relief. Irrespective of instructions, most patients do this on their own, adopting on-demand or intermittent PPI dosing as required for symptom control.59

PPI safety

For short term use, PPIs have proven quite safe. Side effects include headache (<5%) and diarrhea (<5%), both of which are reversible with cessation of therapy. However, with their widespread long term use over the past few decades, the relation between PPIs and a multitude of adverse outcomes has been scrutinized, causing a backlash against PPI use. Adverse consequences are the proposed result of either profound acid inhibition, secondary hypergastrinemia, or idiosyncratic reactions. However, most of this literature stems from observational population based studies and only one relevant randomized controlled trial: a placebo controlled, randomized, double blind trial of 17 598 participants with stable cardiovascular disease randomized to pantoprazole 40 mg daily or placebo as well as one of four anticoagulant regimens.79 Prospective data were collected for a median of three years (53 152 patient y) on a variety of adverse outcomes put forth in population based studies as PPI “risks”: pneumonia, Clostridium difficile infection, other enteric infections, fractures, gastric atrophy, chronic kidney disease, diabetes, chronic obstructive lung disease, dementia, cardiovascular disease, cancer, hospitalizations, and all cause mortality. The only significant difference found between the pantoprazole and placebo groups was for enteric infections (1.4% versus 1.0% in the placebo group; odds ratio, 1.33). For all other safety outcomes, proportions were similar between groups except for C difficile infection, which exhibited a trend to being more common with pantoprazole. Proponents of population based epidemiology argue that the 3 year randomized controlled trial was still too small and too short to detect rare long term adverse events associated with PPI use. Instead they point to the many population based studies and meta-analyses of PPI risks summarized in table 3.80-101 However, the mechanistic hypotheses that link these adverse outcomes to PPI use are without support from experimental studies. Population based studies are subject to unrecognized, uncontrolled bias (for instance, frailty), or recognized but inadequately controlled bias, such that odds ratios of less than 3 in such studies rarely prove to be meaningful.102 Applying that filter to the data in table 3 reduces the significant risks of PPI use to enteric infections and rare instances of acute interstitial nephritis, both
Reflux inhibition and prokinetic drugs

Since transient LES relaxations are a common mechanism of reflux, their pharmacological inhibition represents an attractive treatment target. Baclofen, a GABA<sub>B</sub> agonist inhibits the vagal pathway for transient LES relaxations, but the side effects of somnolence and dizziness limit its clinical utility for GERD. Hence, novel GABA<sub>B</sub> agonists were developed to avoid these side effects. Lesogaberon was the candidate drug that progressed furthest in clinical trials, but phase II clinical trials failed to show clinically significant additive benefit to PPIs and, with only that modest benefit, development was halted. Consequently, baclofen remains the only reflux inhibitor currently available, albeit without that approved indication and with very limiting side effects.

Fig 2 | Results of a dose ranging randomized controlled trial comparing vonoprazan with lansoprazole for healing low and high grade esophagitis. Healing was assessed by endoscopy after two weeks and eight weeks of treatment. Although a trend toward faster healing with high grade esophagitis was evident, none of the differences in healing rates are significant. Data from Ashida, 2015

Fig 3 | The diminishing efficacy of PPIs going from healing esophagitis to treatment for cardinal GERD symptoms with or without coexistent esophagitis. Data are from randomized controlled trials using once daily PPIs. NNT=number needed to treat to benefit one individual
In theory, drugs that augment esophageal motility or gastric emptying can be beneficial in GERD by reducing the occurrence of reflux and/or enhancing the process of esophageal acid clearance. Prucalopride and mosapride are 5-HT4 agonists commercialized as prokinetics with potentially beneficial physiological effects for GERD when tested in normal volunteers. However, neither was shown to be beneficial as add-on therapy to PPIs either in a double blind, placebo controlled, randomized, crossover study of 21 healthy volunteers (prucalopride) or in a randomized trial of 116 esophagitis patients (mosapride). The prokinetic most widely used for GERD is metoclopramide, an antidopaminergic drug that also has 5-HT3 antagonist, 5-HT4 agonist, and cholinomimetic properties. However, no high quality data support the use of metoclopramide as monotherapy or adjunctive therapy in any GERD syndrome. Furthermore, the drug has the potential for substantial central nervous system toxicity (tremor, Parkinsonism, depression, tardive dyskinesia), and clinical guidelines recommend against its use in GERD.

### Visceral hypersensitivity

Evident in table 1, several of the major GERD phenotypes have esophageal or visceral hypersensitivity as a distinguishing feature. Antidepressants may modulate esophageal sensitivity, potentially benefiting these syndromes. Supportive of this, trazodone, a serotonin antagonist and reuptake inhibitor, was more effective than placebo in 29 symptomatic patients with motility abnormalities completing a 6 week, double blind, placebo controlled trial. Similarly, a selective serotonin reuptake inhibitor, citalopram, reduced esophageal acid sensitivity, and significantly improved symptoms in a 10 patient randomized, placebo controlled, crossover, double blind acute study and in a placebo controlled randomized trial of 252 patients with pH impedance defined hypersensitivity (67% vs 23%). However, in an 83 patient randomized, placebo controlled trial testing the efficacy of a low dose tricyclic antidepressant (imipramine) for treating esophageal hypersensitivity and functional heartburn, the response rates (judged by 50% reduction in GERD symptoms) were 37.2% and 37.5% for imipramine and placebo respectively, with no observed difference between patients with hypersensitivity and those with functional heartburn. Imipramine treatment was, however, associated with improved quality of life as assessed by SF-36 score, offering some support to its use.

### Barrett’s esophagus

Retrospective case-control studies report conflicting results as to whether or not medical treatment prevents progression of Barrett’s epithelium to EAC. The Aspirin and Esomeprazole Chemoprevention in Barrett’s metaplasia trial (AspECT) was a large randomized controlled trial intended to clarify the issue. Some 2557 non-dysplastic Barrett’s patients at 84 centers in the UK were randomized to standard or high dose esomeprazole with or without aspirin (four groups) and followed for at least eight years. The primary composite endpoint was time to all cause mortality, EAC, or high grade dysplasia. The high dose PPI and aspirin group was significantly more likely to achieve the composite endpoint, but the effect was driven mainly by improved overall survival rather than reduced progression of Barrett’s. Hence, this remains an open question, with experts differing on their interpretation of these data.

A major advance in the management of Barrett’s pertains to patients with high grade dysplasia and early cancers. Whereas these patients would formerly be treated with esophagectomy, the current standard of practice is complete endoscopic ablation of the Barrett’s segment with endoscopic resection of visible lesions followed by high dose acid suppression and, if necessary, fundoplication. The dominant ablation method used is radiofrequency energy as

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**Table 3 | Summary of observational epidemiology reports (meta-analyses or population based studies) of adverse outcomes associated with long term PPI use. For each adverse outcome, only one report (most recent, largest, or highest quality) is included. Note that these associations do not prove causation and only the adverse outcome of enteric infections has been supported by randomized controlled trial data (see text)**

<table>
<thead>
<tr>
<th>Adverse outcome</th>
<th>OR, HR, or RR with PPI use</th>
<th>95% Confidence interval</th>
<th>Patients analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>1.18</td>
<td>1.53-1.84</td>
<td>20k</td>
</tr>
<tr>
<td>Bone related</td>
<td>1.5</td>
<td>1.16-1.45</td>
<td>1.5m</td>
</tr>
<tr>
<td>Dental implant failure</td>
<td>2.02</td>
<td>1.41-2.88</td>
<td>5k</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>1.2</td>
<td>1.14-1.28</td>
<td>2.1m</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.23</td>
<td>1.06-1.42</td>
<td>100k</td>
</tr>
<tr>
<td>Spine fracture</td>
<td>1.49</td>
<td>1.31-1.68</td>
<td>700k</td>
</tr>
<tr>
<td>Wrist fracture</td>
<td>1.09</td>
<td>0.95-1.20</td>
<td>—</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.55</td>
<td>0.88-2.73</td>
<td>100k</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>2.5</td>
<td>1.74-3.85</td>
<td>900k</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>3.52</td>
<td>0.36-34.49</td>
<td>10k</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1.71</td>
<td>1.20-2.43</td>
<td>7k</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1.25</td>
<td>1.11-1.42</td>
<td>400k</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>1.49</td>
<td>1.73-2.30</td>
<td>400k</td>
</tr>
<tr>
<td>Infections</td>
<td>1.73</td>
<td>1.39-2.15</td>
<td>8k</td>
</tr>
<tr>
<td>C difficile</td>
<td>2.8</td>
<td>3.01-6.08</td>
<td>—</td>
</tr>
<tr>
<td>Recurrent C difficile</td>
<td>1.43</td>
<td>1.30-1.57</td>
<td>7.6m</td>
</tr>
<tr>
<td>Enteric infections</td>
<td>1.71</td>
<td>1.20-2.43</td>
<td>7k</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.55</td>
<td>1.00-2.61</td>
<td>3k</td>
</tr>
<tr>
<td>SIBO</td>
<td>1.44</td>
<td>1.13-1.76</td>
<td>100k</td>
</tr>
<tr>
<td>Kidney related</td>
<td>1.88</td>
<td>1.71-2.07</td>
<td>500k</td>
</tr>
<tr>
<td>Acute interstitial nephritis</td>
<td>3.76</td>
<td>2.36-5.99</td>
<td>600k</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>1.61</td>
<td>1.16-2.22</td>
<td>2.4m</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.32</td>
<td>1.19-1.46</td>
<td>800k</td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>1.88</td>
<td>1.71-2.07</td>
<td>500k</td>
</tr>
<tr>
<td>Neurological</td>
<td>1.23</td>
<td>0.90-1.67</td>
<td>100k</td>
</tr>
<tr>
<td>Alzheimers</td>
<td>0.96</td>
<td>0.83-1.09</td>
<td>400k</td>
</tr>
<tr>
<td>Dementia</td>
<td>1.23</td>
<td>0.90-1.67</td>
<td>100k</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1.32</td>
<td>1.07-1.50</td>
<td>400k</td>
</tr>
<tr>
<td>Risk of fall</td>
<td>2.46</td>
<td>1.42-4.27</td>
<td>40k</td>
</tr>
<tr>
<td>Fundic gland polyps</td>
<td>1.55</td>
<td>1.00-2.61</td>
<td>3k</td>
</tr>
<tr>
<td>Gastric mucosal atrophy</td>
<td>1.44</td>
<td>1.13-1.76</td>
<td>100k</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>2.68</td>
<td>1.73-4.17</td>
<td>0.4k</td>
</tr>
</tbody>
</table>

OR = odds ratio; HR = hazard ratio; RR = risk ratio. k = 10; m = 10.

*Small intestinal bacterial overgrowth.*
reported in a randomized controlled trial involving 127 patients with dysplastic Barrett’s. In that trial, the ablation group had better Barrett’s eradication and developed fewer cancers compared with the sham treated group (77.4% vs 2.3%, P<0.001 and 1.2% vs 9.3%, P=0.045, respectively).

Procedural therapies
Procedural treatments for GERD (surgical or intraluminally performed) have always been both appealing and controversial, balancing the desire for a mechanistic, “curative” treatment against the risk of iatrogenic harm. However, the pursuit of restoring normality to the intricate function of the EGI has repeatedly exposed the challenges of achieving that. The current standard surgical technique is a laparoscopic fundoplication involving reduction of the hiatal hernia (if present), partially closing the dilated diaphragmatic hiatus to approximate its normal size, and bolstering the LES by encircling it either partially (Dor 180°, Toupet 270°) or completely (Nissen 360°) with the mobilized gastric fundus. The Nissen is by far the most commonly done and the only one that has been compared to medical therapy in randomized controlled trials. One multicenter trial enrolled 554 patients with chronic GERD who had initially responded to PPIs and randomized them to either laparoscopic Nissen fundoplication or 20-40 mg esomeprazole.1,16 Estimated remission rates at 5 years, defined as not needing a PPI in the surgical group or adequately controlled symptoms in the PPI group, were 92% with PPIs and 85% with fundoplication (P=0.048). Another randomized controlled trial compared laparoscopic fundoplication to active medical therapy (PPI, baclofen, and/or desipramine) or “control medical management” (PPI and placebo) in 366 veterans with refractory GERD.117 Although the study encountered 79% screening failures, 67% of those treated improved with fundoplication compared with 28% with active medical management and 12% with control medical management (P<0.01 medical vs fundoplication).

Emerging therapies
Although fundoplication can benefit patients poorly managed with PPIs (refractory regurgitation, intolerance of PPIs, uncontrolled recumbent reflux, or worsening lung disease), it suffers from frequent failure with breakdown in 10%-50% of patients within 5-10 years.117-121 Furthermore, side effects of dysphagia and gas bloat due to an inability to belch or vomit are common. As a result, alternative devices and techniques have been developed over the past three decades. Most have failed in practice because of safety issues, lack of efficacy, or both. The two exceptions that remain in current use with supportive outcome data are magnetic sphincter augmentation (MSA) and transoral incisionless fundoplication (TIF).

The MSA device consists of a ring of titanium enshrouded magnetic beads designed to be loosely fitted around the LES laparoscopically. The beads separate when the LES opens during peristalsis and their magnetic attraction then augments sphincter closure. In an uncontrolled trial reporting on 100 GERD patients, MSA achieved the primary outcome of normalizing (or greatly improving) pH-metry in 64% and substantially reduced PPI usage in 93% at 1 year.122 At 5 year follow-up, 85 of these patients had sustained control of reflux symptoms.123 Another MSA study targeted regurgitation dominant GERD that was poorly responsive to once daily PPI. In a prospective study of 152 patients, 89% randomized to MSA reported improvement in regurgitation at 6 months compared with 10% of patients randomized to twice daily PPI (P<0.01).124 The current place of the MSA device in GERD management is evolving, but it is a reversible alternative to fundoplication in patients without high grade esophagitis, >3 cm hiatal hernia, or morbid obesity.

The other procedural treatment in current use is TIF which employs a device fitting over an endoscope to create a facsimile of a 270° fundoplication by intussuscepting the esophagus into the stomach and securing it there with transmural fasteners. A US randomized controlled trial of 87 patients with regurgitation dominant reflux disease without >3 cm hiatal hernia compared TIF and placebo with sham surgery and 40-80 mg omeprazole.125 After six months of treatment, a larger proportion of TIF patients achieved the primary endpoint of elimination of troublesome regurgitation (67% vs 45% for PPI, P<0.05). Another double blind sham controlled study in 44 GERD patients who were chronic PPI users from a European consortium showed similar efficacy.126 As with MSA, the place of TIF in GERD management is evolving, but it too is an alternative to fundoplication in patients without high grade esophagitis, >3 cm hiatal hernias, or morbid obesity.

All surgical and procedural trials have specifically excluded patients with morbid obesity leaving open the question of how to manage them, especially since obesity is an important risk factor for GERD. An emerging strategy is gastric bypass. Although the primary indication for this surgery is weight reduction, a systematic review of four studies examining the effect of laparoscopic Roux-En-Y gastric bypass demonstrated better control of GERD symptoms when compared with lifestyle changes.127 Notably, sleeve gastrectomy and vertical band gastroplasty exacerbate reflux.

Finally, an experimental approach to refractory GERD is bile acid binding. In a multicenter, double blind, placebo controlled trial in 280 patients with confirmed GERD, the addition of a novel bile acid sequestrant to PPIs significantly reduced heartburn and regurgitation compared with adding placebo.128

Conclusion
GERD is a multifaceted disorder encompassing a family of syndromes attributable to, or exacerbated by, gastroesophageal reflux that impart morbidity
through troublesome symptoms and/or injury. GERD is common throughout the world with its epidemiology largely linked to the Western lifestyle and obesity. Because of its prevalence and chronicity, GERD is a huge economic burden. However, apart from the roughly fivefold risk of developing EAC, mortality related to GERD is very rare. The principles of management are both to provide symptomatic relief and to minimize potential health risks through some combination of lifestyle modifications, diagnostic testing, pharmaceuticals to suppress gastric acid secretion, and surgery. However, management needs to be personalized to the specific GERD phenotype recognizing that each has distinct pathophysiological features. Management principles are shown in the summary (box 1).

**Box 1: Summary of GERD management**

**Diagnosis**

Symptom assessment
- With typical heartburn and/or regurgitation, GERD is confirmed by an expected response to treatment

Endoscopy
- The primary test in the evaluation of suspected GERD syndromes
  - Alarm symptoms: (dysphagia, bleeding, vomiting, or unintentional weight loss)
  - Atypical symptoms
  - Unsatisfactory response to empiric PPI therapy
  - Barrett’s/EAC risk—regional guidelines vary regarding the specific indications for screening and surveillance
  - Evaluate for disorders, particularly eosinophilic esophagitis, infectious esophagitis

Prolonged ambulatory esophageal reflux monitoring
- Suspected GERD syndrome without esophagitis (or only Los Angeles grade A)
  - Ascertain the presence and severity of physiologically defined GER
  - Determine if symptoms correlate with reflux events
  - Determine if gastroesophageal reflux is being controlled by therapy

High resolution manometry
- No diagnostic role for GERD

- Indicated to exclude alternative diagnoses (eg, achalasia) and to evaluate peristalsis when procedural therapies are being considered

**Treatment**

Lifestyle modifications
- Tailor to the individual patient’s triggers and symptom patterns
- Emphasize weight loss if at all relevant to the individual

Antacids, alginates, H2RAs
- Mild intermittent symptoms: use on demand
- Breakthrough symptoms while on maintenance PPI therapy

PPIs, PCABs
- Preventive treatment for frequent/severe symptoms, erosive esophagitis, and/or stricture
- Atypical symptoms that respond to empirical 8 week therapeutic trial
- Tailor dosing and patterning of usage to the specific syndrome

Procedural therapies: Nissen fundoplication is the standard
- PPI intolerance
- Regurgitation dominant disease poorly responsive to PPIs
- Uncontrolled recumbent reflux
- Chronic recurrent aspiration causing pulmonary injury (bronchiectasis, pneumonia)

**RESEARCH QUESTIONS**

- How to better define the reflux contribution to myriad putative laryngopharyngeal reflux syndromes?
- How to better identify and treat visceral hypersensitivity as a determinant of reflux syndromes?
- What are effective early detection/prevention strategies for esophageal adenocarcinoma?

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No patients were directly involved in the creation of this article.

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**STATE OF THE ART REVIEW**


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STATE OF THE ART REVIEW


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