Review Article

Role of endoscopy in gastroesophageal reflux disease

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Abstract

Gastroesophageal reflux disease is a condition due to reflux of stomach content in the esophagus causing trouble symptoms or complications or both. GERD is a clinical diagnosis and typically presents with a heartburn and/or regurgitation and a positive response to antacid secretory medications. GERD is the leading outpatient diagnosis among all gastrointestinal disorders in the United States. Approximately 40% of population report occasional symptoms of GERD whereas 10-20% of patients will have symptoms at least once in a week. Recent guidelines from gastrointestinal societies such as American College of Gastroenterology, American Society for Gastrointestinal Endoscopy and American College of Physicians have laid out specific indications regarding role of esophagogastroduodenoscopy in GERD. Despite these recommendations, studies have revealed that one-fifth to two-fifth EGDs may not be clinically indicated, especially where open access endoscopy referral system is used. Traditionally, GERD has been thought to be a disease of the western world. Prevalence rates had been estimated to be lower in Asia when compared to that of the Western Countries. Few recent epidemiological studies in India showed the prevalence of reflux disease in India to be between 8-24%, which is comparable to the western world. The use of EGDs becomes more critical for developing countries such as India where prevalence of GERD and BE is comparable to the western countries but have limited resources. In addition to direct cost for an EGD, it burdens economy with indirect costs such as time off from the work, transportation and any procedural complications. Risk stratifying patients with GERD may therefore prevent unnecessary procedures, harms and costs. The aim of this paper is to review the existing evidence on the role of endoscopy in GERD.

Key words Barrett's esophagus, endoscopy, gastroesophageal reflux disease

Introduction

The Montreal Consensus Conference defines gastroesophageal reflux disease (GERD) as a condition due to reflux of stomach content in the esophagus causing trouble symptoms or complications or both.[1] Endoscopic or histologic changes are not necessary to make the diagnosis. GERD is a clinical diagnosis and typically presents with heartburn and/or regurgitation and a positive response to antacid secretory medications.

GERD is the leading outpatient diagnosis among all gastrointestinal (GI) disorders in the United States. Approximately 40% of the population report occasional symptoms of GERD whereas 10–20% of patients will have symptoms at least once in a week.[2-4] Proton-pump inhibitors (PPIs) are the main stay of GERD therapy. At least, a PPI has been in the list of top-five bestselling medications, both by volume as well as sales in 2007–2012.

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Recent guidelines from GI societies such as American College of Gastroenterology (ACG), American Society for GI Endoscopy (ASGE), and American College of Physicians (ACP) have laid out specific indications regarding role of esophagogastroduodenoscopy (EGD) in GERD. Despite these recommendations, studies have revealed that one-fifth to two-fifth EGDs may not be clinically indicated, especially where open access endoscopy referral system is used.[5] The number of EGDs performed per year in the USA for Medicare patients has increased by 40% in recent years whereas the enrollment has increased only by 13% (www.cms.gov/NonIdentifiableDataFiles). The aim of this paper is to review the existing evidence on the role of endoscopy in GERD.

Burden of Gastroesophageal Reflux Disease in India and Asia

Traditionally, GERD has been thought to be a disease of the Western world. Prevalence rates had been estimated to be lower in Asia when compared to that of the Western countries.[6] Few recent epidemiological studies in India showed the prevalence of reflux disease in India to be between 8% and 24%,[7,8] which is comparable to the Western world. Epidemiological studies have reported variable prevalence of Barrett's esophagus (BE) in Asian population, between 1% and 42%,[9,10] with higher prevalence of short segment nondysplastic BE (NDBE) as compared to long segment NDBE. In India, the prevalence of BE has reported to be between 2.4% and 23.6%.[11,12] The heterogeneity in the findings could be secondary to methods used for diagnosis as well as the selected population being evaluated. In the retrospective study by Punia *et al*.[11] with reported 23.6% prevalence of BE, half of the patients with gastric metaplasia were classified as having BE. So the true prevalence of BE was approximately 10% in GERD patients with typical symptoms. However, it is unclear if this represents a true increase in the prevalence of GERD or is a result of better understanding of the disease symptoms, increased awareness of acid reflux, or the recent high quality epidemiological studies. Nonetheless, the impact of the adaptation of "western diet and lifestyle" increasing obesity, reducing *Helicobacter pylori* frequency, etc., on the increase in the prevalence of GERD cannot be ruled out. In India, the future "Diabetes Capital of the World," the prevalence of GERD and BE may increase further.

Burden of Gastroesophageal Reflux Disease and Utilization of Endoscopy in the USA

Among patient reported symptoms, abdominal pain was the leading cause of outpatient clinic appointments with approximately 16 million visits in 2009.[13] Heartburn and indigestion were the sixth leading symptom that led to 2 million

GI clinic visits. Among all GI disorders, GERD was the number one physician diagnosis in outpatient clinics and the patients discharged from hospitals.[13] There were half a million doctor visits for BE.

Of 6.9 million EGDs performed in 2009, the presence of alarm symptoms such as anemia, weight loss, bleeding, or vomiting was the most common indication (28.4%).[13] GERD alone was an indication for EGD in 19.2% of cases whereas reflux or dysphagia was indicated in 23.9 and 20.3% endoscopies, respectively. An estimated direct cost of all EGDs performed was $12.3 billion. The average direct cost per upper endoscopy was $1,775.[13] Indirect costs include decreased quality of life work, decreased productivity, and time off from work both for the patient and the attendant. Patients with abdominal pain, GERD, and bloating scored similar to those with depression and heart failure in the National Health and Wellness Survey, 2000 which assessed quality of life in terms of physical, mental, and activity impairment.[13]

Role of Endoscopy in the Diagnosis of Gastroesophageal Reflux Disease

The typical symptoms of GERD are regurgitation and heartburn. Atypical symptoms include cough, chest pain, abdominal pain, and extraesophageal symptoms are hoarseness of voice, cough, and asthma. On EGD, approximately 40–50% of patients with prolonged reflux will have findings of esophagitis.[1,14,15] The presence of esophagitis is 90–95% specific but not sensitive for the diagnosis of GERD.[14,16,17] The response to PPI has also been advocated for GERD diagnosis. The problem with this definition is that the response rate to PPI is variable. For patients with severe degree of inflammation, the response rate is as high as 90% whereas for patients with Los Angeles (LA) Grade A or LA Grade B esophagitis, the response rate could be as low as 40–50%.[18,19] Patients with normal esophageal findings on EGD are often referred to as having nonerosive reflux disease.

The most common classification currently used to grade the severity of esophagitis is the LA classification [Table 1 and Figure 1].[20] The LA classification is reliable and has shown good intra-observer and inter-observer agreement among endoscopists. It also correlates well with the amount of acid exposure based on 24 h pH-testing. A limitation of these scoring systems is that the endoscopic findings fail to predict the symptom severity.

Histological Findings in Gastroesophageal Reflux Disease

Initial reports in 1970s suggested that basal cell hyperplasia and elongation of papilla correlated well with the presence of GERD.[21,22] However recent studies, including a large prospective GERD trial (The ProGERD Study),[23] failed to

find any significant difference in basal cell hyperplasia and elongation of papilla in patients with GERD symptoms and with or without erosive changes. In this study, biopsies were obtained 2 cm above the gastroesophageal junction (Z-line). The presence of intraepithelial inflammatory cells had high specificity but low sensitivity as it could be present in normal appearing mucosa in subjects without reflux symptoms.

Dilated intercellular space, seen on transmission electron microscopy has been proposed as one of the diagnostic characteristics of GERD. Intercellular spaces were dilated twice as much in patients with reflux symptoms compared to asymptomatic controls whereas no difference was noted in the symptomatic GERD patients, with and without erosive changes on EGD.[24,25] The findings are not validated and transmission elevation microscopy is not widely available in general practice.

Differential Diagnosis of Esophagitis

In immunocompromised individuals, viral or candida infection can cause esophagitis. Herpes simplex virus (HSV) and cytomegalovirus (CMV) are the most common viral infections. HSV usually affects the distal esophagus and causes small ulcers with normal-appearing intervening mucosa. The ulcers are well circumscribed and have a "volcano-like" appearance. Biopsies should be taken from the edge of an ulcer where viral cytopathic effects are most likely to be present. Multinucleated giant cells, with ground-glass nuclei, and eosinophilic inclusions (Cowdry Type A inclusion bodies) are often seen in histology. On the other hand, CMV ulcers are more linear, longitudinal, or deeper with diffuse esophageal involvement. Large cells containing eosinophilic intranuclear and basophilic intracytoplasmic inclusions, known as cytomegalic cells are often noted in the biopsy. *Candida* esophagitis causes white mucosal plaque such as exudative lesions and biopsy show yeasts and pseudohyphae.

Complications of Long Standing Gastroesophageal Reflux Disease

Endoscopy in Barrett's esophagus

BE is a well-known complication of GERD [Figure 2]. The prevalence of BE is approximately 5% in patients without and 8% with a history of heartburn. Older age, male gender, Caucasian race, and higher body mass index (BMI)[26] are risk factors for BE. BE is the only known precursor lesion of esophageal adenocarcinoma (EAC). Approximately, 90% of BE is nondysplastic. The rate of progression of NDBE and

Table 1: The modified LA classification system for the endoscopic assessment of grade of esophagitis

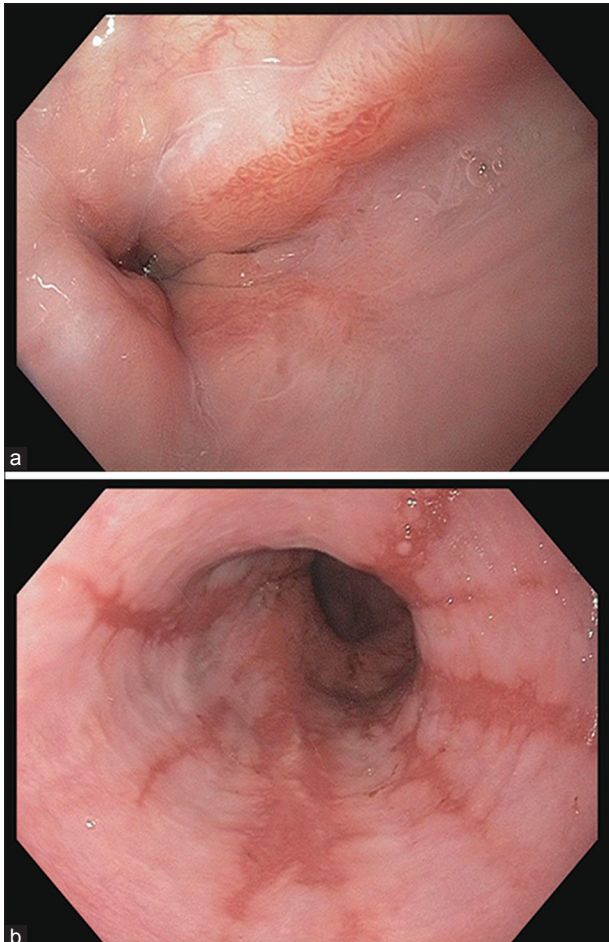| Grade	Description
A	One (or more) mucosal breaks no longer than 5 mm, none of which extends between the tops of the mucosal folds
B	One (or more) mucosal breaks more than 5 mm long, none of which extends between the tops of two mucosal folds
C	One (or more) mucosal breaks that extend between the tops of two or more mucosal folds, but which involve <75% of the esophageal circumference
D	One (or more) mucosal breaks which involve at least 75% of the esophageal circumference

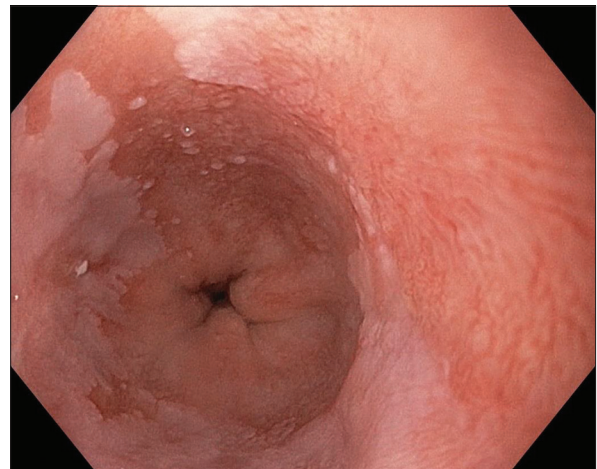**Figure 1:** (a) Grade B esophagitis; (b) Grade D esophagitis

Figure 2: Endoscopic appearance of Barrett's esophagus

low-grade dysplasia (LGD) to EAC is very low; approximately 0.3–0.4% and 0.5–1% per patient year, respectively.[27] Figure 2 shows nondysplastic and EAC.

Given the high prevalence of GERD, the presence of BE without GERD symptoms and low rate of progression of NDBE to EAC, the use of EGD as a population-based screening tool is neither cost effective nor feasible. A cost utility analysis showed that screening of men above the age of 50 with long standing symptoms of GERD to detect adenocarcinoma associated with BE is probably cost-effective. However, even 5-year subsequent surveillance intervals for NDBE patients might exceed the current threshold of cost-effectiveness ratio <$50,000 per Quality Life Year saved.[28]

Given above factors, most GI societies[29-31] and ACP[32] recommend, EGD for BE only in men older than 50 years, with chronic GERD symptoms more than 5 years, with presence of additional risk factors such as nocturnal reflux symptoms, hiatal hernia, elevated BMI, tobacco use, and abdominal obesity. The role of EGD as once in a lifetime screening for BE is controversial. American Gastroenterological Association (AGA) recommends against screening the general population with GERD for BE.[29] If no BE is noted on index EGD when reflux symptoms for more than 5 years, ASGE recommends against further EGD unless there is a development of new high risk symptoms such as anemia, weight loss, or dysphagia.[30] The role of EGD in the GERD patients is summarized in Table 2.

Endoscopy in dysplastic Barrett's esophagus

BE with any grade of dysplasia – LGD or high-grade dysplasia (HGD), should be confirmed by two independent expert pathologists. Once the diagnosis is confirmed, AGA recommends surveillance EGD for LGD every 6 months to 1 year. Currently, ACG and ASGE do not advocate treating patients with LGD except in a select group of people. In patients with high-grade dysplasia (HGD) or EAC, AGA recommends endoscopic eradication or ablation treatment over surgery.[29] In the absence of eradication therapy, surveillance EGD should be done every 3 months. Patients undergoing endoscopic treatment, should have an endoscopic mucosal resection (EMR) followed by an ablative technique in the presence of a visible lesion.[33] EMR is both diagnostic and therapeutic. It allows pathologists to provide accurate diagnosis and disease staging. Endoscopic ablation alone is performed in the absence of a visible lesion or nodule. The role of EGD in surveillance of BE is summarized in Table 3.

Surveillance interval after endoscopic treatment is not clear at this time. Societies recommend surveillance every 3–6 months in the 1st year followed by yearly EGDs in the absence of dysplasia. Common complications of the EMR are bleeding (1–8%), perforation, and stricture (1–24%)

which may need dilation in symptomatic patients. Multiple sessions of EMR alone have shown to cause more stricture as compared to EMR followed by ablation.[34] Among the ablative techniques, radiofrequency ablation (RFA) is preferred. RFA uses ultra-short pulse radiofrequency energy that ablates the dysplastic mucosa to a uniform depth of 0.5–1 mm, while preserving the submucosa – results from the large multi-center trial showed high efficacy rates of eradication of dysplasia (90%) and intestinal metaplasia (IM) (80%). A multi-center study by Gupta *et al.* observed that of patients with BE treated by RFA, 56% were in complete remission after 24 months.[35] However, 33% of these patients had disease recurrence within the next 2 years. Though most recurrences were nondysplastic and endoscopically manageable, authors recommended continued surveillance after RFA. Long-term data on safety and efficacy of carbon dioxide cryotherapy for treatment of neoplastic BE by Canto *et al.* showed that at 1 year, the overall complete response rates were 77% for cancer, 89% for dysplasia, and 94% for HGD. Thus, long-term studies on safety and efficacy of ablation for BE is promising.

Table 2: Role of EGD in GERD

Men and women with alarm symptoms-Dysphagia, bleeding, anemia, weight loss, and recurrent vomiting

Persistence of typical GERD symptoms after therapeutic trial of twice daily PPI for 4-8 weeks

Surveillance for severe esophagitis (LA grade C/D) after a 2 months trial of twice daily PPI to R/O BE

Evaluation for suspected extraesophageal manifestations of GERD

Findings of mass/stricture on imaging studies

Symptom control for dysphagia in patients with benign or malignant stricture

Screening for BE in men with reflux symptoms for more than 5 years, age above 50 and presence of other risk factors such as (nocturnal symptoms, hiatal hernia, abdominal obesity, high body mass index, and tobacco use)

Evaluation of patients undergoing surgical anti-reflux procedures

Evaluation of patients with recurrent reflux symptoms and alarm symptoms such as abdominal pain, vomiting, anemia, or weight loss after anti-reflux surgery

EGD=Esophagogastroduodenoscopy, GERD=Gastroesophageal reflux disease PPI=Proton-pump inhibitors, BE=Barrett's Esophagus, LA=Los Angeles

Table 3: Role of EGD in surveillance of BE

NDBE
   EGD should be performed no more frequently than every 3-5 years, with white-light endoscopy and targeted plus 4-quadrant biopsies at every 2 cm of suspected BE[a,b]
   Repeat EGD at 1 year and then every 3 years[a]

LGD
   Repeat endoscopy within 6 months to confirm the diagnosis, and then, annual surveillance endoscopy using a standard biopsy protocol[b,c]

HGD
   Endoscopic treatment (preferred) or surgery can consider surveillance every 3 months[c]

[a]ACG, [b]ASGE, [c]AGA. EGD=Esophagogastroduodenoscopy, BE=Barrett's Esophagus, LGD=Low-grade dysplasia, HGD=High-grade dysplasia, NDBE=Nondysplastic Barrett's esophagus, ACG=American College of Gastroenterology, ASGE=American Society for Gastrointestinal Endoscopy, AGA=American Gastroenterological Association

Advanced imaging techniques in Barrett's esophagus

White light endoscopy with random biopsies is the standard for detection of IM and neoplasia in patients with BE. In a meta-analysis by Qumseya *et al.*, it was noted that advanced imaging techniques increased the diagnostic yield for detection of dysplasia or cancer by 34%.[36] Virtual chromoendoscopy (narrow band imaging [NBI]) or chromoendoscopy were the advanced imaging technique studied. There was no difference in the diagnostic yield for dysplasia between NBI or chromoendoscopy.[36] NBI highlights surface patterns that correlate with IM and neoplasia in BE. In another study, Sharma *et al.* noted that NBI targeted biopsies can have the same IM detection rate as a high-definition white light examination with the Seattle protocol while requiring fewer biopsies.[37] In addition, NBI targeted biopsies detected more areas with dysplasia. Regular appearing NBI surface patterns did not harbor HGD/cancer, suggesting that biopsies could be avoided in these areas.

Endoscopy in strictures

Long standing reflux disease can cause esophageal strictures. Figure 3 shows a typical peptic stricture. Dysphagia is the chief symptom. The role of endoscopy is to differentiate malignant and benign strictures. The incidence of benign strictures has decreased due to the widespread use of PPIs. Empiric dilation in the absence of symptoms is not recommended.[38] In benign strictures, dilation is attempted as need basis for symptom control. Malignant strictures need self-expandable metallic or frequent dilation as compared to benign strictures for symptom control.

In common practice, nonwire guided mercury or tungsten filled bougies (Maloney or Hurst), wire guided polyvinyl dilators (Savary-Gillard or American), and through-the-scope balloon dilators are used. During dilation, the "rule of three" is followed. No greater than three consecutive dilation in increment of 1 mm should be used in a single session. The exception to this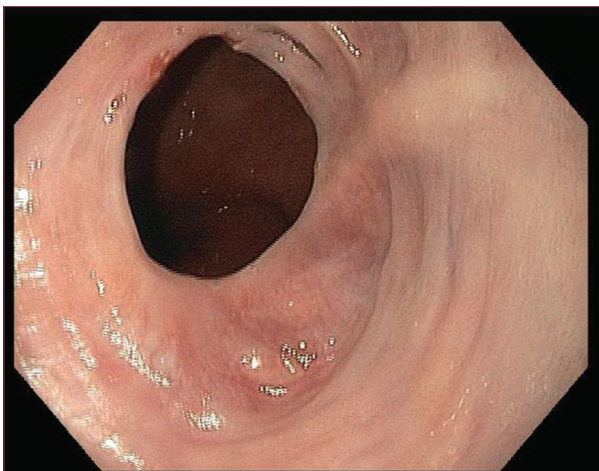 rule is for Schatzki ring, where the largest diameter dilators, usually 16-20 mm is used with intent of disrupting the stricture.[38] Sometimes biopsy/incision of the Schatzki ring is helpful in breaking the ring.

Endoscopy for esophageal adenocarcinoma

Esophageal neoplasia is usually classified according to the internationally accepted Vienna Classification.[39] The Vienna Classification is based upon the histopathological evaluation of endoscopically acquired biopsies [Table 4]. Endoscopy eradication therapies are considered adequate for T1a cancers (involving mucosal layer) as the risk of lymph node metastasis is <1–3%.[40] Few centers consider endoscopic resection for superficial submucosal layer (T1sm1 cancers) provided the tumor is not poorly differentiated or show lymphovascular invasion. The chances of lymph node metastasis are more than 20% in patients with any cancer beyond T1sm1.[41] EMR has shown good results for early EAC in conjunction with RFA. Haidry *et al.* showed that HGD was cleared from 86% of patients, all dysplasia from 81%, and BE from 62% at the 12-month time point, after a mean of 2.5 RFA procedures.[42] Endoscopic submucosal dissection (ESD) is now emerging as an alternative technique. Probst *et al.* showed that ESD is safe with higher complete removal of all tumor with microscopic examination of margins showing no tumor cells (R0 resection) in 83.9%.[43]

Reasons for Overuse of Endoscopy in Gastroesophageal Reflux Disease

Common reasons for overuse of endoscopy are physician preference,[44] patient satisfaction,[45] and prevention of potential malpractice law suit.[46] It has been noted that around 10–40% of EGD are not clinically indicated[47,48] and the surveillance interval for BE is more intense in at least 30% of the patients in the community practice with open access endoscopy referral system.[49,47] The range of EGD utilization for abdominal pain could be anywhere between 10% and 100% of patients enrolled. With increased awareness among patients, those with long standing reflux symptoms without any high risk features would also want to have a screening EGD to rule out any serious pathology. For patients with known BE, the knowledge of harboring a precancerous lesion might cause anxiety and result in frequent surveillance EGDs.

Figure 3: Benign peptic stricture

Table 4: Vienna classification of esophageal neoplasia

Category	Description
1	No dysplasia
2	Indefinite for dysplasia
3	Low-grade intraepithelial neoplasia (low-grade adenoma/dysplasia)
4	High-grade intraepithelial neoplasia (high-grade adenoma/dysplasia, noninvasive carcinoma, or suspicion of invasive carcinoma)
5	Invasive epithelial neoplasia (intramucosal carcinoma, submucosal carcinoma, or beyond)

The common reasons for the failure of GERD treatment are compliance with PPI and adherence to PPI.[50] In a recent study, approximately 40% of primary care practitioners and around 20% of gastroenterologists were not aware of the proper timing and indication of PPI.[51]

Summary and Recommendations on Use of Endoscopy in Gastroesophageal Reflux Disease Patients

In summary, the role of endoscopy in GERD patients is limited. Patients with alarm symptoms such as weight loss, anemia, vomiting, and bleeding should undergo EGD to rule out the presence of strictures or cancer. Benign strictures can be dilated for symptom relief. It should be used to screen BE only in patients with high risk features. Patients with BE should be educated regarding their low risk of cancer and enrollment in endoscopic surveillance programs can be considered.

Patients with reflux symptoms and the absence of high risk features should be treated empirically with PPI for 4–8 weeks. For those patients, who are not responsive to PPI, adherence and compliance to PPI use should be monitored. Changing to a different PPI, doubling the dose, or addition of night-time histamine 2 receptor antagonists are all reasonable options. In the absence of response to conservative treatments, EGD is warranted. For patients with extraesophageal symptoms, a multi-specialty approach with participation of ENT, pulmonary, and cardiology services should be considered to rule other pathologies.

The use of EGDs becomes more critical for developing countries such as India where the prevalence of GERD and BE is comparable to the Western countries but have limited resources. The prevalence of GERD and BE may rise in future in India due to increase in prevalence of metabolic syndrome, aging population, and obesity. In addition to direct cost for an EGD, it burdens the economy with indirect costs such as time off from the work, transportation, and any procedural complications. Risk stratifying patients with GERD may, therefore, prevent unnecessary procedures, harms, and costs. This can be achieved through patient and primary care physician education as well as an emphasis on the current and effective standard of care by gastroenterologists.

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