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# Diagnosis and initial management of Gastroesophageal complications

Afrin Kamal, Michael F. Vaezi, Professor of Medicine and Clinical Director *

*Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, 1301 Medical Center Drive, 1660 TVC, Nashville, TN 37232, United States*

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Chronic esophageal exposure to reflux of gastroduodenal contents can result in complications of GERD including esophageal stricture, Barrett's oesophagus or extraesophageal symptoms such as laryngitis, chronic cough or asthma. Endoscopy is the main diagnostic tool for patients with chronic reflux presenting with dysphagia to visualise esophageal mucosa and identify the underlying pathology. Barrett's oesophagus should be suspected in those with chronic reflux disease. Patients with Barrett's oesophagus should undergo surveillance endoscopy in order to risk stratify to dysplasia or adenocarcinoma. New endoscopic ablative therapies in patients with Barrett's oesophagus and high grade dysplasia are promising new treatment modality for those who may not be candidates for definitive intervention. Given poor sensitivity of diagnostic tests in extraesophageal reflux, empiric therapy with proton pump patients is the initial recommended approach. Diagnostic testing with esophagogastroduodenoscopy and ambulatory pH and impedance monitoring is usually reserved for those unresponsive to acid suppressive therapy. Many uncertainties remain in this group of patients including which patient subgroups might benefit from acid suppressive therapy. Future outcome studies are needed to assess the role of impedance/pH monitoring in this group of patients and to determine who might symptomatically benefit from medical or surgical intervention.



* Corresponding author. Tel.: +1 615 322 3739; fax: +1 615 322 8525.
*E-mail address:* Michael.Vaezi@vanderbilt.edu (M.F. Vaezi).

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## Introduction

Gastroesophageal reflux disease (GERD) is a commonly diagnosed condition with prevalence of 20–30% in the western population [1]. The diagnosis is often based on typical symptoms of heartburn and regurgitation; although GERD may present with atypical symptoms such as chest pain, hoarseness, chronic cough and asthma thus eluding correct diagnosis for some time. Although GERD is associated with more ominous conditions such as esophageal adenocarcinoma, in most it is the patients' reduced quality of life which is the driver of clinical care and diagnostic testing. GERD imposes a significant economic impact to health care system due to medication costs, frequent office visits, and reduced productivity. The annual direct cost for managing the disease is estimated to be more than $9 billion dollars in the USA [2].

GERD occurs when the normal anti-reflux barrier between the stomach and the oesophagus is impaired, either transiently or permanently. Therefore, defects in the esophago-gastric barrier, such as lower esophageal sphincter (LES) incompetence, transient lower esophageal sphincter relaxations (TLESR), and hiatal hernia, are the primary factors involved in the development of GERD [3]. TLESR are the primary mechanism for GER is normal individual and those with mild GERD; while in those with severe disease with complications permanent structural alteration such as low LES pressure or a large hiatal hernia are more likely to be causal [4]. Delayed gastric emptying can also be an underlying and often overlooked contributing factor to the development of GERD. Symptoms and or complications of GERD develop when the offensive factors in the gastroduodenal contents, such as acid, pepsin, bile acids, and trypsin, overcome several lines of esophageal defence, including esophageal acid clearance and mucosal resistance [3]. As more components of esophageal defence break down, reflux severity increases resulting in increased likelihood of esophageal mucosal damage.

Complications of untreated or sub-optimally treated GERD are well known and predominately relate to chronic exposure to gastroduodenal contents resulting in esophageal ulcerations, peptic stricture, Barrett's oesophagus, adenocarcinoma as well as extraesophageal presentations (Table 1). It is generally accepted that GERD complications are far less common representing less than 50% of those diagnosed with reflux disease; however, its true incidence remains elusive due to limited cohort studies. Complications related to reflux disease may develop over time especially in patients who are not appropriately treated. Several over arching caveats about GERD complications include: (1) in those with mucosal disease; especially LA Grade C and D oesophagitis (Fig. 1), discontinuation of acid suppressive therapy leads to recurrence of disease; (2) the majority of patients with Barrett's oesophagus without baseline dysplasia or cancer are unlikely develop dysplasia or cancer in surveillance programs; (3) the association of GERD and extraesophageal symptoms is often over stated in patients initially presenting with the presumed diagnosis; (4) acid suppression using proton pump inhibitors (PPI's) continues to be the therapy of choice as empiric or preventive treatment in complicated GERD.

**Table 1**
Complications of Gastroesophageal reflux.

| Esophageal | Extraesophageal |
|---|---|
| Oesophagitis | Hoarseness |
| Esophageal ulcers | Laryngitis |
| Peptic stricture | Laryngeal nodules |
| Barrett's oesophagus with intestinal metaplasia | Laryngeal cancer |
| Adenocarcinoma | Globus |
| | Asthma |
| | Chronic cough |
| | Chronic bronchitis |
| | Pulmonary fibrosis |
| | Pneumonitis |
| | Chest pain (non-cardiac) |
| | Dental erosions |

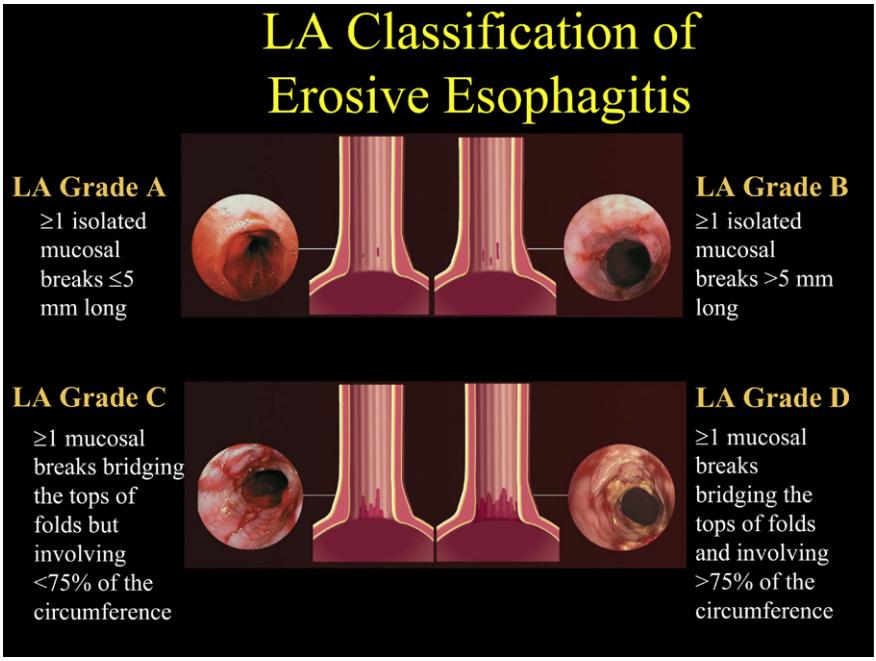


**Fig. 1.** Los Angeles (LA) classification of erosive oesophagitis. Note that mucosal breaks are necessary to yield a diagnosis of oesophagitis. Subtle findings such as erythema or oedema of the gastroesophageal junction are not a part of this classification scheme since they are not specific to GERD.

We will review the current knowledge on complications of GERD and focus the discussion to esophageal strictures, Barrett's oesophagus and extraesophageal reflux diseases such as chronic laryngitis, asthma and cough.

## Esophageal strictures

Esophageal strictures can be separated into two groups: functional and organic. Functional strictures form from increased tone within the muscular wall, while organic is from deposition of collagen and fibrous tissue as a consequence of mucosal injury. Aetiology of benign esophageal strictures are numerous and a limited list is provided in Table 2 [5]. More commonly strictures develop secondary to chronic GERD and this condition is referred to as peptic strictures. This condition is a consequence of chronic exposure to injurious gastroduodenal contents. It may occur in 7–23% of those with GERD and are typically short (<1 cm) and most occur in the distal third of the oesophagus [6] (Fig. 2). Overall the incidence of peptic strictures have declined since 1990's due to increase availability and utilisation of proton pump inhibitors [7].

**Table 2**
Aetiology of benign esophageal strictures.

| |
|---|
| Peptic (GERD) |
| Esophageal rings |
| Eosinophilic oesophagitis |
| Postsurgery |
| Iatrogenic (Irradiation, PDT, Sclerotherapy, Caustic, NG tube) |
| Infectious (CMV, Herpes, HIV, Candida) |
| Crohn's |
| GVHD |
| Pill induced |

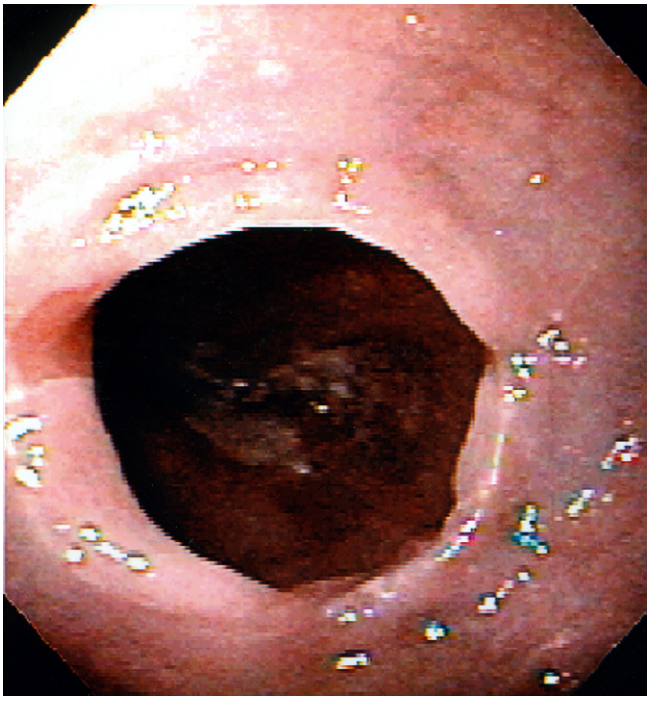

**Fig. 2.** Endoscopic view of a simple distal esophageal stricture. Note the significant narrowing in the esophageal lumen.

*Epidemiology*

Peptic strictures are the most common type of benign esophageal strictures representing 70–75% of esophageal strictures [8]. Less frequent etiologies include eosinophilic oesophagitis, NSAID use, chest irradiation, and esophageal variceal sclerotherapy and others (Table 2) [9]. In the past few years the prevalence of eosinophilic oesophagitis has been increasing in the adult population and this diagnosis should be ruled out in especially young men with food impaction and dysphagia [10].

In patients with de novo diagnosis of peptic strictures, 25–44% may have underlying Barrett's oesophagus [6] which is the reason repeat endoscopy may be necessary post PPI therapy. Risk factors for esophageal stricture formation include long-standing GERD, hiatal hernia, and peptic ulcer disease. In addition, a higher incidence of esophageal strictures is found among patients diagnosed with rheumatoid arthritis, use of disease-modifying anti-rheumatic drugs (DMARDs), and heavy alcohol use [11]. The elderly are especially at increased risk of developing complications of GERD such as esophageal stricture due to disassociation of symptom severity and mucosal disease, poly pharmacy adversely affecting the LES pressure, possible esophageal dysmotility and increasing BMI.

*Pathophysiology*

Benign esophageal strictures are commonly located within the distal third of the oesophagus. Initially narrowing results from reversible oedema and muscular spasm. As acid reflux progresses, chronic inflammation from erosions and ulcerations develop, leading to collagen and scar tissue depositing around epithelial cells. Over time fibrous tissue causes stricture formation within the esophageal lumen, ultimately leading to narrowing and obstruction [6,8,11,12].

'Simple' peptic strictures are characterised as short, focal, straight, and effort-less for the endoscope to pass through (>ten mm in diameter) (Fig. 2). Strictures that are longer, angular, and more narrow

causing difficulty for the endoscope to pass through are referred to as 'complex' strictures (Fig. 3). An alternative classification for peptic stricture scores the strictures based on three parameters (diameter, length and ease of dilation). Strictures are then classified based on the summed scores from the three parameters into type I (mild), type II (moderate) or type III (severe) strictures (Table 3) [13]. However, this classification is less often used clinically.

*Symptoms*

Dysphagia is the most frequent presenting symptom for peptic strictures (Table 4). As strictures narrow the esophageal lumen to less than 12 mm diameter, patients begin to complain of difficulty

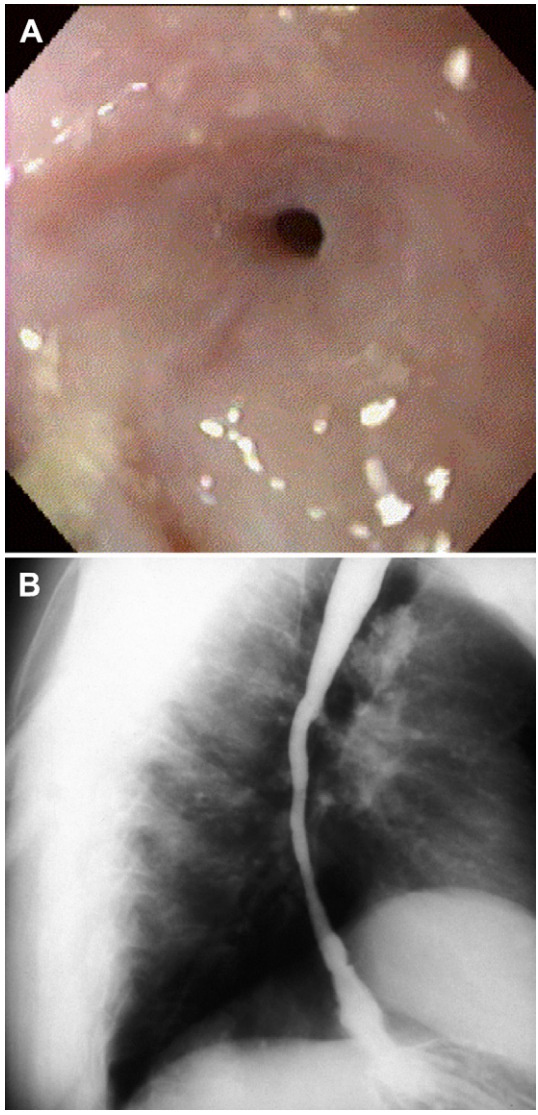


**Fig. 3.** (A) Endoscopic view of a complex and tight esophageal stricture not allowing the passage of a diagnostic upper endoscope. (B) Barium esophagram of the same stricutre extending along the length of the oesophagus.

**Table 3**
Proposed Stricture grading based on ease of dilation, length and diameter of stricture.

| Stricture character | Score |
|---|---|
| Ease of dilation | 1–2 |
| Length | 1–3 |
| Diameter | 1–3 |
| Type I | 3–4 |
| Type II | 5–6 |
| Type III | 7–8 |

swallowing. Dysphagia is usually to solids and a report of dysphagia to both solids and liquids should raise suspension for a motility disorder such as achalasia. Patients' localisation of symptom to cervical region occurs in up to one third of those with distal esophageal stricture and does not rule out distal esophageal origin. A sub-sternal complaint on the other hand usually implicates esophageal location. Other symptoms associated with this condition may include chest pain, heartburn, regurgitation, weight loss, or globus [11]. A history of typical heartburn symptoms is present in greater than 75% of patients with peptic strictures. However, some describe reduction in heartburn symptoms as structuring becomes more severe.

*Diagnosis*

Endoscopy and barium swallow are complementary studies in patients with dysphagia and suspected peptic strictures. Barium esophagram may provide details about the location, diameter and length of the peptic stricture. However, unless a motility disorder is suspected the initial diagnostic testing in those with suspected peptic stricture is endoscopy which provides both the diagnosis and treatment by dilation. The endoscopic appearance of a peptic stricture is usually a smooth stenosis with or without accompanying inflammation (Fig. 2). Patients with high suspicion for a motility disorder such as achalasia may initially benefit from a barium swallow. Barium swallow is also recommended in patients where a complex stricture is suspected, such as patients with history of radiation therapy or caustic ingestion.

*Management*

The goal of therapy is to resolve dysphagia symptoms and reduce frequency of stricture and recurrence. The main stay of treatment for peptic strictures is endoscopy with esophageal dilation accompanied with acid suppressive therapy with PPI's. Two methods of esophageal dilation include: balloon and mechanical (push-type or Bougie) dilators. Function of dilator is to split or circumferentially stretch the stricture. Balloon dilators exert radial force over entire length of the stricture, while mechanical dilators exert longitudinal and radial force, dilating from proximal to distal oesophagus [14,15]. Since balloon dilators apply force at one general area, in theory it is thought to have less shear stress. Although the mechanism of accomplishing dilation differs between the methods, there is no distinct advantage between the two unless it is desired to avoid longitudinal forces, for example in tracheoesophageal voice prosthesis and epidermolysis bullosa [16–19].

**Table 4**
Clinical presentation of peptic stricture.

| |
|---|
| Dysphagia |
| Odynophagia |
| Heartburn |
| Regurgitation |
| Globus |
| Chest pain |

Mechanical dilators can either be passed freely into the oesophagus or introduced through a guide wire. Maloney dilators are the most common dilators used without a guide wire (Fig. 4a). With a tapered tip, the dilator traditionally was filled with mercury. Due to leakage concerns, the element was replaced with tungsten filling. Dilators requiring guide wire provide reassurance (sometimes false reassurance) about the localisation into the oesophagus with Savary-Gilliard being the most commonly used (Fig. 4b). Savary-Gilliard dilators are plastic with a tapered tip, made in various sizes. Advantages to the mechanical dilators are their lower cost and their ability to be reused [20,21].

Balloon dilators also come in two forms: through-the-scope (TTS) and over-the-guide wire (OTW) (Fig. 5). The goal of TTS dilator is to position the balloon in centre at narrowest portion of stricture. After direct visualisation or under fluoro, the balloon is inflated with water (or radio-opaque material for fluoro) to stretch the stricture [22]. Initially balloon dilators were available in two mm increments, which made them unfavourable compared to gradual dilation seen by mechanical dilators. Recent TTS balloons are built to expand 1.5 mm increments at three different diameters, all without replacing the balloons. OTW is useful for narrow lumens or long structures, causing difficulty for an endoscope to pass through. The balloon can thus be positioned between the stricture with the aid of a guide wire.

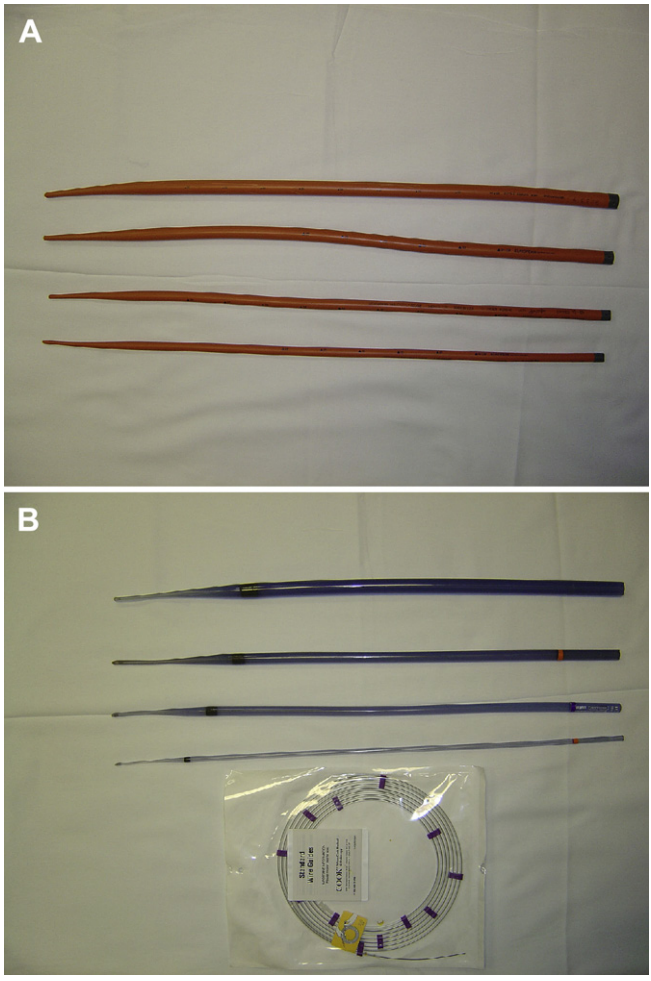


**Fig. 4.** (A) Maloney and (B) Savoury Miller dilators. The latter uses guide wire while the former is a blinded dilation.

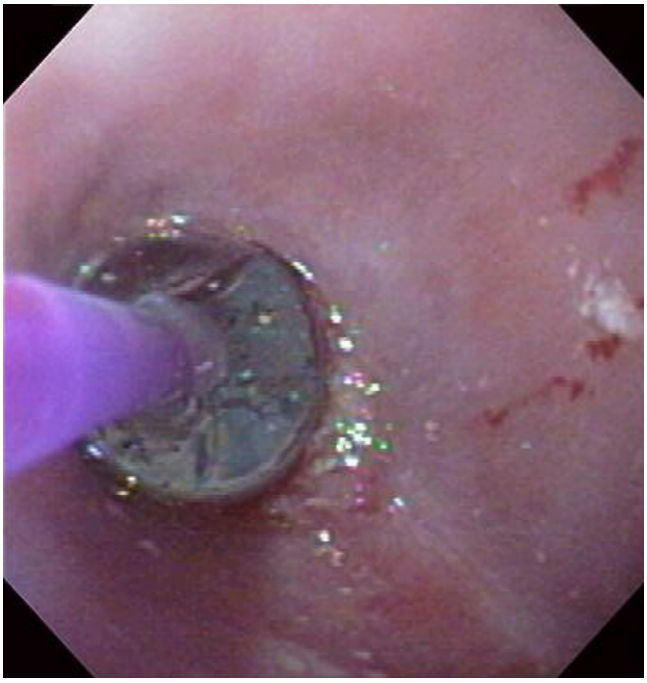

**Fig. 5.** Through-the-scope (TTS) balloon dilators.

Since peptic strictures are more commonly simple, and thus easy to traverse with endoscope, guide wire or balloon dilators are often unnecessary [23]. In complex strictures, such as caused by hiatal hernias or caustic ingestion, the lumen appears tortuous and narrow. Thus complex strictures require use of a guide wire mechanical dilator or balloon, and often under fluoroscopy. In motivated patients who experience recurrent dysphagia, self dilation often with Maloney dilators can be effective [24]. Choosing dilator size depends on stricture diameter. In mechanical and balloon dilators, the target size is approximately the same width as the stricture. This can be identified during initial endoscopy prior to therapeutic dilation. For example a stricture of five to nine mm diameter will require a 12 mm balloon dilator [25]. The general consensus on frequency of dilation per session follows 'the rule of threes'. In a single session no more then three progressive dilations should occur, nor should increments increase by more than two mm (six french). More stringent rules apply to very narrow or long strictures. By applying the rule of threes patients may be protected from adverse effects, such as esophageal perforation [5].

Esophageal dilation may relieve dysphagia with an initial response rate of greater than 80%. However, up to 30% of patients may require repeat dilation within one year. Factors predicting the need for recurrent dilation are poorly defined but include continued exposure to gastroduodenal contents from either severe disease or poor compliance with acid suppressive therapy and strictures that are difficult to dilate in the first dilation session. Esophageal perforation is the most clinically significant complication of endoscopic dilation. At a rate of 0.1–0.4%, the incidence is less for simple strictures. Mechanical and balloon dilators appear to have the same rate of perforation. Other less clinically significant complications include mild bleeding from stricture dilation and bacterial endocarditis in high-risk patients improperly prophylaxed [16–18,24,26–28].

Treatment of peptic stricture with acid suppressive therapy reduces the need for repeat dilation by decreasing the esophageal mucosal exposure to the offending gastroduodenal agents. Healing oesophagitis is vital for strictures to degenerate. When initially studied with $H_2$ blockers, reports suggested improvement in patient symptoms, but the need for re-dilation, and thus complete regression, did not

change compared to placebo [29–31]. Since the advent and use of PPI's, incidence of peptic ulcers has decreased in parallel. Marks et al [32] conducted the first randomised controlled study evaluating the effects of medical acid suppression and decrease in need for dilation. They compared omeprazole vs. ranitidine 150 mg BID (or famotidine 20 mg po BID) in 32 patients with erosive oesophagitis and strictures. After six months patients taking Omeprazole demonstrated higher rate of esophageal healing, improved dysphagia, and fewer dilations [32]. Additionally, in a large randomised, double-blind study by Smith et al [33], 366 patients with peptic strictures were studied assessing the efficacy of omeprazole (20 mg po daily) and ranitidine (150 mg po BID) after one year. As compared to those on H2RA, patients in the PPI treated arm had less need for repeat dilation (30% vs. 46%), less frequency of strictures (41% vs. 60%, $p < 0.01$) and severe oesophagitis [33]. In general, results from randomised and observations studies confirm the higher efficacy of PPIs over $H_2$ blockers in symptoms and frequency of dilations. Even with concomitant PPI use, symptom recurrence in peptic stricture may be as high as 30–40% [17,32,34,35]. Patients with complex strictures, constant heartburn, or nonacid-related strictures had higher risks of recurrence [36]. In the setting of persistent dysphagia, the last dilator size can be used as the starting size [22] and frequent scheduled sessions may be necessary.

Intralesional steroid injection is recommended by some in managing refractory peptic strictures. With its known anti-inflammatory effects, and characteristic reduction in collagen and ultimately scar formation, it has shown to diminish stricture recurrence after initial dilation [5]. Its use is advocated in those undergoing frequent dilations. An added advantage of intralesional steroid may be reduction on the time interval between dilations [37]. In a small RCT of 21 patients with benign esophageal stricture, patients receiving eight mg triamcinolone acetate injections within each quadrant of the muscle had lower frequency of dilations and a significant increase in time between additional dilations. Typically 40 mg/mL corticosteroid diluted with sterile saline in 1:1 ratio is injected into all four quadrants of the stricture [38,39]. In patients with complex or multiple strictures refractory to standard management, surgical resection transgastrically with endoscope can be considered [40].

Finally, with the advent of removable plastic stents, esophageal stent are now being advocated for more benign strictures [41]. In the past, uncovered and partially covered stents have not played a significant role in benign esophageal diseases because of their tendency to rapidly embed themselves in the esophageal wall, making removal difficult and dangerous. Left long term, these stents may erode, occlude, fistulize, or cause other severe problems. However, with the introduction of a fully coated, removable plastic stent (Fig. 6) (Polyflex, Boston Scientific), a host of new applications is being attempted, with varying success. With moderate reported long term success rates these stents suffer from migration as the main complication.

A possible therapeutic algorithm of peptic stricture is summarised in Fig. 7.

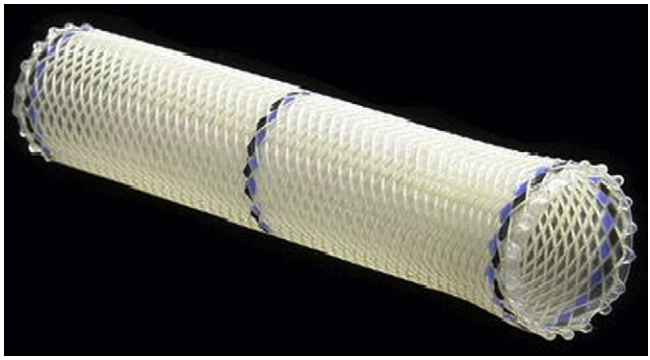

**Fig. 6.** Self-expanding Polyflex stents come in three luminal diameters of 16, 18, and 21 mm with proximal flanges of 20, 23, and 25 mm, respectively. Lengths of nine, 12, and 15 cm are available.

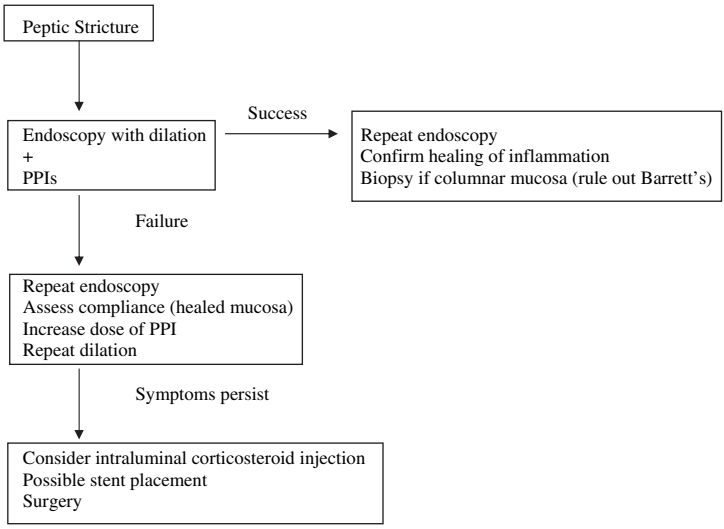


**Fig. 7.** Algorithm for approaching patients with esophageal stricture.

## Barrett's oesophagus

### *Epidemiology*

Esophageal mucosa may undergo metaplastic change into Barrett's epithelium after chronic exposure to acid reflux (Fig. 8). An estimated ten percent of patients with oesophagitis will develop Barrett's oesophagus [42]. It is estimated that 0.9–4.5% of the US population has a diagnosed of Barrett's [43–45] and more commonly encountered among older adults (mean age 55 years) who may be Caucasians or Hispanics. Barrett's is less commonly identified in blacks and Asians. In addition, more males are found diagnosed than females, 2:1. Risk factors to intestinal metaplasia include: advanced age, males, Caucasians, reflux symptoms, and obesity [46–48].

### *Pathophysiology*

Metaplasia is the process of transformation of one fully differentiated cell type into another. Change can occur after prolonged stress or abnormal stimulation. In Barrett's oesophagus, chronic acid reflux (pH $<$ four) induces stress to the underlying squamous cell, injuring the mature squamous cell. This promotes repair and differentiation into immature proliferating cells, triggering columnar metaplasia with intestinal differentiation [49–51]. Many propose metaplastic cells function favourably against chronic reflux by acting more resistant to the injury, compared to its squamous counterpart [52].

In addition to persistent acid injury, exposure to nitric oxide produced from dietary nitrates ($NO_3$) found in green, leafy vegetables, has been associated with chronic inflammation and metaplasia. The cycle of ingested nitrate consists of small intestine absorption, later excreted unchanged into the urine. One quarter of that ingested concentrates within salivary glands, later converted into nitrite ($NO_2$) after bacteria exposure. As nitrite is exposed to gastric acid, the final conversion leads to nitric oxide (NO), a genotoxic and potentially carcinogenic substance [53]. An alternative hypothesis suggests that some cells coexpress squamous and columnar cytokeratin, thus cells can transform from one type to the other in times of stress. Another group suggested Barrett's oesophagus may arise from stem cells that switch to differentiate into columnar cells, rather than squamous, secondary to chronic reflux. These multipotent stem cells inhabit the interpapillary basal layer. While some propose columnar cells originally differentiated as cardiac glands. After exposure to the esophageal lumen, they convert and

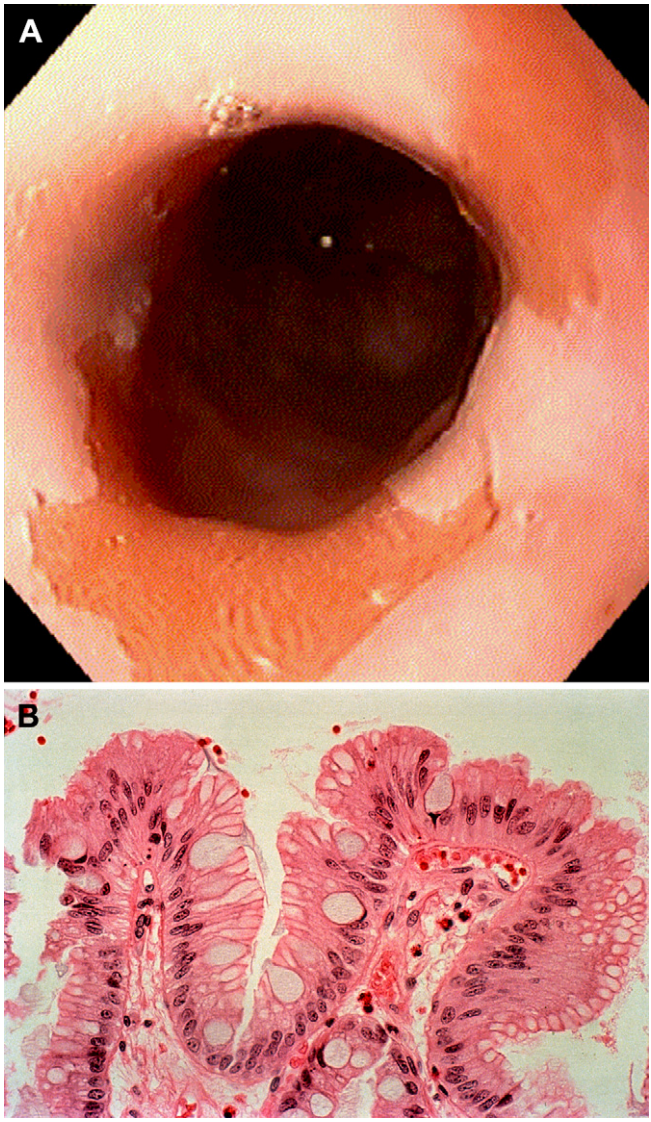


**Fig. 8.** (A) Endoscopic findings associated with Barrett's oesophagus. The white appearing squamous lining of esophageal mucosa is replaced with salmon-pink mucosa characteristic of Barrett's epithelium. Only biopsies can confirm the diagnosis of Barrett's epithelium. (B) Biopsy confirmation of the suspected epithelium above. Note the classic findings of intestinal metaplasia (IM) with goblet cells diagnostic of Barrett's metaplasia.

clonally expand. The developmental process of columnar metaplasia is currently under active research [54–58]. However, most agree that it is the chronic exposure to gastroduodenal contents in GERD which is the underlying pathophysiologic mechanism in Barrett's oesophagus.

*Diagnosis*

Barrett's oesophagus is a histological diagnosis, with characteristic features on endoscopy (Fig. 8). In healthy individuals, the oesophagus is lined by squamous epithelial cells and meets gastric columnar cells at the gastroesophageal junction. In the United States this junction is defined at the proximal end

of the gastric folds, while other countries like Japan define it at the distal end of the lower esophageal palisade vessels [59,60]. As esophageal lining is exposed to chronic acid exposure, 10–15% of people undergo metaplastic transformation resembling intestinal lining. On microscopy mucosa is characterised by columnar cells with presence of goblet cells, an important diagnostic criteria. On endoscopy the once healthy squamous epithelium portrayed as pale, glossy mucousa, is now replaced by red/salmon velvety mucosa (Fig. 8) [42,60].

As individuals develop Barrett's the squamous-columnar junction gradually moves proximally away from the gastroesophageal junction. Distances $>$ three cm from each junctions was termed 'long-segment' while those less were termed 'short-segment'; although the distinction is no longer clinically relevant [59,60]. New imaging techniques such as narrow band imaging (NBI) and chromoendoscopy have allowed endoscopists to better characterise subtle premalignant lesions in the oesophagus. Additionally, confocal laser microscopy provides information at the cellular level during ongoing endoscopy. Initial studies with the new endoscopic modalities are promising but they are still in the research arena and not widely employed in clinical practise.

*Treatment*

Since it is the chronic exposure to acid reflux which is believed to be the contributing factor in Barrett's development, it is not unusual that the main stay of therapy is the use of anti-reflux medications. PPIs are effective in symptom control and healing of oesophagitis in patients with Barrett's oesophagus. However, there are no prospective studies suggesting that PPIs prevent the feared complications from Barrett's oesophagus, namely adenocarcinoma. However, some retrospective observational studies do suggest a possible benefit to PPIs in this regard [61,62]. Multiple endoscopic techniques have been developed aimed at ablating the Barrett's mucosa thereby hoping to decrease the risk of neoplasia. This field is evolving and the latest short term study using radiofrequency ablation is promising but needs long term follow up to ensure complete ablation of at risk mucosa.

Antireflux surgery is also considered an option to manage patients with BE. The disease itself however is not an indication for surgery; only those with symptoms of chronic reflux and non-responsive to proton pump inhibitors are considered for surgical intervention. In a multi-centre European study following 554 patients (60 with BE) randomly designated to laparascopic surgery or esomeprazole 20–40 mg po daily, after three years no significant difference was seen between the two in symptoms and quality of life [63].

*Screening*

Patients with Barrett's oesophagus typically report chronic GERD symptoms. Given association of Barrett's oesophagus with esophageal adenocarcinoma it is rational to consider endoscopic screening in patients with chronic acid reflux. However, this is controversial, since roughly 40% of those with esophageal adenocarcinoma report no prior symptoms of reflux. Knowing that less than five percent of patients diagnosed with adenocarcinoma had known Barrett's, and recognising many with Barrett's denied symptoms prior to diagnosis. According to the American College of Gastroenterology Practise Guidelines published in 2008 [64], 'Screening for Barrett's oesophagus remains controversial because of the lack of documented impact on mortality from esophageal adenocarcinoma'. They suggest that the use of screening in selective population at higher risk remains to be established and should be individualised. What is agreed upon is the need for endoscopy in patients presenting with a complicated disease. These include signs or symptoms of anorexia, weight loss, dysphagia, odynophagia, bleeding, or systemic illness [65].

## Endoscopic surveillance

Barrett's oesophagus is strongly correlated with developing esophageal adenocarcinoma (EAC). However, it is reassuring that progression to EAC is not very common, estimating to 0.5% or less annually [66]. The risk of malignancy increases as epithelial cells become more disordered. Those with long segment Barrett's have a 2–15 times higher risk of cancer than short-segment BE. Dysplasia is

characterised by loss of uniformity within individual cells and architecture. Those with low-grade dysplasia inherit a 0.6%–1.6% risk while those with high-risk have a 6.6% incidence annually. Case-control and cohort studies have shown significant benefit with surveillance [67–73] (Table 5); however, to date there are no randomised controlled studies evaluating surveillance and reduction of mortality. None-the-less the ACG guidelines [64] suggests that there is enough evidence indicating enhanced survival in patients undergoing surveillance. Surveillance is practised by the vast majority of endoscopist in the US and is dependent on the dysplasia grade at initial endoscopy (Table 6).

Surveillance typically involves target biopsy of suspicious area coupled with four-quadrant biopsies every two cm near the area of metaplasia. Focused biopsies increase yield of both low-grade (by 17%) and high-grade (by three percent) compared with random esophageal biopsies [74]. After establishing the baseline status of the metaplastic mucosa in regards to presence of dysplasia, patients are scheduled to return for surveillance (Table 6). Those without dysplasia on two endoscopic exams one year apart can return every three years to observe for dysplastic changes. Once esophageal cells exhibit hyperchromatic nuclei with mitotic figures (low-grade dysplasia), annual surveillance is highly recommended [74].

Management of patients with high grade dyplasia (HGD) is controversial. Since malignancy is on the front-line to many patients with high-grade dysplasia, multiple approaches are developed to eradicate the disease. These methods include esophagectomy, endoscopic mucosal resection (EMR), endoscopic ablation, and photodynamic therapy. The standard treatment in high-grade dysplasia is esophaectomy since adenocarcinoma may be present in as high as 40% of these patients. Surgery should not be taken lightly given a morbidity and mortality of three to five percent and 20–50%, respectively. After surgery BE and early neoplasia can still be detected in some patients, thus endoscopy is still considered necessary in this group. Compared to esophagectomy endoscopic therapy has the advantage of lower adverse effects and being an outpatient procedure. However, lack of long term outcome data with endoscopic therapy is the most noted limitation of this option.

In patients who have focal endoscopic lesions with HGD or adenocarcinoma limited to the mucosa or superior 1/3 of the submucosa, dysplastic tissue can be excised by EMR. The goal of excision is to remove dysplastic tissue that could potentially transform and invade beyond the basement membrane. Once tissue is deeply invaded the risk of metastasis is 47%, limiting EMR effectiveness. Excision is considered safe and allows samples for staging. EMR is associated with 30–40% risk of esophageal stenosis and recurrence of neoplasia may be found in up to 20% of cases [75,76].

*Endoscopic ablation* applies the concept that tissue injury during a dysplastic process can interrupt the steps leading to neoplasia. An example of this is *photodynamic therapy (PDT)*, where a directed photosensitiser accumulates within the tissue, free oxygen radicals form leading to ischaemic necrosis of the tissue. In a randomised study, after three months of PDT coupled with omeprazole was superior to omeprazole alone in the eradication of high-grade dysplasia (77% vs. 39%, $p = 0.004$) and in recurrence of neoplasia (15% vs. 29%, $p = 0.027$) [77,78]. PDT has recently been replaced with radio-frequency ablation which results in much less post ablative mucosal structuring. In a multicenter, sham-controlled trial, 127 patients with dysplastic Barrett's were randomised to either receive *radio-frequency ablation therapy* or sham procedure (control). After 12 months, 90.5% of low-grade dysplasia patients underwent complete eradication after endoscopic ablation compared to 22.7% in the control ($p < 0.001$). Among the high-grade dysplasia, 81.0% underwent complete eradication compared to

**Table 5**
Retrospective Barrett's surveillance studies on patient survival.

| Author | Surveillance (n) | No Surveillance ($n$) | $p$ |
|---|---|---|---|
| Streitz et al [67] | 62% (19) | 20% (58) | 0.007 |
| Peters et al [68] | 90% (17) | 20% (35) | 0.09 |
| Van Sandick et al [69] | 86% (16) | 43% (54) | 0.003 |
| Incarbone et al [70] | 100% (12) | 25% (85) | 0.01 |
| Ferguson et al [71] | 84% (12) | 19% (68) | 0.001 |
| Corley et al [72] | 73% (15) | 13% (8) | 0.001 |
| Foundtoulakis et al [73] | 80% (17) | 31% (74) | 0.008 |

**Table 6**
Dysplasia grade and surveillance interval.

| Dysplasia | Documentation | Follow up |
|---|---|---|
| None | confirmed with two EGD's with biopsy | EGD with biopsies q 3yrs within one yr |
| LGD | biopsy within six months<br>Expert pathologist confirmation | EGD q 1yr until no dysplasia |
| HGD | mucosal irregularity<br>Repeat EGD in three months<br>or expert pathologist confirmation | EMR q 3month surveillance or surgery<br><br>ablation (individualise) |

19.0% in the control. In addition, the endoscopic ablation group experienced less dysplastic progression (3.6% vs. 16.3%, $p = 0.03$) and less neoplastic progression (1.2% vs. 9.3%, $p = 0.045$) [79].

Thus, the choice of esophagectomy, EMR or ablative therapy in patients with HGD depends of patients' clinical presentation, choice and other co-morbid conditions; thus, surveillance in this group needs to be individualised (Table 6).

## Extraesophageal reflux syndromes

Extraesophageal symptoms of GERD may be present when reflux of gastric contents into the oesophagus results in symptoms other than the typical heartburn symptoms (Table 7) [80]. The most common of these include chronic cough, asthma and laryngitis or also known as laryngopharyngeal reflux and will be discussed here.

### *Epidemiology*

The exact prevalence of the various extraesophageal manifestations is unknown. Estimates vary due to differences in definitions and methods used to establish the diagnosis. Classic reflux symptoms are absent in 40–60% of asthmatics, in 57–94% of patients with ENT complaints, and in 43–75% of patients with chronic cough. Up to 78% of patients with chronic sore throat have GERD. four to ten percent of patients who present to otolaryngologists do so because of complaints related to GERD. Thus, GERD should be included in the differential diagnosis of patients presenting with extraesophageal symptoms, especially when alternative diagnoses are excluded [81,82].

In a case population study of 101,366 patients with erosive oesophagitis or strictures discharged from a Veterna Affairs hospital between 1981 and 1994, erosive oesophagitis and stricure were associated with laryngitis (OR 2.01, CI 1.53–2.63), asthma (OR 1.51, CI 1.43–1.59), pneumonia (OR 1.15, CI 1.12–1.18) [83]. A recent systematic review of studies assessing the prevalence of GERD in patients with asthma concluded that there is a significant association between GERD and asthma [84] This study evaluated 28 publications and reported pooled odds ratio of 5.5 (95%CI 1.9–15.8) for studies reporting the prevalence of GERD symptoms in asthmatics and 2.3 (95%CI 1.8–2.8) for those studies measuring the prevalence of asthma in GERD.

### *Pathophysiology*

Two mechanisms are proposed to explain extraesophageal symptoms of GERD - microaspiration (reflux) and vagal stimulation (reflex) [80]. Microaspiration involves the entrance of gastroduodenal contents into the larynx or airways due to a failure of normal protective mechanisms. These chemicals can include acid, pepsin, bile, and pancreatic enzymes. Chronic irritation by these chemicals causes laryngitis, chronic cough, or asthma. In the second mechanism, the presence of acid within the distal oesophagus causes stimulation of acid-sensitive receptors innervated by the vagus nerve. Because the oesophagus and bronchial tree share innervation by the vagal nerve, this stimulation may result in non-cardiac chest pain, cough or asthma.

**Table 7**
Extraesophageal Manifestations of GERD.

| |
|---|
| ENT |
| Laryngitis |
| Sinusitis |
| Otitis media |
| Laryngeal ulcers |
| Granuloma |
| Polyps/vocal cord nodules |
| Laryngeal cancer |
| Chronic sore throat |
| Globus pharyngeus |
| Roenke's oedema |
| Subglottic stenosis |
| Dysphonia |
| Dysgeusia |
| Pulmonary |
| Asthma |
| Chronic cough |
| Pneumonia |
| Bronchitis |
| Interstitial fibrosis |
| Cardiac |
| Chest pain |
| Sinus arrhythmia |
| Other |
| Dental erosions |
| Halitosis |
| Sandifer's syndrome |

*Clinical features*

*Chronic cough*

The American College of Chest Physicians suggest that GERD-related chronic cough typically occurs during the day, in the upright position, and is nonproductive. GERD should be suspected in patients with cough whose symptoms have been chronic, not smokers, not on any cough-inducing medications (such as ACE inhibitors), with normal chest X-ray, and in those in whom there is no evidence of asthma or postnasal drip [85]. Presence of regurgitation especially when in the supine period or worsening symptoms after meals may be useful clues.

*Asthma*

Patients with asthma whose symptoms are worse after meals, or those who do not respond to traditional asthma medications should be suspected of having GERD. Additionally, patients who experience heartburn and regurgitation before the onset of asthma symptoms may have GERD as a potential cause for worsening asthma symptoms. Patients often present with adult onset symptoms that are only partially responsive to aggressive asthma therapies. Most will report presence of heartburn and occasionally regurgitation. Aggressive therapy of both GERD and asthma are indicated in this group of patients in order to provide symptomatic relief.

*Laryngopharyngeal reflux*

Delahunty was the first to suggest that proliferative changes in the laryngeal epithelium may be due to acid reflux in 1972 [86]. Symptoms may include hoarseness, throat clearing, cough, sore or burning throat, dysphagia, and globus sensation. Chronic laryngitis and difficult-to-treat sore throat are associated with acid reflux in as many as 60% of patients [82]. Most patients with laryngeal findings from GERD will have responded to aggressive therapy with PPI's. However, the current dilemma in this field is what the likelihood of association between GERD and laryngeal symptoms may be in those unresponsive to PPI therapy. Most recent data suggest that GERD is likely not the cause of persistent

symptoms in this group. The issue of 'silent' reflux causing laryngeal irritation or symptoms in this group is currently controversial. Failure to diagnose early symptoms of laryngopharyngeal reflux may result in progression to the more serious complications of contact ulcers, granuloma, subglottic stenosis and lower airway disease [87]. However, prospective controlled data in this area are lacking.

*Diagnosis*

Given the nonspecific nature of the extraesophageal symptoms and the poor sensitivity and specificity of diagnostic tests such as pH monitoring, laryngoscopy, or endoscopy for establishing a GERD aetiology, empiric therapy with PPIs has become common practise. Testing is usually indicated in patients with persistent symptoms despite therapy, those with warning signs (ie, dysphagia, weight loss, bleeding), prior to fundoplication, or in those patients with long-standing GERD in order to rule out Barrett's oesophagus. Common tests include endoscopy, and ambulatory proloned pH monitoring.

*Endoscopy*

Oesophagitis is uncommonly seen in extraesophageal reflux patients. In contrast to typical GERD patients, oesophagitis is found in only 10–30% of this group of patients. Therefore, it is neither a sensitive nor specific tool for diagnosing extraesophageal reflux. However, if a patient has warning signs or is considering surgery, endoscopy would be indicated. In most patients presenting with continued symptoms endoscopy is performed not to rule in GERD but to rule out other upper GI structural causes for patients' symptoms.

*Laryngoscopy*

Patients with laryngeal symptoms are often referred to ear, nose and throat (ENT) physicians for laryngoscopy. Findings on laryngoscopy do not necessarily implicate gastric contents as the causative irritants. The initial endoscopic lesions associated with GERD were erosions and lesions such as vocal cord ulcerations. However, erythema and oedema are now considered by many in the ENT community to suggest GERD [88]. The laryngeal findings in reflux laryngitis may include erythematous arytaenoids and a mottled appearance of the interarytenoid region (Fig. 9). Additionally, patients with GERD may exhibit such abnormalities as erythema and oedema of the posterior larynx, vocal cord polyps granuloma, subglottic stenosis, ulcerations, vocal cord nodules, leukoplakia and cancer (Table 7). These findings are not specific for GERD; other causes of these findings may include smoking, alcohol, postnasal drip, viral illness, voice overuse, or environmental allergens. Recent studies suggest that laryngeal abnormalities involving the vocal cords and medial arytaenoid walls may be more specific for GERD [82]. Laryngoscopy in patients with throat symptoms is not to rule in GERD but to rule out cancer and causes other than GERD. The suspicion of GERD in this group is not based on specific laryngeal findings but more on lack of more serious condition and uncertainty for role of other factors.

*pH monitoring*

Twenty-four hour pH monitoring has been used by some to diagnose reflux, but its utility is hampered by poor sensitivity (70–80%) and frequent false negatives (20–50%). Studies are conflicting as to the usefulness of pH monitoring in diagnosing extraesophageal reflux. This may be due to several factors, including variable probe position, the definition of abnormal reflux, day-to-day variability of reflux events, and the intermittent nature of reflux events. The presence of acid in the upper oesophagus and hypopharynx may be seen in up to ten percent of asymptomatic volunteers. Therefore, 24-hour pH monitoring can neither definitively diagnose nor exclude extraesophageal reflux as the cause of patients' symptoms. Wireless pH monitoring may increase the sensitivity of pH monitoring by reducing the day-to-day variability and prolonged monitoring. However, since most patients in whom this test is utilised are symptomatic despite therapy the unresolved question is to perform pH monitoring on or off PPI therapy. Recent data suggest on therapy testing with impedance monitoring may be the single best test [89]. However, this point is controversial and some suggest off therapy testing as the initial diagnostic approach [90]. Impedance/pH monitoring increases the sensitivity of the traditional ambulatory pH testing by detecting nonacid liquid (decreased impedance) or gas reflux (increased impedance). However, the clinical relevance of abnormal impedance findings in patients unresponsive

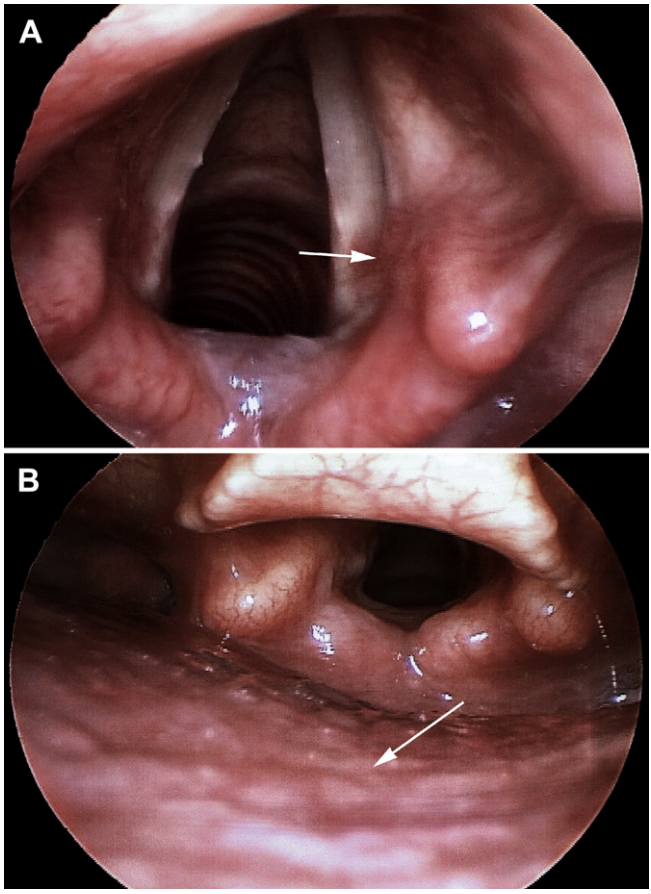


**Fig. 9.** Abnormal Larynx. (A) Arytaenoid Medial Wall Erythema; (B) Posterior Pharyngeal Wall Cobblestoning.

to PPI therapy is uncertain. The most recent AGA guidelines suggest empiric therapy followed by pH monitoring for those unresponsive [91].

*Treatment*

Given the nonspecific nature of the extraesophageal symptoms and the poor sensitivity and specificity of diagnostic tests such as pH monitoring, laryngoscopy, or endoscopy for establishing a GERD aetiology, empiric therapy with PPIs has become common practise (Fig. 9). Most therapeutic trials of these syndromes have used twice daily dosing of PPIs for treatment periods of two to four months. The rationale for this unapproved dosing and indication comes from pH monitoring data demonstrating that the likelihood of normalising esophageal acid exposure with twice daily PPIs in this group of patients is 93–99% [92]; the logic then being that lesser dosing does not exclude the possibility of a poor response because of inadequate acid suppression. Having said that, there are no controlled studies investigating the optimal dosage or duration of PPI therapy in extraesophageal syndromes. The only supportive data for twice daily PPI dosing are uncontrolled open-label studies of suspected reflux laryngitis or asthma [93]. Patients are notoriously difficult to treat and may not respond to traditional therapy, largely because of the over-diagnosis of extraesophageal reflux.

The fact that placebo controlled trials in patients with extraesophageal symptoms show a limited or no benefit from PPI's compared to placebo [94,95], is probably due to several reasons. (1) An overlap in extraesophageal symptoms and signs between GERD and other causes which lead to over-diagnosis of GERD. (2) Multi-factorial nature of the presenting extraesophageal symptoms, with GERD as only one of the causes and (3) the possibility of weakly acidic or non-acid reflux as the aetiology for persistent symptoms in some patients unresponsive to PPI therapy.

Step-down therapy is recommended for patients with suspected extraesophageal reflux (Fig. 10). Initial therapy with BID PPI dosing should be limited with an endpoint of titration to the lowest dose of acid suppression with controlled symptoms or to no acid suppression if symptoms do not improve after two-months of therapy. pH/impedance monitoring on therapy could be considered to help identify that small subgroup that continues to have abnormal esophageal acid or nonacid exposure. However, in most non-responders search for other potential etiologies for patients' symptoms should be explored. Testing off therapy may provide information about the baseline esophageal reflux exposure in this group but does not explain the lack of response to PPI therapy.

Surgery does not seem to benefit patients who do not respond to PPI therapy. Surgical therapy would not be helpful in patients who do not demonstrate LES incompetence or large-volume liquid reflux. Allen and Anvari [96] studied surgical treatment of GERD in treating chronic cough. In their 42 patients, 51% had resolution of cough and 31% had improvement. They later determined that response to PPI predicted surgical outcome. Similarly, in a concurrent controlled study of non-responders to PPI's, Swoger et al [97] established that surgical fundoplication is of limited clinical utility after one year

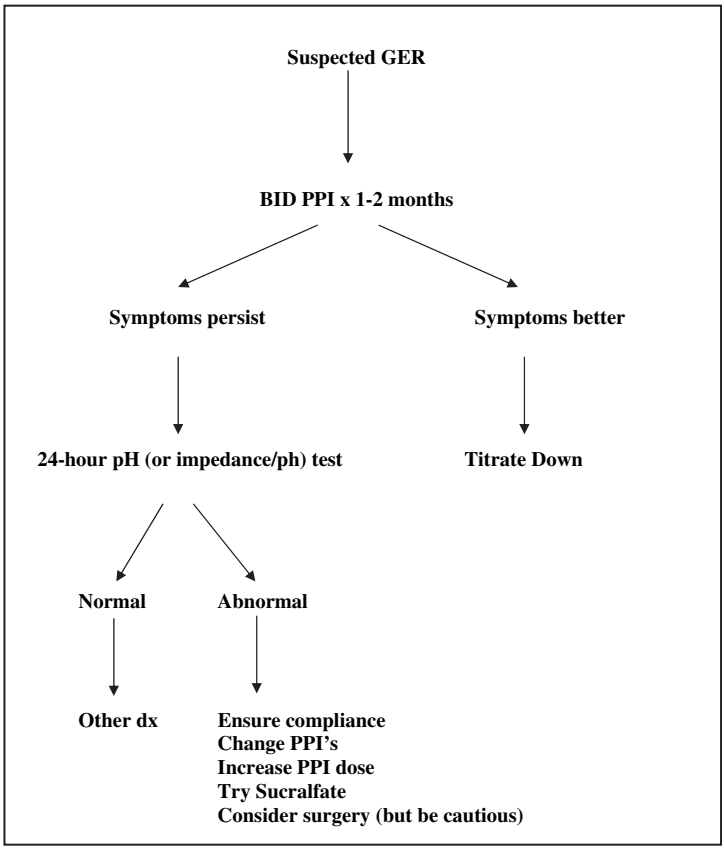


**Fig. 10.** Treatment Algorithm for suspected GER-related extraesophageal symptoms.

follow up of symptoms and objective parameters. A recent study in 17 patients with positive symptom index on impedance monitoring found that surgical fundoplication was successful in 94% of cases [98]. However, the lack of a control group and multiple study biases limit the conclusions from this study. Thus, at this point, surgical fundoplication cannot be recommended to those unresponsive to PPI therapy unless symptoms such as regurgitation are accompanied by endoscopic findings of hiatal hernia and baseline abnormal acid reflux parameters.

**Practice points**

- GERD can be complicated by esophageal stricture, Barrett's oesophagus with accompanying dysplasia or adenocarcinoma.
- Patients with longstanding GERD presenting with dysphagia should undergo endoscopic evaluation to rule out GERD complications.
- Esophageal dilation combined with PPI therapy improves most benign GERD related strictures.
- Most patients with Barrett's oesophagus do not develop dysplasia or cancer.
- Surveillance of patients with Barrett's oesophagus should be tailored to patients and the dysplasia status of the epithelium.
- Radiofrequency ablation of Barrett's epithelium with HGD is a new promising field.
- Patients with suspected extraesophageal reflux symptoms often respond to PPI therapy.
- Patients with suspected extraesophageal symptoms who do not respond to aggressive PPI therapy most likely do not have GERD as the cause of their persistent symptoms.

**Research agenda**

- Long term efficacy of radiofrequency ablation in patients with Barrett's with high grade or low-grade dysplasia and its ultimate role in Barrett's without dysplasia.
- Role of impedance/pH monitoring in extraesophageal reflux.
- Identifying the subgroup of patients who might respond to surgical fundoplication if previously poorly unresponsive to PPI therapy.

## Conflict of interest statement

None.

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