GERD Outlook: A Gastroenterologist's Perspective

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Abbreviations

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ARMS	Anti-reflux mucosectomy
EART	Endoscopic anti-reflux therapy
GEJ	Gastro-esophageal junction
GERD	Gastroesophageal reflux disease
GERD-HRQL	GERD Health-Related Quality of Life
LARS	Laparoscopic anti-reflux surgery
LESP	Lower esophageal sphincter pressure
PPI	Proton pump inhibitors
TF	Transoral fundoplication

The recent availability and expanding application of many novel diagnostic and treatment modalities have led to a dramatic modernization, both medical and surgical, of the management of patients with gastroesophageal reflux disease (GERD) and its complications and have created a need for multidisciplinary interaction and decision-making that crosses the boundaries of traditional medical or surgical practice. Therefore, there are no gastroenterologists' or surgeons' perspectives, but one, of *precision reflux management* that takes into consideration all aspects of the disease and its manifestations and formulates the best possible approach for each individual patient, that may involve medical, endoscopic, or surgical modalities, alone or in combination (Table 15.1).

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Table 15.1 Ten key questions for precision GERD management

1. Is GERD truly present and validated by endoscopy and/or pH monitoring?
2. Does GERD affect the patient's quality of life?
3. Is there a confounding illness that makes GERD worse?
4. Has pharmacologic therapy been optimized?
5. Is there a sliding hiatal hernia that would require repair?
6. Are GERD complications (i.e., strictures, Barrett's esophagus) present?
7. Are the esophageal structure and function adequate to undertake an endoscopic or surgical intervention?
8. Is the patient treatment-naïve or has failed or inadequately responded to previous therapies?
9. Is there significant obesity present that would be amenable to endoscopic or surgical therapy?
10. Are there extra-esophageal manifestations present, either alone or together with typical GER symptoms?
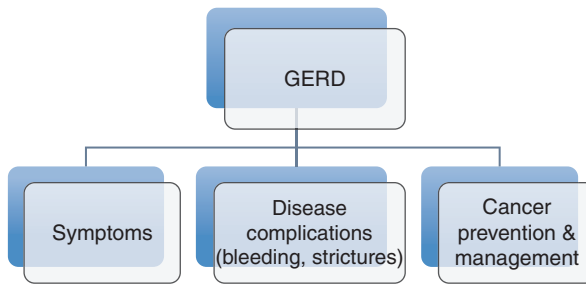
Fig. 15.1 Spectrum of GERD: Clinicians caring for patients with GERD should always consider the symptoms and quality of life (QoL), disease complications (bleeding, strictures, etc.) as well as cancer prevention and management in patients with Barrett's esophagus (BE), dysplasia, and esophageal adenocarcinoma (EAC)

Figure 15.1 highlights the spectrum of GERD seen from the precision reflux management perspective. First and foremost, is the attention to the symptoms, if such symptoms truly reflect abnormal esophageal acid exposure, and to what degree they affect the patient's quality of life, thereby requiring intervention. In the era of increasing recognition of adverse events due to long-term proton pump inhibition (PPI), it is important to establish if such therapy is appropriate and justified [1]. In the patient with refractory GERD, one should examine if pharmacologic management has been optimized and to what degree if there are any confounding illness that would make GERD worse. Although in the modern era of PPI use, disease complications, such as esophageal ulcer bleeding and stricture formation, have become infrequent and are still part of the disease landscape and require expert therapy. Finally, given the rising incidence of esophageal adenocarcinoma, cancer prevention and management of Barrett's esophagus (BE) are essential elements in the initial and long-term management of GERD in all patients but more so in white, obese males [2].
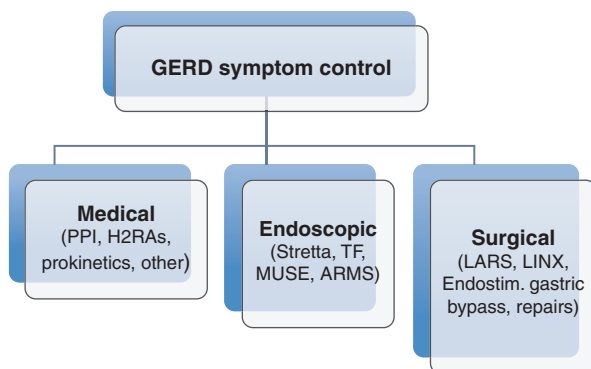
Fig. 15.2 Control of GERD symptoms: Medical (pharmacologic) therapy using proton pump inhibitors (PPI), H2 receptor antagonists (H2RAs), prokinetics, or other agents is cornerstone. For certain, carefully selected patients, endoscopic therapies, such as radiofrequency therapy (Stretta), transoral fundoplication (TF), endoscopic partial fundoplication under ultrasound guidance (MUSE), or anti-reflux mucosectomy (ARMS) may be tried. Laparoscopic options include anti-reflux surgery (LARS), magnetic sphincter implantation (LINX), electrical sphincter stimulation (Endostim), Roux-en-Y bypass for obesity, and hernia repair surgery

Figure 15.2 outlines the various elements of GERD symptom control. Pharmacologic treatment may require therapies beyond PPIs, such as H2 receptor antagonists, prokinetics, or even low-dose tricyclic agents. Although the symptoms of heartburn and acid regurgitation are highly disease specific, they are imperfect and other diagnoses need to be considered. In a patient using PPIs, it is useful to ask what happens if these drugs are transiently discontinued. Under such circumstances, *bona fide* patients with GERD quickly develop heartburn and acid regurgitation (or other more atypical symptoms) while patients with other diagnoses tend to tolerate PPI abstinence for quite some time. The latter group of patients should not be considered as good candidates for invasive procedures but instead be evaluated further to define the underlying reason for their symptoms. Extra-esophageal symptoms, such as noncardiac chest pain, cough, asthma, and hoarseness, are less responsive to any interventions and proof that GERD is their underlying cause and is advised in order to maximize gains.

The best way to validate the diagnosis in a patient with a negative endoscopic examination is ambulatory esophageal pH monitoring that is performed either using a transnasal catheter (impedance/pH) or wirelessly by placing the Bravo pH probe [3]. These tools quantify esophageal acid exposure and are invaluable in establishing the diagnosis of GERD and, further, assessing its magnitude, occurrence in the upright or supine position, and relating acid reflux events to symptoms. If the pH/impedance study is negative, other possibilities, particularly achalasia, esophageal spasm, or gastroparesis, need to be considered. Yet, even if the pH/impedance study is positive, overlap syndromes may occur. For example, in a recent study, pathologic acid reflux was found in 44% of patients with esophageal dysmotility/achalasia and 73% of patients with gastroparesis [4]. Another important question to be addressed

is the presence of regurgitation, or "volume" reflux, particularly while patients are on PPI therapy. Its presence suggests more severe, mostly, supine GERD and also a higher likelihood of underlying hiatal hernia, complicated disease (i.e., Barrett's esophagus), and respiratory manifestations. Regurgitation is a key point in the discussion of pursuing endoscopic and surgical therapies for GERD [5].

Endoscopic anti-reflux therapy (EART) intends to address three key issues: First, the need to eliminate symptoms that are not completely controlled by PPIs; second to eliminate long-term PPI use in those patients who, although well-controlled pharmacologically, are concerned about drug-related adverse events; and third to minimize the need for laparoscopic anti-reflux surgery (LARS) and its complications [6]. Over the past 15 years, these clinical issues have become increasingly prevalent and clinically significant, thereby expanding the potential applicability and clinical value of EART. The *GERD treatment gap* represents the 25–30% of patients with refractory GERD who are not willing to undergo conventional, albeit laparoscopic, fundoplication, mostly because they are afraid of potential long-term side effects, such as difficulty with belching, bloating, and dysphagia [7]. It has also become clear that not all patients with GERD are suitable candidates for such an option and that a careful objective evaluation is needed in order to phenotypically characterize the disease and tailor therapy, aiming at producing the best long-term efficacy and safety.

Currently, there are four EART options available. Radiofrequency therapy of GEJ (Stretta) has the best long-term data [8]. The transoral fundoplication (TF) device creates molding of the GEJ through endoscopic placement of polypropylene suture material; its short-term efficacy and safety have been recently demonstrated in controlled clinical trials. The MUSE™ endoscopic stapling system is a recent technique that creates an endoscopic partial fundoplication under ultrasound guidance, but clinical data is still scant. More recently, the use of conventional endoscopic dissection tools to perform anti-reflux mucosectomy (ARMS) has been reported from Japan.

Several minimally invasive options have entered the realm of surgical GERD management aiming at minimizing the adverse events encountered with laparoscopic anti-reflux surgery, while providing an effective anti-reflux barrier, and they include the magnetic sphincter augmentation (LINX), electrical stimulation of the lower esophageal sphincter (Endostim), gastric bypass surgery in patients with obesity, and, if needed, laparoscopic surgical repairs [9].

Although PPI therapy remains essential in management, the careful assessment of complications, such as strictures or BE, defines the need for other modalities (Fig. 15.3). Esophageal structure is best assessed by endoscopy, first to exclude other conditions (i.e., other forms of esophagitis or cancer), and to carefully define mucosal integrity, ruling out dysplastic Barrett's esophagus that will require attention prior to any endoscopic or surgical therapy for GERD being applied [10]. In order to provide useful information, endoscopy requires attention to the gastroesophageal junction (GEJ) at various levels of air distention, forward and retrograde viewing, and a meticulous detailing of the mucosa (Fig. 15.4). If the distance of the GEJ from the incisors does not vary significantly with insufflation, one can expect
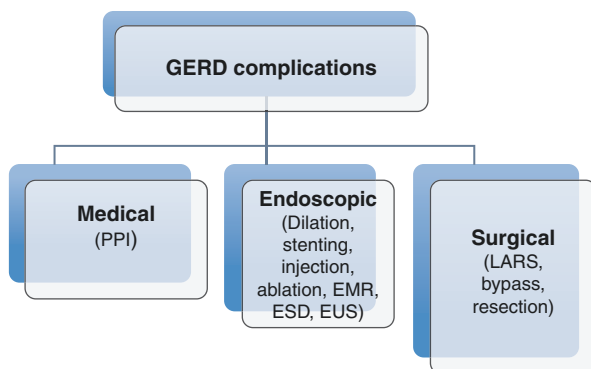
Fig. 15.3 Management of GERD complications. The use of proton pump inhibitors (PPI) remains an adjunctive and important long-term therapy. Endoscopic interventions aim at relieving dysphagia (balloon or wire/bougie dilation, temporary stenting), Barrett's esophagus (BE) ablation and/or endoscopic mucosal resection (EMR), or endoscopic submucosal dissection (ESD). Endoscopic ultrasound (EUS) may be used to clarify the nature of a stricture

Fig. 15.4 Assessment of the gastro-esophageal junction (GEJ). (**a**) Antegrade view revealing a medium-sized sliding hiatal hernia. (**b**) Retroflexed view of the cardia showing the hernia. (**c**) Retroflexed view of the cardia showing changes of a well-positioned Nissen fundoplication

wall fibrosis and esophageal foreshortening. Fluid pooling, stricture, or tissue nodularity imply atony and complicated disease and are expected to be associated with suboptimal endoscopic or surgical outcomes. Retroflexed views of the cardia during endoscopy are essential not only to confirm the type and size of the hernia but also to assess the GEJ using the Hill classification, a grading system that is easy to learn and has been used and validated for over 20 years [11]. The presence, type, and dimensions of a "sliding" hiatal hernia in need of repair and the underlying esophageal structure and function need to be evaluated. Classic "para-esophageal" hernias readily disqualify from endoscopic intervention. The same is true for "mixed" hernias that are typically large enough and fixed to lend themselves to a successful endoscopic repair. On the other hand, properly assessed sliding hernias that are less than 3 cm in length could be amenable to transoral fundoplication (TF). Available evidence thus far has questioned the feasibility and efficacy of the other endoscopic modalities if the hiatal length exceeds 2 cm.
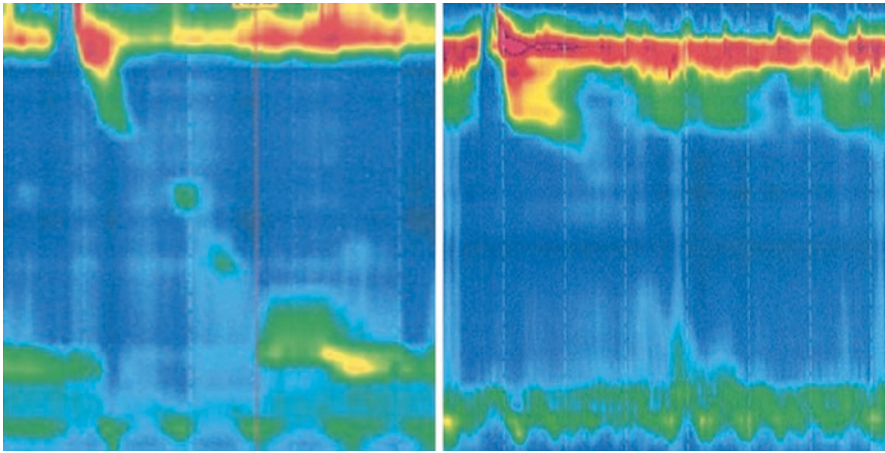
Fig. 15.5 High-resolution esophageal manometry images highlighting ineffective esophageal motility (IEM). (Left panel): Fragmented peristalsis defined as frequent (≥50%) swallows with large (>5 cm) defects in the 20-mmHg isobaric contour; (Right panel): Failed peristalsis with a DCI ≥450 mmHg s cm

Functional assessment mainly aims to exclude achalasia or other forms of severe peristaltic failure that would impede the placement of a magnetic sphincter or a 360° fundoplication and may favor instead a partial 270° (Toupet) fundoplication or a Collis gastroplasty. It is debatable to what degree ineffective esophageal peristalsis (IEM) and other lesser disorders of function detected by high-resolution manometry (HRM) serve as contraindications to surgery or endoscopic management (Fig. 15.5). As a general rule, the creation of a tight anti-reflux barrier may aggravate dysphagia and difficulties with throat clearance and any invasive option needs to be carefully examined and individualized. In general, if a patient with GERD is a candidate for anti-obesity surgery, the performance of Roux-en-Y bypass is the best surgical option. Sleeve gastrectomy is less likely to be associated with complete control of GERD symptoms, but if such symptoms occur postoperatively, radiofrequency therapy of EGJ is feasible and effective [12].

There are very limited data in patients who have previously undergone either endoscopic or surgical therapies for GERD and present with refractory symptoms. Stretta can be performed repeatedly or in a patient post anti-reflux surgery but not after magnetic sphincter implantation, but there is no published data on its efficacy. In a patient presenting with recurrent GERD after anti-reflux surgery, the degree of wrap displacement, if any, plays an essential role in decision-making. If present, there is no role for EART and surgical repair is the only option [13]. Revisional anti-reflux surgery is always more challenging to perform and its outcomes are considered less robust than those of the initial intervention. The use of mesh to close large hiatal defects that contributed to prior failure remains controversial and needs to be individualized. Finally, patients with prior esophageal injury or those with complicated disease, (i.e., long peptic strictures) that are resistant to medical therapy lone or in combination with temporary endoscopic stenting, may require esophagectomy

instead of EART or anti-reflux surgery. The presence of esophageal stricture calls for endoscopic management aiming at excluding malignancy, and expanding and maintaining the luminal diameter of the esophagus, thereby improving dysphagia. Sometimes temporary stenting facilitates long-term management (Fig. 15.6).

The recognition of BE requires further detailed assessment to exclude dysplasia, using high-definition white light endoscopy (HD-WLE), narrow-band imaging (NBI), in vivo confocal microscopy, and Seattle protocol biopsies. Identification and endoscopic resection of mucosal abnormalities are critical in managing dysplastic BE because these areas may harbor esophageal adenocarcinoma (EAC) [14]. Endoscopic eradication therapy (EET), that is, the resection of visible lesions followed by ablation, is now well established as a first-line treatment option in subjects with BE-related dysplasia and mucosal adenocarcinoma (Fig. 15.7) [15, 16]. EET however has raised two concerns. First, is the potential persistence of undetected
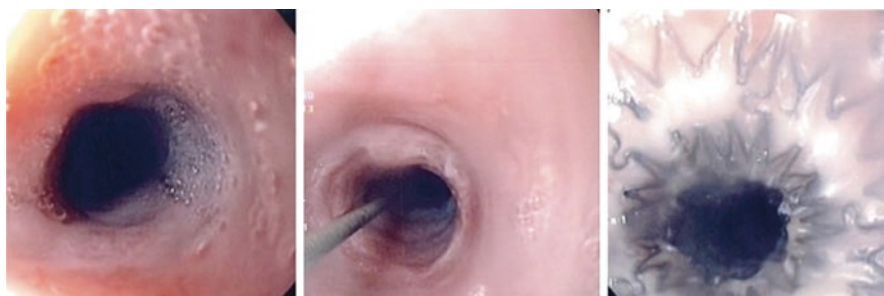
Fig. 15.6 Peptic stricture management. (**a**) Benign appearing mid to distal esophageal stricture that would not allow the passage of the endoscope. (**b**) Wire-based dilation using Savary bougies. (**c**) Endoscopic appearance of a temporary metal stent traversing the stenosis in order to relieve dysphagia
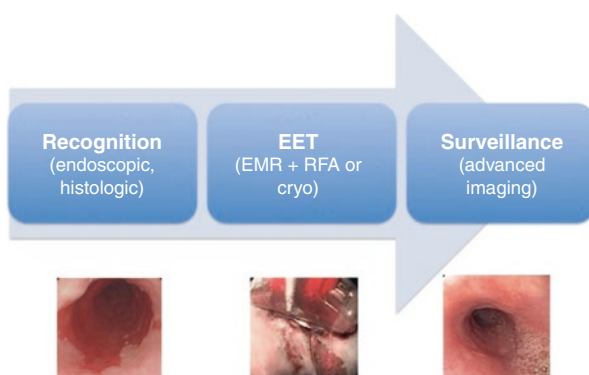
Fig. 15.7 Role of endoscopy in Barrett's esophagus (BE). (**a**) Endoscopy allows recognition and classification of BE and proper histologic diagnosis. (**b**) Endoscopic eradication therapy (EET) ablates the dysplastic mucosa and the surrounding intestinal metaplasia. (**c**) Endoscopic surveillance of the esophagus after ablation usually involves advanced imaging techniques (i.e., volumetric laser endomicroscopy) to detect buried metaplasia or dysplasia

subsquamous BE mucosa (buried BE) that may progress to adenocarcinoma by escaping conventional endoscopic surveillance [17]. Second concern is the rare but documented risk of recurrent BE with dysplasia or adenocarcinoma [18]. Volumetric laser endomicroscopy (VLE) allows rapid visualization of the esophageal wall layers within a few minutes using a laser probe mounted on a balloon. Such rapid scanning of large surface areas of the lamina propria and submucosa with excellent resolution and deeper penetration reliably and safely images the distal esophagus in BE after EET [19] and may accurately to allow targeted tissue acquisition even in ablation-naïve BE patients [20].

Laparoscopic anti-reflux surgery (LARS) is usually preferred in patients with large hiatal hernia, para-esophageal hernia, previously failed EART, in patients with pulmonary manifestations of GERD and in those with Barrett's esophagus resistant to EET. Roux-en-Y bypass surgery is preferred in obese patients with GERD while esophagectomy is reserved for those BE patients with invasive cancer (Fig. 15.8).

In summary, the clinical and phenotypic complexity of GERD requires a detailed, multimodality diagnostic evaluation prior to decision-making for pharmacological, EART or surgical therapies. An individualized selection has to be based on symptoms, clinical presentation, proper disease definition, therapeutic objectives, and available local endoscopic and surgical expertise. As these novel endoscopic and laparoscopic technologies evolve and mature and long-term data becomes available, decision-making will remain in flux but best done at multidisciplinary esophageal centers of excellence.

Compliance with Ethical Standards

Conflict of Interest: The author has equity position with Mederi Therapeutics, C2 Therapeutics, and EndoStim.
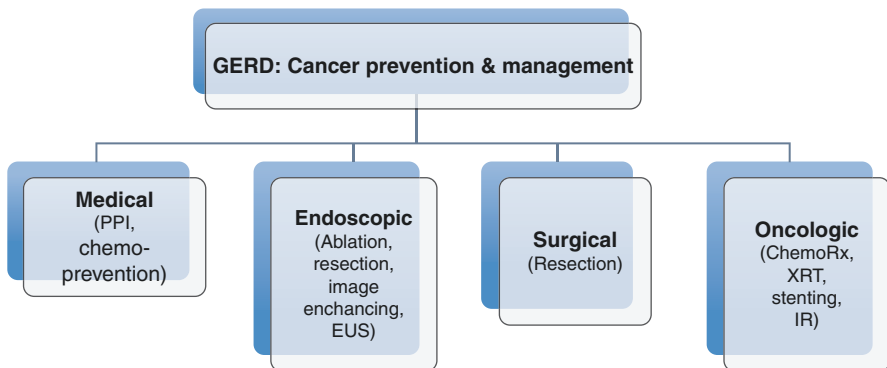
Fig. 15.8 Cancer prevention and management strategies in GERD. Proton pump inhibition (PPI) and/or other agents (i.e., aspirin, statins, and NSAIDs) may have a chemoprevention role in patients with Barrett's esophagus (BE). Advanced endoscopic imaging may identify areas of dysplasia in BE and facilitate ablation or resection of dysplasia and early neoplasia, while endoscopic ultrasound (EUS) facilitates staging. Surgical management involves resection for cancer, while oncologic approaches involve chemotherapy, radiation therapy (XRT), and palliative stenting. Interventional radiologic (IR) techniques assist in tumor staging

Human and Animal Rights and Informed Consent: This chapter does not contain any studies with human or animal subjects performed by the author.

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