Published in final edited form as:
Best Pract Res Clin Gastroenterol. 2010 December ; 24(6): 961–968. doi:10.1016/j.bpg.2010.09.007.

Treatment of GERD Complications (Barrett's, Peptic Stricture) and Extraesophageal Syndromes

Ajay Bansal[*] and **Peter J. Kahrilas**[†]

[*] Department of Medicine, Veterans Affairs Medical Center and University of Kansas, Kansas City, MO

[†] Department of Medicine, The Feinberg School of Medicine, Northwestern University, Chicago, IL

Abstract

Apart from typical reflux symptoms and esophagitis, the clinical presentation of GERD can be dominated by mucosal complications of reflux (Barrett's esophagus, esophageal adenocarcinoma, Peptic structure) or by extra-esophageal syndromes, most notably asthma, laryngitis, or chronic cough. Managing these entities is much less straightforward than with esophagitis. With respect to adenocarcinoma, metaplasia and dysplasia are recognized precursors, but the potential of these lesions to evolve to cancer has not been shown to lessen as a result of treatment, medical or surgical. Consequently, management focuses on strategies to identify and eliminate high grade dysplasia and intramucosal cancer, lesions that are potentially curable by endoscopic ablation or surgical resection. With respect to the extra-esophageal GERD syndromes, these are increasingly recognized as multifactorial conditions with reflux as an exacerbating factor. Treatment trials have been generally disappointing and the clinical challenge remains in accurately identifying afflicted patients who might benefit from more intensive medical or surgical reflux treatment.

Keywords

Barrett's esophagus; esophageal adenocarcinoma; peptic stricture; extra-esophageal GERD

The Montreal definition of reflux disease was developed to broaden the definition of GERD to all potential consequences of reflux (1). With respect to the esophagus, this encompasses peptic structure and the metaplasia-dysplasia sequence that can potentially lead to esophageal adenocarcinoma. In the extra-esophageal domain a host of syndromes including asthma, laryngitis and chronic cough are recognized to be associated with reflux. The following treatise will review treatment data of these entities, highlighting the limitations and uncertainty in current management strategies.

Correspondence: Peter J. Kahrilas, M.D, Northwestern University, Feinberg School of Medicine, Department of Medicine, Division of Gastroenterology, 676 St Clair St, Suite 1400, Chicago, Illinois 60611-2951, 312-695-4016, Fax: 312-695-3999, p-kahrilas@northwestern.edu.

Conflict of Interest Statement

AB: No financial interests to declare

PJK: Dr Kahrilas is a paid consultant for AstraZeneca, Eisai, EndoGastric Solutions, Ironwood, Novartis, Movetis, Reckitt Benckiser, Torax, and Xenoport

Barrett's Esophagus

Does treatment prevent cancer?

While it is clear that proton pump inhibitor (PPI) therapy or anti-reflux surgery heals esophagitis, it is less than certain that either reduces the small risk of adenocarcinoma in GERD. Randomized controlled trials to evaluate this question do not exist. Consequently, secondary endpoints such as progression or regression of metaplasia and the development of the dysplasia have been studied. Three randomized controlled trials (two published only as abstracts) have examined the effect of PPI treatment on metaplasia; two showed a slight (6–8%) decrease in Barrett's area (2,3) whereas the third did not show any reduction (4). Thus, acid suppression does not eliminate metaplasia and has minimal, if any impact on Barrett's length. With respect to the development of dysplasia, retrospective cohort studies (5,6) suggest that acid suppression reduced the incidence of dysplasia if low-grade dysplasia is accepted as an endpoint. That, however, is very controversial. A more definitive trial, comparing PPI therapy to PPI and aspirin in Barrett's using adenocarcinoma as the outcome is ongoing (7).

Data suggesting benefit of anti-reflux surgery with respect to Barrett's progression are also equivocal. A meta-analysis found an overall similar cancer incidence rates between the surgical and the medical groups (3.8/1000 patient-years vs. 4.2/1000 patient-years)(8) when controlled for Barrett's length. More recently, data from a Swedish population-based registry of antireflux surgery patients from 1965 to 2006 (n=14,102), found no impact of surgery on esophageal adenocarcinoma after at least 15 years of follow up (9). Thus, whatever the merits of anti-reflux surgery might otherwise be, prevention of cancer should not weigh on the decision to pursue it.

Should Barrett's esophagus be ablated?

The past 15 years have witnessed the development of a succession of techniques for the endoscopic eradication of Barrett's metaplasia, high-grade dysplasia (HGD) and intramucosal esophageal adenocarcinoma. Two multi-center randomized controlled trials support the use of endoscopic eradication in instances of HGD. The first of these, using photodynamic therapy, succeeded in HGD eradication in 77% of patients with a significantly reduced progression to cancer (13% vs. 28%, $p<0.006$)(10) and sustained 5 year HGD eradication in 77% (11). The more recent trial using radiofrequency ablation achieved HGD eradication in 81% of patients, also with significantly reduced progression to cancer (1.2% vs. 9.3%, $P=0.045$)(12). Uncontrolled trials of endoscopic mucosal resection (13) and cryotherapy (14)) also support endoscopic ablation as an effective therapy for Barrett's related HGD and intramucosal cancer. A retrospective comparison of endoscopic eradication with esophagectomy from Mayo Clinic suggests that overall mortality and long-term survival is comparable in patients with HGD (15). Post endoscopic eradication complications are recognized with risks of perforation (low), bleeding, stricture formation (higher with photodynamic therapy compared to radiofrequency ablation, 15% vs. 6%) and disease recurrence (hence need for continued surveillance). Since head to head comparisons of various endoscopic eradication modalities are not currently available, the choice of therapy will depend on local expertise and availability. In those domains, the relative ease and elegance of radiofrequency ablation makes it an attractive option.

Related to post ablation surveillance is the important issue of "Buried glands" i.e. histologic columnar metaplasia that is under the endoscopically visible neosquamous mucosa. The significance of buried glands is in their potential to become cancer (11). Some studies suggest that endoscopic biopsies are adequate glands (16) while others suggesting them to

be of inadequate depth (17). Consequently, the ideal method for post ablation surveillance is currently unclear and an area of active research.

At the core of the controversial issue of ablation of BE without dysplasia (non-dysplastic Barrett's esophagus) or low-grade dysplasia (LGD) are the progression rates of these lesions. In non-dysplastic Barrett's esophagus, progression rates as low as 0.3% per year have been reported (18,19); the reported progression potential of LGD varies from 0.6% (20) to 13.4% per year (21). This highlights the problems of inter-observer variability and possibly the potential of regression with LGD (22). Proponents of ablating all Barrett's irrespective of dysplasia suggest that the number needed to treat to prevent one cancer during a 5-year follow up is 45 for non-dysplastic Barrett's esophagus and 13 for LGD (23). However, this calculation assumes that the annual progression rate of Barrett's to cancer is linear and constant over time allowing extrapolation from the available "per-patient per-year" incidence rates to a 5 year time frame (19). Furthermore, the projection also ignores the fact that most patients with Barrett's die of unrelated causes during the period of surveillance (18). Additionally, there is a paucity of data demonstrating the durability of Barrett's eradication. Thus, as it stands, ablation of Barrett's does not obviate the need for continued endoscopic surveillance.

Peptic Stricture

Chronic ulcerative esophagitis can lead to scarring and stricture formation, usually in the distal esophagus. With the widespread use of PPIs as healing and maintenance therapy for esophagitis, strictures have become much less of a clinical problem. Using the United Kingdom General Practitioner Database, Ruigomez et al clearly showed a significant decline in the incidence of peptic strictures from 1994 to 2000, the time span paralleling the widespread adoption of PPI therapy for GERD (24). Refractory strictures, characterized by frequent recurrence after dilation, have become even more rare. However, when encountered, refractory strictures can be a significant clinical challenge.

Technique of dilation

Several esophageal dilator designs are available to use in conjunction with endoscopy. Broadly speaking, these are either flexible plastic/hard rubber devices with tapered ends that are passed independently of an endoscope, or balloon dilators that are passed through the instrumentation channel of the endoscope. The most common design of the former have a hollow core to facilitate threading them over a guide wire, which is first positioned across the stricture endoscopically and/or fluoroscopically (Savary dilators). Much opinion, but little controlled data, exist regarding the optimal technique or device to use for esophageal dilation. Clearly, the most important principle is to minimize the risk of esophageal perforation, estimated to occur in about 0.18% of cases (25) when the tip of the dilator penetrates the wall of the esophagus, usually at the area of angulation proximal to the gastroesophageal junction, or when a dilator of excessive diameter is used with a tight stricture. Minimizing this risk amounts to careful placement technique, using fluoroscopy if necessary, and caution with respect to the extent of dilation attempted in a single session. Generally, once a dilator of sufficient diameter to break the mucosa has been used, that is a good stopping point.

The choice between flexible plastic/hard rubber dilators (e.g. Savary) and balloon dilators is a matter of personal preference, availability and experience. Although an initial randomized study suggested that balloon dilators had a longer duration of response than Savary dilators (26), a subsequent trial of 251 subjects (45% peptic stricture, 55% Schatzki ring) failed to confirm any superiority (27). 1-year Kaplan-Meier estimates of repeat dilation with balloon versus Savary dilators were 12% and 9% respectively. Retrospective multivariate modeling,

of 67 peptic stricture patients suggested that persistent heartburn after dilation (OR 23.80, 95% CI 4.4 -125.0, p=0.0002) and presence of a hiatus hernia (OR 5.90, 95% CI 1.90-333.3, p=0.014) were significant predictors for recurrence (28).

Refractory strictures: steroid injections, stents, surgery, or self-dilation?

Although rare, refractory peptic strictures can be very challenging to manage. Intra-lesion steroid injection has been advocated as one method to reduce stricture recurrence. An initial study inclusive of 14 peptic stricture patients suggested a significant reduction in the need for subsequent dilations after 4-quadrant triamcinolone injection in and around the strictures (40 mg diluted to 10–20 mg/ml) (29). This finding was confirmed in a subsequent randomized, double blind, sham-controlled trial of steroid injection therapy in 30 peptic stricture patients (30). After 1 year, significantly fewer patients in the steroid group required further dilation compared to the sham group (13% vs. 60%, P=0.011). Thus, intra-lesion steroid therapy is effective at reducing the need for repeat dilation in refractory peptic stricture patients.

Esophageal stent placement is an alternative method of gradual dilation of an esophageal stricture with encouraging results in case reports and case series. However, the procedure has been associated with complications such as stent migration in up to 60% of patients (31) and only moderate resolution of dysphagia at long-term follow up. A systematic review of 10 studies that used stents to treat benign strictures of varied etiology showed a technical success of 98% but dysphagia resolution in only half the patients (32). Migration occurred within 4 weeks in 24% of patients. Consequently, stents should be considered only in carefully selected patients.

Historically, surgery has been recommended as yet another alternative for peptic structure patients. A cohort study evaluating anti-reflux surgery for peptic strictures showed a reduction in dysphagia scores as well as in the need for further dilation (5.3 sessions/26 months pre-operatively to 1.8 sessions/24 months postoperatively, $p < 0.001$)(33). Although these data are uncontrolled, one could argue that the sub-group of patients with refractory peptic strictures may benefit from anti-reflux surgery if more conservative measures fail.

Finally, self-dilation is an option for highly motivated patients who require frequent dilation. Small case series (34) and case reports support this method, but instance of perforation have also been reported (35). Nonetheless, this method is feasible for the occasional patient who can be adequately educated on the technique.

Extraesophageal GERD Syndromes

The Montreal definition of GERD encompasses instances in which the disease is defined by associated extra-esophageal syndromes (1). Specifically, asthma, laryngitis and chronic cough can be associated with GERD. However, the emerging theme is that these conditions are multifactorial in etiology with reflux being only one of multiple contributing factors. Consequently, although reflux treatment may be part of an effective management strategy for these entities, it is rarely the only element.

Reflux-asthma syndrome

A systematic review of 12 trials evaluated the impact of medical or surgical GERD treatment on asthma in patients with erosive esophagitis found inconsistent benefit (36). A recent large randomized controlled trial of twice daily PPI therapy suggested some benefit in morning peak expiratory flow for patients characterized apriori by nocturnal respiratory and reflux symptoms but no respiratory function benefit in subgroups with only one or the other (37). Another large randomized controlled trial of patients with poorly controlled asthma

found no respiratory function benefit to twice daily PPI therapy, even in a subgroup analysis of those with abnormal esophageal pH monitoring studies (38). On the other hand a small trial in 62 asthmatics did show benefit in overall asthma status with anti-reflux surgery compared to H-2 receptor antagonist therapy or placebo (39). Thus, although it seems that there is a subgroup of asthmatics who benefit from reflux therapy, the treatment effect is usually slight and unpredictable.

Reflux-laryngitis syndrome

A recent meta-analysis of eight randomized controlled trials of PPI therapy for chronic laryngitis found a non-significant benefit (OR 1.28, 95% CI 0.94-1,74) without identifiable predictors for response. However, examining individual studies, the presence of reflux symptoms in association with symptoms of reflux laryngitis appears to predict response. Supporting that concept, of the two largest double-blind, placebo controlled trials of suspected reflux laryngitis, the study that excluded patients with more than mild heartburn had a negative result (40) while that study that included patients with typical reflux symptoms was positive (41). Further support for GERD symptoms as a predictor of response in suspected reflux laryngitis is provided by other uncontrolled and controlled studies (42,43). Another interesting subgroup of patients with laryngeal symptoms are those with heterotopic gastric mucosa in the cervical esophagus (inlet patch). A recent controlled study showed that ablation of the inlet patch improved the symptom of globus in these patients (44).

The utility of antireflux surgery in reflux laryngitis remains to be determined. A non-randomized, but controlled, study of suspected reflux laryngitis patients with laryngeal symptoms (hoarseness, cough, sore throat) refractory to PPI therapy found Nissen fundoplication to be as ineffective as continued medical therapy (10% vs. 6.7% response) (45). While this study did not address the utility of anti-reflux surgery as primary therapy for reflux laryngitis, it argues against employing it in “refractory” cases.

Reflux-cough syndrome

Chronic cough has a diverse set of potential causes that are often elusive. Included in the list is GERD. However, unlike the case with either asthma or laryngitis, chronic cough can be an atypical manifestation of GERD without concomitant esophageal symptoms. Current thinking is that chronic cough of varied etiology is exacerbated by a sensitized broncho-esophageal reflex triggered by reflux (46). Furthermore, not only can reflux cause cough but cough can cause reflux and evidence suggests that this too may be partially the result of a sensitized neural reflex.

With respect to treatment, medical trials in reflux-cough syndrome have been disappointing. A meta-analysis of five PPI trials concluded that PPIs probably have some benefit for some cough patients, but the effect is far from universal (47). Uncontrolled surgical data are somewhat more promising. In a cohort study of 905 Nissen Fundoplication patients, approximately one-fifth of whom underwent surgery for cough, 71% reported improvement in cough at 5 years (48). However, the predictors of response remain ill-defined and the potential benefit of anti-reflux surgery must be weighed against its potential morbidity.

Summary

The major esophageal complications of GERD are esophageal adenocarcinoma and peptic stricture. PPI therapy has been very effective in managing the problem of peptic stricture but has not significantly impacted on the problem of adenocarcinoma or its precursor lesion, Barrett’s esophagus. Thus, major unresolved questions in GERD management are when to

screen patients with endoscopy and what to do in the event of detecting Barrett's esophagus. On the other hand, the findings of high grade dysplasia or intramucosal cancer are clearly actionable. In this case the unanswered question is when to employ the endoscopic eradication therapy, a rapidly emerging option, as opposed to the existing standard of care, esophagectomy.

Potential extra-esophageal manifestations of GERD include asthma, laryngitis, and chronic cough although, in each case, these are usually multifactorial syndromes. Given the low morbidity, PPI trials have become somewhat routine in clinical management when these entities are suspected. The more difficult, unanswered question is what to do in instances of unsuccessful therapy. What is the role of antireflux surgery? What are the clinical predictors of response to reflux therapies, medical or surgical?

Practice Points

Barrett's esophagus management

- Progression from non-dysplastic Barrett's esophagus to adenocarcinoma occurs at a rate of about 0.3% per year
- Neither antisecretory therapy nor anti-reflux surgery eliminates the cancer risk in Barrett's esophagus; it is uncertain whether or not the risk is reduced
- Both esophagectomy and endoscopic eradication therapy reduce the risk of adenocarcinoma in patients with high grade dysplasia
- The natural history and treatment of low grade dysplasia are controversial
- Endoscopic eradication therapy is not recommended with non-dysplastic Barrett's esophagus

Practice Points

Peptic stricture

- Peptic strictures have become a rare problem with the widespread use of PPIs
- Dilation with either through-the-scope balloon or Savary-type dilators is effective in treating peptic stricture and relieving the associated dysphagia
- In rare instances, peptic strictures can be refractory to simple dilation and benefit from endoscopic steroid injection, implanted stents, or anti-reflux surgery

Practice Points

Extra-esophageal GERD syndromes

- Asthma, laryngitis, and chronic cough can be associated with GERD
- Extra-esophageal manifestations of GERD are usually multifactorial
- Treatment benefit for extra-esophageal GERD manifestations is far less predicable than for heartburn or esophagitis

Acknowledgments

Financial support for the project: This work was supported by R01 DK56033 from the Public Health Service (PJK) and a Career Development Grant from the American College of Gastroenterology (AB)

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