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Management of Refractory and Complicated Reflux Esophagitis

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Simple intermittent heartburn with minor or no esophagitis can be treated with simple measures including lifestyle changes and antacids as needed, or H_2 receptor antagonists (H_2RA), and has a good outcome. Problematic reflux includes resistance to therapy, stricture, Barrett's esophagus and aspiration. Severe reflux esophagitis, often resistant to H_2RA therapy, requires more potent treatment with potent acid suppression using proton pump inhibitors, often indefinitely. When complicated by stricture, dilatations with potent acid suppression are needed. Barrett's esophagus is subject to esophagitis, which is no more difficult to treat than other cases of esophagitis. Reflux in Barrett's esophagus should be treated on its own merits without regard to the presence of Barrett's epithelium. Dysplasia leading to adenocarcinoma is a different problem, apparently not influenced by reduced exposure to acid. Indications for antireflux surgery are quite limited and should be carefully analyzed as a cost/risk/benefit problem.

INTRODUCTION

As many as 40 percent of adult Americans experience heartburn at least once a month [1]. Although heartburn is the most common symptom of esophagitis, as many as 70 percent of all persons with intermittent heartburn have no esophagitis [2] and only 60 percent of persons with daily heartburn have esophagitis [3]. Perhaps as many as 2 percent of adults in the U.S. have esophagitis [4], while heartburn and esophagitis are quite uncommon in Japan [5] for unclear reasons.

While the majority of patients with heartburn have minimal or no disease, a number of patients with problematic gastroesophageal reflux (GER)[b] disease require special attention. There are several categories of problematic GER including patients with esophagitis or symptoms refractory to treatment [6, 7, 8], those with rapidly recurring esophagitis [1, 9], those with complications such as stricture and Barrett's esophagus and those with airway aspiration of refluxate. Treatment for each of these states requires understanding of the specific causes of abnormal GER, the extent of the esophageal disease and the natural history of the disorder. Goals for treatment must be defined so that therapy may be appropriately applied and the results measured [1, 10, 11].

BASIS FOR TREATMENT STRATEGIES

In general, gastroesophageal reflux is a physiological phenomenon in which gastric contents intermittently enter the esophagus and are rapidly cleared and neutralized [12]. The highly integrated lower esophageal sphincter (LES) complex accommodates the swallowed bolus, relaxing after swallowing to allow forward passage and preventing reflux at other times, while allowing gas to escape via belching, i.e., discriminating gas and liquid.

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[b]*Abbreviations:* GER, gastroesophageal; LES, lower esophageal sphincter; TLESR, transient LES relaxation; H_2RA, H_2 receptor antagonist; ZES, Zollinger-Ellison syndrome; BAO, basal acid output.

The inappropriate relaxation of the LES (abnormal transient LES relaxation or TLESR [12, 13]) is to be distinguished from a permanently incompetent sphincter (LESP less than 10 mm Hg) which allows free reflux by gravity or pressure differential [12, 14]. Sphincter incompetence (LESP less than 10 mm Hg) in the presence of acid secretion almost always leads to esophagitis, but in one study [15] accounted for only 30 percent of cases of esophagitis. Almost all patients resistant to omeprazole have low LESP [7]. LESP in infants is generally low, but esophagitis is not common. Excessive frequency or duration of TLESR is felt to underlie the majority of the remaining 70 percent of cases of esophagitis [13], presumably coupled with defects in factors protecting the esophageal mucosa [12]. The LES may also be rendered incompetent by an axial hiatal hernia, which often additionally functions as an intrathoracic reservoir of gastric contents so that clearance remains incomplete [12]. Hiatal hernia, however, is present in only 50 percent of patients with esophagitis [6]. Normally, acid gastric contents are rapidly cleared from the esophagus through a combination of reflex responses to acid reflux: propulsive motility is initiated to empty the esophagus and HCO_3^- secreted by the esophagus and from saliva which is reflexively stimulated neutralizes remaining acid. It is not clear how these reflexes operate during sleep when salivary flow largely ceases and swallowing is much diminished. The squamous epithelium of the esophagus is quite impermeable to acid [16, 17]. Maintenance of mucosal integrity is complex and involves EGF, mucus and HCO_3^- secretion, blood flow and cellular responses and proliferation in response to injury [12].

Excessive exposure of the esophagus to acid and pepsin may result from delayed gastric emptying; in the most extreme case persistent vomiting secondary to pyloric stenosis or gastroparesis always causes esophagitis though in the ordinary course of events lesser abnormalities of gastric emptying, which do not cause vomiting, do not probably underlie reflux esophagitis [1]. Massive gastric hypersecretion due to gastrinoma (Zollinger-Ellison syndrome) is frequently associated with esophagitis [19], but in non-ZE hypersecretors with BAO (basal acid output) over 15 meq/hr, esophagitis is uncommon [15, 20]. In general, acid and pepsin secretion are not different between patients with either simple or complicated (stricture, Barrett's) esophagitis and controls matched for age, sex and coexisting disease such as duodenal ulcer [6, 15, 21]. Nevertheless, stringent reduction in esophageal acid exposure is the key to successful treatment of esophagitis [18].

There are no good data defining the conditions necessary to induce and maintain esophagitis in man [12]. We do not know the necessary duration of exposure, the minimum composition of the refluxate, or whether there is any particular time of day or night when the esophagus is more susceptible to damage. In experimental animals, acid alone is much less ulcerogenic even at pH as low as 1.6 [22, 23]. Addition of pepsin to acid at pH 1.6 rapidly resulted in esophagitis [22]. It would thus appear that pepsin is critical to the evolution and maintenance of esophagitis and its effective inactivation at pH greater than 3.5 by adequate acid suppression will allow esophageal healing [14]. Other barrier breakers may allow acid/pepsin access to the baso-lateral membrane with rapid, serious, deleterious effect on the mucosa. Such agents include bile salts, aspirin acting systemically [24], and other drugs like quinaglute, KCl, and tetracycline, among others, acting locally to cause so-called pill esophagitis, which is localized rather than being typical distal reflux esophagitis [25].

Disordered motility as in scleroderma [26] or as a consequence of severe esophagitis [27] prolongs acid/pepsin exposure and compounds the problem.

THE MEASURED APPROACH TO THERAPY

First steps: The management of heartburn starts with a good history

The majority of cases of intermittent heartburn respond readily to antacids or single small doses of H_2 antagonists recently released in non-prescription form [28]. Even a simple increase of salivary flow by the use of chewing gum may suffice [29]. Such patients clearly require no diagnostic evaluation or other treatment and most will respond to change in habits [11], such as reducing the size of meals, especially if the patient eats only one large meal per day. For nocturnal heartburn, the patient should allow three to four hours to elapse between the evening meal, which should be reduced in bulk and fat, and recumbency to permit gastric emptying and the dissipation of fat effect on the LES. Avoidance of a bedtime snack and elevation of the head of the bed is often recommended, though persistence of nocturnal heartburn after change in eating habits might be better managed pharmacologically, e.g., with an evening dose of antacid H_2RA [35] or prokinetic agents [1]. Other measures recommended include weight reduction, especially if symptoms are clearly related to recent weight gain, though the role of obesity *per se* has not been formally distinguished from the concomitant consumption of high-fat foods [30]. Patients should avoid, if possible, foods or drugs that lower LESP, e.g., fats, chocolate, coffee, alcohol; anticholinergics, calcium channel blockers, progesterone, aminophylline or nitrates. Smoking also promotes reflux [31]. The cumulative benefit of dealing with each of these contributing factors is quite enough to manage reflux in the majority of patients with symptoms [11] and results may be readily assessed by the presence or absence of symptoms. Assuming that such patients have minimal or no esophagitis, the natural history is very favorable. Thus, even if grade I esophagitis is present, 50 percent will remain unchanged, a further 45 percent will heal spontaneously and only five percent progress to grade III in three years [32].

When to investigate GER symptoms further

The majority of patients with heartburn can be adequately treated with simple measures without radiographic or endoscopic investigations. Further workup is necessary in those patients with persistent heartburn, dysphagia, non-cardiac chest pain or airway aspiration. Evaluation starts with a barium contrast radiographic study, preferably with cinefluoroscopy recording to confirm and define the extent of reflux including influence of body position, and the effect of increasing intra-abdominal pressure. Such studies should include the use of sized barium tablets to measure stricture diameter. Endoscopy is required to assess the degree and extent of damage; biopsy is indicated to diagnose and classify Barrett's epithelium [33] and to rule out suspected malignancy or infection.

The grading of esophagitis at the outset is important, given the very favorable prognosis of patients with heartburn who have no or only grade I esophagitis [32]. Grade II esophagitis (linear erosions over less than 10 percent of surface) will heal well with H_2RA, or even cisapride [1], and poses no long-term risk to the patient, seldom progressing to severe grades with complications, especially if NSAIDs are avoided [24] and if there is no underlying major motor disorder such as scleroderma. For these patients symptom control is probably an adequate benchmark, even though relapse rates are fairly high [34-37.] Such relapse may require change in treatment.

Grade III and IV esophagitis (severe and/or complicated esophagitis) [1, 9, 34, 38] represent the hard core of the problem. The majority of such cases have severe persistent heartburn [3, 4, 6, 9, 38, 39] or dysphagia and few, if any, remit spontaneously [1-3, 8-10, 39] and most require long term continuous acid suppressing therapy [7-9]. NSAIDs, especially aspirin, may contribute significantly to esophagitis and stricture, and overt or surreptitious use of these drugs should be diligently investigated [24]. Continuing esophagitis

may lead to stricture and decrease in motor function, further compounding the problem. Stricture is moreover a marker for failure to heal [6]. Barrett's esophagus is a separate problem and at first may be obscured by superimposed esophagitis, and may not be diagnosed until the esophagitis is treated. Severe, diffuse esophagitis or discrete esophageal ulcer pose a risk of bleeding, especially in patients with concomitant NSAID use. Endoscopic and radiologic examinations will thus determine the immediate course of treatment and further studies will be indicated by the response to such treatment.

At this point the patient may be treated and further investigation postponed unless results of treatment are suboptimal. Further studies include manometry to define contraction strength and patterns and to measure LES pressure. This study would also uncover undiagnosed aperistalsis [7] including that due to scleroderma, in which refractory esophagitis is common [26]. A 24-hour gastric acid measurement for documentation and quantitation of acid exposure without treatment best defines the relation of symptoms to acid reflux. In patients who fail to respond to treatment with proton pump inhibitors, 24 hour gastric acid measurement on treatment, e.g., with omeprazole 20 mg twice daily, should be done [7, 8, 40, 41]. In patients with concomitant duodenal ulcer or marginal ulcer following gastrectomy, ZES should be excluded by appropriate tests of serum gastrin and gastric analysis [19].

PHARMACOLOGIC TREATMENT FOR PROBLEMATIC REFLUX ESOPHAGITIS

In those cases with problematic esophagitis, grade III or IV, stricture, or Barrett's esophagus, and airway aspiration, specific long term treatment goals should be defined.

Esophagitis resistant to treatment

In the past, resistance to treatment has in practice been generally defined by failure to heal with H_2RA with six to 12 weeks treatment [6-9, 34-38]. In a meta-analysis "duodenal ulcer," doses of H_2RA failed to heal two-thirds of cases of esophagitis [42] and many controlled trials showed no benefit over placebo [1]. Such resistance was soon found to be a function of initial severity of esophagitis, e.g., 78 percent of grade II healed at six weeks compared to 30 percent and 23 percent, respectively, for grade III and IV [34] and ranitidine 150 mg/day or equivalent did not prevent relapse [7, 34-36, 43].

Even though in such patients underlying acid secretion is not different from those who healed [6], the key to effective treatment appears to be acid suppression to elevate gastric juice pH outside the range of peptic proteolytic activity [18, 23], and this may be most effectively achieved by proton pump inhibitors [7, 14, 42, 44]. Because of the greater potency of PPI, so-called resistant esophagitis, i.e., resistant to H_2RA [6, 7] is now almost always treatable with omeprazole or lansoprazole [38, 41-44] at one or two doses per day [7, 41]; a very few patients require higher doses [7, 8] and resistance to therapy has to be redefined in the era of PPI therapy.

Rare cases of resistance to doses greater than 60 mg omeprazole/day are reported [8, 40]. Such resistance to high doses of proton pump inhibitors should be investigated by manometry which almost always shows very low LESP [7, 8] by measurement of gastric secretion on treatment and 24-gastric gastric acid measurements to document at least one source of resistance [8]; other causes such as undisclosed use of NSAIDs [24], underlying ZES [19] or scleroderma [26] should be considered. Acid clearance is decreased in patients with higher grades of esophagitis [27] and both motor activity [8] and acid clearance in those with stricture [8, 27]. Such defects may explain why stricture is such a strong marker for resistant esophagitis (22/30 resistant patients had stricture *vs.* 3/20 who healed) [6], and why there is even initial resistance to omeprazole treatment [9] and slow response, which requires up to two or more months to heal [7-9, 18, 37]. Most or all such patients

require indefinite treatment with proton pump inhibitors because the relapse rate is almost 100 percent [9, 18, 45]. Even on 20 mg omeprazole/day as many as 33 percent of patients relapse in 12 months [7, 8, 37, 38] (generally, however, only to grade I). With relapse, such patients require higher doses for some time [7, 45]. Rarely they should be considered for surgery [10] (see below). No data are available on the outcome of such patients. There are no data on the effect of NSAIDs or their discontinuation on the relapse rate in esophagitis, particularly grade III and IV.

ESOPHAGEAL STRICTURE

Reflux esophagitis, usually at least grade III, may be complicated by stricture which always occurs at the squamo-columnar junction and extends proximally [46]. In cases of Barrett's esophagus, strictures form at the neosquamous-columnar junction [46]. By contrast, strictures due to other causes such as caustic or pill-induced stricture may occur at more proximal locations [25].

The diagnosis of peptic stricture is suggested by progressive dysphagia for solids, generally preceded by prolonged symptomatic reflux. Dysphagia requires diagnosis by barium contrast studies, including sizing of the stricture using barium tablets [46, 47]. When the lumen is less than 12 mm, dysphagia is always present and the patient may present with impaction. Endoscopy is also necessary to determine the degree of esophagitis, the appearance of the stricture, to rule out malignancy and determine whether the Barrett's epithelium is present. Manometry to characterize motility of the body and the LESP are important in planning therapy, while 24-hour ambulatory pH measurement will define the degree of reflux underlying the disorder. Aspirin or other NSAID may contribute to esophagitis and stricture by promoting fibrogenesis [48]. In our patient population 80 percent of stricture patients were currently using NSAIDs (over 80 percent of which was aspirin) compared to 60 percent with esophagitis only and 23 percent of controls [24, 49]. Careful history together with interview of family members and measurement of salicylate in blood should be done in each case. ZES should also be ruled out, especially if there is concomitant duodenal ulcer.

Peptic strictures are frequently associated with abnormally low LESP, and with disordered motility and especially with diminished acid clearance, all of which contribute to the persistence of the esophagitis and the relapse of the stricture requiring repeated dilatation if the cycle of continued reflux with damage is not interrupted [8, 27, 46, 47]. It is not clear whether the disorders of motility and acid clearance are primary or secondary [27] and whether they are reversible [46]. A small number have severe transmural fibrosis and in these the condition is irreversible [50]. In cases of intrinsic loss of motor function, such as scleroderma (or achalasia after Heller myotomy) esophagitis is common (60 percent) and of these half have strictures [26, 51].

Dilatation of the stricture alone without eliminating acid/pepsin reflux is seldom successful. Before potent acid suppressing therapy was available such patients required multiple repeated dilatations [46]. H_2 antagonists are only slightly better than no therapy [45, 52]. However, with the use of long-term omeprazole, dilatation of the stricture and healing of the esophagitis is both feasible and cost-effective [49, 53], virtually eliminating recurrent strictures with omeprazole doses of 20 or 40 mg/day [45, 52]. With this approach surgery is seldom needed. A case can be made for surgery in young persons who might otherwise face a lifetime of expensive medications [10], and in those with airway aspiration persisting during acid suppression.

Surgical antireflux treatment is aimed at the reflux rather than the stricture and risks, results and cost of surgery should be compared to those of proton pump inhibitors combined with dilatation [10, 47]. In any event, surgery should not be performed until the patient has had a thorough course of treatment with dilatations and proton pump inhibitors

to complete healing of the mucosa and resolution of the stricture. At that point the motor function of the esophagus should be again studied, as an aperistaltic esophagus is likely to result in dysphagia and a poor result [50].

There is no good indication for performing simultaneous acid suppressing surgery (vagotomy or gastrectomy). Moreover, these provide another source of unfavorable outcome, especially as vagotomy may cause delayed gastric emptying. If laparoscopic antireflux surgery becomes reliable and good outcome dependable, a better case can be made for such treatment. This is discussed in the following paper by Perdikis et al. Re-operation for failed antireflux surgery and resection of strictures carry high morbidity and mortality [54].

Patients with "pill esophagitis" generally do not require acid suppression therapy unless there is evidence of concomitant reflux disease. Esophageal peptic stricture is a risk factor for pill impaction; in that case severe stricture may result at the location of the reflux-induced primary stricture or Schatzki's ring.

BARRETT'S ESOPHAGUS

In 5 to 12 percent of patients with GER undergoing endoscopy the distal esophagus may be found to be lined with columnar epithelium, so-called Barrett's esophagus (BES). This condition may also be present in young children [55], raising the possibility of a congenital disorder, since in the fetus the esophagus is lined with columnar epithelium, which becomes squamous when fetal length exceeds about 230 mm [56]. In adult life Barrett's esophagus is diagnosed mainly in the age group 40 to 80 [57-59], corresponding to the age range in which symptomatic esophagitis is usually seen [1, 15]. While it is generally thought that Barrett's esophagus results from reflux esophagitis [55, 58, 59], the demographic peculiarities of this condition raise questions about the conventional hypothesis of antecedant acid/pepsin reflux esophagitis with abnormal healing. At least 30 percent of patients with BES have no history of heartburn [59]. BES occurs predominantly in whites (almost 100 percent) and is rare among females who number almost 50 percent of non-Barrett's esophagitis [15] but who are as equally subject to the other more rationally presumed sequel of esophagitis, namely stricture. Thus, in my prior study [15] the proportion of females with esophagitis who had BES was 6.5 percent compared to 28 percent of males ($p < .01$) while the proportions with stricture were 28 percent *vs* 29 percent, respectively.

There are no pathophysiological factors [12] that explain this gender difference, nor its rarity in blacks [59]. Moreover, in a study of 30 patients with BES there was no difference in basal or maximal acid or pepsin secretion between patients with BES and appropriately matched controls [21]. In examining the possible role of acid and pepsin in causing BES, there is little convincing evidence of new development or progression of BES in patients over long term endoscopic observation [57]. Experimentally induced BES in dogs required both removal of the esophageal epithelium and exposure to histamine-stimulated gastric secretion to produce BES epithelium [60]. Another problem in ascribing BES solely to acid/peptic reflux arises from the fact that the extent of the BES appears to be uninfluenced by either reducing acid exposure or failing to do so [57, 58, 61,63]. Antireflux surgery does not result in reduction of extent of BES [55, 61, 63].

Regardless of its pathogenesis, the problems of BES are two-fold; first, in the presence of reflux, BES epithelium is subject to damage, and second, and more serious, is the potential for malignant transformation of Barrett's epithelium to adenocarcinoma [64-67].

BES is said to be subject to more severe esophagitis [59], perhaps due to the generally found lower LESP and the frequently defective motility in the body of the esophagus [68, 69]. One study reported 37 percent of BES in scleroderma [25]. In my own patients the degree of esophagitis and the prevalence of discrete ulcer and stricture were

no higher among BES patients than in age, sex and race-matched controls with esophagitis but without BES [21]. Whether or why the columnar epithelium is more susceptible to damage is not clear since its characteristics as an epithelium, e.g., with respect to resistance to acid, or its ability to secrete mucus and bicarbonate have not been formally established. Esophagitis in BES does, however, heal readily with conventional PPI treatment for superimposed esophagitis [54] but with the same columnar epithelium.

The principal concern about Barrett's esophagus is the potential for adenocarcinoma of the lower esophagus and cardia [64, 67 70, 71]. Adenocarcinoma in this area is associated with BES in about 30 percent of cases, but shares the characteristics of BES in being predominantly (6:1) found in white males [67]. Carcinoma developing in Barrett's epithelium follows a definable course of progressive genomic instability [71] expressed in histological grades of atypia [70]. It is estimated that about 10 percent of patients will develop adenocarcinoma 10 or more years after initial diagnosis [25, 64-66], with relative risk of about 40 over the age-matched controls [59]. What is not clear is whether inflammation (esophagitis) or acid exposure in any way influences this process, either in its initiation or progression. Prevention of reflux by antireflux surgery does not prevent malignant evolution [63, 64, 66, 70, 71]. It is too soon to tell whether strict control of acid secretion now possible with proton pump inhibitors will by itself influence the long term outcome [72], but that too seems not to be the case [61, 62].

Acid suppression does not apparently affect atypia or its progression. In the absence of esophagitis or symptoms, BES *per se* requires no therapy except for the difficult question of dysplasia. New approaches to reversing Barrett's metaplasia, such as the use of laser ablation plus acid suppression [62, 73] are encouraging and may change the whole approach to the problem of malignant potential of BES, especially the difficulty of timing and extent of surgery based on the finding of dysplasia. The treatment of reflux in the presence of BES should therefore be solely determined by the reflux problems — symptoms, esophagitis and aspiration — and not by the BES. A decision to recommend antireflux surgery for proper reflux indications does not alter the need to continue to survey the BES [63, 73, 74] and be guided by the endoscopic and histological findings [61, 70, 71].

With better diagnosis [62, 70] and recently available potent acid suppressing drugs longitudinal studies should help resolve the role of acid and pepsin in the development, evolution and natural history of Barrett's esophagus. The metaplasia/dysplasia and cancer risk that complicate Barrett's may well be a separate problem requiring more than control of acid/pepsin exposure

SUMMARY

Simple heartburn with minor or no esophagitis can be treated with simple measures to control symptoms including lifestyle changes and antacids or use of H_2RA as needed. Problematic reflux esophagitis, resistance to therapy, largely in the more severe degrees of esophagitis, which is often complicated by stricture, requires more potent treatment but is almost always manageable by medical means. Proton pump inhibitors at doses sufficient to raise refluxed gastric juice pH to more than 3.5 or outside the proteolytic optimum for pepsin for most of the day [14, 42, 44] will heal all cases of esophagitis, with rare exceptions, and prevent relapse with little risk in long term use. Strictures respond to dilatation and with esophagitis eliminated do not recur. Barrett's esophagus is as subject as squamous epithelium to reflux esophagitis and is similarly responsive to acid suppression therapy, though BES generally remains unchanged, in extent with or without therapy. The demographics (over 80 percent of BES patients are male and all are white) suggest that BES may not be a straight-forward result of reflux esophagitis. The principal problem of BES is evolution of atypia and malignancy in about 10 percent of BES, and this appears to be independent of acid reflux or its control.

The problem of airway aspiration due to reflux is also generally well managed by adequate acid suppression, though serious episodes of reflux aspiration still may recur [45] and require antireflux surgery. Surgery for BES with dysplasia requires careful consideration and should not be lightly undertaken except in high grade-dysplasia. New approaches such as laser ablation should be vigorously pursued.

Indications for antireflux surgery are limited. Even if laparoscopic techniques make it easier to do, indications should not be relaxed. The best indications are for aspiration and severe reflux disease where the LESP is incompetent and the patient is young enough so that the cost, risk and benefit ratios and long term outcome compare favorably with medical treatment.

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