Medical Management of Esophageal Reflux

Basil I. Hirschowitz

Department of Medicine, School of Medicine,
University of Alabama at Birmingham,
Birmingham, Alabama

(Submitted February 25, 1994; sent for revision June 29, 1994; accepted August 23, 1994)

Gastroesophageal reflux of varying severity is a common disorder for which medical attention is sought at all levels, from pharmacists to specialist physicians and surgeons. This brief overview represents my current understanding of reflux, its effects on the esophagus and my personal approach to treatment of these disorders. Of necessity, because the literature is so extensive (a Medline search on reflux from 1966 to 1993 yielded over 1500 papers.), I have relied in places on the extensive review by Marks and Richter [1]. My paper emphasizes the evaluation and treatment of patients with symptomatic reflux, esophagitis and its complications. It describes why it is important to grade the disorders so that the treatment used is appropriate to the severity of the disease. The more severe the disease, the more specific the diagnostic information needed and the more exacting the treatment. Various treatments and outcomes of therapy are discussed, and a role for surgery is defined. The essence of effective medical treatment of esophagitis is to reduce acidity of the refluxate to a level outside the optimum proteolytic pH range of pepsin, i.e., greater than pH 3.5.

INTRODUCTION

Gastroesophageal reflux is a physiological phenomenon in which gastric contents enter the esophagus intermittently and are rapidly cleared. A complex and finely tuned mechanism involving the lower esophageal sphincter (LES) proper and the pinchock effect of the diaphragm must both accommodate the forward passage of swallowed material (food, saliva) and prevent inappropriate or prolonged reflux from the stomach. The lower esophageal sphincter mechanism must also allow gas or air in the stomach to reflux, resulting in a belch, and at the same time, not permit acid liquid to do the same. The reflux arc, arising from receptors in the gastric fundus surrounding the LES, whereby the LES relaxes when confronted by gas and fails to do so for liquid or acid liquid, has not been elucidated. A similar discrimination between air and liquid exists at the anal sphincter. The inappropriate relaxation of a normal pressure LES is to be distinguished from the incompetent (low pressure, i.e., < 10 mm Hg) sphincter, where reflux occurs by gravity (e.g., by lying down or bending over) and by simple pressure differential between the abdomen and the intrathoracic esophagus.

Massive reflux may reach the pharynx and can then gain access to the larynx and lungs. Normal acid gastric contents refluxing into the esophagus are rapidly and efficiently cleared through a combination of reflex responses: propulsive orderly motility is initiated to empty the esophagus of the bolus, the esophagus secretes neutralizing HCO₃⁻ and

---

"To whom all correspondence should be addressed: Division of Gastroenterology and Hepatology, Department of Medicine, University of Alabama at Birmingham School of Medicine, 406 Lyons-Harrison Research Building, 701 South 19th Street, Birmingham, AL 35294-0007. Tel: (205) 934-7954; Fax: (205) 975-6381.

"Abbreviations: LES, lower esophageal sphincter; ZE, Zollinger-Ellison.
an esophago-salivary reflex likewise initiates the flow of HCO\textsubscript{3}^-/rich saliva. It is not clear whether these reflexes are operative during sleep, when salivary flow ceases. Nocturnal acid reflux is presumably more damaging because of the loss of salivary neutralization.

Moreover, the esophageal squamous mucosa represents a tight epithelium that resists penetration by H\textsuperscript{+}, and probably, in part, under the influence of epidermal growth factor secreted by the salivary glands, desquamated epithelium is replaced and damaged epithelium repaired.

If this continuously balanced mechanism is disrupted by one or more changes in the elements of the equation, esophagitis results; esophagitis, in turn, may have secondary consequences. It is not known whether there is more than one initiating event, though it is clear that acid and pepsin are the major sustaining factors in esophagitis. However, not all reflux, much of which is physiological or very transient, results in esophagitis or even produces symptoms. The threshold for these consequences has not been defined. In the clinical context, we are only concerned with symptoms (heartburn or more rarely laryngitis/pulmonary), with esophagitis and ultimately with the consequences of esophagitis [1].

There are a number of circumstances in which an excess of acid/peptic contents reflux into the esophagus. First, an excess of gastric contents may result from delayed gastric emptying, which may be physiological due to a large fatty meal, or pathological as in diabetic enteroneuropathy or other gastroparesis; the massive hypersecretion of Zollinger-Ellison syndrome may also promote reflux, which is more damaging because the refluxate is excessively acidic. Obesity, ascites and pregnancy promote reflux because of increased abdominal pressure, the latter also reducing LES pressure by altered hormonal status. A low LES pressure is normally present in infants.

In some adults, the LES may be intrinsically weak (< 10 mm Hg), and in most such cases, esophagitis results [1, 2]. However, this defect accounts for no more than 30 percent of cases of esophagitis [2]. The LES may be rendered incompetent by an axial hiatal hernia, which often additionally functions as an intrathoracic reservoir of gastric contents at the thoracic pressure, so that the esophagus is not fully cleared of acid. Hiatal hernia is present in only half the cases of esophagitis. The LES can also be damaged by operations, such as a myotomy for achalasia. The reason why an LES with normal pressure relaxes inappropriately is unknown. This functional defect accounts for many of the remaining cases of reflux. Except in the ZE syndrome, esophagitis is not related to the level of acid secretion [2], though deep reduction in acidity is the key to adequate esophagitis treatment [3-6].

There are no good data defining the conditions necessary to induce esophagitis in man. We do not know the necessary duration of exposure, the minimum composition of the refluxate, nor whether the esophagus is more vulnerable at any particular time of day or night. In experimental animals, acid without pepsin is much less ulcerogenic, and it may be assumed that pepsin is as important in the genesis of esophagitis [7] as it is in its continuance. This hypothesis is strongly supported by the efficacy of omeprazole.

It may be presumed that the barrier-breaking agents, such as bile acids, may allow the development of esophagitis, though with an intact stomach bile or alkaline reflux are probably minor factors in the esophagus. Locally acting medications, such as tablets of aspirin, quinaglutide, tetracycline, ferrous sulfate and KCl among others, are more likely to induce local ulceration rather than conventional "reflux" esophagitis [8], especially in elderly patients with underlying motility disorders. Such lesions may also complicate reflux esophagitis which would require independent treatment.

Disordered clearance in scleroderma prolongs the duration of acid reflux episodes, and the same may apply after myotomy in the astatic esophagus of achalasia.
THE BASIS FOR THERAPY

Treatment requires an understanding of the specific causes of abnormal GE reflux, the extent of the symptom or esophageal disease and the natural history of the disorder. Goals for treatment must be defined so that therapy may be appropriately measured and applied [1, 9, 10].

As many as 40 percent of adult Americans experience heartburn at least monthly, according to a 1988 Gallup poll (cited by Richter [1, 9]). Though heartburn is the commonest symptom of esophagitis, as many as 70 percent of all persons with intermittent heartburn do not have endoscopic evidence of esophagitis [11], and only 61 percent of 77 patients with persistent (daily) heartburn had esophagitis [12]. Overall in the U.S., there is probably about a two percent prevalence of esophagitis [13].

In the greater majority of cases, the occasional episode of heartburn may require no treatment, or it may respond readily to antacids or to single doses of H2 antagonists. Clearly, such patients do not require further diagnostic evaluation or treatment other than simple symptomatic measures. For all patients with mild or intermittent heartburn, change in habits commonly suffices [10], such as reducing the size of meals, especially if the patient eats one heavy meal per day. For nocturnal heartburn, the patient should allow three to four hr to elapse between the large evening meal and bedtime to permit time for gastric emptying, avoid a bedtime snack and elevate the head of the bed. Other measures include weight reduction especially if the patient is obese or if heartburn is related to recent weight gain, avoidance of any foods causing reduced LES pressure (e.g., fats, chocolate, coffee and alcohol), as well as medications that might promote reflux, such as anticholinergics, calcium channel antagonists, progesterone, aminophylline or nitrates. The role of smoking on reflux or healing is not clear [1]. Such simple measures may suffice, and results can be readily assessed by the presence or absence of symptoms. Assuming that the greater majority will have no or minimal esophagitis, the natural history in such cases is very favorable. Thus, 50 percent of patients with Grade I disease will remain unchanged, 45 percent will be healed and only five percent of all mild esophagitis (i.e., Grade I) will have progressed to Grade III in three years [14].

In those patients with persistent heartburn, dysphagia, noncardiac chest pain or laryngo-pulmonary aspiration, further workup is necessary. Such workup should include a barium contrast radiographic examination (preferably with cine-fluoroscopy recording) to confirm reflux and to size stricture if present, as well as endoscopy to establish the degree of esophageal damage. Workup should also include 24-hr pH measurement and manometry to define LES pressure and esophageal contraction patterns, as indicated in patients with unambiguous radiographic results, endoscopy or poor response to therapy and those with atypical symptoms. In patients with concomitant duodenal or postgastrectomy ulcer, serum gastrin should be measured to rule out Zollinger-Ellison syndrome.

The grading of esophagitis (see Refs. 1-4, 16, 23) is important, since Grade I esophagitis has a very favorable outcome, seldom progressing to more advanced disease and healing spontaneously in as many as 50 percent of cases [14]. Such cases may be managed symptomatically with lifestyle changes and, where necessary, supplemented by H2 receptor antagonists. Grade II esophagitis (linear erosions < 10 percent of the surface) will heal well with H2 antagonists, pose no long-term risk to the patients and seldom progress to more serious levels of esophagitis. For many such patients, it may be enough to control symptoms even though the relapse rate is fairly high [16-19]. Grades III and IV (severe and/or complicated esophagitis) represent the hard core of the problem. The majority of such cases have persistent or severe heartburn [12, 20, 21] or dysphagia requiring treatment, and few, if any, remit spontaneously [1, 9, 11, 12, 20, 21]. A careful
history of aspirin use should be taken in every patient with esophagitis, since aspirin may contribute to esophagitis and delay healing [15]. Continuing esophagitis may progress to stricture, and 10 or more percent are said to have Barrett's esophagus [11, 21, 22] (see below). However, even severe esophagitis does not apparently affect survival [23].

PHARMACOLOGIC TREATMENT

Treatment of esophagitis prior to the advent of H₂ antagonists with antacids alone or combined with alginate was largely symptomatic [1, 10] and clinically useful only in mild esophagitis or in patients with occasional heartburn and no esophagitis.

H₂ antagonists were effective in treating duodenal ulcer, but results of treatment of esophagitis were disappointing. At doses and duration of treatment similar to those for duodenal ulcer, fewer than one third of esophagitis cases healed [5], and a majority of controlled trials showed no benefit over placebo [1]. It was soon realized that the degree of esophagitis determined response (see below). It was hoped that ranitidine, a more potent acid suppressor than cimetidine (Figure 1), might be more effective than cimetidine. However, ranitidine may have to be used at larger doses (e.g., 300 mg, four times daily [18]), for longer periods, up to eight weeks, to heal esophagitis. Many patients are, in fact, also resistant to ranitidine [3, 4, 16-18, 24, 25]. Such cases are not necessarily hypersecretors [26]. Most cases resistant to H₂ antagonists have severe esophagitis (Grade III/IV) or stricture [26, 27]. While healing occurred in 78 percent of patients with Grade II esophagitis at six weeks, Grades III and IV had healing rates of 38 percent and 23 percent, respectively [16]. Ranitidine at a dose of 150 mg per day was ineffective in preventing relapse [16]. Similar data were obtained in other studies with ranitidine [18, 21, 25, 28] and other H₂ antagonists, such as famotidine [17] or nizatidine (see Ref. 1). The only H₂ antagonist so far approved for esophageal reflux disease by the FDA is, in fact, ranitidine. Limited data suggest that famotidine and nizatidine could be expected to produce the same results.

Other Drugs

Sucralfate has not been particularly effective in esophagitis [1].

Promotility drugs. (i) Bethanechol is of marginal benefit. (ii) Metoclopramide likewise is of marginal benefit and has the additional disadvantage of causing side effects in almost 30 percent of patients, including fatigue, psychotrophic changes, hirsutism and extrapyramidal symptoms (tardive dyskinesia), which may persist [1]. (iii) Cisapride, a newly released prokinetic agent, lacking the side effects of metoclopramide, increases the LES pressure and improves esophageal and gastric propulsive motility. Cisapride appears to be as effective in healing esophagitis as cimetidine or ranitidine (300 mg per day) and apparently improves the benefit of H₂ antagonists [1]. However, no comparison has been made yet with omeprazole.

Proton pump inhibitors. Treatment of esophagitis, especially Grades III and IV, remained unsatisfactory until the development of omeprazole, which provided for the first time a means of suppressing acid output to a level not achievable in most cases with any but extreme doses of H₂ antagonists. Proton pump inhibitors, acting on the final step of acid secretion, inhibit acid secretion more potently than the H₂ antagonists, regardless of stimulus, with the ability to raise the median pH of gastric contents to levels above 5.0 (Figure 1), whereas H₂ antagonists only achieve median pH levels below 2.0 (Figure 1). With the ability to so potently reduce acid, various studies have shown that the more extreme acid reduction is necessary to heal esophagitis, especially esophagitis of more severe grades [5, 6], most of which are resistant to H₂ antagonist treatment [20-23]. The degree to which acid reflux is diminished by omeprazole at different doses [30] is reflected
in some studies by improvement in healing rates and in the speed and extent of symptom relief [1, 3-5, 24, 27]. Many cases, however, require up to two or more months to achieve full healing [1, 4, 24], and 50 percent of Grade IV patients may be initially resistant to omeprazole [4] due to a combination of inadequate acid suppression and impaired motility-dependent clearance of the esophagus detected by 24-hr pH recordings [27]. These require higher doses and more prolonged courses of treatment. Most, if not all, such patients require indefinite treatment with omeprazole.

Arguing from the knowledge that profound acid suppression is necessary for the healing of esophagitis, especially that resistant to H₂ antagonists, and that omeprazole maintains gastric pH outside the pH optimum range of pepsin (Figure 1), we may assume that pepsin contributes to or is responsible for persistence of non-healing of esophagitis. Moreover, while acid perfusion alone does not produce experimental esophagitis, the addition of pepsin at physiological concentrations does promote the development of lesions. Since basement membrane collagen is a specific substrate for pepsin, one might postulate that pepsin is possibly a specific factor in the initiation as well as the maintenance of esophagitis [7] and that omeprazole is so effective [3, 4, 24, 27, 30] precisely and only because it renders pepsin ineffective [35]. Lansoprazole has a similar action and
is as effective as omeprazole [31, 32] in suppressing acid secretion. It would, therefore, be expected to have a similar therapeutic effect [1].

RELAPSE AND MAINTENANCE

When treatment is stopped, as many as 80 percent or more of severe esophagitis cases relapse within six months of healing, induced by any method of treatment or any dose of omeprazole [4]. Ranitidine (150 mg, twice daily) did not prevent relapse in 90 percent of cases healed on either omeprazole or ranitidine, compared to 33 percent relapse in 12 months on maintenance omeprazole (20 mg per day) [19]. Daily therapy is required for effective maintenance [1], and in many cases, long-term, possibly life-long, treatment with omeprazole is necessary.

Since relapse is almost universal, especially in Grade III/IV esophagitis, surgery may be a reasonable alternative to life-long omeprazole therapy [1, 9]. In the case of surgery, the object is to prevent reflux. The cases most likely to benefit are those with incompetent LES (pressure < 10 mm Hg), especially younger people with potential life-long dependence on omeprazole and those with tracheopulmonary aspiration [9]. In these latter patients, omeprazole may reduce the volume and acidity of the gastric contents, but it does not alter reflux mechanisms nor the frequency of reflux [4].

Chronic use of aspirin or other non-steroidal anti-inflammatory drugs may promote esophagitis or contribute to resistance to therapy or relapse of esophagitis [15]. Mechanisms of these effects have not yet been fully evaluated. Certainly, non-steroidal anti-inflammatory drugs should be proscribed before considering surgery.

COMPLICATIONS

Stricture

Esophageal stricture may be broadly divided into two categories: those associated with or resulting from reflux esophagitis and those due to local action of a variety of pills [8]. Stricture is not the inevitable result of reflux, but some patients have a distinct tendency to stricture, requiring repeated dilatations. Dysphagia predominates and is always present when the lumen diameter is smaller than 12 mm. Heartburn may long precede dysphagia but often ameliorates or disappears with the onset of dysphagia [1]. In such patients, the majority have at least Grade II esophagitis, which is generally resistant to treatment with H2 antagonists, even though acid secretion is not different from controls with esophagitis but without stricture [26]. In such patients, treatment with dilatation is much more effective when combined with adequate long-term acid suppression by omeprazole [22]. With this approach, surgery is seldom required.

In patients with severe grades of esophagitis, the presence of a stricture is a marker for resistance to therapy and for high rates of relapse [26], so that intensive and long-term acid-suppressing therapy with omeprazole combined with esophageal dilatation is indicated [4, 22]. Antireflux surgery is usually successful as well [1] but should be delayed until the esophagitis is healed by omeprazole.

The second group of patients, those with pill esophagitis, is generally older and may or may not give a specific history of an episode of pill impaction. In the majority, with dysphagia predominating. A number have pain, but few have heartburn. The commonest medications involved are quinaglute, doxycyline/tetracycline, potassium tablets, aspirin and ferrous sulfate, which cause acute injury when held up in the esophagus [8]. This may occur because of dysmotility (especially in the elderly), as a result of swallowing in the horizontal posture or because of the presence of a Schatzki ring or reflux stricture. Such lesions may then set up enough inflammation or local spasm
to trap future tablets and so perpetuate a vicious cycle. These cases of stricture are treated by avoidance of the offending medication and dilatation until healed, and they may require local injection of steroids to promote healing. In the absence of reflux (e.g., with mid-esophageal location of stricture), acid suppression is not needed.

Barrett’s Esophagus.

In five to twelve percent of patients with symptomatic reflux undergoing endoscopy, the distal esophagus may be found to be lined with columnar epithelium, so-called Barrett’s esophagus. This condition may be present in young children, raising the possibility that it is a congenital disorder. In adult life, it occurs mostly in age 40-80, more commonly (65-80 percent) in white males and is considered to be the consequence of erosive esophagitis. The importance of this condition is that when the epithelium is of a specialized columnar intestinal type, it carries the potential for malignant transformation to adenocarcinoma [1, 35]. Gastric fundic or junctional epithelium apparently carries no malignant potential, as opposed to intestinal type epithelium. Thus, histologic classification is important in planning surveillance studies [33].

The other significant aspect to Barrett’s epithelium is that it appears to be quite susceptible to reflux damage, frequently presenting with severe grades of esophagitis, frank localized “peptic” ulcer and stricture [22, 33]. There is no indication that these lesions heal more slowly because of the columnar lining [33]. In healing, the epithelium is again covered by the same columnar cells. There is no evidence that the area of columnar metaplasia can be influenced by treatment with acid suppression or elimination of abnormal reflux by surgery. There is also no evidence yet whether effective treatment of the superimposed esophagitis influences the malignant transformation. The whole complex story of Barrett’s esophagus is unfolding at the present time [33]. Questions regarding etiology, natural history, neoplastic transformation and treatment remain incomplete.

COST AND QUALITY OF TREATMENT

Omeprazole is clearly superior to any other medical therapy [1, 19, 25, 27-30]. Because of the high cost of omeprazole (20 mg/day costs $1150/year), various analyses of the cost of alternative treatments have been made. One such study [34] (supported by Merck, Sharp & Dohme) concludes that omeprazole is the most cost-effective treatment in patients in whom conservative (lifestyle) treatment, so-called Plan 1 [10], fails to relieve persistent reflux symptoms. In young persons, antireflux surgery, where indicated, may be preferable, especially if, as it appears, laparoscopic techniques reduce risk and morbidity. For those with reflux and laryngobronchial aspiration not relieved by omeprazole, surgery is indicated.

CONCLUSION

Pharmacologic treatment of reflux esophagitis and its symptoms clearly depends on the adequate suppression of gastric acidity. The threshold for effective treatment appears to be an increase in gastric juice pH to levels outside the optimum for pepsin [35]. Omeprazole (and lansoprazole) inhibitors of the proton pump, but not H₂ antagonists at any reasonable dose, achieves a median pH > 5, with 85 percent of samples above pH 4.0. The optimum pH for pepsin is below 3.5. Thus, as shown in Figure 1, proton pump inhibitors achieve such a pH profile, while H₂ antagonists do not. This concept provides a useful marker for therapeutic effectiveness, which has been determined from results of clinical trials. Until we understand the determinants of susceptibility to mucosal ulceration, acid suppression remains the mainstay of therapy.
REFERENCES

1. Marks, R.D. and Richter, J.E. Gastroesophageal reflux disease. In: Zakim, D., Dannenberg, A.J., eds. Peptic Ulcer Disease and Other Acid-Related Disorders. New York: Academic Research Associates, Inc.:1991.

2. Hirschowitz, B.I. A critical analysis, with appropriate controls, of gastric acid and pepsin secretion in clinical esophagitis. Gastroenterology 101:1149-1158, 1991.

3. Sontag, S.J., Hirschowitz, B.I., Holt, S., Robinson, M.G., Beher, J., Berenson, M.M., McCullough, A., Ippoliti, A.F., Richter, J.E., Ahtaridis, G., McCallum, R.W., Pambianco, D.J., Vlahcevic, R.Z., Johnson, D.A., Collen, M.J., Lyon, D.T., Humphries, T.J., Cagiola, A., and Berman, R.S. Two doses of omeprazole versus placebo in symptomatic erosive esophagitis: the U.S. multicenter study. Gastroenterology 102:109-118, 1992.

4. Hetzel, D.J., Dent, J., Reed, W.D., Narielvala, F.M., MacKinnon, M., McCarthy, J.H., Mitchell, B., Beveridge, B.R., Laurence, B.H., Gibson, G.G., Grant, A.K., Shearman, D.J.C., Whitehead, R., and Buckle, P.J. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. Gastroenterology 95:903-912, 1988.

5. Bell, N.J.V. and Hunt, R.H. Role of gastric acid suppression in the treatment of gastro-oesophageal reflux disease. Gut 33:118-124, 1992.

6. Bell, N.J.V., Burget, D., Howden, C.W., Wilkinson, J., and Hunt, R.H. Appropriate acid suppression for the management of gastro-oesophageal reflux disease. Digestion 51(suppl 1):59-67, 1992.

7. Hirschowitz, B.I. Pepsin in the pathogenesis of peptic ulceration. In: Halter, F., Garner, A., Tytgat, G.N.J., eds. Mechanisms of Peptic Ulcer Healing. Dordrecht, The Netherlands: Kluwer Academic Publishers; 1990, pp. 183-194.

8. Kikendall, J.W., Friedman, A.C., Oyewole, M.A., Fleischer, D., and Johnson, L.F. Pill-induced esophageal injury. Case reports and review of the medical literature. Dig. Dis. Sci. 28:174-182, 1983.

9. Richter, J.E. Surgery for reflux disease: reflections of a gastroenterologist (Editorial). N. Engl. J. Med. 326:825-827, 1992.

10. Kitchin, L.I. and Castell, D.O. Rationale and efficacy of conservative therapy for gastroesophageal reflux disease. Arch. Intern. Med. 151:448-454, 1991.

11. Spechler, S.J. Epidemiology and natural history of gastro-oesophageal reflux disease. Digestion 51(suppl 1):24-29, 1992.

12. Behar, J., Biancani, P., and Sheahan, D.G. Evaluation of esophageal tests in the diagnosis of reflux esophagitis. Gastroenterology 71:9-15, 1976.

13. Wieniebeck, M. and Barnert, J. Epidemiology of reflux disease and reflux esophagitis. Scand. J. Gastroenterol. 24(suppl 156):7-13, 1989.

14. Roesch, W. Erosions of the upper gastrointestinal tract. Clinics in Gastroenterology 7:623-634, 1978.

15. Lanas, A. and Hirschowitz, B.I. Significant role of aspirin use in patients with esophagitis. J. Clin. Gastroenterol. 13:622-627, 1991.

16. Koelz, H.R., Birchnler, R., Bretholz, A., Bron, B., Capitaine, Y., Delmore, G., Fehr, H.F., Fumagalli, I., Gehrig, J., Gonvers, J.J., Halter, F., Hammer, B., Kayasseh, L., Kobler, E., Miller, G., Münst, G., Pelloni, S., Realini, S., Schmid, P., Voiroil, M., and Blum, A.L. Healing and relapse of reflux esophagitis during treatment with ranitidine. Gastroenterology 91:1198-1205, 1986.

17. Sabesin, S.M., Berlin, R.G., Humphries, T.J., Bradstreet, D.C., Walton-Bowen, K.L., and Zaidi, S. Famotidine relieves symptoms of gastroesophageal reflux disease and heals erosions and ulcerations. Arch. Intern. Med. 151:2394-2400, 1991.

18. Johnson, N.J., Boyd, E.J.S., Mills, J.G., and Wood, J.R. Acute treatment of reflux esophagitis: a multicentre trial to compare 150 mg ranitidine b.d. with 300 mg ranitidine q.d.s. Aliment. Pharmacol. Therap. 3:259-266, 1989.

19. Lundell, L., Backman, L., Ekström, P., Enande, L.-K., Falkmer, S., Fausa, O., Grimelius, L., Havu, N., Lind, T., Lönnroth, H., Sandmark, S., Sandzén, B., Unge, P., and Westin, I.H. Prevention of relapse of reflux esophagitis after endoscopic healing: The efficacy and safety of omeprazole compared with ranitidine. Scand. J. Gastroenterol. 26:248-256, 1991.

20. Knill-Jones, R.P., Card, W.I., Crean, C.P., James, W.B., and Spiegelhalter, D.J. The symptoms of gastro-oesophageal reflux and oesophagitis. Scand. J. Gastroenterol. 19(suppl 106):72-76, 1984.
21. Spechler, S.J. Barrett's esophagus: what's new and what to do. Am. J. Gastroenterol. 84:220-223, 1989.
22. Lundell, L. Acid suppression in the long-term treatment of peptic stricture and Barrett's esophagus. Digestion 51(suppl 1):49-58, 1992.
23. Brunnen, P.L., Karmody, A.M., and Needham, C.D. Severe peptic oesophagitis. Gut 10:831-837, 1969.
24. Hetzel, D.J. Controlled clinical trials of omeprazole in the long-term management of reflux disease. Digestion 51(suppl 1):35-42, 1992.
25. Klinkenberg-Knol, E.C. and Meuwissen, S.G.M. Medical therapy of patients with reflux oesophagitis poorly responsive to H2-receptor antagonist therapy. Digestion 51(suppl 1):44-48, 1992.
26. Hirschowitz, B.I. Acid and pepsin secretion in patients with esophagitis refractory to treatment with H2 antagonists. Scand. J. Gastroenterol. 27:449-452, 1992.
27. Klinkenberg-Knol, E.C. and Meuwissen, S.G.M. Combined gastric and oesophageal 24-hour pH monitoring and oesophageal manometry in patients with reflux disease, resistant to treatment with omeprazole. Aliment. Pharmacol. Therap. 4:485-495, 1990.
28. Sandmark, S., Carlsson, R., Fausa, O., and Lundell, L. Omeprazole or ranitidine in the treatment of reflux esophagitis: results of a double-blind, randomized, Scandinavian multicenter study. Scand. J. Gastroenterol. 23:625-632, 1988.
29. Dent, J., Bremner, C.G., Collen, M.J., Haggitt, R.C., and Spechler, S.J. Barrett's oesophagus. Working party report to the world congresses of gastroenterology, Sydney 1990. J. Gastroenterol. Hepatol. 6:1-22, 1991.
30. Hillman, A.L., Bloom, B.S., Fendrick, A.M., and Schwartz, J.S. Cost and quality effects of alternative treatments for persistent gastrooesophageal reflux disease. Arch. Intern. Med. 152:1467-1472, 1992.