Peptic Acid Disorders: Developing a Disease Management Program

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OBJECTIVE:
To review peptic acid disorders and associated treatment costs while developing a disease management program for these situations.

DATA SOURCES:
Medline search and additional health care periodicals known to the author.

STUDY SELECTION:
Clinical and economic references, decision analysis.

DATA EXTRACTION:
Not applicable.

Disease management has been defined as "planned care that in a systematic way is designed to improve outcomes and to lower costs for a population of patients with a given condition." Mark Zitter, president of San Francisco's Zitter Group, has defined disease management as "a comprehensive, integrated approach to care and reimbursement based on the natural course of disease with treatment designed to address the illness with maximum effectiveness and efficiency." The focus on integration is key, since the fragmented nature of health care delivery, focusing on component care, has been identified as one reason for the failure of cost-control efforts in health care in the 1980s. Despite these and several other available definitions, however, disease management is a phrase tossed around to encompass everything from marketing strategies, designed to maximize drug use, to broad brush-stroked overcoats for otherwise thinly veiled, narrowly focused cost-cutting procedures. It has been termed "among the most abused words in the English language."

According to Zitter, true disease management programs contain the following elements:

- Understanding of the disease state, especially cost drivers
- Treatment based on the disease process, rather than on reimbursement for a given therapy
- Patient education and compliance programs
- Management of treatment that cuts across the continuum of care
- Funding the most powerful intervention

Disease management seeks to change the focus of health care from treating acute flare-ups to managing an entire course of disease through an integrated, comprehensive approach. Such an approach can be used in the area of peptic acid diseases. The first element, understanding the disease state, is the focus of this paper.

Using the approach of evidence-based medicine (EBM), guidelines are developed based on objective examination of the literature, not on intuition and unsystematic clinical experience or pathophysiologic rationale. It represents an escape from the "in my experience" approach to medicine. The EBM approach rates literature based on its...
strength, with the highest rating given to prospective, randomized trials. Grade A evidence is based on one or more prospective, randomized, controlled trials with low potentials for false-positive and false-negative errors. Grade B evidence is based on prospective, randomized, controlled trials, but with high false-positive or false-negative error potentials. Grade C evidence is based on nonrandomized, prospective, controlled trials that compare contemporaneous patients or current and former patients, or is based on noncontrolled case studies evaluating 10 or more patients. Grade D evidence is based on a retrospective analysis. Grade E evidence is based on case reports of fewer than 10 patients, personal experience or expert opinion, or indirect evidence found in clinical trials. My institution has added categories of grades for evidence based on a meta-analysis (grade M), evidence based on a decision analysis or pharmacoeconomic analysis (grade Q), and evidence based on a summary (grade S).

PEPTIC ACID DISORDERS

For the purposes of this review, peptic acid disorders are defined as disorders whose primary pathology is associated with oversecretion of gastric acid. Because of some commonality in symptoms and similarities in treatment, three illness will be discussed, peptic ulcer disease (PUD), nonulcer dyspepsia (NUD), and esophagitis. Patients with PUD or NUD most frequently present to their physicians with complaints of epigastric pain and/or discomfort, a constellation of findings often referred to as dyspepsia.

Dyspepsia

Management of the patient presenting with dyspepsia is complicated by multiple options and a diverse differential diagnosis with widely overlapping symptomatology. The term "dyspepsia," although widely used, has escaped clear definition. It has been called "ill-defined" and "vague and misunderstood." Relevant symptoms include abdominal pain or discomfort, postprandial fullness, abdominal bloating, belching, early satiety, anorexia, nausea, vomiting, heartburn, and regurgitation.

For the purposes of this review, the definition established by Talley will be used: abdominal pain or discomfort centered in the upper abdomen.

Some 15% of Americans suffer from dyspepsia on a chronic or recurrent basis. Of those whose dyspeptic symptoms become severe enough to warrant endoscopy, approximately 24% have gastroesophageal reflux disease, 20% peptic ulcer disease, 21% gastroduodenal inflammation without ulcer, and 34% normal mucosa. About 2% have a malignancy. Dyspepsia may account for 2-5% of all visits to primary care physicians and up to 20-40% of consultations with gastroenterologists.

Despite contradictory data, most investigators have concluded that empiric treatment of the patient presenting with dyspepsia—rather than diagnostic work-up through upper gastrointestinal radiography or endoscopy—is rational and cost-effective. In fact, in a position paper, the American College of Physicians recommended an empiric approach, reserving endoscopy for patients who do not respond to initial therapy.

Peptic Ulcer Disease

Some 500,000 new cases of peptic ulcer are diagnosed in the United States each year, and 4.5 million persons experience recurrent ulcers. This illness alone accounts for one million hospitalizations annually with direct expenditures of $1.78 billion for hospital costs, $126.8 million for physician office visits, and $53 million for prescription drugs. Additionally, an estimated indirect cost of $303 million results from lost worktime. These figures do not include the far greater number of persons who self-treat or seek medical advice for nonspecific upper abdominal pain or dyspepsia. The frequency of this disease and its substantial fiscal impact suggests that a targeted approach may improve outcomes and reduce costs. How can these lofty goals be approached?

ROLE OF HELICOBACTER PYLORI IN PEPTIC ULCER DISEASE

Beginning with its isolation and identification in 1983, understanding of the role of Helicobacter (formerly Campylobacter) pylori in the pathogenesis of peptic ulcer disease has grown. A recent Consensus Development Conference of the National Institutes of Health recommended that patients with ulcers who also have H. pylori be treated with appropriate antibiotics targeted at the pathogen. Sound clinical and economic data support this recommendation.

The traditional approach of managing patients with antisecretory agents (histamine H2 antagonists and proton-pump inhibitors) results in high healing rates for both duodenal and gastric ulcers. However, following a four- to eight-week regimen, recurrence is very common. In perhaps the most convincing study to date, Graham et al. demonstrated that concurrent use of antibiotics directed against H. pylori dramatically reduced recurrence rates in patients with duodenal and gastric ulcers, relative to therapy with ranitidine alone. One-year recurrence rates were 12% and 13% for duodenal ulcer and gastric ulcer, respectively, in patients treated with antibiotics, versus 95% and 74%, respectively, in patients treated with an acute regimen of ranitidine alone.

The economic benefit of H. pylori eradication can also be profound. In a noncontrolled trial, 175 patients with PUD and positive for H. pylori were treated with antisecretory therapy and antibiotics; 106 patients had effective eradication of H. pylori. This group had a lower rate of gastrointestinal hemor-
In a well-performed decision analysis, Fendrick et al. analyzed a cohort of 1,000 hypothetical patients presenting with symptoms suggestive of PUD who were not concurrently taking NSAIDs. The decision analysis consisted of five arms: 1. Immediate endoscopy with biopsy for *H. pylori*; 2. Immediate endoscopy without a biopsy (those with documented PUD were assumed to be positive for *H. pylori*, and treated accordingly); 3. Empiric H2-antagonist therapy; 4. Empiric H2-antagonist therapy plus anti-*H. pylori* antibiotics; 5. Empiric H2-antagonist therapy and serologic testing for *H. pylori* (those testing positive for *H. pylori* were then treated accordingly).

The model included an every-six-week assessment of each patient for the presence or absence of recurrent symptoms, *H. pylori* status, and active ulcer disease. For the three empiric arms, any patient developing recurrent symptoms was assumed to have undergone endoscopy. Serology was assumed to be 95% sensitive and specific for current or past infection with *H. pylori*. Finally, eradication of *H. pylori* in patients with NUD was assumed to offer no benefit. A large number of clinical probabilities were included from the medical literature.

Among them were the following:

- **\( \Delta \)** Likelihood of active ulcer disease (20%)
- **\( \Delta \)** *H. pylori* infection if ulcer is present (95%)
- **\( \Delta \)** *H. pylori* infection if ulcer is not present (50%)
- **\( \Delta \)** *H. pylori* eradication with antibiotic therapy (60%)
- **\( \Delta \)** Ulcer healing with antisecretory therapy (75%)
- **\( \Delta \)** Ulcer recurrence in *H. pylori*-positive patients (2.7 per 100 patient-months)
- **\( \Delta \)** Ulcer recurrence in *H. pylori*-negative patients (0.6 per 100 patient-months)

Cost inputs were derived from charges allowed by the Health Care Financing Administration for Medicare. The perspective was that of the payer. Sensitivity analyses were performed for all clinical variables.

The analysis demonstrated that the most cost-effective strategy was empiric antisecretory therapy combined with anti-*H. pylori* antibiotic therapy ($4,155 per ulcer healed). This strategy was followed by empiric antisecretory therapy combined with *H. pylori* serology ($4,541), and empiric antisecretory therapy alone ($4,835). All three of these strategies were far more cost-effective than the two strategies calling for initial endoscopy, $6,984 for endoscopy alone and $8,045 for endoscopy with biopsy. Analysis of total costs demonstrated the same order for the strategies: $818, $894, $952, $1,375, and $1,584, respectively.

Thus, this study demonstrated that, despite an overtreatment rate of 80% (i.e., 80% of those treated do not benefit), the strategy calling for a purely empiric approach is the least costly and most cost-effective. The study did not take into account the possible ill effects of antibiotic...
overprescribing on the development of resistance. For this reason, it may be reasonable to select the serology strategy (e) as an alternative to the current practice (strategy c). The strategy of empirically treating dyspeptic patients who test positively for *H. pylori* is also suggested by Graham and Rabeneck.23

### Optimal Regimen for Treating *H. pylori*

An optimal antibiotic regimen is simple to use, consisting of a single dosing regimen of one or two inexpensive antibiotics with few side effects and a high cure rate. Unfortunately, no such regimen is available in the treatment of *H. pylori*. The classic “triple therapy,” a combination of a bismuth salt, metronidazole, and tetracycline, has consistently demonstrated high eradication rates, usually more than 90–95%. Using amoxicillin in place of tetracycline reduces the eradication rate by about 10%. A one-week course of triple therapy has been demonstrated to be as effective as the original two-week course, with a higher rate of patient compliance, 91% versus 70%.24 Although high eradication and ulcer cure rates have been demonstrated without concurrent antisecretory therapy,25–26 triple therapy is generally combined with an antisecretory agent to reduce pain associated with the ulcer.25

As would be expected, eradication depends on patient compliance with the regimen. In a study by Graham et al.,27 when patients took more than 60% of the total tablets of triple therapy, the eradication rate was 96%; when they took less than 60%, the eradication rate was only 69%. A recent decision analysis concluded that triple therapy would be the optimal regimen if compliance was greater than 53%, assuming a low rate of metronidazole resistance.28

Although side effects such as nausea, vomiting, and diarrhea may occur in 20–25% of patients, drop-out rates in clinical trials have been low, generally less than 8%.21 A pharmacist-based *H. pylori* clinic has reduced expenditures for long-term H₂-receptor antagonists by identifying such patients, testing them for *H. pylori*, and treating those with positive results.29,30 Such a clinic could also attempt to follow-up with patients to improve compliance.

Clearly, some patients cannot or will not take triple therapy. For these patients, alternatives are needed. Additionally, metronidazole resistance is associated with a lower eradication rate.20–24 In two trials of classic triple therapy, eradication rates were 90–96% in patients with metronidazole-susceptible strains, but only 32–36% in patients with metronidazole-resistant strains.31,32 Women appear to be approximately twice as likely as men to harbor metronidazole-resistant strains of *H. pylori*, perhaps because of more frequent metronidazole administration.33,34 If a metronidazole-based regimen is followed by recurrence, an alternative regimen without that agent would be needed.

The initial excitement of a simple omeprazole-amoxicillin regimen has been tempered by reports of eradication rates as low as 37%. The eradication rate can be increased to 80–90% by using very high doses of the proton-pump inhibitor (e.g., omeprazole 120 mg/day),35,36 but such doses are remarkably expensive. Even a 60 mg/day dose of omeprazole when combined with amoxicillin for 10–14 days achieves an eradication of less than 40%.29

A regimen of a proton-pump inhibitor plus metronidazole and clarithromycin may be the optimal back-up to triple therapy. Using a one-week course of relatively low doses of the proton-pump inhibitor (standard doses once or twice a day),

<table>
<thead>
<tr>
<th>Description</th>
<th>Drugs and Dosing</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Traditional triple therapy (BMT)</td>
<td>Bismuth subsalicylate (Pepso Bismol) 2 tablets q.i.d. + metronidazole 250 mg t.i.d. + tetracycline 500 mg q.i.d. for two weeks, Add H₂A or PPI</td>
<td>Extensively researchedb</td>
<td>Large number of tablets (15–17/day) Complex three- and four-times daily regimens If compliance is &lt; 60%, eradication is &lt; 70%. If organism is metronidazole-resistant, eradication rate may be only 30–60%</td>
</tr>
<tr>
<td>Omeprazole + clarithromycin (OC)</td>
<td>Omeprazole 40 mg q.d. + clarithromycin 500 mg t.i.d. for two weeks, followed by omeprazole 20 mg q.d. for two weeks</td>
<td>Simple regimen</td>
<td>Lower eradication rate (70–85%) Expensive</td>
</tr>
<tr>
<td>RBC + clarithromycin</td>
<td>Ranitidine–bismuth citrate 400 mg b.i.d. for four weeks plus clarithromycin 500 mg t.i.d. for two weeks</td>
<td>FDA approved</td>
<td>Lower eradication rate (70–80%) Expensive</td>
</tr>
<tr>
<td>PPI-based triple therapy</td>
<td>Omeprazole 20 mg (or lansoprazole 30 mg) b.i.d. + metronidazole 500 mg (or amoxicillin 1 g) b.i.d. + clarithromycin 500 mg b.i.d. for one week</td>
<td>High eradication rate (85–95%)</td>
<td>Less extensively studied Some experts recommend 10 days (rather than one week)</td>
</tr>
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a Regimens using five tablets per day have also demonstrated efficacy.
b Pending FDA approval.
several investigators have produced eradication rates approaching 90%.\textsuperscript{40-42} A cost-effectiveness analysis concluded that a one-week regimen of omeprazole 20 mg/day, metronidazole 400 mg twice daily, plus clarithromycin 250 mg twice daily was associated with the greatest cost–benefit ratio.\textsuperscript{43}

A simpler regimen consisting of a proton-pump inhibitor plus clarithromycin has been advocated by some. However, in one prospective, randomized trial, the eradication rate associated with a one-week duration of this regimen was only 50%.\textsuperscript{44} In another comparative trial, 14 days of high-dose omeprazole (60 mg/day) plus 10 days of clarithromycin 1500 mg/day achieved an eradication rate of only 59%, whereas a 14-day regimen of omeprazole, clarithromycin, and amoxicillin eradicated \textit{H. pylori} in 90% of cases.\textsuperscript{45} Lansoprazole 30 mg twice daily has also been combined with clarithromycin and amoxicillin to achieve an eradication rate of 90%.\textsuperscript{46} Thus, a regimen of a proton-pump inhibitor with clarithromycin and amoxicillin might prove very useful in recurrences and in areas where metronidazole resistance is common. Another possible regimen in such a situation is bismuth subsalicylate, clarithromycin, plus tetracycline, a two-week regimen of which was associated with an eradication rate of 93%.\textsuperscript{47}

Table 1 summarizes the regimens approved for use by our medical group.

**OPTIMAL TREATMENT STRATEGY FOR ESOPHAGITIS**

In developing a disease management program for acid-related disorders, strategies are required for management of patients with esophagitis. At least three patient populations must be considered, and the strategies for each may differ. First, patients with no specific reflux symptoms have endoscopy for recurrent dyspepsia and a diagnosis of esophagitis results. Some 20% of people with recurrent dyspepsia have esophagitis.\textsuperscript{48} On the other extreme is the patient who presents with heartburn and regurgitation as the dominant symptoms. In these patients, a clinical diagnosis of esophagitis has a sensitivity of 78% and a specificity of 60%.\textsuperscript{49} Because of the high probability of the diagnosis, empiric therapy for these patients is reasonable. Third, some patients have heartburn and/or regurgitation in combination with other dyspeptic complaints, such as epigastric pain or discomfort. For them, the clinical diagnosis of esophagitis cannot be made reliably.\textsuperscript{50,46,47} Unfortunately, only one third of patients with complaints consistent with gastroesophageal reflux will be positively diagnosed using endoscopy.\textsuperscript{46} Thus, additional diagnostic work-up may be necessary.

Unlike duodenitis and gastritis, esophagitis is not associated with \textit{H. pylori}, but such gastroesophageal reflux conditions require an estimated $2–3$ billion of prescription and nonprescription medications annually. The incidence of this disorder is difficult to estimate, since its spectrum of presentation is diverse. Approximately 44% of the adult United States population experiences heartburn at least monthly, 18% twice weekly, and 7% daily.\textsuperscript{51} If esophagitis is indeed diagnosed on endoscopy, the rate of complications is not inconsequential, with 10–20% developing serious complications such as esophageal strictures, 10–15% Barrett’s esophagitis, 2–7% esophageal ulcerations, and 5–10% ultimately requiring surgical repair.\textsuperscript{52} These complications and the chronicity of the disease, leading to repeated physician visits, contribute heavily to the total cost of care of esophagitis.\textsuperscript{46-51}

The initial management of esophagitis includes lifestyle modifications (smoking cessation, weight loss, head elevation during sleep, elimination of caffeine and other foods and beverages that can decrease lower esophageal sphincter tone), antacid therapy, and perhaps nonprescription H2 antagonists. Unfortunately, the degree of symptomatology is not clearly correlated with endoscopic grade of esophagitis.\textsuperscript{53} If grade 2 or greater esophagitis (i.e., erosions) is diagnosed on endoscopy, the illness is considered a chronic one.\textsuperscript{54} Long-term therapy of some sort may therefore be inevitable.

**Acute Treatment of Esophagitis**

Studies using standard doses of H2 antagonists (e.g., cimetidine 400 mg or ranitidine 150 mg twice daily) demonstrated inadequate healing rates of 40–45%.\textsuperscript{46} As a result, the FDA approved a high-dose regimen, consisting of double the standard dose. Even with these higher doses, healing rates have been 68–70% at eight weeks and 57–83% at 12 weeks.\textsuperscript{55} On the other hand, healing rates with proton-pump inhibitors have been consistently better than with H2 antagonists, with healing rates of up to 96% at eight weeks.\textsuperscript{56,57-59}

**Maintenance Treatment of Esophagitis**

Following initial healing of a patient with erosive esophagitis, recurrence is common, with prevalence rates as high as 80% without some form of maintenance therapy.\textsuperscript{60} With maintenance therapy, recurrence rates are substantially diminished. Proton-pump inhibitors reduce one-year recurrence rates to 11–20%. Recurrence rates with H2 antagonists are closer to 50–75%.\textsuperscript{56,57,60} Given the sizable difference in recurrence rates between these two classes of drugs, a reasonable course would be to determine whether the higher cost of the proton-pump inhibitors might be balanced by the higher cost of secondary physician visits and/or examinations associated with the higher failure rates of the H2 antagonists.

Three pharmacoeconomic analyses were performed comparing the total costs of care of omeprazole versus a standard dose of an H2-receptor antagonist,\textsuperscript{61} a high dose of an H2-receptor antagonist,\textsuperscript{62} and a combination of an H2-receptor antagonist and metoclopramide.\textsuperscript{52} In each case, the proton-pump inhibitor was more cost-effective. A subsequent pharmacoeco-
nomic analysis demonstrated that the total cost of care using maintenance doses of lansoprazole would be less than that using brand-name ranitidine and only 3% more than that using generic cimetidine. The improved efficacy, likely associated with higher patient satisfaction scores so important to a managed care organization, would seem to be well worth the few additional dollars. Thus, a strong argument can be made for the use of proton-pump inhibitors in patients with endoscopically confirmed erosive esophagitis.

**OPTIMAL DOSE OF PROTON-PUMP INHIBITORS**

Lower-dose regimens of proton-pump inhibitors have been investigated. In a small, noncontrolled trial, a one-month regimen of omeprazole 20 mg once daily was followed by the same dose given every other day for up to three years in patients with H₂-antagonist-refractory erosive esophagitis. Symptoms were controlled in 92% of cases. A “weekend regimen,” consisting of a three-day-per-week regimen of omeprazole 20 or 40 mg, has been demonstrated to suppress basal and stimulated acid secretion. However, a prospective, randomized trial of the regimen in 87 patients with esophagitis led to disappointing results. Following an acute four- to eight-week regimen of omeprazole 20 mg daily that resulted in cure, patients were randomized to receive omeprazole 10 mg daily or 20 mg three times weekly for a period of six months. Relapse rates were 21% and 54%, respectively. In another trial, 159 patients with healed esophagitis were randomized to receive omeprazole 20 mg daily, omeprazole 20 mg three times weekly, or ranitidine 150 mg twice daily. The rates of continued remission at 12 months were 89%, 32%, and 25%, respectively. Thus, proton-pump inhibitors are substantially more effective than H₂ antagonists at preventing recurrences, and a three-times weekly regimen of a proton-pump inhibitor is less effective than a daily regimen. A reduced-dose regimen given daily may be satisfactory, but it requires further study.

**CONCLUSION**

Managed care organizations can and should take the lead in developing and implementing guidelines for peptic acid diseases with consideration given to the following points:

▲ Peptic ulcer disease not associated with NSAID therapy is curable; only the small minority of patients who are not cured by one or two appropriate antibiotic regimens should receive long-term therapy.

▲ *H. pylori* regimens with high eradication rates should be highly promoted. Consideration can be given to a pharmacist-run clinic or some sort of case manager to follow-up patients to assure compliance.

▲ Primary care practitioners can use the model of Fendrick et al. by seriously considering serology to identify those patients presenting with epigastric pain who have *H. pylori*. Even though many of these patients will have nonulcer dyspepsia and will likely not benefit from antibiotic therapy, the model demonstrates that this strategy is cost-effective.

▲ Patients with erosive esophagitis are clinically and economically best treated with proton-pump inhibitors. Serious consideration should be given to endoscopy for patients with symptoms suggestive of esophagitis, so that those who need these agents can be treated appropriately and those with negative results may be considered for a trial of H₂ antagonists.

▲ References

21. Walsh JH, Peterson WL. The treatment of *He-