

Proton Pump Inhibitors: Cost-Effective Agents for Management of Reflux-Induced Esophagitis

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In this issue, Ofman and colleagues analyze the cost effectiveness of 2 commonly used strategies for the management of gastroesophageal reflux disease (GERD).¹ Affecting up to one third of North Americans at some time and up to 7% daily, GERD can be defined as the pathological reflux of gastric contents into the esophagus. Symptomatically, patients typically complain of heartburn or a burning discomfort arising in the epigastrium or lower chest that radiates upward, although more atypical chest pains, nausea, and swallowing difficulties are not uncommon. In most patients, the esophageal mucosa tolerates this insult well; however, in at least 10% significant inflammation and ulceration occur. These patients are prone to serious complications such as bleeding, stricturing, and less commonly, adenocarcinoma.

The primary pathological alteration in GERD is incompetence of the physiologic barrier between stomach and esophagus: the lower esophageal sphincter (LES). Surgically, this problem can be addressed with procedures such as fundoplication, which is generally reserved for only the most refractory of patients. The vast majority of patients are managed medically. Therapeutic options include lifestyle changes such as smoking cessation and limitation of aggravating factors such as coffee and alcohol, although there is little supportive evidence for these measures in the literature. Over-the-counter antacids, particularly alginates like Gaviscon, often are prescribed for infrequent symptoms. Although pathophysiologically appealing because of their effects on LES pressure and gastrointestinal motility, prokinetics like cisapride are rarely used as first-

line agents because of limited efficacy and potential side effects.

Patients with GERD usually do not have any degree of acid hypersecretion. Despite this, use of acid-reducing medications such as histamine H₂ receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs) is the most efficient approach to management for most patients.

Proton pump inhibitors such as omeprazole and the newer agent rabeprazole are not only far more potent inhibitors of acid secretion than H₂RAs such as ranitidine, but they also have been shown to be more effective in treating both the symptoms and the pathological alterations of GERD.² There has been little debate about this fact since the introduction of PPIs more than a decade ago. However, H₂RAs do provide some relief to most patients, with satisfactory symptom resolution in up to 50%.

Initial concerns about side effects from potent acid suppression have dissipated, making the debate regarding the initial choice for GERD therapy primarily economic. Should initial therapy be with an H₂RA or a PPI? Those advocating a step-up approach would argue that one should use the less expensive H₂RA first, not only because a substantial number of patients will respond well but also because less intensive therapy may encourage more effort toward lifestyle modification. Those advocating the initial use of PPIs would argue that one should take full advantage of a drug that is far more likely to produce both symptomatic and endoscopic remission and that any initial increase in cost would be offset by the ancillary costs incurred by those for whom H₂RA therapy is ineffective.

There is an abundance of literature examining the efficacy of both H₂RAs and PPIs in GERD. Although most studies emphasize endoscopic remission of esophagitis, a significant amount of literature also looks at symptomatic response. Unfortunately, as in most medical conditions, there is a paucity of economic data on which to base policy decisions.

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The decision analysis by Ofman et al makes use of the available literature and incorporates US costs, considering direct medical costs from the perspective of a third-party payer. They focus on a specific GERD population with significant but uncomplicated mucosal damage (grade 2-4 esophagitis) over a 1-year time horizon. This restriction allows very accurate estimation of input variables but tends to limit the generalizability and long-term applicability of the analysis.

Decision analysis is most useful when there are trade-offs inherent in approaching a particular clinical problem. Initially this technique was used when the clinical trade-offs were obvious (eg, side effects of a therapy or investigation vs the potential for therapeutic gain). In recent years, decision analysis has become indispensable in considering economic trade-offs not generally accounted for in clinical trials. It is rare to see a randomized controlled trial with enough power to estimate the frequency of rare outcomes, which may significantly impact overall costs. In addition, trials often have short-term surrogate outcome measures that do not reflect the most clinically relevant outcomes that will drive healthcare utilization, such as need for further physician visits or testing. Trials involving GERD are no exception.

As previously noted, PPIs are an extremely well-tolerated class of medications that have been shown to be superior to H₂RAs. This increased efficacy is accompanied by substantially higher initial drug costs. The trade-off becomes higher initial drug costs versus the costs of investigating and treating the higher number of treatment failures associated with H₂RA therapy.

Not surprisingly, the results of the analysis confirm that PPI therapy is associated with fewer symptomatic recurrences. Therapy with rabeprazole costs approximately \$80 per month more than therapy with ranitidine. How much of that cost difference can be recouped by less subsequent need for physician visits and investigation? This analysis suggests almost all of it. There is an average cost-per-patient difference of less than \$100 over the 1-year time horizon.

When Ofman et al analyzed the data using the incremental cost-effectiveness ratio, it cost approximately \$300 on average to prevent a symptomatic recurrence with rabeprazole. Given the significant impact on health-related quality of life of GERD³ and the effects on economic productivity not accounted for in this analysis, initial PPI therapy in this population appears justified. The argument for initial and maintenance PPI therapy becomes even stronger

when one considers the potential for prevention of future complications such as bleeding, stricturing, and Barrett's metaplasia leading to repeated endoscopy and possibly esophageal cancer.

Perhaps the major limitation of this study is the population considered. Most patients with GERD do not have endoscopically significant esophagitis. Studies suggest that heartburn severity correlates poorly, if at all, with degree of esophagitis. Can the results of this analysis be extrapolated to the 80% to 90% of GERD patients without esophagitis? Certainly we know that endoscopically negative GERD patients respond well to PPI therapy, although there are fewer data on maintenance therapy in these patients.

In discussing their results, Ofman et al analyzed a step-down strategy as well. They estimated that initial rabeprazole therapy followed by maintenance therapy with ranitidine would be almost \$900 less expensive per patient than continuous rabeprazole therapy. In addition, continuous rabeprazole therapy had a considerably higher incremental cost-effectiveness ratio of approximately \$2500 compared with this step-down approach. Because esophagitis recurrence rates approach 50% on H₂RA maintenance therapy, this is not an appealing strategy in patients with endoscopically positive disease. In those with endoscopically negative GERD, however, this approach may represent a reasonable compromise between clinical efficacy and economic considerations.

Until recently, it would be unheard of to use a less effective, less convenient, and less well-tolerated medication purely on the basis of cost. The use of H₂RAs instead of PPIs is one of the best examples of such a policy decision. At least in the case of reflux-induced esophagitis, it appears that cost savings generated by this policy are minimal at best.

... REFERENCES ...

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