Recent Advances in Care: Treatment of Acid-Related Disorders

HIGHLIGHTS

- The Changing Landscape of Health Care
- Current Treatment Trends in Gastric-Reflux Disorders
- Effective Approaches to Acid Suppression
- A Comparison of Proton Pump Inhibitors
Recent Advances in Care: Treatment of Acid-Related Disorders

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Prior to 1980, the paradigm of health care in this country was based on indemnity health plans. Insured patients could choose freely among available providers. Insurers rarely questioned physicians’ decisions. Care was paid for on a fee-for-service basis with providers largely determining the fees. Few health insurance companies saw their job as managing care. Most saw their job as paying the bills.

Yet the 1980s witnessed significant changes. The rapid growth of health care costs and insurance premiums generated pressure from purchasers of health care, including both private payers and the government, to slow the rate of growth. Through the '80s, health care spending continued to rise as a percentage of the gross domestic product (GDP), and by 1990, health care was taking about 12 percent of the total economy. Health care spending was increasing at double-digit rates.1

U.S. health care spending was at about 12 percent of its GDP, while in other developed countries it was about 8 percent.2 Yet U.S. health outcomes were not significantly better; median life expectancy was about the same, and the infant mortality rate was substantially worse.2

Managed care was offered as the way to reduce costs. While managed care organizations (MCOs) were originally formed in the 1940s, their national growth began with the passage of federal health maintenance organization legislation in 1973. Rapid growth of managed care enrollment nationwide occurred in response to the rapid increases in health care costs in the 1980s. Although quality-improvement issues were part of the arguments in favor of managed care, the primary motivation for employers and government to adopt managed care was to contain expenditures.

What happened?
Managed care enrollment increased dramatically during the 1990s. By the late 1990s, about 85 percent of the commercially insured population participated in some form of managed care (e.g., HMO, preferred provider organization, point-of-service plan). In addition, Medicaid recipients were being moved to managed care settings and there was growth in Medicare managed care.

Managed care slowed the growth of health care costs considerably. The annual inflation rate for health care plummeted in the early 1990s, from 4.5 percent above the general rate of inflation down to about 1 percent.3 During the 1990s, there was a change in the relationship between the rates of growth of the economy and the growth of health care expenditures (Figure 1).1 In the middle and latter parts of the decade, the two came together and, in some years the rate of growth of the economy actually exceeded that of health care expenditures. This caused health care spending as a percentage of the economy to plateau, or even fall slightly.

By the late 1990s, decreasing health care inflation rates and a strong economy reduced the pressure on government and employers to control health care costs. Other issues assumed higher business and political priority.

How did managed care reduce costs?
There are only two ways to reduce health care costs: reduce the amount paid per unit of service* and reduce the per capita utilization of services. Most of the reduction in health care costs by managed care plans in the 1990s was due to the negotiation of lower payment rates to health care providers.

The development of new payment systems by Medicare for hospitals and for physicians assisted managed care plans in negotiating lower prices. The Medicare prospective payment system (PPS) replaced cost-based reimbursement for inpatient hospital services beginning in 1983. The Medicare Resource Based Relative Value System (RBRVS) replaced “usual, customary, and rea-

* This can be accomplished by reducing the price for individual services and by shifting from more-expensive to less-expensive services to accomplish the same purpose. Both affect the weighted average price per unit of service.
sonable” (UCR) reimbursement for physician services beginning in 1992.

Medicare became a benchmark for MCOs in their dealings with providers. Some plans have adopted the Medicare fee schedules as a pricing formula. Depending on a plan's market power, some plans have been able to negotiate contracts at less than 100 percent of Medicare rates. Even when a different pricing formula is used, Medicare pricing serves as an important benchmark.

Yet, in recent years, limits on plans' ability to achieve price reductions seem to have been reached. For many reasons, health care providers have been able to negotiate more substantial price increases in the past few years. These reasons include consolidation of hospital systems, creation of independent practice associations to negotiate for physicians, reduced ability of plans to guarantee volume to health care providers due to more inclusive networks, and increased experience in contract negotiation among health care providers.

Utilization management measures by MCOs include, among others, preauthorization, restrictions on direct access to specialists, and selection of physicians with conservative practice styles. While utilization management measures by MCOs have been the focus of political attention, they have never been the main source of cost reductions. Most of the impact of utilization management has been on the use of inpatient hospital services. There has been some impact on the use of physician specialists. Yet the low copayments of managed care plans for office visits to primary care physicians and for prescription drugs may have increased utilization of these services.

Where do we stand today?

Managed care has undoubtedly imposed inconveniences on health care providers and on some patients. Nevertheless, by any objective measurement, the quality of health care delivered through MCOs is as good or better than that delivered through unmanaged indemnity plans. The percentage of enrollees satisfied with their health plans has also remained high. Delivering the same quality of care for a lower cost is good for society as a whole. At the margin, more people will have health insurance when premiums are stable or declining. Fewer people will have health insurance when premiums rise.

Nevertheless, managed care has become the villain in the minds of many consumers and elected officials as a result of backlash from physicians and patients. By the late 1990s, health care providers had won the battle for public opinion and had built a public sense of entitlement to unlimited health care regardless of cost and regardless of contract. The backlash from physicians stemmed from reductions in their income and from the constraints MCOs put on their professional autonomy. While most patients seem to be satisfied with their level of care, there was a dissatisfied minority of patients, a dissatisfied majority of physicians, and a few real horror stories to gain the attention of elected officials. In the booming economy of the 1990s, control of health care costs seemed less important politically. The political goals increasingly became patient choice and restricting the mechanisms managed care plans could use to control costs. This resulted in state and federal legislation for mandated benefits and patient bills of rights.

The number of mandates passed by states increased dramatically during the past five years (Figure 2). These mandates include any-willing-provider legislation, direct access to specialists, the right to sue health plans and employers, provider antitrust exemptions, expanded definitions of medical necessity, and benefit mandates. While each of these mandates contributes just a fraction of a percentage point in increased costs, together they ultimately lead to an increase in the amount charged for health insurance. For example, in Texas, one of the states with the most mandates, mandates account for an additional increase of health care premiums of between 7 percent and 8 percent.

While some of this legislation provides genuine protection for patients, much of it is better seen as protection for health care providers. None of the legislation provides any benefits for people who lose health insurance coverage as a result of higher premium costs.

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**Figure 1** Gross domestic product and health care expenditure annual growth rates, 1990–1999.

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Adapted from CMS.
What issues do we face as a nation?

Although significant changes in the U.S. health care system occurred in the mid-1990s, many changes were undone in the last part of the decade, putting us close today to where we were in 1990 (Figure 3). In 1990, per capita spending on health care was about $2,000. Today, it is about $4,700. U.S. spending per capita is still more than twice the median for other developed countries, as is spending as a percent of national GDP (Figure 4). Yet our infant mortality, life expectancy at birth, and life expectancy at age 65 are worse or not significantly better than other developed countries. So our increased spending is not justified by better health outcomes.

This time, though, public opinion is against the precepts of managed care rather than in favor of them. We are again seeing acceleration in health care expenditures. Recent quotations for health insurance premiums are reported to be 10 to 30 percent higher than in the prior year. Projections from the Social Security Administration predict health care expenditures will rise about 8 percent annually over the next few years and then fall to about 7 percent per year toward the end of the decade. These increases would occur when the economy is projected to grow at about 3 percent (Figure 3). So we will again see health care expenditures rise as a percentage of GDP.

Health care costs will be a growing problem in the next 30 years, as more individuals reach age 65. Today, 13 percent of the population is 65 years or older. In 2030, that figure will rise to 20 percent. Medicare projections from the Centers for Medicare and Medicaid Services (CMS, formerly HCFA) place per capita spending at about $5,700 by the year 2008. Research & Planning Consultants LP projects that with current trends, the figure will be about $9,000 in 2030 (in year 2000 dollars). If accurate, that level of spending would increase health care spending from about 13 percent to about 22 percent of the GDP. These figures are driven not only by the proportion of the population that is older than 65 years, but also by the growth rate of health care expenditures per capita in all age groups.

What is the future?

What does this mean to the nation as a whole? Essentially, if we repeat the experience of the last two decades, we will have health care expenditures growing more rapidly than the economy, leading us back to all the problems we experienced at the end of the 1980s. And as we spend more on health care, dollars are limited for other expenditures that also affect our quality of life. Future health care expenditures may crowd out spending on other social priorities such as education, research and development, and business investment in capital goods. For example, the percentage of the GDP spent on education has not grown since 1970.

Where do we go from here?

The demand for health care services is essentially unlimited, as long as someone else is paying for them. There are four ways to control per-capita health care expenditures: (1) restrict who has access; (2) restrict the treatment; (3) restrict how much care is delivered; and (4) restrict how much providers are paid. Health care at any cost, almost regardless of benefit to the patient, is gaining status as
a political right. To the extent this occurs, market forces are less effective and less acceptable as a means of limiting expenditures. The alternative is a mix of market mechanisms and rationing by government.

While explicit rationing of health care is considered politically taboo, our current systems implicitly ration care. The publicly insured (e.g., Medicaid, children’s health insurance program) have access to a very broad range of services but may have limited access to providers. They may have to wait for care. Those privately insured have access to a broad range of services and providers. The uninsured have very limited access to emergent and urgent services from a limited set of providers. And if you are older than 65, you have essentially unlimited access to care through Medicare with no significant problem of access to providers.

At this time, the Oregon Health Plan is the only public health program in the United States to explicitly address rationing of treatment paid by a health plan. Their system recognizes that while access to health care is a basic right, there is a limit to the amount of money the public sector can devote to health care, and that limited resources necessitate choices about what treatments and conditions can be covered. At present, this approach appears to be the most logical basis for rationing and is consistent with increased emphasis on evidence-based medicine.

While rationing can address some of the equity questions as to how health care is provided, it does not fully address questions of efficiency, efficacy, and quality of care. Physician practice patterns are the most important factor in all three concerns. Because physicians control 85 to 90 percent of health care expenditures, changes within the medical profession have the potential to alter per-capita health care expenditures. Changes may involve how many physicians are trained, how they are paid, and where they practice.

We need to change the paradigm that glorifies individual physician autonomy to a systems paradigm that emphasizes evidence-based medicine and outpatient quality-assurance systems. The lay public believes that the physician knows best, but the average patient has no way to judge whether a physician is following best practices (doing the right thing) and is providing high-quality services (doing the right thing right). Outside the hospital, there is no peer review of physicians except that done by managed care plans. The ability of hospital peer-review systems to require best practices and quality of care for inpatients is questionable.

This creates two issues: First, people resent MCOs overruling their individual physicians. The public has been led to believe that personnel other than physicians within MCOs are overruling their doctors. In fact, the laws in most states actually allow only physicians retained by MCOs to disapprove requested treatment. Second, giving sole authority to the physician translates to no review of his or her work, no preauthorization of treatment to ensure that care is standard and appropriate, and no comparison of practice profiles of physicians to ensure that each individual physician is practicing according to the quality standards set by the experience of a larger group. If managed care plans are not reviewing physician decisions and asking why best practices are not being used, who is?

The focus of state and federal governments on enhanced confidentiality of patient records may interfere with the ability of MCOs to exchange the type of information needed to monitor care, to carry out disease management, and to monitor accountability of and results by individual physicians. If managed care plans are not looking at the overall course of treatment and changes in the patient’s health status, who is?

A political battle is inevitable over the scope of the health care entitlement. Can a health insurance plan limit its offering to a basic package of treatments for certain conditions established, like the Oregon plan, through cost/benefit analysis and a budget constraint? People who want more can buy private supplemental insurance. Alternatively, will the courts and the legislature...
say that no matter what the policy says, any insurance plan must pay for all treatment that could have any benefit to the individual regardless of cost or cost/benefit relationships.

Increasingly health care services are improving quality of life, not simply maintaining life or basic functions. While everyone has an equal right to life, we do not recognize a right to equal quality of life. There has never been a right to equal access to other necessities — housing, food, transportation, etc. — beyond a basic level. A large policy issue will be defining which health care services are basic necessities and hence an entitlement, and which are discretionary expenditures to enhance quality of life. If commercial insurers cannot write limited policies and rely on regulators and courts to respect those limits, then premium rates must be set to cover the risks of unexpected obligations. This prices more people out of the private insurance market and increases the problem of a large and growing uninsured population.

Managed care will survive the public backlash evident today, but in a weakened form. As the economy weakens, and health care costs increase, there will be a renewed interest in reducing expenditures. Younger individuals in this country have grown up within a managed care environment, both as patients and physicians, and accept the practices and general restrictions on care. As older people move out of the system, resistance will begin to dissipate. However, in the current legislative and litigation climate, health insurance plans will, on balance, retreat from managing health care.

If managed care is not the answer to coming increases in U.S. health care costs, what is? Some favor restoring market discipline to individual health care decisions by medical savings accounts. Others favor a single-payer health care system like all other industrialized nations. Both sides have strengths and weaknesses. Neither side believes commercial managed care plans are the correct answer, nor have they determined how to balance physician autonomy with ensuring that patients are treated with best practices applied correctly.

Just as Medicare reimbursement systems became benchmarks for commercial insurance, the results of efforts to reform the Medicare system are likely to be our first indication of the answer the U.S. political system will choose. It is not yet clear whether Congress will enact a broad reform, or whether it will proceed with incremental changes to avoid short-term problems. A serious “train wreck” between health care spending and other federal budget priorities may have to occur before there is the political will for broad reforms.

Summary

The last time the United States experienced rapid increases in health care expenditures in the 1980s, the solution was widespread adoption of managed care by employer-sponsored health plans. To a lesser degree, managed care approaches were adopted for some Medicaid and Medicare enrollees. By the mid-1990s, new Medicare reimbursement policies and the widespread adoption of managed care plans had substantially reduced the growth rate of health care expenditures.

All published studies show that HMOs and other managed care plans have delivered health care of equal or better clinical quality to traditional indemnity insurance plans at a lower cost. Yet as the economy strengthened during the latter ’90s, concerns about overall health care costs lessened, and the public became less willing to accept restrictions on the enrollee’s choice of physician and the physician’s treatment choices. Public opinion turned against the concept of managed care as a result of backlash from both physicians and consumers. Government mandates altered the ability of managed care to deliver on the promise of higher quality at a reduced cost.

Today, health care costs are again rising. The United States is spending significantly more per capita on health care than are other developed nations, with no demonstrable improvement in health outcomes. Estimates suggest that in the next 30 years, health care costs will again rise at a rate faster than that of the economy. Further, rising costs will reflect the impact of an aging population, with more than 20 percent of individuals 65 years or older by the year 2030. Thus, it appears we are again headed for a crisis. However, the environment has changed: As a result of the experience of the last 10 years, the public is now less willing to accept changes to the health care system, and the concept of managed care has negative connotations. Consequently, the crisis may potentially be even worse than that we experienced a decade ago if we are unable to find ways to control health care expenditures.

References

Impact of Acid-Related Disorders
In the United States

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Acid-related disorders, which include duodenal ulcer disease, gastric ulcer disease, Zollinger-Ellison syndrome, and gastroesophageal reflux disease (GERD), are caused by an imbalance between mucosal defense mechanisms and acid secretions. In the United States, the lifetime prevalence of peptic ulcer disease (including duodenal ulcer and gastric ulcer) is about 10 percent. Estimates reveal that about 44 percent of adults have reflux symptoms, from occasional heartburn to severe GERD. The true prevalence of acid-related disorders may be higher, as many who experience symptoms of these conditions are likely to self-medicate and not seek the advice of a physician.

Gastric, duodenal, and esophageal mucosa can all be damaged by acid. In GERD, damage to the esophageal mucosa results from excessive reflux of gastric contents into the lower esophagus, principally due to abnormally frequent relaxation of the lower esophageal sphincter (LES). Reflux disease is a common, chronic disease. Esophagitis is a complication of reflux that develops when mucosal defenses that normally counteract insults on the esophagus succumb to the onslaught of acid pepsin. Esophageal erosions or ulceration develop in about half of individuals with symptomatic GERD. Esophagitis is a complication of reflux that develops when mucosal defenses that normally counteract insults on the esophagus succumb to the onslaught of acid pepsin.

Pathology of acid-related disorders

Figure 1 shows the spectrum of upper gastrointestinal (GI) symptoms. Ulcer-like symptoms are associated with H. pylori infection, chronic use of aspirin and/or NSAIDs, stress, ischemia, or acid hypersecretion. Dysmotility-like symptoms tend to be related to gastric or small-bowel abnormalities. GERD-like symptoms are related to abnormal presence of acid, pepsin, and bile acids in the distal esophagus, complicated by esophageal dysmotility, gastroparesis, and abnormal tissue factors in the esophagus.

Due to more frequent LES relaxations, and in some cases, reduced pressure in the LES, individuals with GERD generally have more episodes of acid reflux than do healthy subjects. The GI contents are most likely to reflux when gastric volume is increased after meals, when the gastric contents are located near the gastroesophageal junction (such as when the patient is bending down), or when gastric pressure is increased (i.e., with obesity,
pregnancy, or binding clothing). The contact of this acid with the esophageal epithelium may be prolonged by abnormal esophageal motility, causing ineffective clearance. The abnormal peristalsis seen in those with GERD is typically more marked in individuals who have severe esophagitis (Figure 2).6 Patients with GERD have delayed gastric emptying, indicating that acid is not cleared from their stomach as rapidly as it is in individuals without reflux disease. The diminished clearance of acid, bile, and food from the stomach allows a greater pool for reflux and increases intraabdominal pressure.

Prolonged contact of acid with the epithelium is central to the development of GERD, which develops when gastric acid overwhelms the intrinsic epithelial defenses and repair mechanisms. Unlike the stomach, which has very tight junctions between the cells and, therefore, does not allow bile salts or acid to diffuse into the mucosa and cause damage, the esophagus is lined by a squamous tissue with gap junctions between the cells. Protection against acid is conferred by overlapping of the cells. When the distal esophagus becomes damaged, however, the cells shrink, pulling apart the junctions and allowing acid and bile salts to enter. Pepsin, a proteolytic enzyme activated when acid facilitates the release of pepsinogen, destroys the tissue in the esophagus. At a pH of 1.3 to 2.3, pepsin increases the severity of mucosal damage and produces inflammation.7 If the pH is above 2.3 to 2.5, the activity of pepsin is reduced, leading to a reduction in damage (Figure 3).8 Peptic activity is markedly reduced at a pH of 4.0 and absent at a pH >5.0; pepsin is denatured and therefore out of the system at a pH >7.0. The cycle is predictable — when protection is lost, injury results; with injury, there is increased sloughing of cells, increased epithelial turnover, and a greater proportion of immature epithelium. Immature epithelium allows more back-diffusion of acid and bile salts, which then stimulate the nervous system, causing the cognition of pain. In short, the acid breakdown of tissue defenses leads to the production of symptoms, erosions, ulceration, and other complications such as bleeding and stricture formation.9

The immature epithelium found in the distal esophagus after injury may have increased potential for malignant transformation, i.e., progression to Barrett’s esophagus and adenocarcinoma. A recently published population-based study in the New England Journal of Medicine from Sweden used personal interviews on the subjects’ history of GERD. Researchers concluded that patients with reflux have a fivefold increased risk of esophageal cancer.10 For patients with moderate or severe reflux symptoms occurring more than three times weekly and persisting for >20 years, the esophageal cancer risk increased significantly. There was no indication in the report whether patients with reflux were treated with a proton pump inhibitor (PPI). This preliminary study suggests that esophageal cancer risk in those with reflux may be an issue and that control or moderation of symptoms may be important.

Recent studies that were conducted in Sweden have indicated major risk factors for the increasing incidence of esophageal adenocarcinoma in association with reflux disease.11-13 In case-control studies, obesity (particularly a body mass index >30 kg/m²) and gastroesophageal reflux were seen as strong risk factors for developing esophageal cancer.11,12 In combination, obesity and reflux symptoms entailed highly increased risk estimates.11 Another study noted the relationship between the
increasing incidence of esophageal adenocarcinoma and the use of LES-relaxing medications. These medications included nitroglycerin, anticholinergics, beta-adrenergic agonists, aminophyllines, and benzodiazepines. The association was especially strong for anticholinergics.\textsuperscript{13}

**Symptoms in acid-related disorders**

Although epigastric pain is the primary symptom of peptic ulcer disease and heartburn is the primary symptom associated with GERD, patients often present with overlapping symptom complexes. Symptoms of ulcer disease and GERD may overlap with symptoms of nonulcer dyspepsia, a condition caused by abnormal upper GI motility associated with altered visceral sensation (Figure 1).\textsuperscript{5} To make the diagnosis, the physician listens to the patient’s description of symptoms and considers the location of the pain, its character, and its relationship to meals. It is also useful to determine whether eating or antacids give relief, as is common in peptic ulcer disease. Ulcer-like symptoms include epigastric pain (relieved by food or antacids) and bleeding, either overt or occult. Dysmotility-like symptoms include early satiety, postprandial bloating, nausea or vomiting, and pain unrelied by intake of food or antacids. GERD-like symptoms include heartburn, regurgitation, and chest pain. Reflux symptoms are insidious in that they come on gradually, tend to persist over time, and force patients to change their lifestyle to accommodate the condition. There is no correlation between the severity of heartburn and the underlying severity of the disease (i.e., esophagitis). Patients with GERD have a difficult time swallowing food. Whereas most healthy individuals will clear a bolus of food in one to two swallows, individuals with GERD will require significantly more swallows (Figure 4).\textsuperscript{14}

**Treating reflux disease**

Studies in the literature report that reflux disease has a significant impact on quality of life as assessed by physical pain, mental well-being, and social interaction. Therefore, GERD should be treated aggressively to relieve symptoms and prevent potential long-term complications.

Although patients present with a number of overlapping symptoms, physicians have found that a patient with two or more reflux-like complaints is usually suffering from reflux disease. This finding has led to the concept of empiric PPI therapy in place of diagnostic endoscopy, which is a more expensive option. Endoscopy may be indicated in a patient who has dysphagia or difficulty swallowing, painful swallowing, anemia (particularly in the elderly), some weight loss, or other signs of bleeding or chest pain; other patients can be treated initially with a PPI. If the symptoms are relieved by the PPI, the individual is most likely suffering from GERD.

Options in treating GERD include histamine-2 receptor antagonists (H\textsubscript{2}RAs), prokinetic agents, PPIs, or a combination of these agents. A review of the literature indicates that the available therapies for treating this disease demonstrate a wide range of effectiveness.

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**Figure 3** Relationship of pH and esophageal damage in a canine model.

**Figure 4** Number of swallows to clear bolus of food significantly greater in patients with reflux compared with healthy subjects.
The enzyme responsible for secretion of hydrogen ions from parietal cells into the gastric lumen, hydrogen-potassium adenosine triphosphatase, is called the proton pump. Compounds that bind this enzyme, known as PPIs, have a profound inhibitory effect on gastric acidity. Currently available PPIs include omeprazole, lanso-prazole, pantoprazole, esomeprazole, and rabeprazole. Results of research in the last 10 to 15 years suggest that the most effective therapy for GERD is a PPI twice or three times daily and that the least effective treatment is to use over-the-counter medicines, including antacids and low-dose H$_2$RAs. The PPIs are effective in GERD because they eliminate acid, thus preventing the release of pepsin and consequent damage to the esophageal mucosa. Effectiveness in treating acid-related disorders may be assessed through measurements of acid suppression, including the degree, the duration (percentage of a 24-hour period), and the length of treatment. An increase in any or all of these parameters results in an increase in the proportion of mucosal healing at any time point. Curing of duodenal ulcer requires steady acid suppression throughout the day. A large study conducted with 1,000 patients found that the pH must reach 3.0 for about 16 hours each day to achieve a 90 percent healing rate. To heal GERD, the critical pH is 4.0. Due to rising concern about the risk of Barrett’s esophagus and esophageal cancer in those with long-term reflux disease, physicians and patients have shown less concern about harmful effects of long-term acid suppression with PPIs.

Almost every algorithm for treating reflux disease suggests the use of step-up therapy. A step-up protocol recommends starting with the least expensive therapy and then modifying treatment according to the patient’s response. If the therapy is ineffective, the next more expensive therapy is tried. If that therapy fails to provide relief, the next therapy is tried; the patient continues through the list until an effective therapy is found. While such treatment initially keeps medication costs down, it ultimately leads to increases in both direct and indirect costs of caring for the patient, because therapy with less expensive options, e.g., H$_2$RAs, is likely to fail. Data from prospective, randomized clinical trials of H$_2$RA therapy in GERD indicate that esophagitis will heal and symptoms will be relieved in only about 50 percent of cases, and there are no data to suggest that a significant proportion of cases will be kept in remission. In addition, tolerance occurs with all H$_2$RAs. When acid is suppressed, histamine receptors on parietal cells are up-regulated. As the dose of the H$_2$RA is increased, the receptors continue to be up-regulated and tolerance develops.

When patients have unrelieved symptoms, there are increased costs of care beyond drug therapy. At a minimum, patients return to the physician’s office for another prescription. Costs may be increased for additional diagnostic tests (e.g., endoscopy), emergency room visits, or hospital admissions for atypical chest pain. The H$_2$RAs should be reserved for mild or intermittent disease and the more effective agents, the PPIs, should be the standard therapy for most patients.

**Summary**

Acid-related disorders are common conditions that negatively impact quality of life for a significant number of people nationwide. The pathology of these conditions involves an imbalance between acid secretion by gastric parietal cells and the ability of upper GI tract mucosa to defend against the effects of the acid. Therefore, therapy is targeted at elevating gastric pH. PPIs are used to control the effects of excessive acid secretion. This class of drugs has a unique mechanism of action that inhibits the final pathway to gastric acid secretion — the parietal cell proton pump.

**References**

Comparative Pharmacology Of Proton Pump Inhibitors

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Gastric acid secretion is regulated by a network of central and peripheral mechanisms. The final step in the process occurs when hydrogen-potassium adenosine triphosphatase (the proton pump) exchanges intracellular hydrogen for extracellular potassium.\(^1,2\) Parietal cells of the gut contain a number of proton pumps. The proton pumps are inactive until they migrate to and extend cysteine residues through the cell wall. Once a proton pump is active, it has the ability to pump hydrogen ions into the secretory canaliculus, creating an acidic environment. The hydrogen ions combine with chlorine to form hydrochloric acid. The formation of hydrochloric acid is dependent on a number of mediators that activate the parietal cell through effects on membrane receptors, ion channels, and signal transduction mechanisms.\(^1\) Proton pump inhibitors (PPIs) block the final step of gastric acid secretion by the parietal cell.

Proton pump inhibitors

The PPIs are substituted benzimidazoles. The agents that belong to this class of drugs include omeprazole, lansoprazole, pantoprazole, esomeprazole, and rabeprazole. All PPIs are effective therapies for control of the excess gastric acid secretion that is associated with acid-related disorders. Whereas all the PPIs currently on the market have been shown to be clinically useful, they do not all have the same pharmacologic and clinical properties. The pharmacokinetic properties of the PPIs are summarized in Table 1. Knowledge of the differences that exist in pharmacology and clinical safety and efficacy may add to the optimal use of these agents for the management of acid-related disorders.

**Activation**

All PPIs are prodrugs that require acid-induced activation. After administration, PPIs are absorbed systematically and then resorbed into the canalicular space. Because the PPIs are weak bases, they become ionized when they are in the acidic environment of the canalicular space. Once ionized, the PPI is trapped in the acidic medium, becoming concentrated at the site of activity. The molecule is protonated, which changes its shape, and it is converted to its active form — a sulfenamide with exposed sulfur atoms. The exposed sulfur atoms bind covalently to the sulfur atoms in the cysteine groups of the protein pump. Once the drug binds to the proton pump, the pump is unable to exchange potassium for hydrogen in the parietal cell and is thus rendered inactive (Figure 1).\(^1\) All the PPIs currently on the market share one common binding site; each also has between one and four additional binding sites.

**Differences in activation.** While the process of activation is generally the same for each of the PPIs, the protonation and activation steps are both pH and drug dependent. The five currently available agents differ in rate of activation, which may impact their onset of action.
action. The rate of acid-induced activation of an individual PPI depends on the reactivity (i.e., the pKₐ) of the molecule. The pKₐ of a PPI is the pH at which half the drug is protonated and half is unionized. The pKₐ values of the PPIs that are currently on the market range from 3.8 to 5.0. The activation rate changes depending on the pH. At an extremely low pH of about 1.2, the activation rates of the various PPIs are all very rapid and similar. Any small differences in activation rates are not clinically significant. At higher pH values, however, there are differences among the PPIs. For example, at a pH of 5.0, activation half-lives for the PPIs vary: approximately 7 minutes for rabeprazole, about 90 minutes for omeprazole and lansoprazole, and approximately 5 hours for pantoprazole (Figure 2). To some extent, these differences are related to the pKₐ of the drugs, with rabeprazole having the highest pKₐ — about 5.0.

The times to onset of action (inhibition of gastric acid) of the various PPIs may correlate with their pKₐ values. For example, because of its greater reactivity, rabeprazole may have a more rapid response to first dose than other PPIs. This effect has been demonstrated both in vivo and in vitro. In an in vitro study using porcine gastric cells, which are similar to human gastric cells, rabeprazole demonstrated 100 percent inhibition of the proton pump after only 5 minutes (Figure 3). This inhibition was maintained throughout the 45-minute study period. Lansoprazole, the second best inhibitor of acid at the initial time point, was associated with only 65 percent inhibition. Lansoprazole provided similar inhibition to rabeprazole, but only after 45 minutes of incubation with the cells. By the end of the study, pantoprazole reached only 50 percent inhibition. These differences can be explained, in part, by the agents’ relative acid stability. Rabeprazole is a more reactive molecule that is rapidly converted to the active sulfenamide derivative. In contrast, pantoprazole is much more stable in an acid environment and its conversion to the active sulfenamide derivative is relatively slow.

Acid secretion. The meaningful clinical end point for patients with acid-related disorders is control of acid secretion. Although all of the PPIs control acid secretion, differences have been noted among the five currently marketed compounds in both the degree of acid control and the consistency of acid control. As an example, Figure 4 portrays data comparing acid secretion in 23 healthy Helicobacter pylori–negative subjects treated in a crossover trial with either rabeprazole 20 mg, omeprazole 20 mg, or placebo once daily before breakfast. Intragastric acidity decreases via the buffering action of ingested food and then increases subsequent to acid secretion. Rabeprazole was associated with a statistically significant reduction in acid production compared to omeprazole for the entire 24-hour period, including three postprandial periods. Rabeprazole also produced an earlier decrease in intragastric acidity. In all subjects, there was a nocturnal spike of acidity beginning between approximately 8:30 and 9:00 PM (nocturnal acid breakthrough). This spike was not quite as high with rabeprazole as with...
omeprazole. These data confirm the hypothesis that rabeprazole is activated quickly and therefore has a more rapid onset of effect when compared to omeprazole.

Among PPIs, rabeprazole has the most significant day-1 effects. Intragastric pH in the 24 hours following administration of a single dose is significantly higher for rabeprazole than for lansoprazole, pantoprazole, or omeprazole (Figure 5). Two studies are available comparing rabeprazole to esomeprazole. Warrington et al. found that rabeprazole 20 mg increased the percent of time that gastric pH was >4.0 significantly more than esomeprazole 20 mg on both day 1 and day 5 (Figure 6). Wilder-Smith et al. compared esomeprazole 40 mg, rabeprazole 20 mg, and placebo and found a significant effect on intragastric pH on day 5 for both drugs, with esomeprazole showing a larger difference than rabeprazole. The median pH and the percent of time pH was >4.0 were markedly lower for rabeprazole in the Wilder-Smith study compared to other studies, however.

Overall potency. Fujisaki et al. demonstrated a tenfold difference in the potency of omeprazole and rabeprazole on a molar basis. This difference was determined by an in vitro study in a porcine parietal cell model. The aim of the experiment was to ascertain the concentration of each of the PPIs required to produce 50 percent inhibition of parietal cell activity. With rabeprazole, 50 percent inhibition was seen at about 0.3 mmol/L. Fifty percent inhibition with omeprazole was noted at approximately 3.0 mmol/L.

Potency differences between omeprazole and rabeprazole appear to influence the consistency of their acid-reducing effects. Consistency of effect was evaluated by reviewing individual patient results from the crossover study published by Williams et al. (Figure 7). The magnitude of suppression is much more consistent with rabeprazole than it is with omeprazole.

Metabolism. The metabolism of each PPI is related to extensive hepatic biotransformation with varying degrees of dependence on cytochrome P450 (CYP) 2C19, a polymorphically distributed enzyme. This effect seems to be very pro-

![FIGURE 3 Intensity of proton pump inhibition after one dose.](image)

**FIGURE 3** Intensity of proton pump inhibition after one dose.

![FIGURE 4 Day-1 effects of rabeprazole and omeprazole in 23 healthy Helicobacter pylori-negative subjects.](image)

**FIGURE 4** Day-1 effects of rabeprazole and omeprazole in 23 healthy *Helicobacter pylori*-negative subjects.

nounced with omeprazole, accounting for the high degree of interpatient variability following administration of this agent. Interpatient variability is also seen with lansoprazole, since its metabolism is similar to that of omeprazole. Nevertheless, because lansoprazole and rabeprazole are less CYP2C19-dependent, they have lower variability ratios.

In the general population, individuals can be classified as either homozygous extensive, heterozygous extensive, or poor metabolizers of PPIs, based on their CYP2C19 enzyme activity. Interpatient variability following omeprazole administration was demonstrated in a study that evaluated the effect of polymorphic metabolism on intragastric pH. Omeprazole (20 mg) had no effect on pH in homozygous extensive (i.e., very rapid) metabo-
Omeprazole also has the idiosyncrasy of inhibiting its own metabolism by acting as both a substrate and an inhibitor of CYP2C19. When the area under the time–plasma concentration curve (AUC) is evaluated, a doubling of omeprazole AUC levels is observed between days 1 and 5. It appears that there is a decreased clearance and accumulation of omeprazole after repeated administration.\

Clinical effect of pharmacologic differences

Gastroesophageal reflux. Healing rates in gastroesophageal reflux disease (GERD) or peptic ulcer disease are essentially the same for all the PPIs. Probably because healing rates are so good with these drugs — about 90 percent — it is difficult to see any clinically significant differences between PPIs in most patients. Differences are detectable, however, in surrogate measures of efficacy such as esophageal acid exposure in individuals with GERD. For example, after the first dose of rabeprazole, there was a significant decrease in acid exposure in patients with documented erosive esophagitis. After 7 days of treatment, these patients had acid exposure within normal limits.

H. pylori eradication. Current H. pylori eradication regimens employ 10- to 14-day therapy. Seven-day therapy for H. pylori eradication would benefit patients, since 7-day regimens would both decrease costs and allow patients to use less medication. Studies have shown that omeprazole therapy for 7 days may lack sufficient efficacy because 3 or 4 days are needed to achieve maximal acid suppression with this PPI. Data from European trials with rabeprazole indicate, however, that 7-day combination therapy with rabeprazole is as effective as the results seen with longer regimens. The superiority of rabeprazole over omeprazole in 1-week eradication regimens may be related to rabeprazole’s ability to more quickly affect acid control and also to rabeprazole’s ability to inhibit H. pylori. All PPIs affect H. pylori, and this activity is typically measured by determining change in urease production. About 0.2–0.3 µmol of rabeprazole will inhibit 50 percent of urease activity; omeprazole and lansoprazole are markedly less potent in their inhibi-
tion of *H. pylori*. This pharmacologic difference may explain the clinical differences.

**On-demand therapy.** Rapidity of onset with rabeprazol e is a pharmacodynamic effect. This effect becomes a more important issue when patients choose to take their PPI on demand for symptom relief rather than when therapy is continuous and long term as in ulcer treatment. Many patients use PPIs as needed in response to symptoms, making the onset of action an important differentiator. In contrast to omeprazole and other PPIs, rabeprazole achieves a maximal effect after the first dose, making it a suitable agent for on-demand therapy.

**Summary**

The PPIs are the most effective therapy to suppress gastric acid secretion. These agents decrease acid secretion by inhibiting parietal cell proton pumps. From chemical and pharmacodynamic points of view, subtle differences that exist among the PPIs may influence clinical activity.

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Acid-related disorders, including gastro-esophageal reflux disease (GERD), duodenal ulcers, and gastric ulcers, are common chronic conditions that have a negative impact on patient quality of life. The pathogenesis of these multifactorial conditions involves an imbalance between acid secretion by gastric parietal cells and the ability of the upper gastrointestinal tract to defend itself against the injurious effects of the acid. Treatment for these disorders focuses on raising gastric pH. Neutralizing acid with antacids or decreasing acid secretion with histamine-2 receptor antagonists (H2RAs) was the standard of care before the introduction of proton pump inhibitors (PPIs). Data from throughout the last decade show PPIs to be the most effective therapy for long-term symptom control and the healing of acid-related diseases.1–4 Ulcers will usually heal when the pH is maintained above 3.0 or 3.5, and the esophagus will heal in patients with GERD if the pH is kept above 4.0. In addition to the degree of acid suppression, the duration of acid suppression is important. PPIs maintain intragastric pH at >4.0 significantly longer than do H2RAs or conventional doses of antacids.5 Clinically, this correlates with more rapid and complete mucosal healing (Figure 1).

Five PPIs are currently on the market: omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole. While the use of PPIs to control acid in GERD is probably the most common application of these drugs, PPIs are also used to control atypical GERD manifestations, including noncardiac chest pain, laryngitis, asthma, and cough associated with reflux. PPIs are also useful for treating duodenal ulcer, gastric ulcer, hyper-secretory conditions like Zollinger-Ellison syndrome, and dyspepsia in patients presenting with GERD-like or ulcer-like symptoms. While all PPIs inhibit the enzyme hydrogen-potassium adenosine triphosphatase (i.e., the proton pump) — not all PPIs have the same pharmacologic and clinical properties. Rates of PPI activation differ based on the reactivity of individual molecules.6 The PPIs also differ in potency (which affects consistency of acid suppression) and metabolism. Rabeprazole is the most rapidly activated of the PPIs.7 Due to its greater reactivity, rabeprazole has a more rapid onset of action and thus a more rapid inhibition of the proton pump when compared with the other PPIs.8,9 After the first dose, rabeprazole creates 88 percent of maximal acid suppression on day 1 of therapy. In contrast, day-1 acid suppression induced by omeprazole is 42 percent of maximum.10

In a study that compared the effects of rabeprazole and omeprazole on the activity of H+,K+-ATPase, which was isolated from porcine gastric mucosa, investigators found a tenfold difference in inhibition of the enzyme between omeprazole and rabeprazole, which influences the consistency of acid-reducing effects.11 The magnitude of suppression is much more consistent with rabeprazole than omeprazole.8 The metabolism of the PPIs also differs based on their degree of dependence on cytochrome P450 (CYP) 2C19, a polymorphically distributed enzyme. A high degree of dependence on CYP2C19 gives rise to more interpatient variability with omeprazole and pantoprazole than with lansoprazole and rabeprazole, which are less dependent on this enzyme.

In the absence of head-to-head clinical studies that compare all the available PPIs in each of the different acid-related disorders, surrogate factors are considered in the selection of an appropriate drug for each patient. Rapid onset of symptom control is extremely important to patients presenting with symptoms of reflux, and rapid symptom control is most meaningful in the first few days of starting treatment in a newly diagnosed patient. It is also critical as more patients use “on-demand” therapy to control their symptoms.

A drug that will consistently control acid during the day as well as at night with once-daily administration is important to ensure patient compliance and minimize the cost of therapy. The drug should demonstrate effective healing and long-term maintenance of healing in patients with ulcers and in those with damage resulting from GERD. Finally, the drug of choice should have min-
imal side effects — including a low potential for drug/drug interactions.

**Symptom control with PPIs**

Only about 5 percent to 10 percent of patients with GERD have erosive disease. Thus, controlling symptoms of reflux and improving patient quality of life become the primary goals of therapy in this population. Symptom frequency in patients with GERD is directly related to the degree of esophageal acid exposure. As the percentage of time increases that esophageal pH remains below 4.0, so does the frequency of symptoms. Optimal therapy necessitates a PPI with a rapid onset of action to raise esophageal pH.

Statistically significant differences in rapidity of symptom relief have been observed in studies comparing rabeprazole to omeprazole. Figure 2 shows data from a study that evaluated the effects of the first 3 days of therapy with these two drugs in patients who had varying degrees of symptom severity due to GERD. Rabeprazole was superior ($P<0.036$) to omeprazole. This difference continued through the first 7 days of therapy.

Rabeprazole has been shown to be superior to omeprazole in achieving rapid symptom relief in patients with active duodenal ulcer. Four weeks after initiating therapy, patients treated with rabeprazole 20 mg had significantly ($P<0.038$) less daytime ulcer pain severity; in addition, they had less ulcer pain frequency and less nighttime ulcer pain severity (Figure 3).

Rabeprazole has also demonstrated superior symptom improvement ($P<0.05$) when compared to treatment with omeprazole in patients with active gastric ulcer. In a randomized study of 227 patients administered either rabeprazole or omeprazole once daily for 3 or 6 weeks, rabeprazole decreased gastric ulcer pain frequency grades at week 3 and significantly at week 6 ($P<0.006$), and decreased daytime pain severity grades significantly at week 3 ($P<0.023$), with a reduction also evident at week 6, albeit not significantly.

Finally, rabeprazole has shown rapid relief of both daytime and nighttime heartburn in patients with endoscopically confirmed erosive esophagitis. Patients had moderate to severe symptoms at baseline and used an interactive voice-response system to report when they achieved mild or no symptoms. The majority of patients — 65 percent — achieved satisfactory relief of both daytime and nighttime heartburn on the first day of therapy. This contrasts with
the level of relief achieved in a similar study with esomeprazole (45 percent) and omeprazole (32 percent) (See Figure 4).16,17

**Healing with PPIs**

Reducing esophageal acid exposure is critical for healing of the esophageal damage evident in many patients with GERD.3 Studies have demonstrated a good correlation between the healing rate of esophagitis at 8 weeks and duration in hours that the intragastric pH is maintained above 4.0. Although similar findings are seen with a pH threshold of 3.0, the relationship is not as strong.5 Thus, achieving a pH >4.0 in the esophagus for as long as possible is an important goal of GERD therapy.18 A study comparing the control of intragastric acidity in healthy, Helicobacter pylori-negative subjects demonstrated the superior decrease in gastric acidity with rabeprazole when compared to omeprazole. During the 24-hour period following the first dose, the mean percentage of time that intragastric pH remained >4.0 was 44.1 percent for rabeprazole and 24.7 percent for omeprazole (P<0.001).8 Because the measurement of healing over several months is a more crude measure, multiple studies with direct comparisons of the different PPIs have, for the most part, failed to show statistically significant differences in healing rates between these compounds. Esomeprazole has shown about a 9 percent improvement over omeprazole in 8-week healing rates of erosive esophagitis in a large, multicenter, double-blind trial.17 All the PPIs produce effective healing. Rabeprazole has been shown to be equivalent to omeprazole in healing rates in both erosive GERD and in healing of duodenal ulcer.14,15

**Maintenance therapy**

GERD is a chronic disease. If therapy is stopped after erosive esophagitis is healed, about 70 percent of patients will experience relapse. Maintenance therapy is therefore important in this setting. All the PPIs maintain healing. Figure 5 shows the percentage of patients in remission while undergoing therapy with either placebo or rabeprazole in two separate studies.19,20 Rabeprazole was significantly better than placebo (P<0.001) for all time points. After 1 year of therapy, GERD continued to be well controlled. At week 52 of the studies, 94 percent to 97 percent of rabeprazole-treated patients had no relapse in daytime heartburn and 91 percent to 98 percent of rabeprazole-treated patients had no relapse in nighttime heartburn.

Patients with Barrett’s esophagus are a special population who typically have more acid exposure than most patients with GERD and a risk of esophageal cancer if acid is left uncontrolled. Rabeprazole has been shown to maintain healing in this group as well, in a 1-year study evaluating maintenance of healing with rabeprazole versus placebo (P<0.006).21

**Extraesophageal indications for PPIs**

Studies with omeprazole have indicated the value of the PPIs in treating noncardiac chest pain; posterior
laryngitis related to reflux, and asthma. Little data are available on the newer PPIs in these indications, but studies are ongoing.

Drug-drug interactions

Interactions of drugs with PPIs can occur either as the drugs are being metabolized through the CYP450 system or at the absorption level, when absorption of the affected drug is dependent on intragastric pH. Omeprazole and lansoprazole have CYP450-related interactions. Due to the nature of their activity, all PPIs affect pH-dependent absorption of drugs such as digoxin and ketoconazole.

Summary

Acid-related disorders are caused by an imbalance between acid secretion by the gastric parietal cells and the defensive mechanisms of the gastrointestinal tract to protect against the effects of acid. Therapy for acid-related disorders focuses on the control of acidity. Data collected throughout the last decade have demonstrated that PPIs are the most effective therapy for acid-related disorders: PPIs have proven superior to H2RAs and antacids in numerous studies. Five PPIs are currently available in the United States. While all PPIs exert their effect through the same basic mechanism of action, they do not have the same pharmacologic and clinical properties. All PPIs are effective in healing and maintenance of gastric and duodenal ulcers and GERD. The PPIs differ, however, in their ability to control symptoms rapidly and consistently. Due to its more rapid rate of activation, rabeprazole results in a faster onset of action and faster symptom control than other PPIs. Studies comparing rabeprazole to omeprazole found statistically significant differences in the rapidity of symptom relief in patients with gastric ulcer, duodenal ulcer, and GERD. Rapid symptom relief is important to the majority of patients, as their symptoms have an impact on their quality of life. Rapid symptom relief is also important in an environment where patients self-medicate on demand, depending on daily symptoms. Rabeprazole has also been shown to have a more consistent suppression of acid, including at night. Optimizing therapy with PPIs necessitates consideration not only of healing rates of the different available treatments but also of the rapidity and consistency of acid suppression that translate clinically into symptom relief.

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**FIGURE 5** Rabeprazole in long-term maintenance of healed erosive GERD.

![Graph showing the effectiveness of rabeprazole compared to placebo in maintaining endoscopic remission over time.](image)
Evidence-Based Health Care: Making Health Policy and Management Decisions

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What is evidence-based medicine?

Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence from clinical care research in the management of individual patients. The evidence must be explicit, meaning that the source of the evidence must be obvious and scientifically justified, especially if used to develop guidelines or algorithms for patient care. Evidence-based medicine integrates three key components in an attempt to deliver the best care: (1) the individual clinical expertise of the provider, (2) the best available external clinical evidence from systematic research, and (3) patients' values and expectations regarding their treatment. Evidence-based medicine is not "cookbook medicine," because it requires the clinical judgment of the physician to extrapolate the published clinical evidence to the care of a specific patient having unique biology, values, and expectations. It is also not "cost-cutting medicine," since evidence-based care may cause costs to rise as well as to fall.

Critics of evidence-based medicine claim that it suppresses the clinical freedom of the clinician. In fact, the opinions, judgment, and expertise of the individual provider are critical to the practice of evidence-based medicine. The proficiency, judgment, and expertise acquired during years of medical practice enhance the application of evidence-based care. The treating physician is best qualified to assess the individual patient's values, preferences, prognosis, and condition at any given time. Good doctors use both their own expertise and the best available external clinical evidence to determine best treatment practices. External clinical evidence may consist of data from relevant clinical trials, knowledge about the precision and accuracy of specific diagnostic tests, or collective information about the efficacy and safety of therapeutic, rehabilitative, and preventive regimens. External clinical evidence may either validate or invalidate previously accepted standards or may suggest replacing those standards with options proven to be more accurate, more efficacious, or safer. External clinical evidence is meant to inform the physician and not to replace clinical judgment and knowledge of the patient.

The randomized clinical trial has become the standard for judging the benefits of a particular intervention and
Evidence-based health care management

As the practice of managed care matures during the coming years, evidence-based medicine has the potential to become an integral part of delivering quality care at an appropriate cost. To fully realize these benefits, managed care organizations will need to:

- Ensure that services and procedures are supported by high-quality evidence. Evidence may be gathered through well-designed, well-executed technology assessments or through critical appraisal of provider practices. An established source of technologic and treatment assessment in health care is the Cochrane database, which evaluates both services and procedures and currently contains over 1,000 assessments of different disease states.

- Ensure that the mix of services and procedures provided is one that will give the greatest benefit to the treated population. This can be done using needs assessments to set priorities for allocating health care resources.

- Ensure that services and procedures are of sufficiently high quality to realize the potential identified in research settings. The efficacy of a new procedure may be defined as its performance in carefully controlled settings, usually in selected patients in the hands of experts. The effectiveness of a new treatment is its performance in routine clinical practice. When innovations are applied in community practice, the results may not be the same as seen in randomized trials, creating the need for ongoing audits of actual outcomes for patients in the community. On occasion, a treatment cannot be adequately transferred from the well-controlled research setting to a general community treatment setting. This problem may be resolved by educating patients and providers about the proper use of technologic innovations. When education does not resolve the issue, it may be that outcomes are poor, costs are higher, or adverse events are more frequent, suggesting that the treatment or procedure may not be as valuable as previously believed. In these cases, the services and procedures may need to be changed.

Realities of evidence-based medicine

Technologic innovation has the potential to deliver treatments that do more harm than good, more good than harm, and treatments of unknown effect.

Therapies that do more harm than good are frequently used as a result of poor or insufficient research that is often based on anecdotal evidence or individual case reports. There are many unfortunate examples of therapies that do more harm than good: the Angelchik prosthesis was promoted as a cure for reflux disease but was later found to have many serious complications. The gastric bubble was proposed as a treatment for obesity and widely adopted in community practice until a randomized controlled trial showed that it was ineffective. It should be recognized that the highest levels of evidence are available for only a small number of medical procedures. Available studies may have enrolled too few patients, looked at the wrong patient population, or introduced unintended bias by their design.

The principles of evidence-based medicine can prevent therapies that do more harm than good from ever being introduced. New therapies or procedures should not be instituted in clinical practice without good data from well-conducted trials. This clarifies the risk and benefits of the procedure and allows patients and physicians to make informed choices. In the future, managed care organizations need to be willing to invest in clinical research related to medical innovations to ensure that they have the data necessary to guide treatment for their members. Managed care organizations also need to be proactive and develop processes to keep abreast of new techniques and new procedures and evaluate the benefits of these innovations.

As evidence-based medicine becomes more accepted, it will be necessary to come to terms with the reality of information overload for physicians. It has been estimated that a physician in internal medicine needs to read 19 articles per day every day to keep abreast of the relevant literature being published. This figure is likely to increase as more information becomes available.

It has been estimated that in an average day, a general practitioner develops an average of 16 unanswered clinical questions. Searching for answers in the litera-
The question is asked, it will be necessary to develop the best evidence to answer the question. A new audit cycle will enable researchers to ask and answer questions efficiently (Figure 1). The new cycle will necessitate that providers and researchers ask a question, gather the evidence, and then set the standard. Once a standard is set, a re-audit will ensure that it is delivering the best outcome. To gather evidence, providers and insur-ers will either need to rely on systematic reviews performed by an independent organization or, if such an organization is not available, will have to invest in the time and resources needed to complete an in-house re-view of the available literature or conduct the relevant clinical trial.

**Summary**

The paradigm for health care delivery in the United States continues to evolve. Patients and physicians are beginning to reject guidelines for treatment that are solely based on cost reduction and are not evidence based. Future managed care guidelines will rely on the best external clinical evidence about the value of any given therapeu-tic intervention combined with individual physician experience and patient choice. Managed care organiza-tions will need to play a greater role in the development, evaluation, and incorporation of clinical trials into their strategies.

**References**

