Less hype, more hope

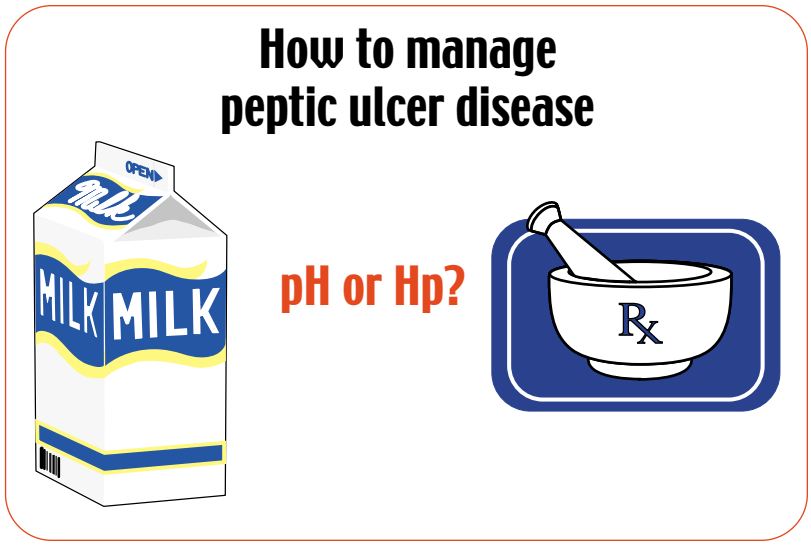
Eldon Shaffer, MD

Once upon a time, not so very long ago, gastroenterology was a cognitive discipline based on art, with little in the way of evidence to support its treatment protocols. In the 1930s there were the Sippy diets for peptic ulcer disease, and later, extirpative gastric surgery. The post-war years witnessed the almost serendipitous discovery that sulfasalazine was effective in treating ulcerative colitis. The introduction of flexible endoscopy in the 1970s led to better clinical trials for peptic ulcer disease, a prelude to the advent of potent acid-reducing agents: H_2-receptor antagonists and, more recently, proton pump inhibitors. Today, there is less hype and more hope: revised concepts of disease, vastly improved diagnostic and therapeutic modalities, and our new friend — the health care directive.

Over the past year, a bacterium and a virus have spawned 2 Canadian consensus conferences that exemplify these advances.

Helicobacter pylori is the ultimate success story. Some 15 years ago, Barry Marshall identified this spiral rod from mucosal biopsy samples of patients with chronic active gastritis and suggested that it caused peptic ulcer disease. The GI community was sceptical, but the relation has proved solid. *H. pylori* is also a factor in the development of gastric malignant disease, specifically gastric carcinoma and B-cell lymphoma. Whatever happened to stress and too much acid?

In the good old days (just a few years ago), ulcers recurred within a year in 85% of treated patients. Curing *H. pylori* infection now means eliminating peptic ulcer disease forever. This has been great news for the pharmaceutical industry. Eradication of *H. pylori* requires at least 2 antibacterial agents given over 10 to 14 days; 3 or 4 agents are needed if therapy is planned for only 7 days. The initial "gold standard" of treatment consisted of bismuth (2 tablets qid), 250 mg metronidazole tid, 500 mg tetracycline qid and an acid-reducing agent, a regimen so complex that many patients gave up, even those in controlled trials, who would have had the benefit of study personnel encouraging compliance. Recent success has involved "PPI-triple therapy": a proton pump inhibitor plus 2 antibiotics (e.g., clarithromycin, metronidazole) in a myriad of combinations. Cure rates exceed 80% to 90%. Such eradication is cost-effective compared with maintenance acid suppression by means of a generic H_2-receptor antagonist administered daily.[1] However, economic evaluations such as that of Taylor and associates[1] do not take into account regional differences in costs and practice, nor do they factor in the rise of antibacterial-resistant organisms.



Clinical trials on ulcer healing are predicated on endoscopy rather than symptomatic presentation. That being the case, does a mucosal defect in the form of an ulcer truly constitute disease? Does efficient drug therapy yield effective clinical practice? In a free market, one would expect competition to drive the price down, yet the advent of 2 new proton pump inhibitors has not significantly diminished the price of treatment. Even better news for Canadians is that *H. pylori* is disappearing from developed countries such as ours because of reduced infection in children. Does this mean that peptic ulcer disease will become a historical curiosity?

The possibility of *H. pylori* eradication has left a pair of unsettled problem areas. Non-ulcer dyspepsia occurs in a large contingent of patients who have ulcer-like symptoms but, according to endoscopic criteria, lack an overt ulcer. Many of these patients also harbour *H. pylori* organisms, which consistently produce gastritis. It is a standard dictum in gastroenterology that gastritis does not necessarily lead to abdominal pain or symptoms. Furthermore, eradicating *H. pylori* has not yielded predictable responses in controlled clinical trials to date. There may be a lesson here. The link between *H. pylori* and both peptic ulcer disease and gastric malignant disease is exciting but should not be extrapolated to all gut complaints, nor should the existence of a link be considered causal in other entities, such as coronary artery disease, merely because of an epidemiologic association.

The second problem area, equally perplexing, is the association between *H. pylori* and significant gastroesophageal reflux disease. Among patients with reflux esophagitis who require chronic therapy with proton pump inhibitors, those with *H. pylori*-associated gastritis tend to experience chronic atrophic gastritis, a likely forerunner of gastric carcinoma. If this association holds true, should we eradicate *H. pylori* in patients likely to receive long-term therapy with a proton pump inhibitor? Ironically, eliminating *H. pylori* increases the need for acid suppression. We are caught between the devil and the deep blue sea of acid.

Viral hepatitis has been in the hepatology news this past year, and not just because of tainted blood problems. Thirty years ago, Bernard Blumberg identified a novel antigen in the blood of patients with leukemia. This discovery led to specific serologic markers to diagnose hepatitis A and B but left a void, designated non-A, non-B hepatitis. We now recognize hepatitis C virus (HCV) as an important cause of chronic liver disease. In 85% of those infected with HCV chronic hepatitis occurs, in 20% cirrhosis eventually develops, and in some, hepatocellular carcinoma occurs. The genetic diversity of HCV allows it to escape immune surveillance, which leads to its persistence in the body. HCV is now the most common indication for liver transplantation. Yet the significance of hepatitis C in Canada is not clear. Between 150 000 and 250 000 people may be infected. Fortunately, with better screening of blood products, the number of cases caused by transfusion has declined to almost zero, so this may be another disappearing disease.

Effective therapy with interferon-α has led to Canadian[2] and US[3] consensus conferences. Interferon-α (3 million units subcutaneously 3 times weekly for 12 months) produces a sustained biochemical response (normalization of alanine aminotransferase levels) and a corresponding disappearance of the marker of viral infection as measured by polymerase chain reaction in 30% to 40% of patients. This is not a terribly pleasant therapy, as most patients experience flu-like symptoms. Furthermore, at $3000 for 6 months, the treatment is not inexpensive. Combining interferon-α and ribavirin may yield a higher sustained response, in about 40% to 50% of patients after 6 months. The odds of success, though, are not great. Treatment should be reserved for those at greatest risk of cirrhosis, as indicated by persistently elevated levels of alanine aminotransferase, positive test results for HCV-RNA in serum, and liver biopsy results showing inflammation and significant fibrosis.

The evidence indicates that these important diseases — peptic ulcer and related entities and hepatitis C — are declining in frequency and that effective treatments are becoming available. Will these successes spell the demise of gastroenterology and hepatology? Fear not. There will be no roving bands of underemployed specialists. New entities and their treatments are coming our way. Stay tuned.

References

1. Taylor JL, Zagarim M, Murphy K, Freston JW. Pharmacoeconomic comparison of treatments for the eradication of *Helicobacter pylori*. *Arch Intern Med* 1997;157:87-97.
2. Sherman M, CASL Hepatitis Consensus Group. Management of viral hepatitis: clinical and public health prospectus — a consensus statement. *Can J Gastroenterol* 1997;11:407-16.
3. National Institutes of Health Consensus Development Conference Panel Statement. Management of hepatitis C. *Hepatology* 1997;26(suppl 1):2S-10S.

Dr. Shaffer is Professor and Head of the Department of Medicine, University of Calgary, Calgary, Alta.