Medical treatment of peptic ulcer disease: Where do we stand?

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ABSTRACT

Peptic ulcer disease is one of the most common and most costly gastrointestinal disorders. Our knowledge of the pathogenesis and treatment of peptic ulcer disease underwent revolutionary changes over the last two decades, starting with the introduction of effective and safe acid suppressive and cytoprotective drugs and culminating with the recognition of Helicobacter Pylori as the major causative factor for peptic ulcer disease. There are enough reasons now to believe that we have a real opportunity to modify the natural history of peptic ulcer disease from the traditional one of chronicity and relapses to effective prevention and cure.

Keywords: Peptic ulcer disease, Helicobacter Pylori, nonsteroidal anti-inflammatory drugs.


After many years of dependence on diet, antacids and anticholinergics in treating peptic ulcer disease (PUD), the introduction of H2-receptor antagonists (H2RAs) in the 1970s marked the beginning of a remarkable new era. These agents were the first drugs to bring rapid relief of ulcer pain, accelerate ulcer healing, markedly reduce ulcer recurrences and possibly reduce ulcer complications when given as long-term maintenance therapy. The later introduction of cytoprotective and potent antisecretory drugs, the proton pump inhibitors (PPIs), markedly expanded our armamentarium of anti-ulcer therapy. All these drugs have proved to be safe and effective. Surgical management, performed not infrequently for ulcer patients previously, became something of a rarity, and is now used mainly for management of ulcer complications. However, when these drugs were discontinued after ulcer healing, ulcers recurred within the following 12 months in up to 70% of cases and can reach 100% in smokers. The relapse rate also remained high after stopping long-term H2RAs maintenance therapy given up to 8 years. On the other hand, about 20% of patients had ulcer relapse while receiving long-term maintenance therapy. It became clear that these new anti-ulcer therapies did not change the natural history of PUD that is characterized by chronicity and frequent relapses: “once an ulcer, always an ulcer”.

Role of Helicobacter Pylori in peptic ulcer disease. Soon after the discovery of Helicobacter Pylori (H pylori) by Marshall and Warren in 1983, a great deal of research was conducted on all matters related to this microorganism, especially with regard to diagnosis and therapy. Heated debate about its pathogenic significance took place within the gastroenterology community until eventually H pylori was established as a major causative factor of PUD. This recognition came mainly from the indirect evidence that eradication of H pylori resulted in marked reduction of ulcer recurrence to less than 10%. H pylori gastritis is present in 90 to 100% of duodenal ulcer patients and in over 70% of gastric ulcer patients. It has been shown also that the
eradication of *H. pylori* reduced the recurrence of ulcer complications. Reinfec
tion rates with *H. pylori* are low in the developed countries, being less than 0.5% per year. How infection of the gastric antrum by *H. pylori* causes ulcer in the duodenum, and why only about one in six patients so infected develop PUD, are matters which are still under research and intense debate. Currently, it is believed that gastric metaplasia containing *H. pylori* in the duodenum is the likely explanation for the development of duodenal ulcer (DU). Certain strains of *H. pylori*, mainly cag A and Vac A positive, which appear to be more aggressive (toxin producing), in conjunction with host factors are felt to be important determining factors for the development of DU in the minority of *H. pylori* infected persons. In addition to the essential *H. pylori* induced mucosal inflammation and NSAIDS intake, other factors like smoking, alcohol and stress are believed to form the basis for the multifactorial pathogenesis of Peptic Ulcer. The resulting disruption of mucosal integrity will render it vulnerable to the attack of gastric acid and acid activated pepsin.

**Anti-*H. pylori* therapy.** The first efficacious anti-*H. pylori* therapy, “triple therapy” (bismuth 120 mg qid, tetracycline hydrochlorid 500 mg qid and metronidazole 400 mg tid, given for two weeks) was introduced at the World Congress of Gastroenterology in Sydney in 1991. Despite the initially reported cure rate of 80 to 90% and the relatively low cost, several drawbacks have limited the wide-spread use of this regimen. Most importantly was the high incidence of resistance of *H. pylori* to metronidazole in the developing countries (about 65%). This resistance is mostly primary and appears to be due to the wide and rather indiscriminate use of this drug in other conditions. In developed countries the resistance to metronidazole has been reported to develop in more than 25% of cases. Poor compliance and the potential for developing side effects are additional disadvantages. Subepithelial colonization of the *H. pylori* and its spiral-helical shape represent additional difficulties for the antibacterial therapy. The optimal treatment of *H. pylori* infection remains to be established. Although *H. pylori* is sensitive to several antibiotics in-vitro, there is no effective single antimicrobial therapy. This discrepancy between the in-vitro and in-vivo efficacy awaits definite explanation. Several combinations of drugs were evaluated and used over the following years. More recently, new, more simplified and effective non-metronidazole based anti-*H. pylori* therapies have been used with cure rates above 90%. These revolutionary developments led to a reappraisal of our previous therapeutic strategies of PUD. The current recommended practice is to attempt a cure of *H. pylori* infection in all infected patients with documented current or past peptic ulcer who are receiving long-term anti-secretory therapy. The recommendation is to give two antibiotics known to be active against *H. pylori* together with either bismuth or an antisecretory agent. PPIs were found to have some anti-*H. pylori* activity in vitro, but in vivo they appear only to suppress the organism. The rationale for giving antisecretory drugs as part of anti-*H. pylori* treatment is the increase of intragastric pH, which enhances the action of the concurrently administered antibiotics. One of the most recommended and efficacious regimens, although expensive, is clarithromycin 500 mg bid, amoxicillin 1 g bid and omeprazole 20 mg bid given for 7 to 10 days. Metronidazole given in a dose of 500 mg tid or tinidazole can be substituted for clarithromycin in sensitive *H. pylori* strains. The standard “triple therapy” still represents a reasonable option in metronidazole sensitive strain. Triple therapy with bismuth, tetracycline and clarithromycin for 14 days is another regimen reported to be effective for metronidazole resistant strains. Quadruple therapy consisting of the standard “triple therapy” combined with a PPI for 7 days has been reported to achieve cure rates above 95% independent of metronidazole resistance. The rule of ranitidine bismuth citrate has yet to be defined. The recommended approach for active ulcers is to continue a full course of antisecretory therapy (standard doses of H, RAs or PPIs) after completing anti-*H. pylori* treatment. For complicated and refractory ulcers, conventional anti-ulcer therapy should be continued until *H. pylori* eradication is confirmed. All matters related to anti-*H. pylori* therapy, such as efficacy and potential side effects, as well as the crucial role of compliance, should be explained to the patient. The cure of *H. pylori* infection obviates the need for costly maintenance therapy. For those who fail *H. pylori* eradication, a re-treatment regimen should be selected after consideration of previous regimen(s) and/or bacterial sensitivity testing. There is ongoing debate in the industrialized countries about the need and benefit for anti-*H. pylori* therapy given for patients with asymptomatic gastritis or non-ulcer dyspepsia. Most authorities do not advocate such therapy and the published data in this regard is contradictory. Considering the high prevalence of *H. pylori* infection in our population and the lack of data documenting the benefit of anti-*H. pylori* therapy in patients with non-ulcer dyspepsia or asymptomatic gastritis, it appears reasonable not to give anti-*H. pylori* therapy for such patients, except probably for those with symptomatic gastroduodenitis.

**NSAID - Associated peptic ulcers.** Nonsteroidal anti-inflammatory drugs (NSAIDs) are the second most common cause of PUD. The prevalence of ulceration in patients on chronic NSAID therapy, has been reported to be between 12% to 30% for gastric and 2% to 19% for duodenal ulcers, with 1.3 to 2% of these patients developing life threatening ulcer...
complication per year of use. The relation between H pylori and NSAIDs with respect to the development of PU is still not clear. When PU develops in a patient infected with H pylori who is taking regular NSAIDs it will not be clear initially which of the two factors is the cause of ulcer. The current recommendation is to give anti-H pylori and anti-ulcer therapy to such patients and, if possible, to discontinue the NSAID and switch the patient to an analgesic alone like paracetamol. Misoprostol, a synthetic prostaglandine E analogue, given in a dose of 200 μg qid or tid, was found to be effective in the prevention of NSAID-induced gastric and duodenal ulcer. Misoprostol is costly and must not be prescribed to women of child bearing age due to their uterotonic action. Other side effects are abdominal pain and diarrhea, mostly dose related. Co-protective therapy is recommended in patients at high risk of ulcer formation and/or complication, namely those with a history of peptic ulcer disease and age greater than 75 years. Patients older than 70 years with serious co-morbid conditions, should also be so treated, as the successful cure of H pylori alone does not eliminate the risk of ulcer recurrence when NSAIDs are resumed. However, the subset of long-term NSAID users who will benefit from the costly prophylactic therapy remains to be better characterized. It is hoped that safer, less ulcerogenic NSAIDs will be developed. One important area of ongoing research is the exploration of new NSAIDs with more selective inhibition of the inflammatory enzyme cyclooxygenase II (COX-II), rather than the prostaglandin producing cyclooxygenase I (COX-I).

**Confirming cure of H pylori infection.** Until a reliable, non invasive and inexpensive method to confirm the cure of H pylori infection becomes available, the verification of H pylori eradication is not necessary except in those patients with a history of complicated or refractory ulcer and in patients with aggressive-recurrent ulcer history. Gastric biopsy or urea breath tests are reliable for this purpose. In case endoscopy is performed, gastric biopsies should be obtained from the antrum and corpus. The urea breath test, when available, is considered the noninvasive method of choice to confirm H pylori eradication. Currently, anti-H pylori antibody IgM is being evaluated as a marker of active inflammation, whereby their disappearance may indicate successful eradication. It is essential to perform these tests not earlier than 4 weeks after H pylori therapy is completed in order to avoid false negative results.

In conclusion, cure of H pylori infection is now strongly recommended in all infected peptic ulcer patients, including those with a history of recurrernt peptic ulcers or complicated ulcers who are under maintenance antisecretory therapy. This will prevent - minimize ulcer recurrence with its potential complications and obviate the need for the costly long-term maintenance therapy. It is essential to provide the most effective therapeutic regimen available in order to ensure high cure rates and minimize the risk of resistance. Currently, only regimens that achieve 90% cure should be prescribed. In view of the rapidity of these extraordinary developments and the intense ongoing research, more advances on the diagnostic and particularly on the therapeutic front are expected. It is hoped that simple, more efficacious and less costly therapies will emerge and that an effective vaccination against H pylori will be developed.

**References**


