Is the decreasing resistance to treat *Helicobacter pylori* the result of improved efficacy?

There is irrefutable evidence linking *Helicobacter pylori* to duodenal ulcers, gastric ulcers and gastric cancer. Whether the organism is causally related to nonulcer dyspepsia is still unclear. Although functional dyspepsia patients form the largest group with *H pylori* infection, to date no convincing evidence has been published that unequivocally demonstrates that compared with placebo, the patient's symptoms are significantly more improved by eradication of the organism. Nevertheless many such patients are receiving anti-helicobacter treatment. The established indications for treatment of *H pylori*, reaffirmed by a recent National Institutes of Health sponsored consensus conference are: all patients with newly diagnosed acute *H pylori*-positive duodenal ulcer; patients with *H pylori* infection and proven relapsing duodenal ulcers (including all patients who are on maintenance therapy for recurrent peptic ulcer disease); and patients with *H pylori*-positive gastric ulcers.

Most of the knowledge about treatment efficacy has been acquired by trial and error rather than by using a planned scientific approach. A major reason for this lack of rationale was the experience, gathered early on, that the in vitro susceptibility of *H pylori* to therapeutic agents is a poor predictor of in vivo behaviour. Numerous combinations of antibiotics have been tried and those with clinical activity against *H pylori* were then evaluated further - 'playing the winners'. It is likely that future treatments may be very different from the ones currently employed.

Whether antibiotics work topically as they pass through the stomach or whether absorption in the small bowel is necessary to achieve eradication of the organisms is not known. There is also little knowledge about the pharmacodynamics and pharmacokinetics of antibiotics across the gastric mucosa. For metronidazole, one of the antibiotics with proven efficacy against *H pylori*, there is evidence that it is secreted across the gastric mucosa, whereas for the penicillins, data are conflicting. Research has been lacking on essential enzyme pathways that *H pylori* needs for its basic metabolism, or on the enzymes that could serve as potential targets for antimicrobial activity. When metronidazole is part of the treatment protocol, eradication rates drop markedly if metronidazole resistance is present. Little is known about the mechanisms by which this resistance develops or is transmitted, although some progress has been reported. *H pylori* lives 'off shore' within the gastric mucus in close proximity to the gastric mucosal cells, but we have only rudimentary knowledge about this 'milieu'. Much remains to be learned about mechanisms of bacterial adhesion to the epithelial cells and the pathways by which inflammation is induced. The minimal inhibitory concentration values of some antimicrobials are known to be pH-dependent and this provides a possible explanation for the benefit of using acid suppression. On the other hand the advantage of acid suppression may be offset by a decrease in the total volume of gastric fluid, resulting in a decrease in the concentrations of antibiotic that can be achieved in the stomach or in the total amount of antibiotic that is secreted across the gastric mucosa.

Where do we stand with regard to treatment options in 1994? To date, the best treatment results are achieved with combinations of three drugs, the so-called triple therapy. The 'classic' triple therapy regimen consists of a bismuth compound in combination with metronidazole (250 to 500 mg tid or qid) and tetracycline (500 mg qid) or amoxycillin (500 mg tid or qid). The combination bismuth-metronidazole-tetracycline appears superior to the combination of bismuth-metronidazole-amoxycillin (94% versus 73% eradication). The duration of treatment generally is for a period of two weeks, but one week may prove equally effective. Compliance is an important predictor of treatment success. Bismuth subsalicylate (usual dose two tablets qid) is the only bismuth preparation available in Canada, but clinical trials using bismuth subcitrate are also starting. The fundamental chemistry of bismuth and the mechanisms by which bismuth compounds act against *H pylori* are poorly understood. Nevertheless, it is clear that various bismuth compounds differ in their bioavailability and that their anti-helicobacter activity may be different.

Omeprazole is the only acid suppressive agent available on the Canadian market that has anti-helicobacter activity, al-
though newly developed proton pump inhibitors, such as lansoprazole, also inhibit the growth of *H. pylori* in vivo.\(^\text{16}\)

Recently, the combination of high dose omeprazole (40 mg bid) with amoxycillin (1 g bid) has shown eradication rates as high as 82%.\(^\text{14}\) However, such high eradication rates using this combination have not been consistently achieved, whereas omeprazole in combination with two antibiotics (metronizadole and amoxycillin, amoxycillin and clarithromycin, or metronizadole and clarithromycin) result in reproducibly high success rates. An advantage of using omeprazole, especially when an acute ulcer is present, is the rapid ulcer healing rate. An interesting aspect of omeprazole treatment is the observation that 20 mg bid is better than 40 mg given once a day.\(^\text{18}\) For omeprazole treatment duration of two weeks may be better than one week.\(^\text{18}\)

Clarithromycin is receiving a lot of attention for use in *H. pylori* eradication. When used as a single agent, eradication rates are as high as 54% which, to date, are the highest for monotherapy against *H. pylori*. Resistance to clarithromycin may develop and the magnitude of this problem needs further investigation.\(^\text{19}\) When clarithromycin is given in combination with a proton pump inhibitor eradication rates of 80% have been achieved.\(^\text{20}\) Additional studies are needed to determine whether dual therapy with clarithromycin and a proton pump inhibitor is sufficient or whether a triple combination is still required to achieve high (greater than 80%) eradication rates consistently.

Although we have made considerable progress in the treatment of *H. pylori* infection much more needs to be learned. The clinician has a number of choices among treatment strategies. Triple therapies, such as bismuth or omeprazole in combination with two antibiotics, are still the best option.

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**REFERENCES**


