Implications of antibiotic resistance in the management of *Helicobacter pylori* infection

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Since its discovery in 1982, *Helicobacter pylori* has quickly and irreversibly established itself as an important pathogen. Treatment of *H pylori* infection has revolutionized the management of peptic ulcer disease. There also is much interest about the role of *H pylori* in gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma (MALToma). The link with cancer has led to new research, especially in the basic sciences. There are several *H pylori* gastric cancer models available that allow for research on the pathogenesis of cancer formation of this chronic infection.

On the clinical side, much of the 1990s were spent on the development of efficacious treatments against *H pylori* infection. The current first- and second-line therapies were largely developed by trial and error in which different combinations of antibiotics were used with either proton pump inhibitors or bismuth-containing compounds. Regimens were refined using the results of numerous smaller and larger studies that evaluated different combinations of drugs.

It is fair to say that little is known about the behaviour of antibiotics in the stomach. In fact, for most compounds, the mechanisms by which they exert their anti-*H pylori* activity are completely unknown. For example, it is not known whether some or all antibiotics kill the helicobacter organism topically as they pass through the stomach or whether first absorption in the proximal small bowel is necessary, with subsequent transfer of the active agent through the systemic circulation to the gastric mucosa. It seems likely that high mucosal concentrations of antibiotics are necessary to reach the helicobacter organisms that live deep in the gastric pits in the gastric mucous layer.

It has become clear that acid suppression markedly im-

proves the efficacy of antibiotics, especially the combination of clarithromycin and amoxicillin, but also clarithromycin and metronidazole. Furthermore, although the bismuth compounds are unable to kill and eradicate all *H pylori* organisms by themselves, they definitely enhance the anti-*H pylori* activity when given concomitantly with other antibiotics such as tetracycline, metronidazole and amoxicillin. Further improvements in success rates can be achieved by combining bismuth compounds with a proton pump inhibitor and two antibiotics.

Soon after treatment trials were launched, it became clear that *H pylori* can develop resistance to antibiotics. For example, *H pylori* is almost universally resistant to the quinolones, which is why these agents are not currently used in the treatment of *H pylori* infection.

Resistance to metronidazole also occurs frequently; resistance to clarithromycin occurs to a lesser extent. Until recently, resistance to amoxicillin and tetracycline was only rarely reported. A point mutation is responsible for clarithromycin resistance. Much progress has also been made in unravelling the mechanisms of metronidazole resistance; this situation is more complicated. Although the *rdx* gene was found to play an important role, it does not completely explain the mechanisms by which metronidazole resistance can develop.

A clinical problem in the evaluation of resistance of *H pylori* to antibiotics is that methods by which this can be determined have not been standardized and may vary. This is especially true for resistance to metronidazole and far less for resistance to clarithromycin. The recently published guidelines by the National Committee for Clinical Laboratory

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Standards (1) on methods to be used for determining resistance also suffer from the problem of suboptimal reproducibility. Clearly, much more work is needed in this area.

In this issue of *The Canadian Journal of Gastroenterology*, the consensus document about the 1999 consensus meeting of the Canadian *Helicobacter* Study Group, which was held in June 1999 in Ottawa, is described (pages 862-868). The topic of the conference was to assess the implications of antibiotic resistance in the management of *H pylori* infection. The consensus document is accompanied by five contributions from different authors (Smaill [pages 871-875], Fallone [pages 879-882], Chiba [pages 885-889], Taylor [pages 891-894] and Lahaie [pages 895-899]). They describe problems in the methodology of assessment of resistance against *H pylori* and provide data about the changing prevalence of resistance in Canada.

It is clear that treatment of *H pylori* infection has come a long way. The current first-line therapy of a proton pump inhibitor with clarithromycin and either amoxicillin or metronidazole, or quadruple therapy consisting of a bismuth compound and proton pump inhibitor together with tetracycline and metronidazole achieve a cure of the infection in 80% to 85% of cases. Unfortunately, although data from

some centres in Canada are available, adequate data about the prevalence of resistance against antibiotics in most of Canada are lacking. This clearly is an important problem that needs to be addressed. It is of paramount importance that clinicians are provided with information about the prevalence of resistance in their area and perhaps more importantly, to monitor changes in the prevalence of resistance. The latter is especially important because this might affect the efficacy of the available therapies. Participants in the consensus conference strongly suggested that some form of monitoring across the country be instituted. To that extent, it is gratifying that a Canada-wide study of antibiotic resistance has been launched. However, clearly more needs to be done, and it is hoped that public health laboratories will show an interest in this important therapeutic area.

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REFERENCES

1. NCCLS. Performance Standards for Antimicrobial Susceptibility Testing; Eighth Informational Supplement. NCCLS document M100-S9. Wayne: NCCLS, 1999
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