Implications of antibiotic resistance in the management of *Helicobacter pylori* infection: Canadian *Helicobacter* Study Group

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RH Hunt, FM Smaill, CA Fallone, PM Sherman, SJ Veldhuyzen van Zanten, ABR Thomson. Implications of antibiotic resistance in the management of *Helicobacter pylori* infection: Canadian *Helicobacter* Study Group. *Can J Gastroenterol* 2000;14(10):862-868. Eradication of *Helicobacter pylori* from the gastric and duodenal mucosa is an important clinical goal in the treatment of infected patients with peptic ulcer disease and other *H pylori*-associated conditions. Although several oral drug combination regimens are associated with eradication rates of approximately 85% in controlled trials, the success rate in patients infected with a resistant strain of *H pylori* is closer to 75%. Resistance to metronidazole and clarithromycin, which are common components of combination treatment regimens, is of greatest concern. Reported rates of *H pylori* resistance to various antibiotics vary considerably. In Canada, the data documenting *H pylori* susceptibility are limited but suggest that resistance to these antibiotics varies geographically and within specific treatment groups. Although susceptibility testing is not a prerequisite for initial treatment of individual patients infected with *H pylori*, formal efforts to identify and monitor both the causes and prevalence of antibiotic resistance across Canada are a much needed step in the ongoing management of this important infection. Recommended

treatment regimens may be useful, even for treating apparently resistant *H pylori* strains. However, it is important to understand the mechanisms of the development of resistant strains to manage patients with treatment failure better.

Key Words: Antibiotic resistance; Clarithromycin; *Helicobacter pylori*; Metronidazole

Incidence de l'antibiorésistance sur le traitement des infections à *Helicobacter pylori*; rapport du groupe canadien d'étude sur *Helicobacter*

RÉSUMÉ : L'éradication d'*Helicobacter pylori* de la muqueuse gastrique et duodénale constitue un objectif clinique important du traitement des ulcères gastro-duodénaux et d'autres affections associées à *H. pylori*. Bien que les taux d'éradication obtenus à l'aide de plusieurs associations médicamenteuses orales jouent autour de 85 % dans les essais contrôlés, le taux de réussite chez les patients infectés à des souches résistantes d'*H. pylori* se rap-

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proche plutôt de 75 %. La résistance au métronidazole et à la clarithromycine, deux constituants souvent utilisés dans les associations médicamenteuses, préoccupe beaucoup. Les taux de résistance signalés à *H. pylori* à divers antibiotiques varient considérablement. On dispose de peu de données sur la sensibilité d'*H. pylori* au Canada, mais elles semblent indiquer que la résistance aux deux antibiotiques en question varie selon les régions et les groupes de traitement. Même s'il n'est pas nécessaire de procéder à des épreuves de sensibilité chez les patients soumis à un premier

traitement contre *H. pylori*, il faudrait déployer des efforts particuliers pour cerner les causes de la résistance aux antibiotiques et en surveiller la prévalence partout au Canada dans le cadre de la lutte continue contre cette infection importante. Les traitements recommandés peuvent s'avérer utiles, même dans les cas de souches d'*H. pylori* apparemment résistantes. Cependant, il est important de comprendre les mécanismes d'apparition des souches résistantes afin d'améliorer la conduite à tenir en cas d'échec du traitement.

Clinicians have adapted rapidly to the recognition of *Helicobacter pylori* infection as an important gastroduodenal pathogen in humans. The first Canadian treatment guidelines were developed by the Canadian *Helicobacter pylori* Study Group in 1997 (1) and were subsequently updated in 1999 (2). The first Canadian guidelines for the management of pediatric *H pylori* infection were published in 1999 (3). Each Canadian guideline, as in Europe (4), the United States (5) and Asia (6), was developed to identify clinical scenarios in which eradication of *H pylori* infection can improve disease outcome and overall patient care. There are many similarities between guidelines developed in Canada and those developed elsewhere, but practice recommendations specific to Canada are useful due to differences in the prevalence of *H pylori* infection and its sequelae, and the structure of the Canadian health care system.

As in most other infectious diseases, resistance of *H pylori* to antimicrobial therapies is of clinical concern. Although the multiple drugs that are necessary for successful eradication regimens may overcome modest degrees of primary resistance to any single antibiotic in the regimen, resistance may have a measurable influence on treatment success (7-13). Therefore, there is a clear need for surveillance of antibiotic resistance to help predict response to treatment and to guide treatment.

The Canadian *Helicobacter* Consensus Conference convened in June 1999, in Ottawa, Ontario, to address the importance of *H pylori* resistance to antibiotics and to develop a framework with which to monitor the patterns of resistance. As in past consensus conferences, there was a broad representation of interest groups (Appendix). Participants included adult and pediatric gastroenterologists, infectious disease specialists, microbiologists, primary care physicians, pharmacologists, pathologists and basic science researchers. Additionally, there were representatives from Canadian federal and provincial governments, observers from the pharmaceutical industry, and invited experts from Europe and the United States. The Consensus Conference was sponsored by the Canadian *Helicobacter* Study Group, the Canadian Association of Gastroenterology, the Canadian Digestive Disease Foundation and the Canadian Society for Clinical Investigation. Major financial support for the Conference was provided through equal unrestricted educational grants from Abbott Laboratories Ltd, AstraZeneca Canada Inc, Axcan Pharma Inc, BYK Canada Inc/Solvay Pharma Inc and Glaxo Wellcome Inc.

BACKGROUND

Treatment guidelines developed in Canada and elsewhere recommend the eradication of *H pylori* infection in patients who develop clinically significant complications from the infection. All individuals infected with *H pylori* develop chronic, active gastritis, but only 10% to 15% of those infected eventually develop adverse consequences such as ulcer, lymphoma or cancer (14,15). The most common complication of *H pylori* infection is peptic ulcer disease. Up to 90% of duodenal ulcers and 70% of gastric ulcers not associated with nonsteroidal anti-inflammatory drugs are caused by *H pylori* infection (16). Eradication of the underlying infection in these cases almost uniformly leads to ulcer healing and prevention of ulcer recurrences (17). The only other disease firmly linked to *H pylori* infection, mucosa-associated lymphoid tissue lymphoma, is rare (18). However, there is epidemiological evidence associating *H pylori* with gastric cancer (19-21). This association led the World Health Organization to designate this organism a group I carcinogen (22). Although it is widely believed that the risk of gastric cancer is reduced in infected individuals whose gastritis resolves following *H pylori* eradication, there are no scientific data yet to support this hypothesis. The possibility that *H pylori* causes or contributes to nonulcer (functional) dyspepsia continues to be the focus of ongoing research initiatives.

H pylori infection is typically acquired in childhood and appears to be a lifelong infection. In Canada, the prevalence of *H pylori* infection in the general adult population is estimated to be near 30%, with higher rates among specific groups (23). For example, in indigenous populations, elderly people and immigrants from developing countries, prevalence rates can exceed 80% (23). In Canada, neither the prevalence of infection nor the relatively low risk of clinical disease justifies the screening and treatment of all infected individuals (1,2). Such a program would be expensive and potentially associated with adverse consequences from widespread antibiotic use. However, the public health perspective on population-based screening programs could change if, for example, eradication of *H pylori* infection is shown to yield a broader spectrum of clinical benefits, such as protection against gastric cancer or functional dyspepsia.

RESISTANCE AND RECOMMENDED ERADICATION STRATEGIES

In the absence of significant antibiotic resistance, high rates of *H pylori* eradication can be achieved with the recommended therapeutic regimens. The most successful regimens

TABLE 1
Recommended and endorsed therapies for the eradication of *Helicobacter pylori*

Recommended therapies

- A twice daily, seven-day regimen of a proton pump inhibitor (PPI) (omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg) or ranitidine bismuth citrate (RBC) 400 mg, clarithromycin 500 mg and amoxicillin 1000 mg; or
- A twice daily, seven-day regimen of a PPI or RBC, clarithromycin 500 or 250 mg, and metronidazole 500 mg.

Endorsed therapies

- A twice daily, seven-day regimen of PPI, metronidazole 500 mg and amoxicillin 1000 mg; or
- A twice daily, seven-day regimen of bismuth subsalicylate two tablets qid, metronidazole 250 mg qid and tetracycline 500 mg qid (bismuth plus metronidazole plus tetracycline [BMT]).

Treatment failure in patients who received metronidazole in the first course

- A twice daily, seven- to 14-day regimen of PPI or RBC, amoxicillin 1000 mg and clarithromycin 500 mg; or
- A 14-day course of PPI plus BMT.

Treatment failure in patients who received amoxicillin in the first course

- PPI or RBC, metronidazole 500 mg and clarithromycin 500 mg; or
- A 14-day course of PPI plus BMT.

Data from reference 2

require three or more drugs to be administered at least twice a day for seven to 14 days. Effective regimens typically include at least two antibiotics in combination with a drug that can substantially raise intragastric pH at the site of infection, such as a proton pump inhibitor (PPI). The current recommended treatment guidelines are given in Table 1. Drugs that raise intragastric pH or buffer acid at the gastric epithelial cell surface appear to increase *H pylori* susceptibility to the bactericidal effects of the antibiotics (24). Many antibiotics are lethal to *H pylori* in vitro, but no single agent has yet achieved acceptable rates of eradication in vivo.

In Canada, two eradication strategies are recommended as first-line therapy for *H pylori*-infected individuals. Both are triple therapies administered twice daily over seven days. One combination consists of a PPI (omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg) or ranitidine bismuth citrate (RBC) 400 mg plus clarithromycin 500 mg and amoxicillin 1000 mg. The other is a PPI or RBC (in the doses outlined above) plus clarithromycin 500 mg and metronidazole 500 mg (2). These combination regimens achieve similar degrees of efficacy in the absence of resistance to the antibiotics.

Another regimen has also been suggested as a potential alternative, despite relative disadvantages: a course of bismuth subsalicylate (two tablets), metronidazole 250 mg and tetracycline 500 mg each taken qid, plus a PPI taken bid for seven to 14 days. Although this regimen is effective, the number of tablets and the frequency of dosing are considered relative obstacles to acceptable patient compliance, and its

use in metronidazole-resistant *H pylori* strains reduces the efficacy of this combination.

Antibiotic resistance poses a significant threat to the success of treatment. However, resistance to just one of the antibiotics in a triple therapy regimen is a relative rather than an absolute predictor of treatment failure. Although the predicted efficacy of a given regimen may be inversely related to the prevalence and the degree of antibiotic resistance, PPI plus metronidazole-containing triple drug regimens have maintained an efficacy rate of up to 76% in the presence of metronidazole-resistant organisms (7). This is one reason why antibiotic susceptibility testing has not been a prerequisite to initial treatment selection.

The risk of treatment failure in patients with a resistant *H pylori* infection who are receiving a triple therapy regimen is estimated to range between 20% and 40% (7,8,10-13). In the large MACH2 controlled trial (7), eradication rates fell from 95% to 76% in patients with a metronidazole-resistant infection receiving triple therapy containing omeprazole, metronidazole and clarithromycin. Trials that evaluated the impact of metronidazole resistance on eradication efficacy have confirmed an adverse influence of metronidazole resistance (8-13). Data evaluating the effect of clarithromycin resistance on treatment failure are limited, but a similar lowering of efficacy was seen in the small proportion of patients with clarithromycin-resistant infections who received clarithromycin in the MACH2 trial (7).

The relative risk of resistance differs among the three antibiotics most commonly employed in eradication regimens in Canada. When defined as a minimal inhibitory concentration (MIC) of drug greater than 8 mg/L, resistance to metronidazole is observed in approximately 20% of the population, with substantially higher rates reported in some groups, such as recent immigrants to Canada from developing countries. Resistance to clarithromycin, defined as a MIC₉₀ greater than 1 mg/L (25-28), ranges between 1% and 5% in most areas of Canada (29,30; CA Fallone, personal communication). Amoxicillin resistance, documented only recently, is extremely rare in Canada.

Although the increased risk of treatment failure means that antimicrobial resistance is an important clinical variable, its impact is predicted to be modest in populations that have a low prevalence of resistant organisms. In Canada, where the prevalence of metronidazole resistance is approximately 20% (CA Fallone, personal communication), the overall treatment failure using a metronidazole-containing regimen would be expected to rise by only 1% to 4% relative to an expected rate of treatment efficacy in a population with no metronidazole resistance (31). However, in areas of the world with a high prevalence of metronidazole resistance, the negative impact on treatment success would be higher and would require consideration of alternative regimens. Hence, it is important to know the rates of resistance in the specific population being treated.

A similar conclusion concerning the impact of clarithromycin resistance is reasonable but cannot be supported by comparable data. In one trial associating clarithromycin

resistance with diminished efficacy among patients receiving triple therapy with a PPI, clarithromycin and metronidazole, only six of 114 patients had evidence of clarithromycin resistance. In another arm of the same trial, two of 113 patients receiving PPI, clarithromycin and amoxicillin had clarithromycin resistance (7). Eradication of *H pylori* infection was successful irrespective of clarithromycin resistance status. In areas such as France, where the prevalence of clarithromycin is higher, the impact of clarithromycin resistance on the efficacy of eradication of *H pylori* may be greater. However, additional data are necessary to develop evidence-based clinical guidelines.

Antibiotic resistance is partially overcome by acid suppression. As a result, routine in vitro susceptibility testing is not warranted for the selection of a treatment regimen if the anticipated prevalence of bacterial resistance is low. In patient populations with a high risk of resistance to a specific drug such as metronidazole, it is reasonable to select an eradication strategy that does not contain this antibiotic.

Susceptibility testing may have a role in patients who have failed an initial course of treatment despite adequate compliance. However, empirical second-line management is also a reasonable alternative. Although there are few data from prospective trials to guide drug selection in patients who have failed an initial course of therapy, it is reasonable to use an alternative first-line regimen for retreatment (32). Longer treatment courses and the addition of another drug, such as quadruple-drug regimens containing two antibiotics and both bismuth and a PPI, have also been advocated for use in treatment failures. The relative efficacy of these strategies needs to be compared prospectively.

Treatment failure does not necessarily confirm the presence of a resistant infection but does create a selective pressure for secondary antibiotic resistance to develop. This emphasizes the need to use an effective first-line strategy initially. Educational programs to convince clinicians and their patients to comply with recommended first-line *H pylori* eradication protocols are likely to prove to be a key step toward circumventing the development of antibiotic resistance and the need to develop additional rescue strategies.

SUSCEPTIBILITY TESTING

The goal of susceptibility testing is to predict the clinical outcome of attempted *H pylori* treatment. However, there are several unique obstacles to obtaining reproducible and reliable results from susceptibility testing of *H pylori* in culture in vitro. For example, there are no universally accepted methods to determine the antibiotic susceptibility of *H pylori*. In addition, in vivo conditions, including antibiotic tissue concentrations and intragastric pH, are difficult to reproduce in vitro. It is unclear what role serum levels of antibiotics have in predicting their bactericidal effect at the site of *H pylori* colonization. Moreover, it is difficult to interpret resistance to a single drug in a multidrug regimen, and there is a wide geographical variability in the breakpoints used to define resistance to metronidazole and clarithromycin in *H pylori* (30) (Table 2). These factors likely explain

TABLE 2
Variability in breakpoints used to define resistance to metronidazole and clarithromycin in *Helicobacter pylori*

Antibiotic	MIC breakpoint	Geographic origin of strains
Metronidazole	≥4	Peru
	>4	Canada/Europe
	≥64	United States
	≥8	Norway
	≥16	Canada joint study
	>8	Montreal, Quebec
	>8	Halifax, Nova Scotia
	>32	Belgium
	>32	Italy
	>32	The Netherlands
Clarithromycin	≥0.125	Peru
	≥2	Canada/Europe
	≥4	Canada joint study
	>2	Montreal, Quebec
	>2	Halifax, Nova Scotia
	>8	Italy
	≥2	United States

MIC Minimal inhibitory concentration. Reproduced with permission from reference 30

why the MIC breakpoints for resistance of individual antibiotics for *H pylori* remain inconsistently defined.

Nevertheless, susceptibility testing guidelines have been developed in both the United States (33) and Europe (F Megraud, personal communication). Both groups provide guidelines with respect to transport of the organism, composition and relative selectivity of the culture media, incubation temperatures and other aspects important for producing reproducible results. There are many areas of agreement between the guidelines, including the use of agar dilution methodology as the standard for susceptibility testing. The advantages of the agar dilution technique are relative reproducibility and the ability to test batches of bacterial isolates. Testing with agar dilution is also labour intensive and, therefore, less practical when evaluating a small number of isolates. Alternatives include disk diffusion, broth microdilution and the E test. However, the standards for the preparation and implementation of these susceptibility testing methods are not as well established as for agar dilution. Studies in Canada suggest that there is reasonable agreement between these methods (34).

A better definition of what constitutes a clinically meaningful MIC will be an important step toward more widespread use of susceptibility testing of *H pylori* infection in the patient care setting. Several breakpoints have been proposed. However, there are few studies that have evaluated the correlation between any specific breakpoint and clinical

cure. For example, even though an MIC greater than 8 mg/L has been used to define resistance to metronidazole, strains with MICs of up to 32 mg/L may be successfully eradicated with first-line therapy. The problem of establishing meaningful definitions of metronidazole resistance is reflected in the distribution of MICs among *H pylori* organisms. Unlike clarithromycin MICs, which are distributed in a bimodal fashion (8), *H pylori* demonstrates a broader range of metronidazole MICs (35).

Clarithromycin resistance is also poorly defined despite its bimodal distribution. Although an MIC of 1 to 2 mg/L for clarithromycin is widely accepted as the threshold of resistance, these values are an imperfect predictor of treatment failure in clinical trials. Alternative breakpoints deserve evaluation to determine MICs in the context of other drugs included in the eradication regimen.

Successful refinements of traditional culture methods, including improvements in the selectivity of the media and the standardization of culture methods, may improve current standards. These refinements would yield techniques that are more accurate and more consistently reproducible. Such standards for primary culture and susceptibility testing are essential for quality control. With the exception of Halifax, no laboratories in Canada routinely perform susceptibility testing on *H pylori* to guide therapeutic decisions. It is important to develop this capability for treatment failures, as well as to monitor national and regional trends in antibiotic resistance. Reproducible results among testing laboratories performing a sufficient number of tests to maintain expertise will be an essential component of such a program.

MECHANISMS OF RESISTANCE

Innovative methods to determine antibiotic resistance are required. Rather than MIC determinations, identification of a genetic mutation conferring resistance is one option that may predict susceptibility more reliably. Resistance of *H pylori* to antibiotics is mediated by genetic mutations that inhibit bactericidal effects. Alternative mechanisms, such as plasmid-borne resistance factors or the production of enzymes analogous to beta-lactamase, have not yet been detected. Specific mutations that confer resistance to metronidazole are located on the *rdx* gene (36). Mutations in *rdx* enfeeble the organism, making it more susceptible to the bactericidal effects of a second antimicrobial agent. This observation appears to explain why metronidazole resistance only modestly compromises the efficacy of triple combination therapies containing metronidazole. *H pylori* strains resistant to clarithromycin develop from one or more specific point mutations in the 23S rRNA of the 50S ribosomal subunit (37). These mutations prevent the ability of clarithromycin to bind to *H pylori* and thereby inhibit the synthesis of a protein that is key for *H pylori* survival. The increasing prevalence of primary resistance of *H pylori* to clarithromycin correlates with the increasing number of prescriptions for these antibiotics (38,39). In Canada, no trials have attempted to evaluate the impact of prescribing trends on the prevalence of *H pylori* resistance.

A systematic approach to tracking trends in *H pylori* antibiotic resistance is needed in Canada. An increase in the prevalence of antimicrobial resistance predicts a reduced probability of treatment success. Early detection of rising rates of resistance could result in appropriate modification of eradication regimens and recommendations, thereby preventing the chain of events described above and helping to maintain an optimal approach to controlling this infection.

GOALS OF SUSCEPTIBILITY TESTING

Some hurdles exist to establishing an optimal system for monitoring antibiotic resistance among *H pylori*-infected patients in Canada. *H pylori* likely will provide unique challenges to resistance monitoring. For example, the evidence that gastric acid secretion has some benefit on antibiotic susceptibility complicates the clinical relevance of in vitro testing. Other confounding variables, including potential differences in eradication successes due to variations in *H pylori* virulence, may provide opportunities for discordant results among laboratories even when employing identical testing protocols.

Such challenges must be confronted in the development of a systematic approach to national and regional monitoring of resistance. Reliable information about trends in antibiotic resistance is an important form of defense against inappropriate antibiotic use. Susceptibility testing may prove to be a valuable tool for managing treatment failures and in reducing the risk of secondary resistance, although this has not yet been investigated. Moreover, the inconsistent association between in vitro susceptibility and successful eradication in the clinical setting further underlines the importance of continued research in this field.

Several organizations, including the National Commission on Clinical Laboratory Testing (33), have attempted to define standards for *H pylori* susceptibility testing. It is also important for coordinating centres in Canada to evaluate the strengths and weaknesses of current standards. These methodologies differ in their relative complexity, accuracy, resource requirements and time to report a result. It is also important to recognize that the best method for serial testing of multiple isolates may not be the most advantageous method for testing a single isolate. As a result, the standards in this country must be developed within the context of specific goals.

A pilot project in Canada will soon be undertaken in which several geographically distributed centres will participate in a collaborative network for *H pylori* sensitivity testing. The methodology for susceptibility testing will be standardized, with the goal of establishing a database that incorporates information about patient characteristics, the strain of organism, and other variables of clinical and research interest. The network will also facilitate clinical trials, including those conducted in patients who fail initial treatment due to antibiotic resistance. This pilot project will permit comparison of results from different laboratories using standardized methods and should eventually improve the quality of care for persons with *H pylori* infection.

APPENDIX: PARTICIPANTS IN THE *HELICOBACTER* STUDY GROUP MEETING

David Armstrong, Scott Barbeau (Byk/Solvay), Alan Barkun (the Canadian Association of Gastroenterology), Linda Best, Michel Boivin, Ted Bosworth (medical writer), Hugh Chaun, Naoki Chiba, Carol Fallone, Nigel Flook (College of Family Physicians of Canada), Youri Glupczynski, Markus Goettke, Ben Gold, Avery Goodwin, David Haldane, Eric Hassall (Canadian Pediatric Association), Paul Hoffman, Richard Hunt, Wendy Johnson, Monika Keelan, Pamela Kibsey, Raymond Lahaie, Yves Levasseur (Abbott), Vivian Loo, Pamela Lyn, Philippa McDonald (Health Protection Branch), Patrick McLean (Axcn), Mario Monteiro, Myron Pyzyk (Byk/Solvay), Phil Sherman (Canadian Pediatric Association), Christina Sibley (Glaxo), Paul Sinclair (Astra), Fiona Smaill (Canadian Society of Infectious Diseases), Wendy Smith (Astra), Jean Spenard (Axcn), Diane Taylor, Vinay Thatte (Health Protection Branch), Alan Thomson, Sander Van Zanten

CONCLUSIONS

Antibiotic resistance is an important risk factor for the failure of current *H pylori* eradication strategies. Efforts to monitor the prevalence of antibiotic resistance among *H pylori*-infected individuals have important public health implications. A national collaborative network of testing laboratories using standardized protocols is likely to play a beneficial role in helping to control this infection. In Canada, there are only limited data on the frequency and impact of *H pylori* resistance. Monitoring of *H pylori* susceptibility to antibiotics may have value for guiding appropriate alternative regimens in patients who fail repeated courses of eradication therapy.

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