Helicobacter pylori antibiotic resistance: Trends over time

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RG Lahaie, C Gaudreau. *Helicobacter pylori* antibiotic resistance: Trends over time. Can J Gastroenterol 2000;14(10): 895-899. Resistance to antibiotics can be a major problem in the treatment of bacterial infections. As the use of antibiotics increases, bacterial resistance to these agents is rising and in many cases is responsible for the failure of treatment regimens. Although the treatment of *Helicobacter pylori* infection requires the use of more than one antibiotic to obtain adequate eradication rates, the efficacy of the currently used antibiotic combinations has been shown to be decreased by resistance to one of the antibiotics. The use of antibiotics in regimens for the treatment of *H pylori* is increasing in many countries, including Canada. This increase is both in the use of these antibiotics alone for the treatment of non-gastrointestinal infections and in their use in association with proton pump inhibitors for the treatment of *H pylori* infection. In several European and Asian countries, where resistance to antibiotics is being monitored, it has been demonstrated that *H pylori* resistance to metronidazole and to clarithromycin increased throughout the 1990s. Thus far, the data available in Canada do not show increased resistance to either of these antibiotics. As for other antibiotics used in the treatment of *H pylori* infection, such as tetracycline and amoxicillin, the rate of resistance to these agents is still very low and does not constitute a significant problem. Because the efficacy of the regimens used in the treatment of *H pylori* infection is compromised by resistance to the antibiotics used, it is important that *H pylori* resistance rates in Canada and throughout the world continue to be monitored. Only with such reliable data can the most optimal regimens be recommended.

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

Helicobacter pylori et résistance aux antibiotiques: Tendances évolutives

RÉSUMÉ : L'antibiorésistance peut poser un problème sérieux pour le traitement des infections bactériennes. Comme l'utilisation des antibiotiques a augmenté, la résistance bactérienne aux médicaments a également augmenté et, dans bien des cas, elle est responsable de l'échec du traitement. Même si le traitement de l'infection à *Helicobacter pylori* exige l'utilisation de plus d'un antibiotique pour atteindre des taux adéquats d'éradication, l'efficacité de l'association actuelle d'antibiotiques a diminué en raison de la résistance à l'un des antibiotiques. Le recours aux antibiotiques pour le traitement des infections à *H. pylori* augmente dans beaucoup de pays, dont le Canada. Cette augmentation s'observe tant en monothérapie pour le traitement d'infections non gastro-intestinales qu'en bithérapie avec les inhibiteurs de la pompe à protons pour le traitement des infections à *H. pylori*. Selon des données recueillies en Europe et en Asie, où la résistance aux antibiotiques fait l'objet de surveillance, la résistance d'*H. pylori* au métronidazole et à la clarithromycine a augmenté tout au long des années 90. Jusqu'à maintenant, les données au Canada ne montrent pas de résistance accrue à l'un ou l'autre de ces antibiotiques. Quant aux autres antibiotiques utilisés dans le traitement des infections à *H. pylori*, par exemple la tétracycline et l'amoxicilline, le taux de résistance à ces médicaments est encore très faible et ne pose pas de problème sérieux. Comme l'efficacité des schémas thérapeutiques mis en œuvre pour combattre les infections à *H. pylori* est compromise par la résistance aux antibiotiques, il est important que les taux de résistance d'*H. pylori* continuent de faire l'objet de surveillance au Canada et partout dans le monde. Ce n'est que munis de données fiables que nous serons en mesure de recommander les meilleurs schémas thérapeutiques qui soient.

Helicobacter pylori infection is an important cause of human gastric and duodenal pathology, and its treatment cures several of these diseases (1). As is the case for most other infections, antibiotic-based therapeutic regimens are the mainstay of *H pylori* treatment. In bacterial infections treated with a single antibiotic, resistance of the bacterium to the antibiotic precludes its use for the treatment of the infection. In the case of *H pylori* treatment, where multiple

drug regimens are used, resistance to one of the antibiotics significantly decreases the efficacy of the regimen (2).

Several studies have documented an increase in the rate of resistance to antibiotics for different bacterial diseases. A recent study from the Minnesota Department of Health showed an important increase in quinolone-resistant *Campylobacter jejuni* infections between 1992 and 1998 (3). Similar increases in antibiotic resistance of this organism were

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Figure 1 Estimated number of prescriptions of clarithromycin (Clari) and metronidazole (Metro) dispensed in Canada from 1994 to 1998. Data were obtained by IMS Health from a representative sample of retail pharmacies throughout Canada and extrapolated to all of Canada. Reproduced with permission from IMS Health

seen in Quebec between 1985 and 1997 (4). The prevalence of *H pylori* resistance to the most frequently used antibiotics varies greatly among countries, from low resistance rates in developed countries to very high resistance rates in developing countries (5). The very high resistance rates to metronidazole in developing countries have been related to frequent use of this antibiotic for the treatment of locally endemic infections such as giardiasis and amoebiasis (6).

To ensure continued optimal efficacy of the antibiotic regimens designed to treat *H pylori* infection, it is important to study the epidemiology of its resistance to antibiotics, to determine whether *H pylori* resistance to antibiotics is increasing over time and to attempt to identify the potential causes of increasing resistance rates.

MECHANISMS OF INCREASED RESISTANCE TO ANTIBIOTICS

Increased resistance to antibiotics often results from increased exposure to these agents. A recent Finnish study has demonstrated a close relation between macrolide use in the community and erythromycin resistance of group A streptococci (7). Increased exposure to antibiotics can result in an increase in antibiotic resistance by one of several mechanisms, such as strain selection, vertical transmission of resistant strains and induced mutations.

The human stomach can be colonized by more than one strain of *H pylori* (8-10). Exposure to a single antibiotic – for example metronidazole – would kill metronidazole-sensitive (Met^S) strains but select out metronidazole-resistant (Met^R) strains. Thus, increased use of metronidazole as a single agent for the treatment of other infections increases selection of Met^R strains, which then become the dominant strain. Also, use of recommended regimens for *H pylori* eradication is expected to result in eradication failure in 5% to 20% of patients who are treated (11). Failure of *H pylori* eradication treatment has also been shown to result in increased resistance to antibiotics – known as secondary resistance (12-15). Therefore, increased antibiotic use in both the adult and the pediatric populations can potentially increase resistance rates. Because this infection is most often acquired by young children, usually before the age of five years (16), and because transmission from parent to child is

an accepted mode of acquisition of the infection (17,18), vertical transmission of resistant strains is expected to increase as the prevalence of resistance increases in the adult population. Thus, transmission of resistant strains to children would result in a slow increase in the prevalence of primary resistance (resistance occurring in patients never treated for *H pylori* infection) through the next generations. Finally, because metronidazole is a potent mutagen (19), increased exposure to this antibiotic may result in an increased frequency of resistance-inducing mutations in bacterial DNA.

Monitoring antibiotic use can, therefore, help in determining and maybe predicting the future of antibiotic resistance in Canada. The principal antibiotics used in the treatment of *H pylori* infection are metronidazole, clarithromycin, amoxicillin and tetracycline. As discussed by Fallone in this issue (pages 879-882), *H pylori* resistance to antibiotics has been shown to be clinically significant only in the case of metronidazole and clarithromycin; resistance to tetracycline and amoxicillin remains relatively rare. In Canada, use of both clarithromycin and metronidazole has been increasing in recent years (Figure 1). This increase has been similar in all provinces in Canada. Although the increased use of clarithromycin and metronidazole is due in part to their increased use for the eradication of *H pylori*, use of either of these antibiotics alone continues to be the most frequent way in which these drugs are prescribed (IMS Health, unpublished data), which may lay the groundwork for future increases in resistance to these antibiotics.

EVOLUTION OF PRIMARY METRONIDAZOLE AND CLARITHROMYCIN RESISTANCE THROUGHOUT THE WORLD

Studies of the evolution of primary resistance to antibiotics must fulfill several criteria to ensure the validity of the results. Strains must be obtained from patients who have not previously been treated for *H pylori* infection. Accepted and validated methods must be used to determine the antibiotic sensitivities of strains obtained from gastric biopsies. These same methods must be used in successive years during which the trends of resistance are being studied. Ideally, the strains studied should be obtained from a representative segment of the population being studied rather than from a small cohort of individuals frequenting a specific institution.

Literature from around the world does not contain many studies that fulfill these criteria. Several authors have nevertheless attempted to study the evolution of resistance to antibiotics used in the treatment of *H pylori* infection. Table 1 illustrates the results of studies looking at the evolution of metronidazole resistance. One North American, three Asian and five European studies on the evolution of metronidazole resistance over time have been published to date. Among these studies, only four stated clearly that the strains were obtained from patients not previously exposed to *H pylori* eradication therapy, three of which showed a significant increase in primary resistance to metronidazole. These trends are illustrated in Figure 2.

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TABLE 1
Published studies of the evolution of metronidazole resistance over time

					Rate of <i>Helicobacter pylori</i> resistance to metronidazole per year (%)										
Author (reference)	Country	Test	Po	n	1980s	1991	1992	1993	1994	1995	1996	1997	1998	P	
Yeoh et al (22)	Singapore	DD	?	69						20	50	62		S	
Teo et al (23)	Singapore	DD	M	381					45	70	82			S	
Ling et al (24)	Hong Kong	DD	P	1015	25	22	53	50	60	73				S	
Lopez-Brea et al (25)	Spain	AD	?	282		9	6	33	19	22					
van der Wouden et al (26)	The Netherlands	E-t	P	1037				7	8	14	32			S	
Xia et al (27)	Ireland	DD	?	1299		32	34	36	39	46				S	
De Koster et al (28)	Belgium	DD	P	1415	25	33	32	28	28	30	33	34	35	S	
Morton and Bardhan (29)	England	DD	?	1215			18	22	33	32	37	37		S	
Lahaie et al (30)	Canada	E-t	P	137				33	34	35	33		42	NS	

Only a few series represent primary resistance rates; most include a mixed population of patients, some of whom have had previous exposure to *H pylori* eradication therapy. ? Not clearly stated; AD Agar dilution; DD Disk diffusion; E-t E-test; n Number of strains; NS Not significant; M Mixed primary and secondary; P Primary; Po Population; S Significant

primary metronidazole resistance remained stable between 1993 and 1996. This resistance rate may have increased in the past two years; recent results obtained from a multicentre study in which the Saint-Luc Gastroenterology Unit participated showed that 15 of 35 (42.8%) strains cultured were resistant to metronidazole by E-test. However, the culture and sensitivity testing for this study were done in a commercial laboratory; therefore, direct comparison with results obtained in the Saint-Luc microbiology laboratory is difficult. Until these strains are restudied in the CHUM laboratory, it is only speculation that there may have been an increase in metronidazole resistance rates in Montreal. It is interesting, however, that Quebec Drug Program data on metronidazole prescriptions dispensed in the past four years show that the use of this antibiotic has doubled in 1997 and 1998 compared with 1995 and 1996.

One North American, one Asian and five European groups (Table 2) have studied the evolution of clarithromycin resistance. Only three of the seven authors clearly stated that the strains were obtained from untreated patients; thus, their data represent primary resistance rates. The generally low resistance rates to clarithromycin make it more difficult

Figure 2) Evolution of metronidazole resistance taken from series clearly stating that the strains studied were obtained from patients not previously exposed to *Helicobacter pylori* eradication therapy. *Significant increase. Belg Belgium; Can Canada; HK Hong Kong; Neth The Netherlands

to see significant trends in the evolution of resistance. This has been our experience; although it seems that resistance to clarithromycin was increasing in Montreal between 1993 and 1996, the number of strains studied was too small for the results to be statistically significant. Only the Belgian series showed a significant increase in primary clarithromycin

TABLE 2
Published studies of the evolution of clarithromycin resistance over time

Rate of <i>Helicobacter pylori</i> resistance to clarithromycin per year (%)														
Author (reference)	Country	Test	Po	n	1980s	1991	1992	1993	1994	1995	1996	1997	1998	P
Takahashi et al (31)	Japan	E-t	P	210	0					21	9	15		NS
Lopez-Brea et al (25)	Spain	AD	?	282		0	0	4	3	4				NS
Xia et al (27)	Ireland	DD	?	1299				5	6	9				NS
De Koster et al (28)	Belgium	DD	P	1415	2.2	0	4	6	9	6	11	13	10	S
Morton and Bardhan (29)	England	DD	?	1215				1	2	4	6	8		S
Camou et al (32)	France	E-t	?	683	8.8	11	10		12			14		
Lahaie et al (30)	Canada	E-t	P	137				1	0	5	8			NS

Only a few series represent primary resistance rates, most including a mixed population of patients some of whom have had previous exposure to *H pylori* eradication therapy. ? Not clearly stated; AD Agar dilution; DD Disk diffusion; E-t E-test; n Number of strains; NS Not significant; Po Population; S Significant

Figure 3) Quebec Drug Program data representing the number of units of metronidazole 250 mg dispensed between 1995 and 1998

Figure 4) Evolution of clarithromycin resistance taken from series clearly stating that the strains studied were obtained from patients not previously exposed to *Helicobacter pylori* eradication therapy. *Significant increase. Belg Belgium; Can Canada; Jap Japan

resistance over time (Figure 3). In Europe, resistance to clarithromycin has only increased in countries where this new macrolide has only just recently been introduced (20). In Canada, clarithromycin was introduced in 1992, and its use has increased greatly between 1994 and 1998 (Figure 1). Although, as mentioned above, too few strains were studied for this trend to be statistically significant, in 1993 and 1994, virtually no resistance to clarithromycin was found, whereas in 1996, 8% of the strains were found to be resistant to this antibiotic. Other Canadian data, however, suggest that clarithromycin resistance remains low, at 1.8% (21).

EVOLUTION OF SECONDARY METRONIDAZOLE AND CLARITHROMYCIN RESISTANCE THROUGHOUT THE WORLD

H. pylori secondary resistance to antibiotics is defined as resistance that occurs after exposure to and failure of eradication therapy. The mechanisms that can explain the development of secondary resistance are similar to those involved in the development of primary resistance, including strain selection and strain mutation. Failure of eradication therapy has clearly been shown to result in an increase in antibiotic resistance (11-14)

Study of the evolution of secondary resistance is limited by the complexity of the methods involved. Indeed, both pretreatment strains and post-treatment strains from all pa-

Figure 5) Evolution of secondary metronidazole resistance as estimated from series including a mixed population of strains isolated from patients not previously treated for *Helicobacter pylori* infection and from patients who failed eradication therapy. *Significant increase. Irel Ireland; Sign Singapore; UK United Kingdom

Figure 6) Evolution of secondary clarithromycin resistance as estimated from series including a mixed population of strains isolated from patients not previously treated for *Helicobacter pylori* infection and from patients who failed eradication therapy. *Significant increase. Irel Ireland; UK United Kingdom

tients who fail eradication therapy are required. Only patients who have pretreatment, sensitive strains, which then become resistant as a result of failure of therapy, can be said to have developed secondary resistance. Although several studies have addressed the question of secondary resistance as a result of treatment failure, to my knowledge, no systematic study on the evolution of secondary resistance over time has been done or published to this date. The closest estimate of the evolution of secondary resistance over time must thus be obtained from studies with mixed populations, including patients not previously treated for *H. pylori* and patients who have had previous *H. pylori* eradication therapy (Tables 1 and 2).

Such estimates of the evolution of secondary resistance to metronidazole and to clarithromycin are illustrated in Figures 4 and 5. Four of the five series studying metronidazole resistance showed a significant increase in resistance rates over time. Only one of the four studies showed a significant increase in resistance to metronidazole, as for clarithromycin (Figure 6).

CONCLUSIONS

Several points need to be kept in mind when attempting to draw conclusions from existing data on the evolution of antibiotic resistance by *H. pylori* over time. First and foremost among these points is whether the published series truly represent primary resistance, including only patients who have

not had previous exposure to *H pylori* eradication therapy. Also, there is usually no information on previous antibiotic use for other infections by the patients included in these studies. Because this is a major factor in the development of antibiotic resistance, more data need to be gathered concerning this important variable. Also, most series gather patients from their immediate surroundings, and one wonders whether these data are representative of the evolution of resistance rates in the country as a whole.

Nevertheless, the available data suggest that primary metronidazole resistance rates are increasing in different areas of the world, including Asia and Europe. The data available for Canada do not show an increase in primary metronidazole resistance between 1993 and 1996. Whether this situation has changed in the past three years, as is suggested by more recent data, remains to be confirmed. Thus far, a significant increase in primary resistance to clarithromycin has been documented in Belgium only. In Canada, resistance rates to clarithromycin remain quite low. The increase in resistance observed in the series reported here did not reach statistical significance because of the low number of strains available.

It is clear that further work needs to be done in this field. Antibiotic use should be monitored, and *H pylori* resistance to antibiotics followed closely throughout the country and in different areas of the world. Obtaining reliable data on these evolving trends will help ensure continued optimization of antibiotic regimens used in the eradication of *H pylori*.

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