Epidemiology of the antibiotic resistance of *Helicobacter pylori* in Canada

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BACKGROUND: The rate of *Helicobacter pylori* resistance to antibiotics determines the cure rate of treatment regimens containing such antibiotics.

AIMS: To review the literature to determine the rates of *H pylori* resistance to metronidazole and clarithromycin in Canada, and whether these rates vary in different regions of Canada.

METHODS: The literature was reviewed extensively for the prevalence of antibiotic-resistant *H pylori* in Canada by searching MEDLINE from January 1980 to May 1999, as well as abstracts of the American Gastroenterology Association Digestive Disease Week, Canadian Digestive Disease Week and The European *H pylori* Study Group Meetings from January 1995 to May 1999.

RESULTS: Eleven studies that estimated *H pylori* resistance to metronidazole resistance and nine that estimated resistance to clarithromycin in Canada were identified. Rates of resistance for metronidazole and clarithromycin varied from 11% to 48% and 0% to 12%, respectively. Studies that obtained their estimates using the E-test and those that did not clearly exclude patients who had undergone previous attempts at *H pylori* eradication had higher estimates of resistance, accounting for this variability in results.

CONCLUSIONS: The prevalence of primary *H pylori* resistance in Canada appears to be 18% to 22% for metronidazole and less than 4% for clarithromycin. These rates appear to be consistent across the different regions studied in Canada, but many regions have not been studied.

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

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CONTEXTE : Le taux de résistance d'*Helicobacter pylori* aux antibiotiques détermine le taux de guérison des schémas thérapeutiques se composant de ces antibiotiques.

BUT : Passer la documentation en revue pour déterminer le taux de résistance d'*H. pylori* au métronidazole et à la clarithromycine au Canada et vérifier si le taux varie selon les régions.

MÉTHODE : On a procédé à un examen exhaustif de la documentation pour déterminer la prévalence de la résistance d'*H. pylori* au métronidazole et à la clarithromycine au Canada en cherchant dans MEDLINE de 1980 à mai 1999 et en lisant les résumés de l'American Gastroenterology Association Digestive Disease Week, de la Semaine canadienne des maladies digestives et des European *H. pylori* Study group Meetings de 1995 à mai 1999.

RÉSULTATS : On a trouvé 11 études dans lesquelles il y avait une évaluation du taux de résistance d'*H. pylori* au métronidazole et neuf, à la clarithromycine au Canada. Les taux de résistance au métronidazole et à la clarithromycine variaient de 11 à 48 % et de 0 à 12 % respectivement. Les études dont l'évaluation reposait sur le test E et celles dans lesquelles l'exclusion des patients ayant déjà été soumis à un traitement d'éradication d'*H. pylori* était incertaine faisaient état de taux de résistance plus élevés, d'où écart des résultats.

CONCLUSION : La prévalence de la résistance d'*H. pylori* au Canada semble osciller entre 18 et 22 % pour le métronidazole et se situer en deçà de 4 % pour la clarithromycine. Les taux semblent relativement homogènes dans les différentes régions étudiées, mais bon nombre de régions n'ont pas fait l'objet d'étude.

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Helicobacter pylori plays a significant role in the pathogenesis of peptic ulcer disease, gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma (1-3). A suggested approach to the treatment of adult patients younger than 45 years old with uninvestigated dyspepsia and without alarming symptoms is to test for *H pylori* infection and treat the patient if this infection is present (3). Hence, treatment of *H pylori*, which has been estimated to be present in approximately 20% to 50% of the Canadian population (4), is increasingly recommended.

The successful cure of *H pylori* infection is dependent on the susceptibility profile of the organism. It is clear that, although certain strains that show in vitro resistance to metronidazole or clarithromycin respond to treatments containing these antibiotics, the success rate of eradication is significantly reduced (5,6). It is thus important to know the susceptibility profiles in each community to recommend the optimal treatment, given that these in vitro resistance rates vary tremendously from one part of the world to another (7).

The present article summarizes the many studies that have documented in vitro susceptibility profiles of *H pylori* strains across Canada and attempts to estimate the true rate of primary (ie, before any treatment directed toward *H pylori*) *H pylori* resistance to metronidazole and clarithromycin.

METHODS

A MEDLINE search was performed for articles published from January 1980 to May 1999. Abstracts from the Canadian Digestive Disease Week, the American Gastroenterology Association Digestive Disease week and the European *H pylori* Study Group meetings from 1995 to 1999 were also searched. In addition, authors across Canada who were known to have worked in the field were asked for any published or upcoming data. The search was for any documentation of *H pylori* susceptibility profiles to any antibiotics. The articles or abstracts identified were then retrieved and analyzed to determine the population studied, whether the study comprised an adult or pediatric population, the diagnosis of the population studied, whether the study comprised previously untreated patients or patients who had previously undergone treatment for *H pylori* eradication, the method used to determine susceptibility, the cutoff used to define a resistant strain and the estimate of resistance. Using the data obtained from these papers, 95% confidence intervals were calculated throughout. If there were any data missing or if certain data were unclear, an attempt was made to contact the author for clarification.

RESULTS

Eleven studies that estimated *H pylori* resistance to metronidazole in Canada were identified. Nine studies estimated resistance to clarithromycin in Canada, and five studies examined resistance to other antibiotics. Only one study identified antibiotic susceptibility profiles in strains obtained from a Canadian pediatric population. Some of the studies examined susceptibility profiles in specific regions or

Figure 1 Point estimates with 95% confidence intervals of metronidazole resistance from the 11 Canadian studies (references 8 to 18 shown from left to right on the graph) are plotted as per region from which these strains were obtained. Studies in which the estimates were determined by E-tests are labelled, as are the studies in which patients who had undergone previous attempts at *Helicobacter pylori* treatment may have been included. If it is assumed that studies that may have included patients who had undergone a previous treatment attempt and studies that use the E-tests may overestimate the rate of primary resistance, one can estimate that the rate of *H pylori* resistance to metronidazole across Canada is about 18% to 22% because this range crosses most of the 95% confidence intervals. Alb Alberta; CND Across Canada; Mtm Maritimes; ON Ontario; PQ Quebec

cities in Canada, whereas other studies obtained their strains from different cities in Canada. Results are presented as per region, in the event that there was any difference in the rates from different regions of Canada.

Resistance to metronidazole: Four studies examined the prevalence of *H pylori* resistance to metronidazole in the Montreal region (8-11). Of these studies, two (8,9) were of duodenal ulcer patients specifically. The four studies were of adult populations, and strains were obtained before the patients had undergone any treatment for *H pylori*. Agar dilution, with a cutoff of 8 mg/L, was used in three studies (8,9,11), whereas the E-test (cutoff 8 mg/L) and disk diffusion (cutoff 20 mm) were used in the other study (10). Resistance to metronidazole was estimated to be 17% (n=119) (9), 20% (n=89) (8) and 11% (n=55) (11) in the studies that used agar dilution, and a higher estimate of 29% to 34% was obtained in the study that used the E-test and disk diffusion (10). The results are graphically demonstrated with their 95% confidence intervals in Figure 1.

One study examined *H pylori* resistance to metronidazole in Alberta by using both the agar dilution and the E-tests (12). The cutoff was 8 mg/L, and the strains were obtained before any treatment attempt had been made. Strains were from adult patients who had *H pylori* gastritis. The prevalence of resistance to metronidazole was found to be 12% when agar dilution was used and 14% when the E-test was used (n=42).

Six studies (13-18) obtained strains from cities across Canada. Five of these studies (13,14,16-18) did not specify whether specimens were only obtained in patients who had

not previously been treated for *H pylori*. Hence, in these studies, some patients may have previously received metronidazole in an attempt to eradicate *H pylori*, thus increasing the prevalence of resistance to metronidazole in that study populations. Because these results may not be true representations of primary resistance of metronidazole, they are labelled differently in Figure 1. Three studies used the agar dilution method (13-15). Wurzer et al (13) examined strains from Montreal and Edmonton in duodenal ulcer patients. They chose 4 mg/L as a cutoff and found a 47% (n=47) prevalence of resistance to metronidazole. However, because of the low cutoff level and because it was not specified whether some strains were obtained from patients who had previously undergone treatment for *H pylori* eradication, this is likely an overestimation of the actual resistance rate in Canada. Fedorak et al (14) examined strains obtained from duodenal ulcer patients in Montreal, Edmonton and Toronto with the use of agar dilution. Their cutoff was 8 mg/L, but it was not specified whether any patients had undergone previous *H pylori* treatment. The rate of metronidazole resistance was 32% (n=48). Best et al (15) examined strains from Montreal, Edmonton and Toronto from adult duodenal ulcer patients. Their study comprised only patients who had not previously undergone treatment for *H pylori* eradication, and 8 mg/L was the cutoff. They found that the prevalence of *H pylori* resistance to metronidazole was 18.8% (n=97), which is closer to the rate obtained in Quebec and Alberta (Figure 1). One abstract (18) that did not specify which method was used obtained a resistance rate of 22% (n=100), which is in keeping with results from the majority of the studies (Figure 1). The other two studies (16,17) used the E-test and obtained rates that were higher than other estimates – 48% (n=64) and 38% (n=77), respectively. Neither study specified whether patients had previously undergone treatment for *H pylori* eradication.

The studies labelled in Figure 1 as not necessarily excluding patients who had undergone prior treatment for *H pylori* were performed across Canada. These studies are often multicentre eradication trials, and most eradication trials allow patients who have had one previous attempt at *H pylori* treatment. Hence, the estimate of *H pylori* primary resistance would be falsely raised in that study group. This is demonstrated in Figure 1, where the studies that did not allow patients who had undergone treatment attempts seem to have lower estimates of resistance than those that may have included previously treated patients. As well, studies that used E-tests tended to have higher estimates than those that used agar dilution. Therefore, the rate of resistance to metronidazole can be estimated from Figure 1. If the above explanations for discrepancies are accepted, the prevalence of resistance to metronidazole is in the range of 18% to 22% across Canada.

Resistance to clarithromycin: One study examined *H pylori* resistance to clarithromycin in the Maritimes. This study used the E-test on strains obtained from adults with peptic ulcer disease or with nonulcer dyspepsia. These patients had not undergone a previous treatment attempt, and the rate of

Figure 2) Point estimates of clarithromycin resistance with 95% confidence intervals from the nine studies (references 8-12,14,15,17,19 shown from left to right on the graph) are plotted as per region from which these strains were obtained. Studies in which the estimates were determined by E-tests are labelled, as are the studies in which patients who had undergone previous attempts at *Helicobacter pylori* treatment may have been included. If one accepts the assumption that studies that may have included patients who had undergone a previous treatment attempt may overestimate the rate of primary resistance, one can estimate that the rate of *H pylori* resistance to clarithromycin across Canada is less than 4% because this rate crosses most of the 95% confidence intervals. Alb Alberta; CND Across Canada; Mt Maritimes; ON Ontario; PQ Quebec

H pylori resistance to clarithromycin was 1.8% (n=162) (19). In the Montreal region, the same four studies that identified resistance to metronidazole estimated resistance to clarithromycin. The prevalence of resistance varied from 0% to 2% (8-11). In Alberta, Taylor et al (12) estimated that resistance to clarithromycin was present in 3% (n=31) of patients with *H pylori* gastritis who previously had not undergone *H pylori* eradication treatment (12). Three studies obtained strains from across Canada (14,15,17). Each study obtained strains from Montreal, Edmonton and Toronto. Two studies estimated *H pylori* resistance to clarithromycin to be 2.1% (n=97) and 1.3% (n=77), respectively (15,17). Fedorak et al (14) estimated resistance to clarithromycin using microbroth dilution and found a very high rate of resistance (11.6%, n=147). It is not clear whether some of the patients had undergone a previous attempt at *H pylori* eradication, potentially accounting for this elevated rate. Figure 2 demonstrates the 95% confidence intervals around the point estimates for each of these studies. If the one outlying estimate is excluded because it likely does not truly represent primary resistance (14), the rate of resistance to clarithromycin across Canada is roughly estimated to be less than 4%.

Other antibiotics: Several studies (8-12,14) have looked at *H pylori* susceptibility profiles to other antibiotics. No resistance was found to amoxicillin or ampicillin, except for one study that found that three of 147 strains were resistant to amoxicillin (2%) (14). One of the three studies that examined azithromycin and roxithromycin resistance found a 2% resistance rate, whereas the other studies found no resistant strains. No resistance was found in one study that searched

for erythromycin resistance nor in the several studies that examined tetracycline resistance.

Pediatric population: Only one study examined the resistance profile of *H pylori* obtained from a pediatric population in Canada (20). The study was of patients with chronic gastritis who had not previously undergone treatment for *H pylori* eradication. Agar dilution was used, and all of the 18 strains were susceptible to metronidazole, tinidazole, erythromycin, azithromycin, ampicillin, doxycycline and ciprofloxacin. One of the 18 strains was resistant to cefixime.

DISCUSSION

This article attempts to summarize the several studies that have estimated *H pylori* resistance to metronidazole, clarithromycin and other antibiotics in Canada. The studies have been analyzed in such a way as to determine the cause of any discrepancies among different estimates. It appears that results obtained using the E-test may be slightly overestimated compared with results obtained using agar dilution. For this reason it is important that future studies adhere to recommendations of the National Committee for Clinical Laboratory Standards (21). In addition, all the studies that tended to have higher estimates of resistance with either metronidazole or clarithromycin were from studies in which the exact population studied was not specified. Namely, it was not specified whether strains were obtained from

patients who had previously undergone a failed attempt at *H pylori* treatment. When treatment with a regimen containing metronidazole fails, a higher number of metronidazole-resistant strains remain (22). The same is true for clarithromycin (23). Hence, the slightly higher estimates of resistance may be due to the inclusion of patients who may have secondary rather than primary resistance.

The region of Canada from which strains were obtained did not seem to affect the rate of resistance. However, most patients in these studies were urban dwellers. We cannot comment on rates of antibiotic resistance in rural dwellers or in certain populations of Canada such as the Native Indians and the Inuit. Studies of strains obtained for these populations would be interesting.

Therefore, in Canada, the prevalence of primary resistance to *H pylori* is estimated to be approximately 20% for metronidazole and approximately 1% to 4% for clarithromycin. The rate of resistance to other macrolides such as azithromycin and roxithromycin appears to be similar to that of clarithromycin. Resistance to other antibiotics is extremely rare. Resistant *H pylori* strains in the pediatric population also appear to be rare.

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