Helicobacter pylori in South America

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LP Castro, LGV Coelho. *Helicobacter pylori* in South America. Can J Gastroenterol 1998;12(7):509-512. *Helicobacter pylori* is the most common chronic bacterial infection in humans. In less developed nations, eg, most South American countries, the prevalence of *H pylori* infection ranges from 70% to 90% of the population. In these countries there is rapid acquisition of the infection in early life, due to poor sanitation, low standards of living conditions and an increased rate of *H pylori* infection. The management of *H pylori* infection in South America is outlined.

Key Words: *Bacterial infection, Epidemiology*, Helicobacter pylori, *South America*

Helicobacter pylori en Amérique du Sud

RÉSUMÉ : *Helicobacter pylori* est l'infection bactérienne chronique la plus courante chez l'être humain. Dans certains pays en voie de développement, notamment dans les pays d'Amérique du Sud, la prévalence de l'infection à *H. pylori* varie de 70 à 90 %. Dans ces pays, on constate une propagation rapide de l'infection en bas âge due aux piètres conditions sanitaires, au faible niveau de vie et au taux accru d'infection à *H. pylori*. Le traitement de l'infection à *H. pylori* en Amérique du Sud est présenté ici.

The discovery of *Helicobacter pylori* and its association with peptic ulcer disease and gastric cancer is now, after more than 14 years of study, well established. The management of the infection caused by *H pylori* in the developing world, and particularly in South America, deserves some consideration, which follows.

BACKGROUND STUDIES

H pylori is the most common chronic bacterial infection in humans. Forty to 50% of the world's population is estimated to be infected, with the highest incidence occurring in older persons and in those living in areas with low standards of sanitation (1). In less developed nations, eg, most South American countries, the prevalence of *H pylori* infection ranges from 70% to 90% of the population. In these countries there is rapid acquisition of the infection in early life, due to poor sanitation and low standards of living conditions (2).

Another cause of the increased prevalence of *H pylori* infection in developing countries is that their population continues to be infected at a rate of 4.8%/year, a rate much higher than that in the developed world (3).

Latin America has been the location of some of the earliest studies looking at the epidemiology of *H pylori* infection. In Lima, Peru, the prevalence of *H pylori* infection was 48% in 407 children aged two months to 12 years; in children from low income families the prevalence was 56%, compared with a prevalence of 32% in children from high income families (4). It was also noted that, in Peru, people from the noncoastal regions of the country had significantly higher rates of infection than those living on the coast (4).

High prevalence rates of *H pylori* infection have also been reported from many other developing countries of Latin America. In Chile, seroprevalence of *H pylori* among city dwellers was approximately 60% in those 15 to 18 years old,

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TABLE 1
Reinfection rates for *Helicobacter pylori* among patients cured of infection

Population (reference)	Interval to define cure	Mean follow-up (years)	# of reinfections	Reinfection rate (%/year)
United States (15)	4 weeks	2.0	0/55	0
Australia (16)	1 year	5.8	2/94	0.4
Finland (17)	6 weeks	1.0	1/84	1.1
United States (18)	4 weeks	1.2	4/118	1.2
Australia (19)	1 year	7.1	3/35	1.2
Belgium (20)	4-6 weeks	2.0	4/158	1.3
France (21)	3 months	2.0	14/69	2.9
United Kingdom (22)	4 weeks	1.1	20/557	3.8
Austria (23)	6-10 weeks	2.0	5/46	5.4
Brazil (24)	3 months	2.9	38/147	8.8

and the increase in the risk of *H pylori* seropositivity was related to increasing age, low socioeconomic status (5) and consumption of vegetables.

Another study from Chile revealed increasing prevalence of *H pylori* antibodies with increasing age (6). In Colombia, the seroprevalence of *H pylori* among poor rural children was 68%, but was 54% among 57 age-matched children from a higher socioeconomic class living in urbanized areas (7). In Costa Rica similar rates were achieved in a serological survey (8). In Brazil, the seroprevalence of *H pylori* in adult asymptomatic blood donors was found to be 62.1% and the prevalence increased with age; the results were validated against culture, urease test and histology (9).

In another study from Brazil, 219 adult volunteers (mean age 36 years) with low economic status were prospectively tested for *H pylori* by serology: 173 (79.0%) were *H pylori*-positive and 46 (21.0%) were *H pylori*-negative. Thirty-five months later volunteers were tested again for *H pylori*. Of the 173 who were *H pylori*-positive, two reverted to *H pylori*-negative status and five of those who tested negative converted to *H pylori*-positive status, yielding an annual infection rate of 4% (10). In a second study from our group, 25 healthy volunteers who were *H pylori*-negative (mean age 30 years) were retested for *H pylori* infection 60 months later by ^{14}C-urea breath test. Six of the 25 had converted to *H pylori*-positive status, yielding an annual infection rate of 4.8% (3). Both of these studies, with virtually the same rate of annual infection, show a high infection rate in adult life, eight times more frequent than the rate of infection in more developed countries, with very few exceptions. The infection rates from other developing countries in Asia and Africa, eg, the Ivory Coast, Nigeria, Kenya, Zaire, Thailand, Vietnam, India and China, are similar to those in Latin America (4,11). Both factors – high prevalence and high acquisition of the infection in early adulthood – will certainly be important when we plan therapeutic strategies and when we study the incidence of reinfections in South America.

H PYLORI TREATMENT STRATEGIES IN SOUTH AMERICA

In the treatment of *H pylori*, South American countries have some unique difficulties including high rates of *H pylori* prevalence and acquisition, and of bacterial resistance and reinfection.

The cost of treatment is another crucial problem in South American countries. Several economic evaluations conducted in a number of developed countries have consistently shown that the treatment of *H pylori* infection with antimicrobial agents and antisecretory drugs, particularly proton pump inhibitors (PPIs), is associated with the lowest cost per ulcer cured (12,13). This is a clear and consistent message: prompt, effective treatment of *H pylori* infection in patients with peptic ulcer disease makes sound economic, as well as clinical, sense. However, the cost of the medication is very expensive, and public or private health insurance do not cover the medication in most South American countries.

Bacterial resistance, particularly to the nitroimidazoles, is another serious problem. Many eradication regimens contain one of the nitroimidazoles – metronidazole or tinidazole. Results obtained with such regimens depend on the sensitivity of the patient's bacterial strain to these agents. The prevalence of nitroimidazole-resistant strains varies widely between geographic locations, but nitroimidazole resistance is growing steadily. There is a high prevalence of primary nitroimidazole resistance in developing countries such as Brazil, with 62% of the population resistant to metronidazole as tested by the agar dilution method (14).

Another problem related to *H pylori* treatment in developing countries is reinfection. In developed countries, reinfection after successful eradication is very uncommon, occurring in 0.5% to 1.5% of cases each year, with most episodes of suspected reinfection representing actual failed therapy and inaccurate assessment of outcome.

Socioeconomic conditions are of the utmost importance in determining the prevalence of *H pylori* infection. In developing countries where family sizes tend to be large, standards of hygiene tend to be low and overcrowding is commonplace, the risk of reinfection with *H pylori* is much higher than that reported in industrialized nations. Table 1 shows the reinfection rate after successful eradication in various long term follow-up studies (15-24). Note that in Brazil, the reinfection rate is much higher than that from the industrialized countries, but it must be stressed that the increase is not related to endoscope cleaning (24).

The risk of reinfection in developing countries depends on many factors, such as the prevalence of infection, standards of hygiene, family size, overcrowding conditions and endoscopy availability. Well-conducted studies with long term follow-up are urgently needed in order to define the true reinfection rate in the developing countries, and particularly in Latin America.

In a previous study from the authors, 269 patients were treated with the combination of furazolidone 200 mg, metronidazole 250 mg and amoxicillin 500 mg tid for five days (Belo Horizonte regimen, 25); the ^{14}C-urea breath was used

to document eradication, which was validated against culture, and showed a 96.5% sensitivity and 100% specificity (26). In patients of low socioeconomic status, reinfection occurred in 70 of 223 (31%). In patients from the private clinic (n=46) the reinfection rate was 8.7%.

When the rate of reinfection in the 269 patients followed for up to 35 months was examined, a clear trend emerged. Successful treatment was noted in 70 of the 223 patients (31%) who were treated at a university hospital but in just four of the 46 (8.7%) who were treated at a private clinic (significant at $P<0.001$).

The same group of 269 patients were later studied in order to evaluate the eventual role of endoscopy in the reinfection rate. A total of 206 of the 269 *H pylori*-positive patients were cured of the infection and followed-up only with a ^{14}C-urea breath test, performed three months and one year after treatment. Results showed that 47 patients (22.8%) were reinfected. Of those 63 patients followed-up with a ^{14}C-urea breath test plus endoscopy, reinfection occurred in 27 patients (42.9%) (24,25).

TREATMENT RECOMMENDATIONS

The evolution of *H pylori* treatment is based on recommendations from groups of experts in different countries under the sponsorship of medical institutions.

In 1990, the Working Party Report from the World Congress of Gastroenterology, in Sydney, Australia, recommended treatment for only those in whom duodenal ulcer was a serious management problem, requiring either continuous medication or consideration for surgery, ie, complicated duodenal ulcers (27).

Four years later, the United States National Institutes of Health Consensus Conference enlarged the indications for treatment, including all patients with peptic ulcer disease with *H pylori* infection in any stage of the disease (28).

In 1995, in Belo Horizonte, Brazil, during the Pan-American Congress of Gastroenterology, the Brazilian Consensus of *H pylori* and Associated Diseases was issued. This report considered two situations where the micro-organism should be treated: first, in duodenal and gastric ulcers and erosive duodenitis (evidence was considered unequivocal in favour of treatment); and, second, in severe antral gastritis, family history of gastric cancer, low grade mucosa-associated lymphoid tissue cancer and hepatic encephalopathy (treatment was considered experimental) (29).

In September 1996, in Mäastricht, Holland, the European *Helicobacter pylori* Study Group organized a meeting of experts and representatives of the national societies of gastroenterology, as well as general practitioners from Europe, in order to establish guidelines on the current management of *H pylori* infection. The Mäastricht Consensus enlarged enormously the indications for treatment, from peptic ulcer disease to asymptomatic *H pylori* infection, causing a lot of controversy among experts worldwide (31).

In February 1997 the Digestive Health Initiative of the American Digestive Health Foundation brought together specialists in gastroenterology, epidemiology, primary care, managed care, pharmacy and nursing, along with the public, to provide opinions on the role of *H pylori* in upper gastrointestinal disease. A number of issues were addressed at the meeting, but treatment recommendations, which relied on regimens approved by the United States Food and Drug Administration, ie, triple or quadruple therapy of two weeks' duration, were in contrast to the current therapeutic regimens used outside the United States of triple therapy given in shorter, more convenient dosing schedules (31).

Finally, in August 1997, delegates representing the professional gastroenterology societies of 17 different countries in the Asia-Pacific region delivered the Asia Pacific Consensus Conference on the Management of *H pylori* Infection. The highlights of this consensus conference were presented at the Alimentary Disease Week, held in Hong Kong, in December 1997. Their recommendations for treatment, in preferential order, are clarithromycin with amoxicillin or metronidazole, plus either a conventional dose of a PPI or ranitidine bismuth citrate, the latter two each taken twice daily for seven days (32).

The ideal therapy for *H pylori* eradication should be simple, safe and free from side effects, with 100% efficacy and low cost, but this treatment has not been achieved. It is not possible to make definite recommendations for the optimal treatment schedule in South America. To our knowledge large multicentre controlled trials on the treatment of *H pylori* infection in South America have not yet been published in this region, so it is difficult to identify the best regimen.

This lack of trials is the reason why the Brazilian Consensus on *H pylori* made only broad recommendations on how to treat *H pylori* infection: seven to 14 days of treatment using a PPI or H_2 receptor antagonist along with two or three of the following antimicrobials: amoxicillin, clarithromycin, metronidazole, furazolidone, bismuth and tetracycline. Furazolidone, a synthetic nitrofuran derivative with a predominantly topical action and no reports of bacterial resistance, is used in many countries of Latin America to treat giardiasis and vaginal infections. It is a very inexpensive drug and should be studied in future therapeutic regimens in developing countries. Recent studies from Colombia show that in areas where metronidazole resistance is high, a four-week course of furazolidone 100 mg qid and bismuth subsalicylate two tablets qid may prove to be the least expensive therapy available.

For retreatment, the Brazilian Consensus issued the following recommendations: a PPI plus three antimicrobials (the same ones recommended for treatment) for seven to 14 days; the same combination of drugs as used in the first attempt at treatment are not to be used, particularly metronidazole or clarithromycin, unless antibiotic sensitivity data are available. Further, no more than three attempts at eradication are to be undertaken because with each new retreatment regimen the eradication rate decreases; if possible, test for antimicrobial susceptibility.

SUMMARY OF *H PYLORI* TREATMENT IN SOUTH AMERICA

- *H pylori* infection is very prevalent in South American countries; 70% to 90% of the adult population are infected.
- There is a rapid acquisition of *H pylori* infection in childhood as well as in adulthood.
- The acquisition of *H pylori* infection in adulthood is eight times more frequent in Brazil than that in the developed world.
- Different studies have shown that the reinfection rate, depending on various factors, such as high rates of prevalence and acquisition, is probably much higher in developing countries: 8.5% in Brazil versus 0.5 to 1.5% in the industrialized world.
- Due to the above factors, the therapeutic approach in South American countries should be directed predominantly at patients with peptic ulcer disease. Other situations should be analyzed individually.
- There is an urgent need for multicentre randomized controlled trials in South America to define their best therapeutic regimens.

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