World Gastroenterology Organisation Global Guidelines

Helicobacter pylori in developing countries

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1 Introduction

Helicobacter pylori (Hp) is found in half the population of the world. Its prevalence is highly variable in relation to geography, ethnicity, age, and socioeconomic factors—high in developing countries and lower in the developed world. In general, however, there has been a decreasing trend in the prevalence of Hp in many parts of the world in recent years.

Direct epidemiologic comparisons of peptic ulcer disease (PUD) between developing and developed countries are complex, as peptic ulcers may be asymptomatic and the availability and accessibility of the tests required for diagnosis vary widely.

In developing countries, Hp infection is a public-health issue. The high prevalence of the infection means that public-health interventions may be required. Therapeutic vaccination is probably the only strategy that would make a decisive difference in the prevalence and incidence of HP throughout the world. The short-term approach, however—provided that resources allow for this—would be a test-and-treat strategy for those who are at risk for peptic ulcer disease or gastric cancer, as well as for those with troublesome dyspepsia.

Note

By Prof. Barry Marshall, Nobel Laureate, Helicobacter Research Laboratory, University of Western Australia, Perth, Australia

Luckily, not all the management methods for *H. pylori* are expensive, and logical analysis of the disease characteristics in each country can lead to an optimal treatment plan. Initially, not all patients with *H. pylori* can be treated, because resources are limited. However, eradication of the ubiquitous "ulcer bug" is the first step in freeing patients with chronic dyspepsia and/or ulcer disease from an expensive lifetime of chronic medication use. Noninvasive "test-and-treat" strategies have to be balanced with clinical factors and an estimate of the possible cancer risk in each patient.

This paper strikes a practical and useful balance. As you develop expertise in your own area, I am sure that you can even improve on the strategies listed here.

Epidemiology—global aspects

Globally, different strains of *H. pylori* appear to be associated with differences in virulence, and the resulting interplay with host factors and environmental factors leads to subsequent differences in the expression of disease. Age, ethnicity, gender, geography and socioeconomic status are all factors that influence the incidence and prevalence of Hp infection.

The overall prevalence is high in developing countries and lower in developed countries and within areas of different countries. There may be similarly wide variations in the prevalence between more affluent urban populations and rural populations.

The principal reasons for these variations involve socioeconomic differences between populations. Transmission of Hp is largely by the oral–oral or fecal–oral routes. A lack of proper sanitation, of safe drinking water, and of basic hygiene, as

well as poor diets and overcrowding, all play a role in determining the overall prevalence of infection.

- The global prevalence of Hp infection is more than 50%.
- The prevalence may vary significantly within and between countries.
- In general, Hp seropositivity rates increase progressively with age, reflecting a cohort phenomenon.
- In developing countries, Hp infection is markedly more prevalent at younger ages than in developed countries.

Table **1** *Helicobacter pylori* infection globally

Country	Age groups	Prevalence
Africa		
Ethiopia	2–4	48%
Ethiopia	6	80%
Ethiopia	Adults	> 95%
Nigeria	5–9	82%
Nigeria	Adults	91%
	Adults	70–90%
Central America		
Guatemala	5–10	51%
Guatemala	Adults	65%
Mexico	5–9	43%
	Adults	70–90%
North America		
Canada	5–18	7.1%
Canada	50–80	23.1%
USA and Canada	Adults	30%
South America		
Bolivia	5	54%
Brazil	6–8	30%
Brazil	10–19	78%
Brazil	Adults	82%
Chile	3–9	36%
Chile	Adults	72%
	Adults	70–90%
Asia		
Bangladesh	0–2	50–60%
Bangladesh	0–4	58%
Bangladesh	8–9	82%
Bangladesh	Adults	> 90%
Hong Kong	6–19	13.1%
India	0–4	22%
India	10–19	87%
India	Adults	88%
India, south	30–79	80.0%
Japan, 3 areas	20–70+	55.4%
Japan, western	Adults	70.1%
Siberia	5	30%
Siberia	15–20	63%
Siberia	Adults	85%
South Korea	16	56.0%
South Korea	≥ 16	40.6%
Sri Lanka	6–19	67%
Sri Lanka	Adults	72%
Taiwan	9–12	11.0%
Taiwan	13–15	12.3%
Taiwan	≥ 25	45.1%
	Adults	50–80%
Australasia		
Australia	1–59	15.4%
	Adults	20%
Europe		
(Eastern)	Adults	70%
(Western)	Adults	30–50%
Albania	16–64	70.7%
Bulgaria	1–17	61.7%
Czech Republic	5–100	42.1%
Estonia	25–50	69%
Germany	50–74	48.8%
Iceland	25–50	36%
Netherlands	2–4	1.2%

Country	Age groups	Prevalence
Serbia	7–18	36.4%
Sweden	25–50	11%
Switzerland	18–85	26.6%
Switzerland	18–85	11.9%
Middle East		
Egypt	3	50%
Egypt	Adults	90%
Libya	1–9	50%
Libya	10–19	84%
Libya	Adults	94%
Saudi Arabia	5–9	40%
Saudi Arabia	Adults	80%
Turkey	6–17	64%
Turkey	Adults	80%

2 Diagnosis of *Helicobacter pylori* infection

Diagnostic tests for Hp infection include endoscopic and nonendoscopic methods. The techniques used may be direct (culture, microscopic demonstration of the organism) or indirect (using urease, stool antigen, or an antibody response as a marker of disease).

The choice of test depends to a large extent on availability and cost, and includes a distinction between tests used to establish a diagnosis of the infection and those used to confirm its eradication. Other important factors are: clinical situation, population prevalence of infection, pretest probability of infection, differences in test performance, and factors that may influence the test results, such as the use of antisecretory treatment and antibiotics.

Table **2** Tests for *Helicobacter pylori* infection

Tests with endoscopy	Rapid urease test (RUT)
	Histology
	Culture *
	Fluorescence in situ hybridization (FISH)
	Molecular approach: polymerase chain reaction (PCR)
Tests without endoscopy	Stool antigen test (SAT) †
	Finger-stick serology test
	Whole blood serology ‡
	^{13}C urea breath test
	^{14}C urea breath test

* Culture may not be practical in all countries; treatment choices are often based on what is known about resistance patterns.

† Despite being a good test, stool antigen testing may be underused due to its high costs in Pakistan and some other countries/regions.

‡ In high-prevalence areas, the definition of the serological cut-off value distinguishing between active infection and background infection may be problematic.

Table **3** Comparison of diagnostic tests for *Helicobacter pylori* infection

Test	Sensitivity	Specificity	Positive predictive value	Comments
Rapid urease test	> 98%	99%	99%	• Rapid and cheap • Post-treatment sensitivity reduced
Histology	> 95%	> 95%		• Detection improved by use of special stains—e.g., the Warthin–Starry silver stain, or the cheaper hematoxylin–eosin (H&E) stain or Giemsa staining protocol
Culture				• Highly specific; poor sensitivity if adequate transport media are not available • Experience/expertise required • Expensive; often not available
PCR				• Sensitive and specific • Not standardized • Considered experimental
ELISA serology	85–92%	79–83%	64%	• Less accurate and does not identify active infection • Reliable predictor of infection in (high-prevalence) developing countries • Not recommended after therapy • Cheap and readily available
$^{13}C/^{14}C$ urea breath test	95%	96%	88%	• Recommended for diagnosis of Hp before treatment • Preferred test for confirming eradication • Not to be performed within 2 weeks of PPI therapy or within 4 weeks of antibiotic therapy • Variable availability
Stool antigen	95%	94%	84%	• Not often used in spite of its high sensitivity and specificity before and after treatment • Should have a more prominent place, as it is inexpensive and noninvasive
Finger-stick serology test				• Very poor and cannot be equated with ELISA serology

ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; PPI, proton-pump inhibitor.

Serological testing is less accurate than breath testing and stool antigen testing, particularly in areas of low Hp prevalence. Its lower positive predictive value has led to concerns in Western countries that antibiotics are possibly being administered unnecessarily after serology testing. However, this traditional view is not universally applicable in countries with a high Hp prevalence. In a low-prevalence area, serology works less well, so that a negative test has more value than a positive test. In a high-prevalence area, a positive serology test can reasonably be accepted as positive.

A rigorous process of identification and exclusion of Hp infection is required.

- In developed countries:
  - — The use of a test-and-treat strategy for younger patients presenting with dyspepsia is declining.
  - — The immediate use of an antisecretory drug (proton-pump inhibitor, PPI) is usually preferred as a first-line treatment when the Hp prevalence is < 20%.
  - — For those aged 50 and older, endoscopy to exclude an upper gastrointestinal malignancy and testing for Hp infection if no malignancy is found remains a logical approach.
  - — Testing for Hp infection should be carried out in younger patients in countries with a high risk of gastric cancer.
- In developing countries in which the rates of ulcer or gastric cancer are high, an empirical test-and-treat approach or initial endoscopy is a more appropriate initial approach than starting treatment with a PPI.

Good practice point

It should be ensured that patients undergoing a breath test, stool antigen test, or endoscopy are free from medication with PPIs or histamine$_2$-receptor antagonists (H_2RAs) for a minimum of 2 weeks and antibiotics for 4 weeks prior to testing.

3 Management of *Helicobacter pylori* infection

The aim of Hp eradication is to cure peptic ulcer disease and reduce the lifetime risk of gastric cancer. While the burden of gastric cancer is increasing—mostly in developing countries, due to increasing longevity—eradication of Hp infection has the potential to reduce the risk of gastric cancer.

The stage in the natural history of the infection at which eradication of Hp prevents gastric cancer is uncertain. There may be a point of no return, before which eradication is successful in preventing later development of gastric cancer. The appearance of mucosal precursor lesions may prove to be this point of no return. Once these precursor lesions have appeared, Hp eradication may no longer be effective in preventing gastric cancer. Since most people are infected soon after birth, these precursor lesions may be occurring quite early in life, and better information in different parts of the world is needed in order to time interventions optimally.

Table **4** Indications for treatment of infection in Hp-positive patients

1	Past or present duodenal and/or gastric ulcer, with or without complications
2	Following resection of gastric cancer
3	Gastric mucosa-associated lymphoid tissue (MALT) lymphoma
4	Atrophic gastritis
5	Dyspepsia
6	Patients with first-degree relatives with gastric cancer
6	Patient's wishes

Hp eradication treatment is supported by numerous consensus groups around the world and is generally safe and well tolerated. The standard treatment is based on multidrug regimens.

- A vaccine is not currently available, and since the exact source of Hp infection is not yet known, it is difficult to make recommendations for ways of avoiding the infection.
- In general, however, it is always wise to observe good public-health measures, to wash hands thoroughly, to eat food that has been properly prepared, and to drink water from a safe, clean source.
- Pediatric patients who require extensive diagnostic work-up for abdominal symptoms should be referred for evaluation by a specialist.
- Hp eradication does not cause gastroesophageal reflux disease (GERD).

Choosing an eradication regimen

The following factors need to be taken into account when choosing a particular treatment approach; they may vary in different continents, countries, and regions. The management of Hp infection in high-prevalence areas should be similar to that in low-prevalence areas.

Table **5** Factors involved in choosing treatment regimens

• Prevalence of Hp infection
• Prevalence of gastric cancer
• Resistance to antibiotics
• Cost level and available budget
• Availability of bismuth
• Availability of endoscopy, Hp tests
• Ethnicity
• Drug allergies and tolerance
• Previous treatments, outcome
• Effectiveness of local treatment
• Ease of administration
• Adverse effects
• Recommended dosages, treatment duration

- **Compliance**

Commitment on the part of the patient is required for three or four different drugs to be taken in combination two to four times a day for up to 14 days, with a likelihood of adverse effects such as malaise, nausea, and diarrhea.

Good practice point

It should always be emphasized to the patient that successful eradication depends on full compliance with the treatment. Time should be taken to counsel the patient, explaining the procedures involved in taking complicated drug therapies such as quadruple therapy and describing the side effects—this will improve compliance and outcome.

First-line treatment regimens

- *Triple-therapy treatment regimens.* PPI + two antibiotics: amoxicillin and clarithromycin, or metronidazole and clarithromycin.
  - — Used and accepted worldwide.
  - — Standard PPI-based therapy fails in up to 30% of patients. Eradication rates have fallen to 70–85% over the last few years, in part due to increasing clarithromycin resistance.
  - — A longer treatment duration may increase eradication rates, but remains controversial; studies suggest an increase to 14 days instead of 7 days.
  - — Cost considerations and compliance issues may still favor 7-day therapy.
  - — Some groups suggest treatment for 10 days.
- *Quadruple therapy.* PPI + bismuth + two antibiotics: amoxicillin + clarithromycin, or metronidazole + tetracycline.
  - — May be cheaper than triple therapy.
  - — More difficult to take than triple therapy.
  - — Equivalent or superior eradication rates.

Antibiotic resistance

Antibiotic resistance is a key factor in the failure of eradication therapy and recurrence of Hp infection. Antibiotic resistance rates are increasing throughout the world. They vary geographically and are higher in developing countries.

Table **6** Antibiotic resistance of *Helicobacter pylori*

Country (year)	No. tested	Amoxi-cillin	Metro-nidazole	Clarithro-mycin	Quino-lones	Furazoli-done	Tetra-cycline
Africa							
Senegal (2009)	40	0%	90%		0%		
Nigeria (1999)	50	0%	55%	13%	13%		
Asia							
India (2003)	259	33%	78%	45%	3%		4%
India(2005)	67	0%	85%	0%		0%	7%
South-East Asia (2006)	72	19%	100%	28%	7%		
Taiwan (2009)	227	0%	27%	11%	9%		

Country (year)	No. tested	Amoxi-cillin	Metro-nidazole	Clarithro-mycin	Quino-lones	Furazoli-done	Tetra-cycline
China (2007)	340	3%	76%	28%			
Thailand (2009)	221	7%	39%	3%			3%
Middle East							
Iran (2007)	101	21%	73%	9%	5%	9%	5%
Egypt (2004)	48	2%	100%	4%	2%		
Saudi Arabia (2002)	223	1%	80%	4%			0.5%
Kuwait (2006)	96	0%	70%	0%			0%
South America							
Argentina (2006)	242			24%			
Brazil (2002)	202		53%	9%			
Colombia (2009)	106	2%	82%	4%			0%

Good practice point

If treatment fails, antibiotic sensitivity testing may be considered, if available, to avoid choosing Hp-resistant antibiotics.

Rescue therapy

There is considerable variation between consensus groups with regard to the optimal "rescue" therapies.

Table **7** Rescue therapies

Rescue options after initial treatment fails	Comments
• Repeat treatment with a different combination of medications	The choice should take account of the local antibiotic resistance of Hp
• PPI b.i.d. + tetracycline 500 mg t.i.d. + bismuth q.i.d. + metronidazole 500 mg t.i.d. × 10 days	Cheap, high pill burden, many side effects
• PPI + amoxicillin 1 g b.i.d. + levofloxacin 500 mg b.i.d. × 10 days	Eradication rate 87%

B.i.d., bis in die (twice a day); q.i.d., quater in die (four times a day); PPI, proton-pump inhibitor; t.i.d., ter in die (three times a day).

4 Cascade information

Cascade for diagnosing Hp—options for developing countries

Table **8** Resource levels and diagnostic options

Resource level *	Diagnostic options
1	Endoscopy with RUT, histology (culture is not practical in most countries)
2	^{13}C UBT
3	^{14}C UBT
4	Stool antigen testing
5	Whole-blood serology (does not distinguish between past and present infection)
6	Finger-stick serology test (cheaper option in high-prevalence areas; new-generation tests are more accurate) †
7	Do no further testing and assume the patient is infected in areas with a very high prevalence and low resources

RUT, rapid urease test; UBT, urea breath test.

* Resource levels 1–7 represent a scale ranging from all resources (level 1) to no resources (level 7).

† Caution: the literature suggests that the accuracy of finger-stick serology is too low for it to be recommended and that new tests are better.

Note 1. The gold standard—endoscopy with rapid urease testing—is not readily available in all parts of the world. Cost-effectiveness considerations play a major role in all resource settings. In low-resource communities, considerations of precision and sensitivity may sometimes be traded against costs and the availability of resources.

Note 2. In some regions where Hp prevalence is very high, diagnostic tests for the infection are not cost-effective. The decision to treat must then assume the presence of Hp infection.

Good practice point

Treat everyone who tests positive—do not test if not intending to treat.

Ten cascade notes for managing Hp

Note 1. In high-prevalence areas with limited resources, a trial of Hp eradication may be used in an appropriate clinical setting. Due to the high cost of medicines, alternatives to PPI triple-therapy combinations, using generic drugs such as furazolidone, may have a place. Generic PPIs are becoming increasingly available around the world.

Note 2. Antibiotic resistance is high in developing countries and is increasing in developed countries. The antibiotics used must be carefully considered, particularly when there is known antibiotic resistance.

Note 3. There is geographic variability in the efficacy of proton-pump inhibitors (PPIs) in the treatment of peptic ulcer disease, due to differences in body weight,

CYP2C19 genetic polymorphisms, and drug response. PPIs relieve pain and heal peptic ulcers more rapidly than H_2-receptor antagonists. While H_2-receptor antagonists do inhibit acid secretion, proton-pump inhibitors are preferable due to their superior efficacy and lack of tachyphylaxis. However, it is still necessary to use them in a twice-daily regimen.

Note 4. Bismuth is a key consideration, as it is not available in all countries. The Maastricht III Consensus Report concluded that the eradication rates and confidence intervals for bismuth-based quadruple therapy and standard triple therapy are broadly similar, and bismuth-based therapy is considerably cheaper than several other choices.

- It has been assumed that bismuth subsalicylate and colloidal bismuth subcitrate are equivalent.
- Poorly absorbed, < 1%.
- Mechanism of action unknown.
- Affordable cost.
- In the 1970s, bismuth salts were associated with neurotoxicity (with high doses used for long periods).
- Bismuth therapies have therefore been banned in some countries, such as France and Japan.

Note 5. Furazolidone has a place in the treatment of Hp in developing countries with a high Hp prevalence and limited resources.

- It has the lowest cost among anti-Hp drugs.
- It is effective against Hp strains with low resistance rates.
- Its mechanism of action is unknown.
- It has been recommended as an alternative option by the Latin American (2000), second Brazilian (2005), WGO (2006), and third Chinese (2008) consensus conferences.
- It has possible genotoxic and carcinogenetic effects in animals.
- It is no longer available in the USA or European Union.

Note 6. Tetracycline is also an effective drug against Hp and can be recommended in eradication regimens. Tetracycline is not only effective against Hp, but also has low resistance and is cheap.

Note 7. Generic drugs are used in many countries, and a lack of adequate quality control may explain treatment failures.

Note 8. In Brazil, patients with a history of allergy to penicillin receive PPI + clarithromycin 500 mg and furazolidone 200 mg twice daily for 7 days.

Note 9. Reports from Asia suggest that 1 week of triple PPI therapy with clarithromycin and amoxicillin is still a useful form of treatment. Metronidazole resistance in Asia is close to 80% (in vitro).

Note 10. Prescribers should be aware of drug resistance patterns in their own area (particularly with regard to clarithromycin) before deciding on a particular regimen.

Gold standard treatment options

Further information on gold standard treatment options is available in the documents listed in Table **9**.

Table **9** Gold standard treatment options

Publisher	Web address
American Gastroenterological Association (2005)	http://www.gastrojournal.org/article/S0016-5085(05)01818-4/fulltext
Second Asia–Pacific Consensus Conference (2009)	http://www.apage.org
Maastricht III (2009)	http://gut.bmj.com/content/56/6/772
American College of Gastroenterology (2007)	http://www.acg.gi.org/physicians/guidelines/ManagementofHpylori.pdf
Third Chinese National Consensus Report (2008)	http://www3.interscience.wiley.com/journal/120835370/abstract
National Institute for Health and Clinical Excellence (NICE), UK (2004)	http://guidance.nice.org.uk/CG17
Scottish Intercollegiate Guidelines Network (SIGN), UK (2003)	http://www.sign.ac.uk/pdf/2009dyspepsiareport.pdf

Treatment options in developing countries

Table **10** Treatment options in developing countries

	Notes
A First-line therapies	
PPI + amoxicillin + clarithromycin, all twice daily for 7 days	• Used and accepted throughout the world • Eradication rates have fallen to 70–85% over the last few years, in part due to increasing resistance to clarithromycin • Cost considerations and compliance issues may favor 7-day therapy • Some groups suggest treatment for 10 or 14 days • Other inexpensive macrolides, such as azithromycin, are available over the counter in developing countries, and macrolide cross-resistance affects eradication rates
In case of a clarithromycin resistance rate of more than 20%: Quadruple therapy: PPI b.i.d. + bismuth + tetracycline + metronidazole all q.i.d. for 7–10 days	• May be cheaper than triple therapy • More difficult to take than triple therapy. A single triple capsule has been shown to facilitate its use • Equivalent eradication rates in comparison with standard triple therapy • In vitro metronidazole resistance may be overcome by prolonging therapy or using high doses of metronidazole

If there is no known clarithromycin resistance or clarithromycin resistance is not likely:

- PPI + amoxicillin + clarithromycin for 7 days
- Quadruple therapy: PPI + bismuth + tetracycline + metronidazole for 7–10 days
- If bismuth not available: concomitant therapy: PPI + clarithromycin + metronidazole + amoxicillin for 14 days
- Furazolidone-containing regimens: PPI + furazolidone + antibiotic is slightly less effective than the standard triple regimens
- Furazolidone can replace amoxicillin in standard triple therapy
- Sequential regimen: 10-day therapy with PPI + amoxicillin for 5 days followed by PPI + clarithromycin and a nitroimidazole (tinidazole) for 5 days

B Second-line therapies, after failure of clarithromycin-containing regimens

- PPI + bismuth + tetracycline + metronidazole for 10–14 days
- PPI + amoxicillin + levofloxacin for 10 days
- PPI + furazolidone + tetracycline + bismuth for 10 days
- PPI + furazolidone + levofloxacin for 10 days
- PPI + amoxicillin + clarithromycin for 7 days
- PPI + amoxicillin + levofloxacin for 10 days
- PPI + furazolidone + levofloxacin for 10 days

C Third-line therapies, after failure of clarithromycin-containing regimens and quadruple therapy

- PPI + amoxicillin + levofloxacin for 10 days
- PPI + amoxicillin + rifabutin for 10 days
- PPI + furazolidone + levofloxacin for 7–10 days

B.i.d., bis in die (twice a day); q.i.d., quater in die (four times a day); PPI, proton-pump inhibitor.

Lower-cost options for limited-resource settings

Table **11** Cost-reducing alternative *Helicobacter pylori* eradication regimens

Alternative regimens	Recommended by
• 7- or 10-day duration instead of 14-day for standard triple therapy	Maastricht III
• Quadruple instead of triple therapy (if bismuth is available)	Maastricht III
• PPI + furazolidone + tetracycline (low-cost option)	Brazil and Latin America Consensus
• Rabeprazole + levofloxacin + furazolidone	Coelho et al., Aliment Pharmacol Ther 2005;21:783–7
• Furazolidone + amoxicillin + omeprazole + bismuth citrate	Darian (Iran)
• Furazolidone + amoxicillin + omeprazole	Massart (Iran)

Alternative regimens	Recommended by
• Furazolidone + lansoprazole + clarithromycin	Coelho et al., Aliment Pharmacol Ther 2003;17:131–6
• PPI + rifabutin + amoxicillin	Xia et al., Expert Opin Pharmacother 2002;3:1301–11 Second Asia–Pacific Consensus Guidelines for *Helicobacter pylori* Infection