WGO Practice Guideline:

Helicobacter pylori in Developing Countries

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Introduction

Barry Marshall

I am delighted to recommend the enclosed guide to *Helicobacter pylori* in developing countries. The guide has been compiled by several world experts in the field with many years of practical clinical experience behind them.

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.

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1 Summary and Abbreviations

Helicobacter is a genus of Gram-negative, microaerophilic bacteria of the family Spirillaceae, consisting of motile, spiral organisms with multiple sheathed flagella. *Helicobacter pylori* (Hp) is common and infects half the world's population. Its prevalence is high in developing countries and lower in the developed world.

In the developing countries, Hp is a public-health issue. The high prevalence of the infection means that public-health interventions need to be developed. Vaccination with a treatment vaccine is probably the only strategy that would make a decisive difference in prevalence and incidence worldwide. The short-term approach, however—and provided that resources allow this—would be a test-and-treat strategy for those at risk for peptic ulcer disease or gastric cancer, as well as for those with serious symptoms of dyspepsia and indigestion.

Hp eradication treatment uses either triple therapy (a PPI + two antibiotics) or quadruple therapy (a PPI + two antibiotics + bismuth) if bismuth is available. Quadruple therapy is cheaper than triple therapy and equally good, and both give very high eradication rates.

The duration of therapy is still a matter of controversy, but there are no large differences in the outcome between 14, 10 and 7 days of therapy, whilst the cost differences involved may be substantial.

Antibiotic resistance is high in the developing countries. In addition, there may be a risk in developing countries that high-quality generic drugs may be forced out of the market by cheap fake medicines.

Abbreviations

CBS	Colloidal bismuth subcitrate
FISH	Fluorescence in-situ hybridization
GERD	Gastroesophageal reflux disease (American spelling; the British spelling is gastro-oesophageal reflux disease, GORD)
GPP	Good practice point
H_2RA	Histamine$_2$-receptor antagonist
IBS	Irritable bowel syndrome
MALT	Mucosa-associated lymphoid tissue (lymphoma)
NSAID	Nonsteroidal anti-inflammatory drug
PCR	Polymerase chain reaction
PPI	Proton-pump inhibitor
NUD	Nonulcer dyspepsia
PMID	PubMed identifier
PUD	Peptic ulcer disease
RBC	Ranitidine bismuth citrate
RUT	Rapid urease test
SAT	Stool antigen test
UBT	Urea breath test

2 Epidemiology

Key Points

- Hp global prevalence is more than 50%.
- Hp prevalence in the developed world is declining.

- Hp prevalence in developing countries is high.
- Hp prevalence may vary significantly within and between countries.

2.1 Global Aspects

Globally, different Hp strains are associated with differences in virulence, interplaying with host factors and environmental factors, with subsequent differences in the expression of disease.

Age, ethnicity, gender, geography and socio-economic 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. Within countries, there may be a similarly wide variation in the prevalence between more affluent urban populations and rural populations.

The principal reasons for variation 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.

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

Country	%
Mexico, Central/ South America	70–90
Africa	70–90
Asia	50–80

Eastern Europe	70
Western Europe	30–50
United States and Canada	30
Australia	20

Table **2** Prevalence of *Helicobacter pylori* in developing countries

Region and country	Adults (> 21 y) (%)	Children
Africa		
Ethiopia	> 95	48% (2–4 y) to 80% (6 y)
Gambia	> 95	95% (5 y)
Nigeria	91	82% (5–9 y)
Asia		
Bangladesh	> 90	58% (0–4 y) to 82% (8–9 y)
China	55	41% (3–12 y)
India	88	22% (0–4 y) to 87% (10–19 y)
Siberia	85	30% (5 y) to 63% (15–20 y)
Sri Lanka	72	67% (6–19 y)
Middle East		
Egypt	90	50% (3 y)
Jordan	82	

Libya	94	50% (1–9 y) to 84% (10–19 y)
Saudi	80	40% (5–9 y)
Turkey	80	64% (6–17 y)
Central America		
Guatemala	65	51% (5–10 y)
Mexico	43% (5–9 y)	
South America		
Bolivia	54% (5 y)	
Brazil	82	30% (6–8 y) to 78% (10–19 y)
Chile	72	36% (3–9 y)
Peru	52% (3 y)	

3 Pathogenesis, Natural History and Associated Conditions

Key Points

- Everyone with Hp will develop gastritis—either antrally predominant gastritis or pangastritis.
- Hp infection is mostly asymptomatic.
- Some 15–20% of infected people will develop PUD.
- Less than 1% of infected people will develop gastric cancer, but there are regional variations.

3.1 Introduction

It is now accepted that Hp is responsible for the pathological processes leading to chronic active gastritis and severe gastroduodenal disease, including peptic ulcer, gastric cancer and gastric MALT lymphoma. All those infected will develop gastritis. Many will remain without symptoms.

Spontaneous remission is uncommon. Only a small proportion will develop clinically significant diseases such as peptic ulcer or gastric cancer.

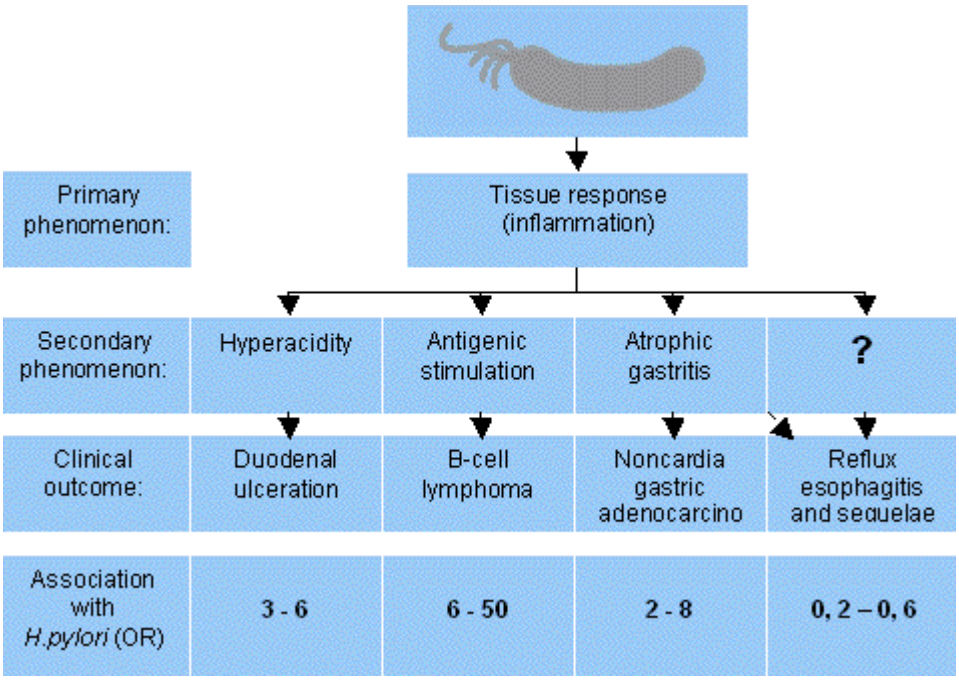

Fig. **1** Pathogenesis and response, based on the Asia–Pacific Consensus Conference (Lam and Talley, 1998).

3.2 Natural History

It is not clear whether the natural history of Hp evolves differently in different parts of the world. Host genetic factors, the Hp strain involved and environmental factors all play a role, and all those infected have chronic active gastritis. Certain strains appear to have survived more effectively during the epidemiological evolution of the disease—for example, cagA-positive strains may survive better than others.

Most individuals infected with Hp never suffer any symptoms related to the infection.

Spontaneous clearance of the infection is unusual. The proportion of people developing serious diseases such as PUD is 15–20%, and fewer than 1% will develop gastric cancer.

Infected persons have a 2–6-fold increased risk of developing gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma in comparison with their uninfected counterparts. The role of Hp in nonulcer dyspepsia remains unclear.

3.3 Helicobacter pylori *Transmission*

It is not known exactly how Hp is transmitted, or why some patients become symptomatic while others do not. The infection is most likely spread at a very young age through the fecal–oral or oral–oral routes. In the developing world especially, possible environmental reservoirs also include contaminated water sources. Iatrogenic spread through contaminated endoscopes has been documented, but can be prevented by proper cleaning of equipment.

In children, the prevalence of Hp infection varies from 10% to 80% in different populations worldwide. By the age of 10, more than 50% of the world's children are infected. Thus, identifying transmission mechanisms in the child is of key importance.

Known risk factors

- Low socio-economic status
- Crowded living conditions
- Several children sleeping in one bed
- Large number of siblings
- Unclean water
- Ethnicity
- Infection present in family members

3.4 Risk of Malignancies and Nonmalignant Diseases

There are substantial differences in the risk of gastric cancer between countries. In China and Japan, for example, the risk of gastric cancer is much higher than that in the United Kingdom or United States. In Africa, on the other hand, life expectancy is low and people may not live long enough for gastric cancer to develop.

The incidence of NSAID-related disease is higher in Western countries, but the incidence of Hp-related ulcer disease is very low.

More research is needed to help us understand the risk factors—for example, of the three ethnic groups making up the population in Malaysia, the Chinese have a much

higher risk of developing gastric cancer than the Indian and Malay populations. The reasons for this are not known.

The African enigma—the very low incidence of gastric cancer in the continent—may have more to do with the average life expectancy of 40 years in many parts of sub-Saharan Africa than with a possible protective effect provided by Hp infection. Recent research from Africa suggests that the African enigma is not just a result of bacterial virulence factors, but instead that host-specific factors such as diet and ethnicity may play a role.

4 Diagnosis of *Helicobacter pylori*

Key Points

- The urea breath test (UBT) is recommended for the diagnosis of Hp before treatment.
- Serology is less accurate and does not identify active infection. However, in developing countries where prevalence is high, serology is a reliable predictor of infection.
- UBT is the preferred test to confirm eradication.
- UBT should not be performed within 2 weeks of PPI therapy or within 4 weeks of antibiotic therapy.
- Stool antigen tests are not often used, in spite of their high sensitivity and specificity. These should have a more prominent place, as they are cheap and noninvasive.

- Finger-stick tests are rarely used; they are very poor and cannot be equated with ELISA serology.
- Serology identifies only a “footprint” and not an active infection.

4.1 Introduction

What are the principal diagnostic tools for identifying Hp? How cost-effective are they in a low-resource setting? What would be an acceptable cascade of options to achieve broadly similar diagnostic ends?

Diagnostic testing for *Helicobacter pylori* is usually divided into endoscopy-based tests and tests not requiring endoscopy. The techniques used may be *direct* (culture, microscopic demonstration of the organism) or *indirect* (using urease or an antibody response as a marker of disease). The choice of test depends on issues such as cost, availability, clinical situation, population prevalence of infection, pretest probability of infection, and factors such as the use of proton-pump inhibitors and antibiotics, which may influence the test results.

Serological testing (sensitivity 92%, specificity 83%) is less accurate than breath testing (sensitivity 95%, specificity 96%) and stool antigen testing (sensitivity 95%, specificity 94%). The lower positive predictive value with serological testing (64% vs. 88% or 84%, respectively) has led to concerns that antibiotics may be administered unnecessarily after serology testing.

However, this is the traditional view in Western countries and it is not entirely 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 may be acceptable.

Good practice point (GPP): Ensure that patients undergoing a breath test, stool antigen test, or endoscopy are free from medication with either a PPI or H_2RA for a minimum of 2 weeks beforehand.

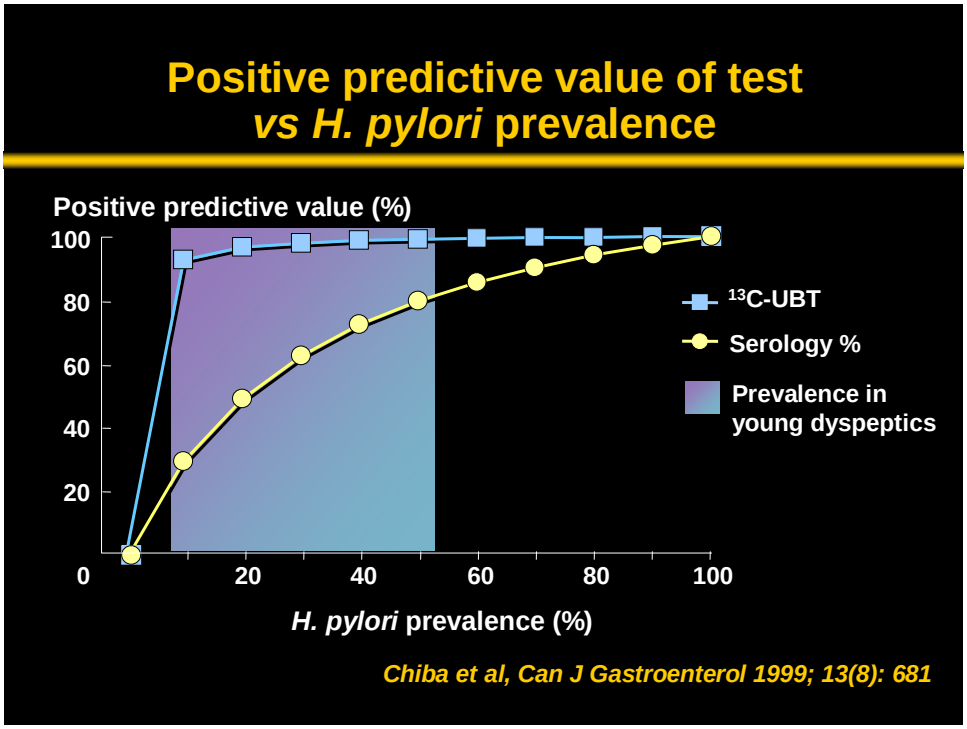

Fig. **2** The positive predictive value of testing in relation to the prevalence of *H. pylori.*

4.2 Symptoms, Signs and Flowcharts

GPP: Dyspeptic patients should be considered for early endoscopy on the basis of the incidence of gastric cancer in a particular country, the presence of alarm features such as weight loss, bleeding, and anemia, and the age of presentation of the patient, with

the cut-off point depending on the age-specific incidence of gastric cancer in that country or region.

Key Dyspepsia Symptoms

- Pain in the epigastrium
- Bloating
- Early satiety
- Bleeding
- Nausea
- Vomiting
- Appetite loss

Common ulcer symptoms include a burning pain in the epigastrium when the stomach is empty, between meals and in the early morning hours, but symptoms can also occur at other times. It may last from minutes to hours and may be relieved by eating or by taking antacids. Less common ulcer symptoms include nausea, vomiting and loss of appetite. Bleeding can also occur; prolonged subclinical bleeding may cause anemia, leading to weakness and fatigue, although hematemesis and/or melena may also occur.

One of the problems with diagnosing Hp is that there are several conditions that can be responsible for generating such symptoms. A rigorous process of identification and exclusion 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 anti-secretory drug (a PPI) is usually preferred. For those aged 50 and older, endoscopy to look for an upper gastrointestinal malignancy and testing for Hp

infection if a malignancy is not found is still a logical approach. Testing should be carried out in younger patients in countries with a high risk of gastric cancer.

In developing countries where ulcer rates or cancer rates are high, an empirical test-and-treat approach or endoscopy would be more appropriate than starting treatment with a PPI.

Dyspepsia Flowcharts

Diagnostic flowchart considerations should take account of local incidence and prevalence as well as local resources, values and preferences. What is acceptable and feasible in one part of the world is not necessarily so in another.

The flowcharts below—based on originals from the Asian–Pacific Guideline on Hp infection—are especially relevant, as they differentiate for areas with a low incidence of gastric cancer, a high incidence of gastric cancer, a low prevalence of Hp infection and a high prevalence of Hp infection but with limited access to endoscopy.

Areas with a high incidence of gastric cancer

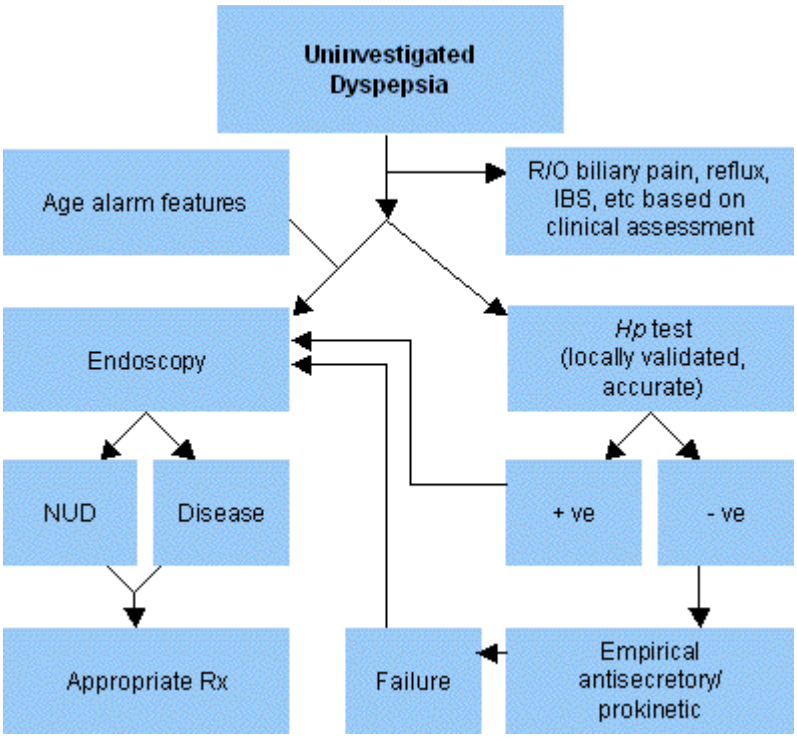

Fig. **3** Dyspepsia flowchart for use in an area with a high incidence of gastric cancer.

Hp test, *Helicobacter pylori* test; IBS, irritable bowel syndrome; NUD, nonulcer dyspepsia; R/O, rule out; Rx, treatment; failure, symptoms persist; +ve, positive; –ve, negative.

Areas with a low incidence of gastric cancer

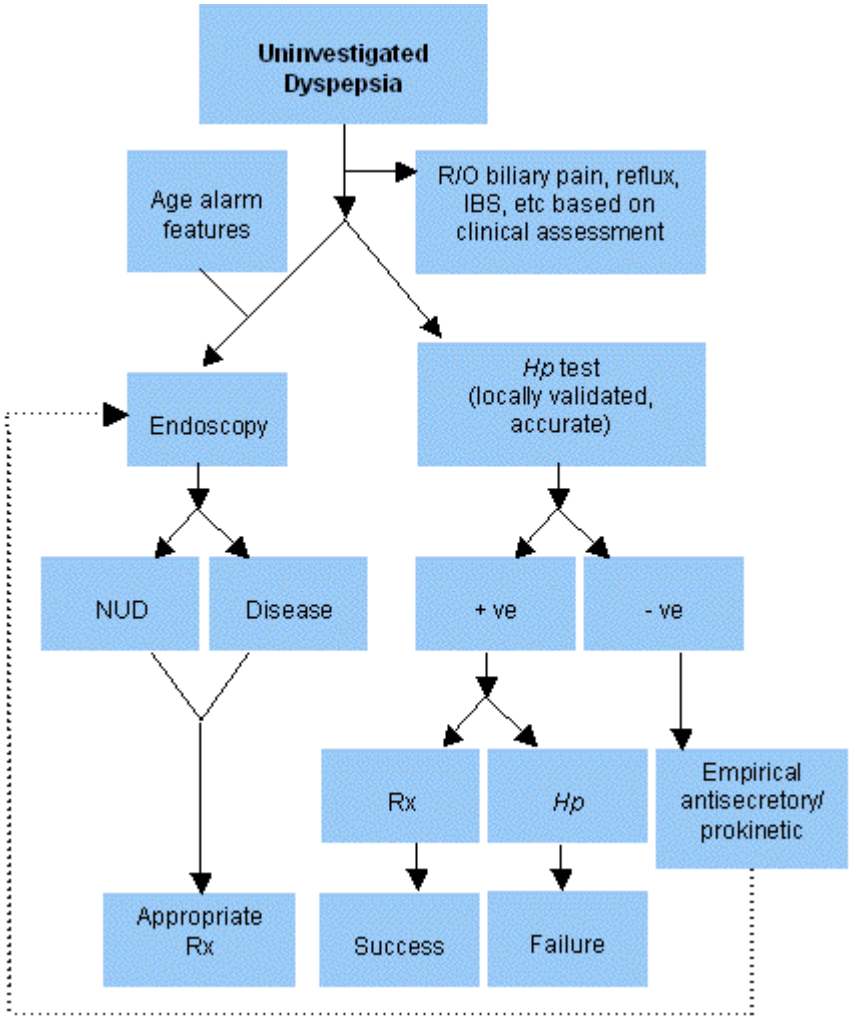

Fig. **4** Dyspepsia flowchart for use in an area with a low incidence of gastric cancer at endoscopy.

Hp test, *Helicobacter pylori* test; IBS, irritable bowel syndrome; NUD, nonulcer dyspepsia; R/O, rule out; Rx, treatment; failure, symptoms persist; success, symptoms resolve; +ve, positive; –ve, negative.

Regions with a high prevalence of Hp infection but limited access to endoscopy

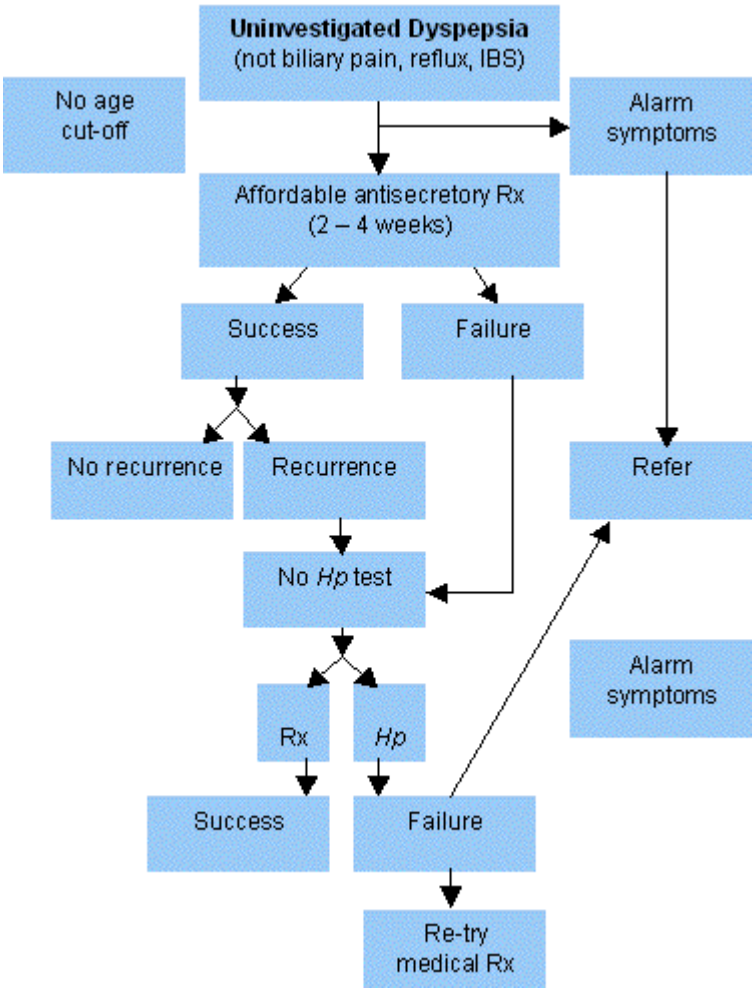

Fig. **5** Dyspepsia flowchart for use in regions with a high prevalence of *Helicobacter pylori* infection but limited access to endoscopy. In these areas, there is much more to be gained from the point of view of cost-effectiveness with an Hp test-and-treat strategy. In Western countries, cost models have shown that the threshold for testing for Hp initially is 20%. While costs are different in other countries, it may well be reasonable to start with acid suppression here.

Hp test, *Helicobacter pylori* test; Rx, treatment; failure, symptoms persist; success, symptoms resolve.

Regions with a low prevalence of Hp infection and easy access to endoscopy

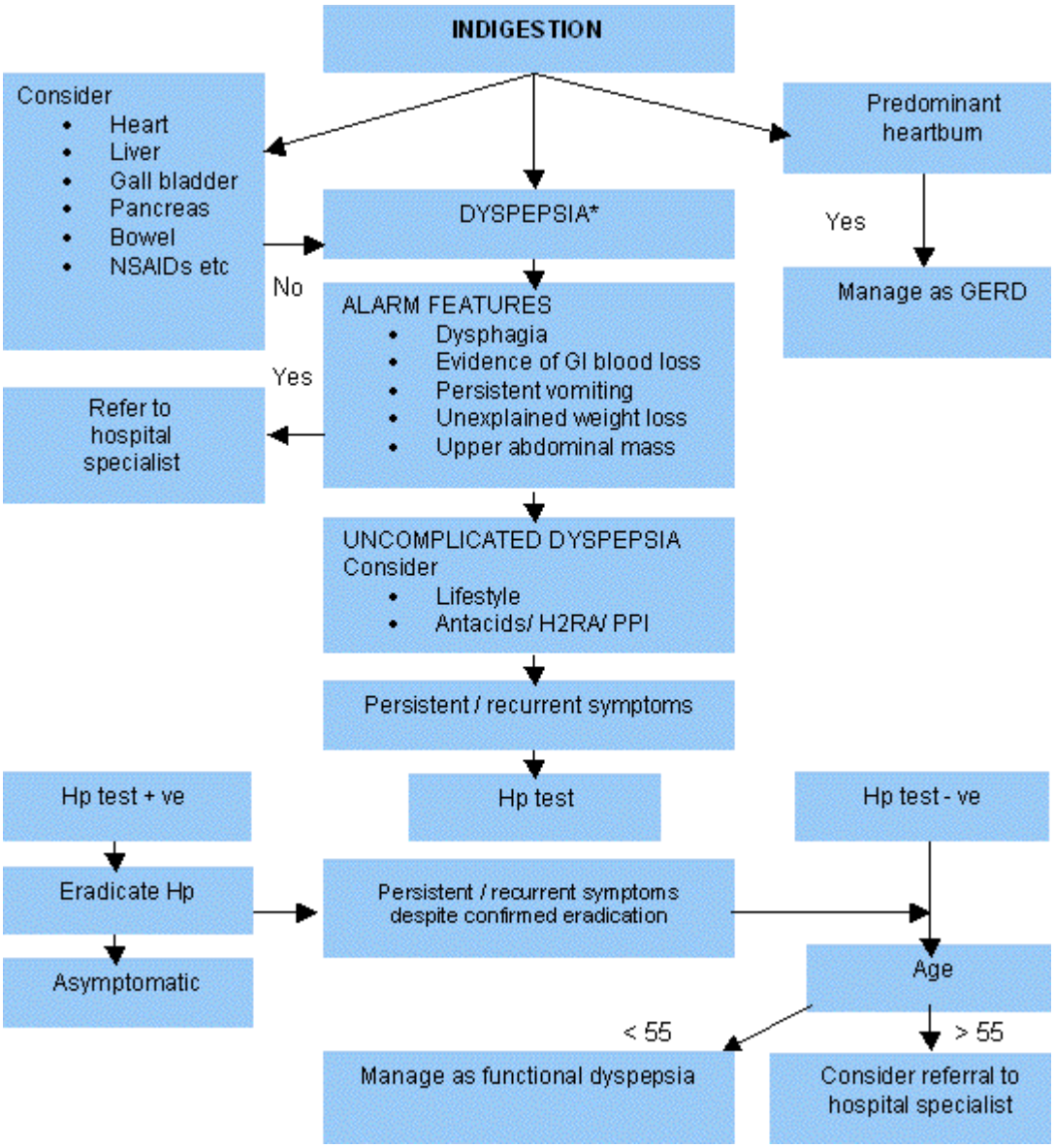

Fig. **6** Dyspepsia flowchart for use in regions of the Western world with a mostly low prevalence of *Helicobacter pylori* infection and easy access to endoscopy.

* Rome II definition. GERD, gastroesophageal reflux disease; H_2RA, histamine$_2$-receptor antagonist; Hp test, *Helicobacter pylori* test; NSAIDs,

nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitor; +-ve, positive; –ve, negative.

4.3 Diagnostic tests for Helicobacter pylori

Key points

- Endoscopy and RUT or culture are key standards.
- There is no single gold standard.
- Breath tests (^{14}C or ^{13}C) are very effective.
- Serology does not determine active infection.
- Serology or finger-stick tests may be a cheap option in low-resource settings.
- Stool antigen tests are of limited use.

Introduction

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 settings, considerations of precision and sensitivity may sometimes be traded against costs and the availability of resources.

In some regions where Hp prevalence is very high, diagnostic tests for Hp are not cost-effective. The decision to treat must assume the presence of Hp. A distinction is usually made between tests performed during endoscopy and tests not requiring endoscopy.

Table **3** Tests for *Helicobacter pylori*

Tests with endoscopy

- Endoscopy and rapid urease test (RUT)
- Fluorescence in-situ hybridization (FISH)
- Molecular approach: polymerase chain reaction (PCR)

Tests without endoscopy

- ^{13}C urea breath test
- ^{14}C urea breath test
- Stool antigen test (SAT)
- Finger-stick test
- Serology/histology

Rapid Urease Test (RUT)

One large or two small antral biopsy specimens are placed in a gel containing urea and a pH indicator. The presence of Hp urease elicits a color change, which often occurs within minutes but may require up to 24 h.

Urea Breath test (UBT)

The patient drinks a labeled urea solution and then exhales into a tube. The urea is labeled with either the nonradioactive isotope ^{13}C or with a minute dose of the radioactive isotope ^{14}C.

If Hp urease is present, the urea is hydrolyzed, and labeled carbon dioxide is detected in breath samples. ^{13}C or ^{14}C urea breath tests are inexpensive and simpler

than endoscopy and are useful for follow-up after treatment in order to confirm successful eradication.

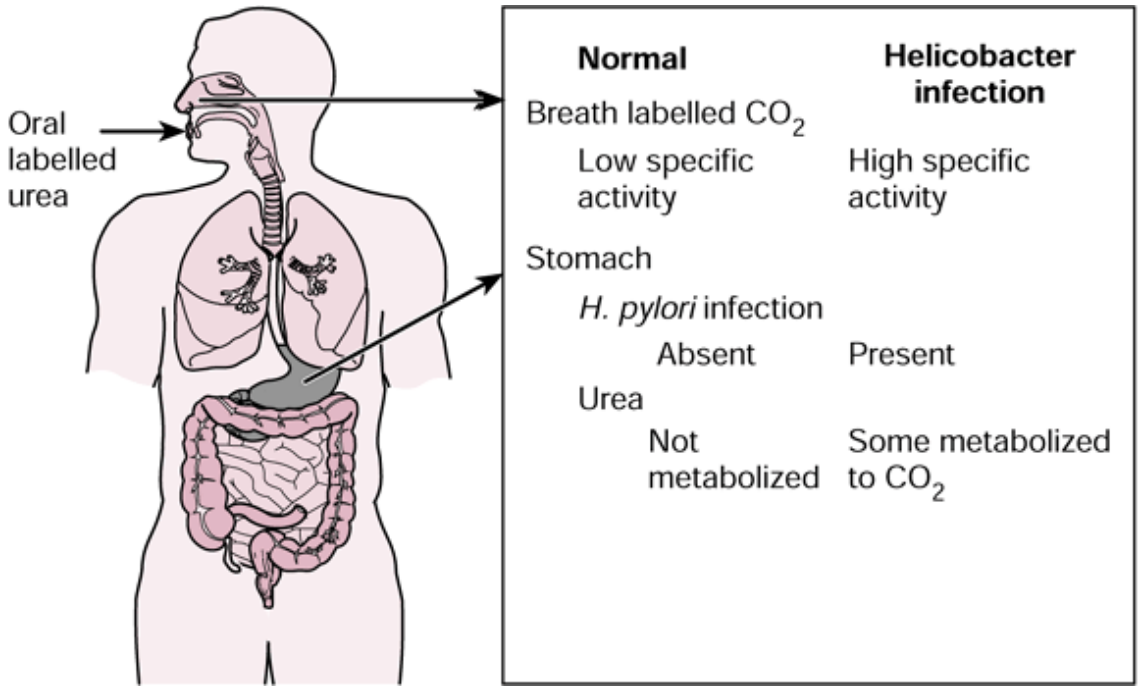

Fig. **7** Urea breath testing.

Serology

The key drawback of serology testing is that it does not measure active infection, since the presence of antibodies may be due to either a current infection or a past infection. However, a negative result is still useful, especially in regions of low prevalence. A positive result would need to be followed up by a second test to confirm active infection in areas of low prevalence.

Stool Antigen Test (SAT)

Stool antigen testing is inexpensive and convenient. It is useful for follow-up after treatment and it may be useful in children. It is not practicable if a cold chain at –20 °C is not available for transporting samples to the laboratory. In most cases, therefore, it is not a realistic option, although a rapid stool card test has recently been developed.

4.4 Maastricht III: Diagnostic Options

In the Maastricht III consensus, it was agreed that UBT and stool antigen tests were the preferred noninvasive diagnostic tests. It was also agreed that certain serological tests with a high accuracy can also be used, although testing for active infection should be carried out with either SAT or UBT.

4.5 Cascade of Diagnostic Options for Developing Countries

Cascade for Diagnosing Hp

1 Endoscopy with RUT or culture

2 ^{13}C UBT

3 ^{14}C UBT

4 Stool antigen testing (not used much outside France)

5 Serology (does not distinguish between past and present infection)

6 Finger-stick test (cheaper option in a high-prevalence area)

7 Do nothing and assume infection in areas with a very high prevalence and low resources

4.6 Differential Diagnosis

Dyspeptic symptoms (listed in section 4.2) may be due to a number of causes other than Hp infection. Hp is associated with different conditions in different parts of the world—for example, parasitosis or giardiasis can produce similar symptoms.

5 Management of *Helicobacter pylori* infection

Key Points

- Both quadruple and triple therapies give very high eradication rates.
- Quadruple therapy (PPIs + antibiotics + bismuth) may be cheaper than triple therapy.
- Resistance to metronidazole and clarithromycin reduces eradication rates.
- Time should be taken to explain the regimen to the patient –this will improve compliance.

5.1 Introduction

GPP: Treat everyone who tests positive but do not test if not intending to treat.

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

- Dyspepsia
- Duodenal ulcer
- Gastric ulcer
- Complicated peptic ulcer disease

- MALToma
- Atrophic gastritis
- Post gastric cancer resection
- Patients with first-degree relatives with gastric cancer
- Patient's wishes

An Hp eradication regimen should normally achieve at least a 90% eradication rate (90% in the per-protocol analysis and 80% in the intention-to-treat analysis) and can be defined as one of the following for at least 1 week:

- PPI triple therapy (PPI plus amoxicillin and clarithromycin)
- H_2RA triple therapy (H_2RA plus amoxicillin and clarithromycin)
- Bismuth triple therapy (bismuth salt and 5-nitroimidazole with either amoxicillin or tetracycline)
- Bismuth quadruple therapy (as bismuth triple therapy, but with PPI in addition)

The aim of Hp eradication is to reduce the lifetime risk of peptic ulcer disease and possibly of gastric cancer. Patients with active gastric or duodenal ulcers or a documented history of ulcer should be tested for Hp infection and treated if found to be infected. First-degree relatives of those with a gastric cancer history should also be tested and treated if positive.

Recent evidence shows an 8% benefit following treatment of *H. pylori* infection in patients with nonulcer dyspepsia. Testing for and treatment of *H. pylori* infection are recommended for low-grade gastric MALT lymphoma and following resection of early gastric cancer.

Retesting after treatment may be prudent for patients with bleeding or otherwise complicated peptic ulcer disease to confirm eradication. Pediatric patients who require extensive diagnostic work-ups for abdominal symptoms should be evaluated by a specialist.

It is uncertain at what stage in the natural history of the infection eradication of Hp prevents gastric cancer. 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 have be effective in preventing gastric cancer.

The management of Hp infection in high-prevalence areas should be similar to that in low-prevalence areas. In high-prevalence areas with limited resources, however, 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.

Maastricht III and Other Options

The Maastricht III treatment options are preferred. However, a number of other treatment options are recommended by different consensus groups around the world. These can be considered as alternative or complementary approaches. A list of complementary Hp treatment approaches recommended by the Asian–Pacific, Asian, African and Latin American consensus groups is included here in the Appendix. There are many factors that need to be taken into account when opting for a particular treatment, and many of these factors may vary in different regions of the world—for

example, the availability of bismuth, the prevalence of Hp infection, the prevalence of gastric cancer, resistance to antibiotics and easy availability of endoscopy.

Quadruple versus Triple Therapy

Bismuth availability is a key factor. Maastricht III shows that 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. Quadruple therapy may be more cost-effective than triple therapy, and it may be a more viable option if a 14-day regimen is chosen. However, quadruple therapy is more difficult to take than triple therapy and compliance may pose a problem.

Availability of Bismuth

Bismuth is not available in all countries. Bismuth has been used for years as a medicine (tripotassium dicitratobismuthate), often in combination with antibiotics. It can also be found as bismuth oxide in hemorrhoid creams and in ointments as bismuth subgallate. In the USA, it is available as bismuth subsalicylate. In the Netherlands and in China, it is available as colloidal bismuth subcitrate (CBS).

Compliance

Some determination is required in order to take three or four different drug combinations two to four times a day for up to 14 days, with at times the likelihood of side effects such as malaise, nausea and diarrhea, and it is advisable to take some time

counseling the patient and explaining the procedures in order to achieve the best compliance and outcome.

The results of the treatment may well be proportionate to the amount of time a physician takes to talk to the patient and explain the process.

GPP: Take time counseling the patient, and explain the procedures involved in taking complicated drug therapies such as quadruple therapy. This will improve the compliance and outcome.

5.2 Treatment Approaches

GPP: Always emphasize that successful eradication depends on compliance with the treatment regimen.

Maastricht III Florence Consensus Report, March 2005

Effective Hp eradication is necessary for good clinical management of Hp infection. Quadruple and triple therapies are the preferred first-line therapies. The choice of a first-line therapy depends on the availability of bismuth and on resistance to metronidazole and clarithromycin.

Antimicrobial resistance continues to be the main reason for treatment failure. Treatment for 14 days shows a 12% advantage over a 7-day course of treatment. However, cost considerations and compliance issues may favor 7-day therapy.

Table **5** The Maastricht III Consensus Report recommendations (further details are listed in the Appendix (section 8.1)

Quadruple therapy	PPI + bismuth + two antibiotics (cheapest option if bismuth available)
Triple therapy	PPI+ clarithromycin + amoxicillin (or metronidazole)
Rescue therapy	Rescue therapies to be based on antimicrobial susceptibility testing

Malfertheiner et al. (in press).

Triple therapy is given twice daily in populations in which the clarithromycin resistance level is less than 20%. An alternative triple therapy consists of a PPI with clarithryomycin and metronidazole, given in populations with a metronidazole resistance level less than 40%.

It was agreed in the Maastricht III consensus that Hp eradication does not cause GERD. Maastricht III also recognized that the burden of gastric cancer is increasing, mostly in developing countries, and that eradication of Hp infection has the potential to reduce the risk of gastric cancer development.

Summary of Treatment Approaches by Different Consensus Groups

Worldwide, many Hp consensus groups have produced or are working on Hp guidelines. A review of the principal publications shows that:

- All groups accept triple therapy with one PPI and two antibiotics (usually clarithromycin + amoxicillin) as the preferred approach if bismuth is not available.
- Quadruple bismuth-based therapies are the most cost-effective (if bismuth is available).
- The antibiotics used must be varied if there is antibiotic resistance.
- Suggestions for treatment duration vary from 7 to 14 days; this is still a matter of controversy.

There is a bewildering configuration of antibiotic combinations. The choice should be based on the available evidence and resources and on local preferences and values.

Table **6** Recommended combinations of antibiotics

	Antibiotic combinations	Recommended by*	Notes
1	PPI + amoxicillin + clarithromycin	a, b, c, d, e, f, g, h	Standard triple therapy; expensive
2	PPI + amoxicillin + metronidazole	a	If < 20% clarithromycin resistance
3	PPI + clarithromycin + metronidazole	a, d, e, g, h	If < 40% metronidazole resistance
4	PPI + clarithromycin + furazolidone	c, e	
5	PPI + clarithromycin + tinidazole	d	
6	PPI/RBC + amoxicillin + furazolidone	e	
7	Bismuth + metronidazole + tetracycline	e	14-day option
8	Bismuth + metronidazole + amoxicillin	e	14-day option
9	Bismuth + furazolidone + clarithromycin	e	
10	PPI + furazolidone + tetracycline	c	Low-cost option

PPI, proton-pump inhibitor; RBC, ranitidine bismuth citrate.

Note 1: the China Consensus group suggests that in first-line therapy (options 1, 3, 7), the PPI can be substituted with an H_2RA such as cimetidine 400 mg, ranitidine 150 mg, or famotidine 20 mg, but that the eradication rate may be lower.

Note 2: the Asian–Pacific Group also suggests alternatives if clarithromycin is not available.

* Key: a, Maastricht III (Malferteiner et al., in press); b, American College of Gastroenterology (Howden and Hunt, 1998); c, Brazil (2004); d, Singapore (Singapore Ministry of Health, 2004); e, China (Chinese Society of Gastroenterology, 2003); f, Spain (Gisbert et al. 2005); g, New Zealand (New Zealand Guidelines Group, 2004); h, Asian–Pacific (Lam and Talley, 1998).

Summary of Low-Cost Treatment Approaches by Different Consensus Groups

Several consensus groups have addressed cost-effectiveness issues and treatments based on cost. It is important to remember always that choosing a treatment on the basis of cost may involve lower eradication rates. Lower-cost treatment may therefore be less cost-effective. All treatment should always be based on evidence and on the associated confidence intervals.

Table **7** Alternative *Helicobacter pylori* eradication regimens

Alternative Hp eradication regimens	Recommended by*	Notes
7-day duration instead of 14-day	Maastricht III	For standard triple therapy
Quadruple instead of triple therapy	Maastricht III	If bismuth available
PPI + furazolidone + tetracycline	Brazil and Latin America	Low-cost option
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)	
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

PPI, proton-pump inhibitor.

5.3 Antibiotic Resistance

Key Points—Global Antibiotic Resistance Rates

- Clarithromycin (5–25%)
- Metronidazole (50–80% in developing countries
- Tetracycline (0–5%)
- Amoxicillin (0–1%)

GPP: In the case of treatment failure, advise a drug sensitivity test to avoid use of Hp-resistant antibiotics.

Triple therapy with a PPI and amoxicillin plus clarithromycin may fail because of resistance to clarithromycin. Resistance to metronidazole, whilst more prevalent, is less important but still significant. Resistance to tetracycline, fluoroquinolones and rifamycin is an emerging issue.

Table **8** Primary resistance of *Helicobacter pylori* to clarithromycin, metronidazole, tetracycline, and amoxicillin in adults in different parts of the world (data from studies including more than 100 strains published during the last 5 years).*

Country	Year(s)	Type of study	Method of testing	Strains tested (n)	Clarithromycin resistance †		Metronidazole resistance †		Tetra-cycline resistance (%)	Amoxi-cillin resistance (%)
					%	95% CI	%	95% CI		
Europe										
Bulgaria	1996–98	3-center	DD	103 ‡	8.7	4.1–15.9	ND		ND	ND
Croatia	2001	Single-center	Etest	196	8.0	4.7–12.9	33	26.6–4.02	ND	0
France	1996–99	Multicenter	AD	659	15.0	12.4–18.0	31.5	28.0–35.3	ND	0
Germany	1995–2000	Single-center	Etest	1644	2.2	1.5–3.0	26.2	24.1–28.4	0	0
Germany	1995–96	Multicenter	Etest	188	4.0	1.9–8.2	32	25.3–39.1	ND	ND
Italy (Central)	1998–2002	Single-center	AD	406	23.4	19.4–27.8	36.7	32.0–41.6	ND	0.2
Italy (North)	1999	Multicenter	Etest	167	1.8	0.4–5.2	14.9	9.9–21.3	ND	0

Netherlands	1997–98	Multicenter	Etest	231	1.7	0–0.4	21.2	16.1–27.1	0	0
Portugal	1990–99	3-center	Etest	132	22.0	15.2–30.0	34.1	26.1–42.8	0	0
Spain	1995–98	Single-center	Etest	235	12.9	8.7–17.7	23.5	18.1–29.3	0.7	0
Sweden	1997–98	Multicenter	AD	203	2.9	1.1–6.3	26.1	20.2–32.6	ND	0
UK	1994–99	Single-center	DD	1064	4.4 [§]	3.3–5.8	40.3	37.4–43.3	0.5	0
UK	1995–98	Single-center		843	3.9	2.7–5.5	36	32.7–39.3	ND	0.4
North America										
Mexico	1995–97	Single-center	Etest	144	25.0	18.2–32.9	76.3	68.6–83.1	ND	0 [#]
USA	1993–99	Multicenter	AD	3439	10.6	9.6–11.7	21.6	20.2–23.0	ND	0.08
USA	1998–99	Multicenter	AD	422	12.0	9.1–15.6	ND		ND	0
USA	2000–01	Multicenter	AD	106	12.2	6.7–20.0	33.9	25.0–43.8	ND	ND
South America										
Brazil	1996–2000		AD	203	9.8	6.1–14.8	53	46.1–60.2	ND	ND

Middle East										
Iran	2002	2-center	DD	120	17.0	10.5–24.6	ND		ND	ND
Israel	2000–01	Single-center	Etest	110	8.2	3.8–15.0	38.2	29.1–47.9	0	0.9
Far East and Australasia										
Hong Kong	1997–2001	Single-center	DD	991	4.5	3.3–6.0	29	26.3–32.0	0.5	0.3
Japan	1995–2000	Single-center	AD	593	11.0	8.6–13.8	9	6.8–11.5	ND	0.3
Japan	1996–99	2-center	AD	388	12.9	9.7–16.6	12.4	9.3–16.1	ND	0
Korea	1994–99	2-center	AD	456	5.9	3.9–8.5	40.6	36.0–45.2	5.3	0
Korea	1996–2000	Single-center	BD	224	5.4	2.8–9.2	41.9	35.4–48.7	ND	ND
Singapore	1993–96	Single-center		459	ND		62.7	58.1–67.2	ND	ND
Singapore	2002	Single-center	AD	120	ND		31.7	23.5–40.8	ND	ND
New Zealand	1993–98	Single-center	DD	225	6.8	3.8–10.8	32	26.0–38.5	ND	ND
China	1995–99	Multicenter	Etest	150	4.0	0.9–7.1	55.3	47.3–63.3	ND	ND

* Megraud, *Drugs* 2004;64:1893–904 (PMID: 15329036); *Gut* 2004;53:1374–84 (PMID: 15306603).

† Global prevalence.

‡ Includes 42 children.

§ Clarithromycin susceptibility performed on 812 strains only.

Transient resistance was observed in 19% of the strains.

AD, agar dilution method; BD, broth dilution method; CI, confidence intervals; DD, disk diffusion method; ND, not determined.

There is considerable variation between consensus groups with regard to the optimal “rescue” therapies. The choice should take account of primary resistance of *Helicobacter pylori* to clarithromycin, metronidazole, tetracycline, and amoxicillin in adults in different parts of the world.

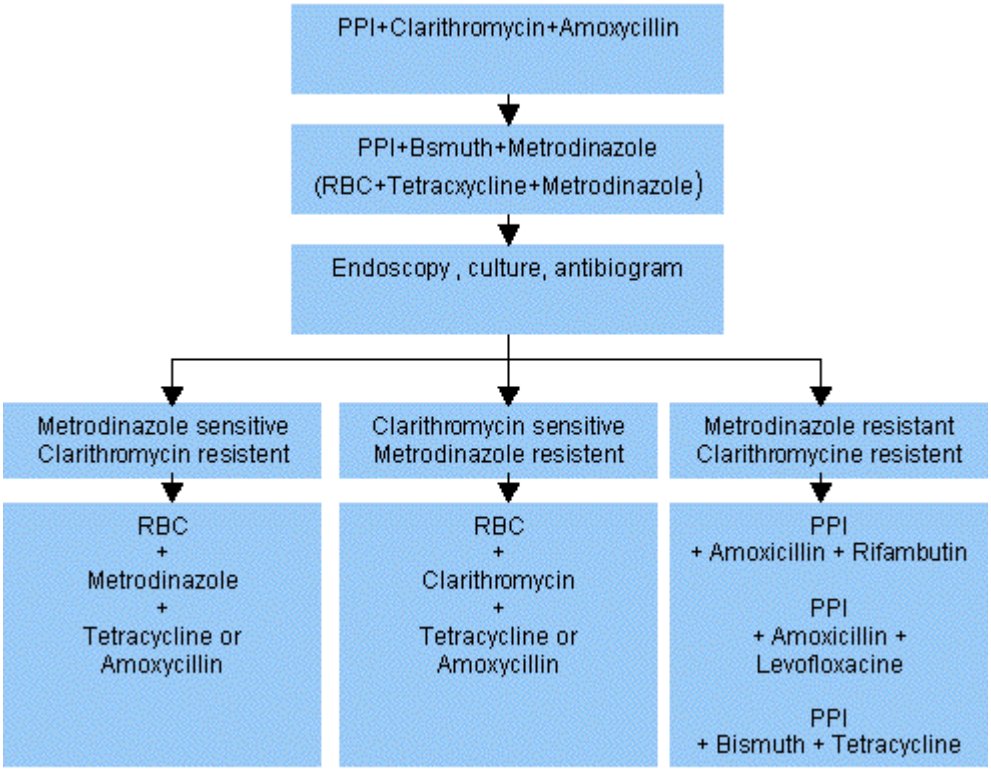

Fig. **8** Rescue therapies (from a western European perspective).

5.4 Prevention

A vaccine is not currently available. Since the source of *H. pylori* infection is not yet known, it is difficult to make recommendations for avoiding the infection. In general, however, it is always wise to wash hands thoroughly, to eat food that has been properly prepared, and to drink water from a safe, clean source.

6 Screening for *Helicobacter pylori* infection

Key Points

- The debate over screening for Hp infection is growing in importance in some developed countries.
- Screening is of particular interest in countries that have a high incidence of gastric cancer.

The question of whether Hp should be eradicated in people who do not present with symptoms is an important one. Detection when there are no symptoms is becoming particularly important in developing countries in which there is a high incidence of gastric cancer. Most consensus statements, guidelines and reviews focus on the treatment of people who present with a clinical problem. But is this cost-effective? Should consideration be given to searching for and detecting infection in the context of a public-health program?

The discovery of Hp infection and the observation that it is responsible for the development of chronic gastritis with atrophy and intestinal metaplasia raises the possibility that the organism is a necessary contributor to the carcinogenic process in most cases of gastric cancer. Early nested epidemiological studies confirmed that infected individuals had a 3–6 times greater risk of developing gastric cancer than uninfected controls. More recent studies suggest that the link is much stronger than this.

There are biologically plausible mechanisms that may explain the association between Hp and gastric cancer. The infection leads to a hyperproliferative state, intragastric concentrations of ascorbic acid are reduced, and the levels of mucosal

reactive oxygen metabolites capable of inducing DNA damage are increased. Hp eradication normalizes gastric cell turnover, luminal ascorbic acid concentrations, and the level of reactive oxygen species in the mucosa.

A systematic review identified 12 nested prospective case–control studies, and meta-analysis suggested that Hp is associated with a 5.9 (95% confidence intervals, 3.4 to 10.3) increase in the odds ratio of developing noncardia gastric cancer. These are not intervention studies, and it is not yet known whether eradication of Hp infection will reduce the risk of gastric cancer.

Two important clinical trials have recently been completed in high-risk gastric cancer areas in Hong Kong and in Beijing. The trial by Wong et al. (2004) concluded that in the subgroup of Hp carriers without precancerous lesions, Hp eradication significantly decreased the development of gastric cancer.

Although research studies have not yet confirmed this, a policy of screening populations for Hp and treating those infected may lead to a reduction in the incidence of gastric cancer. More research is needed to evaluate the efficacy of Hp eradication in preventing gastric neoplasia (gastric adenocarcinoma and MALT lymphoma) in the general population before decisions can be made regarding whether or not screening for Hp in countries with a high incidence of gastric cancer would be cost-effective.

Community screening and eradication of Hp is feasible in the general population and can lead to significant reductions in the number of people who consult for dyspepsia with symptoms 2 years after treatment. The results in Western populations are modest, but the result may be much higher in other populations, due to the elimination of ulcer disease. However, these benefits have to be balanced against the

costs of eradication treatment, so that a targeted eradication strategy in dyspeptic patients may be preferable.

7 Useful Websites, Guidelines and further reading

7.1 Helicobacter pylori*: Relevant Guidelines and Consensus Statements*

American Gastroenterological Association. American Gastroenterological Association medical position statement: evaluation of dyspepsia. Gastroenterology 2005;129:1756–80, http://www.gastrojournal.org/article/PIIS0016508505018184/fulltext (accessed 28 June 2006).

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North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). *Helicobacter pylori* infection in children: recommendations for diagnosis and treatment. http://www.naspghan.org (accessed 19 April 2006).

Scottish Intercollegiate Guidelines Network (SIGN). Dyspepsia: a national clinical guideline. http://www.sign.ac.uk (accessed 19 April 2006).

Singapore Ministry of Health. Management of *Helicobacter pylori* infection. Singapore: Singapore Ministry of Health, 2004. http://www.guideline.gov/summary/summary.aspx?ss=15&doc_id=5947&nbr=3916 (accessed 19 April 2006).

Talley NJ, Vakil N, American College of Gastroenterology. Guidelines for the management of dyspepsia (2005). http://www.acg.gi.org/physicians/guidelines/dyspepsia.pdf (accessed 28 June 2006).

7.2 Further Reading

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Ford AC, Delaney BC, Forman D, Moayyedi P. Eradication therapy for peptic ulcer disease in *Helicobacter pylori* positive patients. Cochrane Database Syst Rev 2006;(2):CD003840. PMID: 16625592.

Frenck RW Jr, Clemens J. *Helicobacter* in the developing world. Microb Infect 2003;5:705–13. PMID: 12814771.

Gisbert JP, Pajares JM. ^{13}C-urea breath test in the diagnosis of *Helicobacter pylori* infection: a critical review. Aliment Pharmacol Ther 2004;201001–17. PMID: 15569102.

Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. Lancet 2002;359:14–22. PMID: 11809181.

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Hunt RH, Bazzoli F. Review article: should NSAID/low-dose aspirin takers be tested routinely for *H. pylori* infection and treated if positive? Implications for primary risk of ulcer and ulcer relapse after initial healing. Aliment Pharmacol Ther 2004;19(Suppl 1):9–16. PMID: 14725573.

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Wong BC, Lam SK, Wong WM, et al. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA 2004;291:187–94. PMID: 14722144.

Zhou LY, Lin SR, Ding SG, et al. The changing trends of the incidence of gastric cancer after *Helicobacter pylori* eradication in the Shangdong area. Chin J Dig Dis 2005;6:114–5. PMID: 16045599.

7.3 Useful Websites

- Centers for Disease Control and Prevention (Atlanta, Georgia). *Helicobacter pylori* and peptic ulcer disease. http://www.cdc.gov/ulcer/md.htm
- Centers for Disease Control and Prevention (Atlanta, Georgia). *Helicobacter pylori* and peptic ulcer disease. http://www.cdc.gov/ulcer/
- National Institute of Clinical Excellence (London). http://www.nice.org.uk
- U.S. National Guideline Clearinghouse. www.guidelines.gov (type “Helicobacter “in the search box).
- The Cochrane Collaboration. www.cochrane.gov
- The Helicobacter Foundation. http://www.helico.com/

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The authors are grateful to Professor Hunt for facilitating access to the Canadian Helicobacter Study Group meeting in Montreal in September 2005, and to Professor Peter Malfertheiner for providing early access to a draft of the Maastricht III report.

8 Appendix 1: Consensus Groups and Other Recommendations

The treatment recommendations listed below are based on published consensus group documents or on articles published or in press prepared by the major gastroenterology societies. Please refer to the full text of the document as available on the relevant website or PMID number listed in section 7 above.

An attempt has been made to rank these consensus statements by evidence and, if this is not transparent from the text of the guideline developer, then by year. WGO-OMGE does not currently take a position on whether recommendations for a particular geographic region should be based on level I evidence from that region or level III evidence coming from trials in a different region.

8.1 Maastricht III (2005)

The Maastricht III consensus is recommended as the preferred approach—certainly for countries in the developed world.

First-line options	
• PPI + clarithromycin + amoxicillin or metronidazole	If < 20% clarithromycin resistance prevalence
• PPI + clarithromycin + metronidazole	Preferable if < 40% metronidazole resistance prevalence
• Quadruple (PPI + bismuth + metronidazole + tetracycline) or furazolidone-based therapies	If bismuth available
Second-line options	
• Best second-line therapy (if bismuth available)	Bismuth-based quadruple therapies
• Best second-line therapy (if bismuth not available)	PPI + (amoxicillin or tetracycline) + metronidazole

Rescue therapy

Rescue therapies must be based on antimicrobial susceptibility testing—this may not always work in developing countries

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Malfertheiner et al. (in press).

It was agreed in the Maastricht III consensus that Hp eradication does not cause GERD. Maastricht III also recognizes that the burden of gastric cancer is increasing, mostly in developing countries, and that eradicating an Hp infection has the potential to reduce the risk of gastric cancer development.

Dosages: Maastricht III did not include dosages.

8.2 Singapore (2004)

Management of *Helicobacter pylori*—Singapore Ministry of Health.

First-line options (7 days)

- PPI * + clarithromycin + amoxicillin
- PPI * + clarithromycin + metronidazole (tinidazole as alternative)

Second-line options (7 days)

- PPI + amoxicillin + metronidazole
- Colloidal bismuth subcitrate + metronidazole + tetracycline

Rescue therapy

- PPI + colloidal bismuth subcitrate + metronidazole + tetracycline

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* Proton-pump inhibitor: lansoprazole 30 mg, omeprazole 20 mg.

Singapore Ministry of Health (2004).

8.3 Helicobacter pylori *Eradication Treatment—Spanish Consensus Conference II (2005)*

First-line treatment

- PPI + clarithromycin + amoxicillin

Second-line options

- PPI + bismuth + tetracycline + metronidazole
- RBC + tetracycline + metronidazole

Rescue therapies (after endoscopy with antibiogram to determine metronidazole and clarithromycin sensitivity and resistance)*y*

- RBC + metronidazole + tetracycline (or amoxicillin)
- RBC + clarithromycin + tetracycline (or amoxicillin)
- PPI + amoxicillin + rifabutin
- PPI + amoxicillin + levofloxacin
- PPI + bismuth + tetracycline + furazolidone

PPI, proton-pump inhibitor; RBC, ranitidine bismuth citrate.

Gisbert et al. (2005).

8.4 American College of Gastroenterology (1998)

Guidelines for the management of dyspepsia.

First-line treatment

- PPI + amoxicillin + clarithromycin

Second-line treatment

- PPI + bismuth + metronidazole + tetracycline

Rescue therapies

- PPI + amoxicillin + rifabutin
- PPI + amoxicillin + levofloxacin
- PPI + amoxicillin + furazolidone

Howden and Hunt (1998).

8.5 Brazil 2004 II Consensus Conference on Helicobacter pylori *Infection*

The 2004 II Consensus Conference on Hp eradication in Brazil includes three options.

1 PPI + clarithromycin 500 + amoxicillin 1 g, twice daily for 7 days

2 PPI + clarithromycin 500 + furazolidone 200, twice daily for 7 days

3 PPI once daily + furazolidone 200 t.i.d. + tetracycline 500 q.i.d. for 7 days

Options 1 and 2 are based on locally available evidence; the third option was included because it represents the only low-cost option in some parts of the country. For the same reason, a 7-day rather than 10-day or 14-day option is a realistic alternative with very little loss of efficacy—Maastricht III showed that treatment with triple therapy for 14 days gives a 12% advantage over 7-day eradication therapy.

Rescue therapy. Furazolidone-based rescue therapies achieve high eradication rates after failure of standard first-line, second-line and rifabutin-based therapies. They are cheaper than standard first-line and second-line therapy and are associated with better compliance and gastric tolerance. These treatments are not suitable for children.

8.6 China (2004)

Consensus on the management of *Helicobacter pylori* infection.

First-line options (7 days)

- PPI/RBC + amoxicillin + clarithromycin
- PPI/RBC + metronidazole + clarithromycin
- PPI/RBC + amoxicillin + furazolidone
- Bismuth + furazolidone + clarithromycin

First-line options (14 days)

- Bismuth + metronidazole + tetracycline
- Bismuth + metronidazole + amoxicillin

Second-line options (7–14 days)

- PPI + bismuth + metronidazole + tetracycline
- PPI + bismuth + furazolidone + tetracycline

PPI, proton-pump inhibitor; RBC, ranitidine bismuth citrate.

Cascade note: In the first-line regimen, the PPI can be substituted with an H_2-receptor antagonist such as cimetidine 400 mg, ranitidine 150 mg, or famotidine 20 mg, but the eradication rate may be lower.

Chinese Society of Gastroenterology (2004).

8.7 Asian–Pacific Consensus Group (1998)

This was the first group to introduce "different management options based on local epidemiology and available resources."

First-line options (7 days)

- PPI + clarithromycin + amoxicillin
- PPI + clarithromycin + metronidazole (tinidazole as alternative)
- RBC + clarithromycin + amoxicillin
- RBC + clarithromycin + metronidazole

If clarithromycin is not available:

- PPI + amoxicillin + metronidazole (for 7 days)
- Colloidal bismuth citrate + metronidazole + tetracycline (for 14 days)

Lam and Talley (1998).

Although drug acquisition costs may be lower, the above two regimens will yield on average a 10% lower eradication rate, and thus their cost-effectiveness may be compromised.

9 Queries and Feedback

The Practice Guidelines Committee welcomes any comments and queries readers may have. Are there any aspects you feel we have neglected? Do you feel that some procedures carry extra risks? You are invited to tell us of your experiences by e-mailing us at guidelines@worldgastroenterology.org.