For the full versions of these articles see bmj.com

Treatment of *Helicobacter pylori* infection

L Fuccio,[1] L Laterza,[1] R M Zagari,[1] V Cennamo,[1] D Grilli,[2] Franco Bazzoli[1]

[1]Department of Internal Medicine and Gastroenterology, University of Bologna, 40138, Bologna, Italy
[2]Department of Economics, University of South Florida, FL 33620, USA

Correspondence to: F Bazzoli
franco.bazzoli@unibo.it

Cite this as: *BMJ* 2008;337:a1454
doi:10.1136/bmj.a1454

Helicobacter pylori is one of the most common human infections, and about half of the world's population carries this organism. Since its discovery in 1984, *H pylori* has been recognised as a major cause of several upper gastrointestinal diseases.[1 2] As with other chronic infectious diseases, several antibiotics must be given simultaneously and sometimes repeated courses of different combinations of antibiotics are needed to eradicate *H pylori*. Eradicating *H pylori* is still a challenge, however, because of the rapidly increasing prevalence of multidrug resistant strains worldwide. In recent years, several randomised controlled trials and meta-analyses have proposed new regimens and treatment strategies for *H pylori* infection. This review will discuss the available treatment strategies for *H pylori* infection and help identify the most effective one.

How common is *H pylori* infection?

The prevalence of *H pylori* varies widely, with more than 80% of adults being infected in Japan and South America compared with around 40% in the United Kingdom and 20% in Scandinavia.[3] Epidemiological evidence suggests that many people acquire the infection in childhood—social deprivation, household crowding, and number of siblings are important risk factors. The prevalence of infection increases with age, although this may be largely a cohort effect. Poorer socioeconomic conditions 60 years ago meant most children were infected with *H pylori*. Although most people over 60 are *H pylori* positive only 10-20% of children are infected today. This is consistent with the reduction over time of *H pylori* related diseases such as peptic ulcer and gastric cancer.

Why should I treat *H pylori* infection?

Several conditions have been linked to *H pylori* infection, and its eradication has consistently been shown to be beneficial (table). Meta-analyses of comparative trials have shown that, when compared with no treatment, eradication provides significant benefit in terms of the healing of peptic ulcers and the prevention of recurrence.[4] Eradication also prevents recurrent bleeding from peptic ulcers.

Several non-randomised observational and prospective studies have supported the role of *H pylori* infection in the development of mucosa associated lymphoid tissue lymphoma. These studies have also shown that eradication of *H pylori* provides durable remission in patients with low grade mucosa associated lymphoid tissue lymphoma.

As reported in our previous review, eradicating *H pylori* provides significant benefit to patients with uninvestigated dyspepsia without alarm features.[5]

The association between gastric cancer and *H pylori* infection has been based on large scale epidemiological studies, meta-analyses of case-control studies, and experimental models.[2] However, it is not known whether eradicating *H pylori* infection can reduce the risk of developing gastric cancer. One large randomised placebo controlled study showed that in patients without precancerous lesions (atrophy, intestinal metaplasia, or dysplasia) at study entry, eradication of *H pylori* significantly decreased the development of gastric cancer compared with placebo.[6]

European guidelines have proposed that eradication should be considered not only in patients who already have gastric cancer, but also in those at increased risk of developing gastric cancer, such as first degree relatives of patients with gastric cancer.[7] American guidelines consider being at high risk for gastric cancer to be a controversial indication for diagnosing and treating *H pylori* infection.[8] Asia-Pacific consensus guidelines recently suggested that *H pylori* infection should be widely screened for and treated to reduce the risk of gastric cancer in populations at high risk.[9]

What are the available treatment regimens and how can we choose between them?

Dual or triple regimens?

Many eradication treatments have been proposed (box). Monotherapies and dual therapies—usually a proton pump inhibitor and one antibiotic—have always had disappointing results.[10 11] A highly effective proton pump inhibitor based triple therapy—composed of omeprazole, tinidazole, and clarithromycin—was first reported in 1993.[12] Shortly after, a similar triple therapy, which used amoxicillin instead of the nitroimidazole and had a

UNANSWERED QUESTIONS

Which is the most cost effective strategy?

Does the eradication rate differ between patients with peptic ulcer disease and non-ulcer dyspepsia?

What factors predict treatment failure other than antibiotic resistance and adherence to therapy?

comparable and highly effective eradication rate, was proposed.[13] Since then, triple therapy of a proton pump inhibitor, clarithromycin, and either amoxicillin or metronidazole has been the most widely recommended eradication treatment.[7 8] Two meta-analyses found that different proton pump inhibitors are equivalent when used in triple therapy, but that double dosing is more effective than single dosing. A meta-analysis of randomised controlled trials has shown that only about 5% of patients have adverse side effects (such as diarrhoea, nausea, and taste disturbance) and these rarely cause discontinuation of treatment.[14]

What is the optimal duration of triple therapies?

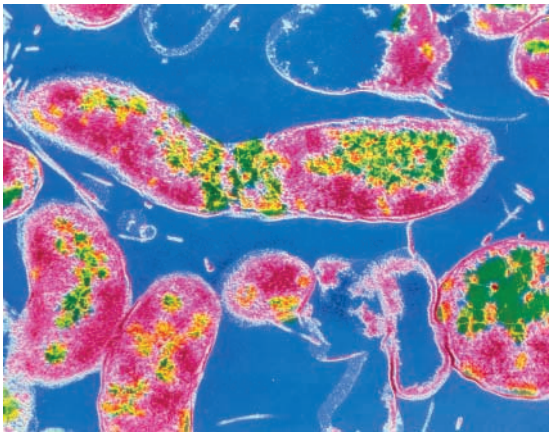
The optimal duration of triple therapies (seven, 10, or 14 days) has been widely debated. Those based on proton pump inhibitors were initially proposed as one week regimens. However, the most recent European and American guidelines now suggest 14 days as the optimal duration for eradicating *H pylori*.[7 8] We recently performed a meta-analysis of randomised controlled trials comparing the efficacy of different durations of proton pump inhibitor based triple therapy and found that extending treatment beyond seven days results in only a slight increase in the rate of *H pylori* eradication.[14] Extending treatment to 10 days produced a 4% increase in eradication, whereas extending it to 14 days led to a 5% increase. As yet, this increase has been seen with the amoxicillin containing regimen only; more research is needed before the effects of extending metronidazole containing triple therapy can be assessed. The increase was higher in patients with non-ulcer dyspepsia (relative risk difference 11%) than in those with peptic ulcer (relative risk difference 2%). In the future, therefore, if these results are confirmed by large well performed randomised controlled trials, different treatment durations might be proposed, depending on the different baseline conditions, and whether patients have non-ulcer dyspepsia or peptic ulcer. These small differences do not seem to be clinically relevant, however, and we think that the standard duration of treatment should be seven days, although 10-14 days may be considered depending on the local success rate.

Why does eradication therapy fail?

Two factors influence the treatment outcome equally—infection with drug resistant *H pylori* and patients' adherence to treatment. A meta-analysis of comparative trials and a systematic review found that drug resistance is the main factor that predicts failure of triple therapy (proton pump inhibitor-clarithromycin-amoxicillin or metronidazole).[15 16] Clarithromycin resistance is the strongest predictor of treatment failure. When the prevalence of clarithromycin resistance in the population reaches 15-20%, the eradication rate of clarithromycin based triple therapy decreases below the recommended threshold of 80%.[15 16] Therefore, in areas with an increased prevalence of clarithromycin resistance (>15-20%), or when patients have previously received a macrolide, clarithromycin based triple therapy should not be used to treat *H pylori* infection.

Conversely, a randomised double blind controlled study showed that metronidazole resistance does not significantly influence the outcome of the nitroimidazole containing regimen,[10] and—on the basis of the results of systematic reviews—this regimen seems to perform better than an amoxicillin containing regimen (amoxicillin-clarithromycin-proton pump inhibitor) in geographical areas with a prevalence of metronidazole resistance of up to 40%.[16 17] The metronidazole containing regimen should also be considered in patients who are allergic to penicillin.

The adherence of patients to their treatment regimen also play a pivotal role in *H pylori* eradication and should be taken into account when a multidrug regimen is proposed. Patients should therefore be fully informed that the success of their treatment depends on their adherence to it.



CNRI/SPL

The culprit: false colour, transmission electron micrograph of *H pylori*

When should quadruple therapy be considered?

A meta-analysis of comparative randomised controlled trials showed that quadruple therapy containing a proton pump inhibitor, bismuth, metronidazole, and tetracycline can achieve a similar eradication rate to clarithromycin based triple therapy (≥80%). It has also been shown that, although the eradication rate of triple therapies falls when clarithromycin resistance increases (>15-20%), the efficacy of non-clarithromycin quadruple therapy remains above 80% under these

Benefits of treating *H pylori* infection

Disease or condition	Benefit	Strength of evidence
Peptic ulcer (active or confirmed history)	Healing; prevention of recurrence; prevention of recurrent bleeding	Meta-analyses[4]; cost effectiveness analysis[4]
Gastric mucosa associated lymphoid tissue lymphoma (low grade)	Durable remission	Non-randomised observational and prospective studies[7 8]
Uninvestigated dyspepsia	Management of dyspepsia symptoms	Meta-analysis[5]; cost effectiveness analysis[5]
Patient at increased risk of developing gastric cancer (first degree relative of patient with gastric cancer; after gastric cancer resection)	Prevention of development or recurrence of non-cardia gastric cancer	Randomised controlled trials[6]; systematic reviews[2]; international guidelines[7-9]

circumstances.[15] Therefore, quadruple therapy could be considered for first line treatment in areas with a high prevalence (>15-20%) of clarithromycin resistance, or in patients who have previously received a macrolide. A meta-analysis of comparative trials found that proton pump inhibitor based quadruple therapy is about 6% (95% confidence interval 3% to 9%) more efficacious when given for more than seven days.[14] The main disadvantage of this regimen is its complexity (a high number of pills taken each day for seven to 14 days), which could influence patients' adherence. However, a meta-analysis found no difference in adherence between patients using quadruple or triple therapy.[15] This study also found that quadruple therapy had a similar incidence of adverse events to that reported for clarithromycin based triple therapy. Cost comparison analyses concluded that the average cost of a 10 day course of quadruple therapy is similar to that of a seven day course of the currently recommended proton pump inhibitor based triple therapies.[18] The main limitation to the worldwide use of quadruple therapy is that bismuth preparations are not available in many countries.

An alternative triple therapy?

In areas with a high prevalence of clarithromycin resistance, an alternative seven day regimen—comprising a proton pump inhibitor, amoxicillin, and metronidazole—has been proposed. A randomised comparative trial performed in Japan showed that, in the presence of metronidazole sensitive strains, this regimen is highly effective (>90% eradication rate) after clarithromycin containing triple therapy fails.[19] However, a meta-analysis found that this regimen was 30% less efficacious in the presence of metronidazole resistance.[20] If confirmed by further studies, this regimen might be considered as an alternative second line treatment in areas with low metronidazole resistance.

Is antimicrobial susceptibility testing essential to *H pylori* eradication?

Antimicrobial susceptibility testing has been recommended to allow treatment to be tailored to the individual patient.[6] Three large randomised comparative clinical trials that evaluated whether first line regimens based on pretreatment susceptibility testing were more effective than empirical triple therapies have produced conflicting results. One trial that enrolled more than 240 patients concluded that tailored treatment did not increase eradication.[21] Conversely, two trials of 259 patients reported a statistically significant increase in eradication in the group randomised to pretreatment antimicrobial susceptibility testing.[22 23]

Furthermore, two large randomised trials comparing susceptibility based and empirical strategies found no difference in eradication between the two strategies in patients attempting eradication for the second time. Notably, susceptibility based treatment does not improve the eradication rate in patients who have already received a clarithromycin based regimen. To reduce treatment failure in these patients a second course of macrolide should be avoided because of the probable presence of resistant strains.

Testing for antimicrobial susceptibility has several limitations. Firstly, in vitro resistance to metronidazole may not accurately reflect in vivo resistance,[15] and metronidazole testing is therefore not recommended routinely, especially as metronidazole resistance is less clinically relevant than clarithromycin resistance. Antimicrobial susceptibility testing is also expensive, it is not widely performed across the country, it is not done routinely in most hospitals, and—most importantly—it is performed on gastric biopsies taken during upper gastrointestinal endoscopy, which is expensive, not well tolerated by all patients, and not indicated in several circumstances (such as uninvestigated dyspepsia). In current clinical practice, the role of antimicrobial susceptibility testing is therefore likely to be marginal.

Is it time to consider sequential therapy for eradicating *H pylori*?

In recent years an alternative treatment strategy, known as sequential therapy, has been proposed for eradicating *H pylori*. It consists of a proton pump inhibitor combined with amoxicillin for five days, followed by a proton pump inhibitor combined with clarithromycin and a nitroimidazole for another five days.[24] The only large randomised double blind placebo controlled trial published to date found that this regimen, despite containing a macrolide, achieved high eradication rates

Standard and third line treatments for eradicating *H pylori*

Standard treatments

Triple therapy: proton pump inhibitor (standard dose) twice daily + clarithromycin 500 mg twice daily + metronidazole 500 mg twice daily or amoxicillin 1000 mg twice daily, for seven, 10, or 14 days

Quadruple therapy: proton pump inhibitor (standard dose) twice daily + metronidazole 500 mg three times daily + tetracycline 500 mg four times daily + bismuth subcitrate 120 mg four times daily, for seven, 10, or 14 days

Third line treatment

Proton pump inhibitor (standard dose) twice daily + amoxicillin 1000 mg twice daily + levofloxacin 500 mg twice daily for 10 days

SOURCES AND SELECTION CRITERIA

This review is based on the results of searches performed on PubMed, Embase, and the *Cochrane Database of Systematic Reviews* using the keywords "*Helicobacter pylori*" and "treatment" (cut-off date May 2008). We also searched the proceedings of the main international congresses (Digestive Diseases Week, United European Gastroenterology Week, and International Workshop of the European Helicobacter Study Group) and published international guidelines. We identified supplementary studies from our personal reference archive and our knowledge of the current literature.

TIPS FOR NON-SPECIALISTS

- Triple and quadruple multidrug regimens are the standard treatment for *H pylori* infection
- A week of triple therapy can be enough to cure *H pylori*
- Avoid using clarithromycin based regimens in patients who have previously been exposed to a macrolide
- Strict adherence to current guidelines significantly reduces treatment failure
- Inform patients that the success of their treatment depends on their adherence to it
- In current clinical practice, antimicrobial susceptibility testing has a limited role
- *Helicobacter pylori* eradication should be confirmed by the urea breath test, at least four weeks after treatment ends
- The annual reinfection rate is low, at least in industrialised countries, so systematic control for recurrence is unnecessary

(88.9%) in clarithromycin resistant strains compared with standard triple therapy (28.6%); both regimens achieved similar results in clarithromycin susceptible strains (94%).[24] A recent meta-analysis of randomised controlled trials comparing first line sequential and standard triple therapies concluded that sequential therapy is superior to standard triple therapy.[25] However, data on sequential therapy have not been confirmed by researchers in countries other than Italy, and it is too early to recommend its use in clinical practice.[25 26] Furthermore, a recent multicentre randomised controlled trial that compared 10 days of sequential therapy with seven days of concomitant therapy (the same antibiotics given at the same time rather than sequentially) concluded that sequential and concomitant administration of the same drugs produced similar results, and that sequential administration might be unnecessarily complex.

When should a levofloxacin based regimen be considered?

A levofloxacin containing regimen, usually a proton pump inhibitor and levofloxacin combined with amoxicillin for 10 days, has been proposed for use when several attempts at eradication have failed.[7 8] Two meta-analyses of trials comparing this levofloxacin based regimen with quadruple therapy confirmed its high efficacy.[27 28] However, although the literature is rapidly expanding, well performed randomised controlled studies and broad validation are needed before it can be recommended. The efficacy of this regimen falls dramatically when *H pylori* are resistant to levofloxacin. Its use should therefore be confined to selected cases, when standard validated treatments have not achieved eradication. Furthermore, the development of levofloxacin resistant microbial strains needs to be avoided, because this antibiotic is a mainstay for treating respiratory tract infections.

What about regimens based on rifabutin and furazolidone?

Regimens based on rifabutin and furazolidone have been proposed as rescue regimens, when validated treatments cannot achieve eradication. The use of rifabutin containing regimens should be limited, however, because this drug can select for resistant strains of *Mycobacterium tuberculosis*. Furthermore, the eradication rate of these regimens is significantly lower than that of levofloxacin containing regimens. This finding, taken together with the increased risk of myelotoxicity and its high cost, prevent it from being recommended in the current *H pylori* treatment strategy.

Furazolidone based triple or quadruple regimens have also been proposed for *H pylori* eradication. The main strengths of this drug are its low cost and the lack of resistance to it. However furazolidone, which is not widely available in Europe and Western countries, has to be used at relatively high doses, which result in a high level of side effects such as diarrhoea. Finally, the available data on efficacy are not consistent and do not allow any definitive conclusion to be reached on furazolidone based regimens.

How can eradication be confirmed?

Follow-up after treatment should be carried out using non-invasive tests with high sensitivity and specificity. Systematic reviews have concluded that the urea breath test is the test of choice[29]; sensitivity and specificity exceed 95% stool antigen testing is an alternative method although it is less accurate than the urea breath test.[29] Invasive methods should be limited to cases where repeat endoscopy is indicated (such as gastric ulcer). Techniques with low sensitivity, such as the rapid urease test, should be avoided; histology based on multiple gastric sampling is preferred. Eradication of *H pylori* should be confirmed at least four weeks after treatment ends.

Can *H pylori* reinfection occur?

Recurrence of *H pylori* infection is infrequent.[30] The few cases that do occur may be caused by recrudescence or reinfection with *H pylori*. Recrudescence occurs when the original strain of *H pylori* recolonises and is detected at a later stage; reinfection occurs when the patient is infected by a new strain of *H pylori*. Large prospective epidemiological studies have shown that the socioeconomic level of the country and the prevalence of *H pylori* in the population are risk factors for reinfection. In industrialised countries, the overall risk of reinfection is estimated at 3.4% per patient year, but this rises to 8.7% in developing countries.[30] In several countries —such as China, South Africa, Poland, and Turkey— recurrence rates are low despite the high prevalence of infection.[30] Recurrence rates decrease with time and beyond the first year become similar to the rate of natural acquisition of *H pylori* infection in adulthood (0.5-2% each year). Reinfection may occur via the oral cavity (dental plaque, tongue) and endoscopy; however, more studies are needed to define the clinical relevance of these potential sources. Most prospective studies have concluded that family members do not act as a reservoir for reinfection, so screening or treating asymptomatic family members to prevent reinfection cannot be justified. Because the annual reinfection rate is low, at least in industrialised countries, it is

SUMMARY POINTS

The prevalence of *H pylori* varies widely and is about 50% in international population studies

Triple and quadruple multidrug regimens are standard treatment

Resistance to clarithromycin and metronidazole and lack of adherence to treatment are the main predictors of treatment failure

The choice of the most effective regimen should be based on the prevalence of antibiotic resistance, especially resistance to clarithromycin and metronidazole

Individualised treatment based on antimicrobial susceptibility has a limited role in *H pylori* eradication strategies

The overall risk of reinfection is estimated at 3.4% per patient year in developed countries, rising to 8.7% in developing countries

unnecessary to control systematically for the recurrence of *H pylori* infection after eradication.

Conclusion

Many alternative treatment regimens have been proposed for the eradication of *H pylori*. The initial management strategy should be based on the prevalence of drug resistance—particularly resistance to clarithromycin. Validated treatments should be preferred to recently proposed ones, which still need validation. Strict adherence to widely accepted guidelines can reduce treatment failure.[31]

Participants: LF, LL, RMZ, and FB helped in the study searches, study selection, data extraction, quality assessment, and drafting of the manuscript. All authors helped critically revise the manuscript for important intellectual content. LF and FB provided administrative, technical, or material support.

Funding: None.
Competing interests: None declared.
Provenance and peer review: Not commissioned; externally peer reviewed.

1 Suerbaum S, Michetti P. Helicobacter pylori infection. *N Engl J Med* 2002;347:1175-86.
2 Fuccio L, Zagari RM, Minardi ME, Bazzoli F. Systematic review: Helicobacter pylori eradication for the prevention of gastric cancer. *Aliment Pharmacol Ther* 2007;25:133-42.
3 Malaty HM. Epidemiology of Helicobacter pylori infection. *Best Pract Res Clin Gastroenterol* 2007;21:205-14.
4 Ford AC, Delaney BC, Forman D, Moayyedi P. Eradication therapy in Helicobacter pylori positive peptic ulcer disease: systematic review and economic analysis. *Am J Gastroenterol* 2004;99:1833-55.
5 Zagari RM, Fuccio L, Bazzoli F. Investigating dyspepsia. *BMJ* 2008;337:a1400.
6 Wong BC, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, et al, China Gastric Cancer Study Group. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004;291:244-5.
7 Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, et al. Current concepts in the management of Helicobacter pylori infection: the Maastricht III consensus report. *Gut* 2007;56:772-81.
8 Chey WD, Wong BCY. American College of Gastroenterology. Guideline on the management of Helicobacter pylori infection. *Am J Gastroenterol* 2007;102:1808-25.
9 Fock KM, Talley N, Moayyedi P, Hunt R, Azuma T, Sugano K, et al. Asia-Pacific consensus guidelines on gastric cancer prevention. *J Gastroenterol Hepatol* 2008;23:351-65.
10 Bazzoli F, Zagari RM, Pozzato P, Varoli O, Fossi S, Ricciardiello L, et al. Evaluation of short low-dose triple therapy for the eradication of Helicobacter pylori by factorial design in a randomized, double-blind, controlled study. *Aliment Pharmacol Ther* 1998;12:439-45.
11 Zagari RM, Bianchi-Porro G, Fiocca R, Gasbarrini G, Roda E, Bazzoli F. Comparison of 1 and 2 weeks of omeprazole, amoxicillin and clarithromycin treatment for Helicobacter pylori eradication: the HYPER study. *Gut* 2007;56:475-9.
12 Bazzoli F, Zagari RM, Fossi S, Pozzato P, Roda A, Roda E. Short-term low-dose triple therapy for the eradication of Helicobacter pylori. *Eur J Gastroenterol Hepatol* 1994;6:773-7.
13 Lamouliatte H. Adjuvant therapy for Helicobacter pylori eradication: role of lansoprazole in clinical studies. *J Clin Gastroenterol* 1995;20(suppl 1):S28-31.
14 Fuccio L, Minardi ME, Zagari RM, Grilli D, Magrini N, Bazzoli F. Meta-analysis: duration of first-line proton-pump inhibitor based triple therapy for Helicobacter pylori eradication. *Ann Intern Med* 2007;147:553.
15 Fischbach LA, Van Zanten SV, Dickason J. Meta-analysis: the efficacy, adverse events, and adherence related to first-line anti-Helicobacter pylori quadruple therapies. *Aliment Pharmacol Ther* 2004;20:1071-82.
16 Megraud F. H. pylori antibiotic resistance: prevalence, importance and advances in testing. *Gut* 2004;53:1374-84.
17 Megraud F. Update on Therapeutic options for Helicobacter pylori-related diseases. *Curr Infect Dis Rep* 2005;7:115-20.
18 Taylor JL, Zagari M, Murphy K, Freston JW. Pharmacoeconomic comparison of treatments for the eradication of Helicobacter pylori. *Arch Intern Med* 1997;157:87-97.
19 Murakami K, Okimoto T, Kodama M, Sato R, Watanabe K, Fujioka T. Evaluation of three different proton pump inhibitors with amoxicillin and metronidazole in retreatment for Helicobacter pylori infection. *J Clin Gastroenterol* 2008;42:139-42.
20 Fischbach L, Evans EL. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for Helicobacter pylori. *Aliment Pharmacol Ther* 2007;26:343-57.
21 Neri M, Milano A, Laterza F, Di Bonaventura G, Piccolomini R, Caldarella MP, et al. Role of antibiotic sensitivity testing before first-line Helicobacter pylori eradication treatments. *Aliment Pharmacol Ther* 2003;18:821-7.
22 Romano M, Marmo R, Cuomo A, De Simone T, Mucherino C, Iovene MR, et al. Pretreatment antimicrobial susceptibility testing is cost saving in the eradication of Helicobacter pylori. *Clin Gastroenterol Hepatol* 2003;1:273-8.
23 Toracchio S, Cellini L, Di Campli E, Cappello G, Malatesta MG, Ferri A, et al. Role of antimicrobial susceptibility testing on efficacy of triple therapy in Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2000;14:1639-43.
24 Vaira D, Zullo A, Vakil N, Gatta L, Ricci C, Perna F, et al. Sequential therapy versus standard triple-drug therapy for Helicobacter pylori eradication: a randomized trial. *Ann Intern Med* 2007;146:556-63.
25 Jafri NS, Hornung CA, Howden CW. Meta-analysis: sequential therapy appears superior to standard therapy for Helicobacter pylori infection in patients naive to treatment. *Ann Intern Med* 2008;148:1-10.
26 Moayyedi P. Sequential regimens for Helicobacter pylori eradication. *Lancet* 2007;370:1010-2.
27 Gisbert JP, Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after Helicobacter pylori treatment failure. *Aliment Pharmacol Ther* 2006;23:35-44.
28 Saad RJ, Schoenfeld P, Kim HM, Chey WD. Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent Helicobacter pylori infection: a meta-analysis. *Am J Gastroenterol* 2006;101:488-96.
29 Gisbert JP, Pajares JM. C-urea breath test in the diagnosis of Helicobacter pylori infection—a critical review. *Aliment Pharm Ther* 2004;20:1001-17.
30 Gisbert JP. The recurrence of Helicobacter pylori infection: incidence and variables influencing it. A critical review. *Am J Gastroenterol* 2005;100:2083-99
31 Rokkas T, Sechopoulos P, Robotis I, Margantinis G, Pistiolas D. Helicobacter pylori eradication rates by adopting regimens proposed by the Maastricht III consensus. *Helicobacter* 2007;12:A403.

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

European Helicobacter Study Group (www.helicobacter.org/)—One of the first international study groups on *Helicobacter pylori* infection and related diseases

Helicobacter Pylori Research Laboratory (http://www.hpylori.com.au/)—Homepage of Professor Barry Marshall, Nobel laureate for his research on *H pylori* infection

Resources for patients

Helicobacter Pylori Foundation (www.helico.com/)—Professor Barry Marshall's foundation dedicated to providing the latest information on the management of *H pylori* infection

Health Protection Agency. *Helicobacter pylori.* (www.hpa.org.uk/infections/topics_az/helicobacter/menu.htm)—Webpage that provides general information and guidelines for the management of *H pylori* infection