Current concepts in medicine

Helicobacter pylori

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Summary

***Helicobacter pylori* infection is a major cause of peptic ulcer disease, and its detection and eradication are now an important part of gastroenterology. Effective regimes are available which will eliminate the organism in about 90% of cases in developed countries.**

Keywords: *Helicobacter pylori*

Helicobacter pylori infection is very common, and affects about half the human race. It is more frequent and acquired earlier in life in poorer and less developed countries. *H pylori* is definitely associated with peptic ulcer disease.^{1 2} It is also regularly associated with antral gastritis, and in some patients the sequence of progression to intestinal metaplasia, dysplasia and carcinoma means that it is a cause of gastric antral carcinoma. However, the overall prevalence of carcinoma of the stomach has been falling for many decades. This has particularly been seen for carcinoma of the gastric antrum, though simultaneously there has been a rise in the prevalence of carcinoma of the proximal stomach and gastro-oesophageal junction. Not only are these latter conditions not caused by *H pylori*, this organism might even have a protective action. It is known that *H pylori* infection is a cause of localised gastric lymphoma (MALToma). Other postulated associations with ischaemic heart disease, migraine and gallstones are unproven and seem unlikely.

Tests for *H pylori*

Where gastroscopy is being undertaken, a convenient way of identifying the organism is by antral biopsy and direct urease testing. This involves immersing the biopsy in either urea solution or buffered urea gel (eg, CLO test) with an indicator. *H pylori* rapidly breaks urea down, generating ammonia, which raises the pH so the indicator changes colour to magenta. The best non-invasive test of active infection is the carbon-14 or carbon-13 urea breath test.^{3 4} This involves taking isotopically labelled urea by mouth and then measuring the excretion of labelled CO₂ in the breath. The distinction between infected and non-infected patients is very clear.

Formal serology using IgG ELISA testing is a satisfactory technique for demonstrating *H pylori* infection in patients who have not been treated. It is especially suitable for epidemiological surveys, but is no use at all for early assessment of effective treatment as it may take 6–12 months for antibody titres to fall or to disappear altogether.⁵

Biopsies taken at endoscopy can also be submitted to microscopy using Giemsa staining, silver staining or even haematoxylin and eosin. This is more cumbersome and no more accurate than urease testing, though histology will allow additional information to be obtained, such as the presence of dysplasia or lymphoma. Formal culture of organisms obtained by gastric biopsy is essential where antimicrobial sensitivity testing is to be undertaken. However, the organism is very fastidious and 10% of cultures will fail in patients known to be infected.

Polymerase chain reaction to identify bacterial DNA in gastric aspirates and biopsies has been used experimentally and certainly will increase the positive diagnostic rate. This technique is probably not suitable for general clinical use.

Not least of the tests for presence of *H pylori* is the demonstration of spontaneous duodenal ulceration. In patients who are not receiving drugs such as aspirin, non-steroidal anti-inflammatory agents (NSAIDs) and steroids, and who do not have hypercalcaemia or gastrinoma, it is the combination of acid in the stomach, *H pylori*, and other factors which leads to duodenal ulceration. An active spontaneous duodenal ulcer generally means current *H pylori* infection unless proved otherwise, though sometimes the causative problem is concealed aspirin or NSAID use.

Usefulness of treatment

There is now clear consensus that patients with spontaneous duodenal ulcers should be treated for *H pylori* infection. In gastric ulcers and where there are confounding factors in duodenal ulcers such as aspirin therapy, direct urease testing or urea breath testing may be required to help the decision on treatment. Benign gastric ulceration is less strongly associated with *H pylori* than duodenal

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Submitted 13 November 1998
Accepted 24 August 1999

First choice 1-week treatments for *H pylori* (lansoprazole and omeprazole are interchangeable in these regimes)

LCM

Lansoprazole 30 mg daily/
Clarithromycin 250 mg
bid/Metronidazole 400 mg bid

OAC

Omeprazole 20 mg bid/Amoxycillin 1 g
bid/Clarithromycin 500 mg bid

RBCCM

Ranitidine Bismuth Citrate 400 mg
bid/Clarithromycin 250 mg
bid/Metronidazole 400 mg bid

RBCAC

Ranitidine Bismuth Citrate 400 mg
bid/Amoxycillin 1 g bid/Clarithromycin
500 mg bid

LTCM

Lansoprazole 30 mg daily/Tetracycline
500 mg bid/Clarithromycin 250 mg
bid/Metronidazole 400 mg bid

Box 1

ulceration, possibly because of the role of NSAID use in causation. The presence of MALToma is the other unequivocal indication for eradication treatment.

Other uses of eradication therapy are contentious. There may be a role for such treatment in chronic dyspepsia treated with anti-secretory therapy over many years, where diagnostic tests for peptic ulceration may be unhelpful. In patients with a family history of gastric carcinoma eradication therapy may be indicated.

The role of eradication treatment in *H pylori* positive functional dyspepsia is contentious.⁶ There is no overall evidence of symptomatic benefit, however, and if it is used, patients must clearly understand that such use is experimental.

Although there is vast literature on different treatment schemes where it is desired to eradicate *H pylori*, it is often difficult to compare studies. There is a general agreement that some sort of anti-secretory treatment together with antibiotics is appropriate. Where proton pump inhibitor (PPI) therapy has been used, neither the dose nor duration of optimal therapy is unequivocal. Omeprazole has been used in a daily dose of 20 mg, 40 mg, and even more. Lansoprazole has been used in doses of 30 and 60 mg daily. There is less information about pantoprazole but this has been used in a dose of 40 mg daily. Rabeprazole is not yet licensed for eradication regimes in Britain. Histamine H2 receptor antagonists such as ranitidine can be used equally successfully.

The duration of PPI therapy in eradication regimes has been variable. Using these agents for one week may be sufficient to facilitate antibiotic eradication therapy, but it seems very likely that a 4-week course will be more effective in achieving rapid complete primary healing of ulcers. Treatment with ranitidine bismuth citrate in combination with antibiotics has been used for 1, 2, and 4 weeks.

The results of *in vitro* antimicrobial sensitivity testing have not translated well in clinical practice.⁹⁻¹⁵ Lansoprazole is more active against *H pylori* than omeprazole but this does not seem to be of importance in combination regimes. In the UK, *H pylori* is always sensitive to amoxycillin, but this is of very low efficacy when used on its own or in combination with omeprazole. There is some resistance to tetracycline and clarithromycin. However, clarithromycin is probably the best of the antibiotics used in treatment of *H pylori* infections, and regimes incorporating this agent have the best success rates. The question of metronidazole resistance is very problematic. It certainly may be an important factor in the developing world, where treatment failures are commoner, and also in migrants from these countries. However, even when apparent metronidazole resistance is demonstrated in micro-aerophilic culture, the organism is often eradicated by metronidazole-containing regimes. Some authors have proposed that *in vitro* metronidazole resistance is irrelevant at least in native Europeans.^{10 12 14} It is of some importance that when cultures are conducted with a short anaerobic phase, apparent metronidazole resistance largely disappears.^{10 12}

Different goals have been described for anti-*Helicobacter* therapy. Audit standards have been set variously at 80% for intention-to-treat results (Maastricht consensus meeting, 1996), or 90% for per-protocol treatment.^{1 2} *H pylori* eradication is probably equivalently demonstrated by direct urease test at endoscopy or urea breath testing.^{4 5} Where endoscopy is undertaken the healing or persistence of peptic ulceration provides another criterion of success. If PPI therapy is given for one week then primary ulcer healing is only seen in 80–85% of duodenal ulcer patients at one month, whereas a one-month course of PPI therapy should heal more than 90% of duodenal ulcers.

Although initially antibiotic and bismuth regimes were given for 2 weeks, a 1-week treatment with appropriate drug combinations is sufficient. Attempts to shorten treatment periods to less than 7 days have not, in general, been successful.

Treatment regimes

FIRST-LINE TRIPLE THERAPY²⁰⁻³¹

The best results currently available have been achieved with regimes which involve the use of a PPI and clarithromycin, together with either a nitro-imidazole or amoxycillin. Examples of these regimes include omeprazole 20 mg daily for one month, clarithromycin 250 mg bid for one week and tinidazole 500 mg bid (metronidazole 400 mg bid is equivalent) for one week.²² Another is lansoprazole 30 mg bid, amoxycillin 1 g bid and clarithromycin 500 mg bid, all given for one week.²⁹ A third simpler and cheaper scheme is lansoprazole 30 mg daily, clarithromycin 250 mg bid and metronidazole 400 mg bid, all given for one week. These schemes will all regularly achieve 90–95% eradication rates.

A useful alternative to PPI therapy is ranitidine bismuth citrate.³²⁻³⁹ This is really a compound of bismuth and ranitidine treatment, and it was hoped that it

Duodenal ulcer disease

- an additional 3 weeks on PPI therapy after anti-*Helicobacter* treatment will increase the early primary healing rate from 80–85% to 90–100%
- *Helicobacter* eradication rates and long-term outcome will probably be the same

Box 2

would both heal ulcers and give high rates of *H pylori* eradication. Regrettably, this proved to be untrue and it was found that additional antibiotics were required. The best results are obtained by using two antibiotics.^{35 36 38 39} Two regimes which can be recommended are ranitidine bismuth citrate 400 mg bid, clarithromycin 250 mg bid, and metronidazole 400 mg bid, all given for one week, or ranitidine bismuth citrate 400 mg bid, amoxycillin 1000 mg bid, and clarithromycin 500 mg bid, all given for one week.

FIRST-LINE QUADRUPLE THERAPY^{40–49}

Lansoprazole 30 mg daily, tetracycline 500 mg bid, clarithromycin 250 mg bid and metronidazole 400 mg bid have given some of the best available results with eradication rates over 95%.⁴⁰ Interestingly, similar regimes including amoxycillin are not so effective.

RESERVE TREATMENT

Triple therapy with a PPI, amoxycillin and metronidazole (eg, omeprazole 20 mg bid, amoxycillin 500 mg tid, and metronidazole 400 mg tid), has not lived up to its early promise.²⁰ Results do not consistently reach audit standards and it is quite common for patients to declare penicillin allergy as a reason for not being able to take the treatment, a problem with all amoxycillin-containing regimes. An interesting alternative scheme was a derivative of the old 'standard' triple therapy. This uses omeprazole 40 mg daily, bismuth chelate 240 mg bid, tetracycline 500 mg qid, and metronidazole 400 mg tid.⁴¹ Although this does give eradication rates of over 90% per protocol, it involves taking a lot of tablets and the high doses of bismuth and tetracycline required mean that patient tolerance is poor.

OBSOLETE TREATMENTS

In 1990 the World Congress of Gastroenterology consensus meeting in Sydney recommended 'standard triple therapy' with bismuth chelate, tetracycline or amoxycillin, and metronidazole for 2 weeks. Patients dislike this treatment because of problems with nausea, diarrhoea, pseudo-melaena and vomiting, and compliance is not good. The overall eradication rates initially proposed have not been confirmed and figures of 82–83% are probably more accurate.³⁸ This treatment is not used by modern British gastroenterologists.

It was hoped, on the basis of sensitivity testing, that simple dual therapy with omeprazole and amoxycillin or clarithromycin would be useful. However, neither of these combinations has proved to be acceptable. Overall, omeprazole and amoxycillin dual therapy yields about a 55% eradication rate, while omeprazole with clarithromycin 500 mg tid (which regularly causes patients to have a metallic taste in the mouth) achieves only an 80% success rate.

All these treatments have been superseded and they should not be used.

Outcome

Enthusiastic attempts at *H pylori* eradication have not been uniformly monitored to assess success. This partly explains why older regimes are still optimistically used. Since treatments are still in a developmental stage it seems a good idea to audit outcome in all patients either by urea breath testing or, if repeat endoscopy is required, by direct urease test. If formal anti-*Helicobacter* therapy has been given at least a year previously then serum IgG ELISA testing will often be helpful, though equivocal results are sometimes a problem.

Where tests indicate that anti-*Helicobacter* therapy has failed, it is useful to give a second and sometimes a third course of treatment. Although it seems logical to choose alternative regimes for this purpose, it may be that simply repeating the initial regime will actually achieve the same result.

Once eradication has been proven, re-infection in adults in developed countries is very uncommon and probably occurs at a level of about 1% per year.⁸ Peptic ulcer relapse will occur at a higher rate than this because of the problem of iatrogenic ulcers related to aspirin and NSAIDs.

The future

Although there have been some remarkable changes in gastroenterology in the *H pylori* age since 1983, more developments may be expected. Attempts are being made to develop a vaccine. If successful, and administered universally to children, this would avoid peptic ulcer and probably reduce the prevalence of gastric antral carcinoma. It could be useful in treatment of adults infected with *H pylori*. Another specific antigen test of active infection is being evaluated (HpSA), but has the disadvantage of requiring a stool sample.

There is a great need for better antibiotics, preferably specific for *H pylori*, which could be used alone and thus avoid the drawbacks of combination therapy. These include interference with bacterial flora and the occasional precipitation of pseudomembranous colitis.

There is a heated debate about whether the only good *Helicobacter* is a dead one. Since the prevalence of gastric antral carcinoma is falling anyway, it is very unlikely that it could be proved that eradication of *H pylori* made any difference overall. Treatment is not without risk. In addition to gastrointestinal side-effects of therapy and the problems of induced antibiotic resistance by wide use of these agents in the community, it is clear that some patients have worse dyspeptic symptoms after treatment than before. There is an increased prevalence of heartburn and actual reflux oesophagitis which has led to some dissatisfied patients. Anti-*H pylori* treatment must not be promoted as a cure-all for dyspepsia, and for the present its use should mainly be restricted to patients with peptic ulcer disease, where we can be confident of curing most patients.

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