Clinical review

Regular review

Treatment of *Helicobacter pylori* infection

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The bacterium *Helicobacter pylori* can infect the stomach during childhood and cause lifelong chronic gastritis, which can lead to peptic ulcer disease. Curing *H pylori* infection cures ulcer disease.[1–5] And since reinfection in adults is extremely rare,[6] adequate treatment permanently cures this former chronic recurrent, serious disease. If ulcers do not recur neither do ulcer perforation or bleeding; quality of life increases,[7] sick leave decreases, and less money is spent on visiting the doctor and drugs.

Antibiotic resistance needs to be taken into account when designing treatment for *H pylori* infection.[8] Over the past decade many different therapies were promoted and recommendations changed rapidly. Most doctors lost track, and a great variety of treatments is being used.[9] In this article we will try to provide a basic framework on which treatment can be based.

Summary points

- The therapeutic goal is to cure *H pylori* infection in all ulcer patients
- Several equally effective regimens are available, but even the best fail in 5-20% of patients
- Antibiotic resistance is usually induced after failure, and initial regimens should not compromise future therapeutic possibilities
- Doctors should choose two complementary regimens, which if used consecutively come close to 100% cure
- Treatment should start with a regimen based on clarithromycin with a back up regimen based on metronidazole unless resistance is above 15%, in which case the order should be reversed
- Triple regimens which combine clarithromycin and metronidazole should not be used as there is no valid empirical back up regimen after failure

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Methods

This article is based largely on our experience in treating *H pylori* infection. We base our recommendations on basic bacteriological principles and on a regularly updated in-house computer database that contains the results of all published therapeutic studies.

Who should be treated?

Treatment to eradicate *H pylori* in patients with a proved ulcer is cost effective and benefits the patient and society.[10] All patients with a history of ulcers, who often use acid suppressants on demand, therefore need to be identified and treated.[3] Whether patients without ulcers benefit from antibiotics is unclear. Empirical antibiotic treatment has been suggested for dyspepsia in order to cure all patients with "hidden" ulcer.[11] In populations with a high incidence of ulcer disease it might be cheaper to prescribe antibiotics to all dyspeptic patients positive for *H pylori* than to investigate all dyspeptic patients to identify those with ulcers.

Selecting a regimen

An evidence based choice of treatment is impossible because we lack large randomised trials comparing the highly effective regimens.[4 8 9 11-13] Dual treatment with proton pump inhibitors is now obsolete due to lack of efficacy. Several triple or quadruple therapies have been sufficiently investigated and seem to be able to cure either 80% (intention to treat) or 90% (per protocol) of patients. The table shows currently useful treatments, but none has surfaced as the final treatment of choice. Metronidazole (or tinidazole) and clarithromycin are the two key antibiotics. Antibiotic resistance against these two drugs, either primary or induced after treatment, is clinically important.[8]

Dual treatments

Dual treatments combining a proton pump inhibitor with either amoxicillin or clarithromycin were popular a few years ago as they were easy to explain and well tolerated. They have now been abandoned because they were not very effective. The newer regimen of 14 days' treatment with ranitidine bismuth citrate plus clarithromycin is effective and has few side effects. In randomised trials it was superior to other dual treatments.[14–16] It is easy to take and therefore attractive for general practice.

Table 1 Treatment regimens which have been repeatedly shown to be effective in eradicating *H pylori*

Length of treatment (days)	Component drugs			
Regimens based on clarithromycin				
14	Ranitidine bismuth citrate 400 mg twice daily	Clarithromycin 500 mg twice daily		
7-10	Ranitidine bismuth citrate 400 mg twice daily	Amoxicillin 1000 mg twice daily	Clarithromycin 500 mg twice daily	
7-10	Proton pump inhibitor twice daily	Amoxicillin 1000 mg twice daily	Clarithromycin 500 mg twice daily	
Regimens based on metronidazole (or tinidazole)				
14	Bismuth compound 4 times/day	Tetracycline 500 mg 4 times/day	Metronidazole 400-500 mg 3-4 times/day	
7-10	Proton pump inhibitor twice daily	Amoxicillin 500 mg 2-3 times/day	Metronidazole 400-500 mg 2-3 times/day	
4-7	Proton pump inhibitor twice daily	Colloidal bismuth subcitrate 4 times/day	Tetracycline 500 mg 4 times/day	Metronidazole 400-500 mg 3-4 times/day
Regimens based on clarithromycin plus metronidazole (or tinidazole)				
7	Ranitidine bismuth citrate 400 mg twice daily	Clarithromycin 500 mg twice daily	Metronidazole 400-500 mg twice daily	
7	Proton pump inhibitor twice daily	Clarithromycin 500 mg twice daily	Metronidazole 400-500 mg twice daily	

Triple treatments

Triple treatment with a bismuth compound, tetracycline (or amoxicillin), and metronidazole is cheap and well investigated.[2 4 5 7-9 11 13] It may cause side effects, but these are usually not severe and have not led to non-compliance in trials.[17 18] It reaches high cure rates in metronidazole sensitive strains after seven days[2 8] but requires 14 days to eradicate a substantial percentage of resistant strains.[2 8 18] This regimen is widely used in cost sensitive markets, but even in the United States it is still popular.[19]

Bismuth triple therapy has mainly been surpassed by seven day triple regimens using proton pump inhibitors; these combine omeprazole, lansoprazole, or pantoprazole with two antibiotics. Most studies use the antibiotics twice daily. There is some evidence that the optimal dose is 20 mg twice daily for omeprazole, 30 mg twice daily for lansoprazole,[20] and 40 mg twice daily for pantoprazole.[21] The appropriate antibiotics are metronidazole (or tinidazole), amoxicillin, and clarithromycin. Several guidelines recommend proton pump inhibitor triple regimens as first line treatment.[4-6 11] Proton pump inhibitors are most commonly combined with amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily. This regimen has fewer side effects then other triple regimens,[22] but it is only moderately effective in clarithromycin resistant strains and secondary resistance is usually induced when treatment fails.

Proton pump inhibitors are sometimes combined with amoxicillin and metronidazole twice or thrice daily. This regimen is only moderately effective in metronidazole resistant strains over seven days.[8 18 23 24] In areas with a high prevalence of resistance treatment should be increased to 10 or 14 days.[18] Regimens combining proton pump inhibitors with metronidazole 400 or 500 mg and clarithromycin 250 mg or 500 mg twice daily are less effective in patients with primary metronidazole or clarithromycin resistance.[22 24 25] If treatment fails the regimen may induce resistance against one or both of the antibiotics used in this regimen.

A new group of triple regimens has been developed that replaces proton pump inhibitors with ranitidine bismuth citrate. These produce less acid suppression but provide the additional antimicrobial action of bismuth. In most patients with sensitive strains replacing proton pump inhibitors with ranitidine bismuth citrate will not increase efficacy, but it might prevent induction of resistance when treatment fails. The cure rate may also be improved in patients with resistant strains, although a very large study will be needed to prove this. So far no clinically important differences have been found in randomised trials directly comparing triple regimens with proton pump inhibitors and those with ranitidine bismuth citrate.

Quadruple treatments

Addition of acid suppressants increases the efficacy of bismuth triple regimens.[26] Quadruple treatment is more effective with proton pump inhibitors then with histamine-2 receptor antagonists[17] and when tetracycline and metronidazole are incorporated. In meta-analyses the quadruple regimen had the highest cure rates,[5 6 12] but it is also the most complicated regimen with the greatest number of tablets each day. Nevertheless, studies have found good compliance, with a drop out rate comparable with that of the easier triple therapies.[17] A course of seven days seems to cure both metronidazole sensitive and resistant strains; sensitive strains are eradicated in four days.[8] The high cure rate at day 4 shows its potency and wide therapeutic window.

Second line treatment

Eradication is more difficult with second line treatment,[27] and repeated regimens might need to be prolonged. Some bacteria can be killed easily (steep kill curve) and other bacteria are more difficult to kill. During treatment the substrains with the steepest kill curve will disappear first. The bacteria that are the least susceptible remain if treatment fails. Bacteria of this "difficult to kill" substrain then increase their numbers and repopulate the stomach. Moreover such remaining strains may also have become resistant against one or both key antibiotics.[28] For obvious reasons patients who do not comply with treatment are overrepresented among those whose treatment fails. These factors may explain the lower cure rates with retreatment. Some authors have reported that in some patients the infection cannot be eradicated,[27] but in our experience this is rare.

Quadruple regimens have been suggested as the optimal second line treatment.[11] Although they have been used successfully after failure of regimens containing clarithromycin,[29-32] results after regimens containing metronidazole were disappointing.[33 34] The large number of "difficult to kill" *H pylori* which have also become resistant to metronidazole is giving concern. This shows that there is as yet no ideal second line treatment.

Logical framework for treatment

If initial antibiotic treatment fails, another attempt must follow and if necessary a third or fourth until the infection is cured in 100% of cases. Ideally follow up treatment should be guided by susceptibility data, but this information is often unavailable. No ulcer patient should be discharged until there is documented proof by endoscopy, breath test, or six month follow up serology that *H pylori* is eliminated.[35] None of the regimens in the table is inferior or superior to another. Even the best regimens fail in 5-20% of cases. We therefore need to focus on what we have to offer to those who are not cured. Since treatment to eradicate *H pylori* is increasing, the number of failures will rise and be of increasing clinical importance. Many of these patients will be referred for specialist care.

The choice of a second line treatment depends on which treatment was used initially. If a clarithromycin based regimen was used a metronidazole based regimen should be used afterwards, and vice versa (fig 1). It seems unwise to use the same antibiotic twice. Doctors should choose a set of two treatment regimens that complement each other and which if used consecutively come close to the desired 100% cure.

The first choice should not be a regimen that combines clarithromycin and metronidazole. Although this regimen is very effective, patients who are not cured will have at least single, and usually double, resistance,[33 34 36 37] and no logical empirical treatment remains afterwards. This is particularly important in areas with a high prevalence of primary metronidazole resistance, where more treatment failures and thus more double resistance will occur.[37] Double resistance could become a serious clinical problem. Endoscopy with culture and susceptibility testing is therefore essential after these regimens in all patients, and especially in patients with positive breath test results, to select further options.

If instead the initial treatment uses either metronidazole or clarithromycin combined with another antibiotic the choice of second line treatment is clear from the beginning and does not depend on culture results. An easier and cheaper follow up schedule can therefore be used with these regimens.[35] Culture and susceptibility testing are required only after a failed second attempt to select a third line treatment (fig 1).

Future trials are needed to study consecutive combinations of treatments. Authors must focus on reporting antimicrobial susceptibility before and after treatment[8 28] and on finding the optimal complementary "back up" regimen to their initial treatment.

Recommendations for treatment

Local (geographical) prevalence of antimicrobial resistance will determine whether it is better to start with a regimen based on clarithromycin or one based on metronidazole.[8 28] Presently clarithromycin resistance is below 10% in most populations. Treatment can therefore usually start with a regimen based on clarithromycin with a seven day quadruple regimen (proton pump inhibitor, bismuth, tetracycline, and metronidazole) as second line treatment (fig 2). Different antibiotics are used in subsequent attempts, and two prospective studies show over 98% overall cure

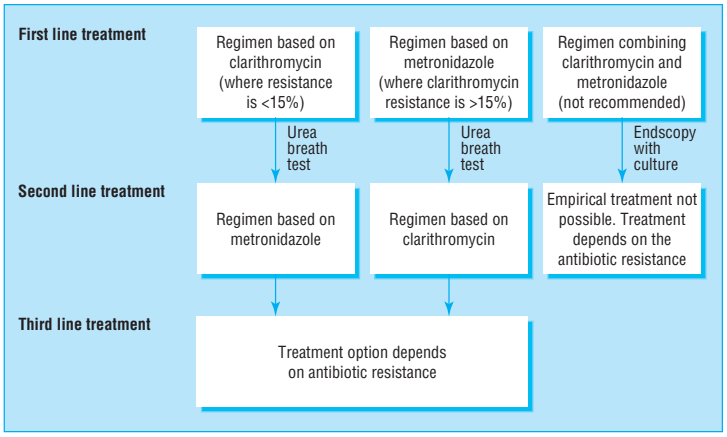

Fig 1 General principles of treatment to eradicate *H pylori*

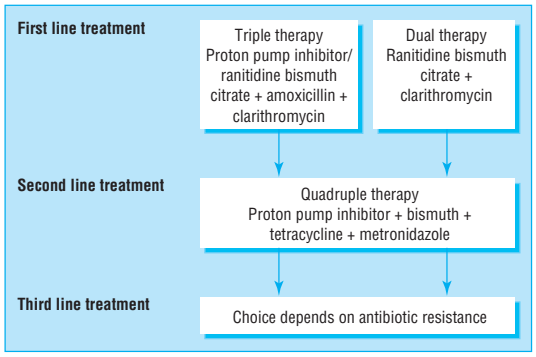

Fig 2 Recommended treatment strategy in areas with low primary prevalence of clarithromycin resistance

with this approach.[31 32] Ranitidine bismuth citrate plus clarithromycin is used for patients with penicillin allergy. Regimens based on metronidazole should be used first if clarithromycin resistance is over 15%. Triple regimens using metronidazole are less effective in primary metronidazole resistant strains,[8 18 23 24] but the quadruple regimen seem to perform well.[8 26] It can therefore be used in almost all populations, and we recommend the quadruple regimen as first line treatment when clarithromycin resistance is a problem. Metronidazole based triple regimens can, however, safely be used in areas with a low prevalence of metronidazole resistance.

Regimens containing both clarithromycin and metronidazole are no more effective than regimens with only one of these antibiotics. Because of problems with resistance we suggest that both key antibiotics should not be used together until a valid empirical back up regimen is available.

In general the likelihood of cure can be increased by increasing the length of treatment. Although seven day treatment is standard for proton pump inhibitor and ranitidine bismuth citrate triple regimens, the success rate can be improved by prescribing a 10-14 day course in patients who have had previous failure or in whom the consequence of failure could be life threatening—for example, patients presenting with complications of ulcer such as bleeding.

Competing interests: Both authors have received funding for speaking or research projects from many different pharmaceutical companies producing some of the drugs mentioned in this paper.

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Obtaining the correct information

The carer of a middle aged man with schizophrenia alerted one of our community nurses that he had had a relapse. Among other symptoms, he was reported to have been receiving information from his salad cream and had stopped attending his day centre. He lived in a private residential care home but had a considerable forensic history and had lived in a special hospital for many years in his youth. More recently, his mental health had improved substantially, and he was free from psychotic symptoms, receiving regular antipsychotic depot injections. During previous relapses, however, he had stopped eating pork as he believed that it made his hair blue and he had killed a cat as he felt it was infesting him with fleas. I immediately arranged a home visit, fearing that he was experiencing delusions or hallucinations and could possibly be dangerous.

When I arrived at his home, I discovered him relaxing in the lounge watching television, and he was surprised at my visit. I found that I had to listen very carefully to understand his speech due to his strong accent and lack of teeth. He explained that he had felt unwell recently because of a bout of diarrhoea and because of this he had stopped attending the day centre. I examined his mental state and inquired at some length about any abnormal experiences. He answered in the negative to all questions. Finally, I mentioned the salad cream. He stated that it caused him inflammation that was responsible for his diarrhoea. I asked if he meant information as suggested by his carer. He laughed and said we had got it all wrong. After a change of diet to eliminate salad cream and potatoes (the other ingredient he identified as harmful), and an increased number of curries (his favourite food), he was free from inflammation and diarrhoea. At one month follow up he experienced no psychotic symptoms and was regularly attending his day centre.

Robert Chaplin *consultant psychiatrist, London*

We welcome articles of up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.