Antimicrobial Treatment of *Helicobacter pylori* Infection

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*Helicobacter pylori* is susceptible to many antimicrobials, but clinically only a few are effective. Two antimicrobials with bismuth or ranitidine or a proton pump inhibitor such as omeprazole are required to achieve a cure rate of >90% and to avoid resistance, which occurs when clarithromycin or metronidazole is the single antimicrobial used. Bismuth plus metronidazole and tetracycline is effective but causes more side effects than does treatment with omeprazole, amoxicillin, and clarithromycin; metronidazole can replace clarithromycin. To ensure a high cure rate, treatment is required for 10 days, but 7-day regimens have sometimes been as successful. A course of ranitidine bismuth citrate for 28 days, given with clarithromycin for the first 14 days, cures 80%–85% of patients, but given with amoxicillin it cures only 74%. In developing countries resistance to metronidazole can reach 95%. An inexpensive regimen is bismuth subsalicylate (two tablets) plus furazolidone (100 mg), four times daily for 4 weeks; however, as this yields a cure rate of only 72%, this regimen is not truly cost-effective.

Although *Helicobacter pylori* is susceptible in vitro to a wide range of antibiotics, in clinical practice only a smaller range of antibiotics have been found to be effective, and two antimicrobials are required to achieve a cure rate of >90%. Some antimicrobials are effective in the normal acid stomach, but others are much more effective when the stomach pH is raised by an acid-reducing drug. *H. pylori* never becomes resistant to some of the clinically active antimicrobials, but it can easily become resistant to others, especially if they are given as single drugs—which is as unwise and unethical as the prescription of one antimicrobial to cure *Mycobacterium tuberculosis* infection.

**Laboratory Tests to Determine the MIC of Antimicrobials Against *H. pylori***

Probably the best method of determining the MICs is the Epsilometer test (Etest; AB BIODISK, Solna, Sweden) [1]. This is a plastic strip containing a predefined continuous and exponential antibiotic gradient of one antibiotic, with various concentrations clearly labelled on the strip. The MIC scale usually covers 15 twofold dilutions, and the strip is placed in the middle of an agar plate that has been inoculated with an isolate of *H. pylori*. After incubation, an elliptical zone of inhibition is seen, with the base at the lowest MIC. This test is usually very easy to read and has been found to be as accurate as the usual reference method—serial dilutions of an antibiotic in agar and inoculation of the agar plate with a standard concentration of *H. pylori*. However, clarithromycin is so active against most strains of *H. pylori* that even the lowest concentration on the Etest strip often produces a very wide zone of inhibition, so only the bottom third of the strip should be placed on the plate to enable reading of the result.

**Development of Resistance to Antimicrobials by *H. pylori***

*H. pylori* readily becomes resistant if any of the following is given as a single antimicrobial: metronidazole or tinidazole [2], ciprofloxacin or rifampin [3], and macrolides such as clarithromycin or azithromycin [3]. Resistance occurs less frequently when clarithromycin is given with omeprazole ([4] and see below). Therefore, none of these drugs should be given as the sole antimicrobial agent to cure infection; each must always be combined with another antibiotic. The resistance rate for each of these antimicrobials should be determined in each geographical area and also among different ethnic groups to guide clinical practice. Clinically effective antibiotics to which *H. pylori* has not demonstrated resistance are bismuth salts, amoxicillin, tetracycline, nitrofurantoin, and furazolidone.

**Raising the pH in the Stomach**

When acid-suppressing drugs are not coprescribed, antimicrobials that work in an acid environment should be given: bismuth salts and nitroimidazoles (metronidazole, tinidazole) and also tetracycline, nitrofurantoin, and furazolidone, whose activity is only slightly impaired in acid conditions [5]. Susceptibility tests of *H. pylori* conducted between pH levels of 5 and 8 showed that there was a 10-fold decrease in the activity of ampicillin and ciprofloxacin at pH 5 compared with that at pH 8 [5]. Thus, amoxicillin, macrolides such as clarithromycin and azithromycin, quinolones such as ciprofloxacin, and rifam-
pin are best prescribed with a proton pump inhibitor (PPI)—omeprazole, lansoprazole, or pantoprazole—or an H2-receptor antagonist such as ranitidine. These acid-suppressing drugs should be given at least twice a day to achieve maximum benefit [6]. Ranitidine is usually given as 300 mg twice daily, but 150 mg twice daily may be as effective. One study of ranitidine plus clarithromycin and metronidazole (involving only 24 patients, however) achieved a 98% cure rate of *H. pylori* infection [7].

### Bismuth Compounds

The first effective therapy that cured >90% of patients was colloidal bismuth subcitrate (CBS; Denol) (120 mg thrice daily) plus tetracycline (500 mg thrice daily) (not doxycycline) and metronidazole (400 mg thrice daily) for 2 weeks [8]. Amoxicillin in place of tetracycline was equally effective, with no reinfection occurring after 1 year [9]. Use of bismuth subsalicylate (Pepto-Bismol, Procter & Gamble, Cincinnati; 524 mg q.d.s.) in place of CBS yielded equally high cure rates. All of these are cheap regimens, but side effects are more frequent than with later therapies such as with omeprazole, clarithromycin, and amoxicillin. Side effects can lead to a drop in compliance and a drop in cure rate, so these consequently are not more cost-effective.

Probably a regimen that involves more than three doses per day is less likely to be acceptable. However, in Australia, in a study of patients who had not been cured by bismuth, tetracycline, and metronidazole, Borody achieved a cure rate of 97% among 125 patients treated five times a day with CBS (120 mg) plus tetracycline (250 mg) and metronidazole (200 mg) and twice daily treatment with omeprazole (20 mg) [10].

### Nitroimidazoles

Variations are found in the rates of resistance, particularly to the nitroimidazoles [3]. In developing countries metronidazole is used extensively to treat gastroenteritis, and strains of *H. pylori* in these countries, or from immigrants from these countries, often show 80%–90% resistance to nitroimidazoles [3]. The resistance rate of *H. pylori* strains from women who have been prescribed metronidazole for vaginal trichomonas infection may be up to 30% [3]. In a recent French study the resistance rate was 50% [11]. However, even when strains were resistant to metronidazole in vitro, a combination of omeprazole, metronidazole, bismuth, and tetracycline given to 165 patients achieved a cure rate of 97.6% [10]. Metronidazole and tinidazole are cheaper than clarithromycin but cause more side effects, usually mild.

### Macrolides

Erythromycin causes abdominal symptoms more frequently than do the newer macrolides, clarithromycin and azithromycin. In Leeds, United Kingdom, among 122 patients given omeprazole (20 mg), erythromycin (250 mg), and tinidazole (500 mg), all thrice daily for 7 days, the cure rate was 86% [12]. A second study, of omeprazole (20 mg once a day) plus erythromycin and tinidazole given to 90 patients yielded a cure rate of 89%. Apparently, all infections with metronidazole-resistant strains were cured [12].

The MIC of clarithromycin for *H. pylori* is 0.03 mg/L, and the concentration of clarithromycin in the stomach is higher when omeprazole is coprescribed. When clarithromycin was given as a single drug without omeprazole, the rate of acquired resistance was 20% [4], but when it was combined with omeprazole, the acquired resistance rate was only 5% [4]; this has also occurred with azithromycin [13]. It is irresponsible to use clarithromycin or azithromycin as the only antimicrobial, even with omeprazole, because this will result in resistant strains of *H. pylori* in the local area, and patients who acquire these resistant strains will not be able to be treated with these macrolides. Thus, when a macrolide is prescribed, another antimicrobial such as metronidazole or amoxicillin must always be given, in addition to omeprazole to raise the pH level in the stomach (see below). When prescribed for 10 days for compliant patients, a combination of omeprazole, clarithromycin, and amoxicillin achieved a cure rate of >90% [4].

In Al Ain, United Arab Emirates, 102 patients were given omeprazole (20 mg), clarithromycin (250 mg, to reduce the frequency of metallic taste), and amoxicillin (500 mg), all thrice daily (for simplicity and to allow for the omission of an occasional dose) for 10 days. An explanation sheet in both English and Arabic was read to each patient. The cure rate was 95%, and the reinfection rate after 1 year was 4% (C.S. Goodwin et al., unpublished data).

### Quinolones and Rifampin

The MIC of most quinolones against *H. pylori* is low, but when ofloxacin was given as monotherapy, resistance among *H. pylori* isolates became apparent very rapidly, with cross-resistance to the other quinolones [14]. Although quinolones may be highly effective when given in combination with another antibiotic plus a PPI, clinical studies of a quinolone combined with another antimicrobial have not yet been reported.

When rifampin was given as monotherapy, resistant strains were isolated from three of eight patients [15]. No clinical studies in which rifampin has been combined with another antimicrobial and a PPI have been reported.

### Ranitidine Bismuth Citrate and Sucralfate

Ranitidine bismuth citrate (RBC) is a new compound. Preliminary reports indicate that RBC given for 28 days and clarithromycin (500 mg twice daily) given for the first 14 days produced a cure rate of 80%–85% [16]. Two small studies have shown that RBC (800 mg b.d.) with amoxicillin (500 mg
q.d.s.) given for 14 days, followed by 14 days of RBC (400 mg b.d.), yielded a cure rate of 74% [17]. One study of sucralfate (1 g 4 times a day for 4 weeks) plus clarithromycin and metronidazole (250 mg and 300 mg, 4 times a day for 2 weeks), given to 35 patients, resulted in a cure rate of 86% [18].

Furazolidone and Bismuth Subsalicylate

Among 25 patients given furazolidone (100 mg four times daily) plus metronidazole (400 mg thrice daily) and amoxicillin (500 mg thrice daily), the cure rate was 72% [19]. However, the use of furazolidone is confined to developing countries, where metronidazole resistance is very high and the cheapest regimen is required. Although the cheapest medication is bismuth subsalicylate (two tablets four times a day) plus furazolidone (100 mg four times a day), the fact that administration of both for 4 weeks produced a cure rate of only 72% means that this is an expensive regimen.

Reliability of Reports of Therapy

To ensure that its results will reliably guide other investigators and practitioners, a study should probably include at least 100 patients. It is well known that among the first 50 or 70 patients a high cure rate may be achieved, but in the next 20 or 30 patients more failures of therapy are often detected. Second, there must be a reliable assessment of cure. Antimicrobial treatment must have been stopped for at least 4 weeks but preferably 6 weeks before testing, and use of a PPI should have ceased at least 4 days before the test. The rapid biopsy urease test is unreliable to assess cure after treatment. Two samples from the antrum and one or two from the fundus must be taken for histology. For culture the same number of samples is required, and the plates must be incubated for 10 days.

If the urea breath test is used to measure cure of the infection, it should probably be performed with multiple samples collected in a bag, from which one sample is taken for measurement of labelled carbon breath; the times of collection, after ingestion of the urea, in an unfasted patient should be after 20, 30, and 40 minutes, and in a fasted patient after 10, 20, and 30 minutes.

Among 706 patients in Birmingham, United Kingdom, who were given omeprazole (20 mg b.d.), amoxicillin (500 mg t.d.s.) and metronidazole (400 mg t.d.s.) for 7 days, the cure rate was 85%. Side effects—mainly loose motions and headaches—occurred in 42% of patients [20]. This suggests that a cure rate of >90% would require treatment for 10 days. A second study in Birmingham of 159 patients receiving 2 weeks of treatment with CBS (120 mg q.d.s.), metronidazole (400 mg t.d.s.), and tetracycline or amoxicillin (500 mg t.d.s.) gave a cure rate of 78%, and side effects occurred in 19% [20]. The latter triple therapy with tetracycline has given higher cure rates of >90% [8] but seems less reliable than regimens with a PPI in place of bismuth.

Possible Reasons for Failure of Therapy

When omeprazole is given and the stomach pH is raised, other bacteria colonize the stomach, and if some of these have a β-lactamase enzyme, then amoxicillin when used as the sole antimicrobial will be destroyed. Moreover, within any one patient there may be more than one strain of H. pylori in the stomach, and among these strains there may be variations in antimicrobial resistance. Ciprofloxacin binds to polyvalent cations, and therefore absorption is reduced by antacids containing magnesium or aluminum [21]. The formulation of a drug as tablet, liquid, or colloidal granules can also alter its effectiveness. Some drugs such as amoxicillin may be more effective when given before meals. However, compliance is probably the most important factor associated with a high cure rate of H. pylori infection. Carefully explaining the treatment method to every patient is the only way to achieve a high cure rate, especially when a regimen is liable to cause side effects.

Drug Interactions

Clarithromycin raises the blood concentration of carbamazepine [22] and digoxin [23], and these effects must be taken into account when clarithromycin is given.

Conclusion

Currently, the regimen that will achieve the best patient compliance and therefore the highest cure rate is a combination of three drugs, amoxicillin (either 500 mg t.d.s. or 1,000 mg b.d.) plus clarithromycin (either 250 mg t.d.s. or 500 mg b.d.) plus either omeprazole (20 mg b.d. or t.d.s.) or ranitidine (300 mg b.d. or t.d.s.), all for 10 days. To ascertain if the infection is cured, the urea breath test performed 6 weeks after the end of therapy is highly accurate and is noninvasive.

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References


