Practical advice on eradicating *Helicobacter pylori* infection

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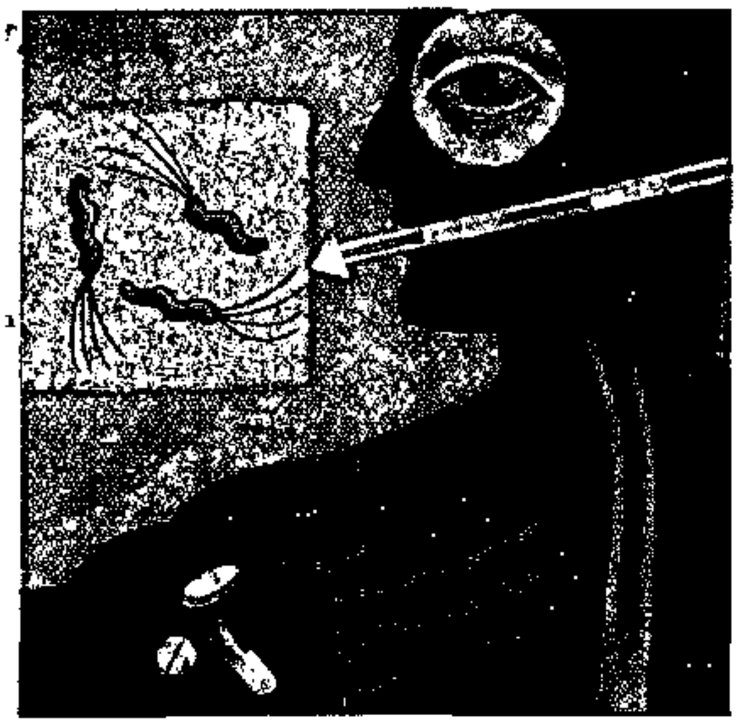
PREVIEW

The days of putting patients with ulcers on a diet of bland food and antacids are past. Today, curing ulcers is simply a matter of eradicating *Helicobacter pylori* infection. Or is that really a simple matter? The authors summarize combination regimens that have been found to be most effective against the organism and discuss what to do when such treatment fails. They also discuss issues to consider in preventing drug resistance, and they provide tips on improving patient compliance, which is vital to successful treatment.

The link between *Helicobacter pylori* infection and ulcer is universally accepted. Diagnosis of uncomplicated ulcer disease is straightforward and inexpensive, and effective therapies are available to cure the infection and heal the ulcer.[1-3] Current thinking in diagnosis and treatment of patients presenting with dyspepsia (figure 1) is that testing for *H pylori* infection should be performed only when the intention is to fully treat it if it is detected. Patients with peptic ulcer disease have clinical improvement after anti–*H pylori* therapy, but this is not necessarily true of patients with nonulcer dyspepsia or gastroesophageal reflux disease. Patients with nonulcer dyspepsia should be warned that treatment cures the infection but may not relieve symptoms.



Management objectives that define the current standard of care are to relieve pain, eliminate maintenance therapy, remove the possibility of recurrence, avoid complications of the disease and its treatment, and prevent development of drug resistance. The following key principles may be useful for primary care physicians who treat patients with peptic ulcer disease:

- Persistent symptoms despite appropriate anti–*H pylori* therapy suggest a cause other than *H pylori* infection.
- Testing for the presence of *H pylori* is mandatory if duodenal ulcer disease is found endoscopically or radiologically.
- In most cases, cure of *H pylori* infection results in cure of peptic ulcer disease (assuming that nonsteroidal anti-inflammatory drugs [NSAIDs] are not being used).
- Long-term antisecretory therapy at maintenance doses may be appropriate in patients with recalcitrant *H pylori* infection or persistent symptoms.

Antacids

Antacids, which can provide pain relief and be obtained without a prescription, were once first-line agents in ulcer care. However, since the advent of histamine$_2$ (H_2) receptor antagonists, many of which are also available without prescription, traditional antacids are considered outmoded in treatment of peptic ulcer disease.

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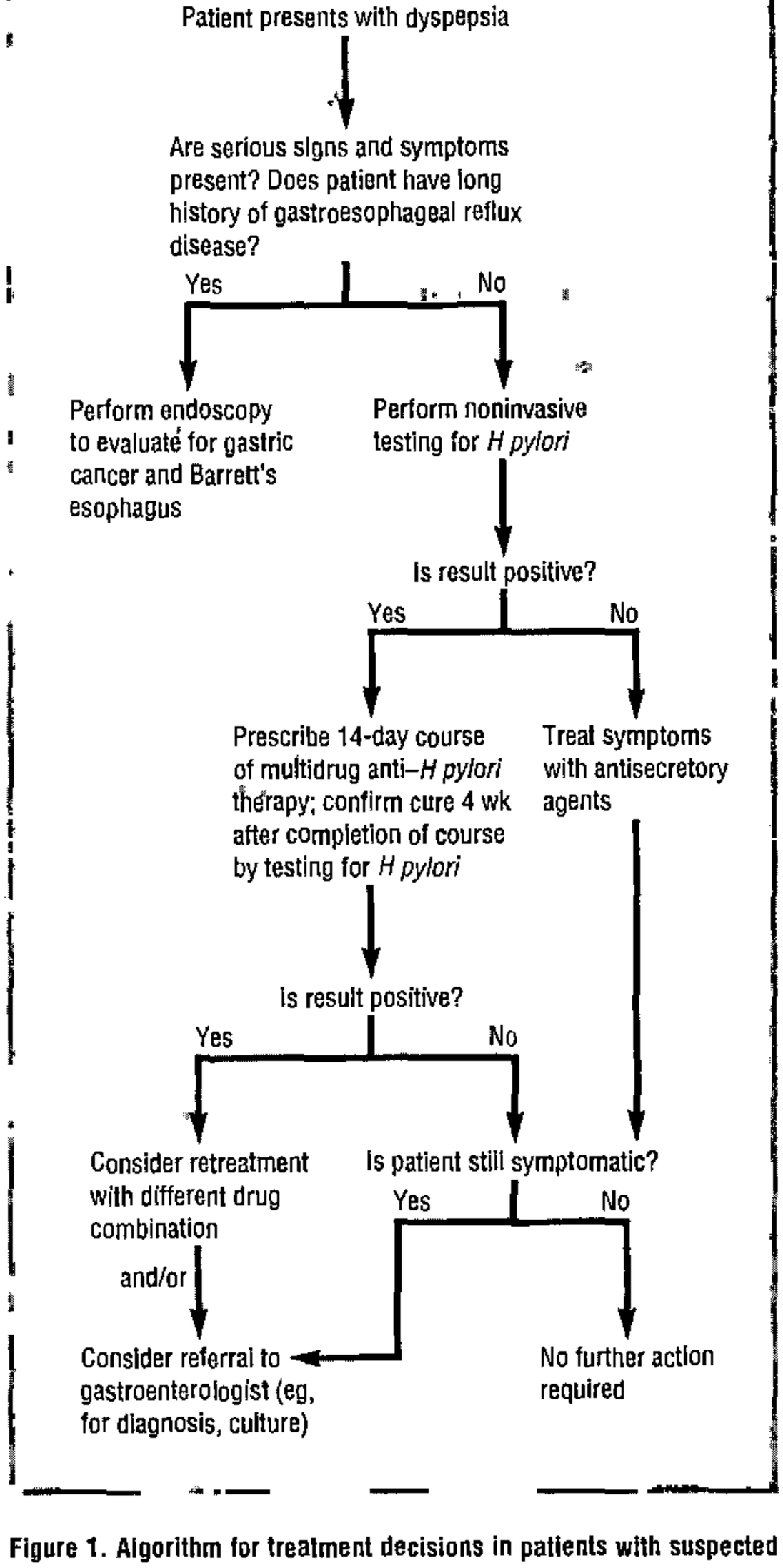

Figure 1. Algorithm for treatment decisions in patients with suspected peptic ulcer disease associated with *Helicobacter pylori* infection.

H_2 receptor antagonists

Cimetidine (Tagamet), famotidine (Pepcid), nizatidine (Axid Pulvules), and ranitidine (Zantac) reversibly inhibit histamine action on the H_2 receptor of the gastric parietal cell. The agents differ in potency and adverse effect profile but not in overall efficacy. The practice of giving the full daily dose with or after the evening meal or at bedtime when therapy is being used to heal an active ulcer is widely accepted. The daily dose is 800 mg for cimetidine, 40 mg for famotidine, and 300 mg for nizatidine and ranitidine. Larger doses increase efficacy in only small increments.

Proton pump inhibitors

Proton pump inhibitors block the action of the hydrogen-potassium-adenosine triphosphatase enzyme, which operates the gut's proton pump, by exchanging hydrogen for potassium across the microvillus membrane. Omeprazole (Prilosec) and lansoprazole (Prevacid) inhibit hydrogen ion secretion from the gastric parietal cells and are the most effective antisecretory agents available. Unlike H_2 receptor antagonists, proton pump inhibitors have direct anti–*H pylori* activity and may be the better choice when combination therapy includes an antibiotic that has reduced effectiveness in acidic environments.[4]

Antimicrobial agents and dosages

H pylori is a gram-negative bacterium; thus, use of antimicrobial agents is critical in curing the infection. Antimicrobial agents used in *H pylori* therapy that have a definite systemic effect include amoxicillin (Amoxil, Trimox, Wymox), clarithromycin (Biaxin), metronidazole (Flagyl, Protostat), and tetracycline hydrochloride. Azithromycin (Zithromax) has also been used but is not as effective as clarithromycin or metronidazole and is not recom-

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Table 1. Combination antimicrobial regimens for peptic ulcer disease

Dual therapies*

- Omeprazole (Prilosec) (40 mg/day for 2 wk, then 20 mg/day for 2 wk)
  and
  Clarithromycin (Biaxin) (500 mg tid for 2 wk)

- Ranitidine bismuth citrate (Tritec) (1 400-mg tablet bid)
  and
  Clarithromycin (500 mg tid)

- Amoxicillin (Amoxil, Trimox, Wymox) (1 g/day in three divided doses)
  and
  Lansoprazole (Prevacid) (30 mg tid)

Quadruple therapy (given for 14 days)

Omeprazole, 20 mg, **or** lansoprazole, 30 mg, once in the morning
and
Bismuth subsalicylate (Bismatrol, Pepto-Bismol), 2 tablets with meals and at bedtime (total daily dose, 8 tablets)
and
Metronidazole (Flagyl, Protostat), 500 mg, with meals (total daily dose, 1,500 mg)
and
Tetracycline, 500 mg, with meals and at bedtime (total daily dose, 2 g)

Triple therapies (given for 14 days)

- BMT therapy:
  Bismuth subsalicylate, 2 tablets with meals and at bedtime
  and
  Metronidazole, 250 mg with meals and at bedtime (total daily dose, 1,000 mg)
  and
  Tetracycline, 500 mg with meals and at bedtime (total daily dose, 2 g)
  or
  A prepackaged triple-therapy agent (Helidac), to be taken qid, has been cleared by the FDA and consists of 525 mg bismuth subsalicylate, 250 mg metronidazole, and 500 mg tetracycline; an antisecretory drug should be added to enhance ulcer healing

- Ranitidine bismuth citrate, 1 tablet (400 mg) bid
  and
  Tetracycline, 500 mg bid
  and
  Clarithromycin **or** metronidazole, 500 mg bid

- Omeprazole,† 20 mg bid, **or** lansoprazole, 30 mg bid
  and
  Clarithromycin, 250 or 500 mg bid
  and
  Metronidazole, 500 mg bid, **or** amoxicillin, 1 g bid
  or
  A prepackaged triple-therapy agent (Prevpac), to be taken bid, has recently been cleared by the FDA and consists of 30 mg lansoprazole, 1 g amoxicillin, and 500 mg clarithromycin

*Although approved by the FDA, not recommended for use as primary therapy because of low cure rates.
†The omeprazole-clarithromycin-amoxicillin combination has been approved for 10-day therapy.

mended.[5] Antimicrobial agents used for *H pylori* infection that act topically within the lumen of the stomach include bismuth salts and furazolidone (Furoxone).[6-8]

H pylori eradication rates are unacceptably low with single-antibiotic therapy.[7,9] Combinations of antibiotics provide the best cure rates, and such regimens are generally used for 14 days.[4,7,8] The tendency in Europe has been to prescribe 7-day therapy, but studies from the United States and Europe have shown that effectiveness of 14-day therapy is superior to both 10-day and 7-day regimens.[8] Therefore, the current trend in Europe is to return to 14-day therapy.

The usual dosages of oral anti–*H pylori* antibiotics are as follows[10,11]:

- Amoxicillin, 2 g/day in divided doses
- Clarithromycin, 500 mg two or three times per day
- Metronidazole, 1 to 1.5 g/day in divided doses
- Tetracycline, 500 mg four times per day
- Bismuth subsalicylate (Bismatrol, Pepto-Bismol), 2 tablets (524 mg) four times per day
- Ranitidine bismuth citrate (Tritec), 1 tablet (150 mg ranitidine and 250 mg bismuth citrate) two times per day
- Furazolidone, 100 mg three times per day

Recommended combination therapy

As noted, for the most part, curing *H pylori* infection cures *H pylori*–associated ulcer disease. A review of 19 published articles found that in patients who were considered cured of *H pylori* infection versus those who were not considered cured, the rate of recurrence was 4% versus 59% for gastric ulcers and 6% versus 67% for duodenal ulcers.[1]

Several articles[7,9-19] support the efficacy, safety, and economic advantages of combination therapy with antibiotics and antisecretory agents for *H pylori*–associated peptic ulcer disease. Factors to consider in selecting combination antimicrobial therapy include rates of efficacy for cure of infection, duration of therapy, adverse effect profile, and cost. Knowledge of the background rate of antibiotic resistance in the population also helps when choosing an appropriate regimen.[8] Among equally effective therapies, the least expensive is preferred. In general, the least expensive therapy is the one that cures the infection. Experienced gastroenterologists advocate that an efficacy rate of 85% to 90% is a legitimate expectation.[9,17] Other factors being equivalent, the favored regimen is the one requiring the fewest doses or allowing medications to be taken together.

Nomenclature for combination antimicrobial therapies with and without healing agents has not been standardized, so considerable confusion may exist among physicians and patients. Therefore, some physicians prefer to list components individually and consistently rather than use such terms as dual therapy and triple therapy.[9]

The Food and Drug Administration (FDA) has approved three dual therapies: omeprazole and clarithromycin, ranitidine bismuth citrate and clarithromycin, and amoxicillin and lansoprazole (table 1). However, dual therapy is not recommended as primary therapy because cure rates for all regimens are less than 85%. Recommended regimens consist of a bismuth preparation or proton pump inhibitor or H_2 receptor antagonist plus two antibiotics (table 1).

The first combination therapy found to be effective, and subsequently approved by the FDA, was bismuth, metronidazole, and tetracycline (BMT therapy). Subsequent studies from Italy showed that combination of a proton pump inhibitor with metronidazole and clarithromycin also was effec-

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tive.[20] Amoxicillin can be substituted for metronidazole. The combinations of lansoprazole or omeprazole plus amoxicillin and clarithromycin have also been approved by the FDA.

Antibiotic resistance

Resistance to antimicrobials is a key issue in overall success of ulcer therapy and should be considered when selecting a combination of agents. The presence of antibiotic-resistant *H pylori* is the most common cause of treatment failure in compliant patients.

H pylori is highly susceptible to the antimicrobial actions of amoxicillin, bismuth salts, clarithromycin, erythromycin, metronidazole, and tetracycline but not to vancomycin (Vancocin, Vancoled), nalidixic acid (NegGram), trimethoprim (Proloprim, Trimpex), or sulfonamides. Clinical efficacy of a particular antimicrobial agent in curing *H pylori* infection is not necessarily predicted by data showing in vitro susceptibility, so understanding how components of therapy work is useful (see box below).

H pylori strains resistant to metronidazole, clarithromycin, tetracycline, and amoxicillin have been described, although resistance to tetracycline and amoxicillin is still uncommon. In the general population, pretreatment resistance is encountered more often with metronidazole than with clarithromycin, presumably because metronidazole has been in use for much longer and in some parts of the world is available without a prescription. Metronidazole resistance has a variable effect. For example, success rates of

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How do common antimicrobial agents destroy *Helicobacter pylori*?

Amoxicillin (Amoxil, Trimox, Wymox) inhibits cell-wall synthesis, has topical intraluminal activity, is stable in acid, and is most active at near-neutral pH. Like penicillin and its other derivatives, amoxicillin binds to specific proteins within bacterial cell walls, including those of *H pylori*. The combination of cell cycle disruption at the time of cell division and direct cell-wall lysis is believed to account for the bactericidal effect of amoxicillin.

Clarithromycin (Biaxin) and tetracycline inhibit bacterial protein synthesis by entering the bacterial cell and binding to receptors on the ribosomal subunits. This inhibits RNA-dependent protein synthesis, resulting in death of the organism. Clarithromycin concentrates in gastric tissue. Tetracycline, which is active at a low pH, has topical intraluminal as well as systemic activity and exerts powerful synergy with bismuth.

Metronidazole (Flagyl, Protostat) has bactericidal effects by producing intracellular products that damage DNA, and it kills bacteria at a concentration only twice that at which it inhibits their growth. Metronidazole diffuses well into all tissues and is relatively insensitive to pH. It enters the bacterial cell and undergoes reductive activation, in which its nitro group is converted to an amino function. Conversion of its molecule into toxic intermediates keeps metronidazole's intracellular concentration low, driving drug uptake into the bacterium, even as DNA and other intracellular components are damaged by exposure to the toxic metabolites.

Bismuth acts by different mechanisms than most other antimicrobials and has complementary effects with most of them. It is topically active, disrupting bacterial cell walls and interfering with other surface phenomena of bacteria. Bismuth lyses the *H pylori* cell wall when the organism is close to the gastric epithelium and thus relatively inaccessible to many other agents. Bismuth also prevents adhesion to the epithelium and inhibits urease and other enzymatic activity.

65% have been reported when BMT therapy was used in patients known to be infected with metronidazole-resistant strains of *H pylori*. In a US population in which 20% to 40% of patients had metronidazole-resistant strains of *H pylori*, the cure rate among those who complied with BMT therapy was 96%.[21]

The nationwide prevalence of clarithromycin-resistant *H pylori* is about 5% but seems to be on the rise. Clarithromycin resistance is potentially problematic, in part because the use of macrolides in general is on the increase, and much clarithromycin resistance is an expression of cross-resistance among macrolides, including erythromycin. The problems inherent in clarithromycin resistance are underscored by findings in patients treated with clarithromycin-based dual combination therapies: Clarithromycin resistance was found in 96% of clinical isolates obtained from patients treated unsuccessfully with clarithromycin and omeprazole.

Resistance renders clarithromycin-based therapies markedly less effective. However, increasing evidence suggests that metronidazole-containing regimens have maintained efficacy against *H pylori* despite the emergence of resistant strains.[22] Neither bismuth citrate nor bismuth subsalicylate has been associated with development of resistance.

The following precepts may provide useful guidance regarding potential resistance in patients being treated for peptic ulcer disease:

- The possibility of resistance should be considered when a 14-day course of combination therapy that is known to be effective for ulcer does not result in cure.
- Antibiotic combinations should not be repeated after treatment failure unless sensitivity to the specific agents is demonstrated in vitro.
- Antimicrobial sensitivities should be determined when courses of therapy that include metronidazole and clarithromycin both fail.

Caveats regarding therapy

Several caveats should be observed in choosing and administering drug treatment in patients with peptic ulcer.

- Patients using bismuth subsalicylate therapy receive almost 2 g of salicylates from the usual dosage of 8 tablets per day. Therefore, they should be cautioned to decrease their use of aspirin or other salicylates while following this regimen.
- Metronidazole may interact with alcohol and cause a reaction resembling that to disulfiram (Antabuse), so patients should be cautioned to avoid alcohol while taking metronidazole.
- The traditional proscription against taking tetracycline with meals does not apply. Clinical trials have shown that both tetracycline and bismuth can be taken with meals (and even with milk products), which suggests that at least part of their activity is topical.
- Substitutions that should *not* be made are ampicillin for amoxicillin, doxycycline for tetracycline, and azithromycin for clarithromycin.

Recommendations for patient compliance

Compliance with recommended therapy is essential to the success of every anti–*H pylori* treatment regi-

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men. In a study of bismuth-based combination antimicrobial therapy, for example, the *H pylori* eradication rate was 96% among patients who took more than 60% of their medication but only 69% among those who took less than 60%.[21]

Patients comply better when they understand the rationale behind their treatment and the consequences of incomplete or inadequate treatment. It is important to use language patients understand when explaining peptic ulcer disease, *H pylori*, the outcome with concomitant NSAID use, and the proper way to take medications. Sometimes, reinforcing teaching messages midway through the treatment course is helpful. Pain relief is a powerful incentive to compliance. Patients may respond to the suggestion that taking anti–*H pylori* medications as directed and tolerating possible adverse effects for only 2 weeks can result in permanent abolition of pain and discomfort.

Two antimicrobial combinations are available in convenient dose packs, which may enhance compliance. Prevpac consists of the proton pump inhibitor lansoprazole plus clarithromycin and amoxicillin, to be taken twice daily. Helidac consists of bismuth subsalicylate, tetracycline, and metronidazole, to be taken four times daily along with an antisecretory drug (either an H_2 receptor antagonist or a proton pump inhibitor). Both dose packs are to be taken for 14 days.

Treatment failure

Failure of combination therapy is an increasingly common problem. Ideally, the second round of therapy should be based on results of antibiotic-susceptibility testing. Unfortunately, such testing is unavailable in most cities, and referral to a center with special interest in *H pylori* is usually impractical.

A rule of thumb is to not use metronidazole or clarithromycin a second time. For example, failure with a proton pump inhibitor and clarithromycin could be followed by a course of BMT. Failure of BMT could be followed by a regimen of a proton pump inhibitor, amoxicillin, and clarithromycin.

A rule of thumb when treatment of *H pylori* infection fails is to not use metronidazole or clarithromycin a second time.

There is increasing interest in quadruple regimens for "salvage" therapy when one or more other courses have failed. Quadruple therapy (table 1) is a modification of BMT therapy: A higher dose (500 mg three times daily) of metronidazole is substituted, and a proton pump inhibitor is added. Overall, quadruple therapy has the best cure rates, but it requires dosing four times daily.

Quadruple therapy can be prescribed by adding a proton pump inhibitor and 42 supplementary 250-mg metronidazole tablets to the Helidac dose pack. Although this results in daily intake of 1.75 g of metronidazole, this is the standard approach after treatment failure used by one of us (D. Y. G.). The perceived advantage is that it combines the convenience of the dose pack with the dosage required to cure most infections (independent of metronidazole resistance).

Summary and conclusions

Peptic ulcer disease associated with *H pylori* infection is curable. The important factors in selecting therapy are efficacy of eradication, prevention of resistance, avoidance or minimization of adverse effects, patient compliance, and cost.

The most effective regimens include a bismuth preparation or antisecretory drug (proton pump inhibitor or H_2 receptor antagonist) plus two antibiotics administered for 14 days. Dual-drug therapies are not recommended. Triple-drug regimens are more likely to eradicate *H pylori* and less likely to generate resistant strains among surviving organisms. In gen-

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eral, cure of the infection should be confirmed 4 weeks after completion of the treatment. Antibiotic resistance is an important consideration in choosing therapy, and patients should be taught the importance of compliance. When treatment fails, antibiotic combinations should not be repeated. Considerations for anti–*H pylori* treatment in a managed care environment mirror those for good medical practice in general, with special attention to stringent cost-control or outcomes-driven measures. **PGM**

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