AMCP's Annual Meeting: Controversies Surrounding *Helicobacter pylori*

Numerous sessions at the AMCP convention in San Francisco focused on practical information about medications. The diagnosis and treatment of *Helicobacter pylori* infection are explored in this feature article.

Attendees at AMCP's Eighth Annual Meeting left San Francisco with no shortage of information and ideas on medications and ways to manage them. The recognition of the role played by *Helicobacter pylori* in gastric and duodenal ulcers and oncolytic conditions were explored in a Saturday morning session. The program was supported by Abbott Laboratories.

BACTERIOLOGY REVOLUTIONIZES ACID PEPTIC DISEASE

"No acid, no ulcer." That dictum, once the basis of thought on treatment of peptic ulcer disease and other acid peptic disorders, has been discarded as the role of *H. pylori* in the disease has become clear over the past 10 years.

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Table 1. Patient Selection for *H. pylori* Eradication Therapy**▲ Who to treat:**

Patients with documented *H. pylori* infections and these clinical conditions:

Active duodenal ulcer

Active gastric ulcer

Past history of gastric or duodenal ulcer

MALT lymphoma

▲ Who not to treat:

Patients with undocumented *H. pylori*

Asymptomatic individuals

General population for prevention of gastric cancer

That message, by Larry Danziger, Pharm.D., and Jay Goldstein, M.D., of the University of Illinois at Chicago, was brought home for listeners by the realization that *H. pylori* infection is now "the most common infectious disease throughout the world today."

THE ORGANISM AND ITS EFFECTS

The *H. pylori* organism is very well adapted to life in the acidic environment of the upper gastrointestinal tract, Danziger explained. Spiral shaped, the organism has two to six flagella providing motility, is microaerophilic, and commits 10% of its protein and energy resources to urease, which splits urea into the basic ammonia and bicarbonate ions. *H. pylori* colonizes the mucous layer over the gastric epithelium only, more commonly in the antrum rather than the body of the stomach. The infection leads to an acute and chronic inflammatory response.

The prevalence of *H. pylori* infection increases with age; some 75% of patients over age 65 years are infected. Spread of the organism is thought to be through the fecal-oral route between family members and those sleeping in the same bed. The prevalence of *H. pylori* infection in patients with specific disorders reads this way:

▲ 100% of those with chronic active gastritis

▲ About 95% of patients with duode-

nal ulcers

▲ About 70% of those with gastric ulcers

Additionally, acid secretion from chronic *H. pylori* infection has been linked to development of gastric metaplasia in the duodenum.

DIAGNOSIS: BALANCING COSTS AND RESULTS

Three choices are available for diagnosis, according to Goldstein. Culture of *H. pylori* is not cost effective, being difficult and expensive to perform and taking seven days for results.

Histology has been the mainstay of diagnosis. The gold standard continues to be staining endoscopic samples using hematoxylin and eosin. Even though the test costs \$250, Goldstein advocates its use, since it is being added to a \$1,000 endoscopic procedure and produces a definitive diagnosis.

Serology is an option for initial diagnosis, but it fails to differentiate between active and treated or prior infection. It is inexpensive and highly sensitive and specific, Goldstein explained. ELISA tests are quantitative, while office-based procedures are qualitative and provide results in four minutes.

More recently available are urea breath tests, which take advantage of the organisms high level of urease production. Just approved by FDA this spring, the tests use urea labeled with radioactive carbon (^{13}C or ^{14}C). The patient takes the radiolabeled urea orally, and 20 minutes later the presence of

radiolabeled carbon dioxide in the breath is measured. The test, highly sensitive and specific, confirms active infection anywhere in the stomach, and costs about \$200–250.

CONTROVERSIES ON WHOM TO TREAT

Goldstein then jumped into the sticky issue of treatment of documented *H. pylori* infections. "We are not going to eradicate the organism," he began, giving the lists of definitive candidates and noncandidates shown in Table 1. Four areas of controversy create most current discussions about when and when not to treat *H. pylori*:

▲ *Helicobacter*-positive dyspepsia

▲ *Helicobacter*-positive gastritis

▲ Individuals with a first-degree relative with gastric cancer

▲ Individuals with a spouse/significant other with an ulcer

The controversy surrounding dyspepsia was explored in detail in the session.

Endoscopy can differentiate among the five types of patients with dyspepsia:

▲ Duodenal ulcer (20%)

▲ Gastric ulcer (5%)

▲ Gastritis (40%)

▲ Other (including reflux disease, 20%)

▲ Normal (15%)

Therapy for *H. pylori* will not aid patients in the last two categories, while those in the first two groups definitely should receive treatment. For patients under age 45, a noninvasive test can be used to aid differentiation. Serology or urea breath tests, if positive, lead to a need for endoscopy and/or anti-*H. pylori* treatment. Patients with negative results can be treated empirically with acid-inhibition therapy.

The main point to remember, Goldstein said, is this: "If you're going to test, you have to treat." Here are his

Table 2. Common *H. pylori* Eradication Regimens**Bismuth triple therapy (14 days; 90% eradication rate)**

Bismuth (PeptoBismol)	2 tabs p.o. q.i.d.
Metronidazole	250 mg p.o. q.i.d.
Tetracycline	500 mg p.o. q.i.d.

PPI dual therapy (14 days; 80% eradication rate)

Omeprazole	40 mg p.o. q.d.
Clarithromycin	500 mg p.o. t.i.d.

PPI triple therapy (14 or fewer days; 90% eradication rate)

Omeprazole	40 mg p.o. q.d.
Clarithromycin	500 mg p.o. t.i.d.
PLUS	
Metronidazole	500 mg p.o. b.i.d.
OR	
Amoxicillin	1,000 mg p.o. b.i.d.

Combination therapy with RBC (80% eradication rate)

Ranitidine/bismuth citrate	400 mg p.o. b.i.d. x 28 days
Clarithromycin	500 mg p.o. t.i.d. x 14 days

thoughts on the best regimens to use for that.

ANTI-*H. PYLORI* PROTOCOLS

Table 2 lists the four most common *H. pylori* protocols. Goldstein emphasized two general treatment guidelines:

- ▲ Monotherapy is unacceptable: it's just going to produce resistance and treatment failures

- ▲ Do not substitute one agent for another (e.g., ampicillin for amoxicillin; azithromycin or erythromycin for clarithromycin)

In addition to bacterial resistance, three other factors influence patient outcomes: innate efficacy, compliance, and side effects. Compliance is a particular problem with *H. pylori* therapy, partially because of the complexity and length of the regimens and also because of the agents' side effects. When the compliance rate with bismuth triple

therapy exceeds 60%, the eradication rate is 95%. However, Goldstein noted, it falls to 69% with lower compliance.

Additionally, metronidazole resistance decreases the efficacy of bismuth triple therapy by 35–65%.

Regimens such as omeprazole plus clarithromycin are much simpler, requiring four tablets/day versus 16 with bismuth triple therapy. The combination of clarithromycin and omeprazole is based on the effects on stomach pH of the antisecretory agent. Proton-pump inhibitors increase the stomach pH, allowing clarithromycin to become more concentrated in the mucosal lining where *H. pylori* colonizes.

After eradication, reinfection rates are quite low, explained Goldstein. Rates per patient-year have ranged from 0.6 to 2.3%. "For each month the patient remains symptom-free," Goldstein summarized, "is one less month of H₂ antagonist therapy under the old schools of thought. Even if the patient

Table 3. Two-Year Direct Cost Model for Duodenal Ulcers

Therapy	Cost (\$)
Bismuth triple therapy	720
Omeprazole/clarithromycin	769
Omeprazole/amoxicillin ^a	1028
H ₂ antagonist maintenance therapy	1701

^a Therapy no longer considered effective.

has other risk factors—such as concomitant therapy with nonsteroidal anti-inflammatory agents, the *H. pylori* status needs to be determined and the patient treated if positive. The avoidance of years of symptomatic therapy will be cost-effective despite the high one-time costs." He provided the cost data in Table 3 in support of his position; the data are based on a two-year period, which Goldstein said was the average length of coverage in a managed care plan.

MICROBE CHANGES THE WORLD OF ULCER THERAPY

With *H. pylori* now firmly established as an etiologic agent for peptic ulcer disease, and the recent recognition of a role for *Chlamydia pneumoniae* in pathogenesis of atherosclerosis (see June *Journal of the American College of Cardiology*), people are wondering what else will turn out to be caused by invisible but ubiquitous bacteria. Certainly, the recognition of the key role played by *H. pylori* has altered completely basic approaches to diagnosis and management of dyspepsia, ulcer, and oncologic conditions of the upper gastrointestinal tract. ■