

Duodenal/Gastric Ulcer

... OVERVIEW ...

It is now established that the overwhelming majority of non-NSAID-induced peptic ulcers are caused by *H. pylori* infection. The goals of treatment are eradication of infection and promotion and maintenance of healing. To achieve these goals, treatment regimens include antibiotics in combination with an agent that promotes healing.

Symptoms of peptic ulcer are not diagnostic. A specific diagnosis is neces-

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sary, which requires diagnostic testing. The diagnosis can be made by endoscopy or by an upper GI barium series plus serologic studies. From a managed care standpoint, either of these techniques is appropriate.

The differential diagnosis of peptic ulcer includes NUD, GERD, and biliary tract disease.

The panel agreed on three main regimens used to treat peptic ulcer. These are: bismuth-based triple antibiotic therapy, PPI-based triple therapy; and dual therapy with a PPI plus one antibiotic. When selecting a regimen, efficacy should be the main priority, since recurrences and hospitalizations are expensive. Thus, again the most effective treatment is the cheapest one, and the most expensive therapy is the least effective.

According to the participants, the two available PPIs are equally safe and effective and either omeprazole or lansoprazole can be used with assurance in a PPI-based regimen. There are some considerations in selecting an antibiotic for eradication of *H. pylori*, including resistance patterns. Clarithromycin appears to be an excellent choice and is associated with only minimal resistance to date.

Other considerations in choosing a regimen include compliance. Compliance decreases as the complexity of regimens increases. Bismuth-based triple therapy, sometimes called "standard triple therapy," requires approximately 16 pills a day for 14 days and can be difficult for patients to follow. Whichever regimen is selected, studies suggest that treatment of acute ulcer should be accompanied by an antisecretory agent for an additional 4 to 6 weeks.

... DISCUSSION HIGHLIGHTS ...

Etiology and Testing

Dr. Fennerty: Classic symptoms of peptic ulcer include pain on awakening, relief of pain by food or antacids, burning pain, and pain in the epigastrium. Symptoms are not specific for gastric or duodenal ulcer disease. For the most part, symptoms are not even suggestive of ulcer disease, since less than one in five people with classic symptoms will actually have an ulcer. The corollary is that one in five asymptomatic patients taking NSAIDS will also have an ulcer. The prevalence of peptic ulcers is less than

1% in the United States. The lifetime incidence is 10% to 15%.

There is probably less than a 1% chance of peptic ulcer in a population under age 50 with dyspeptic symptoms, which is not taking NSAIDs, and in which the *H. pylori* serology is negative.

Peptic ulcer is almost always caused by *H. pylori* infection; the majority of the rest of ulcers in the stomach and duodenum are caused by NSAIDs. Ulcers caused by other diseases are extremely rare.

Dr. Howden: My approach to diagnosis of ulcer depends on the circumstances. If I am endoscoping a patient who has had bleeding or epigastric pain, I will biopsy at the time of endoscopy to check for *H. pylori*. I will also perform a rapid urease test and wait 24 hours to read the results. For duodenal ulcer, I hold the biopsy and send it only if there is a negative rapid urease test.

Dr. Fennerty: A patient with a gastric ulcer should be biopsied at the time of endoscopy to rule out malignancy. The standard of care is no longer just proof of healing. A well-trained endoscopist will take between six and 10 biopsies and that will exclude the diagnosis of cancer with 99% accuracy. Follow-up endoscopy is probably no longer necessary with this approach, but that is remains a controversial issue.

Dr. Freston: Only a small percentage of endoscopists take that many biopsies. I would agree that if one is prepared to do that, then follow-up endoscopy might not be necessary.

Dr. Brandt: It would be reasonable to say that gastroscopy has at least two roles. One is to make a definitive diagnosis and the other is to find the etiology by determining whether or not *H. pylori* is present.

Dr. Howden: People with epigastric symptoms are usually treated by primary care physicians. In these patients, a posi-

tive *H. pylori* serology is useless, since the organism may be present in the stomachs of up to 50% of people. A negative *H. pylori* serology is quite helpful,

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since it has a strong negative predictive value for peptic ulcer. Nonetheless, it is important to keep in mind that serology tests for the presence of *H. pylori* and not for the presence of peptic ulcer.

Dr. Freston: It appears that patients who enjoy relief of symptoms with eradication of *H. pylori* are only those with an ulcer. Only a few patients with positive serology will have ulcers, and they are the ones who will get symptom relief.

The outlier in this discussion is *H. pylori* infection in children, which is a different disease entity with abdominal pain (but no ulcer) that responds to *Helicobacter* therapy.

A serology test is positive or negative and indicates the presence or absence, respectively, of *H. pylori* in about 90% of patients; it is an office-based test that costs about \$20. Positive urea breath tests are probably a bit more sensitive and specific for active *H. pylori* infection but also cost more—between \$150 and \$200. The real value of urea breath testing is for follow-up, which generally is not necessary in patients with uncomplicated ulcer disease.

Follow-up urea breath testing is clearly necessary in patients with complicated ulcers, because these patients can have a devastating recurrence of disease if eradication of *H. pylori* is not achieved.

The presence of *H. pylori* indicates some degree of inflammation. This is called gastritis and is a histologic diagnosis that is not associated with a distinct symptom complex. Physicians have used gastritis as a catchall diagnosis to

explain a patient's dyspeptic symptoms within the context of a negative evaluation, but this is incorrect. The diagnosis of gastritis should never be used outside of a histologic setting. Treatment of gastritis is not necessary; 50% of the world's population has *H. pylori*, and 80% of those infected with it will never develop the peptic disease associated with that infection.

An upper GI barium series and serology will detect the presence of duodenal and gastric ulcer disease with relatively high sensitivity. Less than 10% of patients we treat will present acutely.

We are missing a large group of patients who require treatment; these are people who had well-documented ulcer in the past and are being maintained on H2RAs but have not had their underlying infection eradicated. These patients should be tested for *H. pylori*.

Dr. Brandt: From the managed care viewpoint, there is no difference in cost between an upper GI series plus serology versus endoscopy in evaluating a patient with suspected peptic disease.

Regimen Efficacy and Costs

Dr. Freston: For primary care physicians, the basic decision is when to start the patient on empiric therapy. The issue is whether therapy should be directed by serology and/or endoscopy results.

Dr. Fennerty: First we need to identify the regimens that are appropriate. We have standard bismuth-based triple therapy for 2 weeks; PPI-based triple therapy; or dual therapy. Efficacy with 2 weeks of standard triple therapy is 90%, but this requires taking 16 pills a day for 14 days, which poses tremendous compliance problems. Efficacy with the other two regimens is 70% to 95%.

There is an important difference between efficacy and effectiveness. Efficacy is a term used in clinical trials to mean what is supposed to happen. Effectiveness generally means whether a treatment works in clinical practice.

All the data show that omeprazole and lansoprazole, the two currently available PPIs, are equally effective and interchangeable in these regimens.

Compliance is an important issue. We know that a patient is required to take more than 60% of the prescribed medication to achieve a 90% efficacy rate with standard triple therapy; if that patient takes less than 60% of the medicine, the efficacy rate of standard triple therapy falls to 60%. One study suggested only about 25% of patients take more than 60% of the medications.¹ It appears that when patients are not being paid to participate in a study, their motivation to take the full prescribed amount of medication decreases.

We do know that when you look at overall costs of managing peptic ulcer disease, the direct costs of pharmacologic treatment are less than 10%. Complications and hospitalization account for the lion's share of the cost, so when you are evaluating therapies, effectiveness should be the dominant consideration irrespective of cost of the drug. A regimen that can be used twice a day, such as PPI-based triple therapy, will be associated with better compliance than that achieved with standard triple therapy, and therefore may have greater effectiveness. This will be cheaper in the long run. The cost of the regimen for treating peptic ulcer should never enter into the discussion.

Dr. Sclar: The issue of noncompliance with pharmacotherapy needs to be addressed in treatment guidelines and in the development of disease state management programming.

Dr. Fennerty: One of the things we should not do in a managed care environment is choose a regimen because it costs less to the pharmacy. Effectiveness is the most important criterion. A less effective regimen will end up costing more. A good approach would be to have all three types of regimens available to clinicians. The antibiotics and the PPIs are already on formularies, so it

shouldn't be difficult to implement this strategy from a managed care standpoint.

Dr. Freston: Dr. Fennerty raised a very important point earlier about the difference between efficacy and effectiveness, and one of the factors responsible for this difference is compliance. Compliance should be measurable and entered into the decision.

Dr. Zagari: We are in the preliminary stages of developing a model to assess compliance. Some recent data are helpful in this regard. The Graham study¹ shows a 23% reduction in eradication rate when compliance drops below 60%. In that study compliance was defined as the number of pills taken. Other studies have looked at compliance as a function of regimen complexity and found compliance drops as complexity increases; in other words, compliance is better with a bid regimen and falls off as you go to a tid, then a qid regimen. We think we can combine these data and arrive at a model, which will have to suffice until someone comes up with real world data.

Dr. Fennerty: Vakil and I just published a study² that applied compliance data to modeling of the various available therapies. In that study we found omeprazole/clarithromycin (OC) for 2 weeks costs the same as standard triple therapy over a 2-year follow-up. The cost for OC was about \$768; the cost was \$1,028 for omeprazole/amoxicillin (OA); and the cost with an H2RA was about \$1,791. The increase in cost was due to decreased efficacy. We now know continued H2RA treatment, as well as largely ineffective regimens like OA, are very costly as well as clinically ineffective. Regimens that are appropriate include OC, bismuth-based triple therapy, and PPI-based triple therapy. PPI-based triple therapy for 10 to 14 days is very successful.

Dr. Zagari: That is a good summary of treatments. Any of these three regimens is a good choice, but this message can

get lost in all the discussions about triple versus double antibiotics. The key is to use an effective therapy. All three regimens will be much more effective compared to H2RA maintenance and certainly better than OA, which is still commonly used.

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Dr. Goldenring: One of the important things managed care companies need to pursue is to go back to their databases and identify patients with a diagnosis of ulcer disease who are being maintained on chronic H2RA and change their treatment. We are on the wrong track with these patients and we need to get them properly treated.

Dr. Freston: This is an important message to the primary care physician. If the patient has been on an H2-blocker for prolonged periods, it is important to re-establish the diagnosis. If the patient has ulcers, then treatment should be aimed at eradication of *H. pylori* and healing of the ulcer.

Dr. Saltiel: Most of the data we have is on standard triple therapy. Until we have community-based studies, effectiveness will not be known. The PPI-based triple therapy appears to be the best alternative to classic bismuth-based triple therapy. Some data suggest 1 week of treatment is as good as 2 weeks.

Dr. Freston: European studies show 1 week is sufficient. However, studies in the United States thus far have failed to replicate these results, and it would be prudent for us to treat for 10 to 14 days.

Dr. Fennerty: The US data look different from the European data. Loren Laine's data³ show omeprazole, amoxi-

cillin, and clarithromycin (OAC) is 77% effective at 7 days (compared to 95% in the European literature); 93% effective in 10 days; and 100% effective in 14 days.

Dr. Brandt: What are your treatment recommendations for a patient with a duodenal ulcer identified by endoscopy and a positive guaiac test?

Dr. Howden: I would prescribe PPI-based triple therapy and use it for 2 weeks. Either of the PPIs would be a good choice, because they are interchangeable. I would also definitely use clarithromycin, with either amoxicillin or metronidazole.

Dr. Zagari: I would treat with a PPI and triple antibiotic therapy for 10 days.

Dr. Saltiel: In general, I would use metronidazole, bismuth, and tetracycline and a PPI for 10 to 14 days.

Dr. Goldenring: I would treat with a PPI, metronidazole, and clarithromycin for 10 days.

Drs. Freston, Fennerty, and Potash: We agree with Dr. Howden's choice of PPI-based triple therapy. With an acute ulcer, treat for only 2 weeks. It is not necessary to continue the PPI beyond that.

Dr. Freston: The FDA-approved regimens for acute ulcer include another 14 days of antisecretory therapy.

Dr. Howden: A recent study from Labenz et al in *Deutsch Medizinische Wochenschrift*. [1996;121:3-8] in Germany included more than 100 patients with gastric or duodenal ulcer treated with omeprazole-based antibiotic regimens for 1 week. Four weeks later, endoscopy revealed 97% of the duodenal ulcers and 89% of the gastric ulcers had healed.

Dr. Saltiel: Metronidazole resistance is a factor in effectiveness. There is a major difference in eradication rates for *H. pylori* if the strain is susceptible or resis-

tant to metronidazole. Some experts advocate testing for metronidazole susceptibility.

Dr. Freston: In this country, the background resistance rate for metronidazole is between 15% and 20%, whereas the rate for clarithromycin is between 2% and 5%. This is not as important an issue in the United States as in Europe, and it is mainly relevant for female patients who are often prescribed Flagyl (metronidazole) and are sometimes resistant to it. If I were setting up a disease management plan, I would ask female patients whether they had ever taken metronidazole and if so, use a non-metronidazole-containing regimen.

Dr. Saltiel: I'm not aware of any evidence that shows the inclusion of metronidazole conveys any advantage over amoxicillin in PPI-based triple therapy. Thus, in patients who have been treated previously with metronidazole, a non-metronidazole-based regimen may be preferred. Women have a far greater likelihood of harboring metronidazole-resistant strains than do men.

Dr. Fennerty: Good point. Physicians should think about the drugs they are using. We are responsible for the fate of OA in this country, which became the most widely prescribed regimen for *H. pylori* without US studies to support that practice. Regarding specific drug choices, as far as the data show, PPIs are interchangeable. We can get away without metronidazole. We have enough options to enable us to tailor therapy to specific populations.

Dr. Goldenring: In my view, we should all be more aware of resistance as an issue in infectious disease. Pneumococcus and TB are the current classical examples. We should keep tailoring our regimens with resistance in mind. This leads to treatment considerations for the 10% of patients who recur despite good compliance.

Dr. Fennerty: There are three follow-up studies of re-treatment of treatment failures.⁴⁻⁶ Two of these studies were of OA failures, and the third was of high-dose OA failures. These studies each showed that 14 days of PPI-based therapy was effective in patients who failed on OA. We recommend a regimen that contains antibiotics not previously used. The best option for patients who have failed on standard triple therapy is PPI-based triple therapy for 14 days. The ace-in-the-hole for patients who again fail on PPI-based triple therapy is to put them back on H2RAs.

When setting disease management guidelines for managed care organizations to use as a template, it is important to emphasize the need to wait 4 to 6 weeks after all medication has been stopped before retesting. That includes PPIs. Otherwise, there will be false negatives.

Serologic follow-up is only possible if the clinician has banked serum. A recent paper in the *American Journal of Gastroenterology* [1996;91;85-88] showed that banked serum with a greater than 20% titer drop is an accurate means of detecting eradication of the organism. The problem is that most organizations and most physicians don't save serum. This type of testing is difficult to perform in any environment, because the companion sera have to be run on the same test.

PPI Safety

Dr. Brandt: Our discussion should include the safety profiles of the PPIs.

Dr. Freston: We have a growing database that can give us comfort. Studies show no difference in the safety profiles over 8 weeks of treatment for omeprazole versus ranitidine and placebo. Long-term safety is related to consequences of hypergastrinemia, which most patients will develop to some degree on antisecretory medications. In the rat, hypergastrinemia stimulates the ECL cells to proliferate and form gastric carcinoids. We now know these are char-

acteristics unique to the rat, and this does not happen in humans. In controlled trials, serial gastric biopsies of patients treated with both omeprazole and lansoprazole have not shown any change in the histologic behavior of ECL cells

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that would forecast the eventual development of carcinoids. Over the long history of PPI usage, there has been no report of the development of carcinoids related to PPI treatment. It appears additional factors are necessary for the development of dysplasia, including smoldering, ongoing gastritis due to *H. pylori* infection.

Dr. Fennerty: Safety of PPIs seems to be a nonissue in treatment of gastric disorders.

Treatment Access

Dr. Brandt: What effect will the OTC availability of inhibitors of acid secretion have on patient referral patterns?

Dr. Saltiel: Once patients get used to paying small copayments, they don't want to spend their own money on drugs. The question is whether managed care plans will compete on allowing payment for OTC H2RAs.

Dr. Potash: There will be tremendous pressure from patients to have medication included as part of the pharmacy benefits of insurance plans. If a plan takes the approach of not covering OTC H2RAs, that position will not be tenable for long.

Dr. Goldenring: We have OTC NSAIDs, but we are still prescribing NSAIDs. Acetaminophen is preferable to NSAIDs for elderly patients with ar-

thritis. Many elderly patients with arthritis end up in the hospital with gastric bleeds. If we were going to cover any OTC medication, it should be acetaminophen! Also, cost of medication for both patient and payer, when larger therapeutic doses are truly needed, clearly favors the prescription medication. Therefore, any organization will almost certainly not cover low-dose OTC H2RAs.

Dr. Sclar: Let me suggest patients will procure OTC drugs on their own and self-medicate for long periods of time. I am concerned about the effect of self-treatment practices on the patient's ultimate diagnosis. The impact on health service expenditures needs further evaluation.

Dr. Brandt: As clinicians, we all need to be more concerned about doing a thorough history regarding OTC medications. Elderly patients with arthritis should be asked about OTC medications to see if they are taking NSAIDs. Just because we didn't prescribe a certain drug, doesn't mean they are not taking it.

If we find our patients are taking an OTC H2RA, we can probe more deeply

about why they are taking it, how long they've been taking it, and the quality of their symptom relief. This will influence our clinical judgment.

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