

UPAP CLASS 34
EVIDENCE BASED MEDICINE
WRITE-UP #4
Diagnosis related case:
Triple vs. Quadruple Therapy
for treatments of H. Pylori Gastritis

MM, PAS

I. SOAP NOTE

Refer to attachment.

II. CODING FOR DIAGNOSIS

- A. CPT code: 99213, \$57.00, \$15.00 co-pay
- B. ICD-9: 535.50, gastritis with no hemorrhage
- C. Labs: None done for this visit
 - Meds: from AUCH pocket drug list
 - tetracycline 500 mg, \$7.28
 - Bismuth subsalicylate (Pepto-Bismol Caplets OTC), \$5.99
 - metronidazole 500 mg, \$6.30
 - omeprazole 20 mg, \$34.36

III. SYMPTOM RELATED CASE

N/A

IV. DIAGNOSIS RELATED CASE

Case introduction

J.C. is a 16 year-old Hispanic male who first presented to clinic with abdominal pain in December of 2003. He was given a trial of ranitidine and failed to show to the follow up appointment a month later. JC then presented in April of this year again with abdominal pain and stated that ranitidine was minimally effective so he stopped it after a few days. At that visit, he was then given a trial of Prevacid (samples given) and blood was taken to test for H. pylori antibodies. In the visit of 9-14-04, JC's mother stated that they were never contacted with results of the H. pylori test, which was positive. JC stated that Prevacid effectively controlled his pain so he took it prn pain. However, he run out of Prevacid samples three months ago and the pain continues to recur and it has started to get worse. Refer to soap note for more details. He is taking no other medications. His past medical history is unremarkable.

After discussing the diagnosis of h. pylori gastritis and it's treatment choices, JC and his mother decided to try the quadruple therapy for the eradication of h. pylori mostly due to lack of insurance of coverage.

This case got my attention because I was really concerned that a 16 year-old kid will stick to such a complicated treatment plan. Also, we were thought in our therapeutics class that triple therapy was first line and quadruple was really the last resort for h. pylori eradication. I was really surprised when Dr. Hasby proposed this treatment option.

Gastritis

Etiology

There are three main categories of gastritis: erosive and hemorrhagic, non-erosive and nonspecific, and other specific types of gastritis distinguished by characteristic histologic and endoscopic features like lymphocytic gastritis, hypertrophy naturopathy, granulomatous gastritis and eosinophilic gastritis. Erosive and hemorrhagic gastritis is mostly seen in alcoholics, in about 6% of critically ill patients and roughly half of patients taking NSAIDs on a chronic basis. Pernicious anemia induced gastritis, h. pylori gastritis, and lymphocytic gastritis are the main types of non-erosive gastritis. (1)

H. pylori infection is the most common type of bacterial infection causing gastritis. H. pylori, a spiral gram-negative rod, produces urease, which in turn, catalyzes the hydrolysis of urea to ammonia and carbon dioxide in the stomach. It is hypothesized that the hydroxide ions generated by the equilibration of water with ammonia contribute to gastric mucosal epithelial damage. It is also associated with a transient increase of acid production in the stomach. H. pylori gastritis usually starts in the antrum, causing intense inflammation, and over time it may involve the entire stomach (pangastritis). (4) It is not completely understood how h. pylori is transmitted but most likely is transmitted from person to person via fecal-oral and gastro-oral (exposure to vomitus). (1)

Other less common types of bacterial infection causing gastritis include: helicobacter heilmanii infection, tuberculosis, secondary syphilis, phlegmonous gastritis, caused by a number of bacterial agents, cytomegalovirus. Fungal infections, like those caused by candida albicans and histoplasmosis as well nematode infection, anisakidosis, can also cause infectious gastritis. Debilitated and immunocompromised patients are at the highest risk of suffering from the less common types of infectious gastritis (4)

H&P findings

Signs and symptoms of gastritis depend on the cause and how long the problem has existed. Most of the time signs and symptoms are mild and short lived. (7) Acute h. pylori infection may cause transient nausea and abdominal pain with may last for several days. (1)

Symptoms that present suddenly characterize acute gastritis. Gradual and mild symptoms are usually of chronic gastritis. However, people who suffer from chronic gastritis may have no symptoms at all. (7)

According to an emedicine article on gastritis and peptic ulcer disease the following are common presenting symptoms and physical findings:

- Patients typically present with abdominal pain that has the following characteristics:
 - Epigastric to left upper quadrant
 - Frequently described as burning
 - May radiate to the back
 - Usually occurs 1-5 hours after meals
 - May be relieved by food, antacids (duodenal), or vomiting (gastric)
 - Typically follows a daily pattern specific to patient

- NSAID-induced gastritis or ulcers are usually silent.
- Sudden onset of symptoms may indicate perforation.
- Gastritis may present as bleeding, which is more likely in elderly patients.
- Symptoms consistent with anemia (e.g., fatigue, dyspnea) may manifest.

Physical:

- Epigastric tenderness is present and usually mild.
- Bowel sounds are normal.
- Signs of peritonitis or GI bleeding may manifest. Perform a rectal examination and Hemoccult testing. (6)

Workup

The most sensitive diagnosis method for gastritis is upper endoscopy. It is most indicated when bleeding is present/highly suspected and to rule out more serious conditions like peptic ulcer disease and esophageal varices and patients with suspected gastric lymphoma. During endoscopy gastric biopsy specimens can be obtained and tested for active infection. These biopsies provide more definitive results for h. pylori infection but cost an average of \$150-\$250 dollars. (1)

Endoscopy is rarely indicated for the diagnosis of h. pylori infection alone. Fecal antigen tests or serologic tests are recommended as the most cost effective initial test. Laboratory-based quantitative serologic ELISA tests cost \$40-\$75 dollars on average and have over 90% sensitivity and specificity. Nevertheless, positive serologic tests do not necessarily imply active ongoing infection. For a similar average cost, the fecal antigen immunoassay has a sensitivity and specificity of about 90%. A positive fecal antigen does indicate active infection and is therefore, the preferred non-invasive screening test for h. pylori. C-urea breath tests also have similar sensitivity and specificity and indicate active infection if positive. (1) It's higher cost (\$60-\$300) makes it less permissive, especially for the CHC population/system.

Treatment options

Treatment of gastritis depends on the cause. Starting with life style changes like maintaining a healthy weight, exercising, smoking cessation, avoid or limit alcohol use and healthy eating.

Medications that control and limit stomach acid like following are also used:

- Antacids: Maalox, Mylanta
- Acid blockers: cimetidine, ranitidine, famotidine
- Proton pump inhibitors (PPI): omeprazole, lansoprazole, esomeprazole
- cytoprotective agents: sucralfate, misoprostol

Avoiding medications that have side effects that exacerbate gastritis like NSAIDs is also part of the treatment. (7)

When gastritis is caused by h. pylori infection a combination of a PPI and antibiotics is recommended. This combination therapy has a 90% cure rate. Amoxicillin, clarithromycin, metronidazole and tetracycline are the antibiotics used in different combinations with a PPI for 10-14 days for the triple agent therapy. (7) The quadruple agent therapy includes two of the antibiotics mentioned above, and a PPI plus bismuth

subsaliolate. Metronidazole should be avoided in areas where resistance has been detected.

Treatment with a PPI should continue for 4-8 weeks, after the completion of the 10-14 days of combination therapy, to promote healing of the stomach mucosa. (1)

Prognosis

30-50% of the present population is chronically infected with *h. pylori*. However, only 15 % of patients develop a peptic ulcer. The majority of patients are asymptomatic and suffer no sequelae. Patients with chronic *h. pylori* gastritis have a two to six fold increased risk of developing gastric adenocarcinoma and low grade B cell gastric lymphoma. (1) According to Mayo Clinic untreated gastritis may lead to stomach ulcers and stomach bleeding. However, gastritis is usually not serious, though may decrease quality of life due to pain and discomfort, complications are unusual. (7) Having said that, phlegmonous gastritis has a mortality rate of 65% even when treated aggressively, luckily it is a rare event. (4)

V. CLINICAL QUESTIONS

1. Clinical findings

How do the clinical findings of non-erosive gastritis compare to clinical findings of erosive gastritis?

As mentioned above signs and symptoms of non-erosive gastritis include nausea, vomiting, loss of appetite, belching or bloating and a gnawing or burning ache or pain in the epigastria area. Eating may worsen or improve the discomfort. (7) Erosive gastritis has many similar symptoms like nausea, vomiting, epigastria pain and anorexia. Though, many patients are usually asymptomatic. Clinically, erosive gastritis presents with upper gastrointestinal (GI) bleeding, hematemesis, or “coffee grounds” emesis, or melena. Endoscopic findings don’t correspond to the severity of symptoms experienced by the patient. Bleeding is superficial and rarely becomes hemodynamically significant. (1) Also refer to the H&P findings above.

2. Differential diagnosis.

What is the differential diagnosis for epigastric pain?

The 2004 Current Medical and Diagnosis and Treatment (CMDT) states that the following conditions should be considered in patients with epigastria pain:

- Peptic ulcer
- gastroesophageal reflux
- Gastric cancer
- Biliary tract disease
- Food poisoning
- Viral gastroenteritis
- Functional dyspepsia

If the pain is severe, perforated or penetrating ulcers, pancreatic disease, esophageal rupture aortic aneurysm, gastric volvulus and myocardial colic, should be considered. With upper GI bleeding the differential should include peptic ulcer disease, esophageal varices, Mallory-Weiss tear, and arteriovenous malformations. (1)

3. Clinical epidemiology.

What is the prevalence of h pylori infection in the general US population? Mayo clinic states that up to 20% of young adults and 50% of persons over 60 years of age are infected with h. pylori. The majority of infections happen during childhood. (7) CMDT states that 10% of Caucasians under age 30 are infected and the prevalence increases in non-whites and immigrants from developing countries, where prevalence rates reach up to 80% (7), and decreases as socioeconomic status increases. (1)

4. Etiology.

How does h. pylori cause damage to intestinal mucosa?
Refer to the second paragraph in the etiology section above.



H. pylori bacterium seen with an electron microscope

5. Diagnostic tests.

What are the most commonly used diagnostic tests for h pylori? The Essentials of Family medicine book quotes the following values for sensitivity, specificity, positive and negative likelihood ratios for the tests that are most commonly used for h. pylori detection. (2) Urea breath test, though more expensive, seems superior to the other tests. In our CHC population, where the majority of patient lack insurance, serum IgG antibody is the most cost effective test we can do.

| Test | Sensitivity | Specificity | LR+ | LR - |
|--------------------|-------------|-------------|--------|----------|
| Urea breath test | 0.91-1.0 | 0.96-1.0 | 22-100 | 0.01-0.1 |
| Stool antigen test | 0.94 | 0.92 | 12 | 0.06 |
| Serum IgG test | 0.86-0.96 | 0.75-0.89 | 4-8 | 0.04-0.2 |
| Antibody test | 0.76-0.9 | 0.79-0.98 | 4-8 | 0.2-0.3 |

Also refer to the second paragraph of the workup section above.

6. Therapy.

In adult patients with positive h. pylori test, how do triple therapy compares with quadruple therapy in efficacy, safety, cost and compliance?

“The present meta-analysis suggests that quadruple therapy is slightly more effective than triple therapy for the initial treatment of *H. pylori* infection. Nevertheless, the differences were not statistically significant. Compliance and side effects were also very similar and could not distinguish between triple and quadruple therapy as first line treatment...Antibiotic resistance has a major influence on the effectiveness of eradication therapy...Unlike triple therapy, whose effectiveness is considerably metronidazole-resistant as in metronidazole-sensitive *H. pylori*...A major disadvantage of quadruple therapy is its complicated dosage...In addition, formulations combining tetracycline, metronidazole and a bismuth salt, [like that used in the trial by Laine *et al.*], would facilitate compliance and tolerability and thus overcome a major drawback of quadruple therapy...In conclusion, quadruple therapy provides similar or slightly better results than triple therapy for *H. pylori* eradication. The advantages at present do not seem clear enough to change current polices for *H. pylori* treatment.” (2)

7. Prognosis

What is the prognosis for patients with h. pylori gastritis?
Refer to the prognosis section above.

8. Prevention and education

Are there any life style changes that patient can make to help prevent and control gastritis?

Although gastritis can be caused by many different factors, patients can make many life style changes that can help prevent and Control gastritis. Mayo clinic has the following recommendation for prevention and self care of gastritis:

Prevention/Education

- Eat smaller, more frequent meals to buffer stomach acid secretion, avoid irritating foods such as spicy, citrus or highly seasoned items
- Limit or avoid alcohol. Excessive use of alcohol can irritate and erode the mucous lining of the stomach, causing inflammation and bleeding.
- Don't smoke. Smoking interferes with the protective lining of the stomach, making the stomach more susceptible to the development of gastritis as well as ulcers. Smoking also increases stomach acid and delays stomach healing.
- Switch pain relievers. If possible, avoid taking NSAIDs — aspirin, ibuprofen, ketoprofen and naproxen. These over-the-counter medications can cause or worsen gastritis. Instead, use pain relievers that contain acetaminophen are

suggested.

Self-care

Digestive problems — from simple stomach upset to gastritis — can occur for many reasons, including possibly lifestyle choices patients can control.

- Good eating habits. The manner in which you eat is just as important as what you eat is. Eating moderate proportions, eating at regular times, and relaxing while eating.
- Maintain a healthy weight. Digestive problems can occur no matter what a person's weight is. But heartburn, bloating and constipation tend to be more common in people who are overweight. Maintaining a healthy weight can often help prevent or reduce these symptoms.
- Get plenty of exercise. Aerobic exercise is the most beneficial activity for healthy digestion. Aerobic exercise stimulates the activity of intestinal muscles, helping to move food waste through your intestines more quickly. At least 30 minutes of aerobic activity — walking is one example — most, if not all, days of the week.
- Limit stress. Stress increases stomach acid production and slows digestion, promoting an upset stomach. (7)

9. Experience and meaning

How has the discovery of the link of *h. pylori* to ulcers and gastritis changed the meaning and experience of patients and clinicians?

Early in the 20th century gastritis and ulcers were thought to be caused by stress and diet. Treatment consisted of bed rest and bland diet. Later, excess gastric acid was blamed and antacid drugs were used to treat it. In 1982, Australian physicians Robin Warren and Barry Marshall first identified the link between *h. pylori* and ulcers, concluding that the bacterium, not stress or diet, causes ulcers. The medical community was slow to accept their findings. It wasn't until 1994, when the National Institutes of Health Consensus Development Conference concluded that there is a strong association between *H. pylori* and ulcer disease, and recommended that ulcer and gastritis patients with *H. pylori* infection be treated with antibiotics. A study done in 1995 by the Consumer Research by the American Digestive Health Foundation showed that about 75 percent of ulcer patients were still being treated primarily with H2 blockers, and only 5 percent were receiving antibiotic therapy, and nearly 90 percent of ulcer sufferers were unaware that *H. pylori* causes ulcers. Nearly 90 percent of those with ulcers blame their ulcers on stress or worry, and 60 percent still blame diet. (8)

10. Self-improvement

I think that my main weakness in this case was that fact that I did not document all the pertinent negatives that could have ruled out other more serious conditions in the differential for epigastric pain. The fact that he has a positive *h. pylori* test and we have to treat it doesn't mean that he could not have other more serious condition causing his pain. Also, since I have learned in my therapeutics class that triple agent therapy was the first line treatment I was surprised when Dr. Hasby recommended the quadruple therapy. This is actually what instigated this EBM. I questioned the efficacy and compliance with the quadruple therapy because of the age of the patient and cost. After looking up the prices for the triple vs. quadruple treatments, it made sense that we do the quadruple

therapy since our patient is not insured and his family has limited resources. Quadruple therapy is much cheaper and according to Dr. Hasby even more efficacious.

VI. KEY CLINICAL QUESTION

In adult patients with positive h. pylori test, how do triple therapy compares with quadruple therapy in efficacy, safety, cost and compliance?

“The present meta-analysis suggests that quadruple therapy is slightly more effective than triple therapy for the initial treatment of *H. pylori* infection. Nevertheless, the differences were not statistically significant. Compliance and side effects were also very similar and could not distinguish between triple and quadruple therapy as first line treatment...Antibiotic resistance has a major influence on the effectiveness of eradication therapy...Unlike triple therapy, whose effectiveness is considerably metronidazole-resistant as in metronidazole-sensitive *H. pylori*...A major disadvantage of quadruple therapy is its complicated dosage...In addition, formulation combining tetracycline, metronidazole and a bismuth salt, [like that used in the trial by Laine *et al.*], would facilitate compliance and tolerability and thus overcome a major drawback of quadruple therapy...In conclusion, quadruple therapy provides similar or slightly better results than triple therapy for *H. pylori* eradication. The advantages at present do not seem clear enough to change current policies for *H. pylori* treatment.” (2)

The document by Mayo Clinic, written in September 30, 2004, listed triple therapy for h. pylori eradication as the first line and did not even mentioned quadruple therapy. (7)

CMDT does list 2 different triple therapies and one quadruple combination. (1)

The study above answered my questions about efficacy, side effects and compliance. Cost, however, was not part of this review so I looked up the individual prices for both treatment options. The graphs below show the great price difference between both therapies.

Quadruple therapy

| Medication | Cost |
|------------------------------|----------|
| Omeprazole 20 mg (30 ea) | \$34.36* |
| Metronidazole 500 mg (14 ea) | \$6.30* |
| Tetracycline 500 mg (60 ea) | \$7.28* |
| Pepto-Bismol OTC (30 ea) | \$5.99 |
| Total | \$53.93 |

Triple therapy

| Medication | Cost |
|-------------------------------|----------|
| Omeprazole 20 mg (30 ea) | \$34.36* |
| Clarithromycin 500 mg (20 ea) | \$85.35† |
| Amoxicillin 500 mg (30 ea) | \$5.96* |
| Total | \$125.67 |

*Cost from the AUCH pocket drug list

†Not included in the AUCH program, cost from www.drugstore.com

Search strategy

- Pub med search: “h pylori triple therapy vs. quadruple therapy”, no limits
- 15 hits
- Hit #3: “triple vs. quadruple therapy for treating h pylori: an updated meta-analysis”
- Hit #5: “triple vs. quadruple therapy for treating h pylori: a meta-analysis”
- I printed both articles. The updated version is a *Letter to the editor* and confirms the given in the first article published but including a newly published study.

Level of evidence

- Level 1a: SR (with homogeneity) of RCTs

VII. BIBLIOGRAPHY/REFERENCES

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VIII. APPRAISAL OF THE EVIDENCE

Refer to attachments.

