H.Pylori Related Peptic Ulcer Disease–Overview

Divya Sanganabhatla, R. Shyam Sunder

Abstract: H. pylori are spiral-shaped bacteria that grow in the digestive tract and have a tendency to attack the stomach lining. H. pylori infections are usually harmless, but they're responsible for the majority of ulcers in the stomach and small intestine. H. pylori are adapted to live in the harsh, acidic environment of the stomach. These bacteria can change the environment around them and reduce its acidity so they can survive. The shape of H. pylori allows them to penetrate your stomach lining, where they're protected by mucus and your body's immune cells are not able to reach them. The bacteria can interfere with your immune response and ensure that they're not destroyed. This can lead to stomach problems. These are diagnosed by various tests clinically. After H. pylori is identified in patients with gastritis or a peptic ulcer, the standard procedure is to eradicate the bacterial infection and allow the ulcer to heal. The typical therapy is a one week “triple therapy” consisting of a proton pump inhibitor such as omeprazole and the antibiotics clarithromycin and amoxicillin. There have been different varieties of the “triple therapy” that have been developed. Some varieties may use a different proton pump inhibitor such as pantoprazole or ranisoprazole. They may also replace the amoxicillin with metronidazole for people who are allergic to penicillin. The new revolutions in therapy have made the treatment of peptic ulcers easier and have made it possible to cure the disease. In prior times only the symptoms were treated using antacids, H2-antagonists or proton pump inhibitors alone. Now further advancements have allowed for the treatment process to even decrease from 14 days to a possible 7-10 day treatment period. With advances in the efficacy of proton pump inhibitors a change in the patients diet is not even necessary.

Keywords: Quadruple therapy; Stool test; Triple therapy; Urea breathe test.

I. INTRODUCTION

Since the introduction of Helicobacter pylori to the medical community by Marshall and Warren almost two decades ago, Helicobacter pylori has been the focus of basic biochemical and clinical research and debate. Its relevance to human disease, specifically to peptic ulcer disease, gastritis, and gastric malignancy, is indisputable. Many questions, however, still remain concerning the optimal diagnostic and therapeutic regimens with which to approach the organism Helicobacter pylori is a gram negative, microaerophilic bacterium that can inhabit various areas of the stomach, particularly the antrum. It causes a chronic low-level inflammation of the stomach lining and is strongly linked to the development of duodenal and gastric ulcers and stomach cancer. Over 80% of individuals infected with the bacteria are asymptomatic. The bacterium was initially named Campylobacter pyloridis, then renamed C. pylori (pylori = genitive of pylorus) to correct a Latin grammar error.

When 16S rRNA gene sequencing and other research showed in 1989 that the bacterium did not belong in the genus Campylobacter, it was placed in its own genus, Helicobacter. The genus derived from the ancient Greek "spiral" or "coiled". The specific epithet pylori means "of the pylorus" or pyloric valve (the circular opening leading from the stomach into the duodenum), from the Ancient Greek word πυλωρός, which means gatekeeper. More than 50% of the world’s population harbor Helicobacter pylori in their upper gastrointestinal tract. Infection is more prevalent in developing countries, and incidence is decreasing in Western countries.

II. PATHOGENESIS

The earliest descriptions of the organism classified it as predominately extracellular, gramnegative, flagellated, and motile. With the advancement of biochemical techniques, new information about the pathogenicity and virulence factors of Helicobacter pylori has emerged, indicating that infection by Helicobacter pylori requires a complex interaction of both bacterial and host factors. Investigators have identified several bacterial proteins necessary for colonization of the gastric mucosa by Helicobacter pylori, including proteins active in the transport of the organism to the surface of the mucosa (eg, flagellin, which is encoded on genes flaA and flaB). Once in the presence of the gastric mucosa, bacteria induce a transient hypochlorhydria by an unknown mechanism. The urease enzyme produced by the bacteria alters the microenvironment of the organism to facilitate colonization. Adherence then occurs via interaction between cell-surface glycolipids and adhesins specific to Helicobacter pylori. There also appears to be a role played by proteins called cecropins, which are produced by Helicobacter pylori and inhibit the growth of competing organisms, as well as by a P-type adenosine triphosphatase, which helps prevent excessive alkalinization of the microenvironment by urease. Once attached to gastric mucosa, Helicobacter pylori causes tissue injury by a complex cascade of events that depends on both the organism and the host. Helicobacter pylori, like all gram negative bacteria, has in its cell wall lipopolysaccharide, which acts to disrupt mucosal integrity. Furthermore, Helicobacter pylori release several pathogenic proteins that induce cell injury. For example, the CagA protein, produced by cytotoxic-associated gene A (cagA), is a highly immunogenic protein that may be associated with more severe clinical syndromes, such as duodenal ulcer and gastric adenocarcinoma (although this question is far from settled). There is increasing evidence that CagA positivity is associated with an increased risk for distal, but not proximal, gastric adenocarcinoma. In addition, protein products of the vacuolating cytotoxin A gene (vacA) and the A gene induced.

Revised Version Manuscript Received on November 02, 2017.

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Published By: Blue Eyes Intelligence Engineering & Sciences Publication Pvt. Ltd.
By contact with epithelium (iceA) are known to be associated with mucosal injury. Once colonization of the gastric mucosa has taken place, the immunogenic properties of Helicobacter pylori induce an inflammatory reaction with neutrophilic gastritis that ultimately results in the clinical manifestations of the infection. This process is mediated by host factors, including interleukins 1, 2, 6, 8, and 12; interferon gamma, tumor necrosis factor, T and B lymphocytes and phagocytic cells. These factors mediate injury through release of reactive oxygen species and inflammatory cytokines. Helicobacter pylori additionally appear to increase the rate of mucosal-programmed cell death (also known as apoptosis) (Tandon R et al., 2000).

C. Serologic Tests
Serologic antibody testing detects immunoglobulin G specific to H. pylori in serum and cannot distinguish between an active infection and a past infection. Serologic tests may be most useful in mass population surveys and in patients who cannot stop taking PPIs (e.g., those with gastrointestinal bleeding or continuous NSAID use) because the tests are not affected by PPI or antibiotic use (Chey WD et al., 2007).

A. Urea Breath Tests
Urea breath tests require the ingestion of urea labeled with the nonradioactive isotope carbon 13 or carbon 14. Specificity and sensitivity approach 100%. Urea breath testing is one option for test of cure and should be performed four to six weeks after completion of eradication therapy. Proton pump inhibitors (PPIs) must be stopped for at least two weeks before the test, and accuracy is lower in patients who have had distal gastrectomy. Cost and inconvenience are disadvantages of this test (Moayyedi P et al., 2006).

B. Stool Monoclonal Antigen Tests
Stool antigen tests using monoclonal antibodies are as accurate as urea breath tests if a validated laboratory-based monoclonal test is used (Talley NJ et al., 2005, Malfertheiner P et al., 2012). They are cheaper and require less equipment than urea breath tests. Like urea breath tests, stool antigen tests detect only active infection and can be used as a test of cure. PPIs should be stopped for two weeks before testing, but stool antigen tests are not as affected by PPI use as are urea breath tests.

D. Endoscopy with Biopsy
Endoscopy with biopsy is recommended to rule out cancer and other serious causes in patients 55 years or older, or with one or more alarm symptoms. In patients who have not been taking a PPI within one to two weeks of endoscopy, or bismuth or an antibiotic within four weeks, the rapid urease test performed on the biopsy specimen provides an accurate, inexpensive means of diagnosing H. pylori infection (Chey WD et al., 2007). Patients who have been on these medications will require histology, with or without rapid urease testing. Culture and polymerase chain reaction allow for susceptibility testing but are not readily available for clinical use in the United States.
III. TREATMENT

Eradication of *H. pylori* is recommended in all patients with PUD. First-line therapy should have an eradication rate of more than 80%.

Because pretreatment susceptibility is rarely known to the primary care physician, therapy must be chosen empirically based on regional bacterial resistance patterns, local recommendations, and drug availability. Table 1 includes treatment options; standard triple therapy is a reasonable initial therapy where clarithromycin resistance is low (Ford AC et al., 2006; Gisbert JP et al., 2010; Wu DC et al., 2010).

Table 1: Treatment Regimens for *Helicobacter pylori* Infection

<table>
<thead>
<tr>
<th>TYPE</th>
<th>REGIMEN</th>
<th>DURATION</th>
<th>ERADICATION RATE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td></td>
<td></td>
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<tr>
<td>Standard triple therapy</td>
<td>PPI, amoxicillin 1 g and clarithromycin 500 mg (Biaxin) twice daily</td>
<td>7 to 10 days (up to 14 days)</td>
<td>70% to 85%</td>
<td>Preferred</td>
</tr>
<tr>
<td></td>
<td>PPI, clarithromycin 500 mg, and metronidazole 500 mg (Flagyl) twice daily</td>
<td>10 to 14 days</td>
<td>70% to 85%</td>
<td></td>
</tr>
<tr>
<td>Sequential therapy</td>
<td>PPI and amoxicillin 1 g twice daily, followed by PPI, clarithromycin 500 mg, and tindazole 500 mg (Tindamax) or metronidazole 500 mg twice daily</td>
<td>10 days (5 days for each regimen)</td>
<td>&gt; 84%</td>
<td>Needs validation in the United States</td>
</tr>
<tr>
<td><strong>Second line</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Non–bismuth-based quadruple therapy (concomitant therapy)</td>
<td>PPI, amoxicillin 1 g, clarithromycin 500 mg, and tindazole 500 mg or metronidazole 500 mg twice daily</td>
<td>10 days</td>
<td>90%</td>
<td>Less complex than sequential therapy with similar eradication rates</td>
</tr>
<tr>
<td>Bismuth-based quadruple therapy</td>
<td>Bismuth subsalicylate 525 mg or subcitrate 300 mg, metronidazole 250 mg, and tetracycline 500 mg, four times daily; and PPI twice daily</td>
<td>10 to 14 days</td>
<td>75% to 90%</td>
<td>May also be used if first-line therapy fails</td>
</tr>
<tr>
<td>Levofloxacín-based triple therapy</td>
<td>PPI and amoxicillin 1 g twice daily, and levofloxacín 500 mg (Levaquin) once daily</td>
<td>10 days</td>
<td></td>
<td>Needs validation in United States; should be used as salvage therapy only</td>
</tr>
</tbody>
</table>

*PPI* = proton pump inhibitor.

Eradication heals most duodenal ulcers and greatly diminishes the risk of recurrent bleeding. A systematic review found that treatment of *H. pylori* infection is more effective than antisecretory noneradicating therapy (with or without long-term maintenance antisecretory therapy) in preventing recurrent bleeding from peptic ulcer. Current data suggest that increasing the duration of therapy to 14 days significantly increases the eradication rate.

A. Standard Triple Therapy

A seven- to 10-day triple drug regimen consisting of a PPI, amoxicillin 1 g, and clarithromycin 500 mg (Biaxin) twice daily has long been the first-line therapy to eradicate *H. pylori*. However, increasing resistance to clarithromycin is associated with declining eradication rates, now well below 80% (Houben MH et al., 1999). Therefore, this regimen is not recommended where the prevalence of clarithromycin-resistant strains of *H. pylori* exceeds 15% to 20%.

An alternative triple drug regimen substitutes metronidazole 500 mg twice daily for amoxicillin. Adding probiotics to triple therapy, specifically *Saccharomyces boulardii* and *Lactobacillus*, has been shown to increase eradication rates (absolute increase of 9% and 5%, respectively) and decrease adverse effects of treatment, particularly diarrhea (absolute decrease of 14% and 7%, respectively) (Szajewska H et al., 2010; Zou J, et al., 2009).

B. Sequential Therapy

Sequential therapy consists of a five-day course of a PPI and amoxicillin 1 g taken twice daily, followed by a five-day course of a PPI, clarithromycin 500 mg, and metronidazole 500 mg (Flagyl).
Or tinidazole 500 mg (Tindamax) taken twice daily. The overall eradication rate is 84%, with an eradication rate of 73% for clarithromycin-resistant strains. A recent meta-analysis of available global data revealed that sequential therapy is superior to seven-day triple therapy, but it is not superior to 14-day triple therapy, bismuth-based quadruple therapy, or non–bismuth-based quadruple therapy (Gisbert JP et al., 2011)

Compliance and tolerance rates of sequential therapy are similar to those of triple therapy but cost is lower, especially when the cost of failure of first-line therapy is considered. However, most studies were performed in Italy, and the ACG guideline states that sequential therapy requires validation in the United States (Ford AC et al., 2006) Non–Bismuth-Based Quadruple Therapy (Concomitant Therapy)

This approach involves the addition of metronidazole 500 mg or tinidazole 500 mg twice daily to the standard triple regimen. It is less complex than sequential therapy with similar eradication rates (Molina-Infante et al., 2012). Additionally, non–bismuth-based quadruple therapy may be more effective than sequential therapy in patients with dual antibiotic resistance to clarithromycin and metronidazole (Berning M et al., 2011). It has the highest eradication rate, about 90%, even in areas with high clarithromycin and metronidazole resistance (Lanza FL et al., 2009, Rostom A et al., 2002) but would presumably cost more than sequential therapy because clarithromycin is taken for 10 days.

C. Bismuth-Based Quadruple Therapy

This is the traditional quadruple regimen and includes a bismuth salt (subsalicylate 525 mg or subcitrate potassium 420 mg), metronidazole 250 mg, and tetracycline 375 to 500 mg, all taken four times daily, in addition to a PPI taken twice per day (Chey WD et al., 2011). Bismuth-based quadruple therapy is often employed as salvage therapy if first-line treatment fails, but it may be used as first-line therapy in areas of high resistance or when cost is an important consideration. A three-in-one combination capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline has been developed to help reduce the pill burden, but patients still have to take three capsules four times per day in addition to a PPI. The regimen is usually given for 10 to 14 days.

D. Levofloxacin-Based Triple Therapy

This is a 10-day regimen of a PPI and amoxicillin 1 g twice daily, and levofloxacin 500 mg (Levaquin) once daily. The ACG states that this regimen requires validation in the United States (Ford AC et al., 2006). It should be reserved for second-line therapy and is better tolerated than bismuth-based quadruple therapy (Houben MH et al., 1999).

E. Tailored Therapy

Since antibiotic resistance is the main cause of eradication failure, a tailored therapy that selects the most appropriate regimen to overcome antibiotic resistance would be the optimal treatment. However, tailored therapies are complex and costly. Therefore, a new method to detect antibiotic resistance is needed. One such solution is the polymerase chain reaction (PCR) kit, which uses the dual-priming oligonucleotide-based multiplex PCR test. This kit identifies the presence of point mutations of clarithromycin 23S rRNA that are known to be associated with resistance, namely, A2142G and A2143G, using a PCR (M. Gerrits et al., 2006). The test can be performed with a sample of gastric mucosa and takes only a few hours, making it relatively simple to use; its sensitivity and specificity are approximately 80–85% (T. J. Hwang et al., 2010).

F. Potassium-Competitive Acid Blocker

The potassium-competitive acid blocker (P-CAB), vonoprazan, could improve eradication rates by increasing the intragastric pH and thus increasing bacterial antibiotic susceptibility. Vonoprazan 20 mg demonstrated a more rapid and sustained acid-inhibitory effect than esomeprazole 20 mg or rabeprazole 10 mg (Y. Sakurai et al., 2015). Recent studies revealed that P-CAB-based triple therapy was more effective than PPI-based triple therapy as a first-line H. pylori eradication method (S. Shichijo et al., 2016, K. Murakami et al., 2016, S. Suzuki et al., 2016). Furthermore, even in the presence of clarithromycin-resistant strains, P-CAB-based triple therapy showed good eradication rates that were superior to those for PPI-based triple therapy (76.1% versus 40.2%) (A. Federico et al., 2014).

Figure 5: Drug Mechanism

IV. CONCLUSION

Many studies have determined that novel agents and treatment regimens can improve eradication of H. pylori. With Standard Triple Therapy, high doses of PPI are used which prolongs, therapy duration and increase eradication rates: indeed, in Europe and some regions of Asia these results are improved further with sequential Therapy. Sequential therapy is less affected by antibiotic resistance, which adds value as an alternative treatment. Newer agents, nontraditional therapy, and microtechnology are also expected to play a major role in H. pylori eradication.
REFERENCES


