Patient Selection and Treatment Strategies for H. pylori Eradication

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Abstract

Helicobacter pylori infection remains a significant clinical issue, as it is associated with peptic ulcer disease, dyspepsia, and gastric cancer. H. pylori testing is the standard of care for patients with ulcers, and multiple treatment guidelines recommend H. pylori testing and treatment as a first-line management strategy in patients with dyspepsia. H. pylori is best diagnosed using a real-time test such as the stool antigen test or urea breath test. The most common treatment strategy for H. pylori in the United States is antimicrobial-based triple therapy with a proton pump inhibitor and two antibiotics, although bismuth-containing quadruple therapy should be considered an equivalent first-line treatment based on efficacy and tolerability. Alternative treatment strategies are becoming increasingly important given the rise in the prevalence of drug-resistant strains of H. pylori. Sequential therapy is promising but requires validation in different patient populations. Other treatment options include levofloxacin and rifabutin. Adherence is a key factor in optimizing treatment outcomes and avoiding resistance. Clinicians should therefore discuss issues of adherence, resistance, and side effects with patients at the beginning of treatment in order to maximize adherence and increase the likelihood of attaining H. pylori eradication.
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Clinical Impact of H. pylori in 2009

Helicobacter pylori remains an important clinical issue in 2009. Worldwide, the prevalence of H. pylori still approximates 50%, with the highest rates in developing countries (80–90%) and lower rates in Western Europe (30–50%), North America (30–40%), and Australia (20%). In the United States, prevalence rates rise dramatically by age from 10% in adolescents to 75% in elderly adults, making H. pylori a fairly common commensal organism and pathogen. The prevalence of H. pylori is, however, clearly decreasing in successive birth cohorts, and future practitioners may not encounter H. pylori and its related diseases. For the next 20 or 30 years, however, we will continue to see both the infection and its disease association.

H. pylori, which is usually acquired in the first year or two of life, is more prevalent in environments of crowding, poor sanitation, and poor socioeconomic conditions. As the United States has moved into a modern era characterized by better sanitation, better socioeconomic conditions, and fewer individuals living in a single household, H. pylori transmission and subsequent infection has largely disappeared. Although these trends suggest a fecal/oral route of transmission can occur, H. pylori is primarily transmitted via an oral/oral route. While the organism can be transmitted in daycare centers, recent data indicate that infected mothers are the greatest risk factor for H. pylori transmission in childhood in areas with low H. pylori prevalence.

Given the continued importance of H. pylori, in 2005, the American Gastroenterological Association (AGA) and the American College of Gastroenterology (ACG) independently published new dyspepsia guidelines recommending that patients 55 years of age or younger without alarm features should receive an H. pylori test and treatment followed by acid suppression if symptoms remain. Despite these clear treatment mandates, H. pylori infection is still not being adequately addressed.

Diseases Associated with H. pylori

H. pylori is a lifelong infection with a varied phenotypic expression, which determines the likely clinical outcomes of infection. All patients with H. pylori exhibit a superficial chronic gastritis, which progresses to chronic, active, antral-predominant gastritis in many, if not most, patients. This phenotype is most associated with an elevated risk of duodenal ulcers. Alternatively, superficial gastritis can develop into chronic, active, corpus predominant gastritis, which is associated with an increased risk of gastric ulcers. A third phenotype involves the development of chronic, atrophic pangastritis with severe atrophy and intestinal metaplasia. These patients are probably at the greatest risk for gastric cancer.

It was always presumed that the H. pylori strain was the primary factor in determining the phenotype expressed in each patient. However, research over the last 5–10 years has revealed that although the strain type is important, the patient’s inflammatory response to infection is equally important in determining the disease expression.

Although a variety of diseases have been associated with H. pylori infection (Table 1), the only conditions with an established causal relationship are peptic ulcer disease, dyspepsia, gastric cancer, and a gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Conditions with a possible link include non-ulcer dyspepsia and iron deficiency. H. pylori is not associated with gastroesophageal reflux disease and coronary artery disease.

Effect of H. pylori Treatment on Clinical Outcomes

In the United States, 60–90% of ulcers in patients not taking NSAIDs are directly related to H. pylori. Determining the causal association of H. pylori in ulcer disease in patients taking NSAIDs has been more challenging. Of the gastrointestinal diseases associated with H. pylori, only peptic ulcers have been shown to profoundly benefit from eradication of the infection. In 1998, Laine and colleagues reported that H. pylori eradication in patients with duodenal ulcers is associated with a reduction in the 6-month ulcer recurrence rate from 63–70% to 18–20%. This report provided clear evidence that H. pylori eradication could alter the natural history of chronic ulcer disease.

The relationship between nonulcer dyspepsia and H. pylori is less clear. Several meta-analyses demonstrate that H. pylori treatment offers a much more limited ben-
Table 1. H. pylori Disease Association

<table>
<thead>
<tr>
<th>Disease</th>
<th>H. pylori causation</th>
<th>Effect of H. pylori eradication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic Ulcer Disease (PUD)</td>
<td>Yes</td>
<td>Reduces recurrence</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Yes in some</td>
<td>Symptom improvement in some</td>
</tr>
<tr>
<td>Nonulcer Dyspepsia (NUD)</td>
<td>Possibly in few</td>
<td>Little effect if any</td>
</tr>
<tr>
<td>Gastric Cancer</td>
<td>Yes</td>
<td>Little effect if any</td>
</tr>
<tr>
<td>MALT Lymphoma</td>
<td>Yes</td>
<td>Remission in &gt;50%</td>
</tr>
<tr>
<td>Iron Deficiency Anemia (IDA)</td>
<td>Likely in some</td>
<td>Improvement in some</td>
</tr>
<tr>
<td>NSAID Ulcers</td>
<td>Naïve users?</td>
<td>May reduce incidence</td>
</tr>
<tr>
<td>Gastroesophageal Reflux Disease (GERD)</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Coronary Artery Disease (CAD)</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>


PUD=peptic ulcer disease; NUD=nonulcer dyspepsia; MALT=mucosa-associated lymphoid tissue; IDA=iron-deficiency anemia; NSAID=nonsteroidal anti-inflammatory drug; CAD=coronary artery disease; GERD=gastroesophageal reflux disease.

Table 2. Accuracy of Non-Invasive Tests for H. pylori Infection

<table>
<thead>
<tr>
<th>Test</th>
<th>Percentages (%)</th>
<th>Percentages (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool antigen test</td>
<td>96.1</td>
<td>95.7</td>
</tr>
<tr>
<td>Urea breath test</td>
<td>95.2</td>
<td>89.7</td>
</tr>
<tr>
<td>Serum IgG antibody</td>
<td>85.0</td>
<td>79.0</td>
</tr>
</tbody>
</table>

Selecting Patients for H. pylori Testing

H. pylori testing is the standard of care for patients with ulcers regardless of their history of NSAID use. With regard to dyspepsia, both the AGA and ACG guidelines recommend that for patients 55 years old or younger without alarm features, H. pylori testing and treatment should be a first-line management strategy.5,6 The role of H. pylori testing is less clear for patients with nonulcer dyspepsia, though one could argue for testing those patients as well. Finally, patients with MALT lymphomas should also be tested for H. pylori.

Choosing an H. pylori Diagnostic Test

A variety of H. pylori diagnostic tests are available, including endoscopic tests, multiple serologic tests, and several real-time tests. The serologic tests should no longer be used, based on their limited sensitivity and specificity in populations with a relatively low prevalence of H. pylori. Instead, if the patient is undergoing endoscopy, a biopsy test such as a histology or rapid urease test is an appropriate testing modality. For patients not undergoing endoscopy, one of the real-time, noninvasive tests should be used, such as the stool antigen test, which detects H. pylori antigen in stool, or the urea breath test, which detects 13C-labeled or 14C-labeled CO2 that is expired as a result of H. pylori-associated urease activity present in the stomach.13 Both of these tests are more accurate than the serologic test, with sensitivities and specificities of 90–96%, compared with 79–85% using serology (Table 2). Based on the poor performance of serologic testing in low-prevalence populations and its inability to confirm eradication, the AGA guidelines recommend a real-time test for both the initial diagnosis and for confirming eradication.7

Clinicians may choose between the stool antigen test and the urea breath test based on several convenience factors. The stool antigen test is acquired at home, whereas the urea breath test is performed at the office. The stool antigen test also requires no office staff training, has pediatric labeling, and is less affected by concomitant PPI use and can be used during the continuum of therapy.

Within the category of fecal antigen tests, two types of assays have been developed. The original fecal antigen test,
a polyclonal test, could accurately detect *H. pylori* infection before therapy but was not reliable for proving eradication of *H. pylori* infection after a course of antibiotic therapy. Subsequently, a monoclonal test was developed which is accurate both before and after therapy. Clinicians should verify which of these tests their laboratory is performing in selecting which real-time test to use.

**References**

Selecting a Therapeutic Regimen and Optimizing Outcomes
William D. Chey, MD

The ACG guidelines1 and the Maastricht III Consensus Conference guidelines from Europe2 have endorsed two first-line treatment regimens for *H. pylori* infection. The first option, triple therapy using a proton pump inhibitor (PPI) plus two antibiotics, is more familiar to US clinicians than the second option, bismuth-containing quadruple therapy.

**Triple Therapy for *H. pylori***

The recommended triple therapy regimen for *H. pylori* is a PPI plus clarithromycin (500 mg) and amoxicillin (1 g) or metronidazole (500 mg), with all components taken twice daily for 7–14 days. Randomized, controlled trials conducted in the United States and in other countries have shown eradication rates of 70–80% with this regimen.3 The optimal duration of *H. pylori* therapy remains controversial. After a recent meta-analysis4 suggested that 14 days of therapy may be superior to 7 days, the 2007 ACG *H. pylori* treatment guidelines continued to recommend a treatment duration of 10–14 days.5

The efficacy of triple therapy can be compromised by the presence of drug-resistant strains of *H. pylori*. Clarithromycin resistance is increasing in the United States, and was detected in 13% of patients in 2004.6 Patients with clarithromycin-resistant strains are 40% less likely to attain eradication with triple therapy.7,8 Unfortunately, increasing the dose of clarithromycin does not appear to improve eradication rates. Moreover, recent data suggest that previous macrolide exposure increases the likelihood of harboring clarithromycin-resistant *H. pylori*, which in turn affects the efficacy of triple therapy.9 As such, the recent ACG guidelines recommend that providers ask patients about previous macrolide use, in particular with regard to clarithromycin. Clinicians may want to reconsider the use of traditional triple therapy in patients with previous macrolide exposure.

**Quadruple Therapy for *H. pylori***

The other recommended first-line treatment regimen for *H. pylori* is quadruple therapy consisting of a PPI given twice daily plus bismuth, metronidazole, and tetracycline. Clinical trials of quadruple therapy have investigated a wide range of doses, dosing regimens, and treatment durations, with most studies dosing the drugs four times daily for 7–14 days. Quadruple therapy has typically achieved eradication rates of 75–93%.10,11

Many clinicians have concerns regarding the tolerability of quadruple therapy. However, most side effects associated with the regimen are minor and do not lead to discontinuation of therapy. Another concern is adherence, given the high pill burden associated with the treatment. This issue may be improved by the recent development of a capsule that incorporates bismuth, metronidazole, and tetracycline into a single formulation.11 The FDA-approved dosing regimen with this triple capsule does reduce the overall number of capsules, but still requires dosing four times each day. Studies to address the feasibility of less frequent dosing are eagerly awaited, but have not yet been conducted.

**Efficacy of Triple Therapy Versus Quadruple Therapy***

In a recent meta-analysis, my colleagues and I found that triple therapy and quadruple therapy offer equivalent overall efficacy, with no statistically significant difference in eradication rates (relative risk of quadruple vs triple therapy, 1.002; 95% confidence interval, 0.936–1.073).12 Our analysis also showed no difference in the incidence of side effects or compliance between the two regimens. Based on these findings, clinicians should consider clarithromycin-based triple therapy and bismuth-based quadruple therapy as equal partners when making decisions about first-line therapy in patients with *H. pylori* infection.

**Sequential Therapy***

Sequential therapy is a newer treatment strategy for *H. pylori* treatment in which antimicrobials are administered sequentially rather than concurrently. Although sequential therapy is discussed in the ACG and European guidelines,
neither endorses sequential therapy as a routine first-line treatment option.

The most well studied sequential therapy is a 10-day regimen consisting of a 5-day course of a PPI and amoxicillin given twice daily followed by 5 days of triple therapy with a PPI, clarithromycin, and tinidazole given twice daily. In recent randomized trials from Italy, sequential therapy has yielded modified intention-to-treat eradication rates exceeding 90%. In a meta-analysis of 10 randomized, controlled trials involving 2,747 patients, Jafri and colleagues reported a high intention-to-treat eradication rate with sequential therapy versus clarithromycin-based triple therapy (93% vs 77%). The benefits of sequential therapy were particularly notable in patients infected with clarithromycin-resistant strains of H. pylori. The reasons underlying the improved eradication rates with sequential therapy in patients with clarithromycin resistance are not fully understood. Some-what surprisingly, despite the apparent complexity of the regimen, compliance and tolerability were similar between sequential therapy and triple therapy.

A major limitation of the evidence supporting sequential therapy is that nearly all of the studies have been conducted in Italy, including all 10 trials included in the meta-analysis. In a Spanish study, Sánchez-Delgado and colleagues confirmed a high intention-to-treat eradication rate with sequential therapy of 84%, although this pilot study of 139 patients had no control group of patients receiving triple therapy.

Two other studies presented at Digestive Disease Week 2008 provided additional insight on the efficacy of different treatment strategies. Investigators from Panama conducted a randomized, controlled trial comparing sequential therapy to traditional triple therapy and found no differences in eradication rates. However, the study reported eradication rates above 85% with both regimens, which is higher than has been reported with triple therapy in other parts of the world. A study from Taiwan investigated whether sequential therapy must be given using the current protocol, or whether the four components of sequential therapy would be equally effective if given as concurrent combination therapy. The investigators found no significant differences in eradication rates with sequential versus concurrent therapy.

Thus, many questions remain regarding the optimal treatment strategy. Data suggest that sequential therapy is at least as effective as traditional triple therapy. However, the superiority of sequential therapy over triple therapy requires validation outside of Italy. Indeed, the Panamanian study suggested no significant benefit with sequential therapy over triple therapy. The question of whether the agents in sequential therapy can be given concurrently is another important question. Based on these unanswered questions, it is appropriate that recent guidelines discuss sequential therapy as a possible treatment option but do not formally recommend it as a standard first-line treatment option.

**Confirming Eradication After Treatment**

Although many clinicians are familiar with the indications for initial H. pylori testing, some are falling short on ordering follow-up testing to prove H. pylori eradication after a course of antimicrobial therapy. Real-time testing should be performed after the completion of H. pylori treatment in patients with complicated ulcers, patients with persistent symptoms despite treatment, and in any patient who requests testing. Confirmatory testing should also be performed in patients treated for MALT lymphoma and in those who have undergone resection of early gastric cancer.

Given that 20–25% of patients fail to attain eradication with triple therapy, follow-up testing is crucial for confirming eradication in order to avoid recurrent ulcer complications and other potential consequences of persistent H. pylori infection. Follow-up testing can also avoid an unnecessary second-line therapy in patients with persistent symptoms despite eradication. This is a real possibility, as persistent symptoms do not always equate with the presence of persistent infection, particularly in patients with dyspepsia. Although 70–80% of patients with H. pylori infection are cured by first-line therapy, concurrent symptom improvement can be expected in only 30–50% of patients with dyspepsia. Thus, many patients remain symptomatic after successful eradication of their infection.

Follow-up testing should generally be performed at least 4 weeks after the completion of therapy. Some clinicians instead conduct follow-up testing 4 weeks after the start of therapy, which provides less reliable results.

**References**

Clarithromycin resistance is a major problem in the treatment of *H. pylori* infection, as it causes failure of triple therapy. An estimated 60% of patients with clarithromycin resistance will not achieve eradication with triple therapy, resulting in regrowth of *H. pylori* up to pretreatment levels. However, several alternative treatment strategies are available for these patients.

**Quadruple Therapy**

The foremost treatment alternative for patients with a history of treatment with clarithromycin is the utilization of a regimen that does not contain clarithromycin. The best established regimen in this category is bismuth-based quadruple therapy, which has demonstrated eradication rates as high as 93% among patients with confirmed *H. pylori* infection and of 68% in those who have previously failed clarithromycin-based therapy. Quadruple therapy is therefore my first choice when triple therapy fails, and is the most logical alternative for patients with clarithromycin resistance. In fact, given the rising incidence of clarithromycin resistance and the current endorsement of bismuth-based quadruple therapy as a possible first-line therapy, initial use of quadruple therapy may be indicated in order to minimize the need for multiple therapeutic courses, particularly in those populations where clarithromycin resistance is very prevalent.

**Levofloxacin Triple Therapy**

Another alternative in patients refractory to initial treatment is levofloxacin triple therapy, a 10-day course of PPI, levofloxacin, and amoxicillin. Advantages of levofloxacin include its familiarity among most clinicians, its wide usage, and its fairly positive risk/benefit profile. The major disadvantage of this approach is the high risk of developing levofloxacin resistance. In Germany, levofloxacin resistance can be detected in 22% of *H. pylori* strains. Based on the risk of resistance, levofloxacin should probably not be recommended as an initial second-line treatment. Instead, it is best reserved as a third-line treatment after the failure of both triple and quadruple therapies. Multiple studies and meta-analyses have demonstrated the efficacy of levofloxacin in this setting, although resistance continues to be a concern.

**Rifabutin Triple Therapy**

The other treatment strategy appropriate for second-line or third-line therapy is triple therapy using rifabutin, an antimicrobial drug that has been used in the treatment of microbacterial infections. Studies have demonstrated the efficacy of rifabutin in patients with resistant *H. pylori* infection. A major drawback of the agent is its toxicity, which limits its applicability. Rifabutin is primarily associated with bone marrow suppression, which can result in leukopenia and thrombocytopenia. However, these side effects are relatively uncommon and, therefore, rifabutin is still a viable drug when other treatment regimens have failed.

**Sequential Therapy**

The sequential therapy strategy discussed by Dr. Chey is another treatment alternative for patients with clarithromycin resistance. The regimen is most likely effective as it contains the drugs contained in quadruple therapy—kinetazole, metronidazole, amoxicillin, and a PPI—though administering the drugs sequentially may offer some additional benefit. One theoretical advantage of sequential therapy is that the initial administration of a PPI plus amoxicillin may first weaken the *H. pylori* cell wall, making the organisms more susceptible to the subsequent antimicrobial combination of kinetazole, clarithromycin, and amoxicillin. Sequential therapy has demonstrated high (90%) overall eradication rates even in countries with a high prevalence of clarithromycin resistance. Analyses of patients with documented resistance show that although results with sequential therapy are promising, they do not establish the worldwide efficacy of this approach for patients with clarithromycin resistance. In clinical practice, I typically use triple therapy and quadruple therapy as first-line and second-line treatments before proceeding to other options. I then proceed to levofloxacin triple therapy, followed by sequential therapy or rifabutin, although the order depends on the patient’s treatment history.

**Adherence to *H. pylori* Treatment**

Adherence is an important issue in *H. pylori* treatment, as it is a major unrecognized cause of treatment failure. Among patients taking a 10-day regimen, those who take their
medications for fewer than 6 days have higher failure rates. In a large multicenter trial evaluating triple therapy, 30% of patients with treatment failure had no detectable drug resistance, but did have problems with adherence. Factors important to adherence include the convenience of dosing, side effect profile, and duration of therapy.

Clinicians can take a few simple steps to maximize the likelihood of adherence, which in turn increases treatment efficacy and minimizes drug resistance. First, they can discuss with patients the risk of resistance and its association with adherence. If patients understand that discontinuing clarithromycin-based therapy, for example, leads to clarithromycin resistance in 40–50% of cases, they may be dissuaded from stopping treatment prematurely. Second, clinicians can warn patients about the most common side effects associated with their regimen. I routinely warn patients about temporary taste disturbances with clarithromycin and loose bowel movements with amoxicillin, which can be controlled with immodium if necessary. Patients taking metronidazole are forewarned about metallic taste and dark urine color, whereas patients starting bismuth are warned about black stools, so they do not worry needlessly and discontinue medication abruptly. Warning patients again of side effects associated with their regimen.

Other measures to enhance adherence, such as having a pharmacist call patients to discuss the treatment before and during therapy, also result in improved outcomes. Although such practices may be difficult to implement, they do highlight the importance of spending a few minutes talking with patients about the importance of adherence.

As Dr. Chey discussed, re-treatment should typically be performed a month after the completion of therapy. In my practice, I typically retest patients after approximately 4 weeks and then begin the next round of treatment if necessary. Another reason for waiting to retest and start second-line therapy is to allow patients to recover from side effects of the first course of therapy.

References

**The New AGA Dyspepsia Guideline**

- Symptoms without GERD or NMD:
  - Age > 50
  - Alarm symptoms present
- Endoscopy
- Test for H. pylori
  - Negative
  - Positive
- PPI trial 1 week
- Test for H. pylori
- Reressor/Basal test
- H. pylori negative
- Denote ESG

Adapted from Talley et al. Gastroenterology, 2004;128:1753-1765

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**U.S. Prevalence of H. pylori**

- African American
- Hispanic
- White

Adapted from McCullough and director. Gastroenterology, 2005;128:1753-1765

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**H. pylori: Disease Progression**

- H. pylori infection
- Chronic, active, atrophic gastritis
- Peptic ulcer disease
- Acid secretion

Adapted from Lanza. Am J Gastroenterol. 1999;94:877-889

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**Primary Therapy for H. pylori**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>qid</td>
<td>15-14 d</td>
</tr>
<tr>
<td>Omeprazole 50 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole 500 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI</td>
<td>tid</td>
<td>10-14 d</td>
</tr>
<tr>
<td>Tetracycline 500 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine (priprazine 525 mg or subprazine 42C mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole 350-500 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Chew and Wong. Am J Gastroenterol. 2007;102:1805
Triple vs. Quadruple Therapy for *H. pylori* Infection: A Meta-analysis

- **Percentage**
  - ITT Cure: Triple vs. Quadruple
    - 76 vs. 78%
  - Side Effects: Triple vs. Quadruple
    - 50 vs. 53%

- **8 RCTs**
  - N=1,029

Adapted from Luther et al. *Am J Gastroenterol.* 2000;103:3387

Effect of Antibiotic Resistance on the Efficacy of First-line *H. pylori* Therapies

- **Eradication rate – modified ITT (%)**
  - All patients: Triple vs. Quadruple
    - 76.2 vs. 86.4%
  - Metronidazole: Triple vs. Quadruple
    - 11.8 vs. 14.9%

Adapted from Laine et al. *Am J Gastroenterol.* 2003;98:592

What is Sequential Therapy?

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI + Amoxicillin 1 gm</td>
<td>BID</td>
<td>5 d.</td>
</tr>
<tr>
<td>PPI, Clarithromycin 500 mg,</td>
<td>BID</td>
<td>5 d.</td>
</tr>
<tr>
<td>Tinidazole 500 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Zulu et al. *Am J Pharmaco Ther.* 2003;17:71

Meta-analysis of Sequential vs. Triple Therapy for *H. pylori*

- **10 RCTs**
- Publication bias, only 1 DB, most Italian

- **Success Rate**
  - Sequential: 91 vs. 87%
  - Triple: 72 vs. 87%

Adapted from Jafar et al. *Ann Intern Med.* 2006:145

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