

Brief description of patient problem/setting (summarize the case very briefly)

A 28-year-old female presents with 4 days of abdominal bloating after eating, dyspepsia, and epigastric discomfort. She states she experienced similar symptoms 3 months ago and was diagnosed with a *Helicobacter Pylori* (H.Pylori) infection. In her previous visit, she was prescribed triple therapy, and she states she completed her treatment. Her abdominal exam demonstrates periumbilical and left upper quadrant tenderness to palpation. An in-office urea breath test was performed, a referral to a gastroenterologist was given for a potential endoscopy, and pantoprazole was prescribed. This clinical case involves determining whether her recurrent symptoms are due to persistent H. pylori infection after prior treatment and identifying the most appropriate second-line therapy.

Search Question: In adults with a persistent H.Pylori infection after treatment failure with clarithromycin-based triple therapy, does bismuth- based quadruple therapy, compared to second-line regimens (e.g., levofloxacin-based triple therapy), result in higher rates of eradication?

Question Type: What type of question is this?

☒ **Treatment** ☐ Diagnosis ☐ Prognosis ☐ Screening ☐ Prevalence ☐ Harms

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)?

If a systematic review or meta-analysis is not available, then I would use randomized controlled trials (RCTs) instead because they still provide a high level of evidence. RCTs can reduce bias through blinding and can assess eradication rates between different treatment groups, comparing how each responds to various H.Pylori therapies. I would also consider using large prospective cohort studies as well, since this type of study can monitor outcomes such as evaluating eradication success, and recurrence rates. Retrospective cohort studies can also be valuable in providing early treatment protocols.

PICO Search Terms

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Helicobacter pylori	Bismuth quadruple therapy	Levofloxacin triple therapy	Eradication rate
Persistent H.Pylori	Second-line therapy	Alternative second-line regimens	H.Pylori eradication
H.Pylori eradication failure			Cure rate
Triple therapy failure			

Search tools and strategy used:

Please indicate what databases/tools you used, provide a list of the terms you searched together in each tool, and how many articles were returned using those terms and filters.

Database	Search Terms Used	Number of Results	Filters/Limiters Applied	Notes/Observations
PubMed	Helicobacter pylori AND bismuth quadruple therapy AND treatment failure	121	English language, Published in the last 10 years, RCT or systematic review	Broad coverage of articles that evaluate regimens for persistent H.Pylori infection

Google Scholar	Helicobacter pylori AND second-line therapy	3,040	2020-2026; sorted by relevance, review articles prioritized	Results including systematic reviews and randomized controlled trials evaluating second-line therapies.
CINAHL Complete	Helicobacter pylori AND second-line AND eradication	28	Peer-reviewed, English language, past 10 years	Results focused mainly on randomized controlled trials and other clinical studies evaluating second-line regimens.

A systematic search was conducted using three reliable sources, PubMed, Google Scholar, and CINAHL, to identify relevant studies evaluating treatment, specifically second-line therapy options for H. pylori infection.

Results found:

Identify at least 3 articles (or other appropriate reputable sources) that answer your specific question with the highest available level of evidence.

1. Third-line and rescue therapy for refractory *Helicobacter pylori* infection: A systematic review <https://pmc.ncbi.nlm.nih.gov/articles/PMC9846933/>

Nyssen, O. P., Vaira, D., Saracino, I. M., Fiorini, G., Caldas, M., Bujanda, L., et al. (2023).

Third-line and rescue therapy for refractory *Helicobacter pylori* infection: A systematic review. *Helicobacter*, 28(1), e12936. <https://doi.org/10.1111/hel.12936>

Abstract

Background: Due to increasing resistance rates of *Helicobacter pylori* (H. pylori) to different antibiotics, failures in eradication therapies are becoming more frequent. Even though eradication criteria and treatment algorithms for first-line and second-line therapy against H. pylori infection are well-established, there is no clear recommendation for third-line and rescue therapy in refractory H. pylori infection.

Objective: To perform a systematic review evaluating the efficacy and safety of rescue therapies against refractory H. pylori infection.

Methods: A systematic search of available rescue treatments for refractory H. pylori infection was conducted on the National Library of Medicine's PubMed search platform based on PRISMA guidelines. Randomized or non-randomized clinical trials and observational studies evaluating the effectiveness of H. pylori infection rescue therapies were included.

Results: Twenty-eight studies were included in the analysis. For third-line treatment, mean eradication rates (ITT/PP) were: rifabutin-based triple therapy (81.6%/84.4%), sitafloxacin-based triple therapy (79.4%/81.5%), levofloxacin-based triple therapy (55.7%/60.6%), and metronidazole-based triple therapy (62.0%/63.0%). For third-line quadruple therapy, mean eradication rates were: bismuth quadruple therapy (69.2%/72.1%), BQT-Pylera (88.9%/90.9%), and non-BQT (61.3%/64.2%).

Conclusion: Sitafloxacin-based triple therapy containing vonoprazan is recommended in regions with low macrolide resistance. In regions with known macrolide resistance or unavailability of bismuth, rifabutin-based triple therapy is recommended.

Why I chose this article:

I chose this article because it is a systematic review and was conducted in recent years. It focuses on analyzing treatment for refractory H. Pylori infection, assessing third-line medications, and rescue therapy. This directly aligns with my PICO question, which focuses on treatments for recurrent H. Pylori and assessing failure from clarithromycin triple therapy. This article addresses treatment failure and compares multiple treatments to compare eradication outcomes, including different types of triple therapy and quadruple therapy. Additionally, the article used PRISMA guidelines, which provide a strength to the evidence that helps answer my PICO question. The systematic review also includes both randomized and observational studies, which provide a comprehensive evaluation of treatment strategies. Also, I found it interesting to learn that eradication treatment success depends on the region and its patterns of antibiotic resistance.

Key Points:

1. 28 studies were included that evaluated third-line and rescue therapies for refractory H. Pylori, and included RCT and observational studies
2. Eradication rates were reported for triple therapy and quadruple therapy; rifabutin and sitafloxacin triple therapies had higher rates of success in comparison to levofloxacin-based triple therapy
3. Bismuth-based quadruple therapy showed moderate eradication success, with standardized formulations (Pylera) demonstrating a much higher success rate.
4. Treatment efficacy depended on antibiotic resistance patterns in different regions

2. **A Randomized Control Trial Comparing 2 Levofloxacin-Containing Second-Line Therapies for Helicobacter pylori Eradication** <https://pubmed.ncbi.nlm.nih.gov/27175657/>

Chuah, S. K., Liang, C. M., Lee, C. H., et al. (2016). A randomized control trial comparing 2 levofloxacin-containing second-line therapies for Helicobacter pylori eradication. *Medicine*, 95(19), e3586. <https://doi.org/10.1097/MD.0000000000003586>

Abstract

Background: Lengthy exposure to quinolone-containing triple therapy in Helicobacter pylori eradication leads to the development of drug resistance. Sequential therapy with a quinolone and metronidazole-containing regimen appears to be an effective treatment option.

Objective: To compare the efficacy of 5-plus-5 days' levofloxacin and metronidazole-containing sequential therapy (EALM) with that of 10-day levofloxacin-containing triple therapy (EAL) in second-line H. pylori eradication treatment.

Methods: One hundred and sixty-four patients who had failed H. pylori eradication using standard triple therapy were randomly assigned to either EALM therapy (n=82; esomeprazole 40 mg bid and amoxicillin 1 g bid for 5 days, followed by esomeprazole 40 mg bid, levofloxacin 500 mg qd, and metronidazole 500 mg tid for 5 days) or 10-day EAL therapy (n=82; levofloxacin 500 mg qd, amoxicillin 1 g bid, and esomeprazole 40 mg bid). Follow-up for H. pylori status was performed 4 to 8 weeks later.

Results: Eradication rates for EALM and EAL groups were 90.2% (95% CI 83.7%-96.8%) and 80.5% (95% CI 71.7%-89.2%, P=0.077) in intention-to-treat analysis; and 91.4% (95% CI 85.1%-97.6%) and 81.5% (95% CI 72.8%-90.1%, P=0.067) in per-protocol analysis. Adverse events were 23.5% vs 11.1% (P=0.038) but were mild and well tolerated.

Conclusion: Levofloxacin and metronidazole-containing sequential therapy achieved >90% eradication rate as second-line H. pylori therapy. Dual antibiotic resistance to levofloxacin and metronidazole was the clinical factor influencing efficacy in the sequential therapy group.

Why I chose this article:

I decided to select this article because it is a randomized controlled trial on the second-line treatments for persistent H. Pylori after failed triple therapy. This study directly aligns with my PICO question regarding second-line regimens and eradication success rates. The RCT specifically focused on levofloxacin and metronidazole regimens, which are commonly used as alternative treatments, and this is important when assessing the difference between other first-line therapies. It was interesting to see

that eradication rates were higher with EALM therapy (consisting of PPI, levofloxacin, amoxicillin, and metronidazole) as sequential treatment instead of the typical levofloxacin triple therapy.

Key Points:

1. An RCT was conducted on 164 patients who failed first-line triple therapy.
2. Levofloxacin and metronidazole therapy (EALM) was compared with levofloxacin triple therapy (EAL).
3. Eradication success rates were higher with second-line therapy (90.2%) instead of levofloxacin-based triple therapy (81.5%)

3. Efficacy of second-line regimens for *Helicobacter pylori* eradication treatment: a systematic review and network meta-analysis

<https://bmjopengastro.bmj.com/content/7/1/e000472>

Chang, Y. L., Tung, Y. C., Tu, Y. K., Yeh, H. Z., Yang, J. C., Hsu, P. I., et al. (2020). Efficacy of second-line regimens for *Helicobacter pylori* eradication treatment: a systematic review and network meta-analysis. *BMJ Open Gastroenterology*, 7(1), e000472.

<https://doi.org/10.1136/bmjgast-2020-000472>

Abstract

Current guidelines recommend bismuth-containing quadruple therapy (BQT) and quinolone-containing therapy after failure of first-line *Helicobacter pylori* eradication therapy. However, the optimum regimen of second-line eradication therapy remains elusive.

Objective

To compare the relative efficacy of 16 second-line *H. pylori* eradication regimens through network meta-analysis.

Methods

Three major bibliographic databases were reviewed to enrol relevant randomised controlled trials between January 2000 and September 2018. Network meta-analysis was conducted by STATA software and we performed subgroup analysis in countries with high clarithromycin resistance and high levofloxacin resistance, and in patients with documented failure of first-line triple therapy.

Results

Fifty-four studies totalling 8752 participants who received 16 regimens were eligible for analysis. Compared with a 7-day BQT, use of probiotic add-on therapy during, before, and after second-line antibiotic regimens, quinolone-based sequential therapy for 10–14 days, quinolone-based bismuth

quadruple therapy for 10–14 days, bismuth quadruple therapy for 10–14 days, and quinolone-based triple therapy for 10–14 days were significantly superior to the other regimens. Subgroup analysis of countries with high clarithromycin resistance and high levofloxacin resistance revealed that the ranking of second-line eradication regimens was distributed similarly in each group, as well as in patients with failure of first-line triple therapy.

Conclusion

We conducted a detailed comparison of second-line *H. pylori* regimens according to different antibiotic resistance rates, and the results suggest alternative treatment choices with potential benefits beyond those that could be achieved using salvage therapies recommended by guidelines.

Why I chose this article:

I chose this article since it is a network meta-analysis that compares various second-line therapies for *H. Pylori* after failed first-line treatment. This study analyzes 54 RCT which included over 8,000 participants and also compares 16 second-line therapies; this allows for a broad overview of eradication. This study also answers my PICO question since it emphasizes treatments after failed triple therapy, such as clarithromycin-based triple therapy. Usually, other studies focus on a few regimens, but this one looks at 16, which does give a better understanding of which works best. Additionally, it also assesses the antibiotic resistance, which is important to consider when prescribing even more antibiotics after failed initial treatment.

Key Points:

1. Included 54 RCTs with over 8,000 participants, and compared 16 second-line therapies.
2. Regimens that were prescribed for a longer period of time demonstrated more success in eradication (10 to 14 days versus 7 days).
3. Treatment regimens that included fluoroquinolones or bismuth quadruple therapy demonstrated higher eradication compared to shorter courses

Clinical Bottom line:

Overall, the patient from the case, a 28-year-old female with persistent *H. Pylori* after completing triple therapy, these articles help address this concern for patients like her. Current evidence suggests using longer second-line therapies for complete eradication, stating that extending treatment to 10-14 days is very effective. Based on these sources, it was concluded that bismuth-based quadruple therapy and regimens containing a fluoroquinolone are most effective. The evidence suggests that shorter regimen courses were not as effective. What was one of the most important things to consider as well, was how crucial knowing antibiotic resistance patterns is. Knowing this, the patient from the clinical scenario

would most benefit from a longer course of second-line therapy and taking bismuth quadruple therapy or fluoroquinolone-based therapy. However, to fully eradicate or reduce the risk of failure again, it should overall depend on resistance patterns per region, medication availability, adverse effects to consider, and patient adherence.

RESPONSES:

Hey Tara,

I enjoyed reading your PICO on psoriasis, and when it is appropriate to refer. Your patient case reflects a common condition that patients commonly have and can also be encountered in primary care settings, not just in dermatology, as patients will get referred once seen by their PCP. I remember seeing a case of psoriasis in my family medicine rotation as well, and similarly, the patient presented with silvery scales throughout the body, and had to be referred to dermatology. I think you did a great job highlighting the diagnostic challenges that a primary care provider might face, as this condition has to be distinguished from other skin conditions, such as eczema, which it can be potentially mistaken for. Additionally, you also mentioned how dermatology referral can help provide a more accurate diagnosis, which I agree as it can help when a diagnosis is unclear and this can guide better treatment decisions; this demonstrates how primary care can play a role in early recognition and start initial management as well. Overall, great post on recognizing primary care and dermatology collaboration in managing patients with psoriasis.

Hey Abby,

This is a great topic to discuss for your PICO, because this is commonly encountered in emergency medicine and ambulatory medicine settings. Similarly, in Ambulatory care, I also encountered a patient for a follow-up laceration wound, and found myself wondering what the next appropriate steps would be based on its appearance, if adding steri strips, suture removal, or continued observation would be most appropriate. This is challenging for providers because they have to decide how to manage a laceration, and must think quickly while considering the outcome and any potential complication risks, but I figured this is something we will learn once we become clinicians through repeated exposure. The articles you chose were strong, and one key takeaway I got from them was that the cosmetic outcomes were similar between adhesives and sutures, which suggests that sutures did not necessarily provide better aesthetic results. I also like how you emphasized the advantages and disadvantages of using adhesives, such as shorter procedure time and reduced pain during closure, but a high risk of wound dehiscence. Overall, the evidence provided was strong and answered your PICO question.

Hi Siri,

I thought you chose a great PICO question since it does address a challenging clinical scenario, especially in the geriatric population, with both ESRD and HFrEF, as managing volume overload can be difficult. Your case does highlight how complex cardiorenal syndrome is, and why providers struggle to choose the most effective fluid management strategy. At my Ambulatory Care rotation, I realized how crucial it is to monitor a patient's renal function when they have CKD. I find these cases to be moderate to high complexity, given the meticulous management. From your post, I learned about the concept of ultrafiltration, and a key point that also stood out was how it can reduce heart failure hospitalizations without further worsening renal function. At the same time, your conclusion made it clear that there is limited evidence in improving mortality, which I think is necessary to acknowledge that this can occur in the geriatric demographic with multiple comorbidities. Overall, your post demonstrates how ultrafiltration is an appropriate option, but there are also other options that are still first-line in management, such as diuretics. Great job on tackling this complicated topic.

