

CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on the Management of Refractory *Helicobacter pylori* Infection: Expert Review



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The purpose of this CPU Expert Review is to provide clinicians with guidance on the management of *Helicobacter pylori* after an initial attempt at eradication therapy fails, including best practice advice on specific regimen selection, and consideration of patient and systems factors that contribute to treatment efficacy. This Expert Review is not a formal systematic review, but is based upon a review of the literature to provide practical advice. No formal rating of the strength or quality of the evidence was carried out. Accordingly, a combination of available evidence and consensus-based expert opinion were used to develop these best practice advice statements.

Keywords: Antibiotics; Clinical Management; Proton Pump Inhibitor; CYP2C19; Gastro Neoplasm; Adherence.

BEST PRACTICE ADVICE STATEMENTS

Best Practice Advice 1: The usual cause of refractory *Helicobacter pylori* infection (persistent infection after attempting eradication therapy) is antibiotic resistance. Providers should attempt to identify other contributing etiologies, including inadequate adherence to therapy and insufficient gastric acid suppression.

Best Practice Advice 2: Providers should conduct a thorough review of prior antibiotic exposures. If there is a history of any treatment with macrolides or fluoroquinolones, then clarithromycin- or levofloxacin-based regimens, respectively, should be avoided given the high likelihood of resistance. By contrast, resistance to amoxicillin, tetracycline, and rifabutin is rare, and these can be considered for subsequent therapies in refractory *H pylori* infection.

Best Practice Advice 3: Eradication regimens for *H pylori* are complex and might not be fully comprehended by patients. Barriers to adherence should be explored and addressed prior to prescribing therapy. Providers should explain the rationale for therapy, dosing instructions, expected adverse events, and the importance of completing the full therapeutic course.

Best Practice Advice 4: If bismuth quadruple therapy failed as a first-line treatment, shared decision making between providers and patients should guide selection between (a) levofloxacin- or rifabutin-based triple-therapy regimens with high-dose dual proton pump inhibitor (PPI) and amoxicillin, and (b) an alternative bismuth-containing quadruple therapy, as second-line options.

Best Practice Advice 5: When using metronidazole-containing regimens, providers should consider adequate dosing of metronidazole (1.5–2 g daily in divided doses)

with concomitant bismuth therapy, because this may improve eradication success rates irrespective of observed in vitro metronidazole resistance.

Best Practice Advice 6: In the absence of a history of anaphylaxis, penicillin allergy testing should be considered in a patient labeled as having this allergy in order to delist penicillin as an allergy and potentially enable its use. Amoxicillin should be used at a daily dose of at least 2 g divided 3 times per day or 4 times per day to avoid low trough levels.

Best Practice Advice 7: Inadequate acid suppression is associated with *H pylori* eradication failure. The use of high-dose and more potent PPIs, PPIs not metabolized by CYP2C19, or potassium-competitive acid blockers, if available, should be considered in cases of refractory *H pylori* infection.

Best Practice Advice 8: Longer treatment durations provide higher eradication success rates compared with shorter durations (eg, 14 days vs 7 days). Whenever appropriate, longer treatment durations should be selected for treating refractory *H pylori* infection.

Best Practice Advice 9: In some cases, there should be shared decision making regarding ongoing attempts to eradicate *H pylori*. The potential benefits of *H pylori* eradication should be weighed carefully against the likelihood of adverse effects and inconvenience of repeated exposure to antibiotics and high-dose acid suppression, particularly in vulnerable populations, such as the elderly.

Best Practice Advice 10: After 2 failed therapies with confirmed patient adherence, *H pylori* susceptibility testing should be considered to guide the selection of subsequent regimens.

Best Practice Advice 11: Compiling local data on *H pylori* eradication success rates for each regimen, along with patient demographic and clinical factors (including prior non-*H pylori* antibiotic exposure) is important. Aggregated data should be made publicly available to guide local selection of *H pylori* eradication therapy.

Abbreviations used in this paper: AGA, American Gastroenterological Association; bid, twice a day (dosing); BPA, Best Practice Advice; CagA, cytotoxin-associated gene A; CPU, Clinical Practice Update; IL, interleukin; PPI, proton pump inhibitor; PAL, PPI, amoxicillin, levofloxacin; PAR, PPI, amoxicillin, rifabutin; PBCT, PPI, bismuth, clarithromycin, tetracycline; PBLA, PPI, bismuth, levofloxacin, amoxicillin; PBLT, PPI, bismuth, levofloxacin, tetracycline; PBLM, PPI, bismuth, levofloxacin, metronidazole; PBMT, PPI, bismuth, metronidazole, tetracycline; qd, once per day; qid, four times per day (dosing); tid, three times per day (dosing); VacA, vacuolating cytotoxin A.

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Best Practice Advice 12: Proposed adjunctive therapies, including probiotics, are of unproven benefit as treatment for refractory *H pylori* infection, and thus, their use should be considered experimental.

Helicobacter pylori infection is recognized as one of the most common chronic bacterial infections worldwide, infecting approximately half of the global population.¹ *H pylori* is a World Health Organization-designated carcinogen and the strongest known risk factor for non-cardia gastric adenocarcinoma, the most prevalent form of gastric cancer. It is also causally linked to peptic ulcer disease. Even though only 1% to 3% of infected individuals will develop malignant complications, *H pylori* accounts for 15% of the total cancer burden globally, with up to 89% of all gastric cancer attributable to *H pylori* infection.² Accordingly, all major gastroenterological societies recommend that *H pylori* be eradicated in individuals who test positive.

Downstream consequences of failed treatment include clinical complications related to persistent *H pylori* infection and repeated exposure to antibiotics and high-dose acid suppression, generation of antibiotic resistance in *H pylori* and other organisms, as well as the associated direct and indirect costs to the health care system. Because the likelihood of successful eradication decreases with each subsequent therapeutic attempt, every effort should be made to address factors that might contribute to eradication failure.

Several guidelines exist to help providers choose regimens to eradicate *H pylori* on the first attempt and also include advice on management after initial treatments fail. However, these guidelines are backed by limited high-quality evidence. In general, they rely heavily on trials conducted in populations that are relatively homogenous within geographic borders, albeit ethnically distinct (eg, Asian-Pacific populations). In contrast, the US population comprises individuals with diverse ancestral backgrounds, with correspondingly diverse *H pylori* strains.³

In the United States, the lack of recent comparative clinical trials is coupled with limited knowledge of locoregional *H pylori* antibiotic resistance patterns and of regimen-specific local cure rates, as well as limited contemporary data on temporal trends and relevant demographic details (eg, age, race, and ethnicity). Current national and international guidelines provide limited guidance on how to approach factors other than *H pylori* antibiotic resistance, which might also underlie eradication failure, such as host- and systems-related factors. Collectively, these issues contribute to persistent *H pylori* infection (Figure 1).

The primary objectives of this Clinical Practice Update (CPU) Expert Review are to (1) provide a salient overview of determinants of *H pylori* eradication treatment failure, including host-, microbe-, and systems-related factors as they are currently understood; and (2) leverage these data to provide clinical practitioners with evidence- and consensus-based multimodal Best Practice Advice (BPA) for treating *H pylori* after the first treatment failure. We include a clinically relevant synthesis of contemporary data on the

appropriateness and efficacy, or lack thereof, of specific antimicrobial treatment regimens and adjunctive therapeutic agents for this purpose. The terms “salvage” and “rescue” therapy are commonly used in the literature to describe treatment courses after the initial eradication therapy but without a consistent definition. As such, we avoid the use of these terms. Additionally, to the extent possible, we focus on evidence from North America to ensure that this article is most relevant for US practitioners.

Definition of Refractory Infection

For the purpose of this CPU Expert Review, refractory *H pylori* infection is defined by a persistently positive non-serologic *H pylori* test result (ie, a breath-, stool-, or gastroscopy-based test), at least 4 weeks after 1 or more completed course(s) of a current guideline-recommended first-line *H pylori* eradication therapy, and off of any medications, such as proton-pump inhibitors (PPIs), that might impact the test sensitivity.⁴ Refractory *H pylori* infection should be differentiated from recurrent infection—that is, a nonserologic test that was initially negative after eradication therapy, but then subsequently positive at a later interval—because the latter might be the result of ongoing intrafamilial exposure and may be best addressed by testing household members and treating those who test positive.

Causes of *Helicobacter pylori* Eradication Treatment Failure

Failure to eradicate *H pylori* results from the complex interaction of host-, microbial-, and systems-related factors (Figure 1). Antibiotic resistance (microbial and systems) and patient nonadherence (host and systems) are the 2 most commonly cited reasons for eradication failure. However, because primary eradication failure still occurs despite confirmed antibiotic sensitivity and patient adherence, potentially with higher frequency in refractory *H pylori* specifically, additional factors are likely also relevant. Providers should attempt to identify all contributing etiologies before simply prescribing alternative antibiotics (BPA #1). These factors, along with antibiotic resistance and non-adherence, are described.

Antibiotic Resistance: Mechanisms and Rates

Resistance to several of the antibiotics commonly used in eradication regimens has risen globally over the last 20 years. Rising rates have been linked to prior use of that specific antibiotic, or others within the same class, by the individual as well as with widespread antibiotic consumption at the population level.^{5–7}

Predictably, eradication failure is more likely when an antibiotic to which *H pylori* demonstrates in vitro resistance is included in the regimen. Combining studies of both treatment naïve and refractory *H pylori* infection, in vitro resistance to clarithromycin and levofloxacin are associated with a 7.0-fold (95% CI, 5.2–9.3-fold) and 8.2-fold (95% CI, 3.8–17.6-fold) significantly higher likelihood of treatment

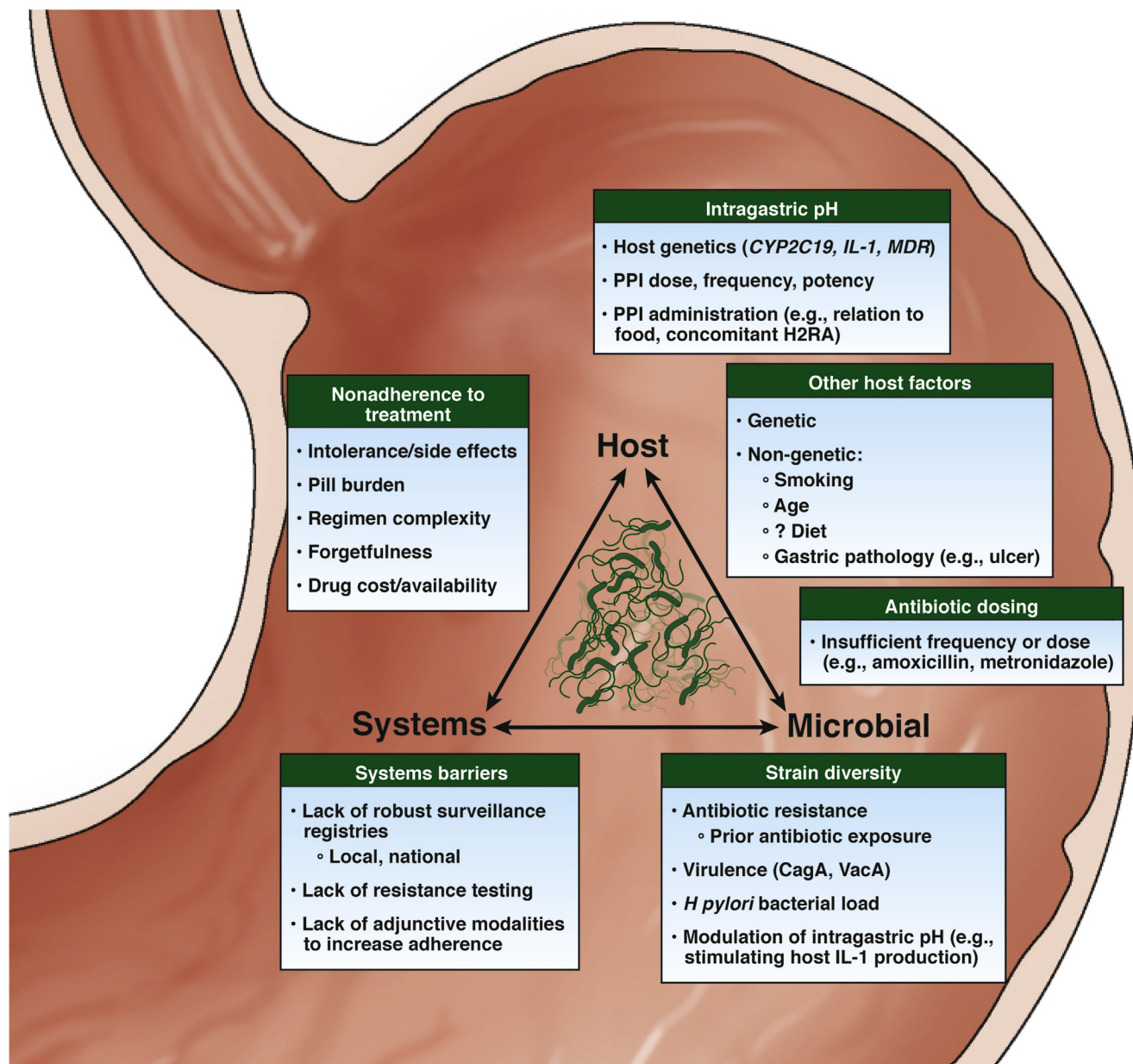


Figure 1. Factors impacting failure to eradicate *H pylori* infection. CagA cytotoxin-associated antigen A; IL, interleukin; VacA, vacuolating cytotoxin A.

failure, respectively, in regimens containing these drugs; whereas in vitro nitroimidazole resistance has relatively less clinical impact, increasing the odds of treatment failure by 2.5-fold (95% CI, 1.8–3.5-fold).⁸ Importantly, selecting eradication therapies based on prior antibiotic exposure is not inferior to selecting therapy based on in vitro antibiotic susceptibility^{9,10} and bypasses the many logistical barriers to obtaining in vitro testing. Accordingly, providers should conduct a thorough review of the medical/pharmacy record and discuss previous medication exposures with the patient and also a pharmacist,¹¹ if available. This should be done before the initial eradication attempt, but is especially critical for successfully treating refractory *H pylori* infection (BPA #2). A national US survey reported that only 38% of

participating providers asked patients about prior antibiotic exposure¹²; thus, there is considerable room for improvement.

The dominant molecular mechanisms responsible for antibiotic resistance in *H pylori* are well established for clarithromycin (usually due to 1 of 3 point mutations in the 23S ribosomal subunit), levofloxacin (mutations in DNA gyrase subunit A), amoxicillin (mutations in penicillin binding protein 1), tetracycline (mutations in genes encoding binding site for ribosomal 16S subunit, or increased efflux), and rifabutin (mutations in *rpoB*, the β subunit of the RNA polymerase gene).¹³

Nitroimidazole resistance is more complicated. It is usually related to mutations within *rdxA*, a gene encoding

a nitroreductase that normally activates nitroimidazoles (eg, metronidazole) from the prodrug state, although changes in drug uptake and efflux may also play a role. The complexity of *rdxA* mutations reported and possible synergy with other redox-associated *H pylori* genes precludes molecular testing of any single point mutation for clinical resistance profiling. Additionally, phenotypic (culture-based) methods are not well standardized for metronidazole resistance testing and can vary by the method used. This may contribute to the relatively low predictive value of in vitro metronidazole resistance testing to treatment outcome.

A comprehensive systematic review and meta-analysis, including data from more than 50,000 patients from 45 countries, found that overall primary resistance rates by global region ranged from 10% to 34% for clarithromycin, 11% to 30% for levofloxacin, and 23% to 56% for metronidazole.⁸ After unsuccessful *H pylori* treatment (secondary resistance), rates increased to 15% to 67% for clarithromycin, 19% to 30% for levofloxacin, and 30% to 65% for metronidazole. In contrast, resistance rates were low for amoxicillin and tetracycline, generally occurring in less than 5% of strains, usually in the 1% to 2% range.⁸ *H pylori* also demonstrates low primary and secondary resistance to rifabutin, based on other reports.^{14,15}

Estimating *H pylori* resistance rates is particularly challenging in the United States because measuring resistance has been uncommon in clinical practice, ultimately equating to very limited contemporary data to guide treatment considerations. In a prospective multicenter US study of 347 strains collected from 1998 to 2002, overall *H pylori* resistance rates (treatment naïve and previously treated combined) were 13% for clarithromycin and 25% for metronidazole.¹⁶ In 128 strains cultured from patients at the Houston Veterans Affairs Medical Center from 2009 to 2013, resistance rates in the 110 treatment-naïve patients were 15% for clarithromycin, 17% for metronidazole, and 29% for levofloxacin, with 15% of strains resistant to more than 1 antibiotic.¹⁷ Most recently, primary resistance rates of 345 strains collected during a multicenter clinical trial were 17% for clarithromycin and 44% for metronidazole.¹⁴ It should be recognized, however, that because *H pylori* infection is most often acquired in childhood, immigrants from countries where *H pylori* is endemic might exhibit antimicrobial resistance patterns characteristic of their native country as opposed to the host country; this again underscores the need for robust surveillance registries that include host demographics.

Nonadherence

The level of adherence to therapy, above which there is negligible incremental benefit for eradication success in refractory *H pylori*, is not known; however, studies demonstrate that adherence to >60% to >90% of the prescribed course might be sufficient for successful eradication, at least in primary *H pylori* infection.^{11,18} The threshold likely varies depending on individual factors and might plausibly be higher for refractory *H pylori*.

Before therapy is prescribed, barriers to adherence should be explored and addressed and the regimen thoroughly discussed. Common barriers include complexity of eradication regimens, associated high pill burden, physical intolerance of medications, poor provider communication, and overall lack of understanding of why therapy is indicated.^{11,19} Based on these considerations, providers who treat *H pylori* infection should provide their patients with anticipatory guidance to help ensure maximum adherence. This specifically includes explaining the rationale for therapy, dosing instructions, expected adverse events, and the importance of completing the full therapeutic course (**BPA #3**).

Two recent large randomized controlled trials from China demonstrated that the use of an interactive smartphone medical application²⁰ and text-based reminders²¹ during treatment improved adherence to primary therapy. These adjunctive systems are worthy of further investigation in the United States for refractory *H pylori* infection and would provide information on which approaches might be more effective in certain populations compared with others; for example, based on characteristics such as age, race and ethnicity, educational level, access, and language. Pillboxes, medication calendars, medication, and counseling from pharmacists may also augment patient adherence.¹¹

Systems-related factors that contribute to refractory *H pylori* infection additionally include lack of robust eradication surveillance registries, lack of widely accessible antibiotic sensitivity testing, practice pattern variability among practitioners with respect to adherence to guideline-recommended therapies,¹² as well as little progress in developing novel anti-*H pylori* therapies.

Host Genetics

Host genetics are also implicated in refractory *H pylori* infection. Polymorphisms that affect intragastric pH, including those of *CYP2C19*, *IL-1B*, and *MDR1*, are especially relevant to successful *H pylori* eradication. *H pylori* is most susceptible to antibiotics when the intragastric pH is consistently between 6 and 8, because this is the optimal pH range for *H pylori* replication. Some antibiotics, including clarithromycin and amoxicillin, also require intragastric acid suppression for maximum efficacy and sustained activity. For example, for gastric pH <2, the half-lives of amoxicillin and clarithromycin are approximately 15.2 ± 0.3 hours and 1.0 ± 0.04 hours, respectively, whereas for gastric pH >7, the half-lives of both antibiotics are >68 hours.²² Hence, in the absence of adequate and sustained acid suppression, *H pylori* can persist despite exposure to antibiotics to which it is otherwise susceptible in vitro.²³

The largest body of literature for host genetics contributing to *H pylori* eradication failure is focused on *CYP2C19*, the cytochrome P450 gene responsible for most of the metabolism of the earlier-generation PPIs. *CYP2C19* polymorphisms giving rise to poor metabolizer phenotypes result in high plasma PPI drug concentrations.²⁴ The

metabolism-enhancing phenotypes of *CYP2C19* are associated with higher rates of eradication failure when PPIs that are heavily metabolized by *CYP2C19* (eg, omeprazole, lansoprazole) are used.²⁵ Because PPIs also have a direct antimicrobial effect and impact *H pylori* bacterial load, *CYP2C19*-induced PPI metabolism also influences *H pylori* persistence independently of intragastric pH.²⁵

Far less data are available on non-*CYP2C19* genetic determinants of intragastric pH (eg, *MDR1*, *IL-1B*) and other host genetic variants, which might contribute to refractory *H. pylori* infection through other mechanisms, such as *H pylori* bacterial load regulation and dysregulation, evasion, or alteration of mucosal immunity.

Studies evaluating *CYP2C19* genotype-guided PPI selection and dosing in refractory *H pylori* infection have been conducted in Asian-Pacific populations, but analogous studies in US populations are lacking. This is an important deficit, because there are substantive racial and ethnic differences in the prevalence of *CYP2C19* variant alleles and genotypes in the United States.^{26,27} Caucasians, non-Hispanic African Americans, and Hispanics have a significantly higher prevalence (57%–71%) of metabolism-enhancing *CYP2C19* phenotypes compared with Asian American ethnic groups (45%), even in population studies of asymptomatic individuals.²⁸ Asian Americans also have the highest prevalence of the poor metabolism genotype.²⁶ Furthermore, Caucasians with extensive metabolizer phenotypes might have even higher clearance of omeprazole compared with some Asian ethnic groups with the same *CYP2C19* genotype,²⁸ suggesting additional genetic or gene-environment interaction determinants might be relevant.

Despite these considerations, current data are insufficient to support genetic polymorphism testing for guiding therapeutic selection in refractory (or primary) eradication therapy. Given the high population prevalence of metabolism-enhancing phenotypes of *CYP2C19* at least in non-Asian groups, empiric selection of strategies that achieve greater intragastric acid suppression might be reasonable in the management of refractory *H pylori* infection. These include higher dosing and/or increased frequency of first-generation PPIs, the use of later generation, more potent PPIs, and selecting potent non-PPI gastric acid suppressors, such as vonoprazan, if available. However, further population-specific data are needed, including comparisons of cost.

Other Host Factors

Nongenetic host-related and lifestyle factors, such as age and smoking, are also associated with eradication treatment failure. One meta-analysis found that patients who smoked vs those who did not smoke were nearly twice as likely to have persistent *H pylori* infection after therapy (odds ratio, 1.95; 95% CI, 1.55–2.45).²⁹ Biological plausibility underlies this association, because smoking increases gastric acid secretion and impairs mucous secretion and gastric blood flow, thus decreasing local antibiotic delivery. Whether smoking cessation, at least while taking eradication therapy, improves eradication success in refractory *H pylori* infection is not established. The data are less consistent for other host

factors, such as comorbid obesity and diabetes, but are important areas for focused research.

Helicobacter pylori Strain Diversity

The high level of *H pylori* strain-specific genetic diversity engenders microbial mechanisms that promote *H pylori* persistence to variable extents. These mechanisms include manipulation and evasion of host immune responses, alteration of the gastric environment, increased bacterial load, enhanced virulence and consequent adverse gastric histopathology, as well as resistance to antimicrobials.^{30,31} Except for antimicrobial resistance, other *H pylori* genetic constituents (eg, cytotoxin-associated gene A, vacuolating cytotoxin A) have not been leveraged in the management of refractory *H pylori* infection but deserve attention.^{32,33}

Proposed Treatment Algorithm

An algorithm for regimen considerations in refractory *H pylori* cases is illustrated in [Figure 2](#) and is based on the initial therapy used and the presence or absence of true penicillin allergy. Of these regimens, only PPI, bismuth, metronidazole, and tetracycline (PBMT) is US Food and Drug Administration-approved for refractory *H pylori* infection. If bismuth-based quadruple therapy failed as a first-line treatment, shared decision making between providers and patients should guide selection between (a) levofloxacin- or rifabutin-based triple-therapy regimens with high-dose dual PPI and amoxicillin, and (b) an alternative bismuth-containing quadruple therapy as second-line options (**BPA #4**).

Owing to rising rates of levofloxacin resistance, levofloxacin should not be considered for treatment unless the *H pylori* strain is known to be sensitive to it or if the population levofloxacin resistance rates are known to be <15% (analogous to the longstanding “rule” regarding clarithromycin usage in triple therapies). However, it is reasonable to consider rifabutin in a triple regimen without prior sensitivity testing because rifabutin and amoxicillin resistance are rare. A recent study demonstrated that the addition of rifabutin to the high-dose amoxicillin and PPI dual regimen improves eradication rates significantly.¹⁴ Although the referenced study used this regimen as first-line therapy, based on these data, it is reasonable to consider PAR (PPI, amoxicillin, and rifabutin) use with high-dose and/or high-potency PPI and amoxicillin 750 mg, 3 times daily, over high-dose dual therapy alone. Optimal dosing of PPIs is provided in [Table 1](#) and is described in text below. We have not included in [Figure 2](#) several other potential regimens, such as concomitant, sequential, or hybrid therapies, due to extremely limited data on their use for refractory *H pylori* infection specifically.⁴

Considerations in Regimen Selection for Refractory *Helicobacter pylori*

There is no shortage of guidelines from international authorities advising on *H pylori* management. Some of the most prominent recent releases are listed in [Table 1](#).^{4,34–36}

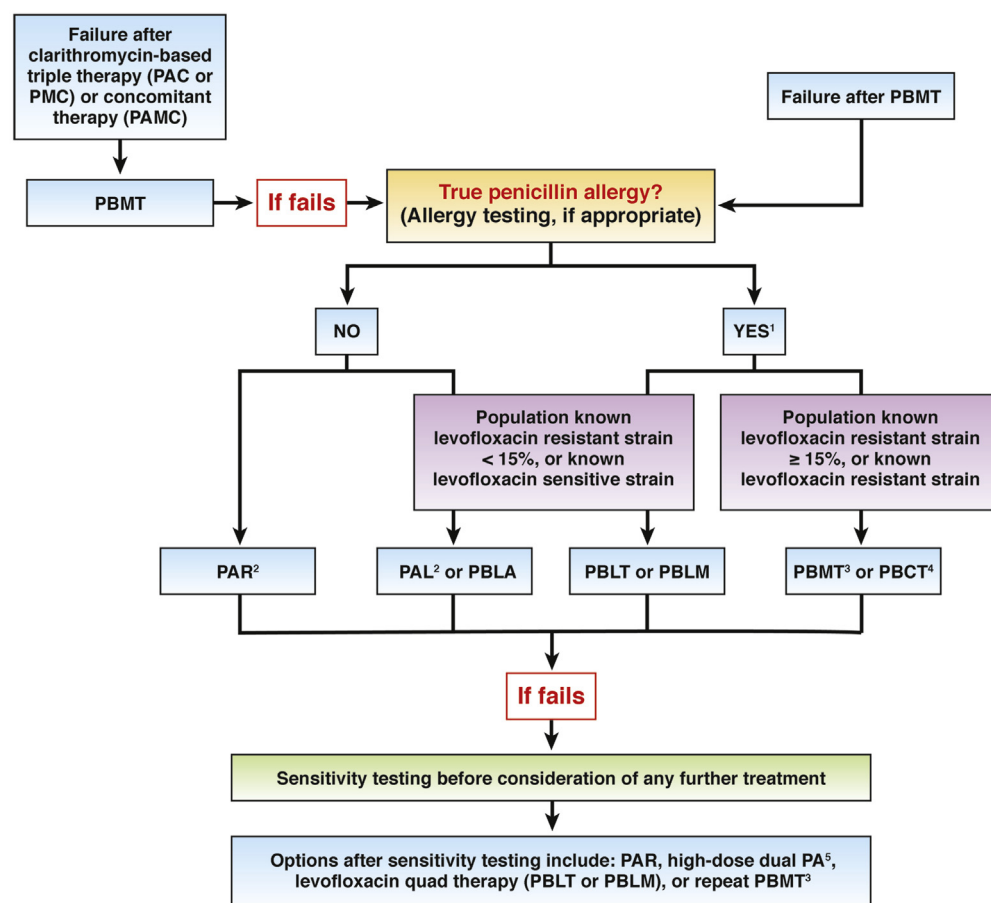


Figure 2. Treatment algorithm for refractory *H pylori* infection. PAL, PPI, amoxicillin, levofloxacin; PAR, PPI, amoxicillin, rifabutin; PBCT, PPI, bismuth, clarithromycin, tetracycline; PBLA, PPI, bismuth, levofloxacin, amoxicillin; PBLT, PPI, bismuth, levofloxacin, tetracycline; PBLM, PPI, bismuth, levofloxacin, metronidazole; PBMT, PPI, bismuth, metronidazole, tetracycline.

¹Limited evidence guiding therapy in individuals with true penicillin allergy

²With high-dose or high-potency PPI, amoxicillin 750 mg TID

³High-dose metronidazole (1.5–2g divided)

⁴Only if clarithromycin sensitive strain

⁵High-dose dual PA = amoxicillin 2–3g daily in 3–4 divided doses + high-dose PPI BID. PA in place of PAR may be considered, although one study from the US demonstrated superiority of PAR compared to PA as first-line treatment (Graham et al. 2020); however, this has not been directly compared in refractory *H pylori* treatment.

P, PPI; C, Clarithromycin; A, Amoxicillin; M, Metronidazole; B, Bismuth; T, Tetracycline; R, Rifabutin; L, Levofloxacin

Overall, the guidance for the management of refractory infection are relatively consistent among the expert groups. However, we must emphasize that the body of evidence underlying their conclusions reflects the general low quality and heterogeneity of clinical studies conducted on refractory *H pylori* infection. Furthermore, most of the trials included in meta-analyses of second-line treatment have investigated treatment after failure of a first-line regimen with clarithromycin-based triple therapy, a regimen that we now appreciate should no longer be used in most regions of the world, including the United States.^{37,38} Lastly, even though incorporation of antibiotic susceptibility testing has been advocated by the Maastricht expert consensus group since the first iteration of their guidelines in 1997,³⁹ the slow uptake of resistance testing around the world persists and continues to propagate empiric selection of eradication

therapy for most refractory *H pylori* infections, especially in the United States.

Nevertheless, several important themes have emerged for guiding treatment of refractory *H pylori* infection. First, given the high resistance rates to clarithromycin and levofloxacin, these antibiotics or others in their class (macrolides and fluoroquinolones, respectively) should not be repeated in subsequent treatment attempts. On the basis of the premise that secondary *H pylori* resistance may have ensued as collateral damage, an antibiotic history of use of any of these drug classes for other indications should be considered when selecting subsequent therapy.⁴ Because primary and secondary resistance to amoxicillin, tetracycline, and rifabutin are very low, these can be used in repeated regimens, even if they have been used previously for *H pylori* eradication or other therapy (BPA #2). Age,

Table 1. Second-Line Therapies for *Helicobacter pylori* Eradication, Based on Selected International Guidelines^a

Regimen failures ^b		Maastricht V/Florence Consensus Report, ³⁶ 2016	Toronto Consensus Report, ³⁴ 2016	American College of Gastroenterology Guidelines, ⁴ 2017	Chinese National Consensus Report, ³⁵ 2018
If clarithromycin-triple fails in first-line	➡	<ul style="list-style-type: none"> • Bismuth quad • Levofloxacin-triple or quad 	<ul style="list-style-type: none"> • Bismuth quad • Levofloxacin triple 	<ul style="list-style-type: none"> • Bismuth quad • Levofloxacin triple 	Not discussed
If bismuth quad fails in first-line	➡	<ul style="list-style-type: none"> • Levofloxacin-triple or quad • In cases of high levofloxacin resistance: <ul style="list-style-type: none"> - Bismuth with other antibiotics - Rifabutin triple 	<ul style="list-style-type: none"> • Levofloxacin triple 	Depending on antibiotic history: <ul style="list-style-type: none"> • Levofloxacin triple • Clarithromycin triple 	<ul style="list-style-type: none"> • Bismuth + PPI + 2 antibiotics not used in the first-line bismuth quad treatment
If nonbismuth quad fails in first-line	➡	<ul style="list-style-type: none"> • Bismuth quad • Levofloxacin triple or quad 	<ul style="list-style-type: none"> • Levofloxacin triple 	Not discussed	Not discussed
If >2 treatment failures	➡	Treatment guided by results of resistance testing	<ul style="list-style-type: none"> • Avoid reusing clarithromycin, levofloxacin, metronidazole • Consider rifabutin triple after >3 failures 	Depending on antibiotic history and population resistance patterns: <ul style="list-style-type: none"> • Concomitant • Rifabutin triple • High-dose dual 	<ul style="list-style-type: none"> • Bismuth + PPI + 2 antibiotics not used in first treatment • Second-line bismuth quad treatments (metronidazole can be reused, but at a higher dose if not already tried)

bid, twice a day; qd, once a day; qid, four times a day; tid, three times a day.

^aMultiple national and multinational *H pylori* management guidelines exist. This table compiles data from 4 of the highest-profile recent publications.

^bRegimens (with usual doses/frequencies/durations): Bismuth quad = bismuth ~300 mg qid, metronidazole 500 mg tid or qid, tetracycline 500 mg qid, PPI bid × 14 days. Concomitant = clarithromycin 500 mg bid, amoxicillin 1 g bid, metronidazole or tinidazole 500 mg bid, PPI bid × 14 days. Clarithromycin triple = clarithromycin 500 mg bid, amoxicillin 1 g bid or metronidazole 500 mg bid, PPI bid × 14 days. Levofloxacin triple = levofloxacin 500 mg qd, amoxicillin 1 g bid, PPI bid × 14 days. Levofloxacin quad = levofloxacin 500 mg qd, PPI bid + 2 antibiotics (multiple variations exist) × 10–14 days. Rifabutin triple = rifabutin 150 or 300 mg daily, amoxicillin 1 g bid, PPI bid × 10 days. High-dose dual = amoxicillin 2–3 g daily in 3–4 split doses, PPI high-dose bid × 14 days. Note: “PPI” implies standard dose unless “high-dose” is specifically stated. Standard dose is as follows: pantoprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, esomeprazole 20 mg, dexlansoprazole 30 mg, and rabeprazole 20 mg. “High-dose” implies double the standard dose.

comorbidities, and concomitant medications should also guide therapeutic selection and factor into shared decision making.

Second, resistance to nitroimidazoles, based on in vitro testing or suspected due to prior nitroimidazole exposure, should not be considered as an “absolute” preclusion for reuse of this antibiotic class for refractory *H pylori* therapy, because, for reasons described above, in vitro resistance does not reliably correlate with *H pylori* eradication failure associated with using this drug. Nitroimidazole resistance might be potentially overcome with dose adjustments and the addition of bismuth.⁵ Higher doses of metronidazole, at least in the 1.5 to 2 g/d range, are also associated with significantly improved eradication rates.⁴⁰ These higher doses might be poorly tolerated due to gastrointestinal and other adverse effects; thus, patients should be advised to consume metronidazole in divided doses (3- to 4-times daily) with food and to avoid alcohol for the therapeutic duration due to a disulfiram-like reaction (BPA #5).

Third, it is now increasingly appreciated that consistently achieving adequate threshold levels of amoxicillin and intragastric acid suppression are important for successful *H pylori* eradication, individually as well as concomitantly, because intragastric pH affects the efficacy and half-life of amoxicillin. Drug dose, frequency, and, for acid suppression, drug potency are relevant, especially with respect to their efficacy as a dual regimen, as well as in other regimens for refractory *H pylori* infection (Figure 2). Amoxicillin was originally given twice daily in clarithromycin-based triple therapy; however, it is now recognized that dividing 2 to 3 g of amoxicillin into at least 3 doses daily avoids low trough levels and improves the efficacy of eradication therapy⁴¹ (BPA #6). Given its value in treating refractory *H pylori* infection, in the absence of anaphylaxis, penicillin allergy testing should be considered to delist penicillin allergy and potentially enable the use of amoxicillin (BPA #6). Despite relatively prevalent medical record documentation of penicillin allergy, true anaphylaxis to penicillin is rare.

Inadequate acid suppression may undermine eradication efforts through a variety of mechanisms, as detailed above. To this end, optimal dosing of PPIs is frequently overlooked when eradication therapy is prescribed, but similar fine-tuning of the acid suppressive prescription may improve eradication outcomes in refractory *H pylori* infection (BPA #7). Providers should also confirm that patients are taking the PPI in a manner that maximizes absorption and activation. Factors such as timing of PPI administration in relation to food (and types of foods) and the impact on absorption, as well as the impact of concomitant medications such as histamine H₂ receptor blockers on PPI activation, should be studied further. Higher dosing, greater frequency (eg, 3- or 4-times daily PPI dosing), and the use of more potent PPIs (eg, esomeprazole or rabeprazole) may be beneficial in cases of refractory *H pylori* infection and similarly warrant further investigation. Vonoprazan, a first-in-class potassium-competitive acid blocker, is a potent intragastric acid suppressor that also bypasses *CYP2C19*-dependent metabolism.

Although not yet available in the United States, trials comparing *CYP2C19*-metabolized PPIs vs vonoprazan are ongoing in the United States (NCT04167670 at clinicaltrials.gov).

Finally, longer treatment durations provide higher eradication rates; thus, a 14-day therapeutic duration should be used for refractory *H pylori* infection (BPA #8).

After multiple failed eradication attempts, the potential benefits of *H pylori* eradication should be weighed carefully against the likelihood of adverse effects and inconvenience of repeated high-dose acid suppression and antibiotic exposure, particularly among individuals who are not at an identifiably higher risk of complications from persistent *H pylori* infection (eg, gastric cancer, peptic ulcer disease); in such scenarios, a shared decision-making approach should be seriously considered, especially in the elderly, those with frailty, and those with intolerance to antibiotics (BPA #9).

Antibiotic Susceptibility-Based Approach

Unlike most infectious diseases where therapy is guided by knowledge of antibiotic sensitivity profiling of the target organism, or at least by knowledge of strains within the relevant geographic region, *H pylori* treatment has remained largely empiric. For refractory cases, it may seem obvious that sensitivity testing should be considered after 2 failed attempts at treatment³⁶ (BPA #10). However, in practice, the situation is complicated by the logistical challenges of obtaining resistance profiles for *H pylori* as well as the lack of convincing data demonstrating superiority of selecting treatment based on sensitivity testing compared with empirically selecting treatment based on prior antibiotic exposure, as further discussed below.

Standard methodology to test for antibiotic sensitivity involves promptly transporting gastric biopsy specimens in sterile containers at room temperature to the receiving microbiology laboratory where they undergo a relatively labor-intensive process to grow up the microbial colonies in microaerophilic conditions over several days. Once it is confirmed that the bacteria are indeed *H pylori*, for example, based on morphology, urease, catalase, and oxidase activity, the bacteria are then tested for viability in the presence of the relevant antibiotics. Because few hospitals or endoscopy centers in the United States offer this service in-house, the biopsy specimens for sensitivity testing are instead usually sent in refrigerated packaging to a commercial laboratory.

We emphasize, though, that in practice, the success rates of obtaining a useful result are much lower than the 80% to 95% success usually reported in research studies. The reasons for the very low success rates outside of a clinical protocol are multifactorial and include delays and errors in sample processing and transport, compounded with the fact that *H pylori* is a fastidious organism and that the success rates of culturing *H pylori* are further decreased by the recent use of PPIs or antibiotics. As an alternative, molecular resistance testing (using a variety of platforms) is simpler, more likely to yield results, and can also be performed on archival specimens, including the formalin-fixed paraffin-embedded gastric biopsy tissue remaining after routine

diagnostic histopathologic testing. This obviates the need for specialized tissue handling by the endoscopist.⁴²

Apart from the practicalities of obtaining *H pylori* antibiotic sensitivity testing, especially in the United States, a note of caution is still warranted when embarking on therapy directed by susceptibility testing (also referred to as “tailored therapy”). The published literature in this area, which derives almost entirely from studies conducted in the Western Pacific, provides little to no evidence that sensitivity-based treatment selection actually results in significantly improved rates of successful *H pylori* eradication over empirically selected second-line regimens.^{10,34,43} High-quality clinical trials of tailored vs empiric therapy after 2 or more failed attempts at eradication are unfortunately lacking in the United States and should be prioritized for future research. Cost-effectiveness analyses will also be valuable, especially if nonendoscopic methods for susceptibility testing, such as molecular testing of stool samples, become a viable option. In the absence of such data, the Maastricht strategy of susceptibility testing after 2 unsuccessful therapies should be considered in most cases (Figure 2) (BPA #10).

Strategies to Advance the Field and Potential Adjunctive Therapies

The most effective strategy for managing refractory *H pylori* is preventing refractory *H pylori* infection by improving success rates of primary eradication therapy.

Personalizing the initial *H pylori* eradication therapy by incorporating individual host genetic, host nongenetic, and microbial factors (Figure 1) might help achieve this by shifting the paradigm away from empiric therapy alone. Population-specific research with particular attention to race, ethnic, and age groups can indicate determinants that impact eradication success in the United States. Regional information of local success rates would further refine regimen selection. The Pan-European Registry on *H pylori* management⁴⁴ is one prototype to emulate. Ideally, such a model would encompass systematic collection and reporting, together with periodic updates of regimen-specific local eradication rates—including regimens for primary and refractory infection—along with relevant nonidentifiable individual-level data such as demographics, smoking history, prior antibiotic exposure, and antibiotic sensitivity data, if available. Aggregated data should be made publicly available to guide local selection of *H pylori* eradication therapy (BPA #11). This information could be used for both initial and refractory treatment choices.

Noninvasive *H pylori* antibiotic sensitivity testing on stool, to supplant the current sensitivity testing using endoscopically obtained samples, would overcome many rate-limiting barriers precluding widespread uptake of sensitivity testing. Molecular testing of stool for the small number of known mutations responsible for clarithromycin or levofloxacin resistance is relatively straightforward, because there are several commercial kits for these purposes that use polymerase chain reaction. However, next-generation sequencing technology offers the potential to

detect the resistance footprint of all antibiotics considered in *H pylori* therapy. While the clinical utility of using stool-based predictions to guide antibiotic therapy remains to be fully determined, collecting this information would galvanize a data pipeline to accelerate the establishment of surveillance registries, which are immediately needed. Hand-in-hand, implementation and adherence to standard quality metrics based on current clinical guidelines, including appropriate eradication confirmation testing in all individuals treated for *H pylori*, would simultaneously advance surveillance programs and ideally attenuate the high practice pattern variability observed in the management of refractory *H pylori* infection.

Despite rising rates of resistance, the global impact of antibiotic overuse, as well as the exorbitant cost associated with treatment failure, which is estimated to be at least \$33 billion in the United States alone,⁴⁵ no truly novel anti-*H pylori* therapies are visible on the horizon. Development of newer antimicrobial agents against *H pylori* should be fostered, as should investigation into repurposing already available antimicrobials with alternative mechanisms of action against *H pylori*. For example, the addition of clavulanic acid to amoxicillin-based regimens has been associated with a 10% to 20% increase in eradication success,⁴⁶ although more rigorous studies are needed.

There are also some promising data for nonantibiotic adjuncts, such as statins^{47–49} and probiotics.^{50–54} Regarding the latter, there is an increasing body of data supporting a benefit of probiotics containing *Lactobacillus* and *Bifidobacterium* on *H pylori* eradication success via an inhibitory effect as well as enhanced patient tolerance of *H pylori* eradication therapy resulting in improved adherence. To date, at least 20 clinical trials and several meta-analyses have evaluated the effect of probiotics on *H pylori* eradication, albeit not necessarily refractory *H pylori*.^{50–54}; these are mostly positive, but there is significant trial heterogeneity and concerns over study quality. Collectively, there are limited data to guide optimal timing, formulation, dosage, duration, and appropriate patient selection for these adjunctive therapies, and their use should therefore be considered experimental (BPA #12). Further rigorous investigation in US populations and specifically in refractory *H pylori* infection would be valuable, particularly given the generally favorable adverse effect and cost profiles of these agents.

Conclusion

H pylori management has become increasingly challenging due to declining eradication success rates coupled with increasing antibiotic resistance, resulting in more *H pylori* infections that are now refractory to first-line therapies. Accordingly, this CPU was developed to provide practitioners with practical advice on how to manage patients whose initial *H pylori* treatment was unsuccessful. When considering the major public health implications associated with persistent *H pylori* infection with respect to disease- and treatment-related complications and cost, there is a clear need to prioritize systematic approaches to improve

rates of successful *H. pylori* eradication with the least number of therapeutic attempts.

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Conflicts of interest

Steven F. Moss serves on the advisory board of Redhill Biopharma and Phathom Pharmaceuticals, and is a consultant for Takeda. The authors report no other disclosures.

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