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Shailja C. Shah, MD MPH, Prasad G. Iyer, MD MS, Steven F. Moss, MD

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

Shailja C. Shah, MD MPH[1, 2], Prasad G. Iyer, MD MS[3], Steven F. Moss, MD[4]

Author Affiliations

1. Division of Gastroenterology, Veterans Affairs Tennessee Valley Health System, Nashville, TN
2. Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, Nashville, TN
3. Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN
4. Division of Gastroenterology, Warren Alpert Medical School of Brown University, Providence, RI

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Corresponding Author

Shailja C Shah
2215 Garland Avenue
Medical Research Building IV, Room 1030-C (mail)
Vanderbilt University Medical Center
Nashville, TN 37213

shailja.c.shah@vumc.org
Fax: 615-343-6229

Abbreviations used in main text, tables, and figures

Abbreviation	Full Term
AGA	American Gastroenterological Association
BID	Two times per day (dosing)
BPA	Best Practice Advice
CPU	Clinical Practice Update
H. pylori	*Helicobacter pylori*
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
RCT	Randomized controlled trial
QID	Four times per day (dosing)
TID	Three times per day (dosing)
US	United States
WHO	World Health Organization
Figure 2 Abbreviations	**Full Term**
A	Amoxicillin
B	Bismuth
C	Clarithromycin
L	Levofloxacin
M	Metronidazole
R	Rifabutin
T	Tetracycline
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

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Abstract

The purpose of this CPU Expert Review is to provide clinicians with guidance on the management of *H. 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.

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Best Practice Advice (BPA) Statements

1. The usual cause of refractory *H. 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.

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.

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.

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, or b) an alternative bismuth-containing quadruple therapy, as second-line options.

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, as this may improve eradication success rates irrespective of observed *in vitro* metronidazole resistance.

6. In the absence of a history of anaphylaxis, penicillin allergy testing should be considered in a patient labelled 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 2g divided TID or QID to avoid low trough levels.

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.

8. Longer treatment durations provide higher eradication success rates compared to shorter durations (e.g. 14 days vs 7 days). Whenever appropriate, longer treatment durations should be selected for treating refractory *H. pylori* infection.

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.

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

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.

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.

Introduction

Helicobacter pylori (H. 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 (WHO)-designated carcinogen and the strongest known risk factor for noncardia gastric adenocarcinoma, the most prevalent form of gastric cancer. It is also causally linked to peptic ulcer disease. Even though only 1-3% 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 healthcare 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; they 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 (e.g. Asian-Pacific populations). In contrast, the United States (US) population comprises individuals with diverse ancestral backgrounds, with correspondingly diverse *H. pylori* strains.[3] In the US, 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 (e.g. 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 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 following 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 in order 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-serological *H. pylori* test (*i.e.,* a breath-, stool-, or gastroscopy-based test), at least 4 weeks following one or more completed course(s) of current guideline-recommended first-line *H. pylori* eradication therapy, and off of any medications that might impact the test sensitivity (e.g. proton-pump inhibitors (PPI)).[4] Refractory *H. pylori* infection should be differentiated from recurrent infection—that is, a non-serological test which was initially negative after eradication therapy, but then subsequently positive at a later interval—as 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.

The causes of *H. pylori* eradication treatment failure (Figure 1)

Failure to eradicate *H. pylori* results from the complex interaction of host-, microbial- and systems-related factors. Antibiotic resistance (microbial and systems) and patient nonadherence (host and systems) are the two 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 nonadherence, are described herein.

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) and 8.2-fold (95% CI, 3.8–17.6) significantly higher likelihood of treatment 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). [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 prior to 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 exposure[12]; 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 one of three 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 beta subunit of 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 (e.g. metronidazole) from the prodrug state, though 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 method used. This may contribute to the relatively low predictive value of *in vitro* metronidazole resistance testing to treatment outcome.

Based on a comprehensive systematic review and meta-analysis, including data from over 50,000 patients from 45 countries, overall primary resistance rates by global region ranged from 10-34% for clarithromycin, 11-30% for levofloxacin and 23-56% for metronidazole.[8] After unsuccessful *H. pylori* treatment (secondary resistance) rates increased to 15-67% for clarithromycin, 19-30% for levofloxacin and 30-65% for metronidazole. In contrast, resistance rates were low for amoxicillin and tetracycline, generally occurring in less than 5% of strains, usually in the 1-2% 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 US because measuring resistance has been uncommon in clinical practice, ultimately equating to very limited contemporary data to guide treatment considerations. In a prospective multi-center 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 2009-2013, 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 one antibiotic.[17] Most recently, primary resistance rates of 345 strains collected during a multi-center 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, as opposed to 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.* Prior to prescribing therapy, 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)**

Recently, two large RCTs from China demonstrated that the use of an interactive smart-phone medical application[20] and text-based reminders[21] during treatment improved adherence to primary therapy. These adjunctive systems are worthy of further investigation in the US for refractory *H. pylori* infection, and would provide information on which approaches might be more effective in certain populations compared to 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 intragastric pH is consistently between 6-8, since 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, while 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 the majority of 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* (e.g. 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]

There are far less data on non-*CYP2C19* genetic determinants of intragastric pH (e.g. *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 since there are substantive racial and ethnic differences in the prevalence of *CYP2C19* variant alleles and genotypes in the US.[26,27] Caucasians, non-Hispanic African Americans, and Hispanics have a significantly higher prevalence (57%-71%) of metabolism-enhancing *CYP2C19* phenotypes compared to 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 to 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

Non-genetic host-related and lifestyle factors, such as age and smoking, are also associated with eradication treatment failure. In one meta-analysis, patients who smoked vs. did not smoke were nearly twice as likely to have persistent *H. pylori* infection following therapy (OR 1.95, 95% CI, 1.55-2.45).[29] Biological plausibility underlies this association, since 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.

H. 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 (e.g. *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 PBMT is FDA-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 proton pump inhibitor (PPI) and amoxicillin, or b) an alternative bismuth-containing quadruple therapy, as second-line options. (**BPA #4**) Due 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 since rifabutin and amoxicillin resistance are rare. A recent study demonstrated that the addition of rifabutin to the high dose amoxicillin, 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 usage with high-dose and/or high-potency PPI and amoxicillin 750mg TID 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 *H. 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]

Overall, the guidance for the management of refractory infection are relatively consistent among the expert groups. However, it should be emphasized 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 metanalyses 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 US.[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 US.

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, fluoroquinolones respectively) should not be repeated in subsequent treatment attempts. Based on the premise that secondary *H. pylori* resistance may have ensued as collateral damage, an antibiotic history of usage 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, comorbidities, and concomitant medications should also guide therapeutic selection and factor into shared decision-making.

Second, resistance to nitroimidazoles, either 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, since, 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 addition of bismuth.[5] Higher doses of metronidazole, at least in the 1.5-2 g/day range, are also associated with significantly improved eradication rates.[40] These higher doses might be poorly tolerated due to gastrointestinal and other side effects; thus patients should be advised to consume metronidazole in divided doses (TID to QID) with food and to avoid alcohol for the therapeutic duration due to a disulfuram-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, both individually as well as concomitantly since 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 2-3g amoxicillin into at least three doses daily avoids low trough levels and improves the efficacy of eradication therapy.[41] (**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 chart 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 prescribing eradication therapy, 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 H_2 receptor blockers on PPI activation should be studied further. Higher dosing, greater frequency (e.g. TID or QID PPI dosing), and the use of more potent PPIs (e.g. 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 US, trials comparing *CYP2C19*-metabolized PPIs versus vonoprazan are ongoing in the US (NCT04167670; 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 identifiably higher risk of complications from persistent *H. pylori* infection (e.g. 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 geographical region, *H. pylori* treatment has remained largely empiric. For refractory cases, it may seem obvious that sensitivity testing should be considered after two failed attempts at treatment.[36] (**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 to empirically selecting treatment based on prior antibiotic exposure, as further discussed below.

Standard methodology to test for antibiotic sensitivity involves promptly transporting gastric biopsies 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 micro-aerophilic 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 US offer this service in-house, the biopsy specimens for sensitivity testing are instead usually sent in refrigerated packaging to a commercial laboratory. It should be emphasized, though, that in practice the success rates of obtaining a useful result are much lower than the 80-95% 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 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 histopathological 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 US, 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.[34,10,43] High quality clinical trials of tailored versus empiric therapy after two or more failed attempts at eradication are unfortunately lacking in the US and should be prioritized for future research. Cost-effectiveness analyses will also be valuable, especially if non-endoscopic modalities for susceptibility testing become a viable option, such as molecular testing of stool samples. In the absence of such data, the Maastricht strategy of susceptibility testing after two 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 non-genetic, 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 US. Regional information of local success rates would further refine regimen selection. The Pan-European Registry on *H. pylori* management[44] 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 utilized for both initial and refractory treatment choices.

Non-invasive *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 of levofloxacin resistance is relatively straightforward, as there are several commercial kits for these purposes that utilize PCR. 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 utilizing 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 (estimated to be at least $33 billion in the US 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 10-20% increase in eradication success[46], although more rigorous studies are needed.

There are also some promising data for non-antibiotic 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 twenty 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 side 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.

526 **Figure Legends**

527 Figure 1. Factors impacting failure to eradicate *H. pylori* infection.

528 Figure 2. Treatment algorithm for refractory *H. pylori* infection.

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Table 1. Second-line therapies for *H. pylori* eradication, based on selected international guidelines*

Regimen Failures	Maastricht V/Florence Consensus Report[1], 2016	Toronto Consensus Report[2], 2016	American College of Gastroenterology Guidelines[3], 2017	Chinese National Consensus Report,[4] 2018
If clarithromycin-triple fails in 1st line	• Bismuth quad • Levofloxacin-triple or quad	• Bismuth quad • levofloxacin triple	• Bismuth quad • Levofloxacin triple	Not discussed
If bismuth quad fails in 1st line	• Levofloxacin-triple or quad • In cases of high levofloxacin resistance: - Bismuth with other antibiotics - Rifabutin triple	• Levofloxacin triple	Depending on antibiotic history: • Levofloxacin triple • Clarithromycin triple	• Bismuth + PPI + 2 antibiotics not used in the 1st line bismuth quad treatment
If non-bismuth quad fails in 1st line	• Bismuth quad • Levofloxacin triple or quad	• Levofloxacin triple	Not discussed	Not discussed
If >2 treatment failures	Treatment guided by results of resistance testing	• Avoid reusing clarithromycin, levofloxacin, metronidazole • Consider rifabutin triple after >3 failures	Depending on antibiotic history and population resistance patterns: • Concomitant • Rifabutin triple • High-dose dual	• Bismuth + PPI + 2 antibiotics not used in 1st treatment • 2nd line bismuth quad treatments (metronidazole can be reused, but at a higher dose if not already tried)

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

1. Abbreviations: bid = two times daily; PPI = proton-pump inhibitor; qid = four times daily; tid = three times daily

2. Regimens (with usual doses/frequencies/durations)
Bismuth quad = bismuth ~300mg qid, metronidazole 500mg tid or qid, tetracycline 500mg qid, PPI bid x 14 days
Concomitant = clarithromycin 500mg bid, amoxicillin 1g bid, metronidazole or tinidazole 500 mg bid, PPI bid x 14 days
Clarithromycin triple = clarithromycin 500mg bid, amoxicillin 1g bid or metronidazole 500 mg bid, PPI bid x 14 days
Levofloxacin triple = levofloxacin 500mg qd, amoxicillin 1g bid, PPI bid x 14 days
Levofloxacin quad = levofloxacin 500mg qd, PPI bid + 2 antibiotics (multiple variations exist) x 10-14 days
Rifabutin triple = rifabutin 150 or 300 mg daily, amoxicillin 1g bid, PPI bid x 10 days
High-dose dual = amoxicillin 2 -3 g daily in 3-4 split doses, PPI high-dose bid x 14 days

Note: "PPI" implies standard dose unless "high-dose" is specifically stated. Standard dose is as follows: pantoprazole 40mg, lansoprazole 30mg, omeprazole 20mg, esomeprazole 20mg, dexlansoprazole 30mg, rabeprazole 20mg. "High-dose" implies double the standard dose.

3. Due to rising rates of levofloxacin resistance, we do not recommend levofloxacin unless the *H. pylori* strain is known to be sensitive to it, or if population levofloxacin resistance rates are known to be <15%. However, it is reasonable to prescribe rifabutin in a triple regimen without prior sensitivity testing since rifabutin and amoxicillin resistance are rare.

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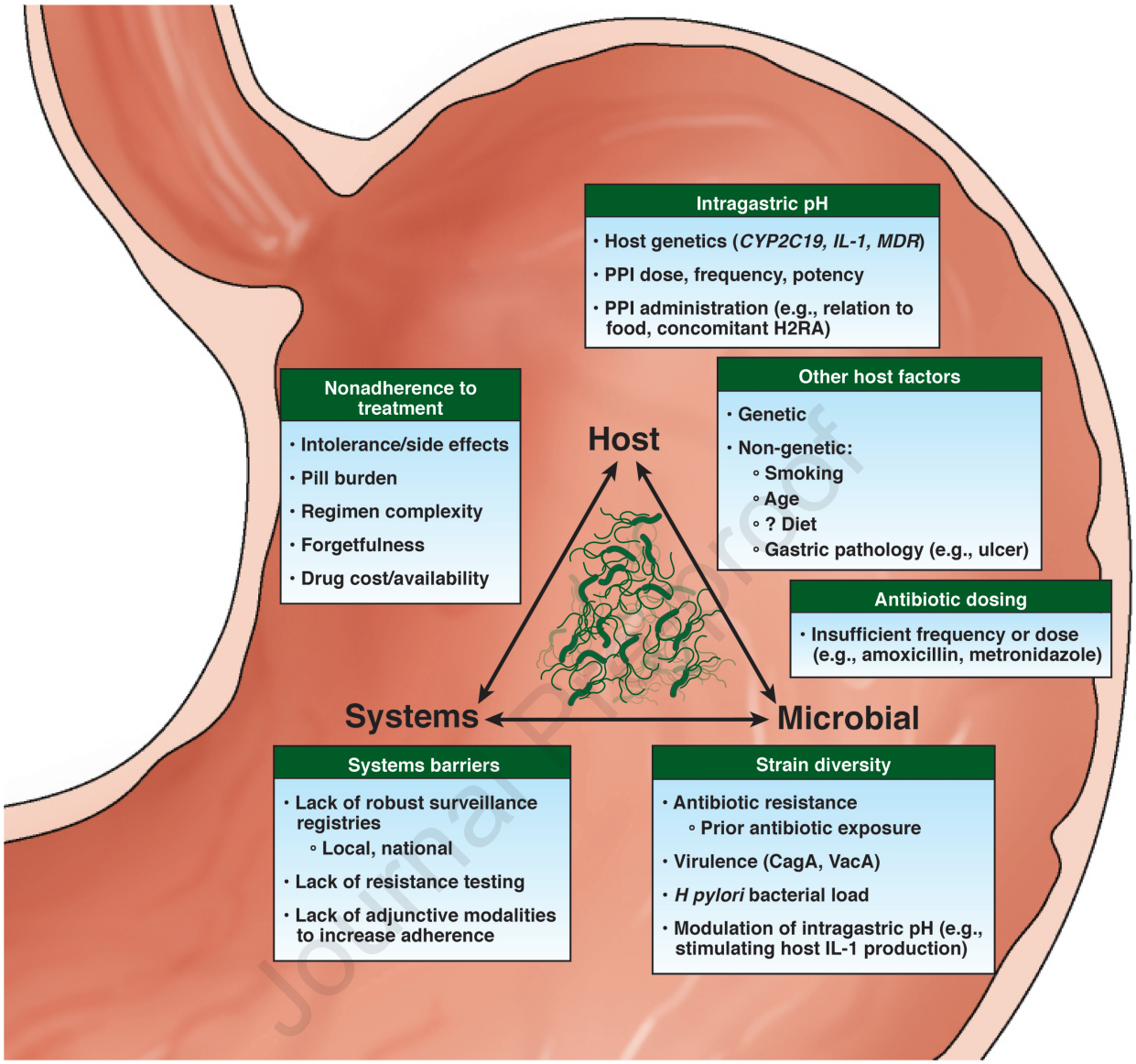

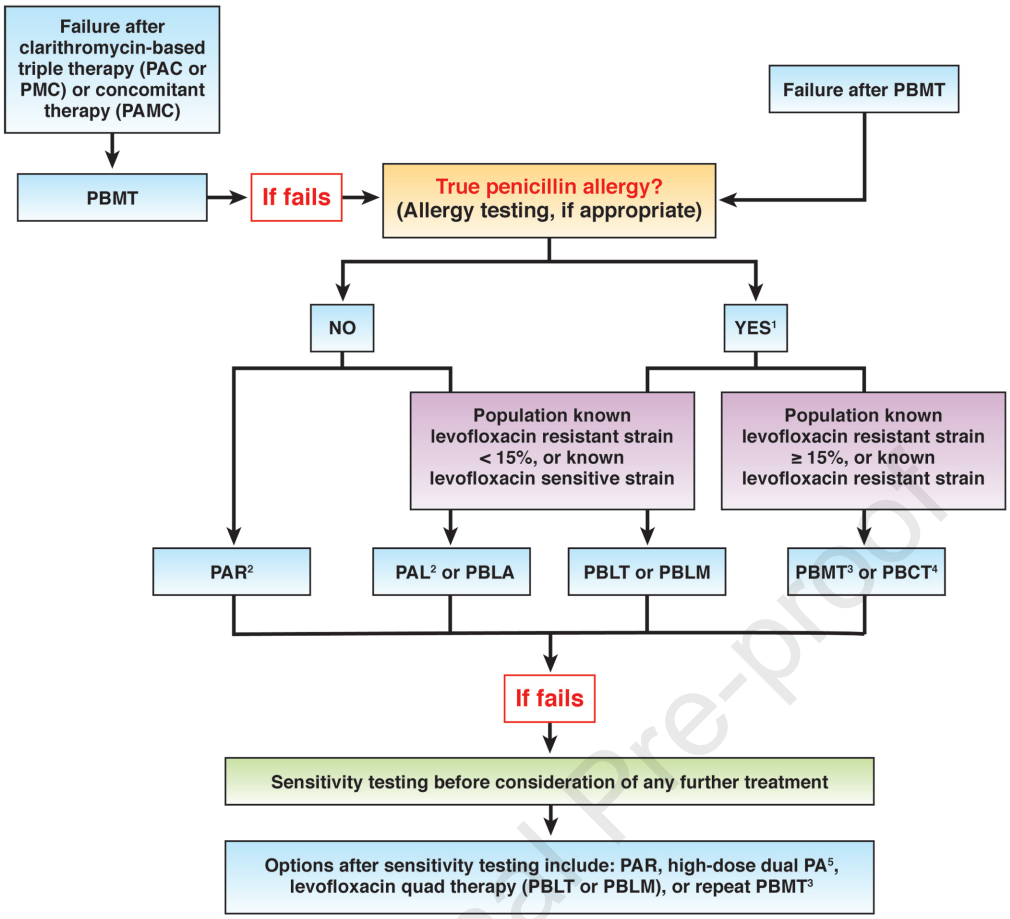

[1]Limited evidence guiding therapy in individuals with true penicillin allergy

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

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

[4]Only if clarithromycin sensitive strain

[5]High-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