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Current and Future Treatment of *Helicobacter pylori* Infections

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Abstract

Helicobacter pylori is one of the most common human pathogens and it has been estimated that about 50% of the world's population is currently infected. The present consensus is that, unless there are compelling reasons, all *H. pylori* infections should be cured. Since the 1990s, different national and international guidelines for the management of *H. pylori*-related diseases have been published and periodically updated regarding indications for treatment, diagnostic procedures, and preferred treatment regimens. Most guidelines provide sophisticated meta-analyses examining the outcome of different regimens done in regions with variable, often high rates of resistance to antibiotics, for which the prevalence and effects of resistance was often ignored. Although successful antimicrobial therapy must be susceptibility-based, increasing antimicrobial resistance and general unavailability of susceptibility testing have required clinicians to generally rely on empiric regimens. Antibiotics resistance of *H. pylori* has reached alarming high levels worldwide, which has an effect to efficacy of treatment. The recommendations should provide regimes for multi-resistant infections or for those where susceptibility testing is unavailable or refused. The first rule is to use only proven locally effective therapies. Because of patient intolerances, drug allergies, and local experiences, the clinicians should have at least two options for first-line therapy. As with any antimicrobial therapy, a thorough review of prior antibiotic use is invaluable to identify the presence of probably resistance. The second key is patient education regarding potential and expected side-effects and the importance of completing the course of antibiotics. We also review here triple therapies, sequential-concomitant, hybrid therapies, bismuth therapies, dual therapy, vonoprazan, modern antibiotic treatments, probiotics and vaccination.

Keywords

Helicobacter pylori; Triple therapy; Sequential therapy; Concomitant therapy; Vonoprazan

1 Introduction

Helicobacter pylori is a Gram-negative spiral-shaped bacterium and human pathogen. *H. pylori* infection causes gastric inflammation and its related diseases: peptic ulcer, gastric cancer, mucosa-associated lymphoid tissue (MALT) lymphoma and a variety of other conditions such as vitamin B12 deficiency, iron deficiency and idiopathic thrombocytopenia (Malfertheiner et al. 2012). *H. pylori* is one of the most common human pathogens and it has been estimated that about 50% of the world's population is currently infected (Williams and Pounder 1999). However, there are substantial geographic differences in the prevalence of infection, being most common in developing countries and infrequent in countries with advanced economies (Hunt et al. 2011). Living in, or birth in, a developing country and low socioeconomic status are associated with increased risk of *H. pylori* infection (Bastos et al. 2013; Bruce and Maarros 2008). Humans are the primary host, and the transmission requires contact with an infected person either directly or through contaminated food or water. Transmission typically occurs within families and most often in childhood. Improvements in household hygiene and living conditions reduce transmission and such improvements are likely the most important factors in decreasing the prevalence of the *H. pylori* infection worldwide (Vale and Vitor 2010). The decline in transmission among children has resulted in a series of age-related cohorts with the prevalence of the infection at age 20, generally describing the lifetime prevalence for that age-cohort (Bastos et al. 2013; Fujimoto et al. 2007). Even within Europe, *H. pylori* prevalence ranges from 11% in Sweden to 60% in Spain (Hunt et al. 2011; Sanchez Ceballos et al. 2007). In China, *H. pylori* prevalence has been reported as high as 83%, but is decreasing rapidly in most areas (Zhang et al. 2014). In the USA, cross-sectional studies of the participants in the National Health and Nutrition Examination Survey (NHANES) III and NHANES 1999–2000 found an overall seropositivity of approximately 30%, which was similar to the prevalence in Canada (Chen and Blaser 2012). In Japan, there has been a progressive and a rapid decline in *H. pylori* prevalence, which is reflected in an overall decrease from 75% in the 1970s to 35% by 2010 (Kamada et al. 2015). The infection is becoming rare in Japanese children with an overall prevalence of <4% and falling.

1.1 *H. pylori* as a Bacterial Infection

H. pylori infection is a bacterial infection, and its growth and survival was shown to be susceptible to a variety of antimicrobials. However, *in vitro* susceptibility did not reliably predict *in vivo* effectiveness and *H. pylori* antimicrobial treatment proved to be more complicated than treatment of other common infections such as bacterial pneumonia, in part because *H. pylori* resides in the human stomach. The stomach presents a hostile environment as it is acidic and to be effective most antibiotics require neutral or near neutral environments. *H. pylori* can also be found deep in the mucosa and even within gastric epithelial cells (Kwok et al. 2002). This wide range of environments complicate delivering active antimicrobial drugs to ensure killing all of the organisms. Other problems have been caused by doctors in that most regimens have been developed using a trial-and-error approach rather than by a systematic strategy.

As with all antimicrobial therapies, treatment success depends on the details of therapy including: susceptibility, doses, formulations, frequency of dosing in relation to meals, use of adjuvants such as anti-secretory drugs, antacids, or probiotics, as well as treatment duration. Few of these important factors have been subjected to detailed clinical assessment and the optimum regimens still remain unknown. The effectiveness of some regimens may also vary in relation to host differences, for example polymorphisms in drug-metabolizing enzyme such as cytochrome P450 2C9 (CYP2C19) can greatly affect effectiveness (Yang and Lin 2010).

2 History of *H. pylori* Therapies

Early experiments showed that, although *H. pylori* was susceptible *in vitro* to many antimicrobials, only a few appeared useful *in vivo*. The first effective regimen, defined as reliably able to produce cure rates of >90%, was a triple therapy of largely acid-independent antimicrobials: bismuth, metronidazole (MTZ), and tetracycline (Graham and Lee 2015). It was soon discovered that its effectiveness was markedly reduced by MTZ resistance and that problem could be partially or completely overcome by increasing the dosage of MTZ to 1.5 g or greater and adding a proton pump inhibitor (PPI). These changes resulted in a quadruple therapy, now commonly called bismuth quadruple therapy. When given for 5–7 days it proved highly effective in MTZ susceptible infections, but required 14 day therapy in the presence of resistance. The second widely used regimen to be introduced, utilized the pH sensitive agents amoxicillin (AMX) and clarithromycin (CLR) and a PPI all given twice a day. To be effective, these pH sensitive antibiotics require bacterial replication. Effective regimens have been described using 200–500 mg of CLR twice a day. Both bismuth quadruple therapy and CAM therapy can reliably achieve 95% or greater cure rates in susceptible infections and adherent patients (Hsu et al. 2017; Macias-Garcia et al. 2018).

Because of convenience, tolerability, and vast marketing support from Pharma, CLR triple therapy became, and still is, one of the most widely prescribed treatment regime worldwide. Best results are obtained with 14-day therapy. However, to obtain marketing advantages, pharmaceutical companies introduced shorter duration CLR triple therapies (7 or 10 instead of 14 days), which were generally associated with a reduction in cure rates from >95% to between 88% and 94%, respectively. This decline was partially obscured by increasing CLR resistance, which was rapidly undermining the effectiveness of the regimen (Thung et al. 2016). In contrast to MTZ resistance, CLR resistance is all-or-none meaning that the presence of CLR resistance effectively reduces the three drug regimen to only AMX and the PPI, which at the doses given resulted in an overall marked fall in cure rates. The rapid rise in CLR resistance was a bystander effect related to high use of macrolides worldwide for respiratory infections. By the year 2000, the *H. pylori* cure rates with CLR were often between 70% and 75%. However, in many countries this regimen was the only one approved which left physicians with few options. Treatment guidelines from various groups and countries continued to recommend short duration CLR triple therapy long after its cure rate had become unacceptably low. In 2012 the Maastricht IV guideline (Malfertheiner et al. 2012) recommended CLR not be used if the prevalence of resistance was 15% or greater, but as clinicians had no access to local resistance rates data, this failed to reduce the continued popularity and use of this obsolete regimen.

2.1 Antibiotic Resistance

Since at least the year 2000, the *H. pylori* eradication rates have been decreasing because of increasing resistance to one or more of the antibiotics (Grad et al. 2012; Graham and Fischbach 2010; Malfertheiner et al. 2012; Savoldi et al. 2018; Selgrad and Malfertheiner 2011). The World Health Organization groups antimicrobial resistance data by region and among east Asian countries the prevalence of CLR resistance is high. MTZ resistance is low only in Japan. Besides, high prevalence resistance to both CLR and MTZ is recognized in Italy, Vietnam, and Mexico as well as China. In northern Europe, there is generally low resistance to CLR also because of restricted use. The prevalence of bacterial resistance is related to the consumption rates of these antibiotics (Graham 2015; Meyer et al. 2002). A 2017 retrospective review from the Netherlands reported increasing resistance rates for CLR (from 9.8% to 18.1%), MTZ (20.7–23.2%), and AMX (6.3–10%) over 10 years (Ruiter et al. 2017). The first systemic reviews of primary antibiotic resistance in the Asia-Pacific region reported mean resistance rates of 17% for CLR, 18% for levofloxacin, and 44% for MTZ. There was significant heterogeneity in resistance rate across different countries (Kuo et al. 2017). The mean overall prevalence of resistance to MTZ is 44% (95% Confidence Interval 39–48) ranging from 10% in Japan to 84% in Bangladesh and 88% in Nepal.

Resistance to AMX is generally less than 1% (Megraud 2004) and overall no significant change in the resistance has been observed (Kobayashi et al. 2007). Kuo and co-workers (2017) reported mean overall prevalence of resistance to levofloxacin of 18% (95% CI 15–22), ranging from 2% to 3% (Bhutan and Malaysia) to 66% in Bangladesh. Subgroup analysis by collection period showed that overall levofloxacin resistance increased from 2% (95% CI 0–13) before 2000 to 27% (95% CI 21–34) during in 2011–2015, with significant between-group heterogeneity. According to data from 2006 to 2015, the overall prevalence of levofloxacin (21%) was higher than those in Europe and Latin America. Resistance to levofloxacin increased over time in all included countries for which data were available. Besides, the resistance to quinolones is in the range of 20% in Europe, 15% in America, and 10% in Asia, and rapidly increasing (Liang et al. 2014).

Because levofloxacin and CLR resistance have increased worldwide such that there are only a few areas where regimens that rely on CLR or levofloxacin are still effective when used as empiric therapy and treatment strategies will need to be adapted to resistance patterns on country-by-country or region-by-region basis (Kuo et al. 2017).

2.1.1 Other Triple Therapies—As noted above, a recent high-quality meta-analysis suggests that the efficacy of both triple therapy with a PPI and AMX plus CLR or MTZ is currently low and clinical unacceptable when given for either 7 days (70% vs. 77%) or 14 days (80% vs. 84%) (Puig et al. 2016). Due to the increase to CLR resistance, levofloxacin, a broad spectrum quinolone, was substituted for CLR in triple therapy. Initial trials utilized 7 and 10 day regimens and failed to achieve even 90% treatment success. Subsequently, it was discovered that a 14-day regimen was highly successful and reliable achieves eradication rates of more than 90% in areas where the local resistance to levofloxacin is low (Savoldi et al. 2018). The worldwide use of quinolones has markedly increased such that fluoroquinolones have joined CLR in no longer being considered acceptable for empiric

therapy except in the few areas where resistance is still low. Among the fourth-generation quinolones (moxifloxacin, sitafloxacin, and gemifloxacin) only sitafloxacin has proven successful in that it remains effective at a higher minimum inhibitory concentration (MIC) than other fluoroquinolones (An et al. 2018). Thus, in regions where sitafloxacin is available it is the only quinolone recommended for empiric therapy.

2.1.2 Sequential-Concomitant, Hybrid Therapies—There are a number of empirically derived 4 drug regimens using AMX, CLR, MTZ, and a PPI. They are named in relation to how the drugs are administered (e.g., sequentially, or all together). They all share the features of providing the best cure rates when given for 14 days and being rendered ineffective by the presence of dual CLR and MTZ (Graham et al. 2014). They all function as if one were giving CLR triple and MTZ triple therapy simultaneously (i.e., the MTZ will kill the CLR-resistant strains, and the CLR will kill the MNZ-resistant strains, such as that only the presence of dual resistant strains will cause this regimen fail). Since simultaneous administration of all 4 drugs always provides results equivalent or superior to the other versions, it is recommended over the other combinations using the same drugs (e.g., sequential therapy). All these regimens arose as empiric therapies in response to failing CLR triple therapy and lack of susceptibility data. It is now recognized that every patient treated receives one unneeded antibiotic (either CLR or MTZ and failures receive two unneeded antibiotics). This regimen was recommended by Maastricht V, the American College of Gastroenterology and Toronto consensus conferences without their recognition or understanding that each one million treatments would also administer approximately 15 tons of unneeded CLR or MTZ (which is actually a potential human carcinogen) (Chey et al. 2017; Fallone et al. 2016; Malfertheiner et al. 2012). This is an extremely high price to pay for failure to provide antimicrobial surveillance programs for *H. pylori* infection (Graham and Shiotani 2008).

2.1.3 Bismuth Therapies—Although bismuth triple therapy and subsequently quadruple therapy were introduced early in the history of *H. pylori*, they became never popular. The issues included intrinsic complexity, the large number of tablets, four times per day administration, side effects, lack of pharmaceutical company support, and importantly markedly negative assessments by key opinion leaders working with CLR triple therapies which were simpler and more tolerable. The combination of high dose MTZ and high dose tetracycline was associated with a high frequency of side effects such as abdominal pain, nausea, and vomiting which often resulted in poor adherence. A proprietary three-in-one capsule (Pylera) containing bismuth subcitrate potassium, MTZ and tetracycline fared no better in the US. Its introduction in Europe, however, coincided with loss of big Pharma support for triple therapy requiring key opinion leaders to re-examine their prior objections and they now found Pylera highly acceptable. Unfortunately, despite all current *H. pylori* treatment guidelines recommending 14-day bismuth quadruple therapy, Pylera is currently packaged as a 10 day regimen. The resulting reduction of cure rates in MTZ resistant infections is likely responsible for the cure rates from Europe being very heterogeneous as they represent combining a group with very high cure rates (i.e., in susceptible infections 7 days were sufficient) and lower cure rates in those with MTZ-resistant infections. In reality, 14 day MTZ triple therapy or 7 day bismuth quadruple therapy would be better tolerated

choices for those with MTZ susceptible infections. The patent on the Pylera formulation expires in December 2018 and hopefully other manufacturers will offer different packaging amenable to using different durations of therapy. Another option is to prescribe generics but these are often difficult to obtain because of difficulties with the supply and availability of both bismuth or tetracycline in Europe and tetracycline in the US.

2.2 Alternate Bismuth Quadruple Therapies

Bismuth-containing quadruple therapy is recommended by the current European, US, Canadian and Chinese guideline (Chey et al. 2017; Fallone et al. 2016; Liu et al. 2018; Malfertheiner et al. 2017). Bismuth is additive adding 20–25% to the outcome of the other components of the quadruple regimen (Graham et al. 2018). Different highly successful bismuth quadruple therapies have been developed in China and are effective despite MTZ resistance. Most use a PPI twice a day, bismuth 220 mg twice a day, along with tetracycline 500 mg four times a day, and either AMX 1 g three times a day or MTZ 400 or 500 mg four times a day for 14 days (Chen et al. 2018; Dore et al. 2016; Zhang et al. 2015). Alternatively, AMX 1 g three times a day has been used to substitute tetracycline in areas, where tetracycline is difficult to obtain. These regimens have proved to be well tolerated and highly successful quadruple therapies.

2.3 Dual Therapy

Dual AMX and PPI therapy has been examined since the year 1989 and in some instances has proven to be highly effective (Unge et al. 1989; reviewed by Dore et al. 1998). The population where it seems most effective is among those with low acid secretion (e.g., significant corpus gastritis). The Food and Drug Administration (FDA) approved regimen is lansoprazole 60 mg three times per day and AMPC 1 g three times a day for 14 days with a cure rate between 60% and 70% (Dore et al. 1998; Laine et al. 1998; Unge et al. 1989). Some recent studies in Taiwan have been proven successful, whereas others from China have not (Graham et al. 2017; Yang et al. 2015; Yang et al. 2011). The major barrier to overcome seems to be the difficulty in obtaining and maintaining the intragastric pH at 6 or greater. This is almost impossible with traditional PPIs, except in the presence of significant corpus inflammation (Graham and Tansel 2018). However, it can be achieved with the newest type of PPI, the potassium-competitive acid blocker (P-CAB) although the dose, dosing frequency, and duration remain to be established (Graham and Dore 2018). Early studies suggest that this will be possible with 14 day therapy and 1 mg AMX three times a day or 500–750 mg four times a day.

AMX is considered a time-dependent antibiotic that is rapidly absorbed into the plasma, but is excreted between 6 and 8 h after administration (Barbhaiya et al. 1979). A dosage of 500–750 mg per 6 h compared with 1000 mg twice daily is more likely to maintain higher plasma concentration of AMX. The bactericidal effect of AMX against *H. pylori* is also pH-dependent because AMX is more stable at a higher intragastric pH (Furuta et al. 2007). Moreover, *H. pylori* replicates when the intragastric pH increases to over 6, and thus become susceptible to AMX. On the contrary, the bacteria move into a non-replicative but viable state when the pH is less than 6 (Scott et al. 1998). Higher PPI dose increases antimicrobial

effectiveness by maintaining a high pH level and it also improves the stability and bioavailability of AMX in gastric juice (Erah et al. 1997).

Kwack and co-workers (2016) reported the high doses of the PPI, liaprazole (80 mg per day) and AMX 3000 mg per day for 14 days as the first line therapy and the cure rate was 79.3%. A meta-analysis of dual therapy as a rescue therapy for *H. pylori* compared to other rescue therapies found eradication rates were almost same, 81.3% vs. 81.5% (Gao et al. 2016). Compliance and adverse events were also same rates compared with others, so some guidelines this regimen is recommended as a rescue treatment.

2.3.1 Vonoprazan—As noted above, vonoprazan is the new P-CAB. The inhibitory effect (pKa 9.4) is largely unaffected by ambient pH and it accumulates in parietal cells under both secreting and resting conditions (Hori et al. 2011). PPIs require 3 or more days to reach full anti-secretory effectiveness, whereas vonoprazan essentially achieves full effectiveness on the first day. Vonoprazan is currently approved in Japan for first-line *H. pylori* eradication with CLR-containing triple therapy and for second-line therapy with MTZ and AMX (Murakami et al. 2016). In the pivotal study, in CLR-susceptible infections both lansoprazole and vonoprazan containing CLR triple therapies cured almost 100% of *H. pylori* infections (Murakami et al. 2013). In contrast, with CLR-resistant strains, the resulting dual therapies (vonoprazan or lansoprazole plus AMX) were markedly different with lansoprazole-AMX curing 40% and vonoprazan-AMX curing 80% (Murakami et al. 2016). Thus, in a comparative trial in the presence of CLR resistance vonoprazan-containing triple therapy will “appear” superior to lansoprazole triple therapy (Jung et al. 2017). However, considered from the prospective of antimicrobial misuse, since 80% of those receiving CLR would have been cured if the CLR had been omitted this regimen utilizes about 3000 kg of unneeded CLR per million cases treated. Clearly, use of vonoprazan in CLR triple therapy needs to be rethought by the Japanese government. (Table 1)

2.3.2 Probiotics—Probiotic supplementation is designed to alter the microbiome and hopefully improve the outcome of *H. pylori* therapy and also reduce side effects of antibiotic therapy such as diarrhea. The interest in probiotics therapy as an adjunct to eradication therapy has resulted in an increasing number of publications and meta-analyses as discussed in detail in Chap. 14 of this book. For example, one recent study reported that the addition of a probiotic reduced the frequency of adverse events from 28.2% to 12.2% (Jung et al. 2018). Oh and co-workers (2016) analyzed the microbiome of patients receiving probiotics compared to those receiving antimicrobial eradication therapy alone and found that although the microbiota were similar, as assessed by metagenomes sequencing, there was a greater proportional shift in functional gene families in those receiving antibiotics compared to those receiving the probiotic (Medilac-S®; *Streptococcus faecium* 9×10^8 and *Bacillus subtilis* 1×10^8). When used with bismuth quadruple therapy, probiotic supplementation resulted in an improvement in eradication rates (92.1% vs. 63.2%) (Shafaghi et al. 2016). Another study reported that the combination of *Bacillus mesentericus*, *Clostridium butyricum*, and *Streptococcus faecalis* was reported to be the optimal probiotic regime for reducing side effects and improving eradication rates when used to supplement the 14-day triple therapy (Wen et al. 2017). A systematic review analyzing 30 Randomized Control

Trials involving 4302 patients reported that the addition of probiotics increased eradication rates by 12.2% analyzed as-per-protocol (PP) and 14.1% intention-to-treat (ITT) (Lau et al. 2016; McFarland et al. 2018). However, the effective strains that produce benefits of increase eradication rate and decrease of side effect have not been established. Overall, the role of probiotics is unclear. And, consensus groups have generally no recommended probiotics (Malfertheiner et al. 2017).

3 Recent Guidelines and Consensus Reports

Since the 1990s, different national and international guidelines for the management of *H. pylori*-related diseases have been published and periodically updated regarding indications for treatment, diagnostic procedures, and preferred treatment regimens (Table 2). All now agree that *H. pylori* is an important human pathogen and whenever feasible, and all with the infection should be offered curative therapy irrespective of whether they currently had clinical manifestation of the infection. This option is currently only practiced in developed countries.

A number of recent major consensus conferences have been published (Chey et al. 2017; El-Serag et al. 2018; Fallone et al. 2016; Liu et al. 2018; Mahachai et al. 2018; Malfertheiner et al. 2017; Sugano et al. 2015). The Kyoto consensus included the designation of *H. pylori* gastritis as an infectious disease with recommendation of treatment for all *H. pylori* infected subjects. This was the first to codify the apparent paradigm shift advocating treatment be no longer reserved for patients with clinical manifestations of the infection. This was followed by the Houston consensus on diagnosis of *H. pylori* infection, which updated indication for considering diagnostic testing (El-Serag et al. 2018). All of the recent consensus conferences recognized the problem of increasing resistance and failure of commonly prescribed regimens. However, most do not engage issues such as rational use of antibiotics, antimicrobial stewardship, the critical role of susceptibility testing and of supplying updated regional, local, or patient-specific susceptibility data. Rather, most guidelines provide sophisticated meta-analyses examining the outcome of different regimens done in regions with variable, often high rates of resistance, for which the prevalence and effects of resistance was often ignored (Graham et al. 2017). This approach resulted in comparisons between incomparable groups not receiving optimal regimens but rather receiving regimes including one or more of the antimicrobials to which drug resistance was induced by *H. pylori* (Chey et al. 2017; Fallone et al. 2016). Many compared regimens proven to be highly successful for treatment of adherent patients with susceptible infections that yielded unacceptably poor cure rates without comments regarding why. Overall, other than the recommendation longer no use certain combinations, most of the conclusions have been of limited value for their expressed purpose of providing up-to-date guidance.

4 Modern Approach to Therapy

In some countries, there are constraints on which anti-*H. pylori* therapies can be used. These constraints include governmental restrictions on which regimes are approved for reimbursement and restrictions may include drugs, doses, and treatment duration. In some regions some commonly recommended antimicrobials and anti-secretory drugs are not

approved for use (examples include bismuth, furazolidone, sitafloxacin, and vonoprazan) or the doses may be restricted, all of which limits the range of available therapies. Approved drugs may also not be available because of shortage or high local cost (e.g., tetracycline in the USA). Finally, the approved regimens may differ from the previously recommended regimens. For example, the bismuth quadruple formulation, Pylera, is packaged for 10 day therapy despite the recommendation, that in the presence of MTZ resistance, it can be given for 14 days. None of these restrictions are consistent with the principles of antimicrobial stewardship, which includes promoting the use of the optimal drug regimes, including drugs, dosing, duration of therapy, and routes of administration as well as take measure to ensure sustainable access to effective therapy (i.e., to prevent development of resistance) (Dyar et al. 2017).

5 Recommended Therapies

Rational antimicrobial therapy is always susceptibility-based and regulatory and government agencies should be encouraged to institute *H. pylori* resistance surveillance programs to provide up-to-date regional and local resistance prevalence reports and treatment guidelines to the physicians for better treatment of their patients. The regulatory agents should only approve highly effective therapies, which should include data about effects of resistances. Regions with different antimicrobial susceptibility patterns may need to promote different strategies.

A general strategy would be to use a susceptibility-based therapy. The order of recommended therapy with susceptible infections is based on using CLR, first because it has the lowest MICs and is generally well tolerated. Levofloxacin is used last, because of the increasing concerns regarding side-effect reflected in Black-box warnings. The recommendations should provide regimens for multi-resistant infections or for those where susceptibility testing is unavailable or refused.

The first rule is to use only proven locally effective therapies (i.e., those that reliably provide cure rates 90%, preferably 95% with patients who are adherent to the therapy). This approach relies on antimicrobials, where resistance is either rare (AMX, bismuth, tetracycline, furazolidone, rifabutin) or can be overcome (MTZ) (Fig. 1). Because of patient intolerances, drug allergies, and local experiences, the clinician should have at least two options for first-line therapy. As with any antimicrobial therapy, a thorough review of prior antibiotic use is invaluable to identify the presence of probably resistance. For example, prior use of a macrolide or quinolone makes resistance to clarithromycin and levofloxacin highly likely. The second key is patient education regarding potential and expected side-effects and the importance of completing the course of antibiotics.

5.1 Approach after Treatment Failure

Treatment failures will occur. One of the most common causes of treatment failure is when the drugs are not taken as prescribed. The problem can lie with the physician for not providing adequate instruction (to the patients, or because of intolerable side effects. With well-chosen treatment and patient education, treatment failures should be rare (e.g., <5%). Another option for failure is the presence of an unusual resistance such as to AMX. For

example, if the region is one with rare CLR resistance and CLR triple therapy is the preferred first choice and is given empirically, failure suggests the patient had preexisting CLR resistance. Where available, the best approach of choosing a second choice therapy is to perform susceptibility testing. If unavailable, a second choice would utilize a different regimen. For example, if the patient was prescribed traditional bismuth quadruple therapy with bismuth, MTZ, tetracycline and a PPI, one could substitute AMX 1 g three times per day for the MTZ. Two failures require susceptibility testing.

5.1.1 Vaccination—Efforts to develop an effective vaccine against *H. pylori* began in the early 1990s (Del Giudice et al. 2009; Salama et al. 2013, see also Chap. 15 of this book). Findings have shown that protection against *H. pylori* infection can be achieved both prophylactically and therapeutically in animal models. However, previous trials of *H. pylori* vaccine candidates have all been at an early stage, with no real efficacy reported (Corthesy et al. 2005; Del Giudice et al. 2009; Malfertheiner et al. 2008). An oral recombinant *H. pylori* vaccine using urease B subunit fused with heat-labile enterotoxin B subunit was developed by Third Military Medical University and Chongqing Kang Wei Biotechnology in China. The vaccine has been assessed in phase 1 and phase 2 clinical trials for preliminary safety, immunogenicity, and optimum dose (unpublished). Zeng and co-workers (2015) reported that oral administration with the *H. pylori* vaccine provided good protection against the infection in children aged 6–15 years up to 1 year after vaccination. Although a previous study of the vaccine's protectiveness showed a mild warning of efficacy, overall protection was sustained up to 3 years. Other recent trials have failed (Zeng et al. 2015). For example, Malfertheiner et al. (2018) reported intramuscular immunization with a vaccine composed of three recombinant *H. pylori* antigens—vacuolating cytotoxin A (VacA), cytotoxin-associated antigen (CagA), and neutrophil-activating protein (NAP)—prevented infection in animal models and was well tolerated and highly immunogenic in healthy adults. However, compared with placebo, the vaccine did not confer additional protection against *H. pylori* infection after challenge with a CagA-positive strain, despite increased systemic humoral responses to *H. pylori* antigens. Clearly, effective vaccination is needed if the problem of very high prevalence of *H. pylori* infection in developing countries is to be solved.

6 Conclusions

There have been several studies in the past year evaluating novel treatment options for *H. pylori*. Debraekeleer and Remaut (2018) reported the future perspective for potential *H. pylori* eradication therapies. *H. pylori* urease has been at the center of attention for many years for the development of more narrow-spectrum treatment or treatment supplements, and several potentially *in vitro* inhibitors have been found. Nevertheless, many suffer from a lack of specificity. The only marketed bacterial urease inhibitor, Acetohydroxamic acid (Lithstat), is approved only as an orphan drug for use in struvite inducing chronic urinary tract infection caused by ureasplitting pathogens. It is not advised for *H. pylori* eradication due to its many and frequent side effects. Two approved and marketed mucolytic agents, erdosteine and N-acetylcysteine (NAC), have suggested to increase *H. pylori* eradication efficiency in clinical trials when given in supplement with triple therapy (Yoon et al. 2016). Nevertheless, they have not made general use due to the high dosage required, increased cost of treatment,

the additional patient discomfort, and increased risk for bleeding peptic ulcers associated with mucolytic agents.

An intervulin (anti-tumor) derivative, AS-1934, was found to have selective anti-*H. pylori* activity, including against antibiotic-resistant strains, without any effect on intestinal bacteria (Ohishi et al. 2018). There have been innumerable *in vitro* studies of agents that inhibit *H. pylori* and some animal studies but almost no human studies. Jeong and co-workers (2018) reported the efficacy of gentamicin-intercalated smectite hybrid-based treatment regimens in the murine model. Kouitcheu Mabeku et al. (2017) reported that *Bryophyllum pinnatum*, a medical plant with antioxidant and antimicrobial properties, could inhibit *H. pylori* growth and also protects gastric mucosa against reactive oxygen species. An Iran group showed the standard triple therapy with curcumin (a turmeric extract) increased *H. pylori* eradication rates and reduced endoscopic inflammation score (Judaki et al. 2017). A study of an Egyptian group suggested high eradication rates with nitazoxanide, which is a very expensive anti-infective drug against protozoa and anaerobic bacteria but also *H. pylori*. When MTZ was replaced with nitazoxanide in triple therapy, the reported eradication rates were 94.6% compared with 60.6% (Shehata et al. 2017).

The future will likely include a new generation PPI plus AMX dual therapy. As noted above, this regimen has been investigated since 1989 (Unge et al. 1989) with variable success (reviewed by Dore et al. 2016). The keys to making this regimen appear to include AMPC dosage and the ability to reliably maintain a high intragastric pH. The introduction of a new class of PPIs, the P-CABs, suggests that this may be possible (Dore et al. 2016; Graham and Dore 2018). The details of therapy have yet to be worked out in terms of doses and durations.

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Fig. 1.

Strategy for incorporation of susceptibility-based therapy against *H. pylori* into practice

The best tolerated and most effective regimens should be used first. For multidrug resistant infections or in instances when therapy must be chosen empirically only regimens proven to be highly effective should be chosen and should emphasize use of drugs for which resistance is rare

Table 1Drug commonly used for *H. pylori* eradication^a

Amoxicillin
Bismuth (subcitrate of subsalicylate)
Clarithromycin (macrolides)
Metronidazole/Tinidazole
Tetracycline HCl
Fluoroquinolones (levofloxacin)
Rifabutin
Proton pump inhibitors

^aAdapted from El-Serag (2018)

Table 2

Recommended regimens for *Helicobacter pylori* eradication

Treatment	Drugs, dosages and duration
Susceptibility-based	No drug allergies
Clarithromycin triple therapy (susceptible to clarithromycin)	Amoxicillin (1 g) and clarithromycin (500 mg) plus a PPI all given twice daily for 14 days (40 mg omeprazole equivalent per dose)
Metronidazole triple therapy (susceptible to metronidazole)	Amoxicillin (1 g) and metronidazole or tinidazole (500 mg) plus a PPI all given twice daily for 14 days (40 mg omeprazole equivalent per dose)
Fluoroquinolone triple therapy (susceptible to fluoroquinolones)	Fluoroquinolone (e.g. levofloxacin 500 mg once daily), plus a PPI and amoxicillin 1 g twice daily for 14 days (40 mg omeprazole equivalent per dose)
Susceptibility-based	Allergic to penicillin
Susceptible to clarithromycin and metronidazole	Clarithromycin (500 mg), and metronidazole or tinidazole (500 mg) plus a PPI (40 mg omeprazole equivalent per dose) all given twice daily for 14 days
Resistant to clarithromycin and/or metronidazole	Bismuth quadruple therapy (see susceptibility testing unavailable)
Empiric therapies	Susceptibility testing unavailable
Bismuth quadruple therapy	Bismuth subsalicylate or bismuth subcitrate 2 tablets 2 or 4 times daily after meals plus tetracycline hydrochloride (500 mg) 4 times daily with meals and at bedtime plus metronidazole (400 or 500 mg) 4 times daily with meals and a PPI twice daily for 14 days.
Prepackaged bismuth quadruple therapy	PYLERA for 14 days; add a PPI b.i.d. (20 mg to 40 mg omeprazole equivalent twice a day)
New bismuth quadruple therapy (amoxicillin replaces tetracycline)	Bismuth 2 tablets 2 or 4 times daily after meals plus metronidazole (400 or 500 mg) four times daily with meals and amoxicillin 1 g three times daily along with a PPI (40 mg omeprazole equivalent or more twice a day) for 14 days.
New bismuth quadruple therapy (amoxicillin replaces metronidazole)	Bismuth 2 tablets 2 or 4 times daily after meals plus tetracycline HCl 500 mg four times daily with meals and amoxicillin 1 g three times daily along with a PPI (40 mg omeprazole equivalent or more twice a day) for 14 days.
Furazolidone quadruple therapy	Furazolidone therapies are obtained by replacing metronidazole in bismuth quadruple therapies with furazolidone 100 mg three times daily
Empiric likely effective regimens	
Rifabutin triple therapy	Rifabutin (150 mg once or twice daily), amoxicillin (1 g three times daily and omeprazole 40 mg (or an equivalent PPI) every 8 h for 14 days.
Rifabutin bismuth therapy	Add bismuth subcitrate or subsalicylate 2 tablets twice daily to above therapy
Experimental regimens	
High dose PPI-amoxicillin dual therapy	PPI (e.g. rabeprazole 40 mg, esomeprazole 40 mg) plus amoxicillin (500–750 mg) all four times daily at approximately 6 h intervals for 14 days (can use 8 h interval at night)
Vonoprazan-amoxicillin dual therapy	Vonoprazan, the potassium competitive acid blocker, 20 mg twice a day plus 500–750 mg amoxicillin every 6 h for 14 days is recommended.
Obsolete regimens	Sequential, hybrid, concomitant therapies, empiric use of triple therapies

Preferred PPI's: 40 mg omeprazole, 60 mg lansoprazole, 20 mg rabeprazole or esomeprazole; pantoprazole not recommended as 40 mg = 9 mg omeprazole