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Choosing Optimal First-line *Helicobacter pylori* Therapy: a View from a Region with High Rates of Antibiotic Resistance

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Abstract

Helicobacter pylori is a gram-negative, microaerophilic spiral bacillus that is associated with life-threatening diseases such as gastric cancer, gastric MALT lymphoma, and peptic ulcer disease. The definition of an effective therapy is one that achieves at least a 90% eradication rate on a per-protocol basis with the first attempt. Eradication rates of *H. pylori* have declined to unacceptable levels worldwide, mostly due to antibiotic resistance and standard triple therapy gradually has lost its efficacy in most counties. However, bismuth quadruple therapy, when prescribed properly, has maintained its effectiveness. Alternative first-line regimens such as sequential and concomitant therapy were developed to substitute for standard triple therapy and were highly effective in the countries where they were developed, but proved susceptible to failure in regions with high rates of antibiotic resistance. Antibiotic resistance rates in Russia are high, however there is lack of data regarding comparative efficacy of first-line eradication options. The authors of this review extrapolate the knowledge of *H. pylori* first-line eradication options in Russia based on data from other countries, as well as from domestic studies. The available data support use of 14-day regimens with concomitant therapy, bismuth quadruple therapy, or furazolidone quadruple therapy for empiric use in adults. In addition, 14-day levofloxacin-containing therapies could be used if resistance is relatively low or lacking as triple therapy or possibly as a 5-day concomitant levofloxacin therapy.

Keywords

Helicobacter pylori; review; first-line eradication; Russia; concomitant therapy; bismuth quadruple therapy; furazolidone quadruple therapy

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CONFLICT OF INTEREST

Doctors Nijevitch, Idrisov, and Akhmadeeva hereby declare that they have no conflicts of interest.

1. INTRODUCTION

Helicobacter pylori is a motile, gram-negative, microaerophilic spiral bacillus with polar flagellae [1]. The infection was first described by Barry Marshall and Robin Warren about 25 years ago when they successfully cultured *H. pylori* from the human stomach. Initially there was concern that it only colonized inflamed mucosa, but when both Morris and Marshall developed gastritis after self-ingestion of the bacteria and the gastritis resolved after cure with antibiotic therapy, it was clear that the organism was the cause of gastritis [2].

Today, *H. pylori* infection is recognized as the major cause of peptic ulcer, gastric cancer, and gastric MALT lymphoma. Gastric cancer is one of the inflammation-associated cancers. Although *H. pylori* influences cell adhesion, proliferation, and apoptosis, it is not clear how it causes gastric adenocarcinoma in addition to causing chronic inflammation [3, 4]. About half of the world's population is infected with *H. pylori* and essentially all who are infected will also have chronic gastritis [2, 5]. *H. pylori* is a common infection and has been linked to many diseases where the association is likely not causal such as associations of *H. pylori* infection in children and upper respiratory tract infections, otitis, periodontal disease, food allergy, sudden infant death syndrome, and short stature [6, 7]. None of these links are proven.

H. pylori prevalence rates are generally much higher in developing countries compared to developed countries. There is a general tendency for the prevalence to decrease coincident with improvements in standards of living and sanitation. There has been a dramatic change in the prevalence of *H. pylori* in Russia over the last decade. For instance, two cross-sectional studies done in children in St Petersburg showed a striking decrease in the prevalence of *H. pylori* within 10 years providing an excellent example of how sensitive *H. pylori* acquisition is to improvements in quality of life and sanitation. In 1995 the overall prevalence of *H. pylori* infection in children in St Petersburg was 44% and decreased to 13% within 10 years. In children younger than 5 years the prevalence was 30%; a decade later the prevalence in the same age group was 2% [8]. However, in other areas of Russia, the prevalence remains high. For example, a 2004 report in Ufa in the middle part of Russia found that *H. pylori* was present in 80% of 225 children with recurrent abdominal pain [9]. Overall, in Russia, *H. pylori* is still common as it is antimicrobial resistance.

H. pylori is usually acquired during childhood [10, 11]. *H. pylori* transmission occurs through person-to-person spread with the most prominent routes being gastro-oral and fecal-oral; unclean water sources are likely important in conditions where sanitation is poor [12]. Rather than being associated with acute infection, *H. pylori* infection is more commonly associated with chronic infections with long latent periods such as syphilis or tuberculosis where the outcomes are severe but many infected patients remain asymptomatic [13]. In children most *H. pylori* infections are asymptomatic and treatment is difficult because many antibiotics cannot be used in children, the rate of resistance to commonly used antibiotics is often high, and recurrences appear more likely [9, 14].

Both invasive and non-invasive methods are used for diagnosis of *H. pylori* infection. Non-invasive approaches include the Urea Breath Test, detection of *H. pylori* antigen in stool and

antibodies against *H. pylori* detection in serum, urine or saliva. Invasive methods include endoscopic biopsy with histological examination, rapid urease test, culture, polymerase chain reaction and fluorescence in situ hybridization [15–18]. However, existing diagnostic methods vary in accuracy and are often used in combination with each other based on the clinical picture in each specific case.

Helicobacter pylori infection is a common and important public health problem in many countries. The challenging questions include when to search for the infection and what treatment should be applied. In this review, features of *H. pylori* infection will be provided in brief, followed by discussion of first-line eradication choices emphasizing the alternative therapies from the perspective of their *pros* and *cons* in regions with high antibiotic resistance and limited resources where antibiotic susceptibility testing is unavailable.

2. TREATMENT

2.1. Treatment Outline

The main principle of any treatment is to use regimens with high effectiveness, good compliance and few side effects. Any infectious disease therapy begins with identification and optimization of treatment regarding drug, dose, formulation, duration, *et cetera* [13]. The goal is to achieve at least a 90% eradication rate on a perprotocol basis on the first attempt [6]. A high initial eradication rate will also help prevent the development of antibiotic resistance, the spread of resistant *H. pylori* strains in the population, the need for repeated treatments and reduce the number who remain infected but are lost to follow-up. *H. pylori* eradication results in healing of gastric mucosal inflammation and halts the progression toward atrophy, cures active peptic ulcers, prevents new ulcers and prevent or reduces gastric cancer incidence in the population [15, 19].

Despite the fact that *H. pylori* been investigated for more than 25 years, its treatment is still challenging, especially in pediatric populations. Years ago, *H. pylori* infection eradication did not seem to be sophisticated and successful cure rates were expected the same as in the treatment of other common infections [20]. However, the cumulated experiences of clinical practitioners worldwide have identified impediments to successful therapy related to both bacterial and host factors [17, 21, 22].

Classic triple therapies include a standard dose of proton pump inhibitor + clarithromycin + amoxicillin or metronidazole/tinidazole, all given twice daily for 7–14 days [6, 15]. While standard triple therapy has recently been undermined by its ineffectiveness for a number of reasons (e.g. the development of high resistance rates) by increasing resistance, the lack of new drugs necessitating the use of old drugs in novel ways (see Table 1 and 2) [15]. Although treatment options have appeared as substitutes for the first-line treatment (e.g. sequential therapy, concomitant therapy, bismuth quadruple therapy, hybrid or dual-concomitant therapy and bismuth containing quadruple therapy) it remains unclear which treatment option should be labeled as a “gold standard”.

2.2. Background and Drugs Efficacy

Many drug combinations have been employed for *H. pylori* eradication. Interestingly, decades ago a combination of colloidal bismuth subcitrate, tetracycline and amoxicillin or metronidazole/tinidazole was the most effective in the treatment of *H. pylori* infection in adults [23]. This regimen had no pharmaceutical company sponsor and was largely replaced by regimens containing a proton pump inhibitor (PPI), and combinations of metronidazole, amoxicillin and clarithromycin [24]. These combinations achieved high eradication rates initially but treatment success rapidly fell because of resistance to metronidazole and clarithromycin. However, they remain effective in areas where resistance remains low [25]. Ranitidine bismuth-citrate in combination with amoxicillin and tinidazole also proved effective including in Russian children [26].

PPI's have a number of modes of action: increasing pH which makes most antibiotics more effective, preventing destruction of the antibiotic in the acidic stomach, inhibiting *H. pylori*, and increasing the antibiotic concentrations in the stomach and gastric mucosa [27]. The apparent advantages of PPI-containing therapy include few side effects, enhanced effectiveness of antimicrobial therapy and prompt pain relief for those with ulcer disease.

Clarithromycin has excellent activity against *H. pylori*, at a neutral pH clarithromycin was significantly more active than other macrolides [28]. Amoxicillin is one of the most widely used antimicrobials for *H. pylori* infection. It is bactericidal, but is less effective in the stationary growth phase or against cell-adherent or slowly growing *H. pylori* [27]. Metronidazole is also one of the most commonly used antimicrobials and a crucial component of the many multidrug *H. pylori* therapies. Metronidazole diffuses well into all tissues and is acid stable. It is a prodrug that is activated by bacterial enzymes and is bactericidal against *H. pylori* due to disruption of DNA and inhibition of bacterial nucleic acid synthesis [29]. Levofloxacin is a third-generation fluoroquinolone whose antibacterial mechanism involves inhibition of bacterial type II topoisomerase. Topoisomerase controls DNA topology in DNA replication and repair and the drug blocks DNA replication by inhibiting bacterial DNA gyrase A subunit and topoisomerase IV activity, thus it has a bactericidal effect [30]. Levofloxacin is usually not used in pediatric patients due to its harmful effect to articular cartilage in young child; however the data regarding fluoroquinolone usage in pediatrics remains contraindicating [31, 32].

Other drugs used in *H. pylori* eradication include tetracycline, furazolidone, and rifabutin. Nitrofurantoin-containing therapies using either nifuratel or furazolidone have produced good cure rates even among those who failed prior therapy [33]. Furazolidone is inexpensive and does not tend to produce drug resistance [34]. However these drugs are used less commonly as initial therapy and are rarely included as first-line regimens in Western countries.

Probiotics, living or attenuated nonpathogenic microorganisms, are also used in *H. pylori* treatment and recent studies have suggested a positive effect of probiotics as adjuvant therapy to reduce the frequency of antibiotic induced side-effects [15, 35]. Recommendations for probiotics use are axiomatic; they are classically used to reduce side effects of antibiotics regardless of patients' health condition. Probiotics have a number of potential beneficial effects such as an ability to bind to epithelial cells, occupy the digestive

tract, suppress pathogenic flora including *Helicobacter* species, and influence metabolic reactions [36].

2.3. Treatment Failures Due to Antimicrobial Resistance

There are many bacterial and host factors that affect treatment outcomes regardless of the choice of first-line therapy. The main bacterial factor is antibiotic resistance, and the primary host factor is compliance with the regimen [21]. Antibiotic resistant *H. pylori* strains are increasingly common worldwide. For instance, in Russia the average resistance to metronidazole and clarithromycin is about 30% and 25% respectively [37]. Almost one-third (e.g., 29.3%) of *H. pylori* strains obtained from children living in the Ural area of Russia had mutations suggesting the presence of clarithromycin resistance (A2142G or A2143G mutant). *RdxA* gene deletion was found in 46.3% of isolates [38].

A meta-analysis of 31 studies from 1993 to 2009 reported the overall *H. pylori* antibiotic resistance rates worldwide as 11.2% for amoxicillin, 17.2% for clarithromycin, 26.7% for metronidazole, 5.9% for tetracycline, 16.2% for levofloxacin, and 9.6% for multidrug-containing therapies with resistances being significantly higher in female than in male patients. In contrast, data from Europe demonstrated primary *H. pylori* resistance rates (1998, 2001 and 2007/2008) for metronidazole: 24.7%, 33.3%, and 35.6%, for clarithromycin: 1.1%, 3.7%, and 3.3% with no cases of amoxicillin resistance [40]. The pattern of antibiotic resistance in a recent study conducted in Europe reported resistance rates among adults as 34.9% for metronidazole, 17.5% for clarithromycin, and 14.1% for levofloxacin. Clarithromycin and levofloxacin were significantly more common in Western/Central and Southern Europe (>20%) than in Northern European countries (<10%) [41].

The data of amoxicillin resistance remains conflicting and overall, it is rare. Amoxicillin resistance, when it occurs in *H. pylori*, is generally due to alterations in penicillin binding proteins. Three substitutions—*Ser* 414 *Arg*, *Thr* 556 *Ser*, and *Asn* 562—have been reported in multiple clinical isolates, suggesting that these are the most common amino acid changes in *PBP1* connected to amoxicillin resistance [42].

Clarithromycin resistance is one of the major limiting factors reducing the efficacy of clarithromycin in initial eradication regimens [42]. Furthermore, in most countries the high rate of clarithromycin resistance no longer allows its empirical use in most *H. pylori* eradication regimens [41]. Common mutations related with clarithromycin resistance are the adenine transitions at positions 2142 and 2143 of rRNA (A2143G and A2143C), while the change of adenine to cytosine at position 2142 (A2142C) is less common. These mutations are responsible for more than 90% of clarithromycin resistance in developed countries; Russia is no exception [21, 43].

Unfortunately, besides macrolide resistance, the widespread use of metronidazole has resulted in an increase in the prevalence of *H. pylori* resistant strains to nitroimidazoles leading to treatment failures [33]. The results of a study conducted by Kwon *et al.* showed that alterations in both the *rdxA* and *frxA* genes of *H. pylori* were required in moderate and high-level metronidazole resistance and that metronidazole resistance that developed during *H. pylori* therapy containing metronidazole was most likely to involve a single sensitive

strain infection rather than a coinfection with a metronidazole-resistant strain [44]. However, metronidazole resistance can be overcome, at least partially, in some regimens by increasing the dose and duration of therapy [21].

Obviously, an increase in the prevalence of *H. pylori* resistant strains leads to increasing treatment failure. However, most often treatment failure is predictable if one knows the outcome with susceptible strains and the effect of resistance to each antibiotic individually and/or in combinations such that one should be able to predict the outcome for an individual patient [13].

Outcome can be predicted using a general treatment equation [45]. For instance, if one prescribes standard triple therapy including a PPI + amoxicillin + clarithromycin to a patient with a clarithromycin resistant infection, clarithromycin drops out of the equation and the bacteria functionally receive only a dual PPI + amoxicillin therapy.

3. MODERN FIRST-LINE TREATMENT OPTIONS

3.1. Preview

According to the latest updates of guidelines for *H. pylori* therapy of adults and children, the choice of first-line treatment options should be based on the local prevalence of resistance [6, 15]. Russia is no exception and traditionally triple therapy with a proton pump inhibitor-amoxicillin/metronidazole or clarithromycin/metronidazole is no longer effective as an empiric regimen [46, 47]. As noted above, standard triple therapy with clarithromycin or metronidazole is ineffective when resistance to the primary antibiotic (clarithromycin or metronidazole is present) and thus they should not be used in areas where resistance is more than 5% (for 7-day therapy) or 10–15% for 14-day therapy or more importantly, in any patient who has received macrolides in the past. The same is true for 10-day sequential therapy which provides about 75% success with metronidazole resistance and 80% success with clarithromycin resistance. Because 14-day concomitant therapy is only affected by dual clarithromycin and metronidazole resistance, however, it is the therapy of choice among clarithromycin containing regimens. Antibiotic susceptibility testing pretreatment at least for clarithromycin should be performed in high antibiotic resistance environments before any clarithromycin-containing regimen is used.

Currently, the best approach is to choose therapy based on antimicrobial susceptibility testing [15]. If that is unavailable, the choices with the highest effectiveness are 14-day concomitant therapy (e.g., twice a day PPI, amoxicillin, clarithromycin and metronidazole), 14-day bismuth quadruple therapy, or bismuth furazolidone quadruple therapy (Table 2). In regions where fluoroquinolone resistance is rare, 14-day levofloxacin or 5-day levofloxacin concomitant therapy are good choices, but unfortunately, quinolone resistance has been increasing rapidly such that the admonition to first test for resistance has become increasingly important.

3.2. Standard Triple Therapy (Generally Now an Obsolete Regimen)

Standard triple therapies include a standard dose of proton pump inhibitor + clarithromycin + amoxicillin or metronidazole/tinidazole, all given twice daily for 7–14 days with 14 days

being preferred [6, 15]. However, the eradication rate with these "classic" first-line triple regimens are relatively low (71–65%) in most countries including Russia and other European regions [46–48]. Therefore, this regimen is obsolete except in areas with low clarithromycin resistance rates. It is also recommended that antibiotic susceptibility testing for clarithromycin should be performed initially in high antibiotic resistance environments [6].

3.3. Sequential Therapy (Obsolete Except in Specific Regions)

Sequential therapy was established in 2000 by Italian scientists and was later found to be a promising substitution for standard triple therapy [49]. The sequential therapy is a simple dual therapy including PPI plus amoxicillin was initially given for the first 5 days followed by a triple therapy including PPI, clarithromycin, and tinidazole for the remaining 5 days; thus sequential administration aggregates to a 10-day complete treatment regimen [50]. The first 5-day phase includes the administration of amoxicillin which reduces bacterial load and favors the successive efficacy of the 5-day phase with clarithromycin-tinidazole [51]. It has recently been recognized that 14-day sequential is superior to 10-day therapy. However, both 10 and 14 days sequential therapy are markedly influenced by metronidazole resistance (e.g., success falling to approximately 75%) [19]. The initial enthusiasm for sequential therapy arose because the initial studies were done in Italy where metronidazole resistance was low [50]. Subsequent studies in other regions with higher rates of metronidazole resistance such as Taiwan, Korea, Panama, Spain, Poland, Thailand, and India have shown it to be relatively ineffective (e.g., treatment success of 80% or less) [26, 52–56] and it should be considered obsolete except in regions with low rates of metronidazole resistance. In any area where clarithromycin and metronidazole resistance are present but not high (e.g., metronidazole resistance <20%), 14-day concomitant will be superior to sequential therapy. Sequential therapy is also complicated such that if a clarithromycin-containing regimen is to be used, concomitant therapy is recommended because of the simplicity and effectiveness.

3.4. Advantages of Concomitant Therapy

Concomitant therapy consists of PPI plus amoxicillin, clarithromycin, and metronidazole given simultaneously. This option was first introduced as a substitute for standard triple therapy in 1998 by Treiber *et al.* and Okada *et al.*; in both studies 5-day concomitant therapy produced intention-to-treat eradication rates of >90% [57, 58]. Later in Hong Kong, the so-called 1-week "non-bismuth quadruple therapy" with omeprazole, clarithromycin, amoxicillin, and metronidazole was claimed an effective treatment of *H. pylori* in children in a population with a high incidence of metronidazole resistant strains. Further studies showed a high efficacy eradication rate of concomitant therapy as well. The advantage of concomitant therapy was recently depicted in the Zullo's review, highlighting pooled estimates of the five randomized controlled trials with an average eradication rate of 91.1% in 3428 patient receiving concomitant therapy [21, 59, 60]. Eradication rates depended on the number of days of eradication; data from a study conducted in 2009 revealed correlation of efficacy with duration of therapy: 85% within 3 days, 89% within 5 days and 92% within 10 days (i.e., eradication rates increase with the treatment duration) [61]. Recent data suggests that nowadays only 14-day concomitant therapy appears to be effective in the areas

with high antibiotic resistance rates [62]. Therefore concomitant therapy should only be prescribed as a 14-day regimen in the areas with high antibiotic resistance such as Russia.

3.5. Other Types of First-Line Therapy

Bismuth-containing quadruple therapy is generally metronidazole+ tetracycline+ bismuth +PPI for 10–14 days and is also recommended as a first line therapy for adults [37]. The 14-day regimen is preferred. Bismuth-containing quadruple therapy has shown promising results as a first-line therapy in a number of studies worldwide [63–65].

The efficacy of ranitidine bismuth-containing triple therapies has also been demonstrated as retreatments. The advantage of traditional 14-day bismuth quadruple therapy is that it overcomes metronidazole resistance. In contrast, the effectiveness in the presence of metronidazole resistance is significantly less with 10-day therapy and very poor with 7-day therapy. The down side of this regimen is poor compliance, which tends to be lower than with non-bismuth quadruple therapies. In most regions, where dual metronidazole-clarithromycin resistance is uncommon, 14-day concomitant therapy is possibly the best first choice with bismuth quadruple therapy being reserved for those with penicillin allergy and as treatment for failure of the 14-day concomitant therapy.

In the central part of Russia other variants of first-line therapies have been emerging as well, for instance a study evaluated empiric nifuratel, amoxicillin, and bismuth triple therapy for *H. pylori* eradication in children. Drugs were prescribed in standard doses for 10 days. Seventy-three children (48 boys, 25 girls, age range 9–14) were treated. *H. pylori* was eradicated in 63 patients (86%; 95% confidence interval: 76.6–93.2; intention-to-treat and per protocol). There were no serious adverse reactions and no withdrawals due to any side-effects. All of the side effects were self-limiting (dark stools, urine discoloration, blackening of the tongue, and others). The study concluded that the combination of nifuratel, bismuth subcitrate, and amoxicillin is an effective and tolerable regimen for *H. pylori* eradication [46]. Possibly, the success would have been higher with 14-day therapy, and studies are needed to optimize the regimen.

Recent studies in China have highlighted the feasibility of furazolidone-containing 4 drug regimens. The Liang *et al.* prospective single-center study has shown that 14-day therapy with a PPI, bismuth, furazolidone and either amoxicillin or tetracycline were very effective despite resistance to other commonly used antibiotics (Table 2) [66]. A tetracycline-containing regimen might be used for patients allergic to penicillins. Apparently, high doses of tetracycline and metronidasole were associated with high risk of side effects (such as fatigue, nausea, head and stomach aches). Frankly, furazolidone-including regimens are effective, however again compliance is often a problem.

3.6. Compliance and Use Challenges

Side effects of the first-line therapy are similar regardless of the type of regimen (e.g., standard, sequential *et c.*). However, compliance to the therapy is the major outcome-influencing factor. Good compliance is defined as the consumption of more than 90% of the prescribed drugs.

Any pharmacologic therapy has side effects, and drugs used for *H. pylori* eradication infection are not exceptions. For example, the use of tinidazole, metronidazole, clarithromycin, or amoxicillin has been associated with nonspecific adverse effects such as anorexia, constipation, dizziness, dysgeusia, dyspepsia, headaches, vomiting and weakness [67]. However, most are generally well-tolerated, and the dropout rate from side effects is generally low. Tinidazole/ metronidazole is contraindicated for patients younger than 3 years old, women in their first trimester of pregnancy and women who are lactating. There is also data supporting carcinogenic effects of tinidazole, metronidazole and possibly furazolidone [68]. Clarithromycin is contraindicated for patients with history of QT prolongation or ventricular cardiac arrhythmia and patients taking statins, as statins are extensively metabolized by CYP3A4 [67]. Of course, the risk of individual sensitivity for each drug should be considered by physicians.

There are a number of studies with comparative data regarding side effects and compliance of *H. pylori* eradication methods. For instance, in a study conducted by Urgesi *et al.* of clarithromycin-containing regimens, no patient discontinued treatment, however 17.5% patients who received standard triple therapy and 15% patients who received sequential therapy reported minor side effects. The most frequent side effects in both groups were nausea, bloating and mild diarrhea [69]. In a pediatric case-control study conducted in Ufa (Russia) revealing the efficacy of 10-day sequential therapy versus standard triple therapy, the most common side effects were nausea, anorexia, headaches, vomiting and diarrhea with no significant differences in either group [70]. However, some drugs such as furazolidone and high-dose tetracycline are particularly likely to be associated with side effects such that extra effort should be made to provide information to the patient about potential side effects and the importance of completing the regimen.

4. CONCLUSIONS

An acceptable *Helicobacter pylori* eradication therapy should achieve at least a 90% cure rate on a per-protocol basis on the first attempt [6]. Antibiotic resistance is one of the leading obstacles to successful eradication of *H. pylori* worldwide. The prevalence of antimicrobial resistance is now so high that all patients should be considered as potential hosts of resistant strains [71]. Numerous drugs have been tested for their *H. pylori* eradication efficacy with combination therapy proving to be most effective. When deciding on which therapy to use for an individual patient, one must consider the maximum treatment success obtainable if the infecting strains are resistant to one or more of the antibiotics used. For example, with 7-day standard clarithromycin-containing triple therapy and clarithromycin is likely to be curative in less than 20% of cases. With a 14-day regimen, success will not exceed 50%. With 10-day sequential therapy, the maximum achievable effectiveness in the presence of clarithromycin is an unacceptable 80%, for metronidazole resistance 75% and for dual resistance less than 20%. Clearly, neither standard triple therapy nor 10-day sequential therapy should be prescribed for a patient for whom resistance is likely either on the basis of history (*i.e.*, use of the drugs) or knowledge of the background prevalence in the society or ethnic group. In most regions tetracycline resistance in bismuth quadruple therapy is rare and one only needs to consider the effect of metronidazole resistance. In the presence of metronidazole resistance, treatment success is related to doses

and duration (e.g., approximately 75% with 7 days, increasing to mid-80% for 10-day therapy and 95% for 14-day therapy. Thus, the recommendation is to only prescribe 14-day therapy if resistance status is unknown,.

It is obvious that the treatment should be chosen according to local peculiarities regarding *H. pylori* drugs resistance. If antibiotic susceptibility testing is unavailable in a given region, one can rely on the success rates of individual regimens making post-treatment test of cure critical for further decision-making. Available up-to-date literature supports the use of 14-day therapies with concomitant therapy, bismuth quadruple therapy, or furazolidone quadruple therapy for empiric use in adults. In addition 14 day levofloxacin-containing therapies could be used if resistance is low or lacking as triple therapy or possibly as a 5-day concomitant therapy.

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Table 1

Empiric first line therapy for adults from regions with rare antibiotic resistance.

Treatment		Regimen*			Duration
Standard Triple Therapy		PPI	clarithromycin	amoxicillin or metronidazole	14-days
Sequential Therapy	Stage 1	PPI		amoxicillin	7-days
	Stage 2	PPI	clarithromycin		7-days
Concomitant Therapy		PPI	clarithromycin	amoxicillin	14-days
Bismuth quadruple Therapy		PPI	tetracycline	bismuth	10–14 days (14 days preferred)
Levofloxacin triple Therapy		PPI	levofloxacin	amoxicillin	14 days
Levofloxacin concomitant Therapy		PPI	levofloxacin	amoxicillin	5 days

PPI – full dose of proton pump inhibitors (e.g., 40 mg of omeprazole or its equivalent); bismuth standard dose q.i.d.; clarithromycin 500 mg b.i.d.; amoxicillin 1 g b.i.d.; metronidazole 500 mg b.i.d.; tetracycline 500 mg q.i.d, levofloxacin 500 mg once daily

Table 2

Empiric first line therapy for adults from regions with high rates of antibiotic resistance.

Treatment		Regimen*			Duration
Hybrid therapy	Stage 1	PPI		amoxicillin	
	Stage 2	PPI	clarithromycin	amoxicillin	metronidazole
Concomitant Therapy		PPI	clarithromycin	amoxicillin	metronidazole
Bismuth quadruple Therapy		PPI	tetracycline	bismuth	metronidazole
Furazolidone quadruple Therapy		PPI	tetracycline or amoxicillin *	bismuth	furazolidone

PPI – full dose of proton pump inhibitors (e.g., 40 mg of omeprazole or its equivalent); bismuth standard dose q.i.d.; clarithromycin 500 mg b.i.d.; amoxicillin 1 g. b.i.d. (*1 g t.i.d. with the furazolidone regimen); metronidazole 500 mg. b.i.d.; tetracycline 500 mg q.i.d.; furazolidone 100 mg t.i.d.