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Eradication of *Helicobacter pylori* infection

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Abstract

Helicobacter pylori infects about 50% of the world's population, causing at a minimum chronic gastritis. A subset of infected patients will ultimately develop gastric or duodenal ulcer disease, gastric adenocarcinoma, or MALT (mucosa-associated lymphoid tissue) lymphoma. Eradication of *H. pylori* requires complex regimens that include acid suppression and multiple antibiotics. The efficacy of treatment using what were once considered standard regimens have declined in recent years, mainly due to widespread development of antibiotic resistance. Addition of bismuth to standard triple therapy regimens, use of alternate antibiotics, or development of alternative regimens using known therapies in novel combinations, have improved treatment efficacy in specific populations, but overall success of eradication remains less than ideal. Novel regimens under investigation either *in vivo* or *in vitro*, involving increased acid suppression ideally with fewer antibiotics or development of non-antibiotic treatment targets show promise for future therapy.

Keywords

Helicobacter pylori; gastric acid; antibiotic resistance; eradication

Introduction

Helicobacter pylori, a gram negative bacteria that infects the normal acid secreting human stomach, was first connected to the development of ulcer disease in 1984 [1]. The bacteria infects about 50% of the world's population, leading to gastritis in 100% of those infected, and a fraction of those individuals will ultimately develop gastric or duodenal ulcer disease, gastric adenocarcinoma, or MALT (mucosa-associated lymphoid tissue) lymphoma [2-6]. *H. pylori* was designated as a class one or definite carcinogen by the World Health Organization on the basis of the established connection with gastric cancer [7, 8]. The worldwide burden of gastric cancer is high. Gastric cancer is the 4th most common cancer and the 2nd most

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common cause of cancer death [9]. Eradication of *H. pylori* infection leads to improvement or resolution of associated pathology, underscoring the importance of effective therapy. Successful treatment of *H. pylori* leads to ulcer healing rates of >90% and is effective in preventing recurrence of bleeding [10-12]. Low-grade MALT lymphoma, in the absence of genetic translocations, can be treated by eradication of *H. pylori* [13-15]. Eradication of *H. pylori* is proven to be beneficial for prevention of gastric cancer [16] and leads to eventual regression of acute and chronic inflammation [17]. Success rates of standard therapy regimens, typically including acid suppression and multiple antibiotics, has fallen below the acceptable level of 80% in many parts of the world [18]. The reason for the decline in treatment success appears to be multifactorial, involving issues such as expanding antibiotic resistance, patient compliance, and host and bacterial factors that alter the efficacy of treatment [19]. Antibiotic resistance is generally believed to be the major contributor to treatment failure, underscoring the importance of understanding why current regimens fail and identifying new treatment regimens.

Scientific basis for standard therapy

H. pylori colonizes an acidic niche in the human stomach. It was originally believed that, even though the gastric lumen has a median pH near 1.4 in normal acid secreting humans [20], the actual site of infection was closer to neutral pH due to a pH gradient through the mucus layer [21]. These studies were done with glass-tipped microelectrodes, and may have been hindered by technique due to difficulty in diffusion of protons through the electrodes. Several studies in the interim have provided evidence for a more acidic environment at the site of infection. Later work using mircoelectrodes in mice have suggested that the presence of *H. pylori* removes any potential barriers to proton diffusion [22]. Fluorescent dye studies completed in externalized stomachs of anesthetized mice also suggested an acidic pH at the gastric surface, regardless of the presence of a mucus layer [23]. The gastric surface pH is a combination of regulation of acid and alkali secretion to a specific set point rather than a result of trapping of buffers or protons under the mucus layer [23]. Transcriptome studies done *in vitro* at acidic and neutral pH and in bacteria collected from infected gerbils demonstrated that genes regulated by acidic pH *in vitro* show similar changes in expression in the gerbil stomach, again suggesting acidic pH at the site of infection [24]. *H. pylori* typically infects the gastric antrum but the infection predominates in the gastric body with acid suppressive therapy [25-28], providing additional evidence that the bacteria are adapted to live in a very specific environment with regard to local pH.

In apparent conflict with the need for *H. pylori* to inhabit an acidic niche, the bacteria are bioenergetically neutralophiles, meaning they are able to survive between pH 4-8 and grow between pH 6-8. The bioenergetic profile has been confirmed using studies measuring membrane potential [29]. The bacteria have adapted to survive in their very specific niche through a mechanism termed acid acclimation, or the ability to maintain periplasmic pH near neutral in an acidic environment [30]. This is distinct from the acid resistance mechanisms seen in other bacteria that merely have to survive passage through the stomach and designed to moderately elevate cytoplasmic pH [31]. Acid acclimation in *H. pylori* is centered on a neutral pH optimum cytoplasmic urease enzyme, which hydrolyzes urea into carbonic acid and ammonia, and an inner membrane localized, proton gated urea channel,

UreI [30, 32, 33]. A periplasmic-localized α-carbonic anhydrase enzyme contributes to periplasmic buffering by catalyzing the conversion of carbon dioxide produced by urease into bicarbonate [30]. The bacteria are able to sense environmental pH via the use of two-component signaling systems, which are able to stimulate protein trafficking, facilitating periplasmic alkalization, and increase transcription of acid acclimation genes [34].

Acid acclimation and *H. pylori* bioenergetics are critical to successful treatment protocols. Available regimens are classically based on acid suppression and multiple antibiotics. The bacteria are uniquely adapted to survive in the acidic environment of the stomach, but based on their status as neutralophiles, a smaller fraction of the bacteria will actually be dividing or growing in acid as compared to more neutral pH. This is demonstrated in transcriptome studies, where genes involved in cell division and cell wall synthesis are up-regulated at neutral pH [35]. Most antibiotics used to treat *H. pylori* are dependent on bacterial growth and will work on bacteria that are actively dividing, which will occur more readily with adequate acid suppression [35]. *H. pylori* that are not dividing at the time of antibiotic administration will not be killed by the antibiotics, leaving a small population of viable bacteria that can restore colonization of the stomach once the antibiotics are stopped. This is considered a form of pheonotypic resistance, where treatment can fail despite appropriate antibiotic coverage [36, 37]. Medications currently available for acid blockade, at recommended doses, will not consistently achieve the sustained pH change required to mimic the bactericidal effect seen in *in vitro* studies [35, 38].

Standard triple and bismuth-containing quadruple therapy

Standard first line treatment for *H. pylori* infection has classically been triple therapy with BID PPI, clarithromycin, and either metronidazole or amoxicillin. Clarithromycin is bacteriostatic and inhibits protein synthesis by binding to the 50S ribosomal subunit. Metronidazole is bactericidal and works via activation within the bacteria, leading to production of toxic metabolites. Amoxicillin is bactericidal and inhibits synthesis of bacterial cell walls. Efficacy is equivalent when using either amoxicillin or metronidazole [39]. Use of high dose BID PPI will increase cure rates with standard therapy regimens by 6-10% [40]. Treatment duration is important as well, as a fourteen day dosing schedule increased efficacy of eradication by 5-6% when compared to a seven day regimen, without causing a significant difference in side effect profile [41-43]. Standard triple therapy was initially acceptably efficacious, with treatment success ranging from >80% to >90% in the early 1990s [44, 45]. Success of this regimen has declined globally over time, dropping to unacceptable levels in many regions [46, 19]. The main identified reason for treatment failure with standard triple therapy is resistance to clarithromycin, with compliance, bacterial load, and strain differences also identified as potential contributing factors [47]. Clarithromycin resistance is mediated either by point mutations that prevent antibiotic binding to the ribosome or via development of antibiotic efflux channels [48, 49]. When deciding to use standard triple therapy, it is important to review a patient's prior antibiotic use since past exposure to any of the macrolide antibiotics may predict clarithromycin resistance [50]. Current guidelines suggest that standard triple therapy should not be used if regional levels of clarithromycin resistance are >15-20% [47]. Metronidazole resistance, mediated by mutations leading to inactivation of the bacterial enzymes needed to activate the

antibiotic, is also fairly prevalent worldwide [51, 52]. Like clarithromycin, prior exposure to metronidazole is an important factor in treatment success [50]. Two important differences exist when comparing metronidazole resistance to clarithromycin resistance. Metronidazole resistance has remained more stable worldwide while clarithromycin resistance has increased [53]. Metronidazole resistance can also be overcome by increasing the antibiotic dose [54, 55]. Amoxicillin resistance, mediated by a variety of different mechanisms including mutations in penicillin binding proteins, decreased permeability for the antibiotic, or development of efflux pumps, is extremely rare in *H. pylori* [47, 56].

In the case of failed standard triple therapy, or as first line therapy in regions of high clarithromycin resistance, bismuth-containing quadruple regimens can be considered [47]. These regimens consist of BID PPI, bismuth, and two antibiotics [47], ideally for fourteen days, and have overall improved efficacy compared with triple therapy in regions with higher levels of clarithromycin or metronidazole resistance [57]. Several recent studies have confirmed efficacy of adding bismuth to clarithromycin or levofloxacin-containing regimens, even in the setting of either high levels of resistance or known resistance based on susceptibility testing. Cure rates across these studies were either >90% for fourteen day regimens or demonstrated improvement from region-based expected eradication levels of 30-40% up to 70-85% [58-61, 55]. Resistance of *H. pylori* to bismuth has not been reported [62-64]. The mechanism of action of bismuth on *H. pylori* is not definitively known. Bismuth preparations, on rare occasions, have been noted to have some independent bactericidal action against *H. pylori* [65-67]. Bismuth has mainly a local effect on *H. pylori*, as absorption is not required for efficacy [68]. Older *in vitro* studies suggest that bismuth may work against *H. pylori* via deposition both on the surface of the bacteria and in the region between the cell wall and the cytoplasmic membrane, disrupting critical bacterial functions [69, 70]. More recent *in vitro* work suggests that bismuth impedes proton entry into the bacteria, allowing for up-regulation of growth-dependent genes and increased efficacy of growth-dependent antibiotics [71]. The downsides to bismuth-containing quadruple therapy include increased complexity of the regimens and increased side-effect potential, which may interfere with compliance. Having a non-antibiotic component as part of a widely-used regimen has the long-term benefit of durability of response, without the concern for development of resistance over time.

Alternative antibiotics

Rising resistance rates and antibiotic availability in different regions may necessitate the use of different antibiotics beyond the standard therapy protocols. The most common antibiotic used in second line or salvage therapies is levofloxacin. Levofloxacin works by inhibiting bacterial topoisomerase II [72]. In most cases of failed 1st line therapy, it is assumed that antibiotic resistance may have played a role, and antibiotics should be altered [37]. Triple therapy with levofloxacin replacing clarithromycin, given that amoxicillin resistance is extremely rare, is a recommended 2nd line regimen [47]. Levofloxacin can also be substituted for clarithromycin in a variety of alternative regimens based on local resistance patterns. Levofloxacin and other fluoroquinolones are widely used for a variety of bacterial infections and levofloxacin should not be considered for treatment of *H. pylori* in patients with a history of chronic infections treated with this class of antibiotics [47]. Due to its

widespread and growing use worldwide, the incidence of levofloxacin-resistant *H. pylori* is growing rapidly [37]. Resistance is typically caused by point mutations in the H. pylori DNA gyrase [73, 74]. 14-day triple therapy with levofloxacin will not reach the target of 90% success if the local resistance rate is over 12%, and addition of bismuth requires a local resistance rate of under 25% [75, 60]. Overall, levofloxacin can be considered as a reasonable 2nd line regimen if local clarithromycin resistance exceeds 15-20% and levofloxacin resistance is less than 10%, or as part of an empiric salvage regimen in areas of low fluoroquinolone resistance [47, 76].

Tetracycline is bactericidal and works by inhibiting protein synthesis. Tetracycline resistance, mediated either by efflux proteins or ribosomal protection proteins [77], is less prevalent worldwide than resistance to clarithromycin, metronidazole, or levofloxacin. In patients in Taiwan receiving a 2nd course of treatment for a prior failure, addition of tetracycline to PPI, bismuth, and amoxicillin was more effective than addition of metronidazole [78]. Use of tetracycline has become more prominent since the introduction of Pylera®, a combined pill containing bismuth, tetracycline, and metronidazole that can be taken four times daily in combination with a twice daily PPI. The benefit of this combined pill formulation is the likelihood of improved patient compliance. Use of Pylera® resulted in eradication rates of 80-93% in a series of studies conducted in populations who were either treatment naïve or had failed 1 treatment course [79-82]. A more recent study looked at effectiveness of this regimen in patients with known resistance to metronidazole, clarithromycin, and levofloxacin or who had failed multiple prior treatment courses, and found eradication rates of 83% (intention to treat) and 87% (per-protocol) [83]. These numbers are encouraging especially in the setting of known metronidazole resistance and in a difficult to treat population. Tetracycline should be considered as a part of 2nd line or salvage regimens, typically as a part of bismuth-containing quadruple therapy regimens, especially in areas where antibiotic resistance is of high concern.

Rifabutin is a bactericidal antibiotic that works by blocking bacterial RNA polymerase. Resistance of *H. pylori* to rifabutin is very low, about 1% overall [37], typically mediated by genomic point mutations [84, 85]. The most commonly used rifabutin-containing regimen is in combination with a PPI and amoxicillin for 14 days, with greater efficacy (over 90%) seen when using high doses of both the PPI and amoxicillin [86, 87]. The mean success rate of regimens containing rifabutin is 73% according to a comprehensive review completed in 2012 [88]. Rifabutin should only be used as a salvage therapy due to the potential for creating resistance to mycobacteria and the risk of side effects such as myelotoxicity [88].

Alternative regimens

Several alternative treatment regimens designed to overcome the problems faced with standard protocols have been developed and extensively tested. Sequential therapy is a 10 day regimen which begins with five days of BID PPI and amoxicillin (or levofloxacin if penicillin-allergic), with discontinuation of amoxicillin and initiation of clarithromycin and metronidazole for treatment days 6-10 [47, 89, 90]. This regimen can be extended to 14 days, with reported superiority over standard triple therapy for 14 days in a recent multi-center study completed in Taiwan [91]. The rationale for this regimen is that the amoxicillin

is used to help overcome clarithromycin resistance. By disrupting bacterial cell walls, amoxicillin interferes with the activation of clarithromycin efflux channels in resistant organisms [89, 49]. Sequential therapy is considered first line treatment in regions of high clarithromycin resistance where bismuth is not readily available [47]. In one analysis, sequential therapy was shown to be effective 75% of the time in clarithromycin-resistant strains [92]. A recent meta-analysis demonstrated that 14 day sequential therapy was a more effective first-line regimen than 14 day triple therapy [93]. The downsides to sequential therapy include challenges with patient compliance with a complex regimen and the potential to either foster resistance to multiple antibiotics or limit salvage options in the event of treatment failure [94, 76].

Concomitant therapy, or non-bismuth quadruple therapy, includes a PPI and 3 antibiotics, typically clarithromycin, amoxicillin, and metronidazole, ideally for 14 days. This regimen is superior to standard triple therapy as demonstrated in a recent randomized controlled trial and multiple meta-analyses [95-97]. The appeal of this regimen as compared to sequential therapy is that there is no need to change antibiotics half way through the treatment course, which is easier for patients and should boost compliance [37]. This regimen shows reasonable success in areas of high clarithromycin or metronidazole resistance, but efficacy drops when the prevalence of strains resistant to both antibiotics is greater than 15%, such as Latin America, Turkey, or Korea [98].

Hybrid therapy is a combination of sequential and concomitant therapy, starting with seven days of PPI and amoxicillin, followed by addition of clarithromycin and metronidazole (4-drug regimen) for the final seven days [99]. Reverse hybrid therapy involves all four drugs for the first seven days, followed by amoxicillin and PPI for the final seven days [100]. Since medications are added during treatment rather than changed, this regimen should be simpler than sequential therapy. There is less overall antibiotic exposure than with concomitant therapy, potentially making this regimen more attractive in regions where it is effective. Similar to concomitant therapy, effectiveness will be decreased in regions with high prevalence of strains with combined metronidazole and clarithromycin resistance [98]. Success rates, as expected, are region-dependent [37]. A meta-analysis completed in early 2015 showed overall similar efficacy when comparing hybrid, concomitant, and sequential therapies [101]. A meta-analysis completed later in 2015 included eight studies and 2516 enrolled subjects and again showed hybrid therapy was similar to sequential therapy and to concomitant therapy in terms of success rate and concluded that hybrid therapy was overall effective and well-tolerated [100]. Based on the available literature, the overall decision to choose an alternative regimen should be based on local resistance patterns, prior antibiotic exposures (relating to *H. pylori* treatment or other infections), and expected patient compliance.

The future of therapy

The two most significant barriers to effective treatment for *H. pylori* infection are antibiotic resistance and patient compliance. With this in mind, the future of treatment needs to be focused on either simpler regimens, use of antibiotics with less chance of development of resistance, or development of non-antibiotic regimens targeting the ability of the bacteria to

survive in the stomach. Both primary and secondary resistance of *H. pylori* to amoxicillin are very rare [102¯104], making this antibiotic a viable candidate for study of dual therapy regimens with PPIs. Dual therapy with PPI and amoxicillin has been studied in different formats for over 20 years, but consistency in results has not been established, and fine tuning is likely required to establish this regimen as a standard treatment protocol. A meta-analysis completed in 1994 suggested a >80% eradication rate with omeprazole 20mg BID and amoxicillin >2g total daily and hinted at the importance of acid suppression in these regimens. Success rates of 30-50% were seen with similar dual regimens in 1995 and 1998 [105, 106], but most significantly, the 1998 study highlighted the importance of profound acid suppression. The only significant factors in successful eradication with PPI-amoxicillin dual therapy were percent time >pH 4 and continuous time >pH 6 [106]. More recently, the recognition of P450 CYP 2C19 polymorphisms that affect the metabolism of PPIs has presented a possible mechanism of treatment failure. Poor metabolizers, who are able to maintain a higher intra-gastric pH on PPI therapy, have a better response to dual therapy regardless of PPI dose, but genotype is less of a factor as PPI doses are increased [107]. Amoxicillin dosing frequency is an important factor as well. Amoxicillin, unlike many other antibiotics used in *H. pylori* treatment regimens, is time-dependent, not concentration-dependent, so time above MIC is an important factor in efficacy [108, 109]. A regimen of four times daily rabeprazole (20mg) and four times daily amoxicillin (750mg) for 14 days was recently shown to be superior to standard treatment regimens in a Taiwanese population [110]. Optimization of acid suppression may ultimately lead to a standard dual therapy regimen that is effective worldwide.

High dose PPI use in dual or standard therapy regimens may ultimately be replaced by more potent acid suppressive agents. The potassium competitive inhibitor of the gastric H,K-ATPase, vonoprazan, is coming into clinical use in Asia and has the benefit of a more rapid and sustained acid inhibitory effect regardless of CYP 2C19 genotype [111]. Use of vonoprazan in place of PPI has shown early promise in recent studies of Japanese populations, with an eradication rate of 70.2% using vonoprazan, amoxicillin, and clarithromycin as second line therapy in patients who have failed first line treatment with rabeprazole, amoxicillin, and clarithromycin and a 92.7% success rate of first line therapy with vonoprazan, amoxicillin, and clarithromycin [112, 113].

Non-antibiotic regimens would be the ideal for future management of *H. pylori* infection as this would avoid the concerning issue of worsening widespread antibiotic resistance. Potential treatments would target the components of acid acclimation that allow the bacteria to colonize the stomach, such as the urea channel, the two-component signaling systems that detect medium pH, or the carbonic anhydrase enzymes. Inhibition or gene knockout of α-carbonic anhydrase has shown promise *in vitro* as a potential treatment target in the presence of acid [30]. Acetazolamide, a carbonic anhydrase inhibitor used clinically for altitude sickness or alkalosis, were shown to have benefit for ulcer healing prior to the discovery of *H. pylori* [114]. One pilot study done in humans, looking at efficacy of acetazolamide in eradication of *H. pylori*, was unsuccessful, but the dose and duration of treatment were likely inappropriate [115, 116]. Use of non-antibiotic targeted treatments of this nature would require attention to obstacles not only of dose and duration, but also to targeted treatment to bacteria in the gastric lumen.

Conclusions

H. pylori is a highly prevalent global pathogen that causes chronic inflammation in all who are infected, carries a risk of advanced disease including ulcers and gastric cancer, and faces growing challenges with treatment efficacy. Standard triple therapy with proton pump inhibitor, clarithromycin, and either amoxicillin or metronidazole is no longer sufficiently efficacious in many parts of the world due to antibiotic resistance patterns. New regimens with bismuth, different antibiotics, or different combinations of standard antibiotics have shown variable promise. As antibiotic use for a variety of different infections increases, the problems inherent with the use of primarily antibiotic-based regimens for *H. pylori* will only increase. Use of enhanced acid suppression to improve efficacy of growth-dependent antibiotics, preference for regimens including antibiotics with lower risk for resistance, and continued focus on the search for non-antibiotic treatment targets will shape the future of treatment for *H. pylori*. Choice of regimens for patients in the present time should be based on knowledge of local resistance patterns and antibiotic use, patient history, and accommodations to facilitate optimal compliance.

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