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TOPIC HIGHLIGHT

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Helicobacter pylori: Future perspectives in therapy reflecting three decades of experience

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Abstract

The rising prevalence of antibiotic resistance has created a need to reassess the established *Helicobacter pylori* (*H. pylori*) eradication protocols, and to develop new ones. Various bacterial and host factors are evaluated, and their contribution to eradication failure is estimated. For a long time being considered the cornerstone eradication scheme, the standard triple therapy has been replaced with novel, more efficient regimens, namely sequential and concomitant, along with the emergence of a new design of bismuth quadruple therapy. A rescue levofloxacin based regimen has overcome the fear of therapy failure due to higher prevalence of dual resistant (clarithromycin and metronidazole) *H. pylori*. Culture-free and efficient susceptibility test are reestablishing the concept of tailored therapy, making eradication success close to originally desirable rates. Alleviating therapy side effects and improving patient compliance are as important as choosing appropriate eradication schemes, so various probiotic compound supplements are taken into consideration. Finally, we summarize the emerging efforts and obstacles in creating efficient *H. pylori* vaccine.

Key words: *Helicobacter pylori*; Eradication therapy; Antibiotic resistance; First line therapy; Rescue therapy; Sequential therapy; Bismuth-containing quadruple therapy; Concomitant quadruple therapy; Hybrid (dual-concomitant) therapy

Core tip: In this article the authors have made a review of the most important literature with knowledge of various factors affecting *Helicobacter pylori* eradication success. The paper presents an analysis of established and new eradication regimens, as well as factors affecting their performance. Since the last 3 decades many new developments appeared in the field of this intriguing infection, along with implementation of recently published guidelines. Authors made a new look to future perspectives in managing this complex infection.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative, microaerophilic bacterium inhabiting human stomach, first isolated by Warren and Marshall in 1983, and that has since then become a point of interest worldwide[1]. It is a major pathogen causing gastric and duodenal ulcer, gastric cancer and mucosa-associated lymphoid tissue

lymphoma[2,3]. Recently, it has been linked to extragastric malignancies such as colorectal adenocarcinoma and nonmalignant diseases such as iron deficiency anemia, idiopathic thrombocytopenic purpura and vitamin B_{12} deficiency, with new data on its role in neurodegenerative diseases and metabolic syndrome[2,4,5].

During three decades of *H. pylori* eradication, various therapeutic protocols have emerged, with the standard triple therapy recently succeeding generally bellow 80%, far away from the originally expected rate of > 90%[6-9]. Possible factors causing progressive eradication therapy failure have been evaluated, with the consensus that antibiotic resistance and patient compliance are the most important ones[6-9]. Accordingly, common opinion is that local antibiotic resistance screening and detailed evaluation of patient prior antibiotic usage, are main steps in preventing further eradication rate decline[2,7,9,10-12].

In this article we will review the most important results of various established and novel eradication protocols and the factors affecting them, along with a look to new perspectives in managing this complex and intriguing infection.

BACTERIA AND HOST INFLUENCING ERADICATION

There are multiple factors, concerning both the bacteria and the host, making *H. pylori* eradication so difficult. Factors affecting proton pump inhibitor metabolism and bioavailability, such as CYP2C19 and MDR1 polymorphism, and the IL-1B polymorphism affecting intragastric acidity, were implied in eradication success rate, with fast metabolizers and acid hypersecretory found to have lower therapy success[6,13,14]. Several studies have shown lower eradication rates in patients with non-ulcer dyspepsia compared to peptic ulcer disease. The reason may be that patients with non-ulcer dyspepsia seem to be infected with less virulent, slow-proliferating strains, making them less susceptible toward antibiotics, with those strains more frequently being resistant to clarithromycin[13,14]. More contradictory data were published about negative impact of increased body mass, diabetes and smoking on eradication rate[13,15]. Finally, before evaluating any cause of eradication failure, physicians must be aware of patient compliance, as those taking < 80% of their treatment regimen have a high chance of failure and subsequent antimicrobial resistance[12,14].

Multiple bacterial factors are influencing eradication therapy success rate, with the development of resistance to antibiotics as the most important[9,10,16]. Recent multicenter study by Megraud *et al*[16] showed that resistance rates in Europe for adults were 17.5% for clarithromycin, 14.1% for levofloxacin and 34.9% for metronidazole, with rates higher in Western/Central and Southern Europe than in Northern Europe. A steady increase in clarithromycin resistance and almost doubling of levofloxacin resistance was noted, linked with an increase in outpatient antibiotic usage[7,16,17]. As opposed to emerging resistance to previously mentioned antibiotics, resistance to amoxicillin, bismuth, furazolidone and tetracycline remains low[9]. The implication of antibiotic resistance is mainly accentuated with clarithromycin. In the case of clarithromycin resistance the rate of success of clarithromycin-containing regimen is very low (10%-30%). Metronidazole resistance is associated with 5%-25% lower eradication rate[10,18]. Levofloxacin, as metronidazole resistance can be overcome with increasing the length of treatment and using bismuth in quadruple therapy[16,19]. Other contributing factors are the presence of dormant coccoid bacterial forms, the density of *H. pylori* in the stomach, virulence factor status, biofilm formation, intracellular location of the bacteria and the presence of multistrain infection[13-15,20,21]. The presence of dormant, non-replicating bacteria causes phenotypic resistance, which is a form of reversible antibiotic resistance causing treatment failure[9].

FIRST LINE ESTABLISHED AND NOVEL TREATMENT OPTIONS

Standard triple therapy (proton pump inhibitor-PPI, clarithromycin, amoxicillin or metronidazole for 7-14 d) was a cornerstone of *H. pylori* treatment for years, recently gaining unacceptable eradication rates, mainly due to increase in clarithromycin resistance. According to new Maastricht guidelines, it is not advisable to use standard triple therapy in areas with clarithromycin resistance over 15%-20%, what lead to revival of some forgotten regimens, and construction and evolution of new ones[6,8]. Considering the fact that it is possible to overcome the resistance to metronidazole and that resistance to certain antibiotics rarely develops, new eradication schemes of various duration and dosage with strong inhibition of acid secretion, have been constructed to bypass triple therapy failure[16].

Bismuth-containing quadruple therapy represents alternative to standard triple therapy in areas with low clarithromycin resistance and the main first-line therapeutic option for areas with high prevalence of clarithromycin resistance. Consisting of bismuth salt, tetracycline and metronidazole it is effective independently of clarithromycin resistance. By using this regimen at full doses and for 14 d one can expect 95% or greater treatment success, irrespective of the level of metronidazole resistance[22]. Therapy for 7, and likely 10 d is very susceptible to metronidazole resistance, however, the prevalence of resistance, which results in a decrease in outcome to less than 90%, is probably approximately 30%[18]. Unfortunately recent meta-analysis, evaluating empirical approach with bismuth-containing quadruple or standard triple eradication regimen, revealed suboptimal data (78.3% and 77% eradication therapy success)[23]. Possible negative effects of metronidazole resistance could be resolved with increased dosage and longer duration of treatment (10-14 d). This regimen has been sometimes marginalized through literature considering the unavail-

ability of bismuth salts and tetracycline worldwide, complex dosing scheme, not yet known optimal dose and adverse effects[6]. After a study by Malfertheiner *et al*[24] and Venerito *et al*[25] in 2011, a revival of a quadruple regime consisting of PPI with a 3 in 1 capsule containing bismuth subcitrate potassium, metronidazole and tetracycline has emerged with improved eradication success exceeding 90%.

The PPI component of *H. pylori* eradication regimens has a major influence on overall therapy success, due to its intrinsic antibacterial effect, and more importantly the possibility to convert the nonproliferating, dormant forms of bacteria into active, proliferating forms by raising pH, leading to higher antibiotic efficacy[26]. Recent studies with new generation PPIs (esomeprazole and rabeprazole) have shown their higher potency in raising pH irrespective of CYP2C19 polymorphism, with eradication rate improvement[27,28].

First developed in Italy in the 90s, sequential therapy (5 d PPI and amoxicillin, followed by 5 d PPI, clarithromycin and metronidazole), is a regime that was proven to be more efficacious than triple therapy in many studies[8,29-32]. Recent multicenter randomized trial in Taiwan showed superiority of sequential over standard triple therapy, adding to its confirmation on population outside Italy[33]. The ability to eradicate the clarithromycin resistant bacteria has been demonstrated, and a sequential therapy has been already included in the recent consensus report as a valid first line option in geographic regions with high clarithromycin resistance[6]. Possible limitation of this regimen could be related to inferior results in treatment of dual resistant strains[30]. The level of metronidazole resistance determines the level of clarithromycin resistance required for eradication regimen success to decrease to < 90%. In low clarithromycin resistance areas metronidazole resistance undermines 10 d sequential therapy when it reaches 20%, and 14 d sequential therapy at approximately 30%. If metronidazole resistance is absent or low, sequential therapy for 10 or 14 d is very mildly affected with clarithromycin resistance. The complexity of sequential therapy was frequently reported as a possible problem of that regimen. Since this issue was never objectively evaluated, comparative studies of different therapy regimens (by using questionnaire, by prescriptive time evaluation *etc.*) are needed. The mechanism behind sequential therapy success is thought to be the disruption of the bacterial wall with initial 5 d of amoxicillin therapy, what prevents formation of efflux channels and consequent resistance for clarithromycin[15,34]. Nevertheless, a lot of authors have been hypothesizing that the use of 3 antibiotics, rather than the sequential scheme of administration, adds to this regime efficacy[15,35,36]. In this situation, adding to complexity and possible lower adherence to therapy, complexity of sequential administration would be unnecessary.

Two novel eradication regimens, namely concomitant (PPI, clarithromycin, amoxicillin, metronidazole for 10 d) and hybrid (PPI and amoxicillin for 7 d, followed by PPI, amoxicillin, clarithromycin and metronidazole for 7 d), have proven their efficacy over triple and sequential therapy in the last few years, especially with dual (clarithromycin and metronidazole) resistant strains[15,37-43]. Several studies have demonstrated that concomitant therapy is more effective (with comparable side effects) than standard triple therapy, although highly variable efficacy is reported with concomitant therapy and optimal treatment duration is not defined[36,44]. Most of these studies were performed with shorter (5-7 d) schemes. Meta-analyses and recent head-to-head comparison in Thailand have shown that the outcome of concomitant therapy is duration dependent[44-46]. Unsatisfactory results have been recently reported even when this scheme was adopted for two weeks. One of the findings of a large randomized trial in Latin America showed that 14 d triple therapy is more effective than 5 d concomitant or 10 d sequential therapy[47]. Geographic variations in the pattern of *H. pylori* resistance to antibiotics might account for some of these discrepancies in results, accentuating the need for implementation of local resistance pattern knowledge in generalized eradication therapy recommendations. Some of the advantages of non-bismuth quadruple regimens over the sequential regimen are longer duration of all the prescribed antibiotics, and broader validation in randomized controlled trials (RCT) of wider geographical regions[39]. A recent RCT in Spain over 338 patients, showed a slight advantage of concomitant over sequential therapy, allowing close to 90% eradication rates[34]. Non-bismuth eradication schemes are recommended as first line therapy in areas with high clarithromycin resistance (> 15%-20%) where bismuth containing quadruple therapy is not locally available[6]. The problem with empirical application of concomitant regimen is dual metronidazole-clarithromycin resistance. Before final conclusions on topic of concurrent *vs* sequential regimen further wider geographical region studies are essential in populations with high dual resistance.

A recently proposed hybrid therapy has been proven equally effective to 14 d concomitant regimen in a pilot study (ITT eradication rate 90% *vs* 92%)[37]. Therefore it could be considered in the same populations where concomitant therapy is recommended. This is a novel regimen, with only few evaluation studies published, so the optimal therapy duration and success rates in populations with high dual resistance are still not defined. This protocol is more complicated than those earlier proposed, with retained complex sequential approach and possible higher side effects rates because of concomitant treatment in the second phase. According to the preliminary data it is associated with comparable side effect profile and therefore merits consideration in further comparative studies in order to define final conclusions[10].

When considering an eradication protocol in first, and especially multiple therapy line failure, it is of utmost importance to reassess patients compliance and prior antibiotic usage, to design a scheme according to local resistance patterns and therapy success, and always confirm successful eradication[6,7,9,10,15]. Because of emergence

of resistance to previously used antibiotic, it is advisable not to use the same antibiotic after therapy failure, and to modify the scheme duration, dosage and antisecretory effect, with addition of antibiotics for which resistance rarely develops[48,49]. After second line treatment failure it is recommended to perform culture and susceptibility testing prior to third line treatment[6]. An expert agreement is that culture susceptibility testing before first or second line therapy is not advisable. With known obstacles of culture susceptibility testing, such as the need for endoscopic examination, the fact that culture is time-consuming, costly and not 100% sensitive and that susceptibility knowledge is not always followed with accordant eradication, highly effective empiric first line and rescue regimens can achieve acceptable results[8,15,50].

RESCUE REGIMENS

Several rescue regimens have been evaluated in recent years, especially with worldwide rise of clarithromycin and metronidazole resistance. Bismuth quadruple regimes are recommended as first and second line treatment options in areas of high clarithromycin resistance[6]. Based on analysis of 30 studies, after first line standard triple regimen, mean second line bismuth quadruple regimes yielded 77% eradication therapy success. Major determinants of eradication efficacy were metronidazole dosage and treatment duration[49].

Another rescue regimen recommended by the Maastricht guidelines for second and third line therapy, is the triple levofloxacin protocol (PPI, levofloxacin and amoxicillin for 10-14 d)[6]. It is especially valuable in situations where sequential and concomitant regimens where used, and where highly possibly dual resistant bacteria emerged[49,51]. Recently Gisbert *et al*[52] evaluated levofloxacin rescue therapy after sequential and concomitant treatment, and presented an encouraging eradication rate of 75%. When comparing levofloxacin triple therapy to bismuth quadruple therapy, which fails in around 20%-30% of patients, several meta-analyses have shown better outcomes with the levofloxacin regimen[48,53]. Besides being established as a rescue protocol, levofloxacin based therapy has proven its efficacy as a first line treatment, although not generally recommended due to rapid emergence of fluoroquinolone resistance and adverse effects[8,15,53]. In contrast to metronidazole there is no dose dependent-effect in overcoming levofloxacin resistance (eradication protocols becomes ineffective when resistance reaches 13%). In a randomized controlled study by Federico *et al*[35], a 5 d levofloxacin concomitant and 10 d sequential scheme in treatment naïve patients, achieved per-protocol eradication rates of 96.5% and 95.5%, respectively. An interesting study from Australia, evaluating fluoroquinolone containing regimens, showed high eradication rates around 95% with quadruple therapy consisting of PPI, amoxicillin or bismuth subcitrate, rifabutin and ciprofloxacin, in patients who failed at least one therapy course[54]. Considering overall resistance issues, possibly better fluoroquinolone-containing regimens include fluoroquinolone-bismuth therapy and fluoroquinolone concomitant therapy. Since neither of this protocol has been optimized or tested widely, generally they should be used as tailored therapies especially in the context of the emerging levofloxacin resistance[10].

Aside from tailored therapy according to culture susceptibility testing, few antibiotics with practically inexistent resistance have been evaluated. Rifabutin, a rifamycin derivate commonly used to treat *Mycobacterium avium-intracellulare*, has shown promising eradication rates in patients with several therapy failures. The eradication rates for second-, third- and forth and more line therapies are 79%, 66% and 70% respectively[55]. It is marginalized in *H. pylori* treatment due to its high cost, severe side effects, primarily myelotoxicity, and possibility of multiresistant *Mycobacterium tuberculosis* emergence[56]. Additional studies are needed to optimize the regimen in terms of dose and duration. Due to low primary bacterial resistance, furazolidone was evaluated as a multiple failure rescue regimen, but has not found an established position, mainly due to its possible genotoxic and carcinogenic effect[57].

WHAT THE FUTURE BRINGS?

As evident from myriad emerging studies evaluating established and creating new *H. pylori* eradication schemes recently, a consensus therapy has not yet been achieved. Main factors for eradication therapy failure are antibiotic resistance and poor patient compliance[10]. With regard to before mentioned culture susceptibility testing deficiencies and highly effective first and second line empirical treatments, the so-called "tailored" eradication therapy has not yet taken effect. With the development of non-invasive, rapid and culture-free susceptibility tests, primarily for clarithromycin and levofloxacin, it would be easier to perform tailored therapy even for treatment of naïve patients, with achievement of originally expected eradication rate of > 95%[9,17]. The use of polymerase chain reaction, a fast and inexpensive, culture-free method for susceptibility testing, was proven to improve the eradication rate when used to create tailored therapy[58]. Recently a study from Taiwan was published, evaluating genotypic resistance-guided third-line sequential therapy and showing promising eradication results. Genotypic resistance testing is more convenient and rapid than standard culture susceptibility testing, with a possibility to determine resistance even from stool samples[59]. With more efficient susceptibility testing, local resistance surveillance would be easier to perform, adding to higher success of eradication therapy in general[7,9]. While waiting for generally available and reliable noninvasive susceptibility tests, allowing unrestricted application of tailored therapy, we should keep in mind that success rate of proposed regimens justify in many instances empirical application of first- and second- line therapies. Even with possibility that sometimes local or regional expert treatment guidelines will not be strictly in line with gen-

eral ones, optimal approach is to use regimens that have been proven to be reliably excellent locally and/or regionally. Expert decisions should be based on knowledge of regional resistance patterns (obtained from imperative regional antimicrobial surveillance programs), local clinical experience with regard to which regimens are best effective and available and history of prior patient drug exposure. The regimen of the highest predicted success rate should apply with confirmation of successful eradication outcome. This approach allows us screening for possible increase in appearance of antimicrobial resistance in everyday clinical practice.

Besides the importance of knowing detailed patient antibiotic usage history and the ability of the physician to persuade the patient to take the medicines according to plan, a lot of effort is being made to reduce eradication therapy side effects. Various probiotic compounds containing *Lactobacillus*, *Bifidobacterium*, *Saccharomyces* and other benevolent bacteria, have been evaluated in improving eradication rate and reducing therapy side effects. Their contribution to eradication therapy is accomplished through direct antibacterial effect, modulation of host immune response and stabilization of the mucosal barrier[60,61]. Few recent studies have shown beneficial effect of probiotic compounds on eradication rate and on diminishing therapy side effects, although results from different studies are contradictory, suggesting a need for further evaluation[61-63].

Development of a vaccine against *H. pylori* infection is an ultimate goal for eradicating all the negative effects of this versatile bacterium. There are several reasons for the fact that an efficient vaccine has not yet been developed. It took many years for the scientific community to acknowledge the contribution of *H. pylori* in peptic ulcer disease, and especially its carcinogenic potential. Another important factor is the complicated host immune response, along with considerable genetic diversity of *H. pylori*, what hampers the technical path in developing the vaccine. At last, due to a long period between *H. pylori* acquisition and manifestation of disease, especially gastric cancer, there is a general climate making development of the vaccine slow and inefficient[64,65].

CONCLUSION

A simple and uncomplicated path in *H. pylori* eradication has been recently disturbed with progressive bacterial resistance for cornerstone antibiotics. With the development and implementation of novel eradication regimens the situation looks more promising, although the final answer to *H. pylori* infection has not yet been established. Hopefully, non-invasive and rapid susceptibility tests will take place in strengthening the tailored therapy concept, and efficient vaccine will obviate the need for *H. pylori* induced disease management.

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