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REVIEW

Vaccine against *Helicobacter pylori*: Inevitable approach

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Abstract

Over three decades have passed since the discovery of *Helicobacter pylori* (*H. pylori*), and yet many questions about its treatment remain unanswered. For example, there is no certainty regarding continued use of current antibiotic therapy against *H. pylori*. The bad news is that even combined regimens are also unable to eradicate bacterial colonization. The worst problem with *H. pylori* chemotherapy is that even if we identify the most successful regimen, it cannot eliminate the risk of re-infection. This problem is further complicated by the fact that clinicians have no information as to whether probiotics are useful or not. Moreover, to date, we have no large scale produced vaccine effective against *H. pylori*. Due to the relatively rapid and abundant dissemination of guidelines globally reported concerning management of gastric cancer prevention and therapeutic regimens, clinicians may choose a vaccine as better effective weapon against *H. pylori*. Therefore, a radical shift in adopted strategies is needed to guide ultimate decisions regarding *H. pylori* management. In light of failures in vaccine projects, we should identify better vaccine design targeting conserved/essential genes. The unique character and persistence of *H. pylori* pose obstacles to making an effective vaccine. Preferably, in developing countries, the best reasonable and logical approach is to recommend prophylactic *H. pylori* vaccine among children as an obligatory national program to limit primary colonization. Trying to produce a therapeutic vaccine would be postponed until later. In reality, we should not forget to prescribe narrow spectrum antibiotics. In the current review, I draw a route to define the best adopted strategy against this rogue bacterium.

Key words: *Helicobacter pylori*; Vaccine; Eradication; Probiotic

Core tip: This review article for first time discusses actual approaches regarding management of *Helicobacter pylori* (*H. pylori*) infection; whether we should continue current strategies or focus on various directions. Primary *H. pylori* colonization usually happens in childhood and lasts for decades if not treated. An ultimate strategy regarding the infection must be the complete eradication of the bacterium.

Herein, we provide specific recommendations on elimination of *H. pylori* with vaccination as well as addressing the preventive vaccine against the bacterium rather than continuing defeated solutions including probiotics or antibiotic therapy.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is one of the most successful human pathogens. Following two important events (first successful isolation of the *H. pylori* in 1983 and secondly; Nobel Prize in medicine in 2005), increasing attention is focused on the human gastric inhabitant and soon after, everyone was surprised by its globally high prevalence (approximately 50%)[1,2]. Soon after the discovery of *H. pylori* in 1983, a new era of research had been initiated in microbiology of the human upper gastrointestinal tract. In 1994, *H. pylori* was recognized as a type (I) carcinogen by the Agency for Research and Cancer. To date, no other bacterial species considered as such a carcinogenic agent. This spiral bacterium plays a determining role in pathobiology of gastric ulcer (GU), duodenal ulcer (DU), gastric cancer (GC) and mucosa-associated lymphoid tissue (MALT) lymphoma[3]. *H. pylori* colonization and subsequent clinical manifestation can induce problematic disorders, if not treated efficiently[4-6]. Historically, the stomach was considered to be sterile organ for a long time due to the strong acidity (pH < 2), which eliminates all types of organisms (fungi, bacteria, viruses and parasites). Among ingested microorganisms, *H. pylori* is a site-specific and symbolic microbe, because of its extraordinary capability for colonizing in hostile environment of human stomach[7,8]. Despite high numbers of infected individuals, only a small proportion develops GC (< 1%), 8%-10% develop DU and GU, and less than 1% suffers from MALT lymphoma. The rest of infected individuals can remain asymptomatic their whole life[9]. Bacterial capability to pick up the exogenous DNA (transformation/conjugation) generates highly diverse offspring even in a single colonized individual[10]. The remarkable diversity (genetically and phenotypically) observed in *H. pylori* can explain existence of various populations, and also answer questions regarding its genomic plasticity. *H. pylori* can acquire resistant genotypes, thus it rapidly entered the MDR (multi resistant drug) list. In clinical practice, quick emergence of resistance raised worries about accurate management of this bacterium[11-13]. In the case of *H. pylori*, we know that gastric acidic output, bacterial genotype, low patient compliance, alcoholism and smoking can result in antibiotic treatment failure[13,14]. After this increasing trend of antibiotic resistance, scientists were looking for better options for dealing with this microbe. Another side of the coin is that *H. pylori* can use natural mechanisms to become a persistent bug against human immune system. The main mechanism adopted by the bacterium to ensure gastric residency lifelong is not clear but antibiotic resistance is one of them at least. During the three decades that we have known about *H. pylori*, there have been many different questions raised; How to treat infections? Who should be treated? Do we need to consider probiotics as adjuvant in therapeutic regimen of *H. pylori*? Shall we recommend vaccine? If yes, how to design an effective vaccine[15-17]? The first interpretation out of the above questions is that *H. pylori* is a smart pathogen, and has adapted to become a resident in gastric mucosa[18]. Because of these concerns, clinicians decided to think about the most useful weapon in the battle against this mysterious bacterium. It should not be forgotten that complete bacterial clearance is a good idea to prevent those severe gastroduodenal disorders[19-21]. Choosing the best way to defeat the bacterium was a challenging step concerning this gastric microbe. In order to choose the best strategy against the bacterium, one should first consider all attributed items and availabilities, and then new roadmap would automatically emerge. For example, antibiotic therapy and vaccination are the two major approaches to defeat the microorganisms. Additionally, some alternative solutions are also used against *H. pylori*, although the success of these solutions remains controversial. In the current article, the available data is discussed in light of finding the best strategy against this rogue bacterium. Finally, we aim to draw a universal roadmap for dealing with *H. pylori* infection.

APPROACHES TO DEFEAT *H. PYLORI*

The role of *H. pylori* in emergence of gastric cancer and other severe gastroduodenal diseases had already convinced many clinicians that we may have underestimated this microorganism[22]. Elimination of *H. pylori* (definite decision) has been frequently speculated as an effective strategy to cure peptic ulcer disease as well as gastric cancer[6,23,24]. While a decision had been taken to eliminate the bacterium, the question remains about the appropriate strategy to achieve this goal. Not surprisingly, antibiotics are the first choice; although a long list of failed therapeutic regimens still comes up[25-27]. As expected, antibiotics are not the only available tools applied against *H. pylori* and other options can be theorized as well. For example, probiotics are the next proposed solution. Accordingly, a long list of alternative options (probiotics, new synthesized drugs and vaccines) against *H. pylori* infection have already been proposed. It seems that our ability to directly combat *H. pylori* is drastically

being affected by increasing rates of antibiotic resistance and ineffectiveness of other aforementioned solutions. Herein, we describe proposed interventions against *H. pylori* infection.

Antibiotics

The bactericidal effect of penicillin discovered by Fleming at 1929 on *Streptococcus* was the first promising step to defeat microbes using antibiotics[28,29]. After decades, scientists are still struggling with large number of organic chemicals and materials to find/apply better antibiotics for killing bacteria. Despite a large number of potent molecules, we are facing with large number of failed therapeutic regimens consisted by these new antibiotics. Nowadays, antimicrobial resistance is a critical issue in management of infectious diseases[30,31]. To our knowledge, *H. pylori* had shown no diversion from this microbial rule. Because of this, three various therapeutic lines in terms of international guidelines have been published. However, clinics have no certainty about the best strategy to achieve an efficient treatment against *H. pylori*[23,32-37].

First line therapy: While no monotherapy is useful to eradicate *H. pylori*, application of regimens consisting more than one treatment is inevitable. First-line triple therapy [amoxicillin + clarithromycin and proton pump inhibitors (PPI)] is the most prescribed regimen worldwide[38]. Notably, this is a recommended therapy for regions with low clarithromycin resistance (< 15%)[36,39,40]. In regions with higher rates of clarithromycin resistance (> 20%), modified formulation (metronidazole, tetracycline or bismuth salicylate) is highly recommended as well as hybrid and concomitant therapies which showed sufficient efficacies to be involved in these regions[6,33,36]. In standard therapy, increased doses of PPI can be used due to higher biological activity and stability[26,41]. As it sounds, clarithromycin resistance rate has a crucial role to determine effectiveness of combined regimen, particularly in first line therapy. Consequently, the wide use of clarithromycin in gastrointestinal and respiratory infections caused a raise rate of exposure to this antibiotic, which can be attributed to the current status of resistance. However, due to the increasing level of resistance to all antibiotics listed in first line therapy, the efficacy of the regimen is falling to unacceptable levels in most countries[6,31]. Currently, use of fluoroquinolone is able to change the low efficacy of first line therapy[13,42].

Second line therapy: The medical community soon realized that first line therapy against *H. pylori* is not sufficient to defeat the infection. It became a basic rationale to define and establish *H. pylori* second line therapy. Indeed, second line therapy is a quadruple treatment and it may be split in two different regimens: with or without bismuth salicylate[38,43]. This regimen consists of bismuth salicylate, metronidazole, tetracycline, and PPI. The novel aspect of these antibiotics in second line therapy is the addition fluoroquinolone to this therapeutic regimen. Using fluoroquinolone and its increasing antibiotic resistance became an Achilles' heel for second line therapy of *H. pylori*. Levofloxacin-based therapy showed a satisfactory efficacy as second line therapy[44]. However, metronidazole-based and moxifloxacin-based therapies achieved a good eradication rates following failed first line therapy[43,45-47]. In brief, a major difference in drug prescription for second line therapy is to increase the dosage, which can be accompanied with adverse side effects[6,23,27,36]. Side effects reported following the prescription of second line therapy led to emergence of a third line therapy as an alternative, or maybe last, chemotherapeutic option. Levofloxacin-based therapy was reported to be useful second line treatment following defeated concomitant therapy in regions with high rate of antibiotic resistance to clarithromycin.

Third line therapy: In patients with treatment failure according to the first and second lines, clinicians have to think about a smarter strategy to defeat the bacterium in this challenging war[48]. It has been firmly indicated that antimicrobial susceptibility tests must be performed prior to initiating the third line regimen in any population worldwide. Antimicrobial susceptibility tests are mandatory only in third line therapy, while it would be better to have these data before prescribing any therapeutic regimens. Choosing the best efficient antibiotic to use as third line therapy is a major challenge in treatment of *H. pylori* infection. It appears that rifabutin may be worthwhile agent and its contribution in third line therapy may be even underestimated[49]. Rifabutin-based therapy revealed that good eradication rate and it can be achieved after both failed therapies (first and second line)[43,49,50]. The main limitation in treatment regimens with rifabutin is its adverse effects and serious myelotoxicity[51]. In addition, more usage of rifabutin can cause higher rates of antibiotic resistance, as reported from *Mycobacterium tuberculosis* treatment. Rifabutin is usually considered as anti-tuberculosis drug and clinicians should think about it cautiously. The optimal duration of treatment for third line therapy as well as other therapeutic regimens was already discussed in various guidelines[30,52-54]. As the story about third line therapy is similar to what happened with former treatment regimens, we have long way to go to find the best eradication strategy against this rogue microorganism.

Last words about antibiotics: For sure, antibiotics are only given to symptomatic patients, and asymptomatic individuals are still under risk of

development of their simple symptoms to severe digestive diseases, including gastric cancer. This is a major problem in managing *H. pylori* infection; a key point that could be covered by administration of an effective vaccine. While these results for all therapeutic lines appear ineffective, each will clearly require careful considerations to increase their overall effectiveness in various populations worldwide. There are two main problems; first, continued design and application of novel antibiotics against *H. pylori* will likely progress slowly, and secondly, with such skyrocketing rates of antibiotic resistance, efficacy of most first and second lines therapies are around zero[55-62]. Altogether, we are becoming disappointed with current antibiotic therapy. However, final success to achieve this solution cannot arise without involvement of better intervention such as smarter strategies concerning the *H. pylori* infection. The big problem with antibiotic treatment is that even if we have the most successful therapeutic regimen, it cannot ensure re-infection protection. In conclusion, different approaches, rather than just antibiotic regimens, should be considered in *H. pylori* management. Taken together, we have to continue this approach while working on better solutions. Indeed, antibiotics are helpful but not the best possible intervention for *H. pylori* infection.

Probiotics

Probiotics are live bacterium which enable to survive in the gastric mucosa and alter microbiota composition, causing beneficial effects if administrated (mostly as oral supplement) properly, as defined by the World Health Organization[63]. Mostly, they are bacterial strains, but include some yeast such as *Saccharomyces boulardii*[64-67]. It has been reported that antibiotic-associated diarrhea is the most common side-effect of *H. pylori* eradication, which can be alleviated with probiotic consumption[68,69]. The aforementioned news promoted clinicians to increase their initiatives to for more research on probiotics in recent years. Indeed, the rationale of recommendation for probiotics as pro-fermentation microbes is its benefits including: (1) stimulation of mucin production which results in effective immune response; (2) induction of acid secretion which causes reduction in *H. pylori* density in the stomach; (3) protection by competing on host receptors with other human pathogens; and (4) immune response modulation which results in higher protection against pathogenic agents[70-72]. Recently, following the increased report of treatment failure, using probiotics as adjuvants can increase the effectiveness of *H. pylori* therapy[15,24,73]. To date, *Lactobacilli* have shown better responses in clinical trials[23,49]. Taking this into account, *in vitro* studies have already shown beneficial effects of consumed *lactobacilli* against *H. pylori* infection but more detailed investigations are required[74,75]. Different strains of *Lactobacilli* were examined to determine the best adjuvant in combination with triple therapy against *H. pylori* infection, however, and regardless of a large number of studies, it is soon to fully elucidate all aspects of its molecular mechanism[68,76,77]. Despite recent progress, many questions are left unanswered in finding the best formulation (including suitable microorganism, dosage and duration of the administration)[15]. In animal and human models, prior studies have shown that actual role of probiotic bacteria and their biologic effects linked with eradication of *H. pylori* need to be examined[78-80]. Conclusively, human and probiotics are in the early stages of collaboration toward defeating *H. pylori,* and we hope that in the near future, associated research can meet the demands in clinics and the market.

Last words about the probiotics: Probiotics may serve as an alternative approach to fight the current dilemma of management of antimicrobial resistance. The protective effects of probiotics (mostly including Bifidobacterium and Lactobacillus) on colonization of *H. pylori* in digestive tract have been widely investigated[78-80]. As noted in several reviews, most of the probiotics that are already examined are listed as beneficial for both healthy individuals and patients. To date, various strains of probiotics with or without adjuvant were used to assist *H. pylori* elimination. With regard to variable results disclosed so far, probiotics can be only used to aid clinicians for increasing efficacy of antibiotic therapy, mostly with compensation of human microflora. So far, exaggerated claims regarding probiotics should be limited until consistent findings from large scale studies are achieved. Apart from the fact that probiotics are chosen to tackle the *H. pylori* infection or assist clinicians to defeat antibiotic resistance, we are not in a position to limit our options with it. *H. pylori* is a major gastric pathogen and we should not ignore even less effective options to defeat the microbe. Taking together, probiotics cannot stand as the final and best solution suggested for *H. pylori* infection.

Vaccine

As expected and seen above, both primary and secondary regimens were not completely successful in eliminating *H. pylori* colonization, so we have to think more on proposed alternatives and practical options[25,41,43,45,81]. In the case of probiotics, lack of knowledge of their actual mechanism of action and also inconsistent findings of their applications were the main reasons not to consider them in management of *H. pylori*. *H. pylori* vaccine design and its application was started a couple of years following its groundbreaking discovery[82-85]. Indeed, the issue is underestimated, since there is no efficient vaccine in clinical practice yet. In other words, vaccination against *H. pylori* remains the most challenging issue for developing countries, where relatively high prevalence

of infection is a public health challenge[86-90]. Although we are sure about who should receive the vaccine and which vaccine candidates should be administrated, a better approach is to continue for finding answers rather than ignoring the primary question. The good news is that current awareness of clinicians regarding vaccination effects to reduce gastric cancer rate, especially in developing countries provide an initiative panel to invite researchers for more attempts in this issue. Consequently, an apparent progress was made on production of this efficient vaccine against *H. pylori* infection[91-93]. Accordingly, there is still an impetus for developing such a protective vaccine. As already mentioned, both antibiotic therapy and probiotics are inadequate strategies in the battle against *H. pylori*. Thus, the last available weapon is a vaccine. The remaining unresolved issues for vaccine production are: (1) complicated host immune response to the pathogen; and (2) high genetic diversity in *H. pylori*. Since with application of the vaccine clinicians can guarantee the protection and reduced risk of re-infection, it would be preferable to recommend vaccine in both developing and developed countries. As it sounds, the best weapon in the war against *H. pylori* is vaccination, thus we should search for better vaccine formulations and adjuvants to make vaccines for eradicating this rogue chronic infection. Unfortunately, we have had several failures in developing *H. pylori* vaccine candidates, such as whole cells extract, flagellar antigens, adhesion antigens, and also urease[94-96]. It seems that to produce and generate an effective/protective *H. pylori* vaccine only two major topics should be addressed; (1) best adjuvant; and (2) best selected antigen. In the case of adjuvant, there is a narrow range of options, since many lack approval for human application[25,91,97].

CONCLUSION

Introduction of a Gram negative microaerophilic bacterium was one of the main groundbreaking events in gastroenterology. Unfortunately, high resistance rates had been reported to all prescribed primary and secondary antibiotics. As such, we should try other strategies to manage this chronic infection and prevent associated severe digestive diseases. The best alternatives would be a prophylactic vaccine. Recently, Zeng *et al*[91], in a randomized trial at clinical phase 3, produced an oral vaccine which may change our primary views toward *H. pylori* vaccines. The good news is that Zeng *et al*[91] reported a good prophylactic aspects for this vaccine, however, they need to work on therapeutic potential which its likely application can easily help clinicians to eliminate *H. pylori* worldwide. To be honest, no one can ignore all aforementioned obstacles to produce this vaccine; but this is the only way to go in order to best manage the gastroduodenal disorders. Better vaccine formulation, better adjuvant, better antigen delivery system, and designing an oral vaccine without booster are the main aspects need to be considered in future work. We predict that in the close future, a prophylactic vaccine will enter to the market and it can solve all aforementioned questions. In conclusion, despite all disclosed difficulties to produce effective vaccine against the *H. pylori*, the current workflow should be promoted and continued. In other words, vaccination is an inevitable approach even if we do not have a globally prescribed therapeutic/prophylactic vaccine.

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