

Helicobacter pylori Infection in Iran: A New Perspective

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ABSTRACT

With 22 deaths per day due to gastric cancer, Iran is certainly an attractive country for all kinds of research associated with *H. pylori* infection. Unfortunately, there are no reliable data on the virulence factors, vaccine and prevalence of the infection in Iran. Numerous anti-*H. pylori* therapies are available, although there is still no effective and ideal treatment in clinical settings. Currently, successful vaccine candidates are already examined in animal models, but have repeatedly failed upon attempts to translate the vaccine into humans. A national study with standard test, which can detect *H. pylori* infection among symptomatic and asymptomatic individuals, is necessary to find the actual prevalence of the infection in Iran. Current knowledge about prevalence, treatment and vaccines of *H. pylori* seems incomplete. Conclusively, it is worthwhile to note that *H. pylori* infection in developing countries such as Iran needs urgent reconsideration for all associated aspects.

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Key words: *Helicobacter pylori*; Prevalence; Vaccines; Virulence; Iran

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a highly adapted gastric pathogen that chronically infects more than half of the world's population. Due to the potentially etiologic roles in diverse gastroduodenal diseases, *H. pylori* research has become cross-disciplinary, incorporating both microbiologists and gastroenterologists^[1]. Every year, thousands of papers are released about different aspects of *H. pylori*; a fact which indicates the importance of this gastric pathogen. Undeniably, *H. pylori* is known as a high genetically variable bacterium which colonizes the gastric epithelium lifelong if not treated efficiently^[2-5]; a fascinating story which has not been repeated for other human bacteria. Complex and causal links between different *H. pylori* virulence factors and various digestive diseases provide additional evidence that the bacterium is a serious clinical problem. Broadly described, Iran is a country with 77 million inhabitants, and relatively high prevalence of *H. pylori* infection^[6,7]. Unfortunately, 22 deaths per day made Iran the top country in mortality risk for gastric cancer in the world. Research on *H. pylori* in Iran has an old history which has been started by Dr. Emami-Ahari nearly 30 years ago^[8,9] in a private clinic. He successfully cured thousands of patients with peptic ulcers by antibiotic therapy^[9]. Remarkably, his findings were underestimated at the time, until later, when Marshall and Warren showed clinical importance of *H. pylori* existence in stomach^[10]. Until now, many studies performed based on Iranian *H. pylori* strains, but a comprehensive and concluding article about current available data is lacking. This review article surveys available knowledge concerning *H. pylori* in Iran and focuses on the prevalence, vaccine, virulence factors and current therapy, which are critical for national and international researchers.

PREVALENCE

The prevalence of *H. pylori* infection is strongly defined by three independent items. The first and most important is acquisition age (Figure 1). Second is the rate of re-infection, which can affect on actual prevalence of infection. In other words, treatment failures can result in subsequent re-infection of *H. pylori*. Third, survival of the colonized infection is the last affecting factor on prevalence

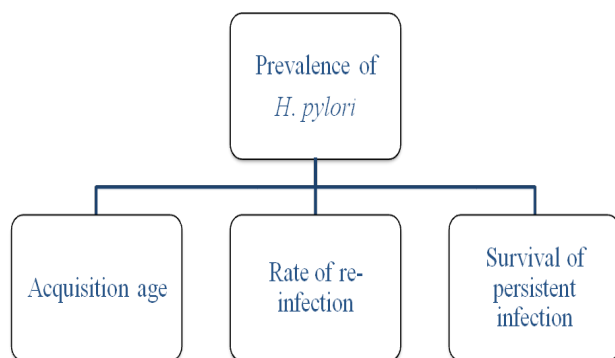


Figure 1 Schematic view of affecting items on prevalence of *H. pylori* in a region.

of *H. pylori* in communities. Altogether, varied rates observed in prevalence of *H. pylori* obtained from different regions are due to the wide range of age of primary colonization^[11]. Indeed, childhood *H. pylori* exposure can be considered as likely major determinant of gastroduodenal disorders in this country. However, higher levels of hygiene in communities can increase the age of first exposure to the bacterium, thereby reducing total prevalence of *H. pylori*. Of result, a national preventive guideline for decreasing the prevalence of *H. pylori* infection seems necessary. The overall prevalence of *H. pylori* infection in Iran varies geographically, but remains relatively high; 40% to 90% in different states (South to North of Iran)^[12-14]. However, using different detecting assays such as ELISA, PCR and urease breath test (UBT) which explain the bias observed in reported rates from various states. In different studies from northern Iran, the prevalence is between 78-90%, a range that is higher than rest of country (especially the south)^[13,15-17]. In a report from west of Iran, the prevalence of serologically positive subjects was reported to be 71%, which is relatively higher than previously published data^[18]. However, in a study from Golestan, near the Mazandaran sea, prevalence of serologically positive subjects was found to be 67%, a rate which was lower than another study from Babol (83%), which is located on the same side of the country^[15,19]. Talebi Bezmin Abadi *et al*^[20] found more than 95% of subjects are *H. pylori* positive in the north of Iran. In Tehran, the capital, *H. pylori* infection rate detected by serologic tests was reportedly near 70%^[21]. Overall, the prevalence of *H. pylori* infection is gradually increasing in Iran. A national study with standard and accurate tests, which can detect *H. pylori* infection among symptomatic and asymptomatic individuals, is necessary to find an actual prevalence of the infection among the Iranian population. Moreover, the matter of re-infection of *H. pylori* should be considered even after effective eradication treatment. The striking observed discrepancy from various studies may be due to the differences between techniques and population size. Remarkably, studies performed on young people are demonstrating *H. pylori* is a prevalent infectious agent, which presents an urgent call for new adopted strategies in hygiene and health^[22-24]. Indeed, studies aimed to estimate the actual prevalence of *H. pylori* infection among the Iranian population on a large scale are necessary. Overall, as expected, the prevalence of *H. pylori* infection among symptomatic subjects was higher than asymptomatic individuals. High incidence of *H. pylori* (even in asymptomatic individuals) should be considered as an alarming status that needs attention. Conclusively, the status of health care, hygiene and socioeconomical levels of life in Iran can easily explain different prevalence rate of *H. pylori* among the Iranian population.

VIRULENCE FACTORS

Virulence factors determine the ability of a bacterium to induce specific disease^[25,26]. With this regard, several virulence-associated genes of *H. pylori*, such as *cagA*, *homB*, *oipA*, *babA2* and *dupA*, are thought to have a crucial role in the associated gastroduodenal pathogenesis^[27-32]. Mainly, some studies performed in Iran reported a specific association between certain virulence factors and specific diseases^[31,33-36], but have not been extensively studied for all virulence factors^[37-39]. *cagA* is the most investigated *H. pylori* virulence factor, which showed a significant correlation with atrophic lesions, gastric cancer and gastritis^[33,40-44]. Similar to Western countries, *cagA* was reported to be linked to the more severe gastroduodenal diseases among the Iranian strains^[33,45,46]. Duodenal ulcer-promoting (*dupA*) gene is the only introduced virulence factor of *H. pylori* associated with a differential susceptibility to gastric cancer and duodenal ulcer^[47], therefore; it may be considered as a disease-specific biomarker in Iran. After *dupA* was shown to be a putative virulence factor of *H. pylori*, it was thought that Iran might be a good region to evaluate the validity of this newly proposed disease biomarker^[48]. In spite of the first study by Douraghi and *et al*^[48], which indicates presence of *dupA* in nearly half of *H. pylori* strains, Talebi Bezmin Abadi *et al* reported less *dupA* positivity (~40%)^[28]. To our knowledge, no newer study has addressed the link between *dupA* harboring strains and disease specificity of colonized individuals. Iranian studies have yielded inconsistent findings, which are insufficient to suggest hypotheses about *H. pylori* virulence factors as disease-specific biomarkers. Of note, next generation of sequence technology, which can provide a lot of genomic information with less costs and time than before, can enable scientists to design experiments to identify the real *H. pylori* virulence factors.

TREATMENT

H. pylori is a persistent spiral microorganism that survives in extremely harsh niche of the stomach, and remains in the human gastric mucosa for life if not treated efficiently. Optimistically, the main goal of *H. pylori* treatment is the clearance of the microbe. *H. pylori* therapy has primarily involved antibiotics; however, continuous therapeutic failures caused reconsideration concerning prescribed regimens. More recently, antibiotic resistance has been increased sharply, while conversely, multi-drug therapies resulted in reduced the patient's compliance^[12,49,50]. The most recommended treatment for first line therapy in locations where clarithromycin resistance is less than 20% is a proton pump inhibitor (PPI), clarithromycin, and either metronidazole (first choice) or amoxicillin (second choice), for 14 days (Triple therapy)^[51,52]. Moreover, these triple therapy regimens can be supplemented by the addition of bismuth in geographical areas where antibiotic resistance is relatively high (second line therapy)^[51-53]. Undoubtedly, since bismuth is not allowed in some countries (such as Iran), a combination of a (PPI) and either amoxicillin or tetracycline can be prescribed^[53]. In fact, in 1994 there was a study^[54] examined a triple regimen among the Iranian population consisting a bismuth subcitrate, tetracycline and metronidazole with an acceptable eradication rate (80%) in metronidazole sensitive strains of *H. pylori* and 64% in metronidazole resistant strains. Although, lack of further investigation caused scarcity of information on this suggested therapeutic regimen in Iran. Recently, in a study from northern Iran, Fakheri *et al* compared a sequential regimen with a bismuth-based quadruple therapy that contains a short course of furazolidone in eradication. They suggested the furazolidone-containing regimen as

superior^[55]. Similarly to what was seen in mid eastern countries^[22], in Iran, resistance rates to clarithromycin is increasing, an alarming message which calls for reconsidering current adopted strategies in *H. pylori* therapy^[49,56,57]. Briefly, the best results for *H. pylori* eradication in Iran were achieved with quadruple therapy using omeprazole, amoxicillin, bismuth with either furazolidone 200 mg twice daily or clarithromycin 500 mg twice daily^[58]. Broadly defined, re-infection can affect on the final outcome of *H. pylori* colonization, however, in developing countries such as Yemen and Iran, the problem is even worse. The *H. pylori* re-infection rate among Iranian population was reported to be ~21%^[59]. The high incidence of *H. pylori* re-infection likely contributes to the fact that treatment failures ranks as major problem in Iranian symptomatic population. Without antibiotic susceptibility data, prediction of treatment failures would be difficult in Iran. The resistance of *H. pylori* to above mentioned therapy may increase; therefore, a surveillance system seems necessary to update current data especially about regions with less antibiotic resistance rates^[60]. It is urgent to investigate the best first-line eradication regimen for using in regions with high rate of antibiotics resistance in the Iranian population as soon as possible.

VACCINES

During the relatively short period of time after *H. pylori* discovery, a long list of different putative and protective *H. pylori*-derived antigens such as cytotoxin-associated antigen (cagA), vacuolating cytotoxin A (vacA), urease subunits, neutrophil-activating protein and oipA had been prepared as candidates to produce an effective prophylactic or even therapeutic vaccine against this microorganism^[61-66]. In one of the first studies, Najar Peerayeh *et al*^[67] showed potential value of HpaA as recombinant immunogenic to produce useful *H. pylori* vaccine, although they were unable to validate this data within animal and human model. Hajikhani *et al* found UreB332-HpaA to be a proper vaccine candidate, which is worthwhile to examine in future studies of Iranian *H. pylori* strains^[68]. In a later study, recombinant VacA protein showed antigenic and immunogenic properties; therefore, it has been introduced for next candidate of *H. pylori* vaccine development^[69]. Similar to Hasanzadeh *et al*, Talebkhan *et al* suggested that recombinant VacA s1m1 can be a good *H. pylori* s1m1 vaccine candidate^[70]. Additionally, in 2013, Farjadi *et al* reported 65kd CagA protein as a vaccine candidate^[71]. Talebkhan *et al* showed that recombinant Omp18 plus cholera toxin can stimulate sufficient immunization against *H. pylori* in C57BL/6 mice^[72]. From the wide array of recent vaccine investigations, it seems that *H. pylori* vaccine development in Iran is not a priority for clinicians and researchers. It is likely that most of studies were not published due to the lack of evidence in animal models. However, to date, most vaccine attempts have not worked in humans^[61,62,73]. As a result, the current status for vaccine research in Iran is not unexpected. In brief, the main reasons for *H. pylori* vaccine failure can be listed as follows; (1) lack of knowledge about models of transmission, exact reservoirs (such as dental plaque or oral candida albicans); (2) heterogeneity of *H. pylori* genome; (3) complex and poorly understood immunology of the stomach; (4) insufficient financial sponsorship, and eventually; and (5) high ability of the bacterium to avoid human immune system. In fact, much knowledge of the potential *H. pylori* vaccine has been accumulated in Iran, much of it is rather uncontrolled or invalidated, and findings have not been consistently replicated and confirmed in other laboratories. Reinvestment in current health and medical budgets can refresh ongoing research flow on *H. pylori* vaccine projects in Iran.

H. PYLORI PROSPECTIVE IN IRAN

While several *H. pylori* strains carry a variety of virulence factors in Iran, cagA was significantly associated with severe gastroduodenal diseases such as gastric malignancy in Northern Iran, where the incidence of gastric cancer is the highest rate found in Iran. Based on the studies described in this review, it is obvious that increasing prevalence of *H. pylori* infection will likely lead to much more therapeutic failures in Iran, and it ideally may lead to new attempts to generate an effective vaccine in the near future. High prevalence and accessibility of *H. pylori* strains, in addition to the relatively high incidence of gastrointestinal disorders reported from the Iran, provide a suitable location for clinical research. Therefore, Iran can serve a practical model to design, produce and use therapeutic and prophylactic vaccines. Of note, elimination of all *H. pylori* strains is not feasible in Iran, but treating the high groups risk such as gastric cancer or other severe digestive diseases can be an option at least in the near future.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests and received no financial support.

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