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# Expanding the knowledge of Helicobacter pylori – new directions, new challenges

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**Summary**

**Introduction**

Helicobacter pylori (H. pylori) infection is prevalent worldwide. As it is a known carcinogen, causing multitude of gastrointestinal end extra-gastric disorders, the eradication therapy is now indicated for every patient diagnosed with this infection. This approach may prove however to be improper, since it is now known, that not every strain of this species is pathogenic, therapy may be unsuccessful and drug resistance is ever increasing problem.

**A brief description of the state of knowledge:**

H. pylori is a species representing multiple strains with distinct regional genetic markup. Its prevalence is high in the general population, but in the recent years there have been reports of decreased presence in the developed countries. This paper reviews most important known genetic diversity markers and their impact on virulence and toxicity of species. It also covers possible new ways to combat the infection.

**Conclusion**

With increased possibility of genetic sequencing, there may be possibility for custom-tailored eradication therapy of H. pylori in the future.

**Key words:** Helicobacter pylori, genetics, pathogenicity, analysis,

## Introduction and purpose

Helicobacter pylori is a Gram-negative bacteria, commonly found in human stomach. Although it was first cultured in 1982 by Marshall and Warren, the various helicobacter species were known for almost 100 before that [1]. Since the first culture, the knowledge about this bacterium has been vastly expanded. There are known multiple strains of H. pylori, along with different clinical impact, virulence factors and susceptibility to treatment. While usually it is possible to isolate singular strain from a patient, multiple infections (multiple genetically distinct strains) were reported. There were also reports of mixed infections, where

different genetical strains can have varying susceptibility to antibiotics [2]. H. pylori infection is prevalent in the general population, with various sources around the world reporting 12,8-90% prevalence, although there was no unified method for detecting the infection among researchers [3]. Majority of carriers are symptomless, but H. pylori can cause multitude of disorders, mainly in the gastrointestinal tract, including known carcinogenic potential, but also stomach and duodenal ulcers, gastritis and important factor in development of mucosa-associated lymphoid tissue (MALT) lymphoma [4]. Recent studies explore the potential effect on other systems, including neurological, cardiac, metabolic, respiratory, dermatological and hematological diseases[5]. Current consensus of European Helicobacter and Microbiota Study Group (Maastricht V/Florence) states that every patient diagnosed with H. pylori infection should be treated regardless of presence of clinical manifestations. There is however lack of evidence for efficiency of mass eradication programs, with possible emergence of antibiotic resistance and notable potential side effects of the therapy [6]. This article reviews recent development in knowledge about H. pylori epidemiology, virulence and antibiotic resistance among various strains of the bacterium.

**State of the knowledge**

While the H. pylori infection is relatively common, there is shared downward trend of the prevalence of H. pylori in the developed world. The recent studies in children yielded results as low as 0,5% of the studied population (in the 2-4 year age group) [7], which suggests possibility of complete eradication. These results were replicated in another study [8], in which the prevalence in age group 0-11 was reported to be 0,6%. However, both studies noted that this was only applicable to countries with high hygienic standards, with marked increase of presence of infection in adolescence.

So far there is no known method of transmission. The most common routes are thought to be human to human, specifically oral-oral (via shared utensils, or physical contact) and fecal-oral. As mentioned above, the low prevalence in children indicates that typical parent-child transmission may not be applicable. This is in contrast to previous statements, that family setting, may be the deciding factor [9, 10]. The possible new routes include animal to human transmission, through contaminated water and food sources, or direct contact with animals [8].

Once acquired, the infection persists through person’s life. For the bacterium to survive in highly acidic environment of the stomach, it had to develop various virulence genes. In fact there is evidence of high adaptability to the new environment, with new subpopulations of H.

pylori constantly emerging in different regions of the world. Recent studies highlighted that in the span of 500 years of migration to the Latin America, already there have been sequenced distinct genomes specific to these populations [11]. This diversity is also present when analyzing severity of the infection across the world, and manifests itself is in virulence factors. Thanks to the rapid development of genome sequencing, various virulence factors have been described and classified. These have been divided into two main groups, one consisting of adhesins and outer membrane proteins, which enable bacterium to colonize the gastric mucosa, another consisting of secreted and injected proteins, that through its cytotoxic effect induce inflammation, which leads to clinical symptoms that the patient may experience [12,13].

The main proteins included in the adhesin and OMP group, that are currently investigated for possible promotion of the diseases associated with H. pylori infection, are: blood group antigen binding protein (*bab*), which enables binding to mucosal blood group antigens of Levis$^{b}$ system, outer membrane proteins (*hom*), out of which the most studied member, *homB* has been proven to enable adherence to host epithelial cells of the stomach, as well as promote cellular production of IL-8 *in vitro*, sialic acid binding adhesin (sab), which binds to sialyl-Lewis$^{x}$ and sialyl-Lewis$^{a}$ receptors, enabling adherence [12,13].

The another group of virulence genes are the cytotoxic protein producing genes. The studies in this group focus on vacuolating cytotoxin (VacA), the cytotoxin-associated genes (*cag)*, producing protein CagA. While CagA presence has been shown to have strong correlation with oncogenesis, the VacA gene is present in all studied H. pylori strains, however with different vacuolating ability [13].

There are also virulence genes that were not classified into those two groups. Of those, duodenal ulcer promoting (*dupA)* gene presence was proven to elicit IL-8 production in gastric epithelial cells, leading to antral gastritis [13]. There is also a gene named the induced by contact with epithelium (*iceA*) locus which initially was associated with various gastric disease states, however more recent studies could not prove a strong correlaton between *IceA* presence and clinical manifestation of the disease [12].

Because of the possible polymorphisms in one group of proteins expressed in population, these studies produced so far mixed results in different populations. For example in *bab* family of proteins, out of three paralogues (A, B, C), a single strain can express one, two or three simultaneously, with numerous combinations possible. This further confounds the

studies in this field, which currently is heavily influenced by geography of populations studied [12].

Another important direction in H. pylori genome study is exploration of antibiotic resistance genes. Because of widespread antibiotic use, there has been shown a marked increase of resistance to standard therapy regimen, which currently is a choice of two antibiotics (out of tetracycline, metronidazole, clarithromycin and amoxicillin), proton pump inhibitor and bismuth salt used simultaneously for 10-14 days [6]. There have been reports of multidrug-resistant H. pylori strains [14]. Recently, a multitude of possible mechanisms of resistance have been described along genes responsible for the mechanism [15]. Classic method of recognizing antibiotic resistance, the culture from gastric biopsy and antimicrobial susceptibility test may be unsuccessful and time consuming. Thus it is recommended to move to genotypic methods due to higher sensitivity, particularly in the regions of high clarithromycin resistance [6, 15]. The possibility of PCR and fluorescence in-situ hybridization testing is explored, which offers greater accuracy [15].

## Conclusion

Despite of observed lower prevalence of H. pylori infection in developed countries, it remains an important factor not only in gastroduodenal diseases, but also in extra-gastric disorders. Because it is a species with high adaptability to environment, the efforts to dampen its influence in developing countries are hampered due to increased antibiotic resistance. There is also particular concern for precision of the therapy. Despite being an infectious disease, it is not certain whether routine therapy in case of symptomless infection is indicated, as there are also possible beneficial aspects of the bacterial colonization. The side effects of the therapy, especially antibiotic use in conjunction with bismuth salt may overweight the benefits. The new approach, which promotes recognition of pathogenic strains and tailoring the eradication therapy to the particular strain is needed. These struggles may however prove to be unnecessary on a large scale, since there is increasing evidence, that improving the conditions of life in society is the best solution of the problem.

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