**Editorial**                                                                                          **Open Access**

# *Helicobacter Pylori* Infection: Strains Virulence and Antibiotics Activity

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## Editorial

*Helicobacter pylori (Hp)* was first isolated in culture media by Warren and Marshall in 1983. It is a Gram-negative, spiral-shaped bacterium, with positive findings for urease, oxidase and catalase. The bacterium colonizes the human gastric epithelium. *Helicobacter pylori* is the main cause of chronic active gastritis, peptic ulcer disease, gastric carcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. Further, epidemiological and eradication studies have demonstrated a casual relationship between *Helicobacter pylori* infections and endothelial dysfunction, leading to vascular diseases [1]. Generally, the colonization occurs primarily during childhood especially in the developing areas, usually in the same family for a cohort effect. This colonization is widely asymptomatic even if a long-lasting infection can be established in some subjects. Infection is virtually lifelong in the absence of treatment, implying that evasion of the host response is efficient [2].

The infection outcome mainly depends on three factors: environmental settings, strain virulence and host response.

## Environmental settings

The cigarette smoking is a major risk factor for duodenal ulceration among *Helicobacter pylori*-infected persons. Other important factors include stress, childhood living conditions, diet, alcohol and NSAIDs (non- steroidal anti-inflammatory drugs) use [3].

## Strain Virulence

Gastric colonization is a prerequisite for *Helicobacter pylori*-associated disease and this is mediated by both flagella and urease: mutant strains lacking these features cannot establish infection. Adhesion by adhesins to epithelial gastric cells is important for the beginning of infection and for the enhanced inflammatory response. *Helicobacter pylori* has been reported to be genetically extremely variable and this heterogeneity is proposed to be involved in the ability of *Helicobacter pylori* to cause different diseases, detrimental and non-detrimental chronic infections [4].

*Helicobacter pylori* is well adapted to the human host as evidenced by its chronical persistence in the gastric niche and by the finding that the bacterial surface carries structures (antigens) which are identical to those found on human cells. Certainly man adapts physiologically to infection during his lifetime and treatment can lead to problems such as reflux oesophagitis. In view of these real problems, it would seem preferable to screen for and treat only strains that are known to cause disease.

In *Helicobacter pylori* a lot of virulence determinants have been detected affecting the infection course. Two important factors (CagA and VacA) are on the basis of both *Helicobacter pylori* virulence and its antibiotic resistance [5].

The expression of *Helicobacter pylori* vacA gene leads to the production of a vacuolating cytotoxic protein VacA, (present only in about 40% of isolates), which is responsible for inducing the formation of acidic vacuoles. The vacA gene contains two variables regions: the s- (signal) region encoding part of the signal peptide with the N-terminus of the mature protein (hydrophilic part) and the m- (middle) region encoding C-terminal portion of the final processed polypeptide (hydrophobic part within the p58 domain). These regions are both cleaved upon secretion to yield a mature toxin monomer of 87-95 kilodaltons. A further region of the vacA gene [i- (intermediate) region] has been reported in literature to be associated with gastric cancer being consequently considered a better predictor of *Helicobacter pylori* strain carcinogenic potential than signal region (s) or mid region (m) [6]. The s-region exists as s1 or s2 allelic types. The m-region occurs as a m1 or m2 allele. Each vacA allele can consist of any combination of signal sequence and mid region except s2m1. The combinations between the s and m region determine the strains virulence and are correlated with the disease. In many populations where vacA polymorphism has been found, the combination of s1m1 alleles was the most toxigenic and has been shown to be associated with duodenal and gastric ulceration, making this allelic form an important determinant of disease-associated *Helicobacter pylori* strains.

CagA region and cag A island are further virulence factors of *Helicobacter pylori* strains. The cagA-positive strain increases the risk of development of atrophic gastritis and mucosal inflammation and it is a marker for the cag pathogenicity island (cag PAI). The presence of CagA protein is strongly correlated with duodenal ulcer, neutrophil infiltration and gastric adenocarcinoma.

In our previous article [7] we found that the most virulent strains and those that showed a dual simultaneous clarithromycin (CLA) and metronidazole (MZ) resistance, mainly belonged to the genotype cagA-positive and vacA s1m1 whereas the less virulent and more susceptible strains belonged to the genotype cagA-negative and vacA s2m2.

## Host Response

The evasion of host response is efficient. Antibodies of the humoral immunity are not protective against the infection whereas the natural and acquired immunity determines the strong inflammatory response present during the infection course. In this way, the immune response to *Helicobacter pylori* rarely results in the clearance of microorganism [8].

## Treatment of *Helicobacter pylori*

Treatment regimens for *Helicobacter pylori* that have been used over the past decade are declining in efficacy and the treatment of *Helicobacter pylori* infection is bedevilled by drug-resistant strains. The leading causes of treatment failure are antimicrobial resistance and non-adherence to therapy. *Helicobacter pylori* is in fact a microorganism which can easily acquire resistance to antimicrobial agents. Furthermore, the patterns of resistance to antimicrobials may change with time, considering that in countries where CLA resistance is progressively higher, the use of MZ-based therapies is introduced, leading to subsequent MZ-resistance. Moreover, often the *in vitro* results do not correlate with *in vivo* efficacy [9].

Recently it was also reported that multiple strains can colonize within a single stomach with differences in genotype distribution between different gastric locations such as antrum, corpus and fundus as well as differences in minimum inhibitory concentrations of isolated *H. pylori*. Heteroresistance (HR) is defined as the co-existence of the susceptible and resistant bacteria in the same sample. The HR is difficult to be detected by the phenotypic drug susceptibility tests which cannot identify the different strains if the resistant isolates account for less than 30% of the total bacterial populations. Data on heteroresistance are however controversial, indicating that no single biopsy site can be considered representative of antimicrobial susceptibility testing [10].

*H. pylori* infection is increasingly difficult to treat. The new guidelines for the cure of *Helicobacter pylori* recommend to prolong the therapy from 10 to 14 days [11]. For the first line therapy a concomitant non-bismuth quadruple therapy (proton pump inhibitor, PPI+amoxicillin+metronidazole+clarithromycin, PAMC) or traditional bismuth quadruple therapy (PPI+bismuth+metronidazole+tetracycline, PBMT) are recommended.

The triple therapy (PPI+clarithromycin and either amoxicillin or metronidazole) should be considered only in areas where the resistance to CLA is low (<15%) or where a high eradication success with these regimens (>85%) is well known. Recommended rescue therapies include PBMT and therapy based on the use of levofloxacin (PPI+amoxicillin+levofloxacin, PAL). The use of rifabutin should be confined to patients who failed at least 3 previous regimens. Moreover the guidelines discourage the addition of probiotics for reducing the side effects of the therapy or for increasing the eradication rates because the evidence in support of this thesis is very low. Optimal treatment of *Helicobacter pylori* should require the susceptibility tests *in vitro* but this option includes, first of all, an endoscopy and besides it is an expensive and time consuming method. The Toronto Consensus Group for the treatment of *Helicobacter pylori* infection has agreed that the treatment choice must be based other than on the susceptibility tests also and mainly on the prevalence of antibiotic-resistance as well as on the eradication patterns of specific therapies in the local population. When these informations are not available, the empiric alternative for the adults, based on the literature data, includes quadruple therapies PAMC or PBMT for 14 days [11].

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