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Chapter 1

Introductory Chapter: *Helicobacter pylori* - An Overview of an Old Human Microorganism

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1. Introduction

The human stomach is an unfriendly place for most infective bacteria probably due to the very low pH found in this place. However, the first isolation of a spiral-shaped, Gram-negative and microaerophilic bacterium in 1982 by Warren and Marshall [1] significantly changed the concepts of gastric microbiology.

Initially, this bacterium was named *Campylobacter pyloridis*, but analysis of nucleic acid sequence and ultrastructural studies besides the helical shape allowed differentiation of this genus to *Helicobacter*. Finally, the species was named *pylori* because it can be found most often in the antral mucosa, near the pylorus [2].

Helicobacter pylori (*H. pylori*) organisms are 2.5–5.0 μm long and 0.5–1.0 μm wide, with two to six unipolar-sheathed flagella, which are essential for bacterial motility [3]. It has been described that bacteria can exist in three different morphologic forms: the viable and culturable spiral form, the viable but nonculturable (VBNC) coccoid form which are less virulent, and the nonviable degenerative *H. pylori* form [4].

Colonization with *H. pylori* is commonly acquired during childhood and induces chronic gastritis in all infected individuals unless specific treatment is given [5, 6]. While over 80% of infected subjects remain asymptomatic [7], *H. pylori* chronic infection has been associated with the development of various clinical disorders of the upper gastrointestinal tract, such as chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma [8]. In fact, *H. pylori* infection is a significant risk factor for the development of gastric cancer, and bacterium is classified as a group I carcinogen by the World Health Organization [9].

Although *H. pylori* is primarily responsible for the upper gastrointestinal diseases, only 10% of people colonized with this bacterium portray disease symptoms. It suggests that host and bacterial factors also contributed to differences in *H. pylori* pathogenicity [10, 11]. For instance, the risk of developing gastric cancer is also related to genetic characteristics of the host and environmental factors, which, associated with specific bacterial strain characteristics, influence the severity of the chronic inflammatory response [12, 13].

H. pylori is perhaps the most ubiquitous and successful human pathogen, since it colonizes the stomach of more than 50% of the world population [14, 15]. It has been demonstrated that *H. pylori* has a long period of coevolution with humans, going back at least since human migration out of Africa about 60,000 years ago [16, 17]. There are very well-characterized mechanisms of adaptation which was developed by ancestral *H. pylori* over the time. Through selection and coevolution, this bacterium established measures which actively and passively avoid the human immune response [18].

H. pylori infection results in recruitment of neutrophils, lymphocytes, and macrophages into the gastric mucosa through the induction of several cytokines such as TNF-α, IL-6, and IL-8 [19, 20]. It is believed that the immune response during infection plays an important role in the pathogenesis. *H. pylori* successfully establishes a chronic infection by achieving a delicate balance between inducing immune response and surviving in the inflammatory milieu by using an array of important virulence factors [15].

H. pylori presents important virulence factors which are essential both for bacterium colonization and maintenance in the human stomach (such as urease and flagella) and for the interaction with the gastric epithelial cells, the bacterial adhesins (blood group antigen-binding adhesion (BabA), sialic acid-binding adhesion (SabA), AlpA and AlpB, HopZ, and OipA). Besides, virulence factors involved in gastric inflammation are important for the development of chronic infection and clinical symptoms of gastrointestinal diseases (the principal are cytotoxin-associated gene-pathogenicity island (cagPAI), vacuolating cytotoxin A (VacA), and duodenal ulcer promoting gene (dupA)).

2. Epidemiology of *H. pylori* infection

The *H. pylori* infection has emerged as one of the most common chronic bacterial infections worldwide and affects more than half of the world's population, with clinical signs of infection only manifesting in <20% of these individuals [21].

H. pylori is thought to be indigenous to the human population and is well adapted to existing in the human stomach for the lifetime of its host [22] unless eradication using appropriate chemotherapeutic agents is successful. Lifelong colonization seems to be due to the ability of some strains of *H. pylori* to both adapt to the host's immunological responses and to also withstand the constantly changing gastric environment [23].

The rate of *H. pylori* infection differs among groups as well as within the population. Strains from different geographical areas exhibit phylogeographic features [24–26]. The genomic

patters of *H. pylori* have been shown to be extremely diverse, and gastric mucosa may be colonized by strains with small differences in the genomic patterns suggesting subtype variation [27].

The prevalence of *H. pylori* infection varies widely by geographic area, age, race, and socioeconomic status. While the infection is on a fast decline in the most of the Western countries, mainly due to the success of therapeutic regimens and improved personal and community hygiene that prevents reinfection, in developing countries, the prevalence rates can reach 90% and is higher among individuals belonging to low socioeconomic status group [28, 29]. It occurs especially due to failure of treatment and emergence of drug resistance [25, 30].

Most studies suggest that males and females are infected at approximately the same rates [31–33]. In spite of it, a meta-analysis population-based study reported a male predominance of *H. pylori*-related diseases in adults but not in children [34].

The infection probably occurs in the childhood, and children are often infected by a strain with a genetic fingerprint identical to that of their parents [35]. Besides, local prevalence of *H. pylori* within a country also should be considered, and there are estimates that infection is more common in rural developing areas than in urban developed ones [36].

Moreover, differences by ethnic and racial groups are evident [31, 32, 37]. In addition, the main risk factors of *H. pylori* infection, especially if present during childhood, have been associated with socioeconomic status. Malaty and Graham [38] demonstrated that there is probably an inverse correlation between prevalence and socioeconomic status. It has also been reported that overcrowding, such as living in a crowded environment, sibship size, number of persons or children in the home, number of persons per room, crowding index, and living in an institutionalized population, is a situation consistently related to *H. pylori* positivity [39–42].

Finally, it is important to consider that the pathogenetic role of *H. pylori* in gastroduodenal pathologies has been elucidated and confirmed in the past 30 years [43] redirecting the scientific and medical understanding of great part of gastrointestinal diseases. The development of effective therapies against *H. pylori* infection has progressed, and its successful eradication leads to healing of chronic active gastritis and reverses inflammation of the mucosa. In spite of it, the challenge nowadays is gastric cancer and the understanding of gastric carcinogenesis, almost always associated with *H. pylori* long-term infection [44].

3. Transmission pathways

Although the natural niche for *H. pylori* is the human stomach, some questions about other possible reservoirs for bacterium have been appearing in the last years. Nevertheless, most part of the questions about the transmission of *H. pylori* remains unclear, and, because of it, the possible modes of transmission are still unknown. Consequently, the routes of transmission of *H. pylori* are supposed to occur via an array of different pathways.

Some important studies have reported and highlighted the importance of *H. pylori* biofilms, the presence of coccoid forms within the biofilm, and resistance, providing insight into the prevalence of coccoid forms in the gastric mucosa. These reports are very important because these can bring a better understanding about the mechanisms behind recalcitrant coccoid states and how they can phenotypically shift into more virulent spiral forms [21, 45–47].

The infection is typically acquired in early childhood and once established commonly persists throughout life unless treated. Person-to-person transmission within the family appears to be the predominant mode of transmission, particularly from mothers to children and among siblings, indicating that intimate contact is important [29, 48–50]. The route of transmission is uncertain, but the gastro-oral, oral-oral, and fecal-oral routes are likely possibilities.

The community and environment may play additional roles for *H. pylori* transmission in some settings. Molecular analyses show that the microorganism is also present in various aquatic environments suggesting that human-fecal-contaminated water sources could be a plausible reservoir of the pathogen. The persistence of the environment virulent *H. pylori* strain in a clustered state, such as the biofilm, suggests a long-term survival of the bacterial community outside the host, enabling bacterial transmission with important clinical repercussions [21, 46]. In addition, zoonotic transmission by houseflies [51–53] and some domestic animals such as dogs, cats, and sheep [54–56], as well as iatrogenic transmission [57, 58], have been proposed. Besides, there can be factors both from host and bacterium which may modify the acquisition and persistence of *H. pylori* infection.

Another possibility of *H. pylori* transmission which has been extensively reported is the water. The contamination of drinking water by human feces has been suggested as one of the possible routes of *H. pylori* transmission, and it has been demonstrated that the microorganism is present in the so-called viable but nonculturable state in this unsuitable environment, meaning that their role in fecal-oral transmission via contaminated water sources cannot be disregarded [47, 59]. The first evidences of water transmission route were obtained in studies developed in some Latin American countries—Peru, Colombia, Chile, and Venezuela—and since then *H. pylori* has been detected in several water sources, including lakes, rivers, tap water, well water, irrigation water, and sea water, and also in water distribution systems. Consequently, it can be hypothesized that drinking water could be the pathway for returning to humans [14]. Consequently, it can be suggested that water can serve as an intermediate source in the fecal-oral transmission of *H. pylori*, acting as a reservoir in which this pathogen can survive for long periods.

4. *H. pylori* eradication therapies

The principal cases in which *H. pylori* have to be eradicated have been discussed in several guidelines worldwide, also considering that this microorganism is sensitive to only a few medications, and their widespread use in other kind of infections has led to a reduction in their effectiveness against the bacterium.

The infection is typically treated with combinations of two to three antibiotics along with a proton pump inhibitor (PPI), taken concomitantly or sequentially for periods ranging from 3

to 14 days. In spite of it, there is no treatment regimen which guarantees cure of *H. pylori* infection in 100% of patients. Individuals should be asked about any previous antibiotic uses, information that has to be taken into consideration when choosing an *H. pylori* treatment regimen.

Clarithromycin triple therapy consisting of a PPI, clarithromycin, and amoxicillin or metronidazole for 14 days remains a recommended treatment option in regions where *H. pylori* clarithromycin resistance is known to be <15% and in patients with no previous history of macrolide exposure for any reason. Bismuth quadruple therapy consisting of a PPI, bismuth, tetracycline, and a nitroimidazole for 10–14 days is a recommended first-line treatment option. Concomitant therapy consisting of a PPI, clarithromycin, amoxicillin, and nitroimidazole for 10–14 days is a recommended first-line treatment option. Levofloxacin triple therapy consisting of a PPI, levofloxacin, and amoxicillin for 10–14 days is a suggested first-line treatment option. Finally, fluoroquinolone sequential therapy consisting of a PPI and amoxicillin for 5–7 days followed by a PPI, fluoroquinolone, and nitroimidazole for 5–7 days is a suggested first-line treatment option [60–62].

This book comprehends important chapters that will certainly clarify the understanding of this microorganism infection, which affects half of the world population, despite promoting clinical symptoms and disease in only a small part of the infected individuals.

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