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REVIEW – EPIDEMIOLOGY OF *HELICOBACTER PYLORI* INFECTION

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Abstract: The routes and modes of transmission of *Helicobacter pylori* infection are still unproven. This is the most important part of its epidemiology. The fecal-oral (person-to-person, foodborne, environmental patterns) and the oral-oral (or gastro-oral predominantly in childhood and associated with vomiting) routes of transmission are assumed to be most likely. Recently, fecal transplantation has been used for treatment, but the possible transmission of *H. pylori* during oral capsule-based fecal microbiota transplantation was found negative. Occupational exposure occurs in hospital-acquired infections. One of the important modes of transmission is intrafamilial. A new family-based strategy for *H. pylori* infection prevention and control (FBCM) has been implemented in China. FBCM is more cost-effective and efficient for the prevention of gastric cancer. In the last year, studies on the prevalence of *H. pylori* among patients with oncological diseases (gastric carcinoma, colorectal carcinoma, pancreatic cancer, etc.), as well as the prevalence of mutations associated with antibiotic resistance, prevailed. The low level of awareness regarding one of the main risk factors for stomach cancer is striking. The knowledge of veterinarians about the zoonotic potential and risk of Helicobacter spp. are also insufficient. The gut microbiota could influence people's health and play a key role in the pathogenesis of Alzheimer's disease. A role for the complement component C3-C3aR signaling on brain functionality via *H. pylori* outer membrane vesicles passing biological barriers was found to be involved in the development of Alzheimer's disease. The optimal serum level of vitamin D has an independent protective effect against *H. pylori* infection.

Keywords: Prevalence, Risk factors, Modes of transmission, Routes of transmission, Family outbreaks, Reinfection, Recurrence.

INTRODUCTION

Helicobacter pylori is the main etiological factor for chronic gastritis, peptic ulcer disease, gastric carcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. In this review, data on the epidemiology of *H. pylori* infection published between April 2022 and March 2023 are presented. Mainly publications in English were searched in PubMed, PubMed Central and Google Scholar. Combinations of the following keywords were used: "*Helicobacter pylori*", "prevalence", "source of infection", "risk factors", "mode of transmission", "route of transmission", "acquisition of *H. pylori* infection", "fecal-oral", "oral-oral", "recurrence", "reinfection", and "family outbreaks".

PREVALENCE OF *HELICOBACTER PYLORI* INFECTION

In the last year, numerous studies on the prevalence of *H. pylori* among patients with oncological diseases (gastric carcinoma, colorectal carcinoma, pancreatic cancer, etc.) as well as the prevalence of mutations associated with antibiotic resistance, were carried out. Alaridah et al[1] conducted an investigation among 933 persons from the general population in Jordan concerning knowledge and information on *H. pylori*. Gastric cancer occupies one of the top places in terms of frequency among neoplasms in the country. Despite that and the fact that 63% of the participants have a higher education, 68.7% have a low level of awareness regarding the main risk factors for stomach

cancer[1]. The authors of another article included patients in over 360 hospitals in the USA (18-65 years old, 47,714,750 in total) to assess the risk of colorectal carcinoma associated with *H. pylori* infection. This large population-based study is the first one demonstrating the link between *H. pylori* infection and the risk of colorectal carcinoma (OR 1.89, 95%CI: 1.69-2.10)[2].

In another case-control study from the USA, 5 prospective cohorts were investigated to determine an association between *H. pylori* infection and pancreatic carcinoma. The authors concluded that *H. pylori* infection was not associated with a higher risk of developing pancreatic cancer (OR 0.83, 95% CI: 0.65-1.06)[3]. The aim of a Mexican study was to detect the prevalence of mutations associated with clarithromycin resistance and the link between virulence factors in patients infected with *H. pylori*. Clarithromycin-based therapy is essential for *H. pylori* eradication. The authors reported a >15% prevalence of mutations associated with clarithromycin resistance and a link between *cag*A and *vac*A genotypes and 23S rRNA gene mutations. The most frequent mutations were A2143G (56%) and A2142C (25%)[4]. There are many challenges related to *H. pylori* infection. For more than four decades, numerous studies have been performed on an effective eradication therapy, vaccine prevention, interruption of transmission routes, and risk factors. The World Gastroenterology Organisation (WGO) revised its *H. pylori* guidelines using a "cascade" approach that summarizes the basic management principles consistent with local resources and experience[5].

In the study of Fekadu et al[6] the authors analyzed 22 studies from 9 African countries (population 2,163) to compute the *H. pylori* eradication rate in Africa. The pooled eradication rate was 79% (95% CI: 75%-82%), with a heterogeneity (I^2) of 93.02%. From observational studies, a higher eradication rate was reported (85%) in comparison with randomized control trials (77%). The highest eradication rate (90%) was found in Ethiopia and the lowest in Ivory Coast (22.3%). Eradication regimes will have an impact on the prevalence and incidence of *H. pylori* infection in Africa in the long term as well.

A cross-sectional study by Awan et al[7] was performed in Pakistan on 1,160 cases, and 48% were positive for *H. pylori.* The purpose of this study was to determine the prevalence and main characteristics of *H. pylori* infection. The prevalence was higher in the following categories: 20–40-year-old men, illiterate people, those consuming food from restaurants, those who use municipal water, and those having pets or other animal contact. The prevalence of *H. pylori* was also associated with socio-demographic variables.

ROUTES (MODES) OF TRANSMISSION OF *HELICOBACTER PYLORI* INFECTION

Duan et al[8] investigated the main routes and modes of *H. pylori* transmission and the relevant prevention and antiepidemic measures. They concluded that the fecal-oral route (person-to-person, foodborne, environmental patterns) is the most common route of transmission and that the oral-oral route is not universal. The gastro-oral route occurs predominantly in childhood and is associated with vomiting. There are hypotheses for anal-oral and genital-oral routes. Hospital-acquired infections occur as an occupational exposure.

Recently, fecal microbiota transplantation has been used for treatment. This procedure consists of introducing feces collected from a healthy donor into the gastrointestinal tract of a recipient. It is, therefore, important to investigate the possibility of transmission of etiological agents of infectious diseases. No evidence of *H. pylori* transmission *via* oral capsule-based fecal microbiota transplantation could be found (0%, 95%CI: 0-11%)[9].

Rarely has *H. pylori* been isolated from the environment, including water. Ekundayo et al[10] performed a systematic review and meta-analysis to investigate the prevalence of *H. pylori* in drinking water. They found a global prevalence of 15.7% (95%CI: 7.98-27.5) which varied significantly according to the sampling technique, the detection method, and the time period. The highest prevalence was found in the years 1990-1999 (41.24%). The prevalence of *H. pylori* is endemic in drinking water regardless of the regional improvement of water supplies.

To investigate the role of houseflies as a vector for the spread of *H. pylori* infection, 902 wild houseflies, identified as *Musca domestica*, were captured, and 60 of them were tested for the *H. pylori*-specific 16S *rRNA* gene. The authors concluded that the gut of houseflies could be an environment for the transfer of *H. pylori* antibiotic-resistance genes. However, the most interesting conclusion is that wasp venom has an antibacterial activity greater than more than four antibiotics used for *H. pylori* eradication[11]. The objective of another study was to detect some zoonotic species of

Helicobacter spp. in companion dogs. Due to the detection of two *Helicobacter* spp. (*Helicobacter heilmannii* and *Helicobacter bilis*), improving the owners' knowledge of this finding is important, regardless of the minor role of fecal-oral transmission in the particular study[12].

In the study by Cortez Nunes et al[13], the authors aimed to evaluate the knowledge of veterinarians (149 specialists) concerning the zoonotic potential and risk of *Helicobacter* spp.; 76.2% of the pet veterinarians did not include the genus *Helicobacter* in the differential diagnosis of gastritis in animals. A significant number of veterinarians did not consider *Helicobacter suis* as a zoonotic agent. An increase in knowledge about the zoonotic risk and potential of *Helicobacter* genus is needed. It is possible that animal-to-human transmission occurs for the acquisition of *H. pylori* and the so-called 'non-*Helicobacter pylori* Helicobacters' (NHPH) from domestic animals. In a study carried out in Taipei, Taiwan, the prevalence of *Helicobacter* species in canines was found to be 75.79%. The detected species were *Helicobacter canis, H. pylori*, *Helicobacter canicola, H. bilis, Helicobacter canadensis* and *Helicobacter typhlonius*[14].

The coccoid forms of *H. pylori* are a way for the bacterium to survive in an unfavorable environment. They are defined as a viable but non-culturable state which could play a role in the transmission of infection. The morphological changes and the dynamics of the growth of spiral forms were examined. The results showed that after exposure to sterile distilled water, the bacteria transform into coccoid forms and lose their growth ability. This is lethal for *H. Pylori,* and it is unlikely that the coccoid forms will survive in a viable state in an aquatic environment[15,16].

The NHPH species have been detected in the gastrointestinal tract of many species. They could be transmitted to human beings directly or by contaminated sources (meat, water) from the relevant animals: pigs, dogs, and cats. NHPH could be etiological agents of gastritis, peptic ulcer disease and gastric MALT lymphoma. Their transmission mechanisms, prevalence, pathogenesis, and eradication regimes must be clarified[17].

FAMILY OUTBREAKS OF *HELICOBACTER PYLORI* INFECTION

A family-based research including 282 families with 772 subjects was conducted in China to investigate the *H. pylori* infection status, risk factors, and modes of transmission in the same households. The spouse co-infection rate was 34.84%, 34.55% of these families being infected by the same strain. According to this study, the marriage duration leads to an increase in the incidence rate, but a higher level of education was associated with a significantly lower infection rate[18].

One of the most important modes of transmission is intrafamilial. In Shandong, China, another prospective cohort study of families was conducted for 6 months (1,173 persons from 386 families). They found an infection rate of 36.7%. The recommendation compliance for eradication treatment, confirmation testing, and gastroscopy was 69.3% (271/391), 32.5% (88/271), and 6.1% (19/309), respectively. The conclusion points to unsatisfactory compliance with the *H. pylori* screening and treatment program. The significant risk factors for lower compliance were male gender, and living in a non-urban area for treatment recommendations; more than one infected family member, and a lower family income, for confirmation testing recommendations and being asymptomatic for gastroscopy recommendations[19].

A cohort of 686 young couples was investigated for potential *H. pylori* risk factors and the possibility of intrafamilial transmission. The significant risk factors were gender, living in rural areas, and the presence of more than three siblings. They did not report any interspousal mode of acquisition of *H. pylori* infection[20]. To investigate the risk factors for an intrafamilial mode of transmission of *H. pylori* infection, a large examination of 10,735 families was performed, also in China, a country with a high prevalence of this infection. The risk factors significantly associated were *H. pylori*-positive family members (OR 2.72, 95%CI: 1.86 to 4.00), place of residence in more infected areas (OR 1.83, 95%CI: 1.57 to 2.13), and a large household (OR 1.97, 95%CI: 1.76 to 2.21). Strategic changes are needed to affect the prevalence of infection associated with family-based management and public health programs for disease prevention[21]. Jung et al[22] performed a large cohort study on 1,888,815 patients after *H. pylori* eradication therapy. The authors' aim was to compare the risk of gastric carcinoma after *H. pylori* eradication at different ages. An earlier treatment minimized the risk and prevented the development of gastric cancer[22].

A new family-based strategy for *H. pylori* infection prevention and control management (FBCM) has been implemented in China. If either or both of the parents was infected by *H. pylori*, their children from 18 years of age were screened by ^{13}C-UBT for *H. pylori* infection, and those positive

children and parents received an eradication treatment. Ma et al[23] conducted an economic investigation on the cost-effectiveness of this strategy. To prevent gastric cancer in a cohort of 1 million asymptomatic Chinese families, FBCM and screen-and-treat strategies prevented 1,010 and 1,201 new gastric cancer cases, reduced 2,809 and 3,339 gastric cancer-related deaths, and saved 956,971 and 1,137,549 QALYs, respectively, when compared with no-screen strategy. Cost-effectiveness analysis showed that the FBCM strategy cost $9.18/QALY, and the screen-and-treat strategy cost $12.08/QALY for gastric cancer prevention when compared with no-screen strategy[23].

RISK FACTORS FOR ACQUISITION OF *HELICOBACTER PYLORI* INFECTION

Another cross-sectional study was conducted in Ethiopia on 373 patients with dyspepsia to assess the risk factors for the acquisition of *H. pylori* infection using the stool antigen test. The predictors of *H. pylori* infection found were overcrowding or having more than four children (AOR = 7.5, 95%CI: 1.7-33.6, $p = 0.008$), poor hygiene or absence of a latrine in the house (AOR = 4.3, 95%CI: 1-17.8, p = 0.043) and drinking river water (AOR = 12.5, 95%CI: 1.5- 105, $p = 0.021$)[24].

The link between the occurrence of gastrointestinal diseases in *H. pylori*-positive patients and some habits like smoking and coffee drinking was investigated in Saudi Arabia by a descriptive cross-sectional study. The conclusion is in favor of a significant association with the habit of drinking coffee but not with smoking[25]. A cross-sectional study to evaluate the risk factors for *H. pylori* acquisition among 161 children (5-13 years old) was performed in Brazil. The authors did not find differences in the sociodemographic characteristics between *H. pylori* positive and *H. pylori* negative children and the prevalence was very similar to that found in developed countries[26].

With regard to the successful eradication of *H. pylori,* the factors with very important roles are the iatrogenic ones. In a study of 508 patients for whom *H. pylori* eradication failed, 17.5% used unadapted antibiotics with high resistance rates in triple therapy, and 11.2% used two antibiotics with high resistance rates in quadruple therapy. Physicians need to improve their knowledge of eradication regimens and antibiotic resistance in relevant geographic areas[27].

The gut microbiota can influence the people's health and play a key role in the pathogenesis of many diseases including Alzheimer's disease. According to Xie et al[28] *H. pylori* outer membrane vesicles, acting as carriers of virulence factors, could pass the biological barriers and reach the brain. They identified the role of the complement component C3-C3aR signaling on brain functionality *via H. pylori* outer membrane vesicles in the development of Alzheimer's disease.

Habbash et al[29] performed a retrospective, cross-sectional study including 200 participants to assess the prevalence of *H. pylori* infection in Bahraini patients in gastroenterology clinics. The prevalence was 55.5%. The authors concluded that a high education level, consumption of honey, coffee, green tea, and an optimal serum level of vitamin D had independent protective effects against *H. pylori* infection. Elshair et al[30] conducted a cross-sectional study to analyze socioeconomic characteristics for the prevalence of *H. pylori* infection in Japan, especially the level of education and sibling number in 3,423 subjects. The results showed that socioeconomic lifestyle and sibling number were significantly linked to the prevalence of the infection.

Another meta-analysis using a random-effect model explored the prevalence of *H. pylori* infection and the risk factors for the acquisition of infection in military personnel (from 16 studies). The highest prevalence was found in Asia (50.2%). The risk factors were predominantly overcrowding in the family, age and environmental features[31].

RECURRENCE AND REINFECTION

The oral cavity is a potential reservoir of *H. pylori*. It is associated with the development of oral diseases, the failure of successful eradication, and reinfection. Zhang et al[32] analyzed evidence for the presence of viable forms of *H. pylori* in the oral cavity as well as the mutual influence between them and other oral bacteria. The purpose of the study was to investigate the role of HLA gene polymorphism in *H. pylori* infection in Egypt. These results are in favor of the conclusion that HLA-DPA1rs3077AA and/or HLA-DQ-rs3920AG genotypes are linked as potential risk factors for the occurrence, recurrence and chronicity of *H. pylori* infection[33]. A meta-analysis including 12 studies, analyzing 226,086

patients found a prevalence of *H. pylori* in the oral cavity from 5.4 to 83.3%. A random-effects model was used to analyze *H. pylori* in oral dental plaque. The conclusion indicated no evidence that the presence of *H. pylori* in oral plaque can cause reinfection of the stomach[34,35].

It is known that a successful *H. pylori* eradication can lead to a complete remission of gastric MALT lymphoma. In one case, after the successful eradication and histologic remission, the patient was exposed to vomitus or feces from older people in a nursing home. The recurrence of gastric MALT lymphoma was observed because of an *H. pylori* reinfection. A complete remission of the gastric MALT lymphoma was established only after the second successful eradication. A subsequent infection led to a third eradication regimen and relevant successful eradication. After advising on good hygiene practice, the remission was achieved again[36].

Cho et al[37] evaluated the recurrence rate of hyperplastic polyps in the stomach after endoscopic resection and successful *H. pylori* eradication. Convincing data are available that the eradication of *H. pylori* contributes to reducing the recurrence of the hyperplastic polyps after their endoscopic resection. Zhang et al[38] studied the effects of inflammatory cytokines on eradication and recurrence of *H. pylori* infection. The authors concluded that higher levels of IL-1β, IL-6, and TNF-α may influence the recurrence rate of *H. pylori* infection in children. Reinfection of *H. pylori* infection in Vietnam occurs very often, as well as the increasing resistance against antibiotics. The consensus of the Vietnam Association of Gastroenterology (32 experts) provided updated recommendations on the management of *H. pylori* infection. The panel reached a consensus concerning strategies to prevent *H. pylori* reinfection[39].

CONCLUSIONS

Although the prevalence of *H. pylori* infection is well described, the routes and modes of transmission are still unproven. The fecal-oral (person-to-person, foodborne, environmental) and the oral-oral routes of transmission are assumed to be most likely. Some researchers investigated the possibility of *H. pylori* transmission *via* oral capsule-based fecal microbiota transplantation but did not find positive results. In the last year, studies on the prevalence of *H. pylori* among patients with oncological diseases as well as the prevalence of mutations associated with antibiotic resistance prevailed. The low level of awareness regarding *H. pylori* as the main risk factor for stomach cancer is striking. The knowledge of veterinarians about the zoonotic potential and risk of acquisition of *Helicobacter* spp. are insufficient as well. A new family-based strategy for *H. pylori* infection prevention and control was found to be more cost-effective and efficient for the prevention of gastric cancer in China.

Conflict of Interest

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