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New insights regarding *Helicobacter pylori* infection in children

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ABSTRACT

Helicobacter pylori (H. pylori) are one of the most common infections during childhood, and if left untreated it might persist lifelong resulting in severe complications such as gastric malignancies. The epidemiology of this infection has wide variations along the continents, countries and sub-regions being related mainly to the socio-economic status, hygiene and sanitary conditions. Nevertheless, a descending trend of *H. pylori* prevalence was noticed worldwide during the last decades, fact that might decrease in time the incidence of gastric cancer in adults. The diagnosis of this infection remains tricky in children and the selection of the most effective diagnostic tool is essential in order to early diagnose *H. pylori* associated gastropathies and extraintestinal manifestations. In spite of the lack of symptoms which occurs especially in pediatric subjects, *H. pylori* infection might result in severe damage to the gastric mucosa and further complications requiring close monitoring after the eradication regimen. Therefore, multiple non-invasive and invasive methods were designed to identify properly the presence of this bacterium within the individual's stomach and for enabling the clinician to use to most adequate method based on its sensitivity and specificity, but also based on the specific clinical situations. Aside from the well-known standard triple therapy used for the eradication of this infection, multiple other regimens were lately proposed in order to prevent failure of eradication. Moreover, probiotics were recently proved to improve the eradication rate, and at the same time to decrease the side effects of the antibiotics therapy. The proper eradication of *H. pylori* infection during childhood remains the cornerstone in preventing gastric cancer during adulthood.

Keywords: *Helicobacter pylori* infection, children, diagnosis, treatment

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is one of the most common chronic infections in pediatric population and its long persistence might trigger several life threatening complications such as gastric cancer, being proved that 8 in 10 gastric cancers among adults are attributable to this bacterium [1]. In terms of prevalence, studies worldwide revealed important discrepancies among different geographic areas mainly due to hygiene conditions and socioeconomic status, but other factors have also been reported to be involved in these differences such as older age, having a mother or a sibling infected with this bacterium, a large number of family members, room or bed-sharing, as well as drinking unboiled or non-treated water [2–6]. Prenatal transmission was another hypothesis meant to explain the discrepancies regarding *H. pylori* infection prevalence worldwide [7], but this route was indicated to be highly unlikely since studies reported no traces of *H. pylori* DNA at the level of the placenta of positive pregnant women for *H. pylori* infection [8]. Moreover, recent findings showed that none of the children born to infected mothers were positive for *H. pylori* infection although they have been followed-up for three months after birth [9].

Although most of the studies reported recently proved a descending trend of *H. pylori* in terms of prevalence across all geographic areas, estimating a decrease in this prevalence from 39% before 2000 to 26% in 2010 [10], the precise prevalence rate is difficult to be established in children since it is well-known that symptoms are rather uncommon in this

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age group. Thus, studies indicated that only 5% of the positive children develop *H. pylori*-related gastropathies like gastritis, gastric ulcer or other extraintestinal manifestations including iron refractory deficiency anemia, growth retardation, or thrombocytopenia [5,11]. Among the few studies performed in order to identify the prevalence of this infection in children, in 2017 it was estimated that the global prevalence of this infection during childhood reaches up to 33%, but the authors did not assess the discrepancies between geographic areas, sub-regions or countries [12]. The descending worldwide prevalence of *H. pylori* infection might be explained by the major improvements in environmental and living conditions, but also in socio-economic status even in the developing areas enabling better sanitation and promoting a decrease in *H. pylori* transmission [10].

Reports from the United States of America (USA) pointed out a mild decrease in *H. pylori* prevalence after the year 2000, but at the same time highlighted an increase in the morbidity and mortality rates due to gastric cancer [13,14]. A study performed on the populations from Caribbean, Central and South America concluded that the incidence rate of this neoplasia varies among these regions between genders as it follows: 8.7 per 100,000 men versus 5.1 females in Caribbean America, 8.1 per 100,000 men as compared to 6.3 females in Central America, and 12.7 per 100,000 men in comparison to 6.9 per 100,000 women in South America [13]. Thus, male gender seems to be more predisposed to developing *H. pylori* gastric cancer. Further studies from USA estimated an overall prevalence of *H. pylori* infection between 50 and 60%, and even above [15–17]. These rates seem to vary even depending on subregions since the prevalence in Alaska Native people was proved to resemble to that of developing countries [18–21], and as a consequence gastric cancer remains the third most-common cause of cancer-related death in this area [20,22,23]. Moreover, no descending trend was noticed a long time in these geographic areas, especially in terms of rural areas from Alaska [24]. In Mexico, the prevalence of *H. pylori* infection during childhood depends also on the sub-regions, but studies definitely pointed out a cert decrease in prevalence lately [25].

In Africa, the discrepancies were proved to be even more expressed [26]. Thus, while the prevalence rate in Ethiopian schoolchildren was estimated at approximately 65.7% [27], in the same population from Kassala city, East of Sudan, the prevalence was found to be of only 21.8% [28]. Similar prevalence rates were also reported in Nigeria [26]. Contrariwise, a recent meta-analysis found Nigeria to be the area with the highest *H. pylori* prevalence worldwide, of 87.7% [15]. The same authors concluded that Africa represents in fact the continent with the most increased prevalence rate of this infection (70.1%), followed by 69.4% in South America and 66.6% in Asia [15]. In terms of pediatric population, a study from Kenya pointed out a higher rate in this age group, of 73.3% as compared to 54.8% in adults [29]. The reports from Uganda and Ethiopia revealed lower rates varying between 44.3% and 52.2% in the same age group [30,31]. The lowest prevalence rate was noticed in children from Ghana, of only 14.2% [32].

The same descending trends of *H. pylori* prevalence were noticed also in Asia [26]. Thus, according to a recent study from Northern Jordan published in 2022, the prevalence rate in school-aged children was estimated at 14.6% [33] as compared to a previous report on the same population, where the prevalence was reported to be much higher, of 55.5% [34]. Contrariwise, a study which included adults from Jordan pointed out a prevalence of almost 90% in terms of *H. pylori* infection [35]. Another study on Iraqi children indicated a prevalence of 27% in young ages with a considerable increase up to 58% until the age of 18 years [36]. Contrariwise, studies from Saudi Arabia mentioned that almost one third of the children under the age of 10 years living in this area tested positive for *H. pylori* infection [37]. In terms of healthy children from Saudi Arabia the seroprevalence of this infection was found to reach 40% [38]. An even higher prevalence was noticed in symptomatic children from Yemen, of 65% [39]. Contrariwise, a study from Nepal indicated a prevalence of only 16%, but the authors found that 75% of the children under 10 years of age tested positive for *H. pylori* infection when stool antigen was assessed [40]. An increased colonization rate, of 42.7% was also noticed in Iran [41], but wide variations were reported in this area, between 30.6% and 82% [42]. In pediatric subjects from Iran, 42% were found to be positive for this infection, the authors stating that more than 50% of this population acquired the infection during the last decades [43]. The prevalence rate in Chinese children was reported to vary between 18.6% and 24.1% [44,45]. The studies performed in Japan indicated a decreasing prevalence rate from 72.7% in 1974 to almost 40% in 2014 [46]. Similarly, children from Korea also displayed a decrease in *H. pylori* infection prevalence from 60-85% (1994) to 12.5-28.9% (2015) [47]. Nevertheless, more than 50% of the healthy Israeli children aged between 6-9 years were found to be positive for *H. pylori* infection [48].

Europe follows the same patterns as previously mentioned continents concerning *H. pylori* infection prevalence [26]. Consequently, a major decrease in gastric cancer incidence was as well as its related mortality rates was noticed in several countries from Europe [23,49,50]. Taking into account that Portugal had the highest rates regarding gastric cancer in the European Union [51,52], a study which included teenagers with the age between 13-17 years from Portugal noticed that the prevalence rate of *H. pylori* infection was high even at the age of 13 years (66.2%), and persisted at this increased rates throughout adolescence [53]. Similar rates were reported also by other studies performed on the same age populations from Portugal [54]. A considerable decrease in prevalence of this infection, of approximately 2.5-fold lower as compared to previous reports was noticed in Bulgarian children [55]. Similarly, a German study underlined an even lower prevalence, of 6.5% [56]. Moreover, the same descending trend was also reported in Norway [57], Netherlands [58–60], Finland [61,62], Denmark [63] and the United Kingdom [64,65]. Among these countries, Netherlands was found to have the lowest *H. pylori* prevalence in children with the age between 1-17 years [66]. Nevertheless, it seems that genetic background has an even stronger influence on *H. pylori* acquisition since according to a study performed on Belgian children, the prevalence rate ranged between 3.2% in those with Belgian parents and 60% in pediatric subjects with parents originating from high prevalence countries [67].

DIAGNOSIS

It is a well-documented fact that children with *H. pylori* infection are commonly asymptomatic or they present unspecific symptoms. Aside from the common lack of symptoms in pediatric patients, the diagnosis of this infection is also burdened by the wide-spectrum of extraintestinal manifestations associated with this infection [68]. Several extraintestinal manifestations were attributed to *H. pylori* infection-associated subclinical inflammatory status such as iron deficiency anemia, idiopathic thrombocytopenic purpura, vitamin B_{12} deficiency, growth retardation [69], or less common manifestations like arterial hypertension, acute coronary artery disease, stroke, diabetes, arterial stiffness in diabetic patients, thyroid disease, eczema, rosacea, chronic hives, glaucoma, Alzheimer or Parkinson's disease [2,69].

Considering that most of the pediatric patients with *H. pylori* infection do not commonly present symptoms, but even in these situations the infection still causes damage at the level of gastric mucosa resulting in gastritis or peptic ulcer. Moreover, the eradication of this infection is recommended even in those without symptoms [70,71], and the selection of the most effective diagnostic method is crucial in pediatric patients. The recent guidelines recommend *H. pylori* testing in the following target groups: patient with peptic ulcer, especially those who undergo treatment with non-steroidal anti-inflammatory drugs or aspirin, as well as those with a history of peptic ulcer; individuals who complain of dyspeptic symptoms originating from high prevalence areas; patients with gastritis, especially those following long-term treatment with proton pump inhibitors; patients with gastric cancer, localized early stage MALToma, or those at increased risk to develop gastric cancer; but also patients with iron deficiency anemia, thrombocytopenic purpura and vitamin B_{12} deficiency [72].

In terms of *H. pylori* testing, the diagnostic tools are divided into invasive (endoscopy, rapid urease test, histopathological exam and culture) and non-invasive tests (serology, urea breath test and stool antigen). Endoscopy has the main advantage of allowing the visualization and assessment of gastric mucosa in order to identify macroscopic anomalies and suspect lesions, but at the same time this invasive tool enables the examiner to take biopsy samples from the gastric mucosa allowing their further evaluation using rapid urease test, histopathological exam and culture [72]. Its limitation regarding the diagnosis of *H. pylori* infection consists in the large number of macroscopic lesions that might result from different stages of gastric inflammation starting with active inflammation or atrophy to intestinal metaplasia [73]. These limitations were recently mitigated through the development of certain new endoscopic-based methods such as narrow band imaging, blue laser imaging or other linked color imaging tools [74,75]. Moreover, magnifying endoscopy has recently emerged in order to improve the diagnosis of *H. pylori* infection being proved that 'pit plus vascular patterns' are significantly associated with this infection [76]. The macroscopic images that suggest the presence of *H. pylori* infection include the well-known atrophy and nodularity aspects, but also diffuse erythema, mucosal edema or hypertrophy of the mucosal folds [77,78]. Rapid urease test is another important invasive test which according to the Maastricht V Consensus Report is recommended for the diagnosis of *H. pylori* infection, but not for assessing its eradication [72]. Both false-negative and false-positive reactions can occur when using rapid urease test. Thus, false-negative reactions might occur in the setting of low-bacterial colonization (<10^4 bacterial cells), evaluation of gastric biopsy from areas with atrophy, metaplasia of recent hemorrhagic ulcers, but also after recent antibiotic use or bismuth, proton pump inhibitors and H_2-receptor agonists [79–81]. Although less common, false positive reactions appear usually when other urease-producing bacteria colonize the gastric mucosa such as *Proteus mirabilis*, *Streptococcus salivarius*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Enterobacter cloacae*, and *Staphylococcus capitits* [81–83]. The specificity of rapid urease test reaches up to 95-100%, while its sensitivity might be as high as 85-95% [79,84]. Histopathological exam from gastric biopsy specimen is used for the primary diagnosis of *H. pylori* infection when upper endoscopy is required [76]. Although the sensitivity of the histopathological exam depends on several factors such as the quality, size, location, the stain used, and frequency of the biopsy varying between 50-95%, the specificity is very high, reaching even 100% [81,85]. Moreover, histopathological exam is extremely useful in diagnosing precancerous lesions like intestinal metaplasia and atrophic gastritis [86]. The culture performed from gastric biopsy provides important information concerning the biological, morphological, and biochemical properties of *H. pylori*, and at the same times enables the determination of antibiotic resistance patterns [79]. Similar to the histopathological exam, culture has a specificity between 50-90%, and a specificity of 100% [87,88]. False negative reactions are usually related to host and environmental factors such as alcohol consumption, upper gastrointestinal bleeding, low bacterial density, and proton pump inhibitors, H_2-receptor agonists or antibiotic intake; but also poor sample quality, delayed transport of biopsy samples or inadequate transportation by exposing the biopsy sample to aerobic conditions, issue related to method, and microbiologist's lack of experience [79]. The limitations of culture include laborious processing involving strict transportation condition for the preservation of the bacterium in a viable state, high costs related to special laboratory equipment and reagents, microaerophilic conditions consisting in an oxygen content below 5% [76].

Urea breath test is recommended for the diagnosis of *H. pylori* infection in both children between 3 and 11 years of age, and adults [73,89], but at the same time this test might be useful for monitoring the eradication of this infection after minimum 4 weeks after treatment completion [72]. The test is also suitable for patients who underwent gastrectomy, and those who were recently administered antibiotics or proton pump inhibitors [90]. Albeit, urea breath test has a very good specificity, even of 100%, the sensitivity varies depending on the patients age, between 93.5-95% in children below the age of 6 years, and 96.6-97.7% in children above 6 years [91]. Serology tests have several advantages such as a high accuracy for detecting *H. pylori* infection in children under the age of 12 years [92], wide availability, low costs, they do not require special equipment [86], and they are not influenced by recent treatment with proton pump inhibitors, antibiotics, bismuth compounds, atrophic gastritis and gastrointestinal bleeding [72]. However, these tests are not useful for primary diagnosis of *H. pylori* infection, but rather for the screening of this infection [93]. Several studies pointed out that serology test present a specificity between 79-90% and a sensitivity between 76-80% [76,94]. Stool antigen-based tests are recommended for both primary diagnosis and eradication monitoring due to their increased specificity (97.6%) and sensitivity (95.5%) [79,95]. These tests have also further advantages like easy-to-use and rapidity and low cost, but they should be avoided in patients with watery stools or acute diarrhea [94]. Moreover, they should not be used earlier than 4 weeks after the completion of antibiotics and bismuth therapy, and 2 weeks after treatment with proton pump inhibitors [94]. However, false negative results might occur in patients with constipation, low bacterial load, persistent gastrointestinal hemorrhage, and ununiform distribution of antigen in the sample [94,95].

Molecular tests, either invasive or non-invasive although a very good alternative, are not commonly used in practice for the diagnosis of *H. pylori* especially due to their related high costs [86].

TREATMENT

Multiple issues emerged recently in terms of *H. pylori* eradication due to the wide-spectrum of antimicrobial resistance as a result of non-judicious antibiotic use for several other pathologies. The guidelines recommend the use of standard triple therapy for the eradication of *H. pylori* infection consisting in two antibiotics such as amoxicillin and clarithromycin or metronidazole in combination with a proton pump inhibitor [96,97]. The length of antibiotic treatment is usually 10-14 days, while the proton pump inhibitor should be administered for 30 days. Although the efficacy of this therapy was more than 90% in the 1990s, it decreased recently to led than 70% mainly due to the increased number of resistant *H. pylori* strains to the most commonly used antibiotics like clarithromycin and metronidazole, but even to levofloxacin [98,99] [49,50]. Therefore, recent study focused more and more on assessing the role of probiotics in eradicating *H. pylori*.

It is worth mentioning that aside from the standard triple therapy, experts proposed lately several eradication strategies such as bismuth quadruple therapy consisting of metronidazole, tetracycline, and bismuth associated with a proton pump inhibitor for 14 days [100]; non-bismuth quadruple concomitant therapy involved amoxicillin, metronidazole, and clarithromycin along with a proton pump inhibitor for 10-14 days [101]; sequential therapy includes 5 days of amoxicillin, which will be further associated with clarithromycin and metronidazole for the next 5 days combined with a proton pump inhibitor during all the 10 days [5]; and hybrid therapy which recommends the use of amoxicillin associated with a proton pump inhibitor for 7 days followed by the combination between amoxicillin, metronidazole, clarithromycin and a proton pump inhibitor for another 7 days [101]. Another option proposed by several studies is represented by the replacement of clarithromycin with levofloxacin [62], but it is usually recommended as a second-line regimen in the setting of resistance to either clarithromycin or metronidazole [68].

The effect of probiotics in eradicating *H. pylori* infection is not yet fully understood, but it was proven so far that although they do not have the ability to eradicate this infection, they are extremely useful in diminishing antibiotic-associated side effects like diarrhea, abdominal distention or taste disorders [101]. Moreover, several studies proved that if added to the standard triple therapy, they increase the eradication rate [101].

CONCLUSIONS

H. pylori remain a complex infection with a multi-systemic impact and long-term life-threatening complications. Thus, the advances regarding the diagnosis of treatment should be updated in clinical practice in order to provide the best outcome for each patient. In terms of pediatric patients, these advances are even more challenging since the effective early eradication of this infection remains the cornerstone in the prevention of gastric cancer during adulthood.

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