Update in Pathophysiology and Management of *Helicobacter pylori* in Children

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Abstract: Objective: The aim of this study is to review *Helicobacter pylori* in children describing its epidemiology, pathophysiology, clinical presentations and management**. Data summary** *Helicobacter pylori* is one of the most common chronic bacterial infection worldwide. *Helicobacter pylori* infection is the main etiological factor for chronic gastritis, most peptic ulcers and gastric adenocarcinoma and lymphoma. Recently a potential role of *Helicobacter pylori* in other gastrointestinal as well as several extra-intestinal pathologies is being evaluated. Standard triple therapy should be abandoned in areas of high clarithromycin resistance. **Conclusion:** Several diseases have been reported to be associated with Helicobacter pylori infection. Its role in some hematologic conditions has been fully validated and included in the current guidelines. Further studies are still needed to evaluate the role of Helicobacter pylori in other diseases. Choice of the diagnostic test for each patient depends on several factors. Clarithromycin is critically important as it negatively impacts the efficacy of the chosen therapeutic regimen.

Keywords: Helicobacter pylori, children, pathophysiology, management.

1- Introduction

Helicobacter pylori (*H. pylori*) is a micro-aerophilic, Gram negative, slow-growing, spiral-shaped, and flagellated organism .It infects more than half of the world's human population. *H. pylori* colonization itself does not cause any symptoms. Approximately 10% of infected individuals develop peptic ulcer disease, 1% to 3% develop gastric adenocarcinoma, and less than 0.1% develop mucosa-associated lymphoid tissue (MALT) lymphoma. The role of *H. pylori* in other gastrointestinal diseases is widely debated[1].

Several diseases from outside of the gastrointestinal tract have been associated with *H. pylori* infection. It has a proven role in some hematologic conditions, such as immune thrombocytopenic purpura, idiopathic sideropenic anemia, and vitamin B12 deficiency and is included in the current guidelines .Its association with other diseases still needs further evaluation [2].

Diagnostic methods to detect *H. pylori* infection are diverse and classified as invasive and non-invasive. The choice of one method or another depends on several factors, such as the availability of diagnostic tests, need to perform an endoscopy, cost, accessibility, advantages and disadvantages of each method and age of patient [3].

Triple therapy is the standard treatment for *H. pylori*. Clarithromycin resistance is the major cause of eradication failure of the standard triple therapy.

It should be abandoned in areas of high clarithromycin resistance [4].

Objectives

The aim of this study is to review *H. pylori* in children describing its epidemiology, pathophysiology, clinical presentations and management**.**

Data summary

Data source

Data were obtained from previous literatures, reviews and studies as well as medical websites (PubMed) and scientific journals.

Study selection

Selection was performed by supervisors for the study of the update in pathophysiology and management of *Helicobacter pylori* infection in children.

Data extraction

In this review, data from published studies were manually extracted and summarized.

Data synthesis

In this review, the data indicated that several studies of *H. pylori* pathophysiology, clinical presentations and management were included. There are different presentations and different regimens for management. We obtained our data by studying the different clinical presentations and recent approaches and recommendations for its management.

Bacteriology

Helicobacter pylori were 1st observed more than 100 years ago and their association with gastritis has

been recognized since the 1970s. The true implication of these microbes was not fully realized until 1982, when Marshal and Warren identified and subsequently cultured the bacterium, *Campylobacter pyloridis*, later reclassified as *Helicobacer pylori*. In recognition of their very important discovery, they were awarded the 2005 Nobel Prize for medicine and physiology [1].

H. *pylori* is a spiral shaped, slow growing, microaerophilic gram negative bacterium measuring 3.5 micron in length and 0.5 micron in width .*In vitro* it is a slow growing organism that can be cultured on blood agar or selective media such as Skirrow's media, incubated at 37C° in 5% oxygen atmosphere for 3 to 7 days. Small uniformly sized, translucent bacterial colonies form and the organisms can be morphologically characterized by Gram stain and their typical spiral or rod shaped appearance .High power microscopy reveals that the organism has two to seven unipolar sheathed flagellae which enhance its motility through viscous solutions. The organism biochemically characterized as catalase, oxidase and urease positive [5].

Epidemiology

H. *pylori* is the most common chronic bacterial infection in human. Conservative estimates suggest that 50 percent of the world's population is affected .Infection is more frequent and acquired at an earlier age in developing countries compared with industrialized nations .The risk of infection acquisition is related to socioeconomic status and living condition early in life. Hereditary susceptibility hasn't been proven yet, however some studies suggest that members of certain ethnic and racial groups have a higher rate of infection that is not entirely explained by socioeconomic differences [1].

Transmission of H. *pylori* is still not entirely clarified. Human to human spread through oral-oral or fecal –oral route is thought to be the most plausible. Humans appear to be the major reservoir of infection, however H. *pylori* has been isolated from primates. Intrafamilial clustering of infection support person to person transmission .Infected individuals are more likely to have infected spouses and children. Organisms have been identified in dental plaque, but it is not known if the dental plaque can serve as a source or reservoir of infection [6].

Pathophysiology and immune response to H. pylori

Although H. *pylori* doesn't invade the mucosa, it renders it vulnerable to acid damage by disrupting the mucous layer , liberating enzymes and toxins and adhering to gastric epithelium ,in addition to the host immune response and inflammatory reaction . The chronic inflammation leads to changes of the gastric acid secretory physiology and chronic gastritis that is

asymptomatic and does not progress in most cases . In some cases altered secretion coupled with tissue injury leads to peptic ulcer disease, while in other cases progresses to gastric atrophy, intestinal metaplasia and gastric carcinoma or rarely due to persistent immune stimulation of gastric lymphoid tissue to gastric lymphoma [7].

Certain Helicobacter pylori virulence factors and host genetic polymorphism are known to affect the clinical outcome of H. *pylori* infection .Functional differences of different *Helicobacter pylori* strains lead to virulence differences. All H. *pylori* strains contain the gene coding for Vac A, however only those strains that encode the Cag A pthogenitcity island PA1 co express VacA. Strains producing Vac A and CagA cause more intense tissue inflammation and cytokine production [8].

Diseases related to H.pylori

The life time risk of H. *pylori* related disease is less than 20 percent . Up to 85 percent of infected individuals never experience symptoms or complications . Individuals infected with H. *pylori* have approximately 10 percent life time risk of developing peptic ulcer, 1-3 percent risk of acquiring gastric adenocarcinoma and less than 0.1 percent to develop gastric mucosa associated lymphoid tissue lymphoma [8].

Recently a potential role of H. *pylori* in other gastrointestinal diseases , such as gastroesophageal reflux disease (GERD), non ulcer dyspepsia and recurrent abdominal pain (RAP) in children as well as several extra- intestinal pathologies, such as iron deficiency anaemia (IDA), growth retardation, idiopathic thrombocytopenic purpura (ITP), asthma and other allergic disorders is being evaluated [9].

Gastrointestinal manifestations

Acute H.pylori gastritis:

Despite the high prevalence of H. *pylori* and chronic H. *pylori* gastritis, few examples of spontaneous acute infection are diagnosed. The initial infection usually produce no symptoms. Even those who develop dyspeptic symptoms or mild illness consisting of epigastric pain, nausea and vomiting are not immediately investigated for the cause [10].

Chronic H. pylori gastritis

It affects two third of the world's population .It is one of the most common chronic inflammatory disorders of human being. The condition is usually asymptomatic. The usual natural history of H. *pylori* gastritis is of an antral predominant early stage that is associated with exaggerated gastrin release and reduced somatostatin release This precipitates an increase in acid secretion enough to cause duodenal ulcer in some patients. With continued inflammation, gastrin and acid producing cells are gradually lost precipitating fall in acid secretion and the

development of atrophy and intestinal metaplasia. This scenario is accelerated with chronic proton pump inhibitors (PPIs) therapy [10].

Peptic ulcer

Peptic ulcer disease is the most common pathology associated with *H. pylori* infection, the life time risk is approximately 10%. The majority of patients with duodenal ulcer are infected with *H. pylori*, however it was found to be absent in almost 30 % of patients with documented duodenal ulcer and these patients were found to have shorter symptoms and had history of NSAIDs use . Eradication of *Helicobacter pylori* prevent DU recurrence and bleeding .The pathogenesis of ulcer formation includes different mechanisms such as, increased acid secretion, gastric metaplasia, ,increased production of inflammatory cytokines and down regulation of several important mucosal defense factors [11].

Gastric cancer

The international agency for research on cancer (IARC) declared *H. pylori* as a group 1 human carcinogen for gastric adenocarcinoma. Despite the clear association between Helicobacter pylori and gastric adenocarcinoma, only a minority of infected individuals will develop gastric cancer after long period of persistent infection .Eradication of *H. pylori* appears to reduce the risk of gastric cancer in high risk populations, but even if treatment reduces the risk, difficulties with screening and treating would be large given the worldwide prevalence of *H. pylori* [12].

Mucosa associated lymphoid tissue lymphoma (MALT)oma.

It occurs commonly in middle and old age. Only small number of cases have been reported in both immune competent and immune compromised children. The clinical manifestations includes epigastric pain, anorexia, weight loss, haematemesis and melena. The most dramatic evidence supporting a pathogenic role for *H. pylori* in MALT oma is remission of the tumor following eradication with antibiotic therapy [13].

Functional dyspepsia and recurrent abdominal pain

The role of *H. pylori* infection as a cause of non- ulcer or functional dyspepsia was one of the most debated controversies in the medical community. Currently test-and-treat strategy is appropriate for uninvestigated dyspepsia in high prevalence populations. Urea breath test and stool antigen testing are acceptable non-invasive tests for *H. pylori* infection in this setting. This approach is subject to local cost benefit considerations and not applicable to patients with alarm symptoms, or older patients. Recurrent abdominal pain (RAP) is not an indication for a test and treatment strategy. Most previous studies found no association between RAP and *H. pylori* infection in children [14].

Gastroesophageal reflux disease

The interaction between *H. pylori* infection and gastroesophageal reflux disease (GERD) has been widely debated. *H. pylori* has been found to be inversely correlated to the prevalence and severity of GERD and its consequences. Certain studies have shown aggravation of esophagitis after eradication .The suggested mechanisms include presence of atrophic or significant body gastritis that lead to post-eradication increase in acid output, decreased buffering by the organism and masking of reflux by acid neutralizing medications given for *H. pylori* related diseases eradication [15]**.** Other studies failed to find any association between *H. pylori* eradication and aggravation of reflux disease [16].

The risks and benefits of *H. pylori* eradication are less well defined and the risks are outweighed by those of continued *H. pylori* infection especially in children who are the target for preventive eradication of *H. pylori* [9].

The current conclusions include that in spite of this confirmed inverse relationship, *H. pylori* status has no effect on symptom severity or recurrence and treatment efficacy in GERD. *H. pylori* eradication doesn't exacerbate the disease [14].

Extra gastrointestinal manifestations

Epidemiological studies have also revealed a correlation between *H. pylori* infection and some diseases localized outside the stomach. In addition to its role in some haematologic conditions such as, immune thrombocytopenic purpura(ITP), iron deficiency anaemia (IDA) and vitamin B12 deficiency which were included in the current guidelines, several other conditions such as, growth retardation in children ,asthma and other allergic diseases, cardiovascular disorders, diabetes mellitus ,hepatobiliary and neurologic diseases have also shown promising results [17].

Iron deficiency anemia

In the last two decades an association between *H. pylori* and pediatric IDA has been established especially unexplained or refractory IDA .It was also concluded that eradication of *H. pylori* leads to improvement of iron stores and anemia. A strategy of population based screening and treatment of *H. pylori*to prevent IDA is not recommended .Currently eradication of *H. pylori* is indicated in cases that are refractory to iron supplementation and in the case of frequent relapses assuming that other causes have been excluded [18].

Immune thrombocytopenic purpura (ITP)

Following an association with *H. pylori* was reported, a note of considerable improvement of platelet count after *H. pylori* eradication has been

observed. Screening patients with ITP is now recommended [17].

Growth retardation

The available evidence regarding *H. pylori* infection and its effect on growth parameters in children is controversial and still needs further evaluation. Some investigators evaluated the relationship between *H. pylori* infection and growth parameters. They concluded that symptomatic infection does not appear to influence linear growth [19] .

Other cross-sectional studies proved the positive association between *H. pylori* infection and growth retardation despite similar socioeconomic status between *H. pylori* positive and negative cases .The mechanisms suggested to explain *H. pylori* effect on growth parameters include *H. pylori* associated dyspepsia, the chronic effect of systemic inflammatory mediators and the low plasma ghrelin level associated with *H. pylori* infection [20].

Bronchial asthma

The associations between *H. pylori* and asthma were contradictory. Further studies are still needed to test the strength of association between *H. pylori* status and asthma risk. A meta-analysis found that asthmatic patients have a significantly lower prevalence of *H. pylori* infection than controls [21]. In other studies the negative association between *H. pylori* and asthma is reported to be weak [22].

The lack of *H. pylori* early exposure has been suggested to be an important determinant of asthma risk in childhood .An infection in the early phase of life is essential for the normal maturation of the immune system, and achieving a balance between T helper type 1 (protective immunity) and T-helper type 2 (allergic diseases) . [23].

Investigations

Diagnostic testing can be divided into invasive (rapid or biopsy urease test, histology and bacterial culture and sensitivity) and non- invasive (urea breath test, stool antigen test and serology) techniques. The choice of a suitable test depends upon different factors such as cost, availability, clinical situation, population prevalence of infection, pretest probability of infection and other factors such as the use of PPI and antibiotics that may influence certain test results [3].

Testing is indicated in patients with active peptic ulcer or past history of documented ulcer, gastric MALT lymphoma, pathologically proven gastric atrophy, metaplasia and gastric adenocarcinoma. Test and treat strategy is indicated for uninvestigated dyspepsia under age of 55 with no alarm signs. Other indications include asymptomatic individuals with a family history of gastric cancer, patients on long term PPIs , prior to long treatment

with NSAIDs, in ITP , Unexplained or refractory IDA and vit B12 deficiency [14].

Testing for *H. pylori* is not justified by current evidence in functional abdominal pain, otitis media, upper respiratory tract infections, periodontal disease, food allergy, SIDS and short stature [9].

PPIs or antibiotics should be stopped at least two and four weeks respectively before testing by culture, histology, rapid urease test,urea breath test (UBT),or stool antigen test (SAT). If it's not possible validated IgG can be performed. UBT is the most commonly used non- invasive test for children although it has some limitations in children under five years [3].

The diagnostic accuracy of (SAT) is equivalent to UBT, if a validated laboratory based monoclonal test is used. Serological tests can't be used alone to diagnose *Helicobacter pylori* infection or to monitor for eradication .Culture and sensitivity testing is mainly beneficial for patients with refractory infection not responding to first and second lines therapies .The optimal time to test for eradication therapy success should be at least 4 weeks after the end of treatment [24].

Treatment

The goal of *H. pylori* treatment is complete elimination of the organism. Once this is achieved, re-infection rates are low, thus the benefit of treatment is durable. The main reasons for eradication failure of *H. pylori* infection include antibiotic resistance, poor compliance and rapid metabolism of PPIs.[4].

Clarithromycin resistance is the major cause of eradication failure of the standard triple therapy .The eradication rate of standard triple therapy is 88% in clarithromycin sensitive strains versus 18% in clarithromycin resistant strains, therefore the background of clarithromycin resistance is critically important as it negatively impacts the efficacy of standard triple therapy**.** A systemic review showed that the rate of clarithromycin resistant strains ranged from 49% (Spain) to 1% (Netherland) world wide [25].

With the rising prevalence of antimicrobial resistance, the treatment success of standard triple therapy has recently declined to unacceptable levels in most countries. Several treatment regimens have been evaluated for *H. pylori* eradication. These regimens are classified into three lines [26]

Novel first-line anti- *H. pylori* therapies include sequential therapy, concomitant quadruple therapy, hybrid (dual-concomitant) therapy and bismuth-containing quadruple therapy. After failure of standard triple therapy, a bismuth-containing quadruple therapy comprising a proton pump inhibitor (PPI), bismuth, tetracycline and

metronidazole can be employed as a rescue treatment. Recently, triple therapy combining a PPI, levofloxacin and amoxicillin has been proposed as an alternative to the standard rescue therapy [4].

In areas of high clarithromycin resistance, bismuth containing quadruple treatments are recommended for first line empirical treatment. IF this regimen is not available sequential treatment or non bismuth quadruple treatment is recommended [14].

Most guidelines suggest that patients requiring third-line therapy should be referred to a medical center and treated according to the antibiotic susceptibility test .Alternatively, an empirical therapy such as levofloxacin-based or furazolidone-based therapies can be employed to terminate *H. pylori* infection if antimicrobial sensitivity data are unavailable [25].

Certain probiotic and prebiotic show promising results as an adjuvant treatment. It reduces side effects of the therapeutic drugs and increases the eradication rate of different regimens [26].

Preventive measures should be aimed at interrupting *H. pylori* transmission. Public health efforts have to be directed towards achievement of acceptable standards of living conditions and environmental sanitation including safe drinking water, proper sewage disposal and education programmes for personnal hygienic practice giving special importance for hand washing [6].

Discussion

H. pylori is the most common chronic bacterial infection in humans. Conservative estimates suggest that 50% of the world's population is affected . Higher prevalence rates are present in developing countries due to lower socioeconomic conditions . Most infections are acquired during childhood .Person to person transmission of *H. pylori* through either fecal-oral or oral-oral is the most likely route of infection [6].

H. pylori infection causes chronic gastritis which is mostly asymptomatic in the majority of carriers but is considered a risk factor for the development of peptic ulcer and the two gastric malignancies, mucosa associated lymphoid tissue lymphoma and gastric adenocarcinoma [27].

Screening children with a positive family history of gastric cancer for *H. pylori* is indicated. Screaninig and treatment of *H. pylori* for gastric cancer prevention is recommended in high risk populations [14].

Recurrent abdominal pain is not an indication for a test and treatment strategy. The current recommendation regarding non ulcer dyspepsia and *H. pylori* states that a test-and-treat strategy is appropriate for uninvestigated dyspepsia in high prevalence populations .This approach is subject to local cost benefit considerations and is not applicable to patients with alarm symptoms, or older patients [14].

The relation between *H. pylori* infection and GERD is a matter of controversery and further studies are still needed in this aspect. *Yaghoobi et al.* [15] have shown aggrevation of esophagitis after eradication of *H. pylori.* Another study of *Elitsur et al.*[16] failed to find any association between *H. pylori* eradication and aggrevation of reflux disease . The current recommendations include that in spite of the confirmed inverse relationship between *H. pylori* and GERD, *H. pylori* status has no effect on symptom severity , recurrence or treatment efficacy in GERD . *H. pylori* eradication doesn't exacerbate the disease [28].

Many associations between extra gastrointestinal diseases and *H. pylori* have been studied. Currently ITP, unexplained or refractory IDA and vitamin B12 deficiency are the only extra gastrointestinal indications for *H. pylori* testing and eradication [28].

Further studies are still needed to reveal the role of *H. pylori* infection as a risk of asthma .A meta-analysis of *Zhou et al.* [21] found that asthmatic patients have a significantly lower prevalence of *H. pylori* infection than controls. In other studies such as that of *Wang et al.* [22] the negative association is reported to be weak.

The available evidence regarding *H. pylori* infection and its effects on growth parameters is controversial and still needs further evaluation. *Dehghani et al.* [19]

Evaluated the relationship between *H. pylori* infection and growth parameters. They concluded that symptomatic infection does not appear to influence linear growth .Other cross-sectional study of *Gulcan et al.* [20] proved the positive association between *H. pylori* infection and growth retardation despite similar socioeconomic status between *H. pylori* positive and negative cases .

The choice of a suitable test depends on different factors such as cost, availability, clinical situation, population prevalence of infection, pretest probability of infection and other factors such as the use of PPI and antibiotics that may influence certain test results [29]. UBT is the most commonly used non- invasive test for children. The diagnostic accuracy of (SAT) is equivalent to UBT, if laboratory based monoclonal test is used [3].

Clarithromycin resistance is the major cause of treatment failure of *H. pylori*. Choice of a certain regimen should be based on the local rate of clarithromycin resistance. Treatment success of standard triple therapy has recently declined to

unacceptable levels in most countries, therefore several treatment regimens have been evaluated for *H. pylori* eradication. The available regimens are classified into three lines of therapy [26].

Conclusion

Preventive measures should be aimed at interrupting *H. pylori* transmission. The primary goal of clinical investigation for gastrointestinal problems is to determine the underlying cause of the symptoms and not solely the presence of *H. pylori*. Test and treat strategy is not recommended in children with recurrent abdominal pain, while it is appropriate management for non - ulcer dyspepsia with no alarm symptoms. Screening for *H. pylori* status is now recommended in cases of unexplained and refractory IDA, in cases of ITP,andvit B12 deficiency. *H. pylori* role in several other diseases still needs further evaluation. The background rate of antibiotic resistance mainly to clarithromycin is critically important as it negatively impacts the efficacy of the chosen therapeutic regimen.

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