Helicobacter Pylori Infection in Children

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Abstract

*H. pylori* is a widely prevalent and important component of gastric microbiology. It is usually acquired in childhood. It is more common in poorer sections of society, especially of developing countries. It can cause peptic ulcer disease and dyspepsia. It is a potent carcinogen responsible for gastric adenocarcinoma and gastric lymphoma. *H. pylori* infection should be suspected in children with history suggestive of hyperacidity and in those who have a first-degree family member with gastric cancer. Diagnosis relies on endoscopy and biopsy. Non-invasive tests on breath, stool, serum, urine, and saliva can also diagnose *H. pylori* infection reliably. Treatment in children involves a triple regimen comprising of proton pump inhibitor or bismuth compounds with either two antibiotics or one antibiotic and an imidazole. This eradicates the organism in >90% of the patients. The above tests may need to be repeated to confirm on clearance of the bacterial infection. Awareness of *H. pylori* infection is vital due to its high rate of colonization and risk of gastric malignancies.

Introduction

*Helicobacter pylori* (*H. pylori*) is an important pathogen of paediatric gastroenterology [1, 2]. They are acquired in early childhood [3-7], and are more common in socially deprived people of the developing countries [2, 8, 9]. More than half of the world’s population is infected with this bacteria [10, 11]. Infection rates are similar in both sexes, though some studies have noted a slight male predominance [2]. Prevalence increases with age and it is more common in Asians and Africans [2, 11-13]. The clinical implication of this infection in children is still in the evolution phase. *H. pylori* infection in children differs from that in adults in its prevalence, presence, site and degree of gastric/duodenal inflammation, lesser likelihood of gastric malignancies, problems in diagnosis and higher rate of antibiotic resistance [14].

History

*H. pylori* is a gram-negative helical microaerophilic flagellated bacterium found in the sterile gastric mucosa of majority of the world’s population [15]. Bacterial presence in stomach was known as early as in the late 19th century. However these were dispelled as contaminants from digested foods rather than true colonizers [10, 16]. It was only 3 decades back that there was renewed interest in the microbiology of the stomach with the discovery and successful isolation and culture of the *H. pylori* (formerly called *Campylobacter pylori*) [17-19]. Further research showed that these organisms caused a variety of gastrointestinal disorders such as chronic/atrophic gastritis, peptic ulcer disease, gastric non-Hodgkin’s lymphoma and gastric adenocarcinoma [10].

Prevalence

*Helicobacter pylori* prevalence varies depending on the geographic region, age, race, ethnicity and socio-economic status of individual. *Helicobacter pylori* reside in more than 80% of the stomach of people in the developing world and 40% of those in the western world. High prevalence has been found in general population from Bangladesh, Brazil, Russia, Mexico and Korea. It has also been noted to be high in institutionalized adults from UK and other countries [20-26]. The lowest reported has been in Czech Republic at 7.1% in children < 15 years of age [27]. Decline in prevalence has been noted in the Western figures. The number of people colonized is inversely proportional to the socioeconomic status, and increases with age [28, 29].

Microbiological characteristics

*H. pylori* belongs to the genus Helicobacter, family Helicobacteraceae, order Campylobacterales, and ? subdivision of Proteobacteria. It is an S-shaped gram-negative rod measuring 2-5 μm in length and 0.5-1 μm in width. It has 1-3 turns but acquires rod or coccoid shape with prolonged in vitro culture or after antibiotic therapy [30-32]. The coccoid forms are considered as dead cells, but some believe that they are viable but nonculturable bacilli [33]. This helical organism is motile by means of 2-6 sheathed unipolar flagella; about 3 μm long with a bulb at the end [34]. Unlike most enteric bacteria, *H. pylori* lacks fimbrial adhesions. Its cell envelope consists of an outer and
inner plasma membranes separated by a 30 nm thick periplasm. The dense cytoplasm contains nucleoid material, ribosomes and intracellular polyphosphate granules [35, 36]. Cytoplasmic aggregates containing iron are present in these bacteria and they represent tools for survival during inhospitable circumstances [37].

_H.pylori_ requires low oxygen concentrations of 2-5%, 5-10% CO₂, high humidity, 37°C temperature and neutral pH for optimal growth. It is fastidious requiring complex blood or serum supplemented growth media [10]. Columbia or brucella agar supplemented with lysed horse or sheep blood or fetal or newborn calf serum is routinely used solid media for culture and isolation. Brucella, Mueller-Hinton or brain heart infusion broth enriched with 2-10% calf serum or 0.2-1.0% α-cyclodextrins are the liquid growth media recommended. 98-100% humid conditions are provided to the media. The specimen needs to be cultured for at least 14 days and _H.pylori_ forms small, smooth, translucent colonies [38]. It is urease, catalase, and oxidase positive. _H.pylori_ can metabolize glucose but not other sugars [10, 39-41]. Due to the enzyme urease, it can degrade urea forming ammonia and bicarbonate which facilitates its survival and growth in the acidic gastric environment. These neutralise the gastric pH and are cytotoxic for the gastric cells. _H.pylori_ can withstand short periods of exposure to pH < 4 [42, 43]. Its motility and abundance of urease enzyme assists its penetration into the gastric mucus layer.

### Transmission and pathogenesis

The exact route of transmission of _H.pylori_ remains elusive. But it is believed to spread via direct human-to-human transmission through oral-oral, feco-oral or both routes. _H.pylori_ is present in saliva, vomitus, gastric reflux material and stools of infected individuals and non-human primates [44-47]. Overcrowding is a risk factor for acquisition of _H.pylori_ infection in children [48, 49]. Contaminated water and food also act as sources of infection [50, 51]. But since _H.pylori_ cannot withstand high oxygen, high temperatures and paucity of nutrients in the environment, it does not remain viable in inhospitable conditions. Hence direct person-to-person transmission is thought to be still the main mode of transmission of this infection in children [10].

Colonization by _H.pylori_ does not imply disease but its presence increases lifetime risk of the child getting peptic ulcer disease or gastric cancer by 10-20% and 1-2% respectively [52-55]. This risk is dependent on a complex interplay between bacterial, host and environmental factors. _H.pylori_ is able to withstand the hostile acidic milieu of the stomach due to its urease-secreting capacity. Their spiral structure and flagellae assist in their movements into the neutral gastric mucus layer. Here they induce an inflammatory process of Th1 type; involving neutrophiles, mononuclear cells, and T-helper 1 cells [56]. They initially cause acute gastritis and hypochlorhydria, followed by chronic gastritis and/or atrophic gastritis [57, 58]. The infection may resolve [59] or progress to peptic ulcer disease. Studies carried out in the developed world have shown that eradication of _H. pylori_ reduces risk of recurrence in peptic ulcer disease [10, 60]. With increasing time, there is loss of normal gastric mucosa architecture, destruction of gastric glands, epithelial cell damage, fibrosis, DNA damage, mutations, and intestinal metaplasia and dysplasia [61]. These effects could lead to gastric adenocarcinoma [62-64]. Risk of gastric cancer is elevated 10 times and hence _H.pylori_ has been labelled as a class I carcinogen by World Health Organization [65]. When one clone of B cells proliferates, gastric lymphoma ensues [10, 66].

### Clinical features

_H.pylori_ is usually acquired during early childhood [67]. It may be asymptomatic. Even in cases with histologically proven chronic gastritis, symptoms may be lacking [10]. In some, it gives rise to symptoms of peptic ulcer disease or its complications [54]. There may be non-ulcer dyspepsia, or refractory iron-deficiency anemia [68-70]. In long-standing cases, gastric cancer or lymphoma may be seen [62, 66]. The symptoms result due to the complex, less understood interaction between the bacterial, host and environmental factors. Child's stature and weight is usually not affected due to _H.pylori_ colonization but there may be anorexia and weight loss due to peptic ulcer disease [71]. A number of extragastrointestinal disorders such as coronary artery disease, idiopathic urticaria, rosacea, scleroderma, otitis media, upper airway infections, periodontal disease, food allergy, sudden infant death syndrome, idiopathic thrombocytopenia, short stature, autoimmune diseases, Raynaud’s phenomenon, migraine, and Guillain-Barre syndrome have been thought to be due to _H.pylori_ infection [10, 72, 73]. Various mechanisms have been postulated for this association. But more randomized studies are needed.
to confirm the role of *H. pylori* in these disorders [14, 74-76]. However in case of idiopathic thrombocytopenic purpura, the association is more or less confirmed in adults due to the fact that eradication of *H. pylori* was found to improve thrombocyte counts [77-79]. However in children this cause-effect relationship has yet not been proven. Recent studies in mice have shown that *H. pylori* infection can protect against asthma. Overuse of antibiotics has abolished this ancestral, native microflora leading to immune upset and asthma [80].

**Diagnosis**

A multitude of tests can be used to diagnose presence of *H. pylori* in the stomach. Invasive endoscopy and culture, histopathology, rapid urease test, polymerase chain reaction (PCR) or fluorescence in-situ hybridization (FISH) is feasible in children and is considered the gold standard for diagnosis of *H. pylori* infection [81-85]. Culture of the bacteria from biopsied gastric tissue has 100% specificity but its sensitivity is lower. 2 of 3 of the above tests performed should be negative to rule out *H. pylori* infection. Urea breath test is the alternative non-invasive gold standard for diagnosis of *H. pylori*. It is safe, reliable and useful with specificity and sensitivity of >95%. However, it needs patient cooperation hence it is not possible in infants, toddlers, and in some children with special needs. Instrument required is also expensive. In this, patient is made to swallow urea labelled with isotope C$^{13}$ or C$^{14}$. Urea is broken down by urease of *H. pylori*, CO$_2$ is released and excreted through the breath. Measurement of labelled CO$_2$ before and 20-30 minutes after urea ingestion is performed. The difference gives an indication about presence of gastric *H. pylori* [86]. The above two tests could also be used to evaluate success of eradication of *H. pylori* after treatment. Fecal antigen test detects *H. pylori* antigen in stool of patient [87]. It is also a simple, non-invasive and reliable test. It however cannot be used to confirm success of eradication therapy. Serological testing for antibodies to *H. pylori* has lower specificity and sensitivity and cannot be used for routine screening. It is mainly used for epidemiological surveys. It cannot however be relied on for estimation of success of anti- *H. pylori* therapy due to immunological memory. Saliva could be used for measurement of immunoglobulin G against *H. pylori* non-invasively and this has been found to be quite reliable [88-93]. These tests are indicated in children with history suggestive of peptic ulcer disease, those with first-degree relatives with gastric cancer, and in children with refractory iron-deficiency anaemia where other causes have been ruled out. They are not indicated in children with functional abdominal pain or idiopathic thrombocytopenia [94, 95].

**Treatment**

*H. pylori* is susceptible to a number of antibiotics in vitro but in vivo these fail as monotherapy due to bacterial resistance. Resistance is mainly due to point mutations on the bacterial chromosomes (nonsense, missense, and silent mutations). These may involve various genes such as redox-related genes or 23S rRNA [96]. Clarithromycin can eradicate this infection in 40% of users when taken two times a day for 10-14 days [97, 98]. For better clearence, ‘concomitant’ (standard triple or quadruple) or ‘sequential’ therapies are preferred. This implies combining 2-3 antibiotics with either proton pump inhibitor [PPI] or bismuth salts. Combining PPI with dual antibiotics improves eradication rate from 9.4% to 74.2% [99]. This triple regime is considered as first line therapy in pediatric guidelines for *H. pylori* [94, 100, 101]. PPI+amoxicillin+imidazole or PPI+amoxicillin+clarithromycin or bismuth salts+amoxicillin+imidazole is recommended. In sequential therapy, PPI+amoxicillin for 5 days followed by PPI+clarithromycin+imidazole for 5 days are used. However, failing clearance rates have been reported with this recommended treatment either due to non-compliance due to adverse effects and/or due to antibiotic resistance [102, 103]. In such cases, susceptibility testing guided therapy is effective and cures >90% of children treated [104-108]. Therapies may need to be individualized based on age, other demographic parameters and host polymorphisms. Use of probiotic, *Saccharomyces Boulardi* could serve as a useful adjunct to antibiotic therapy [109, 110].

PPI decreases gastric acidity and it aids in bacterial eradication. Mechanism of action of bismuth is unknown but in vivo and in vitro studies have proven it to be effective in eliminating *H. pylori* [111-113]. It is supposed to lyse cell walls, prevent adherence of bacteria to epithelium and inhibit urease enzyme. The antibiotics and imidazole drugs used are bactericidal. Amoxicillin, macrolides [clarithromycin or azithromycin], imidazoles [metronidazole or tinidazole], or tetracycline are employed [114]. Rifabutin and furazolidone are used as second-line drugs in metronidazole-resistant cases [115-119]. Fluoroquinolones such as ciprofloxacin and levofloxacin, rifampin, streptomycin can be used but offer no advantages over the recommended first-line...
antibacterial agents [120-122]. Some studies have shown that bismuth-based therapies are more effective and less costly than PPI-based therapies [102]. However, unpleasant taste and unpalatability of bismuth raises concern about the compliance of bismuth-based therapies and hence its ultimate clearance rates. Longer duration of therapy enhances eradication rates in children [123] (Table 1).

see Illustration 1

A non-invasive test to confirm eradication of *H. pylori* should be done after 4-8 weeks of treatment. In case of failure of therapy, use of different antibiotics, adding bismuth, increasing dose and/or duration helps. Endoscopy and susceptibility studies may be needed to guide therapy.

Besides proper treatment, vaccination could control this infection. Trials on vaccines for prevention are ongoing and have shown promising results. Suitable immunogens, adjuvants and route of immunization could improve outcomes [124-127]. If human trials are successful, it could have important health-related implications.

Conclusions

*H. pylori* colonization is common in pediatric age group. Symptoms due to this though uncommon do occur, and would need proper diagnosis and treatment. The goal of therapy is to eradicate the organism in the first attempt and avoid development of resistance. Adherence to prescribed therapy should be ensured. This would greatly aid in minimising later risk of dysplasia and gastric cancer and gastric lymphoma.

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Illustrations

Illustration 1

Table 1: Dosages of drugs recommended for H. pylori infection:

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxycillin</td>
<td>50 mg/kg/day upto 1 gm two times a day</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>15 mg/kg/day upto 500 mg two times a day</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>1 mg/kg/day upto 20 mg two times a day</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>20 mg/kg/day upto 500 mg two times a day</td>
</tr>
<tr>
<td>Bismuth subsalicylate</td>
<td>1 tablet (262 mg) 4 times a day or 15 ml (17.6 mg/ml liquid) 4 times a day</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>50 mg/kg/day upto 1 gm two times a day</td>
</tr>
<tr>
<td>Ranitidine bismuth-citrate</td>
<td>1 tablet 4 times a day</td>
</tr>
</tbody>
</table>
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