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WJG, 2000 February; 6(1):20-31
World Journal of Gastroenterology
 ISSN 1007-9327

Helicobacter pylori infection

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Subject headings *Helicobacter pylori*, gastritis; Helicobacter infection

IS THERE ANYTHING NEW?

Helicobacter pylori has been for many years a forgotten bacterium, since the first report on this spiral organism dated from the 19th century[1]. As early as in 1906, an association between a spiral organism and gastric carcinom a was suggested[2]. Doenges reported in 1938 that on autopsy not less than 40% of human stomachs were found to be invaded by spiral organisms[3]. In 1940, the therapeutic effect of bismuth in patients with peptic ulcer in the presence of spiral bacteria in the stomach was reported[4]. Then, interest in this bacterium decreased. In 1982, two Australian researchers, Marshall and Warren, rediscovered the microbe[5], and called it at first *Campylobacter pylori*, later *Helicobacter pylori*. Today, the complete genome (1590 genes) of *H. pylori* has been unmasked[6] and published on the internet (http://www.tigr.org), probably paving the way for sequencing the genome of other organisms, including that of humans within a few years[7].

WHY IS *Helicobacter pylori* SO IMPORTANT?

There is unequivocal evidence that *H. pylori* can be considered as a healthcare issue because of the mortality associated with the infection, due to the risk of ulcer bleeding and gastric cancer. Infection with *H. pylori* results in the development of gastritis in all infected humans, including children and adolescents[8]. Peptic ulcer disease is a major cause of morbidity and distal gastric adenocarcinoma, which is the second biggest cancer killer worldwide[9]. However, the majority of infected individuals remain free of symptoms throughout their lifetime; only a small number present with peptic ulcer disease (lifetime risk 15%), and an even smaller proportion will develop gastric neoplasms including (mucosa-associated lymphoid tissue) lymphoma and adenocarcinoma (lifetime risk 0.1%)[10]. Overall, *H. pylori* can be discovered in 92% of children with duodenal ulcers and in 25% of children with gastric ulcers[11]. *H. pylori* infection is contracted primarily in childhood, and infection from childhood appears to enhance the risk for carcinogenesis[12].

ABOUT THE BACTERIUM: VIRULENCE

The microaerophilic, gram-negative, urease-producing *H. pylori* fulfills each of Koch's postulates[8]. In the normal living form, it is a spiral-s haped bacterium, but the coccoid form can also cause lesions. The bacterium colonizes the stomach of man and induces severe mucosal inflammation and a local and systemic immune response. It is capable of changing its membrane potential at external pH from 3.0 to 7.0 in order to maintain a neutral internal pH[13]. Not all *H. pylori* strains are created equally[14]; and not all are associated with clinical symptoms.

Some virulence factors such as urease and flagella are present in all strains and are necessary for pathogenesis and colonization. Flagella, and thus motility, are needed for persistent gastric colonization[15]. The gene FlbA is needed for flagellar expression[16]. Enzymes produced by *H. pylori* have mostly metabolic, antioxidant and toxic properties[17]; most of these are produced by all isolates tested. Urease is required to establish infection, and is located intra and extra-cellularly[15]. It is a nickel-containing metallo-enzyme, consisting of two structural subunits, UreA and UreB[18]. Urease is primarily a cytoplasmic enzyme[19], and hydrolyzes urea to bicarbonate and ammonia, resulting in a net increase in the ambient pH. Ammonia is a nutrient for the bacteria, and causes lesions to the gastric epithelium by many different mechanisms[20]. Surface urease helps protect against acid exposure, but it is as yet unclear why it is found on bacteria deep underneath gastric mucus where the pH is thought to be neutral. Because there is no obvious urease export machinery, it has been suggested that some bacteria undergo autolysis, which released proteins, including active urease are absorbed onto the surface of remaining intact bacteria[19,21]. Urease might function as an adhesin, although this suggestion has also been contradicted[22]. Ureasest imulates the

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Received 1999-05-19 **Accepted** 1999-08-15

release of a variety inflammatory cytokines including interleukin- beta, interleukin-6, tumor necrosis factor-alfa, and chemokines such as interleukin-8[23]. Although the exact mechanism by which urease functions in the pathogenesis of gastric disease remains unclear, it is likely that urease is an important virulence factor.

H. pylori can produce different kinds of phospholipases weakening the hydrop hobicity of the gastric mucous and mucosa. Phospholipase can also generate ulcer ogenic substances[24]. Many other enzymes, such as mucinase, neuraminidase, fucosidase, alcohol dehydrogenase, etc. have been reported[20].

The vacuolating cytotoxin A (VacA) gene is present in all strains, but is only expressed in 50% of *H. pylori* isolates[25]. The vacuolating activity of VacA is increased by exposure to acidic pH values[26]. The vacuoles a re formed by merging of late endosomes and the mechanism causing this has been determined[27]. The VacA gene exhibits different allelic combinations. Strains with the gene s1/m1 have the highest levels of cytotoxic activity; colonize the stomach more densely and are correlated with peptic ulcer, atrophic gastritis and gastric cancer; s2/m2 strains have no toxic activity[20,28].

Other virulence factors, such as "cytotoxic-associated gene A" (cagA)encoded proteins are only found in a proportion of the strains. This might explain why not all strains are associated with clinical symptoms, although both cagA and the s1 vacA allele are unreliable as single markers in determining the risk of deve loping peptic ulcer disease[29]. The cagA protein is a cryptic 128 kDa immunodominant antigen produced by *H. pylori*. CagA is a marker for a larger cluster of genes (40 different genes[20]carried on a pathogenicity island that exhibits variability between strains[30].CagA+ strains produce increased amounts of interleukin 8[30]. Gastric atrophy, duodenal ulceration and gastric carcinoma are more common in patients infected with CagA+ than with Cag A-strains[31]. CagA negative strains are very rare in some Far East countries such as China and Korea but frequent in some other areas such as Hong Kong, and are reported to be not a marker of specific disease in these regions[32]. However, allelic variations in the cagA protein are found in different parts of the world. In Western countries, cagA positive strains are associated with gastric atrophy and peptic ulcer disease[33]. But, there appears also to be no association between cagA and clinical symptoms or ulcers in children[32,34]. Other putative virulence determinants are being discovered, such as the neutrophil-activating protein (napA) gene, a gene "induced by contact with epithelium" (iceA1), etc[20]. However, according to the recent data, it is suggested that there is no correlation between the degree of inflammation and the presence of the cag-pathogenicity island, cytotoxin production, vacA alleles associated with cytotoxin expression in children[35].

Auto-immunity and host mimicry by expression of blood group antigens may be a relevant phenomenon. Adhesion of *H. pylori* is nonspecific although preferential to epithelial cells and is enhanced at low pH, inducing epithelial cell reorganization and causing deep invagination of the apical membrane, explaining resistance to topical antibiotic treatment[36]. One host receptor for adhesion appears to be a blood group O antigen, possibly explaining why ulcers are more common in people with this blood group[37]. The *H. pylori* lipopolysac charide (LPS) or endotoxin is unusually biologically inert compared with that from other bacteria. However, the mechanisms by which *H. pylori* LPS stimulates cells appears similar to that of other types of bacterial LPS[38].*H. pylori* LPS often contains Lewis x and Lewis y blood group antigens that are identical to those occurring in the gastric mucosa[39]. *H. pylori* presents bacterial epitopes to the host which are similar to the structure on host gastric epithelium; therefore, the host reacts with an auto-antibody response recognizing gastric mucosa inducing atrophic gastritis[40]. Patients with a large parietal cell mass and high acid secretion will have a predominantly antral gastritis, predisposing to duodenal ulcer[41]. People with a small parietal mass and low acid output (or people on proton pomp inhibitors) will be more prone to develop atrophic gastritis and gastric malignancy[41]. The variability in occurrence of gastric cancer in different parts of the world may only be partly explained by the prevalence of *H. pylori*. Apoptosis of gastric epithelial cells is increased in *H. pylori* infection, stimulating crypt cell proliferation, increasing the risk for mutagenesis[42]. Atrophic gastritis enhances the development of intestinal metaplasia, and is related to the intestinal type of gastric carcinoma but not to diffuse gastric carcinoma[43]. Intestinal metaplasia is related to atrophic gastritis, which is on its turn related to *H. pylori* infection.

Symptoms

H. pylori infection in children is mostly asymptomatic and not associated with specific gastrointestinal symptoms[44]. *H. pylori* gastritis, in the absence of duodenal ulcer, does not appear to be associated with specific symptoms[11,45-49]. After eradication of *H. pylori* infection, symptoms are

improved only in those children with duodenal disease[46]. Children with *H. pylori* gastritis cannot be distinguished from noninfected children on the basis of initial symptoms[45,49]. Many studies failed to demonstrate a difference in *H. pylori* infection rate in children with or without recurrent abdominal pain[11,49-51], although others did find this association[52]. Recurrent abdominal pain would occur during the acute phase of *H. pylori* infection[52]. It is unclear whether children with recurrent abdominal pain with *H. pylori* represent a different entity to those without *H. pylori*. *H. pylori* positive children might more often have pain related to meals than *H. pylori* negative children. Ulcer-like symptoms may be more closely associated with the infection than other symptom complexes[53].

In adults, a significantly lower *H. pylori* prevalence was reported in patients with gastro-esophageal reflux disease[54]. The role of *H. pylori* in duodenogastric reflux is unclear. A decreased mean acid output in subjects with *H. pylori* gastritis might explain the inverse relation between reflux and *H. pylori*. Heartburn and epigastric pain might be more frequent in *H. pylori* infected patients. Pooled data from 18 studies suggest that the prevalence of *H. pylori* was greater in patients with dyspepsia than in controls[53]. It is unclear whether *H. pylori* changes gastric emptying rate or not, although most data have suggested that gastric emptying is normal[55-57]. In adults, *H. pylori* is also beyond any doubt associated with an incre ased incidence of gastrointestinal cancer. However, the high prevalence of early *H. pylori* infection and chronic gastritis in children contrasts with the rarity of gastric cancer in black African[58]. Nevertheless, acquisition in infancy is in general considered to be a significant risk factor to develop gastric carcinoma[48].

Similar to other chronic inflammatory conditions, infection with *H. pylori* has been linked to reduced growth[59-65], although socioeconomic factors confuse the issue. Tumor necrosis factor-alpha is inversely correlated with growth, and is increased in *H. pylori*[66]. However, studies have also failed to find differences in hemoglobin, leukocytes, thrombocytes, weight and height[50,67]. Differences in growth seem to be limited to the developing countries[62,63]. It has been speculated that *H. pylori* acquired in infancy could be “the key that opens the door” to enteric infection leading to recurrent diarrhea, malnutrition and growth failure[62]. There is, however, no difference in diarrhea prevalence in relation to *H. pylori* status[68]. After control for socioeconomic status, there is no difference in the height of adults with and without *H. pylori*. *H. pylori* seropositivity is related to a late menarche[69,70]. Socioeconomic status and malnutrition does not explain late menarche, since elevated body mass index is also independently associated with *H. pylori* in the same population[70]. Incidentally, anemia, hemoptysis and vertigo have been reported[71,72].

The association of *H. pylori* with extra-digestive diseases, such as functional vascular diseases and skin and endocrine autoimmune diseases, has been described[73-76]. An interesting relationship between seropositivity to *H. pylori*, serum glucose and non-insulin dependent diabetes mellitus is worthy of further attention. Recent studies suggest that the association between *H. pylori* and coronary heart disease is rather weak[65,73]. Primary Raynaud ‘s phenomenon, observed in young women, which is defined by an intermittent vas ospasm of the arterioles of the distal limbs that occurs mostly following exposure to cold or emotional stimuli, may be related to *H. pylori* in some cases[74]. *H. pylori* may in addition cause headache[74]. Vasoactive substances, such as cytokines (interleukins, interferon, gamma, TNF-alpha), prostaglandins, leukotrienes, oxyradicals, C-reactive protein and fibrinogen are released in chronic infection[74]. Henoch-Sch-nlein purpura and Sj-gren’s syndrome have been correlated with the bacterium. Many patients with autoimmune thyroid diseases a re infected with type I cytotoxic cagA-positive strains[75]. Rosacea and recurrent urticaria may also be associated with *H. pylori* infection[76]. Alopecia areata is related to atrophic gastritis and pernicious anemia, and thus with *H. pylori*[74]. Until now, *H. pylori* has not yet been reported to cause hepatitis in human. Although a mice *Helicobacter* species has been reported to cause hepatitis in germfree mice, and *H. pylori* has been identified in the gallbladders of human[77,78]. An Italian group showed a positive correlation between food allergy and *H. pylori*[79].

H. pylori in infants and children

Independent risk factors for *H. pylori* infection in infants and children include living in lower socioeconomic and overcrowded circumstances and sharing a bed with a parent. Human lactoferrin can support *H. pylori* growth *in vitro* and *H. pylori* binding lactoferrin has now been identified. Infants born to seropositive mothers passively acquire maternal *H. pylori* IgG[80,81]. Transplacentally transferred maternal anti-*H. pylori* IgG lasts until about the third month of life in most infants and disappears from nearly all by 6 months[80]. IgA in mother’s milk can protect the infant from *H. pylori*

infection[82]. However, whether breast feeding is related to a low or high prevalence of *H. pylori* infection in infants remains unclear[80,83,84] (protective effect of mother's milk versus intimate contact between infant and *H. pylori* positive mother). At the age of 14 months, 7.5% of infants in a p opulation with a seroprevalence in 62% of young adults, had acquired *H. pylori* , an event demonstrated by a rise in IgM, quickly disappearing and preceding IgG[80,85,86]. In Belgium, less than 1% of infants are seropositive at the age of 1 year[87] (seropositivity in young adults is about 30%)[87,88]. In Finland, 4% of children under the age of 7 years have a positive serology[89].

Approximately 30% of 53 children (16/53) with dyspepsia were infected with *H. pylori* in the antrum, and about half of them a cytotoxic train was present (anti-Cag A antibodies in 64% and anti-vacA antibodies in 43%)[90]. In only 6/53 children, the *H. pylori* was also detected in the gastric body[9 0]. Clinical evaluation showed a significant difference in favor of subjects positive for *H. pylori* only for epigastric burning and/or pain[90].

Clinical symptoms associated with *H. pylori* infection have been reported in patients with human immunodeficiency virus (HIV)-1[91,92]. Although *H. pylori* has been said to be rare in HIV-1 infected individuals (e.g., be cause of the repetitive and multiple administrations of antibiotics and immunoglobulins)[92], recent data suggest that the prevalence of *H. pylori* infection in HIV-1 infected children is comparable to the prevalence in the non-infected control population[91].

Diagnostic and screening tools

A large number of invasive and non-invasive methods have been used to diagnose *H. pylori* infection in humans[93]. Culture of the organism is a standard method for the diagnosis of bacterial infection. *H. pylori* can be cultured from gastric biopsies. Culture of *H. pylori* requires a microaerobic atmosphere of 5% oxygen with 5%-10% CO_2. When *H. pylori* is cultivated on biopsy, sensitivity to antibiotics should be tested[94]. Whether coccoidal forms also grow in blood agar or not is controversial[95,96].

Histologic examination of Giemsa or Warthin-Starry stained gastric biopsy specimens is widely used for the diagnosis. The Sydney criteria for the classification of gastritis have been revised[97]. Gastric biopsy urease tests make use of a change in color of phenol red which is present in the medium because of a pH increase related to the digestion of urea by the urease. Four rapid urease tests are available commercially: CLO-test (Delta West Ltd, Bentley, Australia), Hpfast (GI Supply, Philadelphia, USA) and PyloriTek (Serin Research Corporation, Elkhart, USA), Jatrox (Röhm Pharma GMBH, Weiterstadt, Germany), although many hospitals prepare their own urease tests. These commercial tests have a high specificity and sensitivity and provide comparable results[98]. PyloriTek has a shorter reading time than CLO-test[99]. Antral and corpus biopsies provide comparable results, and in combination they increase the sensitivity by 4.3%[100]. Although these biopsy urease tests have a high degree of sensitivity in adults, false negative results are common in children, possibly because of a smaller bacterial load[101].

Molecular methods for biopsy material or other biological samples and current PCR methods for molecular fingerprinting of *H. pylori* have been developed[102,103]. PCR techniques can quantitate the bacterial load in gastric samples[103,104]. Several molecular methods have been applied to typing *H. pylori* isolates and demonstrating their genomic diversity. Unfortunately, all these tests necessitate endoscopy[103].

Magnetic beads coated with anti-*H. pylori* rabbit antibodies permit detection of less than 10-million organisms per gram of feces[105]. PCR-detect ion of *H. pylori* in feces is hindered by the presence of inhibitors of Taq polymerase, complex polysaccharides which can be eliminated by filtration on Qiagen and dilution. But, immunomagnetic separation-PCR is recently reported to be simple, rapid and reliable[106]. Nevertheless, the technique is not available as routine.

The ability to detect antibodies in saliva rather than in serum would improve antibody tests by avoiding the need for blood collection[107]. Sensitivity (84% - 93%) and specificity (70% - 82%) are too low, but comparable to rapid whole blood diagnostic tests[107-109]. The discovery of the potential importance of the cagA-pathogenicity island has stimulated interest in the specific detection of the CagA protein.

Serologic testing for IgG antibodies against *H. pylori* requires validation of the assay in children, since antibody levels differ in children and adults, probably because of the duration of infection and the differences in bacterial load[85,106,110,111]. In addition, commercially available serologic tests demonstrate lower accuracy compared with testing in a research setting[112], with sometimes up 33% false positive and 25% false negative results[111,113,114]. Serology is more and more frequently reported to be unsatisfactory for screening for *H. pylori* infection in children[106,111]. Testing should not rely on office

tests[94]. After eradication, there is a slow decline in antibody titer. Many patients remain seropositive 1 year after eradication[115]. At acquisition of the infection, there is a temporary rise in IgM[80,85,86,111,116]. IgA is also reported to be a useful serologic screening tool[117]. Immunoblot has become the reference method used to confirm doubtful results[118]. Specific serologies for cytoxic strains may be helpful in selecting patients for treatment[90].

Carbon-13 and C-14 breath tests are based on the fact that urease from *H. pylori* will hydrolyze the ingested labeled urea into ammonia and labeled bicarbonate, which is exhaled as labeled carbon dioxide[18]. Whether a test meal should be given, or whether the labeled urea should simply be given after a period of fasting, or whether addition of citric acid would be beneficial is not clear[119-121]. A standardized and simplified C-13 breath test was recently described in children[122]. The high sensitivity and specificity of the 13 C-breath test in the detection of *H. pylori* infection in children has been unequivocally demonstrated[90,123,124]. The best cut off value is obtained after 30 minutes[120]. False positive results can occur because of the presence of other urease containing gastric bacteria or because of extra- gastric bacterial urea metabolism (seldom). False negative results are mainly due to fast gastric emptying or previously administered urease-inhibiting drugs, such as antibiotics or bismuth-containing salts. There is a close correlation between the urea breath test and the intragastric bacterial load[100,125], which is on its turn related to the severity of the gastritis. Unfortunately, carbon-13 breath tests are still expensive in many parts of the world. A less expensive method for the analysis of 13C-labeled carbon dioxide is nondispersive infrared spectrometry, with a comparable sensitivity and specificity[126]. But, infrared spectrometry necessitates larger volumes of expired air, making the technique less suitable for (small) children. Alternatively, measurement of 14C-labeled carbon dioxide with a scintillation counter is relatively inexpensive[127]. Although the dose required for one test is not greater than the natural background radiation, the use of 14C is considered unethical in pregnant women, adolescents and children because of its extremely long half-life, since 14C may be incorporated into the bicarbonate pool[128]. The urea breath test is in general accepted to be the most reliable noninvasive diagnostic method[90,129]. The urea breath test detects only current infection and can be used to screen for *H. pylori* infection and as the sole method for assessing eradication, and to evaluate treatment efficacy[129].

Epidemiology

The prevalence of *H. pylori* infection in many populations and/or subgroups is currently well documented. The overall prevalence of *H. pylori* in children is 10% in developed countries but can be as high as 30%-40% in children from lower socioeconomic classes[48]. In developing countries, the prevalence of *H. pylori* in children ranges from 80% to 100%[48]. Like many other childhood bacterial infections, *H. pylori* is most frequently acquired in the preschool age group, with the associated effects of family size, clustering in families, low socioeconomic status and education and variable risks associated with gender[89,130,131]. Recent sociocultural changes may result in changes in infection rates in children[132], which is an important argument for the cohort effect. In general, it is thought that spontaneous eradication of *H. pylori* infection is extremely rare[133,134]. However, recently some authors have suggested that from 1.5% up to 10% or even 20% of spontaneous eradication occurs in a period of 6 months during childhood[111,135,136]. Although, others still report a zero incidence of seroreversion[89]. These discrepancies may, however, be related to the methodology (serology versus urea breath test). Recent epidemiologic data suggest that serology underestimates *H. pylori* infection in children[106,111], and antibodies may persist a lthough *H. pylori* disappeared.

In the developed world, acquisition by adults and children is approximately 1% to 3% per decade[131,136,137], which will result in a dramatic decrease in *H. pylori* infection in that part of the world in the coming decades. In The Netherlands, about 40% of the 60-69-year-old population is seropositive[137]; since the prevalence in adolescents is below 10%[138], it can be speculated that the seropositivity of this cohort will probably not be higher than 25% when reaching the age of 70 years. In Gambia, the prevalence of a positive breath test at the age of 3 months is about 19%, increasing to 84% at 30 months[111].

Re-infection probably does not occur frequently and is, in many cases, consider ed recrudescence after treatment failure[139]. Re-infection rates vary strongly with the effectiveness of the treatment protocol[139,140]. In Chile, re-infection occurred in 4.2% after 1 year, with a treatment protocol that was 82% effective[141,142]. Annual user-relapse rate in children wit h duodenal ulcer in whom *H. pylori* was eradicated was reported to be 9%[143]. The percentage of re-infection does not appear to be much higher in developing countries than in developed regions. As a consequence, there is little reason for treating an entire family to prevent re-

infection, although spread from one adult to another has been suggested[144]. Others do suggest family treatment[183]. It seems more likely that re-infection comes from an external source. Of course, a more detailed specification of the *H. pylori* strain will contribute to the answer whether re-infection rather than relapse occurs. Repetitive extragenetic palindromic-PCR can group isolates into clusters that appear to have a different clinical expression[102]. Oligonucleotide probes containing short repetitive sequence motifs can differentiate between different isolates of *H. pylori*[146].

The major mode(s) of transmission of *H. pylori* are still unknown, oral-oral, gastro-oral and fecal-oral have been proposed[147,148]. Infected parents, especially mothers, may play a key role in transmission of *H. pylori* within families[81,149]. Houseflies could serve as vectors for *H. pylori*[150]. Pets have been suggested as well as contradicted to be vectors[151]. There is considerable evidence of transmission of oral bacteria between spouses and between family members[144]. Vomiting and gastroesophageal reflux might also be a mode of oral-oral contamination[152]. Mode of spread remains an active area of study, with water as a source of contamination still of potential interest. The coccoid form can cause cellular changes similar to the spiral form[153], and may serve as the infectious form in environmental sources such as water[154]. Studies on external water sources in Peru revealed PCR products of *H. pylori* in the municipal water, increasing 12 -times the risk for infection[155]. The examples of studies in Peru and Chile suggest a role for water as a vehicle, but it does not seem to be the main route of acquisition since many studies in Korea[132], Taiwan, or Turkey do not support this hypothesis.

Host response to H. pylori

Another factor contributing to the heterogenecity of *H. pylori* associated symptoms is the variability in host response to the infection. Duodenal bicarbonate secretion is decreased in ulcer patients, and returns to normal after eradication of *H. pylori*[156,157]. Acute *H. pylori* infection has been as so ciated with hypochlorhydria, possibly by stimulating the production of a histamine-3 receptor agonist, which inhibits gastric acid output. In contradiction to this finding is the observation that the same histamine-3 receptor agonist can stimulate parietal cells to produce acid via the histamine-2 receptor[158]. Identification of Lewis carbohydrate structures on *H. pylori* lipopolys accharide may provide an explanation for the development of autoantibodies, reacting with gastric mucosa ("molecular mimicry")[159].

Treatment

Currently, there are no guidelines on the need to treat children[48]. The regimens that have been studied to date have used bismuth preparations, H_2-receptor antagonists, ranitidine bismuth citrate, proton pump inhibitors and various antibiotics. The goal of any treatment should achieve an eradication rate of over 80% on a rigorous intention-to-treat basis[94]. Most European *H. pylori* study groups now recommend (in adults) a triple regimen: a twice daily dose of proton pump inhibitor (PPI) in combination with two antibiotics [from the following 3 groups: clarithromycin; amoxicillin; nitroimidazoles (metron idazole or tinidazole)] for 1 week[94,160,161]. There are no specificr ecommendations for children yet[162]. It has been hypothesized that combination therapy is more effective because of the synergistic mechanisms between different drugs. The requirement is for a simple, well-tolerated regimen, with which it is easy to comply with, and is cost-effective. In a recent Irish study in children, the therapeutic approach consisted of colloidal bismuth subcitrate (480 mg/1.73 m^2 body surface for 4 weeks) in combination with amoxicillin (750 mg/ day for 2 weeks) or metronidazole (20 mg / kg / day for 2 weeks)[120]. In most European countries, eradication treatment in children consists usually of a PPI in combination with amoxicillin and either clarithromycin or nitroimidazole, based on the sensitivity of the prevailing strains. Although antibiograms are needed, there seems to be major discrepancy between *in vitro* testing and *in vivo* efficacy. Resistance to amoxicillin has recently been reported, but seems rare[163]. Resistance to macrolides is rising with increasing use of the drugs, and for both macrolides and nitroimidazoles there is a huge regional variation in resistance patterns. Especially the determination of resistance to metronidazole may be relevant in regions with a high percentage of resistance[164].

Bismuth triple therapy continues to achieve high eradication rates worldwide (78%-89%). Side effects leading to diminished patient compliance and the marked decline of eradication efficacy in cases of metronidazole resistance are considered to be the major drawbacks of this therapy. PPI dual therapy is better tolerate d with fewer side effects than is bismuth triple therapy. The mean eradication rates vary from 55% to 75%, and the extremes lie between 24% and 93%. PPI triple therapies have been shown to be very effective against *H. pylori* with an eradication rate 80 % - 90 %. Eradication rate in children with 2 weeks of treatment with clarithromycin, amoxicillin and proton pump inhibitors (omeprazole or lansopr azole) is reported to be 75 % and 92 %, respectively[165,166].

Omeprazole, clarithromycin and metronidazole or tinidazole for 7 days are reported to cause eradication in 87% and 89%[167,168]. Dual therapy for 2 weeks with omeprazole and amoxicillin causes eradication in 70% of infected children, whereas a ddition of clarithromycin for 2 weeks increases the eradication rate up to 92%[169]. Amoxicillin, bismuth and metronidazole were reported to eradicate *H. pylori* in 96% of infected children[143]. Quadruple therapy leads to a mean eradication rate of 96%. Thus, based on efficacy PPI triple or bismuth triple therapy are recommended as first-line treatment[170]. The cost of PPI versus bismuth should be considered. However, compliance strongly influence the eradication rate, and may explain why, in contradiction to experience in adults, in children two drugs for 2 weeks are sometimes found to be equally effective than triple therapy for 1 week[171].

Eradication therapy is not recommended for all *H. pylori* infected adults and children[162]. However, the complex relationship between *H. pylori* and gastrointestinal cancer might stimulate physicians to prescribe eradication treatment, even in the absence of scientific evidence, especially in countries with a strong impact of legislation on health care, as in the case in the US in children, not one randomized prospective placebo-controlled study had been conduct ed. Whether children with symptomatic *H. pylori* gastritis alone will benefit from treatment is debated[90,121]. Well-designed clinical trials showing a therapeutic gain of *H. pylori* treatment over placebo are still missing, with the exception in duodenal ulcer patients. The cost-benefit ratio of avoiding endoscopy in dyspeptic patients is only worthwhile considering if the cost of end oscopy is greater than $500 USD[172], as is the case in the USA; while the cost of upper gastrointestinal tract endoscopy in Belgium and Finland is only about $100 and $170 USD, respectively[173].

Nevertheless, recommendations differ in Europe and the USA. The European consensus states that scientific evidence for the improvement of functional dyspepsia is equivocal, but the overall evaluation taking into account the expected benefit on the gastritis status makes it worthwhile to consider eradication therapy in such patients. In Europe, it is accepted, although not unanimously, that young patients, aged below 45 years, without alarm symptoms (anemia, weight loss, dysphagia, palpable mass, malabsorption, etc.) and who test positive for *H. pylori* for the first time with validated serology or breath test, can be treated with eradication therapy without further investigations (thus without endoscopy)[94,160]. However, in the USA, the present consensus states that there is no scientific evidence to recommend treatment for *H. pylori* in the absence of an established peptic ulcer disease[156]. As a consequence, according to the North American consensus, non-invasive testing cannot replace endoscopy in t he initial diagnosis of *H. pylori* related gastrointestinal diseases (not in children either)[174]. Eradication of *H. pylori* in patients who do not benefit from it may unnecessarily increase the risk of resistance of *H. pylori* to antibiotics.

H. pylori and non-steroid anti-inflammatory drugs (NSAIDs) are both ulcerogens; however, NSAIDs are not frequently prescribed in children, and moreover, there seems to be no cooperative effect between them. Consequently, eradication of *H. pylori* prior to NSAID administration is not recommended in the USA. In Europe, eradication of *H. pylori* before NSAIDs is considered "advisable".

Elimination of *H. pylori* increases the risk of developing gastroesophageal reflux and reflux esophagitis[157,175]. *H. pylori* eradication results in a marked decrease in the pH-increasing effect of omeprazole and ranitidine[176]. Nevertheless, long-term acid suppressive therapy with proton pump in hibitors (and to a lesser extent with H_2-antagonists) for reflux disease in *H. pylori* positive patients enhances the development of atrophic gastritis if *H. pylori* has not been eradicated beforehand[177,178].

Eradication of *H. pylori* can be demonstrated by normalization of histology and negative culture of gastric biopsies, or with the use of urea breath tests[94]. With respect to serology, a 50% fall in antibody titers is indicative of successful elimination. However, this usually requires up to 6 months to occur[179]. When follow-up tests for eradication of *H. pylori* are necessary, they should not be made earlier than 4 weeks after cessation of treatment[94]. The bacterial load could influence the success rate of eradicating treatment[180].

Knowledge of the *H. pylori* genome provides major new insights into many aspects. Conversion of pyruvate to acetyl-CoA uses an unusual enzyme, only previously found in free-living bacteria from extreme environments[181]and the genome sequence shows that acetyl-CoA is likely to be a crucial intermediary in several biosynthetic pathways. Therefore, blocking the enzyme should allow effective and selective drug activity against *H. pylori*. The same is true for many other enzymes.

Vaccination

Study of the *H. pylori* outer membrane is important for both understanding the pathogenicity but also

for development of vaccines since the outer membrane is involved in adherence to the host epithelium and stimulation of the host immune response. Vaccines should be able to confer preventive and curative immunity on humans. Oral immunization with a recombinant urease given in the absence of a mucosal adjuvant has been assessed unsuccessfully in *H. pylori* infected volunteers[182]. However, recently, the recombinant *H. pylori* urease was given with an *E. coli* heat-lable toxin, provoking diarrhea in the majority of the volunteers, a side-effect which disappeared when the dose was reduced, but also showing an increase in urease specific IgA producing cells and a decrease in the density of gastric colonization by *H. pylori*[183].

IgA antibodies are expected to play a prominent role in protection, since *H. pylori* is a non-invasive pathogen at the luminal surface of the gastric mucosa. This hypothesis has been supported by the observation that milk IgA protects infants against *H. pylori* infection[82]. IgA and immunoglobulin G1 (I gG1) depend on T-helper type 2 (Th2) cells. According to different recent experiments, immunization is associated with an elevation of IgG1 levels, indicative of a Th2 cellular immune response, which might be a significant mechanism[184-186]. The field of vaccination is still very controversial, and is being extensively studied.

CONCLUSION

Helicobacter pylori infection is worldwide one of the most frequent infectious diseases. There is a huge discrepancy in prevalence and incidence between the industrialized countries and the rest of the world (Africa, Asia, South-Americ a). Infection occurs mainly in children. Well-designed studies to identify thos e infected children who are at risk of developing complications or have symptoms due to the infection are still lacking[171]. Because of the cohort-effect which is related to the socio-economic status and/or hygienic circumstances, the annual infection rate in the Western world is dramatically decreasing. If this observation is confirmed, it can be speculated that a decrease in incidence of peptic ulcer disease and gastric cancer may occur in the more industrialized countries during the next decades. However, duodenal ulcer and gastric cancer are only related to some more virulent strains. Many children remain asymptomatic, and a clear relation between *H. pylori* and symptoms has only been demonstrated for ulcer-related symptoms. In addition, peptic ulcers are rare in childhood. Treatment of *H. pylori* is indicated in duodenal ulcer diseases. The relation between chronic abdominal pain, functional dyspepsia, and *H. pylori* is unclear.

Screening tests, including serology or the urea breath test, are of interest for epidemiological studies. The urea breath test evaluates the actual colonization; serum antibodies might persist after eradication, which is only rarely spontaneous. According to the European consensus, eradication therapy can be considered in a child with functional dyspepsia and positive screening test. According to the North American consensus, treatment is only recommended in the presence of ulcer, necessitating endoscopy.

H. pylori strains are not created equal since important virulence factors are not detectable in all strains. The continuous decline of *H. pylori* prevalence as a result of changes in living conditions and active treatment is not unanimously considered to be beneficial[14]. Unfortunately, screening tests rely on virulence factors which are detectable in all strains. Vaccines are not expected to be available in the near future.

Nevertheless, improvement of the socio-economic status and hygienic circumstances in all countries will result in a dramatic decrease of *H. pylori*.

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Edited by Ma JY