

Is *Helicobacter pylori* always a "bad guy"?

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Abstract

Various clinical presentations have been ascribed to *Helicobacter (H.) pylori*. Most importantly, *H. pylori* is considered the leading cause of gastric cancer worldwide and because of that, in adult population, it is listed as a number one carcinogen. However, children are less prone to develop *H. pylori* related serious diseases such as peptic ulcer disease (PUD) and cases of malignancy are only sporadically reported. On the other hand, there is an increasing level of evidence suggesting that *H. pylori* in children could also have a beneficial effect. Recently, several data confirmed previously described inverse relationship of *H. pylori* infection and gastroesophageal reflux disease. Furthermore, it has been hypothesized that an increased prevalence of allergic diseases could be, at least partially, explained by the decreased incidence of *H. pylori* infection. *H. pylori* can, to some degree, influence immunological response. It has an ability to promote high proinflammatory cytokine expression in the gastric mucosa shifting immunity towards Th1 response, which could be a plausible explanation for the down-regulated clinical expression of allergies (including asthma) in patients with *H. pylori* gastritis. Based on these findings the aim of this review is to present “pros and cons” for *H. pylori* eradication in children.

Introduction

Children differ from adults in respect to *Helicobacter (H.) pylori* infection regarding the prevalence of the infection, low rate of severe diseases associated with *H. pylori*, almost an absence of gastric malignancies, age-specific problems with diagnostic tests and treatment strategies, and importantly, a higher rate of antibiotic resistance [1]. The incidence of infection varies between countries and is very low in Western and Northern Europe, far below 10% and, on the other hand, very high, in developing countries where it can be up to 80% [2]. In children, *H. pylori* is associated with increasing antibiotic resistance rate [3, 4], which is the highest for clarithromycin with prevalence of even more than 30% in treatment naïve children in some European countries [5-9]. Based on all the differences of *H. pylori* infection in children comparing to adults, European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and Northern American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) updated the guidelines for detection and treatment of *H. pylori* in children [1]. The guidelines stated that there are not enough data to determine whether *H. pylori* should be eradicated in the absence of peptic ulcer disease (PUD). It is, therefore, the aim of this review to summarize currently available evidence and to present “pros and cons” for the eradication of *H. pylori* in children.

When to look for *H. pylori* in children?

Updated ESPGHAN and NASPGHAN recommendation state that routine search for *H. pylori* is not justified due to the very low incidence of PUD and even lower incidence of gastric carcinoma [1]. All other symptoms including abdominal complaints such as pain, cramps and nausea are very common in pediatric population. Usually, they are unspecific and very often caused by functional gastrointestinal disorders. Spee et al. performed a meta-analysis on the relationship between recurrent abdominal pain (RAP) and *H. pylori* infection in children and found no evidence for any relation between RAP and *H. pylori* infection in children [10]. An older study from Germany including 1221 children [11] found that RAP was associated to social and familial factors (single-parent household, family history of PUD, or functional pain), and not to *H. pylori* status of the child. Similar results were reported by Tindberg et al [12] in school-aged children and also in a very recent Italian study [13]. Based on these results, there is not enough evidence to support a causal relation between *H. pylori* gastritis and abdominal pain in the absence of ulcer disease. Searching for *H. pylori* is, therefore not recommend in children

that otherwise fulfill the criteria of functional abdominal pain, unless upper endoscopy is performed during the diagnostic workup in search for organic disease [1, 14, 15].

Furthermore, the association between *H. pylori* infection and iron deficiency anemia has been widely studied [16, 17], but it is often difficult to distinguish between iron deficiency anemia due to *H. pylori* infection and to the other confounding factors such as poor nutritional status or another underlying disease [17]. Although there are clinical trials which found that eradication therapy alone increases hemoglobin levels even without iron substitution [18], not all clinical trials confirmed this positive effect [19, 20]. Based on all mentioned above, currently available guidelines recommend that in children with unexplained iron deficiency anemia testing for *H. pylori* infection may be considered [1]. Regarding idiopathic thrombocytopenic purpura (ITP), guidelines for adults recommend that *H. pylori* should be sought and eradicated in a case of ITP [21]. The studies in children are limited, included very small number of patients and yield contradictory results [22-26]. Subsequently, guidelines in children found not enough evidence for causal relation for *H. pylori* and ITP [1].

For other diseases, such as upper respiratory disease, periodontal disease or food allergy there is no evidence that in pediatric patients search for *H. pylori* should be performed [1].

Eradicate or not?

Eradication therapy for pediatric patients comprises of two antibiotics (amoxicillin and imidazole or clarithromycin) and the proton pump inhibitor used together or as a sequential therapy or use of bismuth salts with proton pump inhibitor and imidazole [1]. Although the aim is to achieve an eradication rate above 90%, it is currently much lower (around 65%) [27]. Moreover, the level of recurrence is rather high; performed meta-analysis found overall annual recurrence rate of 2.7% in developed countries and 13% in developing countries [28]. In pediatrics, studies on the incidence of *H. pylori* reinfection after eradication therapy are scarce, whereby the reinfection is mostly attributed to intrafamilial transmission, with the rate varying between 1.9 and 9.6% [29].

Undoubtedly, eradication should be recommended in children with PUD [1]. However whether to treat *H. pylori*-associated gastritis without duodenal or gastric ulcer is still not clear. Currently available recommendation state that the decision should be made by the clinician taking into consideration the potential risks and benefits of the treatment in every individual patient [1].

Factor strongly supporting eradication in adults is the potential carcinogenic effect of *H. pylori*. It is well known that infection is usually transmitted during the childhood and commonly persists throughout adulthood unless it is treated. In adults, gastrointestinal diseases associated with *H. pylori* colonization are well recognized and, besides chronic active gastritis, duodenal and gastric ulcer, also include malignancies such as primary gastric B-cell lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma [30]. *H. pylori* infection leads in all infected individuals to a chronic active gastritis, which can proceed to gastric mucosal atrophy and intestinal metaplasia, and finally to the development of gastric cancer [31]. Therefore, atrophy and intestinal metaplasia are considered as precancerous lesions, and *H. pylori* eradication therapy is preventive measure for gastric cancer [21]. Moreover, eradication of *H. pylori* is well recognized as the initial therapy for early stage gastric MALT lymphoma [32].

On the contrary, malignancies associated with *H. pylori* are sporadically reported in children. An interesting case report found that a child with PUD and *H. pylori* infection subsequently developed high-grade B-cell lymphoma [33]. Paper stated that the lymphoma resolved within two months after *H. pylori* eradication and without chemotherapy or radiotherapy. Regression of gastric lymphoma was also seen in a 14-year-old girl after the treatment of *H. pylori* infection and chemotherapy [34]. There are several more case reports which indicate connection between *H. pylori* infection and gastric lymphomas in children [35, 36]. All these data indicate that *H. pylori* could be associated with malignancies in children; however the risk seems to be substantially lower than in adults.

Furthermore, the carcinogenic risk is modified by strain-specific bacterial factors and host responses [37]. Taking all that into account the indications for eradication should not be the same in all areas. Current evidence suggests that in high-risk populations such as China, the eradication of *H. pylori* may have the potential to decrease the risk of gastric cancer [38]. In support of this is a recent report which found that in the population with high risk of gastric cancer even children have a high prevalence of *H. pylori* virulence markers - *cagA* gene and *vacA* s1alleles [39]. Moreover, guidelines also strongly support testing for *H. pylori* in children with first-degree relatives with gastric carcinoma and if *H. pylori* is confirmed eradication should be offered [1].

Other malignancy associated with *H. pylori* is colorectal cancer [40-42]. This hypothesis is based on the observation that infection with *H. pylori* leads to an increase of plasma gastrin level which stimulates mucosal cell proliferation [31]. Two meta-analyses reported that there is a modest increase in the risk of colorectal cancer

due to *H. pylori* infection [43, 44]. However, the included studies had several weaknesses such as a small sample size and high heterogeneity. Recently, a large population-based case control study was conducted in Germany to investigate the association between *H. pylori* and colorectal cancer [45]. The authors performed a stratified analysis which showed increased risk confined to left-sided colorectal cancer. All those data were found for adult patients and in children there are only reports which associate *H. pylori* infection with colorectal juvenile polyps but no further association to colorectal malignancy could be made [46].

Pro eradication is also a data which implicates that eradication of *H. pylori* has a positive effect on growth velocity [47-51]. However, ESPGHAN and NASPGHAN group did not find enough evidence which would support this finding and justify the eradication in order to improve growth [1]. Recently published study on 295 school-aged children followed for 3.7 years [52], found that after the study period *H. pylori* eradicated group grow significantly better compared to non-treated group. However, the effect could not be limited only to eradication of infection as *H. pylori* is often associated with poorer socioeconomic status and children who were not able to clear the infection could have had other risk factors causing a shorter stature. Thus, current evidence does not support eradication of *H. pylori* in order to improve growth in children.

There are several factors opposing the need for the *H. pylori* eradication such as already mentioned low incidence of PUD and malignancy in children [1]. Moreover, spontaneous clearance of *H. pylori* has been shown in children, being more pronounced in younger age [53, 54] and in some areas of the world where it can reach above 4% per year [55, 56].

In addition, it seems that there are diseases which negatively correlate with *H. pylori*. First of all, it has been reported that adult patients with *H. pylori* infection have a lower risk for gastroesophageal reflux disease (GERD) [57, 58]. However, eradication of *H. pylori* in adults was not associated with exacerbation of GERD [59]. Guidelines for adult patients, therefore, indicate that there is a negative association between GERD and infection of *H. pylori*, however, the eradication of *H. pylori* should be recommended regardless of the presence of GERD [21].

Several pediatric studies also reported lower incidence of GERD in children infected with *H. pylori* [60]; Iranian study included 263 pediatric patients and found significantly lower prevalence of *H. pylori* among patients with GERD [61]. Moreover, Fixa et al. explained a decrease in PUD and increase of reflux esophagitis in the past 18 years with a diminishing prevalence of *H. pylori* infection in the studied pediatric population [62]. This negative

association could be explained by several mechanisms including post-eradication increase in acid output and diminished buffering capacity due to reduced ammonia production after the *H. pylori* clearance [57]. However, there are also opposite data in pediatric patients showing positive correlation between the *H. pylori* infection and the prevalence of GERD [63-65].

Furthermore, several recent pediatric studies reported on the negative correlation between the *H. pylori* infection and the prevalence of allergy; the large retrospective study from Israel determined *H. pylori* with urea breath test and found inversed association between *H. pylori* and pediatric asthma [66]. Moreover, a study from Chile found less frequent *H. pylori* infection in children with severe allergy comparing to children with mild or no allergic diseases [67]. Similar finding was also described in developing country where *H. pylori* infected toddlers from Ethiopia had significantly lower risk of skin allergies [68]. This negative association between allergic diseases and *H. pylori* infection in children supports the possibility that a specific microbe could have a dual role, being in symbiosis with the host during an early life while in the later life acts as a pathogen [69]. There are several proposed mechanisms how *H. pylori* could reduce risk for allergy. It has been found that in children *H. pylori*-induced inflammatory response is associated with significant increase of pro-inflammatory cytokines, mainly IFN- γ , TGF- β and IL-10 promoting a Th1 type of immune response which does not support atopy [70-72]. In addition, Amedei et al. found that *H. pylori* neutrophil activating protein added to antigen-induced T-cell lines can cause shift in the cytokine profile from a Th2 to Th1 profile [73].

This association between the *H. pylori* and the atopic disorders was not confirmed in all studies [74]. However, it is tempting to hypothesize that we have lived with *H. pylori* for tens of thousands of years and it is highly unlikely that it will disappear without causing any consequence; meaning that the infection with *H. pylori* could have at least some positive effects on our immune system [75].

Conclusion

Currently available evidence strongly discourages the “test and treat” strategy in children [1]. In contrast to adults, there is no evidence that eradication of *H. pylori* in the absence of PUD can have beneficial effect on reduction of malignancies or on the improvement of abdominal symptoms in children. Therefore, the indication to search for *H. pylori* in children should be limited to clinical presentations suggestive of organic disease.

Eradication of infection, in order to prevent cancer, should be limited to countries with a very high incidence of

gastric cancer. However, it is still not clear whether patients, in whom it was decided against eradication, should be followed, and if yes for how long and how often. This could be a subject for further research. Finally, there are data indicating that *H. pylori* infection could be beneficial for the reduction of allergic diseases and of GERD but more studies are needed to clarify a possible causal relationship.

List of Abbreviations: *H. pylori* – *Helicobacter pylori*; ESPGHAN - European Society for Pediatric Gastroenterology, Hepatology and Nutrition; NASPGHAN - Northern American Society for Pediatric Gastroenterology, Hepatology and Nutrition; PUD - peptic ulcer disease; RAP - recurrent abdominal pain; MALT - mucosa-associated lymphoid tissue lymphoma.

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