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Perspectives on Noninvasive Screening of *Helicobacter pylori* Infection in Children

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Helicobacter pylori (*H. pylori*) infection is a large worldwide infection and a major cause of gastric cancer; it is essentially acquired in early childhood. Working Group Meeting of the International Agency for Research on Cancer (IARC) (2013) [1] and a global consensus meeting held in Kyoto, Japan aimed at evaluation of the management of *H. pylori*-related gastritis [2] have reached in the conclusion that eradication of *H. pylori* can prevent gastric cancer, and recommend that all carriers of *H. pylori* should be treated to eradicate this pathogen. Among the available strategies, screen-and-treat for *H. pylori* infection was considered to be the best approach to decrease cancer risk; however, implementation of this strategy on the population level, and especially when considering pediatric populations, requires a systematic approach [3].

The prevalence of *H. pylori* in children varies, with lower incidence rates in developed countries compared to developing countries (up to 10-15% and 70%, respectively) [4,5]. Most subjects are infected during early childhood; in developing countries, 50% of children are infected by the age of 5 years [6]. Unlike in adults, a 'test-and-treat' strategy is not and has never been recommended in children, since correlation between abdominal pain and *H. pylori* gastritis, in absence of peptic ulcer disease is still debated [4]. ESPGHAN/NASPGHAN report that abdominal complaints such as pain, nausea, or other dyspeptic symptoms are nonspecific and can be caused by different organic diseases within and outside the digestive tract. These diseases may be missed or their diagnosis and treatment delayed, if a noninvasive test for *H. pylori* infection is positive and treatment initiated. Children younger than 8 years old, or even as old as 12 years, may not be able to provide accurate descriptions of the degree, character, and location of pain [7].

There is an indication that *H. pylori* eradication is associated with a reduction in childhood growth and benefits nutritional status [8]. Early exposure to infections may predispose children and adolescents to such chronic diseases as iron-deficiency anemia and idiopathic thrombocytopenic purpura [9,10] as well as significantly increase the risk of gastric cancer [11].

While screening of *H. pylori* infection in adults primarily aims at prevention and early treatment of gastric cancer, the objectives of population-level screening and management of the infection in pediatrics are different and rather aim at decreasing of an overall global burden of *H. pylori*-associated gastro-duodenal and extra gastric diseases.

Nowadays, the initial diagnosis of *H. pylori* infection in children should be based on either a positive histopathology plus or a positive rapid urease test or a positive culture [7]. While applications of noninvasive tests such as the 13C-urea breath test (UBT), and enzyme-linked immunosorbent assay (ELISA) test for detection of *H. pylori* antigen in stool are limited to verifying eradication after therapy and testing for *H. pylori* in children with first-degree relatives with gastric cancer, and refractory iron-deficiency anemia in which other causes have been ruled out [4].

Although in certain population more than a half of the children are chronically infected with this Gram-negative bacterium, most of them remain asymptomatic. Who develops disease depends on strain virulence, host genetic susceptibility, and environmental factors. In particular, gastric cancer develops in only 1%-3% of *H. pylori* infected people in 40 years or longer [12]. It is known that not all strains of *H. pylori* are equivalent in their pathogenic and carcinogenic potential and that those expressing an immunodominant peptide determinant called *CagA* (cytotoxin associated gene A), are endowed with an increased inflammatory and carcinogenic properties [12]. Therefore it is of particular interest to screen subjects infected with *CagA* positive bacteria and to carry out the prophylactic eradication treatment using more targeted approach, which has a potential to decrease use of antibiotics and positively impact the eradication success rates.

However, no diagnostic tool allowing real-time and handy testing and differentiation of toxigenic strains of *H. pylori,* suitable for screening purposes is readily available in clinical setting. A new step towards more strain-specific *H. pylori* diagnostics is a sensory-based analysis of human exhaled gas profile based on the principles of Yanson point-contact spectroscopy [13] for the real-time differentiation of *CagA H. pylori* strains by specific volatiles emitted by the bacteria [14]. Distinctive properties and performance of the novel point-contact nano sensors essentially exceeding those of existing analogues allow performing real-time analysis of multi-component gas mixtures. Recent clinical trial demonstrated that certain parameters of response curves of the point-contact nano sensors were significantly different in *cagA* positive *H. pylori* adolescent patients with gastric dyspepsia, which makes a promising prerequisite for the development of a new real-time diagnostic tool. Such strain-specific approach to *H. pylori* testing opens a new perspective for designing a screening program for prevention of *H. pylori*-related diseases including gastric cancer at the population level in children.

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