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Editorial

To culture on not to culture? That is the question for the primary care physician

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In spite of the increase in number of non-invasive diagnostic tools for *Helicobacter pylori* in children, the ultimate solution (gold standard) has not yet been discovered. This reality is not unexpected, considering the various factors that may affect the accuracy rate of any diagnostic tool. Those factors include the prevalence of the disease in the tested community, the number of infected children included in the study, the demographic data of the children involved (young vs. older age, race and ethnicity), the commercial availability of the tested tool, its reliable cut-off value for the pediatric age group, and more. It is thus understandable, why different expert committees from Europe and North America are "chasing" the published data every so often, and revising their recommendations accordingly [1–3].

In this issue of Journal of Pediatric Infectious Diseases, Argentieri et al. [4] reported the accuracy of various invasive and non-invasive diagnostic tools for detection of *H. pylori* infection in Italian children. In this presumed retrospective study, 215 children were evaluated for *H. pylori* infection by invasive [tissue biopsy, rapid urease test (RUT), and culture], and non-invasive (stool antigen) methods. The authors chose histology alone as the gold standard test and compared the rest of the diagnostic tools to histology. In addition, positive culture samples were examined for antimicrobial susceptibility using the E-test strip. The standard minimum inhibitory concentration values for resistance were used to determine susceptibility to the tested antibiotics (metronidazole, clarithromycin, and amoxicillin). The authors reported a low sensitivity rate for culture (90.6%), RUT (70.3%), and stool antigen (57.8%), compared to histology. The resistance to the tested antibiotics was as follows: metronidazole 27.6%, clarithromycin 20.7%, and amoxicillin none [4].

Surprisingly, in spite of several methodological weakness of study of Argentieri et al. [4], the results of their study fell within the range of the published data. Previous data have shown that the overall accuracy rate of stool antigen (polyclonal) is within 67–100% [5–9], the accuracy rate for tissue culture is in the range of 55–100% [9–13], and the accuracy rate of the RUT is within the range of 75–100% [11,13–15]. Unfortunately, these data demonstrate exactly why each test alone cannot be considered adequate to be the gold standard for the diagnosis of *H. pylori* infection in children.

For example, except for positive culture alone, no diagnostic tool is currently accepted as a reference test (gold standard) for *H. pylori* infection, and many recent publications are defining positive infected children as children with at least two positive invasive tests: positive histology and positive RUT, or one positive inva-

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sive test and a positive urea breath test [16,17]. Due to the patchy distribution of the bacteria in the stomach, more than one biopsy is required to assess positive histology, and better if taken from several anatomical places of the stomach, i.e.: antrum and body. In the present study, histology (one biopsy) alone was defined as the gold standard. It would be interesting to calculate what would have been the sensitivity rate of the examined diagnostic tools, if positive culture and positive histology were the reference.

Although positive tissue culture confirms a positive infection, negative culture does not rule out infection. As the authors stated, *H. pylori* bacterium is a fastidious bacteria, difficult to culture, and needs very special conditions to grow. Previous data have shown that even the most experienced microbiology research laboratories have less than 100% success rate in growing the bacteria; and much lower rates are reported from routine, community hospital laboratories [16,18]. It is no surprise that many practicing physicians in Europe and North America do not utilized culture in their clinical practice [19]. The authors are commended for their high success rate achieved in their microbiology laboratory. It is more likely that the true number of positive children in their study was 58 (positive culture) rather 64 (positive histology). Obviously, when the data is re-calculated with this number in mind, a different accuracy rate will result [4].

The RUT is notoriously dependent upon the concentration of the bacteria within the biopsy. Consequently, a higher rate of accuracy is reported in the adult population compared to the pediatric population [14,15,20]. Moreover, the rate within the pediatric population will differ according to the pediatric population studies, i.e.: age of the participating children, the community tested (socioeconomic differences), and other determinants. Micro-environmental conditions at the stomach level (pH, antibiotics) as well as genetics have been established as important factors that affect the growth of the bacteria. In the present study, the author reported no antibiotic therapy within one month of endoscopy, but no demographic data was provided [4].

The stool antigen test, specifically the polyclonal type was initially considered promising [8,21]. Unfortunately, further studies by other groups showed much lower accuracy rate [7,16,22], and the attractiveness of this test for children has been replaced by the new monoclonal stool antigen tests which recently appeared in the market [13,17]. Those diagnostic tests seemed to have better accuracy rate; but further validation studies in different pediatric communities are yet warranted.

The increase rate of anti-microbial resistance of the bacteria has been one of the major explanations implicated in the low eradication rate reported in the adult and pediatric population [23–25]. Increase rate of bacterial resistance to metronidazole and clarithromicin was reported in different pediatric studies [26–28], encouraging the primary care physicians to obtain bacteriogram before prescribing medications. Although this approach seems reasonable, logical, and probably improves eradication rate and patient satisfaction, recent publications have challenged this approach [18]. In this publication, the authors showed that the sensitivity based treatment protocol for metronidazole resistant bacteria is not cost effective (increases eradication rate by 5%), but is cost effective for clarithromycin resistant bacteria. Moreover, in patients with metronidazole resistant bacteria, metronidazole base therapy eradicated the bacteria in up to 42% of patients [4]. The data suggest that "laboratory resistant" may not always translate into treatment failure, and it is antibiotic specific. The tissue culture procedure of *H. pylori* is cumbersome, difficult to obtain, expensive, and mainly unavailable for most practicing physicians around the world. Thus, it is mandatory to establish its clinical importance before embarking on another recommendation that no practicing physician can follow. More prospectively, blind-controlled studies in children are needed to establish this necessity. In the present study, the therapeutic antibiotic regimen, follow-up clinical data, and eradication rate were not provided; thus, no assessment of this point could be done.

In conclusion, the study by Argentieri et al. [4] provided us the opportunity to examine the existing difficulties of evaluating the different invasive and non-invasive diagnostic tests for *H. pylori* infection in children. Future studies are needed to find a non-invasive test that will genuinely meet the accuracy level needed to establish the gold standard test for *H. pylori* infection in children.

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