Reviewer's report

Title: 13C-Urea Breath Test Threshold Calculation and Evaluation for the Detection of Helicobacter pylori Infection in Children

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Reviewer: Prof Francois Mion

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

This study deals with the question of threshold calculation of the urea breath test in children. As mentioned by the authors, several articles have already been published on this subject, both in the adult and pediatric population. The authors use original statistical methods to calculate the optimal threshold of the test: I am not very familiar with these methods, and a review of their manuscript by a statistician would be advisable.

I have several concerns regarding the work presented here, that should be addressed by the authors before a decision of publication is made:

1) first, the proposed threshold of 5.3 or 5.8 delta is significantly higher than recently published threshold around 3 delta (the authors should add the threshold of the Gambian study (ref 16) that is missing in the background section): the authors should comment on these discrepancies in the discussion section. Of note is the fact that their Hp negative population has a much higher delta value (median at 2.4) than what is usually reported in the literature (see Delvin et al. JPGN 1999;25:59-62, mean delta value of Hp negative children at 0.97). My feeling is that differences are mainly due to the way UBTs are performed (test meal, citric acid and so on), and that thresholds should be validated by each lab for its own population rather than looking for universal standardisation.

2) Methods are not adequately described: it is unclear whether citric acid was given with the urea, and this is an important point, since it has been shown that citric acid solution may increase the distinction between Hp positive and negative subjects (see Eggers et al. Eur J Gastroenterol Hepatol 1990;2:437-44, or Leodolter et al. Aliment Pharmacol Ther 1999;13:1057-62 ) (the meal may also decrease the efficacy of the test to distinguish between positive and negative subjects as it may increase the 13CO2 enrichment per se ); it is unclear whether the presence of Hp on the four biopsy specimens was required to state that a patient was Hp positive (in this case, this may explain why their cut-off value is so high), or if the presence of Hp on one biopsy was regarded as sufficient. A second lecture of histological slides with predefined criteria for the diagnosis of Hp infection would be of interest, and the pathologist could then be associated as an author of the paper; it is also unclear how urea was administered and how breath sampling was managed in children younger than 4 (difficulties may arise in this population for the ingestion of urea and to obtain adequate breath samples at the correct time: this may explain the much larger SD of their threshold compared to the other age groups); authors should comment on the fact that the UBT comparison with histology was performed in children...
older than 5, while a significant proportion of UBTs performed alone were so in children much younger.  
3) Minor points: instead of "Hp-antigens" (line 4 of background section), probably read "anti-Hp antibodies"; table 1: what "BM (methods of analysis)" stands for? it is not clear to me what the values of the vertical axis of figure 1 represent: it would be better is actual number of patients were represented (otherwise indicate on the figure the significance of the scale); in figures 2 and 3, plots A and B are probably inverted, if I understand correctly the legends; in figure 3, adding the words sensitivity and specificity under their corresponding curves will increase the understanding of the figure.

Competing interests:

This reviewer was a member of the European BIOMED project which funding helped for the realisation of this study.
This reviewer was however not involved in the design, realisation or interpretation of this work.