Author's response to reviews

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

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PDF covering letter
Dear Editor,

Thank you for sending us the reviewer’s report on our manuscript “{$^{13}$C-Urea Breath Test Threshold Calculation and Evaluation for the Detection of Helicobacter pylori Infection in Children”}. The reviewer’s detailed comments are very helpful. Now, we would like to re-submit our manuscript after revising it according to the reviewer’s concerns.

In the following, we address these concerns point by point:

Although several articles have already been published internationally, there are few studies on children with only small numbers of subjects investigated. Therefore, we sought to analyze our voluminous available data in depth and with robust methods.

1. The presented threshold (5.3 to 5.8 ‰) is in line with thresholds found by others: 4.8 to 5.0 ‰ (Kindermann 2000), 4.5 ‰ (Bazzoli 2000) and with the Gambian study cited also by the reviewer: 5.47 ‰ (Thomas 1999). However, only the first report investigated a large number of subjects; the second examined 65 children and the Gambian study validated the breath test results in only 14 children with histology, although results of more than 1500 UBTs in 247 children were analyzed. In the manuscript, we added the Gambian study's threshold to the background section.

Averages and ranges previously reported for those subjects who were negative on biopsy were 2 to 3 ‰ (Thomas 1999), 0.53 to 1.22 ‰ (Kindermann 2000), 1.5 ± 0.8 ‰ (Kalach 1998, 100 children) and 0.97 ‰ in the study cited (Delvin 1999). In the latter study, the range of original measurements was -0.2 to 2.83 ‰. However, these measurements were not modeled as in our study for the purpose of threshold calculating. Instead, a threshold value was arbitrarily chosen (such as 3 ‰).

In contrast, it was indeed the intention of our study to not choose a threshold, but to feed all measurements into a suitable model, which then provided an analytical and robust estimator for thresholds. Thus, our delta values in negative children are not directly comparable to the cited values.

We would therefore not necessarily attribute differences to the way the UBTs are performed. Many investigators used values obtained 30 minutes after {$^{13}$C} ingestion and rather similar test meals (Bazzoli 2000).

In contrast to adults, UBT meals for children do generally not contain citric acid because citric acid is disliked by children for its taste. We also deliberately did not give apple juice (which is acidic as citric acid) because of the contained {$^{13}$C} sugar compounds. These points also apply to the beginning of the reviewer’s 2. paragraph. To our knowledge, the application of citric acid is standard in adults, as shown by the cited references.
2. We now included a statement on the test meal composition (as explained above) in the methods section.

Our prospective study required HP to be present in at least one biopsy specimen. When positive biopsies occurred, these were always positive in both of the two antral biopsy specimens. Inconsistently, the corpus mucosa was positive in addition to the two positive antral specimens.

The pathologist was blinded to all specimens; established staining methods and criteria were applied (Caspary 1996). We included these methodological clarifications into the corresponding section of our manuscript.

With regard to children younger than four years, we experienced no insurmountable problems in our earlier feasibility study (Kehrt 1997). In detail: If a child could not expire into the collection bag, breath samples were collected by applying a breath mask with two unidirectional valves connected to a breath bag, permitting the child to breathe freely. The normal respiratory activity filled the bag, from which a sample was drawn and transferred to an evacuated tube (Kehrt 1997).

In children younger than four years, analyses of histology (in conjunction with UBT values) were not done because children in almost no case presented with symptoms indicating endoscopy. We now included this information into our manuscript.

3. According to the reviewer’s suggestion, we corrected our manuscript (“anti-HP antibodies”). The unclear abbreviations in table 1 are now explained in a corresponding legend.

The vertical axis of figure 1 represents the bin height that is scaled to give a unit area under the curve, as stated in the calculations section.

We apologize for confusingly interchanging the A and B plots on figures 2 and 3.

According to the suggestion, we also added curve labels to figure 3.

We would appreciate very much if our revised manuscript is suitable for publication.

Sincerely

Ralf Preud'homme

References