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Answering reviewers

In the paper, "Limitations of urease test in diagnosis of pediatric *Helicobacter pylori* infection", the authors Seo et al. give a very interesting overview of experiences using this test in children, with the observation of lower sensitivity, in particular in small children, and discussion of possible reasons, obstacles and consequences. The paper is well written, the language is near perfect, the figures are nice, and the conclusions are convincing.

→ Thank you for your consideration and kind advice. All authors discussed it carefully. We removed our data and added the Table and copied the figure from the published article.

Although the work basically is intended to be a review, the authors present some interesting results of their own research. Here, they should also report their methodology, including materials and methods. For example, the authors describe that they compared the time points at which the positive result occurred, dividing these into 0-1 hour, 1-6 hours, and 6-24 hours, leading to higher sensitivity especially in the younger age group. However, this type of long-term incubation of the assessment probe is not further explained, which should be done. Further, no error bars or calculations of significance are given.

- Thank you for your advice. We removed our data in original manuscript because it is review article.**
- As your comment, the time for reading the urease test is important and we added next sentence in the introduction.**
- The last sentence of the page 1 in Introduction. "The time at which the urease test turns positive depends on the concentration of the bacteria and the temperature. Most commercially available urease tests will turn positive within 2-3 hours, but it is best to retain those samples**

that appear negative for 24 hours, regardless of the age of the patient [Reference 14].”

Besides, there are no figures or tables showing analyses of other authors. At least, results of other groups should be presented a bit more in detail in a review.

→ We agreed with you. So, we added the table and the copied the figure from the published article with permission. We changed all paragraphs in the “EFFECT OF THE NUMBER OF GASTRIC BIOPSY SPECIMENS” and most sentences in the “EFFECT OF BIOPSY SITE ON UREASE TEST RESULTS”.

→ “Table 1. Summary of the studies on the effect of biopsy sites and biopsy numbers on the positivity rate of the urease test

	<i>Published year</i>	<i>Number of participants/patients</i>	<i>Mean age (years)</i>	<i>Conditions compared</i>	<i>Positivity rate of urease test (%)</i>
<i>Siddique, et al. [24]</i>	2008	100 adults	36.1	One biopsy	
				Two biopsies	52
				Three biopsies	68
				Four biopsies	76
<i>Seo, et al. [19]</i>	2014	255 children	NA*	One biopsy	32.2
				Three biopsies	40.1
<i>Moon, et al. [25]</i>	2012	214 adults	53.6	Antrum body	58.9
				Antrum + body	62.1
				Antrum + body	69.2
<i>Lan, et al. [26]</i>	2012	164 adults	NA*	Antrum + corpus	83.3 100

→ Figure 1. The positivity rate and positive timing of the urease test both in the antrum and body according to age. The positivity rate of the urease test in the antrum was higher in 20-29 years group comparing with that in other three age groups, and the positivity rate of the urease test in the body decreased with increasing age (P <0.0001). The highest positivity timing was within 1 hour in the 20-29 years group, and within 6-24 hours in children (P <0.0001). The proportions of positive reactions within 1 hour (the darkest red color)

were similar for the antrum and body in all groups. Reproduced from Seo JH, et al. Pediatr Gastroenterol Hepatol Nutr 2013;16:34-40, with permission of Korean Society of Pediatric Gastroenterology, Hepatology and Nutrition^[20]."

Possible methodological obstacles both regarding urease and histological analyses should be given more in detail, and in the conclusion, a clear recommendation should be given: which number of biopsies should be done at which age group, in order to prove or clearly exclude helicobacter infection, and which incubation time should be standard.

- ➔ **Thank you for your advice and we changed the sentence in conclusion as follow.**
- ➔ **As you know, the most commonly suggested obstacles of the low sensitivity of urease test and histology in children are low density of bacteria and patchy distribution. Other possible obstacle is the size of biopsy forcep but previous our study showed that the positivity rate of urease test and the degree of gastritis were higher in adults than in children when using same biopsy forcep.**
- ➔ **"Use of 3 or more biopsy samples from both the antrum and body would improve the sensitivity of *H. pylori* detection in children under 5 years old. "**

Minor Points: p. 5 Instead of ...years (n = 224)[20].positive results... Better write ...years (n = 224)[20]. Positive results...

- ➔ **Thank you! We corrected "positive" to "Positive".**

p.7 the sentence In most patients, biopsy specimens were taken from the antrum because antral area for heaviest colonization for *H. pylori* may be the lesser curve at the angulus, in the prepyloric region[26]. appears a bit confuse and should be reorganised.

- ➔ **Thank you for your suggestion. We changed the sentence as follow.**
- ➔ ***In most patients, biopsy specimens were taken from the antrum because one biopsy from the gastric angle for urease test had the maximum probability for detecting *H. pylori* infection [26].***