ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Importance of Delta Over Baseline Values in Predicting the Severity of *Helicobacter pylori* Infection in Children

Çocuklarda *Helicobacter pylori* Enfeksiyonunun Şiddetini Tespit Etmede Başlangıca göre Delta Değerlerinin Önemi

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Abstract

Introduction: Although severe forms of the disease are seen in adults, the *Helicobacter pylori (H. pylori)* infection is usually acquired during childhood. Therefore, prompt diagnosis of *H. pylori* infection in childhood is of prime importance. In the present study, we aimed to identify the sensitivity and specificity of 13C urea breath test (UBT) in the diagnosis of *H. pylori* infection and to assess the severity of the disease with delta over baseline (DOB) values.

Materials and Methods: UBT was administered to 200 children who presented with epigastric pain and/or nausea. Esophagogastroduodenoscopy (EGD) was performed in patients. UBT results were compared with histopathological findings. In the Area Under the ROC Curve analysis, a cutoff DOB value was found for the severity of *H. pylori* infection.

Results: 193 children with a mean age of 13.50±2.98 years were included in the analysis. Of these, 71 (36.8%) patients had a positive UBT and 122 (63.2%) had a negative UBT. EGD was performed in 60 out of 71 patients with positive UBT and in 30 out of 122 patients with negative UBT. The sensitivity and specificity of UBT were 85.1% and 100%. DOB was found to be a significant predictor of moderate/marked *H. pylori* density at a cutoff value of 6%.

Conclusions: The positive correlation detected between the level of DOB values and the density of *H. pylori* and inflammatory activity can be an advantage for detecting the severity of disease

Keywords
H. pylori, child, urea breath test

Anahtar kelimeler
H. pylori, çocuk, üre nefes testi

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Öz

Giriş: Yetişkinlerde ağır formları görülmekle birlikte, *Helicobacter pylori (H. pylori)* enfeksiyonu genellikle çocukluk çağında kazanılır. Bu nedenle, çocukluk çağında *H. pylori* enfeksiyonunun erken tanısı çok önemlidir. Bu çalışmada, *H. pylori* enfeksiyonu tanısında 13C üre nefes testinin (ÜNT) duyarlılığını ve özgüllüğünü bulmayı, delta değeri (DOB) ile hastalığın şiddetini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Epigastrik ağrı ve/veya bulantı şikayeti ile başvuran 200 çocuğa UBT uygulandı. Hastalara özofagogastroduodenoskopi (ÖGD) yapıldı. ÜNT sonuçları histopatolojik bulgularla karşılaştırıldı. ROC eğrisi analizi ile *H. pylori* enfeksiyonunun şiddeti için bir belirleyici DOB değeri bulundu.

Bulgular: Yaş ortalaması 13,50±2,98 yıl olan 193 hasta araştırmaya alındı. Bu hastaların 71'i (%36,8) ÜNT pozitif, 122'si (%63,2) negatif olarak tespit edildi. ÜNT pozitif olan 71 hastanın 60'ına, ÜNT negatif olan 122 hastanın 30'una ÖGD yapıldı. ÜNT'nin duyarlılığı %85,1, özgüllüğü %100 tespit edildi. Orta/belirgin *H. pylori* yoğunluğu için DOB kesim değeri %6 olarak bulundu.

Sonuç: DOB değerleri ile *H. pylori* yoğunluğu ve enflamatuar aktivite arasındaki pozitif korelasyon, hastalığın şiddetini tespit etmek için bir avantaj olabilir.

Introduction

Helicobacter pylori (H. pylori) is a flagellated, gram-negative microaerophilic bacterium infecting over 50% of world's population with higher prevalence in developing countries (1). It is also a common cause of peptic ulcer, gastric cancer and MALT lymphoma and although adults are usually diagnosed with severe forms of the disease, the infection is usually acquired during childhood (2). Failure to administer an effective eradication therapy in the early stages of the infection may lead to long-term complications. Therefore, prompt diagnosis of the infection in childhood is of prime importance.

Both invasive and noninvasive methods are currently used for the diagnosis of *H. pylori* infection. Among these, invasive tests include histopathological examination, culture analysis, and rapid urease test (RUT), while noninvasive tests are serological tests that do not require endoscopic examination, including urea breath test (UBT), stool antigen test, and antibody tests in blood, salivary, and urine.

The UBT is an accurate noninvasive test for detecting *H. pylori* infection which is based on the activity of bacterial urease in the presence of isotopically labeled urea. If bacteria are present in the stomach, the urea is hydrolyzed into carbon dioxide (CO_2) and ammonia. Labeled CO2 diffuses in the blood and is cleared from the lungs in exhaled breath and is usually measured by isotope ratio mass spectrometry (IRMS).

Literature indicates that UBT is a cheaper, safer and more useful method than invasive tests in the diagnosis of *H. pylori* infection. Additionally, UBT has been reported to have a sensitivity and specificity of greater than 90% (3). The European *H. pylori* Study Group recommended UBT for the diagnosis and assessment of *H. pylori* infection after eradication treatment (2). According to the European and North American Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN and NASPGHAN) guidelines, UBT is a reliable test to determine whether *H. pylori* has been eradicated (4).

On the other hand, the optimal standardization of a delta over baseline (DOB) value has not yet been achieved. In a previous study, a cutoff value of 5% was determined based on the Standard European protocol for the differentiation of positive and negative UBT results (5). In later years, this value was reduced to 3.5% by Johnston et al. based on their Receiver Operating Characteristic (ROC) curve analysis (6). Subsequently, the value was determined as 3% by Mion et al. via cluster analysis (7). Similarly, this value has been shown to vary among children as well, whereby a cutoff value of 7% has been recommended for children aged under six years and a value of 4% has been proposed for children aged over six years (8). Additionally, it has been shown that this value may be affected by numerous other factors such as gender, ethnic origin, hunger, and drug use (9).

The present study was designed to investigate the sensitivity and specificity of UBT and to determine an optimal cutoff value for DOB in the diagnosis of *H. pylori* infection.

Materials and Methods

Study Population

The prospective study included a total of 200 children aged 4-18 years who were admitted to Pediatric Gastroenterology Clinic with symptoms including epigastric pain and/or nausea that persisted for more than one month and underwent ^{13}C urea breath test between November 2015 and August 2016. Exclusion criteria included the use of antibiotics within the last four weeks, acid suppressive drugs within the last four weeks, and H_2 receptor blocker within the last two days before testing.

Study Protocol

After 4 hours of fasting, a basal breath sample was collected by blowing into a specially designed bag and patients received 1 g citric acid and 75 mg ^{13}C-labelled urea in 100 ml water respectively. After 30 minutes, a secondary breath sample was collected.

The ^{13}C-UBT was performed both at baseline and at 30 min using a dispersive infrared spectrometer (Heli FAN plus, Fischer ANalysen Instrumente GmbH, Germany). The results were considered positive when the DOB value was >4%.

Upper Gastrointestinal Endoscopy

Esophagogastroduodenoscopy (EGD) was performed under general anesthesia by the same pediatric gastroenterologist. Tissue samples were obtained from the antrum and then were sent for histopathological examination.

Histopathology

The specimens were fixed in 10% formaldehyde and then processed in paraffin and sectioned. The paraffin blocks were stained with hematoxylin-eosin and graded in terms of active inflammation, chronic inflammation, and *H. pylori* density according to the updated Sydney System which is based on a four-point scale (0=none, 1=slight, 2=moderate, 3=marked) (10).

The study was approved by Medical School Ethical Committee. Patients and parents were briefed about the study and provided a signed informed consent form.

Statistical Analysis

Data were analyzed using SPSS for Windows version 22.0 (IBM SPSS Inc., Armonk, NY, USA). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the UBT test were calculated. Groups were compared using Independent Samples t-test and Mann-Whitney U test. A receiver operating characteristic (ROC) curve analysis with the Area Under the ROC Curve (AUC) was performed, whereby an AUC value of 1 was accepted to indicate perfect accuracy, a value of >0.9 to indicate high accuracy, and a value between 0.7 and 0.9 to indicate moderate accuracy.

Results

The ^{13}C-UBT was administered to 200 patients, among whom 7 patients were excluded due to various technical reasons. As a result, 193 children were included in the study, including 134 (69.4%) girls and 59 (30.6%) boys with a mean age of 13.50±2.98 (range, 4-18) years and a median age of 14 years.

Of the 193 children, 71 (36.8%) of them had a positive UBT and 122 (63.2%) had a negative UBT. The mean DOB value was 32.63±22.25 (median, 28.00; range, 4.2-111.8) in the positive UBT group and was 0.92±0.89 (median, 0.70; range: 0.1-3,9) in the negative UBT group and a significant difference was found between the two groups ($p<0.05$).

Upper gastrointestinal endoscopy was performed in 60 (84.5%) out of 71 patients with positive UBT and in 30 (24.6%) out of 122 patients with negative UBT. The flowchart of the study is shown in Figure 1.

In the histological examination, the *H. pylori* density was graded as Grade 1 in 7, Grade 2 in 21, and Grade 3 in 32 patients in the positive UBT group and was graded as Grade 0 in 20, Grade 1 in 3, and Grade 2 in 4, and Grade 3 in 3 patients in the negative UBT group (Table 1). In terms of inflammatory activity, 4 patients were graded as Grade 1, 34 patients as Grade 2, and 22 patients as Grade 3 in the positive UBT group and 22 patients were graded as Grade 1, 5 patients as Grade 2, and 3 patients as Grade 3 in the negative UBT group (Table 1).

The sensitivity and specificity of UBT were 85.1% (CI 95%, 75.3-92.9%) and 100% (CI 95%, 83.2-100%), respectively. The PPV and NPV were 100% (CI 95%, 94-100%) and 66.7% (CI 95%, 47.2-82.7%), respectively.

In the AUC analysis, DOB was found to be a significant predictor of *H. pylori* at a cutoff value of 2% (AUC=0.913, $p<0.05$, 95% CI: 85.2-97.4%),

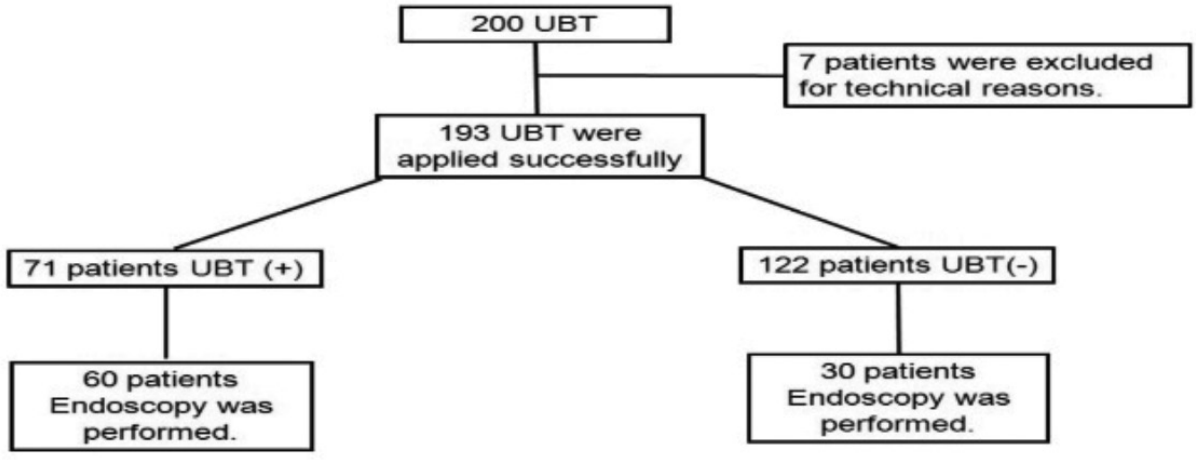

Figure 1. A flowchart of the study.

with a sensitivity and specificity of 90% and 80%, respectively (Figure 2A). Moreover, DOB was also found to be a significant predictor of moderate/marked *H. pylori* density at a cutoff value of 6% (AUC=0.806, p<0.05, 95% CI: 69.5-91.8%), with a sensitivity and specificity of 89.8% and 80.6%, respectively (Figure 2B). Similarly, DOB was revealed to be a significant predictor of marked *H. pylori* density at a cutoff value of 8.05% (AUC=0.680, p<0.05, 95% CI: 57.0-79.0%), with a sensitivity and specificity of 88.2% and 51.8%, respectively (Figure 2C).

On the other hand, a positive correlation was found between the level of DOB values and *H. pylori* density (p<0.01) and inflammatory activity (p<0.01) (Figure 3,4).

Discussion

About one-third of all children worldwide are infected with *H. pylori*. Since patients often present with insignificant symptoms such as dyspepsia and nausea, *H. pylori* infection can be difficult to diagnose, particularly in children. According to ESPGHAN and the European Society of Gastrointestinal Endoscopy (ESGE) Guidelines, endoscopy indications in children are highly limited. However, endoscopy is indicated in the presence of alarming symptoms such as weight loss, failure to thrive, unexplained anemia, dysphagia or odynophagia, and recurrent vomiting (11). Accumulating evidence suggests that an invasive technique is mandatory for the diagnosis of *H. pylori* while a noninvasive technique could be employed for follow-up examinations after the eradication therapy (2). Accordingly, the primary aim of future studies should be to determine an optimal noninvasive test with an acceptable sensitivity and specificity and thereby to reduce the need for invasive tests in the diagnosis of *H. pylori*.

To date, numerous noninvasive tests have been developed for the diagnosis of *H. pylori*, including serological tests (blood, saliva), fecal antigen test, and UBT, and also there have been several studies comparing these tests (3,12,13). The American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA) recommend

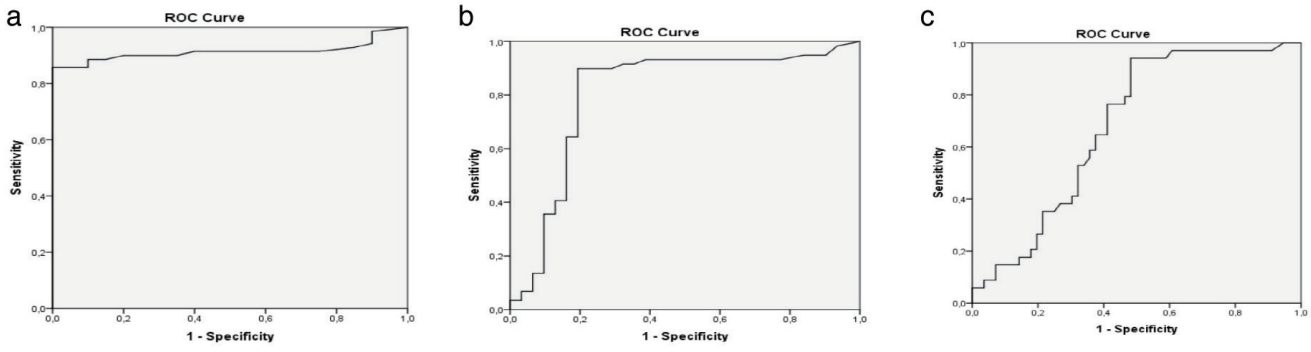

Figure 2. ROC curves for relationship between UBT and *Helicobacter pylori* density.
a) DOB for predicting *H. pylori* in patients (AUROC: 0.913, p<0.05, 95% CI: 85.2 - 97.4) with a cut off ratio value of 2.00%.
b) DOB for predicting moderate/marked *H. pylori* density in patients (AUROC: 0.806, p<0.05, 95% CI: 69.5 - 91.8) with a cut off ratio value of 6.00%.
c) DOB for predicting marked *H. pylori* density in patients (AUROC: 0.680, p<0.05, 95% CI: 57.0 - 79.0) with a cut off ratio value of 8.05%.

Table 1. Correlations between UBT results and *Helicobacter pylori* density and inflammatory activity

Density of *H. pylori*	Grade 0	Grade 1	Grade 2	Grade 3	Total	p
UBT (+)	0	7	21	32	60	<0.001
UBT (-)	20	3	4	3	30	
Inflammatory Activity						
UBT (+)	0	4	34	22	60	<0.001
UBT (-)	0	22	5	3	30	

UBT and fecal antigen test for the diagnosis of active *H. pylori* infection (14). In the present study, we assessed the value of UBT and also evaluated the role of DOB value in the diagnosis of *H. pylori* infection.

In our study, the sensitivity and specificity of UBT in comparison to histopathological diagnosis were 85.1% and 100%, respectively. These values have been shown to vary in numerous studies. Kalach et al. reported the sensitivity and specificity of UBT as 93.3% and 100% (15) and Rowland et al. reported them as 100% and 97.6%, respectively (16), while Delvin et al. reported a value of 100% for both sensitivity and specificity (17). A Turkish study by Kuloğlu et al. reported them as 92.5% and 85.5% (18) while an Iranian study by Honar et al. reported them as 76.2% and 69.2%, respectively (1). In a Cochrane study reported in 2018, the sensitivity and specificity

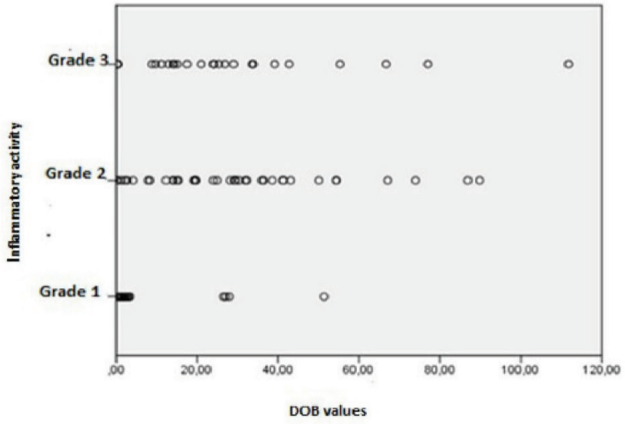

Figure 3. The relationship between the level of DOB values and inflammatory activity (p<0.01).

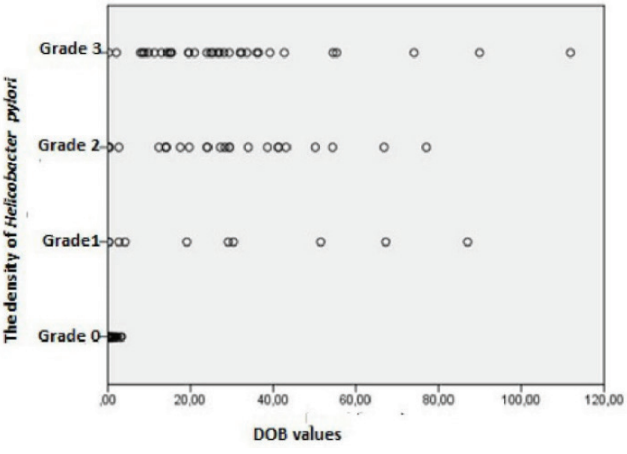

Figure 4. The relationship between the level of DOB values and the density *Helicobacter pylori* (p<0.01).

were 90% and 94% for UBT-^{13}C, respectively, and the authors indicated that UBT had a high diagnostic accuracy in people without a history of gastrectomy and in patients with no recent use of antibiotics and proton pump inhibitors (19). A meta-analysis by Zhou et al. indicated that the sensitivity and specificity were 90% and 94%, respectively, and the AUC was 0.986. The authors also noted that the heterogeneity (age, gender, test administration) in these values could be associated with the differences in testing intervals and thus a standardization is needed (20). Another study proposed that this standardization could be achieved with mathematical approaches such as the finite mixture model (FMM) (21).

Literature indicates that the UBT studies in children are relatively less limited. Leal et al. reported a systematic review and meta-analyses in 2011 and showed that UBT is a reliable test in all ages, with a sensitivity and specificity of 95.9% and 95.7%, respectively (2). On the other hand, there are some studies suggesting that different DOB values are needed in the assessment of children. Yang et al. recommended a cutoff value of 7% for children aged under six years and a value of 4% for children aged over six years (8). In contrast, a previous meta-analysis proposed that the cutoff value should be at least 6% for the diagnosis of children aged under six years (2). These high cutoff values could be associated that the higher frequency of urease-producing bacteria such as *Streptococcus salivarius, Proteus mirabilis*, and *Klebsiella pneumonia* in the oral cavity in children. Additionally, these values could also be attributed to the relatively higher standard 13C urea doses based on age and body weight in children (9). In our study, the optimal cutoff value of DOB for the diagnosis of moderate/marked *H. pylori* infection was determined as 6%.

In our study, a positive correlation was found between the level of DOB values and *H. pylori* density and inflammatory activity, which could be a useful factor in the assessment of disease severity. To our knowledge, this relationship has been documented in a limited number of studies. Chang et al. reported that UBT is a reliable test for the assessment of *H. pylori* density and the activity and degree of gastritis (22,23). Nawacki et al. found a relationship between DOB values and endoscopic findings and reported that peptic ulcer was diagnosed in patients with a DOB

value of >20% (24). In the present study, although no evaluation of endoscopic findings was performed, marked *H. pylori* density was detected in patients with a DOB value of >8.05%. Based on these findings, we suggest that the cutoff value of DOB could be a guiding factor in the assessment of endoscopy indication. Nevertheless, further studies are needed to substantiate this hypothesis.

Endoscopy is an invasive and expensive diagnostic method requiring special monitoring, equipment, small endoscopes, and skilled nurses and physicians (25). Moreover, it is also difficult to convince parents and patients for an endoscopic examination under anesthesia. For all these reasons, a reliable, cost-effective, and noninvasive test is needed for the diagnosis of *H. pylori* infection. In this regard, UBT could be suitable alternative to endoscopy since it has no side effects and is also easy to administered. In a previous comprehensive study, Boklage et al. reported that UBT was revealed as a favorable cost-effective test in the diagnosis of *H. pylori* infection due to high patient adherence, long-term consequences, and excellent test performance (26). On the other hand, another study argued that the UBT results may change based on several factors including isotope dosing, fasting time, duration of breath collection, cutoff value, and the amount of citric acid and gastric emptying (27). Additionally, normal CO2 has been reported to vary based on age, gender, and basal metabolic rate (28). Nevertheless, UBT has been shown to be a less reliable test for children aged under six years mainly because young children produce relatively less endogenous CO2 due to their low body weight and height (2), which, in turn, could lead to false positive results. In light of these findings, we recommend that a standardization program such as FMM should be administered in children as well and that further studies are needed.

Study Limitations

Our study was limited since it had a small number of patients in the control group and the performance of the UBT test could not be confirmed by a third diagnostic method such as RUT. Secondly, no evaluation of endoscopic findings was performed and there were only two patients aged under six years.

Conclusion

In conclusion, UBT can be a safe, cost-effective non-invasive diagnostic test. DOB values, despite being affected by numerous factors, could provide useful information regarding disease severity. Further studies administering a standardization program such as FMM and determining cutoff values based on different variables are needed to reduce the need for invasive techniques. Based on these findings, the cut-off value of DOB could be a guiding factor in the assessment of endoscopy indication.

Ethics

Ethics Committee Approval: The study was approved by Medical School Ethical Committee. Patients and parents were briefed about the study and provided a signed informed consent form.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Honar N, Minazadeh A, Shakibazad N, et al. Diagnostic accuracy of urea breath test for H. pylori infection in children with dyspepsia in comparison to histopathology. Arq Gastroenterol. 2016;53:108-12.
2. Leal YA, Flores LL, Fuentes-Pananá EM, et al. 13C-urea breath test for the diagnosis of Helicobacter pylori infection in children: a systematic review and meta-analysis. Helicobacter. 2011;16:327-37.
3. Atkinson NS, Braden B. Helicobacter Pylori Infection: Diagnostic Strategies in Primary Diagnosis and After Therapy. Dig Dis Sci. 2016;61:19-24.
4. Koletzko S, Jones NL, Goodman KJ, et al. Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. J Pediatr Gastroenterol Nutr. 2011;53:230-43.
5. Eggers RH, Kulp A, Tegeler R. A methodological analysis of the 13Curea breath test for detection of Helicobacter pylori infections: high sensitivity and specificity within 30 min using 75 mg of 13C-urea. Eur J Gastro Hepatol. 1990;2:437-44.
6. Johnston BJ, Levi S, Johnson PG. Cut-off point for 13C-urea breath test. Gut. 1996;39:A122.
7. Mion F, Rosner G, Rousseau M, Minaire Y. 13C-urea breath test for Helicobacter pylori: Cut-off point determination by cluster analysis. Clin Sci. 1997;93:3-6.
8. Yang HR, Seo JK. Diagnostic accuracy of the C-urea breath test in children: adjustment of the cut-off value according to age. J Gastroenterol Hepatol. 2005;20:264-9.
9. Perets TT, Gingold-Belfer R, Leibovitzh H, et al. Optimization of (13) C-urea breath test threshold levels for the detection of Helicobacter pylori infection in a national referral laboratory. J Clin Lab Anal. 2019;33:e22674.

10. Dixon MF, Genta RM, Harley JH, et al. Classification and grading of gastritis. The updated Sydney system. Am J Surg Pathol 1996; 20: 1161-81.
11. Thomson M, Tringali A, Landi R, et al. Pediatric Gastrointestinal Endoscopy: European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and European Society of Gastrointestinal Endoscopy (ESGE) Guidelines Endoscopy. 2017;49:83-91.
12. Miftahussurur M, Yamaoka Y. Diagnostic Methods of Helicobacter pylori Infection for Epidemiological Studies: Critical Importance of Indirect Test Validation. Biomed Res Int. 2016;2016:4819423.
13. Tiryaki Z, Yilmaz-Ciftdoğan D, Kasirga E. Diagnostic value of stool antigen and antibody tests for Helicobacter pylori infection in Turkish children with upper gastrointestinal complaints before and after eradication. Turk J Pediatr. 2010;52:505-11.
14. Talley NJ. American Gastroenterological Association medical position statement: evaluation of dyspepsia. Gastroenterology. 2005;129: 1753-5.
15. Kalach N, Briet F, Raymond J, et al. The 13carbon urea breath test for the noninvasive detection of Helicobacter pylori in children: comparison with culture and determination of minimum analysis requirements. J Pediatr Gastroenterol Nutr.1998;26:291-6.
16. Rowland M, Lambert I, Gormally S, et al. Carbon 13-labeled urea breath test for the diagnosis of Helicobacter pylori infection in children. J Pediatr. 1997;131:815-20.
17. Delvin EE, Brazier JL, Deslandres C, et al. Accuracy of the [13C]-urea breath test in diagnosing Helicobacter pylori gastritis in pediatric patients. J Pediatr Gastroenterol Nutr.1999;28:59-62.
18. Kuloglu Z, Kansu A, Kirsaclioglu CT, Ustundag G, et al. A rapid lateral flow stool antigen immunoassay and (14)C-urea breath test for the diagnosis and eradication of Helicobacter pylori infection in children. Diagn Microbiol Infect Dis. 2008;62:351-6.
19. Best LM, Takwoingi Y, Siddique S, et al. Non-invasive diagnostic tests for Helicobacter pylori infection. Cochrane Database Syst Rev. 2018;3:CD012080.
20. Zhou Q, Li L, Ai Y, Pan Z, Guo M, Han J. Diagnostic accuracy of the (14)C-urea breath test in Helicobacter pylori infections: a meta-analysis. Wien Klin Wochenschr. 2017;129(1-2):38-45.
21. Li ZX, Huang LL, Liu C, Formichella L, Zhang Y, Wang YM, Zhang L, Ma JL, Liu WD, Ulm K, Wang JX, Zhang L, Bajbouj M, Li M, Vieth M, Quante M, Zhou T, Wang LH, Suchanek S, Soutschek E, Schmid R, Classen M, You WC, Gerhard M, Pan KF. Cut-off optimization for (13)C-urea breath test in a community-based trial by mathematic,histology and serology approach. Sci Rep. 2017;7(1):2072.
22. Chang YW, Min SK, Kim KJ, et al.Delta (13)C-urea breath test value is a useful indicator for Helicobacter pylori eradication in patients with functional dyspepsia. J Gastroenterol Hepatol. 2003;18:726-31.
23. Chang MC, Chang YT, Sun CT, et al. Quantitative correlation of Helicobacter pylori stool antigen (HpSA) test with 13C-urea breath test (13C-UBT) by the updated Sydney grading system of gastritis. Hepatogastroenterology. 2002;49:576-9.
24. Nawacki Ł, Czyż A, Bryk P, Kozieł D, Stępień R, Głuszek S. Can urea breath test (UBT) replace rapid urea test (RUT)? Pol Przegl Chir. 2018;90(5):44-8.
25. Lang T. Interfaces in Pediatric Gastrointestinal Endoscopy: Who Should Do It? Visc Med. 2016;32:7-11.
26. Boklage SH, Mangel AW, Ramamohan V,et al. Impact of patient adherence on the cost-effectiveness of noninvasive tests for the initial diagnosis of Helicobacter pylori infection in the United States. Patient Prefer Adherence. 2016;10:45-55.
27. Fock K. M, Katelaris P, Sugano K, et al. "Second Asia-Pacific consensus guidelines for Helicobacter pylori infection," Journal of Gastroenterology and Hepatology, 2009;24: 1587-1600.
28. Elitsur Y, Tolia V, Gilger MA, et al. Urea breath test in children: the United States prospective, multicenter study. Helicobacter. 2009;14:134-40.