

The Sensitivity and Specificity of the Modified Helicobacter Test INFAI Using New Test Meal with ¹³C-UBT in Helicobacter Pylori Positive and Negative Patients with Dyspepsia Taking PPI

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¹³C-Urea breath test

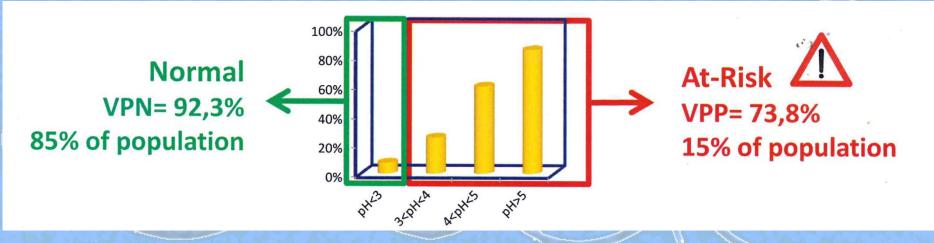
- The ¹³C-urea UBT remains the best test to diagnose H pylori infection
- Statement 4: In patients treated with PPIs: (1) if possible, PPI should be stopped for 2 weeks before testing by culture, histology, rapid urease test, UBT or stool test.
- Evidence level: 1b Grade of recommendation: A
- In the studies with patients on PPI therapy the accuracy of UBT has a 10% - 40% rate of false-negative results.

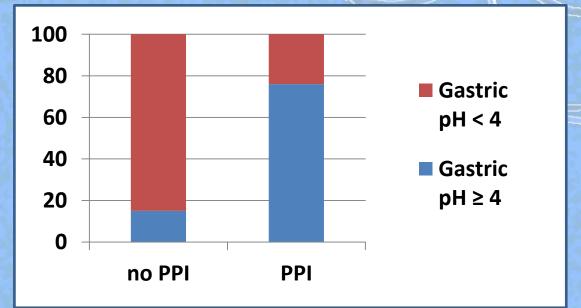
PPI use decrease sensitivity of UBT for detecting H pylori infection

- Several studies have shown that by increasing the gastric pH, PPI use leads to local changes in the stomach. The bacterial load decreases, especially in the antrum
- PPI use increase pH in the stomach, reduces H pylori urease activity, decrease urease entrance into bacteria, have direct antibacterial efect
- Available UBT should be used 14 days after stopping PPI

Malfertheiner P, et al. Gut 2012; 61: 646-64 Graham DY, et al. Am J Gastroenterol 2003; 98: 1005–1009

Why urease activity reduces by patient taking PPI?





Standard UBT

- ¹³C-labeled urea:
 - 75 mg (45 mg in children)
- Test meal:
 - Citric acid (1-4 g in 200 ml water) or orange juice (200 ml)
- Citric acid:
 - Decreases gastric emptying
 - Increases gastric acidity

Clinical important questions

What is the highest dose of citric acid that a patient can tolerate?

The highest concentration of citric acid used until now was 4.2 g in 200 ml water (Graham DY. Am J Gastroenterol 1999; 94: 1214-7)

- Is citric acid the only acid that can be used?
- What is the best acid (or combination of acids) for the test meal, when the patient is using PPI?

False Negative Urea Breath Tests With Proton Pump Inhibitors

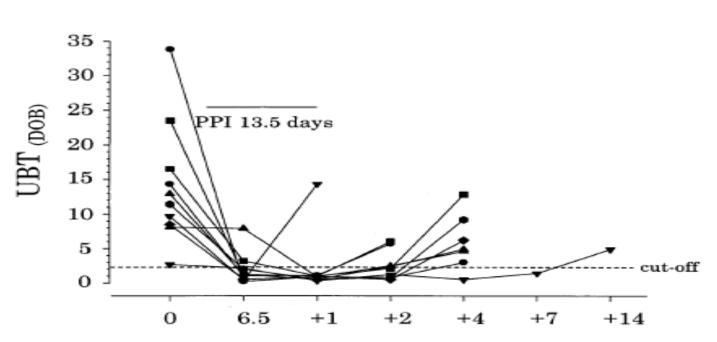
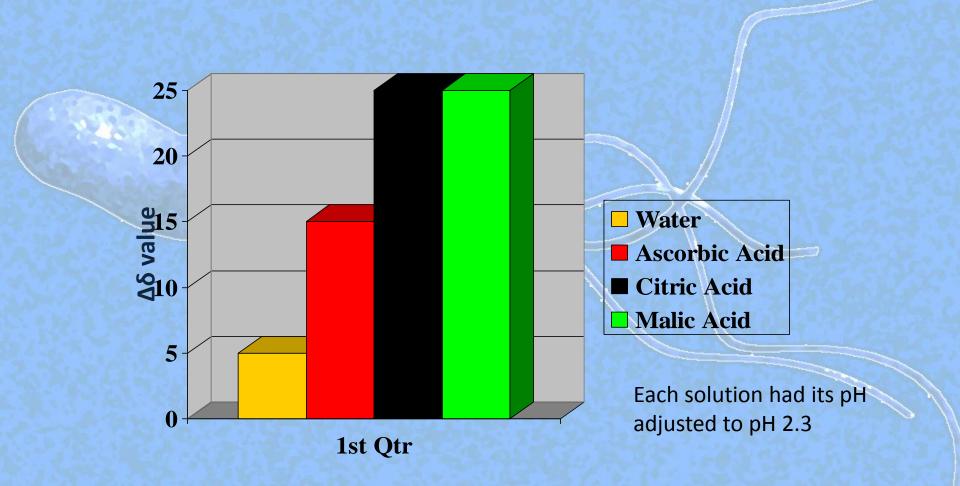


Figure 2. UBT results for the 10 subjects who developed transient false negative UBT results during therapy with omeprazole. All recovered by 14 days post-therapy. DOB, delta over baseline.

Is acid the only mechanism of action of citric acid?



Graham et al., Aliment Pharmacol Ther 2005; 21; 1145-1148

Clinical Trial - Study objectives

Primary Objective: The sensitivity of the ¹³C-UBT (UBT) test using the new test meal for Helicobacter pylori (Hp) in patients with dyspepsia taking a proton pump inhibitor (PPI) with one day break of medication.

Secondary Objectives: The specificity of the ¹³C-UBT using the new test meal for Hp in patients with dyspepsia taking PPI with one day break of medication. The safety and tolerance of the new test meal.

Study number: HPTM11/J/08 EudraCT-Nr.: 2008-008010-39

New test meal Refex® ¹³C-UBT to detect *Hp* in patients on PPI

Inclusion criteria:

- Male and female patients of at least 18 years of age
- Positive or negative standard ¹³C-UBT at screening.
- Diagnosis of Hp infection confirmed or excluded by combination of culture, histology and rapid urease test on samples obtained by endoscopy
- Written informed consent of the patient.

Exclusion criteria:

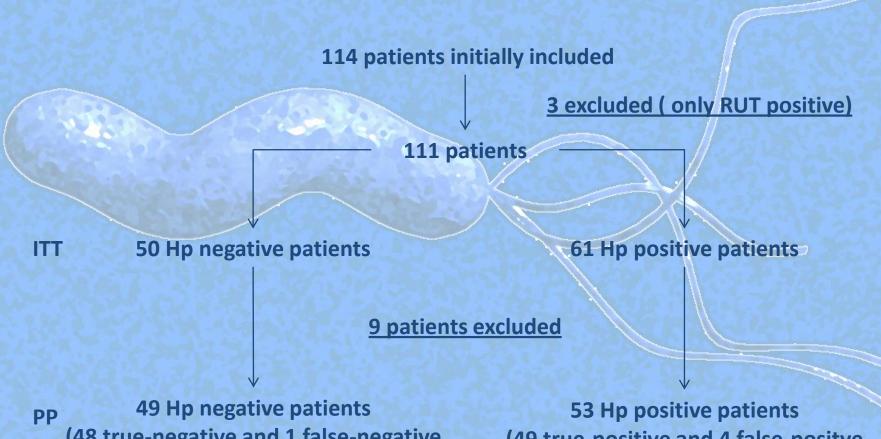
- Previous Hp eradication therapy.
- Intake of PPI, H2 receptor antagonists, NSAIDs, antibiotics, antisecretory
- drugs, bismuth compounds, or sucralfate in the 4 weeks prior to enrolment.
- Manifest coagulopathy or any other disorder according to which
- endoscopy and/or biopsies are contraindicated.
- Participation in a clinical trial with another not approved drug
- within 30 days before entering the study and/or previous
- participation in this study.
- Pregnancy

New test meal Refex® ¹³C-UBT to detect *Hp* in patients on PPI

- 111 consecutive patients, 61 Hp +, 50 Hp -
- Hp +/- based on RUT, histology, UBT, culture
- Nexium® (Esomeprazole) 40 mg x 29 days
- Analysis after one day stop on day 30
- The new test meal Refex® consist of 5,5 g (Citric acid, Malic acid and Tartaric acid)
- Delta value for positive UBT = 2,5‰.

Patient Population and Results of Hp diagnosis

(based on study diagnostic criteria and UBT with new test meal)



(48 true-negative and 1 false-negative based on a new test meal UBT)

(49 true-positive and 4 false-positive based on a new test meal UBT)

Sensitivity of the ¹³C-UBT test using the new test meal Refex® for Hp

	Population	Result of UBT with Refex®	Diagnos infec	is of Hp ction	Sensitivity	95% CI
l			Positive	Negative		
	ITT (N = 111)	Positive	50 (80.6%)	1 (2.0%)	80.65%	70.81% -
		Negative	12 (19.4%)	48 (98.0%)		90.48 %
	PP (N = 102)	Positive	49 (92.5%)	1 (2.0%)	92.45%	85.34% -
		Negative	4 (7.5%)	48 (98.0%)		99.56

CI: confidence interval, N: number of patients,

The specificity of the 13C-UBT test using the new test meal Refex® for Hp

Population	Result of UBT with Refex®		sis of Hp ction	Specificity	95% CI
		Positive	Negative		
ITT (N = 111)	Positive	50 (80.6%)	1 (2.0%)	97.96 %	94.00 %-
	Negative	12 (19.4%)	48 (98,0 %)		100.00 %
PP (N = 102)	Positive	49 (92.5%)	1 (2.0%)	97.96 %	94.00 %-
	Negative	4 (7.5%)	48 (98.0%)		100.00 %

CI: confidence interval, N: number of patients,

Patients 29 days on PPI medication, one day stop, different cut-off points 2 ‰, 2.5 ‰, 3 ‰

Cut-Off	Sensitivity	Specificity	PPV	NPV	Accuracy
2 ‰	92,45 %	97,95 %	98,00 %	92,31 %	95,10 %
2.5 ‰	92,45 %	97,96 %	98,00 %	92,31 %	95,10 %
3 ‰	86,79 %	97,96 %	97,87 %	87,27 %	92,16 %

How can we increase urease activity by patient taking PPI?

urease activity strong correlates with pH in stomach

- lowering pH (opens Urel channel for urea)
- providing Nickel to Hp
- chosing suitable cut-off point (delta value 2,5%)

New test meal Refex® 13C-UBT

- new test meal Refex® contains 5,5 g Citric acid, Malic acid and Tartaric acid
- Refex® supports:
 - lowering pH in stomach with the new test meal
 - new cut-off point (delta value 2,5%)
 - one day stop of PPI

New advance in UBT

New test meal Refex® (combination of citric acid, malic acid, tartaric acid) and using a <u>cut-off point of 2.5 ‰ allows the reliable detection of Hp</u>, while patient is on PPI, with <u>only one day PPI stop</u>.

Comparison Carbon-14 and Carbon-13 Breath Tests

	Comparison Carbon-14 and Carbon-13 Breath Tests							
	Carbon-14	Carbon-13	Carbon-12					
radioactive decay	radioactive, Half-Life: 5730 years beta-decay (0,157 MeV)	non-radioactive	non-radioactive					
natural abundance	1 part per trillion	1%	99%					
isotope mass	14 u (8 protons + 6 neutrons)	13 u (7 protons + 6 neutrons)	12 u (6 protons + 6 neutrons)					
breath test application	for diagnostic breath test for Hp urea labelled with approximately 37 kBq (37000 decays per second) C-14 is fed to a patient	for diagnostic breath test for Hp 75mg of urea labelled with approximately 99% C-13 is fed to a patient						
	cannot be used in children, pregnant or breast-feeding persons	approved for use in children, pregnant or breast-feeding persons						
	not registered as medical product, only as TAEK license	registered as medical product						
interpretation criteria	< 50 dpm at 10 min: negative for Hp	< 4 ‰: negative for Hp						
	50-190 dpm at 10 min: borderline, not detectable for Hp							
	> 200 dpm at 10 min: positive for Hp	> 4 ‰: positive for Hp						
sensitivity and specificity	lower than C-13 urea breath test	higher sensitivity and specificity						
expiry date	6 month	36 month						
radiation after test performance	described in attachment	no radiation						
transport	requires special transport for radioactive compounds	easy transport						
analysis	special department for radioactive compounds necessary	no requirements						

Radiation of Organs after C-14 Test Performance

Normal patient		Helicobacter pylori positive patient		
Organ	(microGy/MBq)	Organ	(microGy/ MBq)	
Or gan		0		
Bladder	120	Bone surfaces	120	
Bone surfaces	33	Bladder	110	
Stomach	30	Red marrow	97	
Red marrow	29	Stomach	83	
Adrenals	24	Adrenals	76	
Breast	24	Breast	76	
Oesophagus	24	Oesophagus	76	
Gall bladder	24	Gall bladder	76	
Brain	24	Brain	76	
Heart	24	Heart	76	
Skin	24	Skin	76	
Liver	24	Liver	76	
Lungs	24	Lungs	76	
Spleen	24	Spleen	76	
Muscles	24	Muscles	76	
Kidneys	24	Kidneys	76	
Ovaries	24	Ovaries	76	
Pancreas	24	Pancreas	76	
Thyroid	24	Thyroid	76	
Testes	24	Testes	76	
Thymus	24	Thymus	76	
Colon	24	Colon	76	
Jejunum	24	Jejunum	76	
Uterus	24	Uterus	76	
Remaining organs	24	Remaining	76	
2 2		organs		
Effective dose	31	Effective dose	81	
(microSv/MBq)		(microSv/MBq)		

Addendum to ICRP 53. ICRP publication 80. Ann ICRP 1998; Vol. 28 No. 3