Ελικοβακτηρίδιο του πυλωρού και… εκρίζωση

Μ. ΜΥΛΩΝΑΚΗ

Γαστρεντερολόγος

Επιμελήτρια Β'

Γενικό Κρατικό Νοσοκομείο Νίκαιας

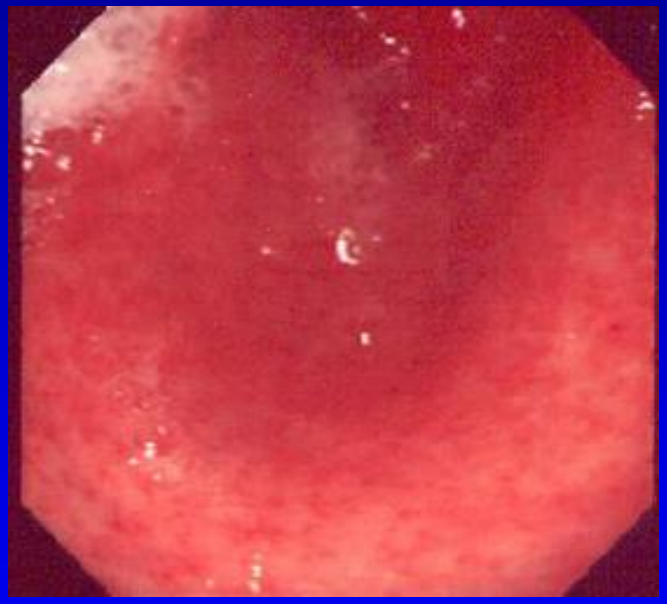
Γυναίκα ηλικίας 40 ετών με επιγαστραλγία από 6μήνου και ήπια σιδηροπενική αναιμία από έτους προσέρχεται για διερεύνηση.

- Υπερχοληστερολαιμία υπό αγωγή
- ***Κολονοσκόπηση:*** αραιά εκκολπώματα σιγμοειδούς χωρίς φλεγμονή
  - Άλγος ΑΛΒ + δυσκοιλιότητα
- ***U/S: κοιλίας και έσω γεννητικών οργάνων***
  - λιπώδης διήθηση ήπατος,

Εργαστηριακός έλεγχος

- **Σιδηροπενική αναιμία.**
  - ***Ht: 33.8%, Hb: 10.9gr/dl,*** MCV: 71, MCH: 24, MCHC: 31
  - Fe:55μg/dl, φερριτίνη: 8 ng/ml,
  - Αντισώματα κοιλιοκάκης (-)…..
- **Mayer κοπράνων x 3 (-)**

Ενδοσκόπηση



Γαστροπάθεια άντρου και σώματος

Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report

P Malfertheiner, F Megraud, C O'Morain, F Bazzoli, E El-Omar, D Graham, R Hunt, T Rokkas, N Vakil, E J Kuipers and The European Helicobacter Study Group (EHSG)

Box 1: Recommendations

1. *H pylori* eradication is appropriate for patients infected with *H pylori* and investigated non-ulcer dyspepsia.

Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report

P Malfertheiner, F Megraud, C O'Morain, F Bazzoli, E El-Omar, D Graham, R Hunt, T Rokkas, N Vakil, E J Kuipers and The European Helicobacter Study Group (EHSG)

Box 4: Recommendations

H pylori infection should be sought for and treated in patients with:

1. Unexplained iron deficiency anemia.
2. Idiopathic thrombocytopenic purpura.

H pylori has no proven role in other extraintestinal diseases.

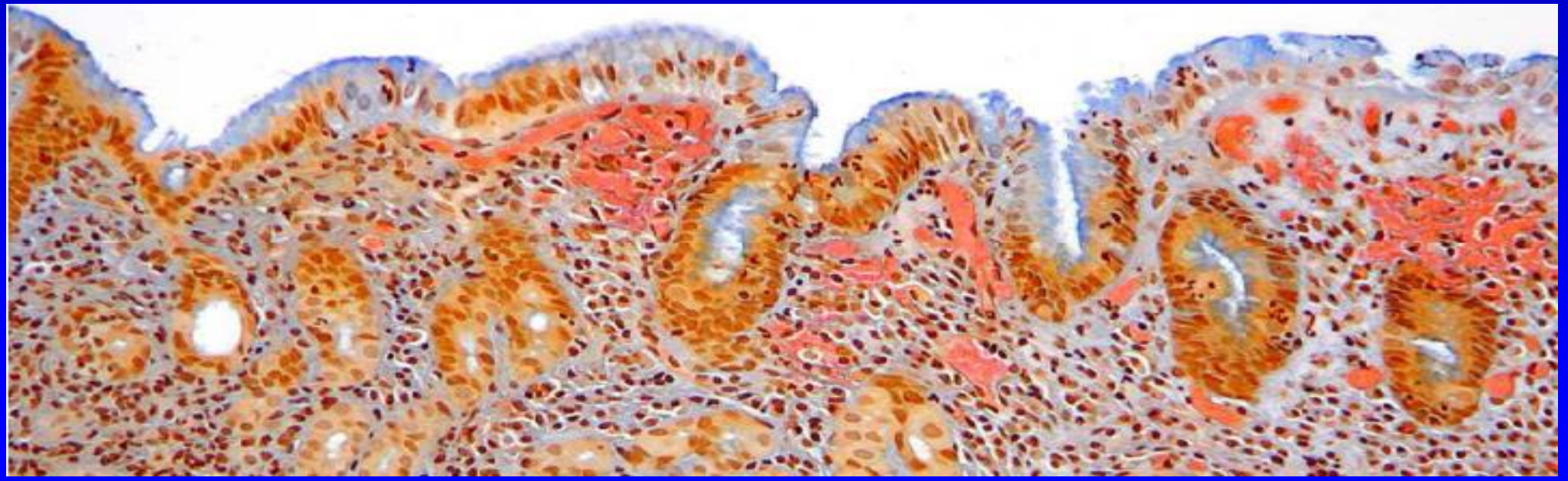
ΕΡΩΤΗΣΗ 1

Ποιο διαγνωστικό test θα χρησιμοποιήσουμε στην ασθενή?

- Test ουρεάσης (CLO test)
- Βιοψία
- Βιοψία-καλλιέργεια και δοκιμασία ευαισθησίας σε αντιβιοτικά
- ***CLO test και βιοψία***

Διαγνωστικές δοκιμασίες: αποτελέσματα

- ***CLO test (-)***
- ***Βιοψία: Hp (-)*** *χρόνια ενεργός πανγαστρίτιδα*



Ιστολογική εξέταση:

διαγνωστική ακρίβεια ανεύρεσης H.pylori

Ευαισθησία της τροποποιημένης Giemsa χρώσης ~90%

Leung χρώση~>90%

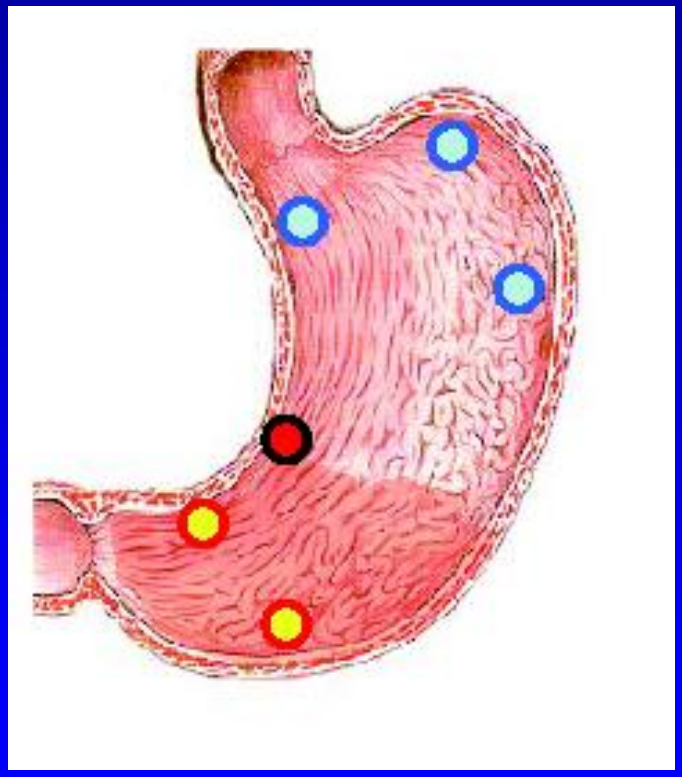
Ανοσοιστοχημεία για H.pylori >97%

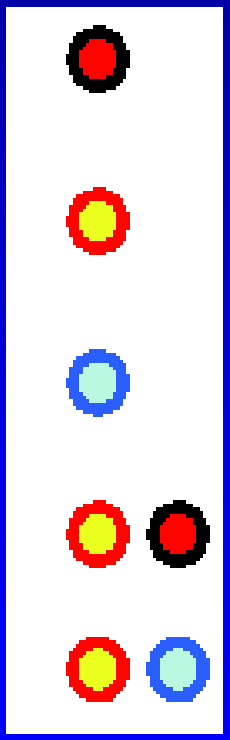
Laine et al, Gastrointestinal Endoscopy 1997;45:463

Vantanian et al, Mod Pathol 1998;11:72

Toulaymat et al, Arch Pathol Lab Med 1999;123: 778

Λήψη βιοψίας:
διαγνωστική ακρίβεια ανεύρεσης H. pylori





Γαστρική γωνία: 94%

Άντρο: 85-92%

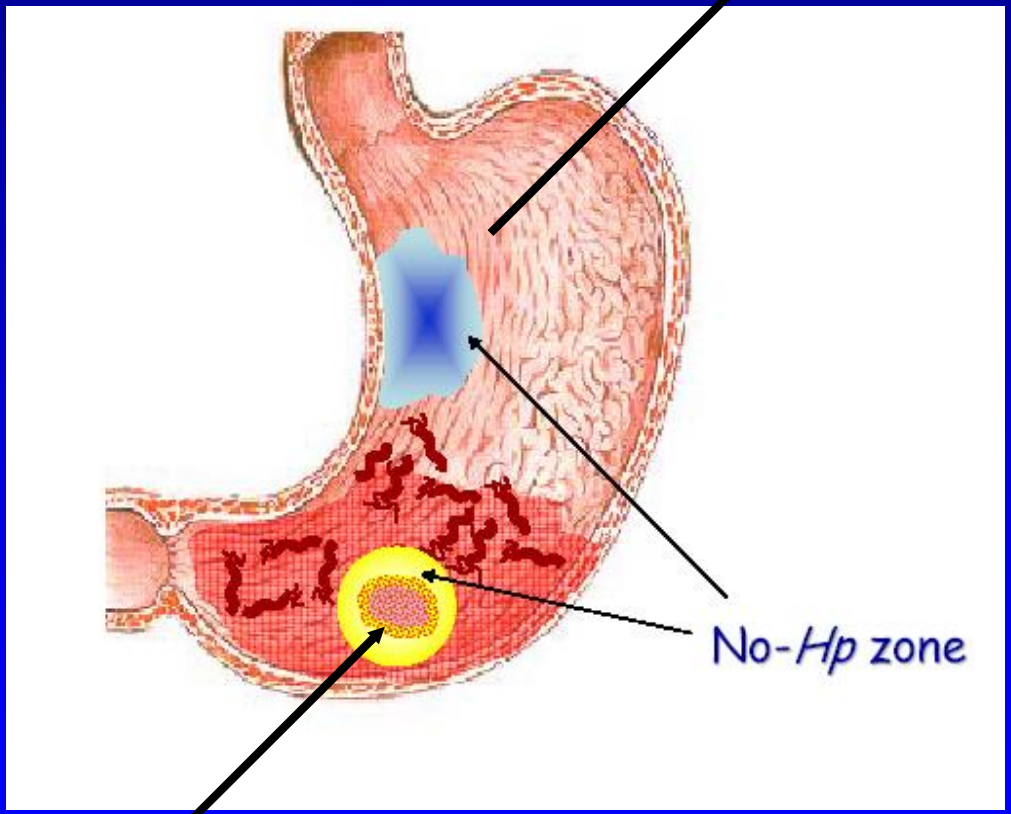
75-85%

99%

95%

Genta & Graham. Gastrointest Endosc 1994 ;40: 342

Δειγματοληπτικό λάθος: Ειδικές περιπτώσεις



Λαμβάνει ο ασθενής PPI's ?

- Η Ομεπραζόλη ↓ τον αριθμό των H.pylori
- 1/3 των 56 βιοψιών από το άντρο μετατράπηκαν σε H.pylori (-)

Graham et al. Am J Gastroenterol 2003;98: 1005

Διακοπή των PPI's για 14 ημέρες πριν την εξέταση

Διακοπή των H2-ανταγωνιστών μια ημέρα πριν την εξέταση

Λαμβάνει ο ασθενής PPI's ?

- Ψευδώς αρνητικά UBT αποτελέσματα από 2.2% (παντοπραζόλη) σε 16.6% (λανσοπραζόλη)
- Μείωση της ευαισθησίας (98% vs 83%) της ανίχνευσης αντιγόνου στα κόπρανα (πολυκλωνική EIA)

Levine et al. Aliment Pharmacol Ther 2004;20: 117

Gatta L, et al. Am J Gastroenterol 2004;99: 823

ΕΡΩΤΗΣΗ 2

Ποια μη επεμβατική δοκιμασία θα προτείνουμε?

- ***UBT***
- Ανίχνευση αντιγόνου στα κόπρανα (ΕΙΑ)
- ***Ορολογικός έλεγχος***

Σε 14 ημ

Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report

P Malfertheiner, F Megraud, C O'Morain, F Bazzoli, E El-Omar, D Graham, R Hunt, T Rokkas, N Vakil, E J Kuipers and The European Helicobacter Study Group (EHSG)

Box 5: Recommendations

Serology should be considered as a diagnostic test when others could be false negative, such as in patients with:

1. Bleeding ulcers, gastric atrophy, MALT lymphoma.
2. Recent or current use of PPIs and antibiotics.

ΕΡΩΤΗΣΗ 3

Ποια αγωγή πρέπει να χορηγηθεί στην ασθενή?

- ***PPI's + AMO + CLA***
- PPI's + MET + CLA
- PPI's + BIS + TET + MET

- Αντοχή στην μετρονιδαζόλη: 40-50%

κλαριθρομυκίνη: 13% (.. > 20%??)

Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report

P Malfertheiner, F Megraud, C O'Morain, F Bazzoli, E El-Omar, D Graham, R Hunt, T Rokkas, N Vakil, E J Kuipers and The European Helicobacter Study Group (EHSG)

PPI-clarithromycin-amoxicillin or metronidazole treatment is the recommended first choice treatment in populations with less than 15–20% clarithromycin resistance. In populations with less than 40% metronidazole resistance PPI-clarithromycin-metronidazole is preferable. Quadruple treatments are alternative first choice treatments.

ΕΡΩΤΗΣΗ 4

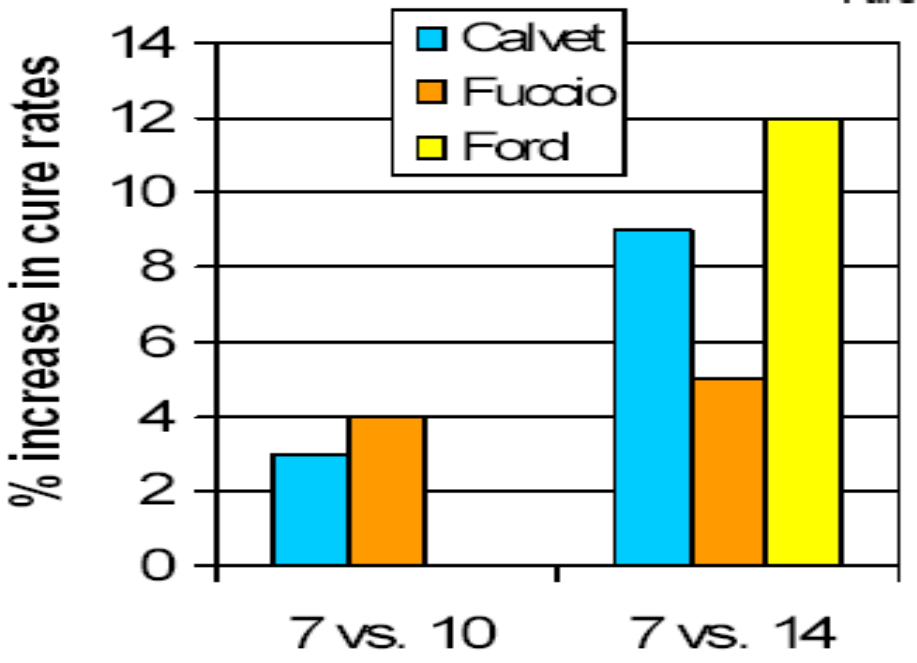
Ποιο το χρονικό διάστημα χορήγησης της αγωγής?

- 7 ημέρες
- ***10 ημέρες***
- 14 ημέρες

Διάρκεια Θεραπείας

Increasing the length of treatment

- At least 7 days (Maastricht II)
- 14-day treatment / 7-day acceptable if good local results (Maastricht III)



Calvet APT2000, Ford Can J Gastro2003, Fuccio Ann Intern Med 2007

Box 11: Recommendations

1. For PPI (standard dose bid), clarithromycin (500 mg bid), amoxicillin (1000 mg bid) or metronidazole (400 or 500 mg bid), 14 day treatment is more effective than seven days (by 12% (95% confidence interval 7% to 17%). A seven day treatment may be acceptable where local studies show that it is effective.

Εκρίζωση (PPI's+AMO+CLA):

7ημ (75%) vs 10 ημ (81%)vs 14ημ (90%)

Karatapanis S, et al.Helicobacter 2007;12:404

ΕΡΩΤΗΣΗ 5

Πως και πότε θα ελέγξουμε την εκρίζωση του H. pylori ?

- ***UBT***
- Αντιγόνο κοπράνων
- CLO test - Βιοψία
- Ορολογικός έλεγχος

Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report

P Malfertheiner, F Megraud, C O'Morain, F Bazzoli, E El-Omar, D Graham, R Hunt, T Rokkas, N Vakil, E J Kuipers and The European Helicobacter Study Group (EHSG)

Box 9: Recommendations

H pylori eradication should be confirmed at least four weeks after treatment.

1. A UBT is recommended if available.
2. If not available, a laboratory based stool test, preferably using monoclonal antibodies, could be used.

Γιατί αποτυγχάνει η θεραπεία 1ης γραμμής?

- ***Αντοχή στα αντιμικροβιακά***
  - ***CLA: ⬇ ποσοστού εκρίζωσης: 87.8% vs 18.3%***
- Μη συμμόρφωση του ασθενή
- Άλλοι λόγοι

Georgopoulos S, et al. Dig Dis Sci 2000;45: 63-67

Θεραπεία 2ης γραμμής

Τετραπλή θεραπεία για 10-14ημ

PPI / 12ωρο

Μετρονιδαζόλη 500mg x 3

Τετρακυκλίνη 500mg x 4

Τρικαλιούχο δικιτρικό βισμούθιο 300mg x 4

Αναμενόμενη συμμόρφωση σε θεραπεία ανά /6h ~50%

PPI's –AMO ή τετρακυκλίνη + μετρονιδαζόλη

Claxton Clin Therap 2001

Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report

P Malfertheiner, F Megraud, C O'Morain, F Bazzoli, E El-Omar, D Graham, R Hunt, T Rokkas, N Vakil, E J Kuipers and The European Helicobacter Study Group (EHSG)

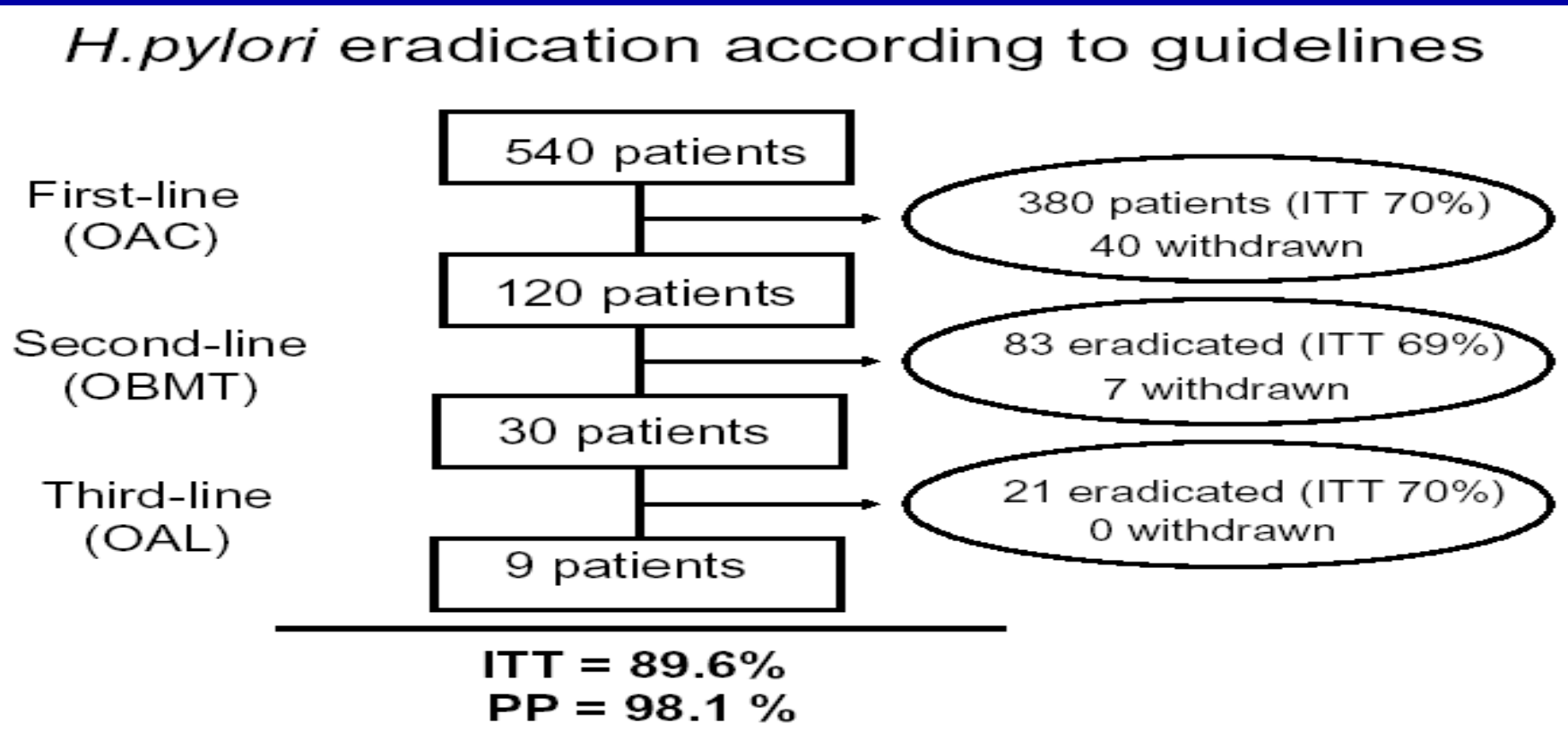
Μετά τη 2η αποτυχία εκρίζωσης, η θεραπεία πρέπει να στηρίζεται σε δοκιμασία ευαισθησίας στα αντιβιοτικά

Θεραπεία 2ης και 3ης γραμμής

- Τετραπλή θεραπεία
- Τριπλή θεραπεία με ***λεβοφλοξασίνη,*** ριφαμπουτίνη, φουραζολιδόνη
- Διαδοχικό σχήμα εκρίζωσης (sequential regimen)

PPI's/12ωρο + AMO 1gr/12ωρο + ΛΕΒΟ 500mg /12ωρο για 10 ημέρες

Cumulative *H. pylori* Eradication Rates in Clinical Practice by Adopting First and Second-Line Regimens Proposed by the Maastricht III Consensus and a Third-Line Empirical Regimen



Rokkas T, et al. Am J Gastroenterol 2009; 104: 21

Διαδοχικό σχήμα εκρίζωσης (10 ημέρες)

1

PPI / 12ωρο

AMO 1gr/ 12ωρο 5 ημέρες

2

PPI / 12ωρο 5 ημέρες

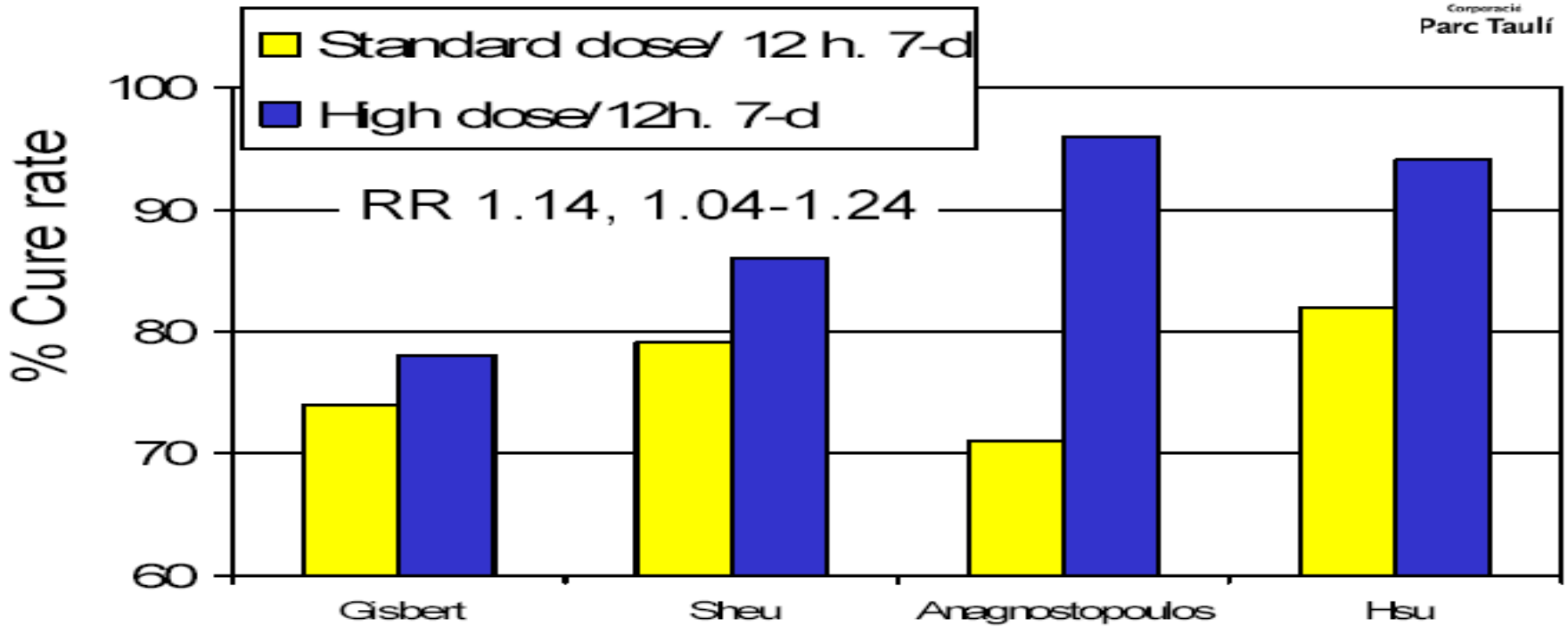
MET 500mg/ 12ωρο

CLA 500mg/12 ωρο

Zullo A, et al. Aliment Pharmacol Ther 2003; 17: 719


ΕΥΧΑΡΙΣΤΩ

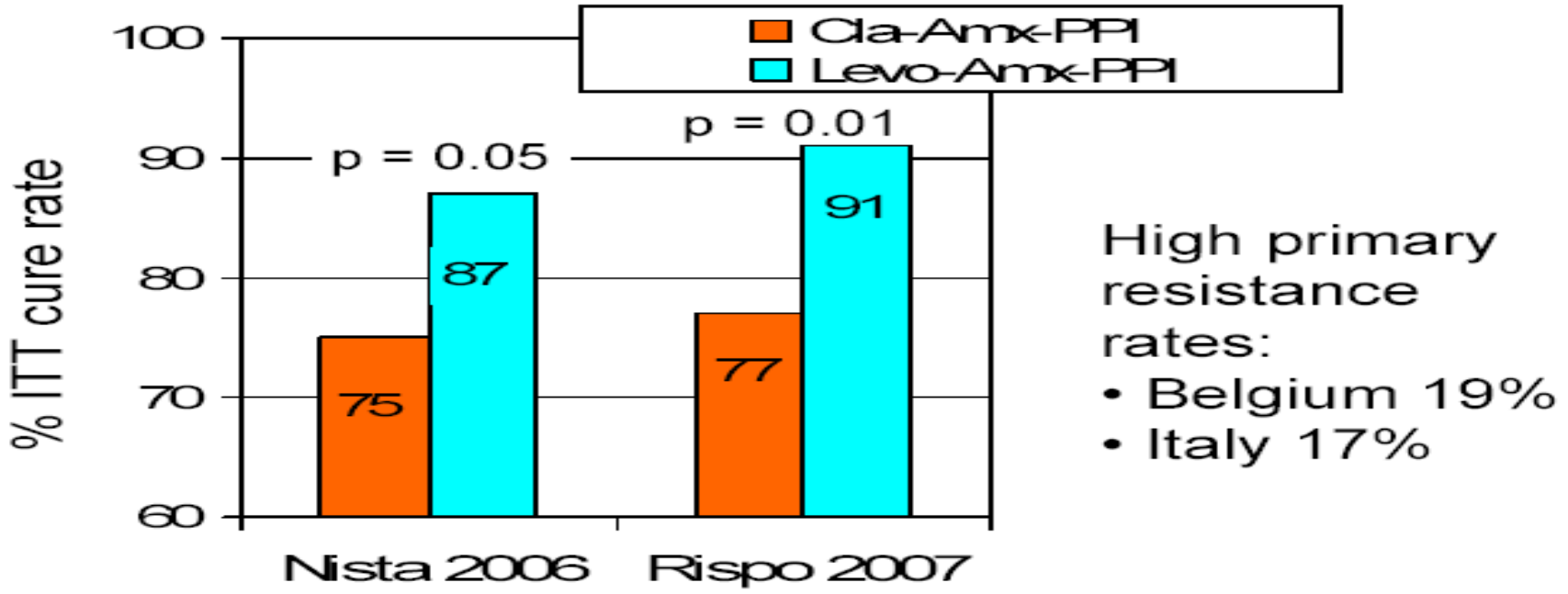
Clinical studies



Gisbert AJG 2005, Sheu APT 2004, Anagnostopoulos J Clin Gastroenterol 2004,Hsu, AJG 2005

Τριπλή θεραπεία

Levofloxacin-based triple therapy



High primary resistance rates:

- Belgium 19%
- Italy 17%

Nista, AJG 2006, Rispo UEGW 2007, Zullo, APT 2007, Burette UEGW 2007

Second-line and Rescue therapy for persistent *H.pylori* infection

Guidelines

- Bismuth-based quadruple therapy (10 or 14 days)
- PPI-amoxicillin or tetracycline and metronidazole if bismuth is not available
- Rescue therapy should be based on antimicrobial susceptibility testing

Maastricht III, Gut 2007

- Bismuth-based quadruple therapy for 7-14 days
- Levofloxacin-based triple therapy for 10 days, which requires validation in the U.S.

ACG Guideline, Am J Gastroenterol 2007

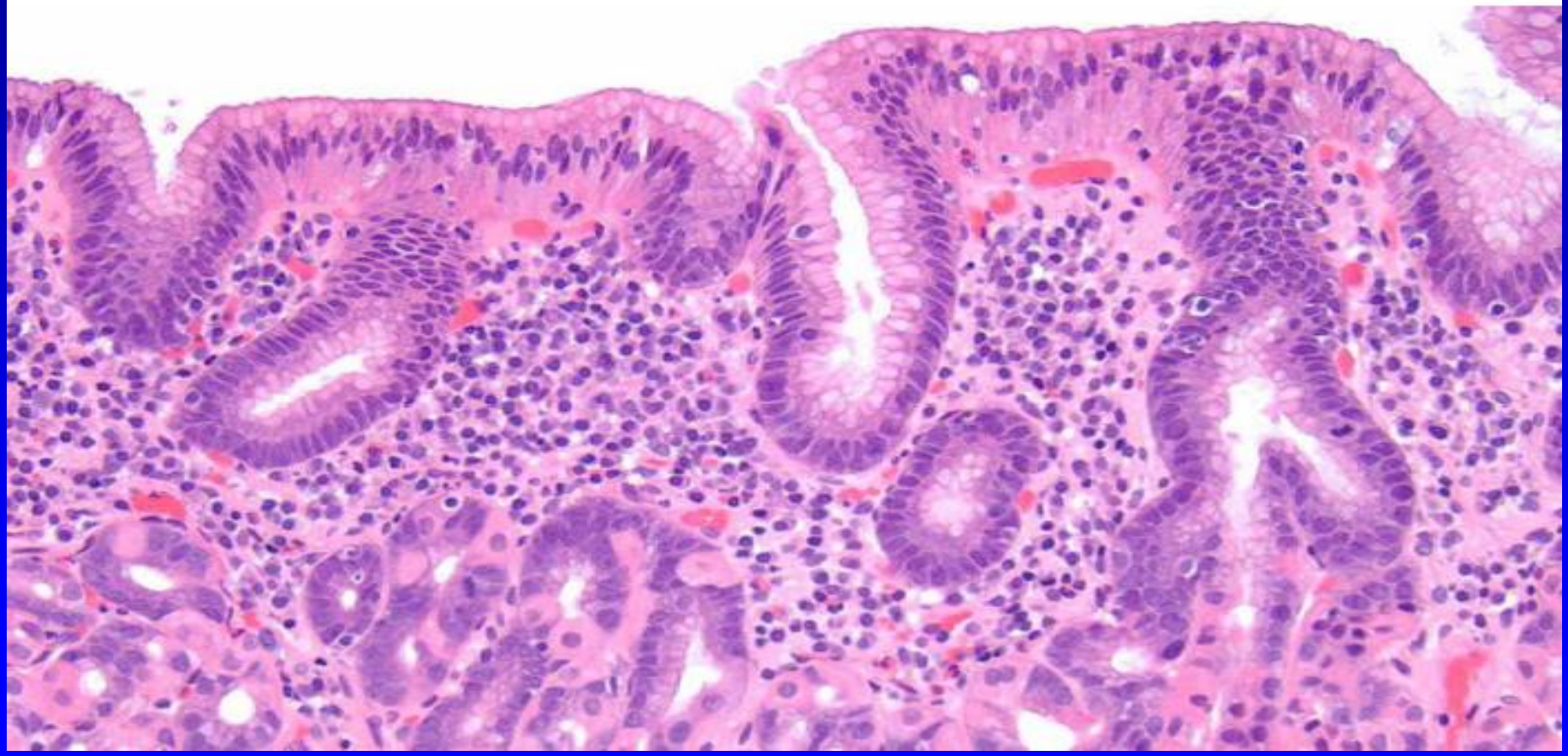
Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report

P Malfertheiner, F Megraud, C O'Morain, F Bazzoli, E El-Omar, D Graham, R Hunt, T Rokkas, N Vakil, E J Kuipers and The European Helicobacter Study Group (EHSG)

Box 1: Recommendations

1. *H pylori* eradication is appropriate for patients infected with *H pylori* and investigated non-ulcer dyspepsia.

H. pylori-infected patients treated with antibiotics for other reasons may have **chronic inactive gastritis**, but almost never *CAG* without detectable organisms



ΕΡΩΤΗΣΗ 3

Στον ασθενή πρέπει να συσταθεί

❷ Μακροχρόνια λήψη PPI

❸ Έλεγχο για παρουσία ελικοβακτηριδίου και εκρίζωση επί θετικού αποτελέσματος

❹ Καμία γαστροπροστασία

#1 Does The Patient Need Treatment?

Carefully review the Maastrich Guidelines

- Histology:
  - Normal Corpus (less need to treat)
  - intestinal Metaplasia (more need to treat)
- Physiology
  - Acid symptoms, low gastric pH (less need)
  - History of GERD or DU (less need)

Sequential treatment

Corporació Parc Taulí

- More effective than 7 (1,2,3) and 10 days (4) of triple therapy
- Not affected by risk factors of triple therapy failure (1,2-4)

1) De Francesco, V. Dig Liver Dis 2004
2) Zullo, A . Aliment Pharmacol Ther 2003
3) Francavilla, R. Gastroenterology 2005
4) De Francesco, V. Aliment Pharmacol Ther 2004

Who to treat (Maastricht Consensus 2002)

Strongly recommended indications

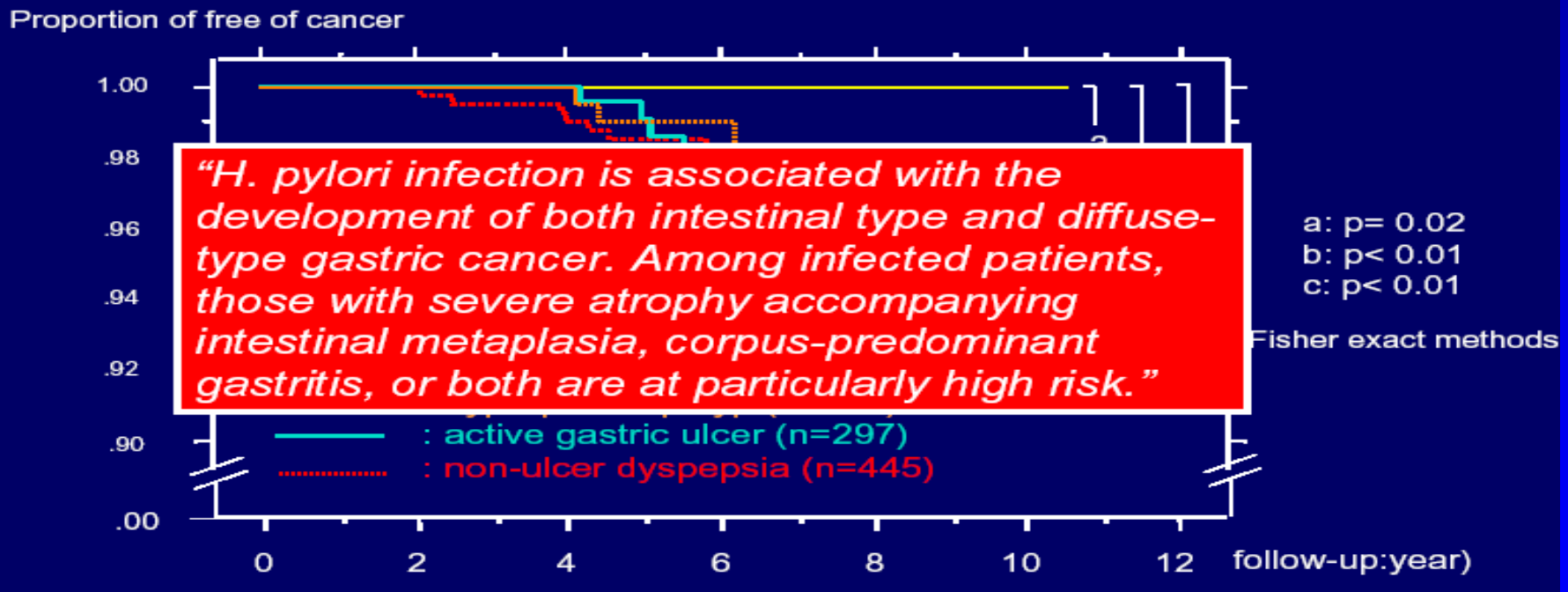
Indication (*H. pylori* positive)	**Scientific evidence**
DU/GU (active or not)	1
MALToma	2
Atrophic gastritis	2
Post-gastric cancer resection	3
First degree relatives of gastric CA patients	3
Patient wishes (after consultation)	4

1 = proven double blind etc,
2 = provenUCT,
3 = strong evidence but no trials,
4 = no evidence of harm and it makes sense.

Advisable indication and relevant statements

Indications (*H. pylori* positive)	**Scientific evidence**
Functional dyspepsia (symptoms but no ulcer)	
• *H. pylori* eradication is an appropriate option	2
• This leads to long-term symptom improvement in a subset of patients	2
GERD	
H. pylori eradication:	
• Is not associated with GERD development in most cases	3
• Does not exacerbate existing GERD	3
H. pylori should be eradicated, though, in patients requiring long term profound acid suppression	3
NSAIDs	
H. pylori eradication:	
• Reduces the incidence of ulcer, given prior to NSAID use	2
• Alone, is insufficient to prevent recurrent ulcer bleeding in high risk NSAID users	2
• *H. pylori* and NSAIDs/aspirin are independent risk factors for PUD	1
• Does not enhance healing of GU or DU in patients receiving antisecretory therapy who continue to take NSAIDs	2

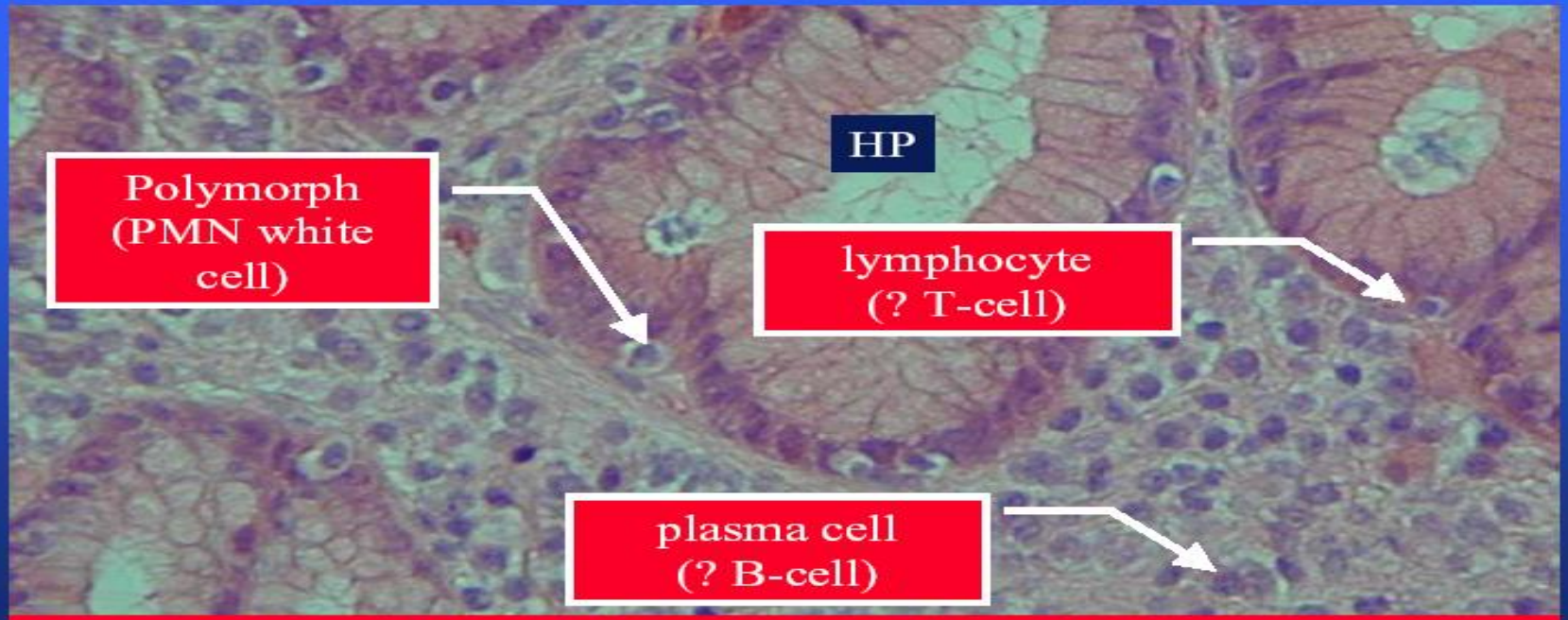
Endoscopic findings and the development of gastric cancer



"H. pylori infection is associated with the development of both intestinal type and diffuse-type gastric cancer. Among infected patients, those with severe atrophy accompanying intestinal metaplasia, corpus-predominant gastritis, or both are at particularly high risk."

Uemura et al. N Engl J Med, Vol. 345, No. 11

Chronic Active Gastritis



Regardless of Hp-toxin status;
Gastritis is always present in Hp infection.

Pro's and Con's of Various Tests

- Serology
  - Sensitive
  - No preparation required
  - Less expensive
- Breath test etc.
  - Sensitive and specific
  - Requires preparation (fasting)
  - Must avoid medications suppressing Hp
    - » Acid pump blockers (esomeprazole etc) 1 week
    - » Pepto bismol / bismuth etc.
    - » Antibiotics

Post Therapy Diagnosis

- Use a test for "active disease"
  - i.e. actual Hp organisms
  - Urea Breath Test
  - Stool antigen
  - Biopsy
- Serology **ONLY** if nothing else available
  - Cannot confirm cure in short term
  - If serology changes from POS to NEG then cure is likely
    - » So wait 6 months then do it
    - » Ignore result if positive – and do a breath test
    - » Accept result if negative

Positive serology may remain for 2 years after therapy
t is very worrying and confusing for patients and doctors!

Antibiotic Agents which can be Re-Used

- Amoxicillin
- Bismuth
- Tetracycline
- Furazolidone

HP almost never becomes resistant to these

Choose These Drugs Only Once

- Clarithromycin
- Metronidazole
- 'Floxacins (e.g. levofloxacin)
- Rifamycins (e.g. rifabutin)

HP almost 'always' becomes resistant to these

Increasing PPI dosage

Corporació Parc Taulí

- od PPI ↓effective than bd PPI in triple therapy
- 10%- 20% of GERD patients show insufficient acid inhibition on twice-daily PPI
- Europe: > 80% Extensive (rapid) Metabolizers (EM) of PPIs
- Triple therapy: EM: ↓↓ eradication rates vs. Poor Metabolizers ($p<0.0001$)

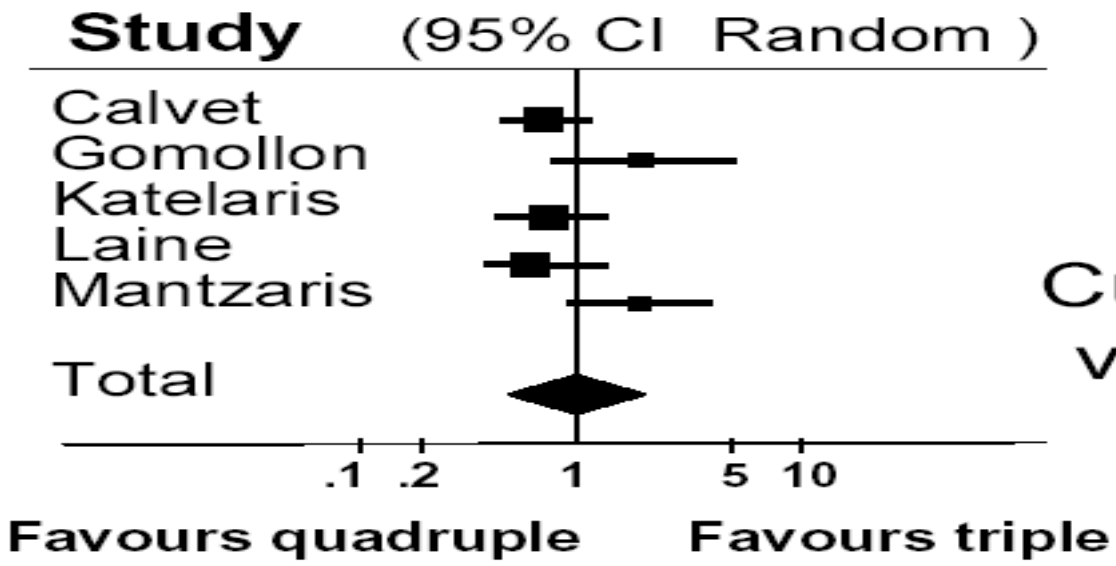
Vallve APT 2002, Mainie Gut 2006, Padol AJG 2006

Alternatives?

Corporació Parc Taulí

1. Quadruple therapy
2. Levofloxacin based triple therapy
3. Sequential therapy

Triple vs. Quadruple therapy



Cure rate: 80%
vs. 79% triple

Gené, APT 2003

Sequential therapy, cure rates

Author	year	n	ITT Cure (%)
Zullo	2000	52	98
De Francesco	2001	63	94
Focareta	2002	94	96
Zullo	2003	522	92
Hassan	2003	152	93
Focareta	2003	174	95
De Francesco	2004	162	93
De Francesco	2004	45	96
De Francesco	2004	116	95
Francavilla	2005	38	95
Zullo	2005	89	95
Zullo	2005	40	95
Scaccianone	2005	72	95
Francavilla	2006	40	95
Vaira	2007	146	91
Total		1805	93.5

Zullo, Gut 2007, Sanchez-Delgado DDW 2007

Country	Year	Clari	Metro
USA	1999-2002	12.9	25.1
Europe			
Bulgaria	1996-2004	12.6	25.6
Finland	2000-2002	2	38
Italy	2004-2005	21.3	-
The Netherlands	1997-2002	1	14.4
Sweden	1998-2001	1.5	16.2
UK	2000-2003	7	24
Middle East			
Iran	2001-2002	16.7	57.5
Kuwait	2003-2005	0	67
Asia			
Hong Kong	2003-2004	7.8	39.2
Bangladesh	1999-2001	10	77.5
Africa			
Kenya	2003-2004	6.4	100

Vakil & Megraud, Gastroenterology 2007

Susceptibility-based *vs* empirical strategy in second-line treatment

Randomized, open study (n = 82)

Regimen	**PP(%)**	**ITT(%)**	**p**
Susceptibility-based strategy	83.3	81.6	NS
PPI-A-M_{10}	94.7	92.4	

Miwa H et al. APT 2003

Susceptibility-based *vs* empirical strategy in second-line treatment

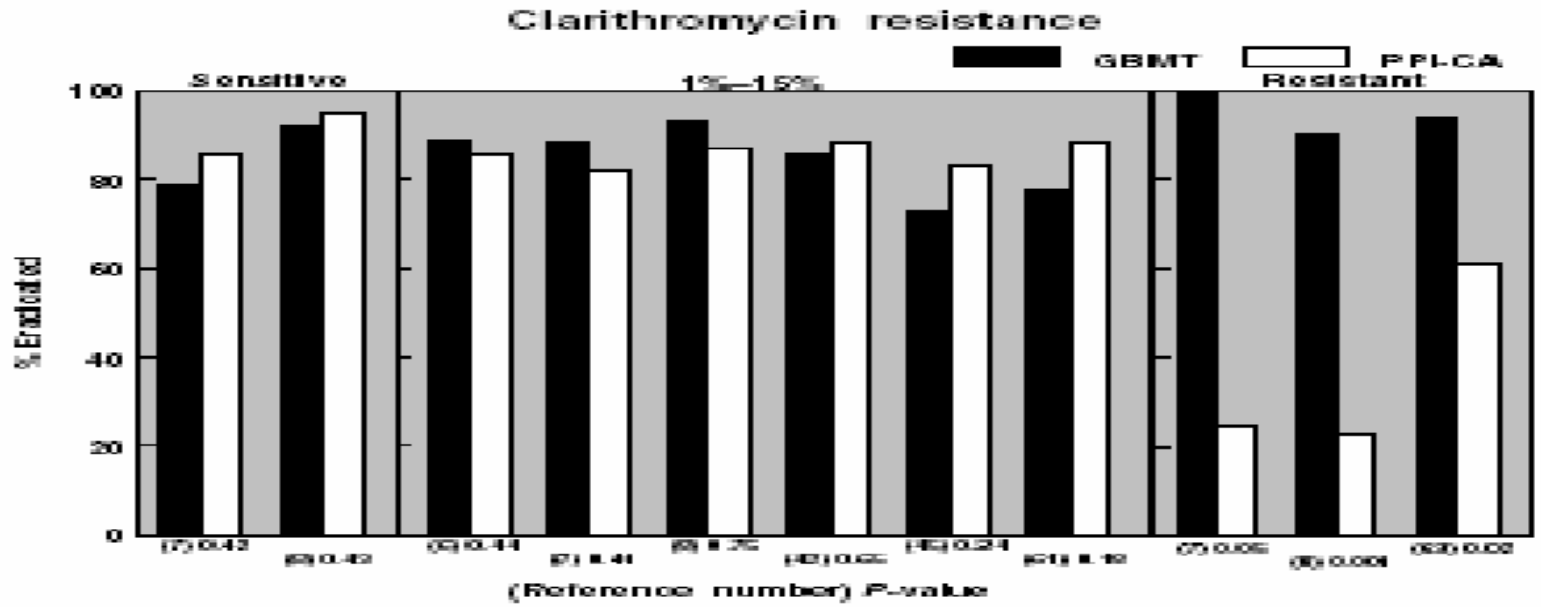
Randomized, open, parallel-group (n = 287)

Regimen	**PP(%)**	**ITT(%)**
Susceptibility-based strategy	78.3*	74.3 *
OAM_{14}	72.1	63.2
OAC_{7}	50.0 *	47.4 *
OAC_{14}	34.1*	34.5 *

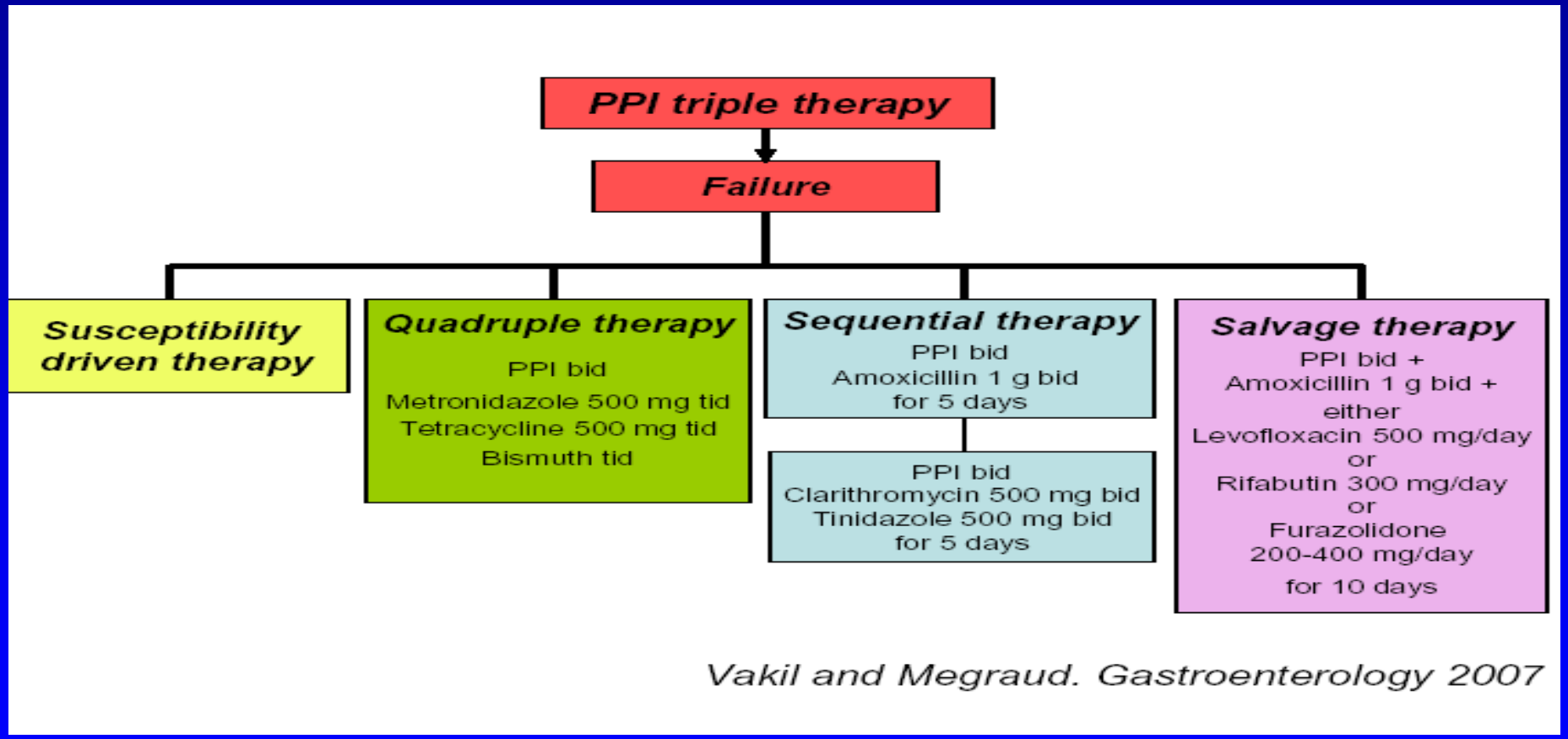
**p<0.01*

Lamouliatte H et al. APT 2003

Eradication rate of *H. pylori* in studies comparing Quadruple PPI-BMT and triple PPI-CA therapies by the prevalence of clarithromycin resistance



Fishbach LA et al, APT 2004



Vakil and Megraud. Gastroenterology 2007

Sequential therapy 5OA+5OMC for clarithromycin-resistant strains

	Eradication rate		
Regimen	Clari-S (n/n)	Clari-R (n/n)	Clari+ Metro-R (n/n)
Sequential therapy	94.7% (108/114)	89% (8/9)	0% (0/4)
Triple therapy	94.5% (86/91)	29% (6/21)	29% (2/7)

Vaira et al. Ann Intern Med 2007

Initial Diagnosis

- Serology is sensitive (95%)
  - But specificity not perfect (80%)
  - In areas of low prevalence, confirm
- Confirm with a test for "active disease"
  - i.e. actual Hp organisms
  - Urea Breath Test
  - Stool antigen
  - Biopsy