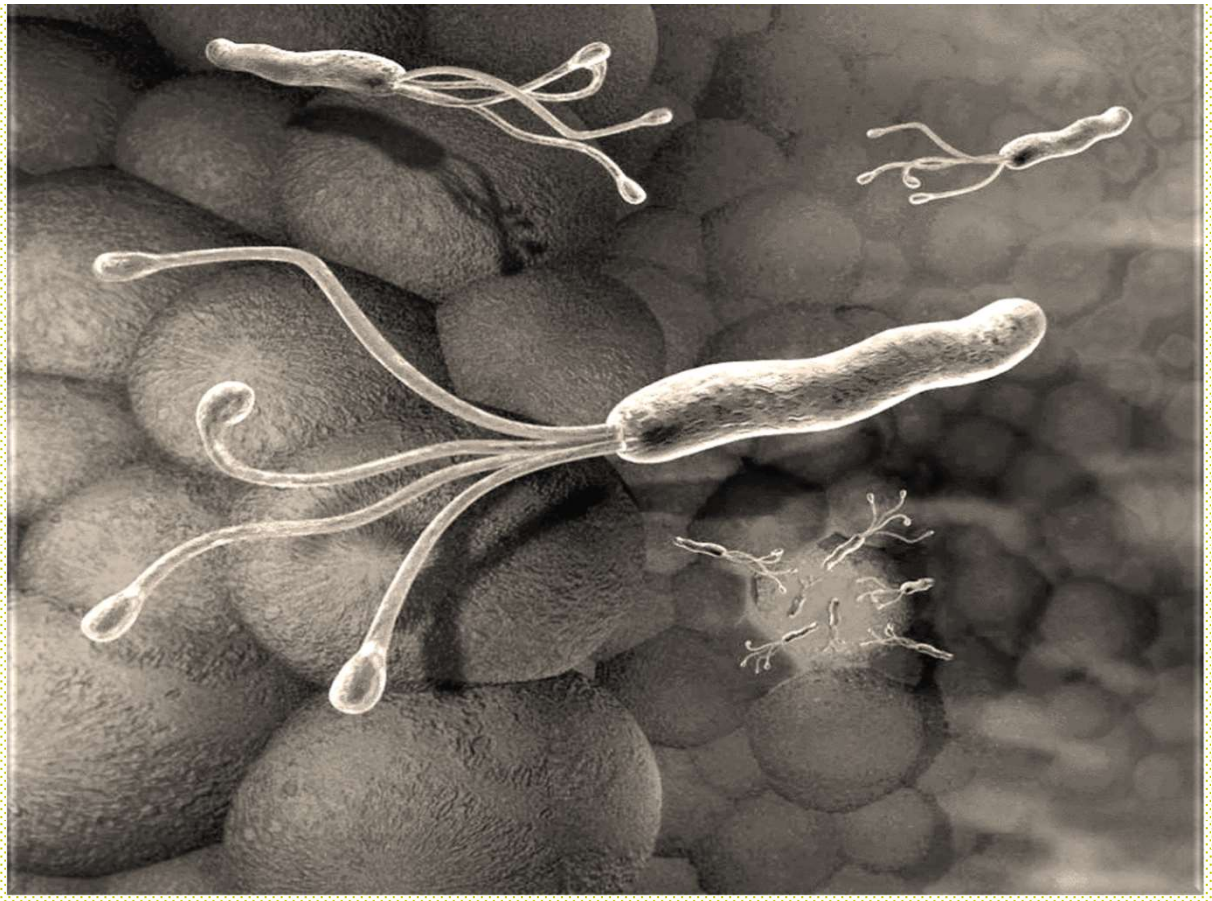
AIGO Lazio
incontra i medici del territorio



- Spiraliforme
- Gram negativo
- Flagellato
- Microaerofilo
- Ureasi positivo
- Genoma noto

Helicobacter pylori

TUTTO CHIARO?

“Non sei mai fregato veramente finchè hai da parte una buona storia da raccontare e qualcuno a cui raccontarla”

Il pianista sull’oceano
Alessandro Baricco

Warren JR, Marshall BJ. *Lancet 1983;i:1273-5.*

UNIDENTIFIED CURVED BACILLI ON GASTRIC EPITHELIUM IN ACTIVE CHRONIC GASTRITIS

SIR,—Gastric microbiology has been sadly neglected. Half the patients coming to gastroscopy and biopsy show bacterial colonisation of their stomachs, a colonisation remarkable for the constancy of both the bacteria involved and the associated histological changes. During the past three years I have observed small curved and S-shaped bacilli in 135 gastric biopsy specimens. The bacteria were closely associated with the surface epithelium, both within and between the gastric pits. Distribution was continuous, patchy, or focal. They were difficult to see with haematoxylin and eosin stain, but stained well by the Warthin-Starry silver method (figure).

I have classified gastric biopsy findings according to the type of inflammation, regardless of other features, as "no inflammation", "chronic gastritis" (CG), or "active chronic gastritis" (ACG). CG shows more small round cells than normal while ACG is characterised by an increase in polymorphonuclear neutrophil leucocytes, besides the features of CG. It was unusual to find no inflammation. CG usually showed superficial oedema of the mucosa. The leucocytes in ACG were usually focal and superficial, in and near the surface epithelium. In many cases they only infiltrated the necks of occasional gastric glands. The superficial epithelium was often irregular, with reduced mucinogenesis and a cobblestone surface.

When there was no inflammation bacteria were rare. Bacteria were often found in CG, but were rarely numerous. The curved bacilli were almost always present in ACG, often in large numbers and often growing between the cells of the surface epithelium (figure). The constant morphology of these bacteria and their intimate relationship with the mucosal architecture contrasted with the heterogeneous bacteria often seen in the surface debris. There was normally a layer of mucous secretion on the surface of the mucosa. When this layer was intact, the debris was spread over it, while the curved bacilli were on the epithelium beneath, closely spread over the surface (figure).

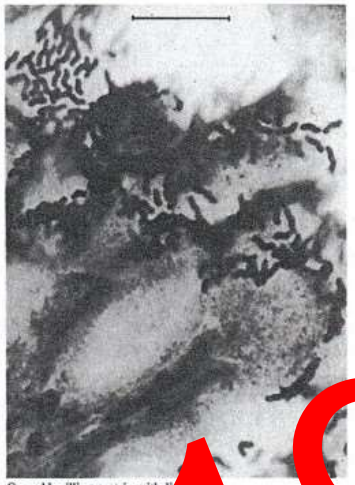
The curved bacilli and the associated histological changes may be present in any part of the stomach, but they were seen most consistently in the gastric antrum. Inflammation, with no bacteria, occurred in mucosa near focal lesions such as carcinoma or peptic ulcer. In such cases, the leucocytes were spread through the full thickness of the nearby mucosa, in contrast to the superficial infiltration associated with the bacteria. Both the bacteria and the typical histological changes were commonly found in mucosa unaffected by the focal lesion.

The extraordinary features of these bacteria are that they are almost unknown to clinicians and pathologists alike, that they are closely associated with granulocyte infiltration, and that they are present in about half of our routine gastric biopsy specimens in numbers large enough to see on routine histology. The only other organism I have found actively growing in the stomach is *Candida*, sometimes seen in the floor of peptic ulcers. These bacteria were not mentioned in two major studies of gastrointestinal microbiology[1,2] possibly because of their unusual atmospheric requirements and slow growth in culture (described by Dr B. Marshall in the accompanying letter). They were mentioned in passing by Fung et al.[3]

How the bacteria survive is uncertain. There is a pH gradient from acid in the gastric lumen to near neutral in the mucosal vessels. The bacteria grow in close contact with the epithelium, presumably near the neutral end of this gradient, and are protected by the overlying mucus.

The identification and clinical significance of this bacterium remain uncertain. By light microscopy it resembles *Campylobacter jejuni* but cannot be classified by reference to *Bergey's Manual of*

1. Gray JDA, Shiner M. Influence of gastric pH on gastric and jejunal flora. *Gut* 1967; **8**: 574–81.
2. Drasar BS, Shiner M, McLeod GM. Studies on the intestinal flora I: The bacterial flora of the gastrointestinal tract in healthy and achlorhydric persons. *Gastroenterology* 1969; **56**: 71–79.
3. Fung WP, Papadimitriou JM, Matz LR. Endoscopic, histological and ultrastructural correlations in chronic gastritis. *Am J Gastroenterol* 1979; **71**: 269–79.



Curved bacilli on gastric epitheli

Section is cut at acute angle to ... surface, forming ... between epithelial cells. (Warth... y silv... bar = 10 μm.)

Determinative Bacteriology. The stomach ... not be viewed as a sterile organ with no permanent flora ... eria in numbers sufficient to see by light microscopy are cl... sociated with a active form of gastritis, a cause of considerabl... dity (dyspeptic disease). These organisms should be re... d and their significance investigated.

Department of Pathology,
Royal Perth Hospital,
Perth, Western Australia 6001

J. ROBIN WARREN

SIR,—The above description of S-shaped spiral bacteria in the gastric antrum, by my colleague Dr J. R. Warren, raises the following questions: why have they not been seen before; are they pathogens or merely commensals in a damaged mucosa; and are they campylobacters?

In 1938 Doenges[1] found "spirochaetes" in 43% of 242 stomachs at necropsy but drew no conclusions because autolysis had rendered most of the specimens unsuitable for pathological diagnosis. Freedburg and Barron[2] studied 35 partial gastrectomy specimens and found "spirochaetes" in 37%, after a long search. They concluded that the bacteria colonised the tissue near benign or malignant ulcers as non-pathogenic opportunists. When Palmer[3] examined 1140 gastric suction biopsy specimens he did not use silver stains, so, not surprisingly, he found "no structure which could reasonably be considered to be of a spirochaetal nature". He concluded that the gastric "spirochaetes" were oral contaminants which multiplied only in post mortem specimens or close to ulcers. Since that time, the spiral bacteria have rarely been mentioned, except as curiosities,[4] and the subject was not reopened with the

1. Doenges JL. Spirochaetes in the gastric glands of *Macacus rhesus* and humans without definite history of related disease. *Proc Soc Exp Med Biol* 1938; **26**: 536–38.
2. Freedburg AS, Barron LE. The presence of spirochaetes in human gastric mucosa. *Am J Dig Dis* 1940; **7**: 443–45.
3. Palmer ED. Investigation of the gastric spirochaetes of the human? *Gastroenterology* 1954; **27**: 218–20.
4. Ito S. Anatomic structure of the gastric mucosa. In: Heidel US, Cody CF, eds. Handbook of physiology, section 6: Alimentary canal, vol II: Secretion. Washington, DC: American Physiological Society, 1967: 705–41.

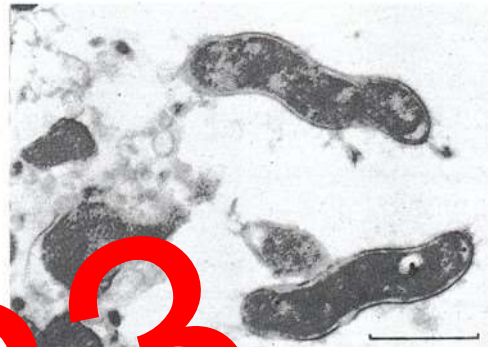


Fig 1—Thin-s... micrograph showing spiral bacteri... face of a mucous cell in gastric biopsy specimen. (Bar = 1 μm.)

...f gastros... biopsy. Silver staining is not routine ... the bacteria have been overlook... In othe... tis spira... bacteria ... well known an... thought ... commensals[5] (e... nges[6] ...em in all ... three ... ys). They usuall... more ... and inhabi... cid-secreting gastr... dus.[5] In cats ... often occupy ... the car... of the oxyntic ce... ggesting tolerance to acid.[6] The ...imal ... do not caus... inflammatory response, and no ...ness ha... with them. Investigatio... cteria in man has been hampered by the ...lse assumption that the bacteria were the same as those in animals ...nd would therefore be acid-tolerant inhabitants of the fundus. Warren's bacteria are, however, shorter, with only one or two spirals and resemble campylobacters rather than spirochaetes. They live beneath the mucus of the gastric antrum well away from the acid-secreting cells.

We have cultured the bacteria from antral biopsy specimens, using *Campylobacter* isolation techniques. They are microaerophilic and grow on moist chocolate agar at 37°C, showing up in 3–4 days as a faint transparent layer. They are about 0·5 μm in diameter and 2·5 μm in length, appearing as short spirals with one or two wavelengths (fig 1). The bacteria have smooth coats with up to five sheathed flagellae arising from one end (fig 2). In some cells, including dividing forms, flagellae may be seen at both ends and in negative stain preparations they have bulbous tips, presumably an artefact.[7]

These bacteria do not fit any known species either morphologically or biochemical. Similar sheathed flagellae have been described in vibrios[7] but micro-aerophilic vibrios have now

5. Lockard VG, Boler RK. Ultrastructure of a spiraled micro-organism in the gastric mucosa of dogs. *Am J Vet Res* 1970; **31**: 1453–62.
6. Vial JD, Orrego H. Electron microscope observations on the fine structure of parietal cells. *J Biophys Biochem Cytol* 1960; **7**: 367–72.
7. Glauert AM, Kerridge D, Horne RW. The fine structure and mode of attachment of the sheathed flagellum of *Vibrio metchnikovii*. *J Cell Biol* 1963; **18**: 327–36.
8. Shewan JM, Veron M. Genus I vibrio. In: Buchanan RE, Gibbons NE, eds. Bergey's manual of determinative microbiology, 8th ed. Baltimore: Williams & Wilkins, 1974: 341.

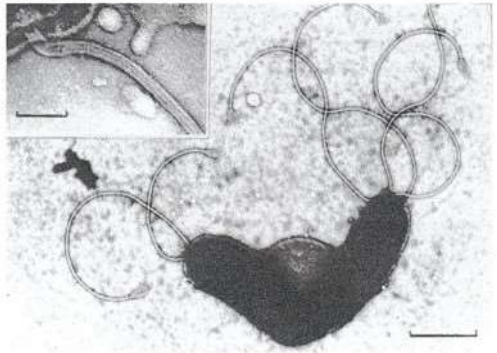
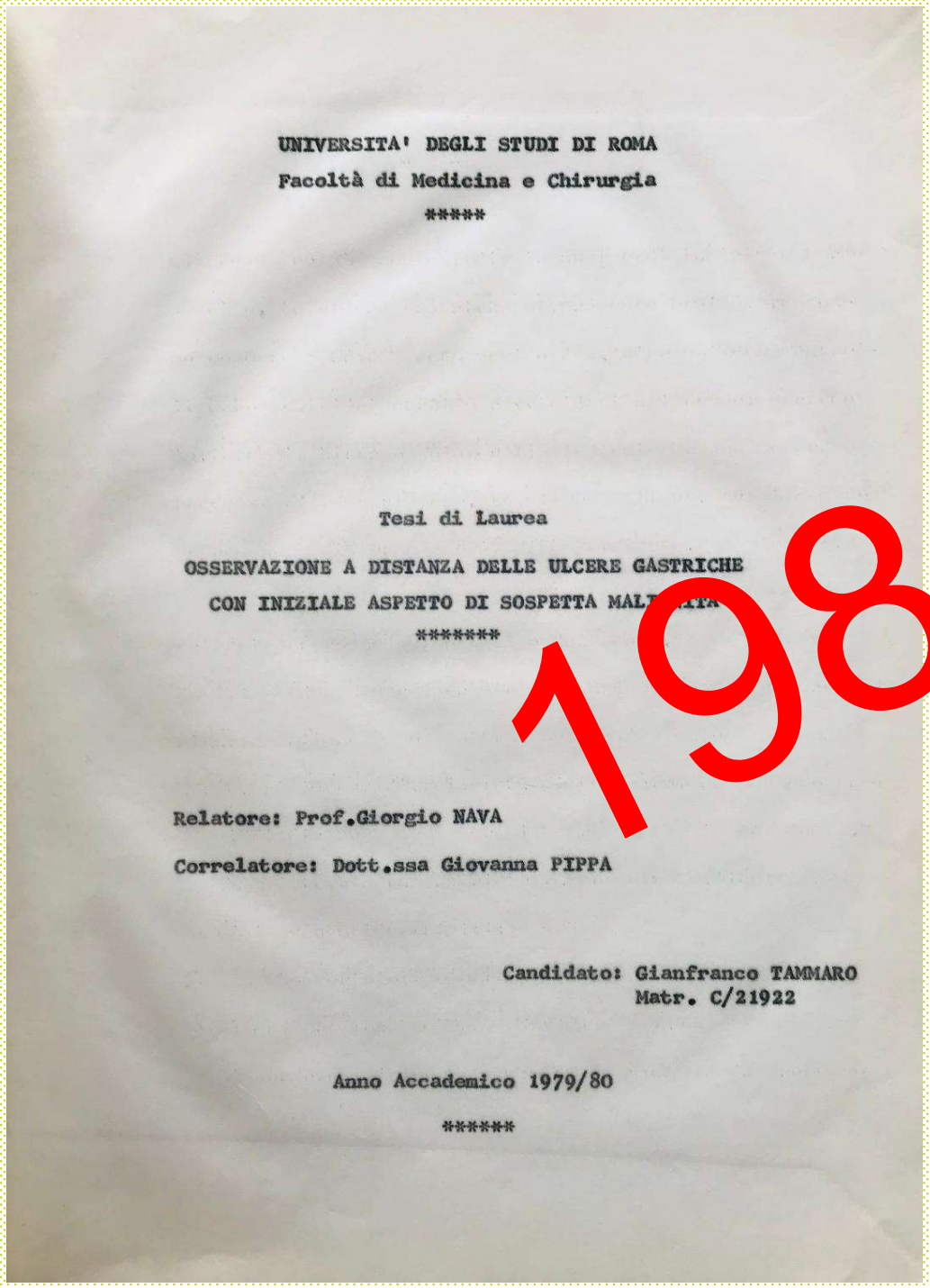


Fig 2—Negative stain micrograph of dividing bacterium from broth culture.

Multiple polar flagellae have terminal bulbs, (2% phosphotungstate, pH 6·8; bar = 1 μm.) Inset: detail showing sheathbed flagellum and basal disc associated with plasma membrane. (3% ammonium molybdate, pH 6·5; bar = 100 nm.)

1983



UNIVERSITA' DEGLI STUDI DI ROMA

Facoltà di Medicina e Chirurgia

*****

Tesi di Laurea

OSSERVAZIONE A DISTANZA DELLE ULCERE GASTRICHE
CON INIZIALE ASPETTO DI SOSPETTA MALI[illegible]

****

Relatore: Prof.Giorgio NAVA

Correlatore: Dott.ssa Giovanna PIPPA

Candidato: Gianfranco TAMMARO
Matr. C/21922

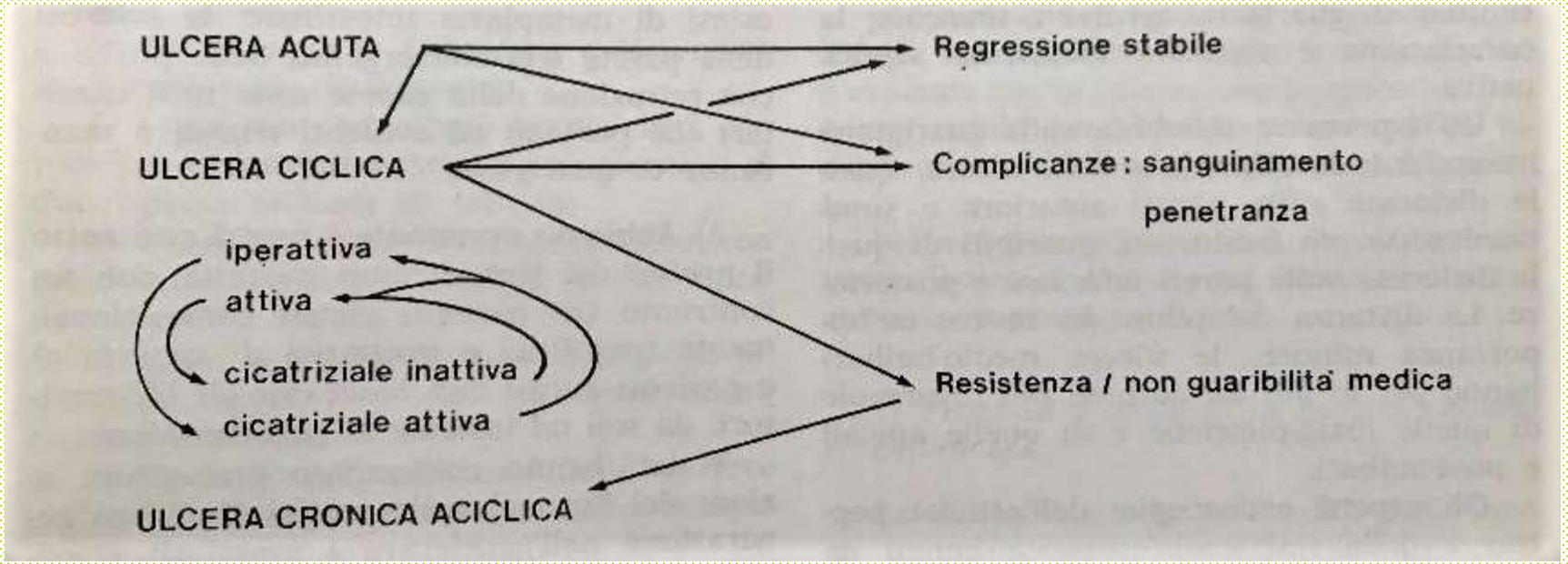
Anno Accademico 1979/80

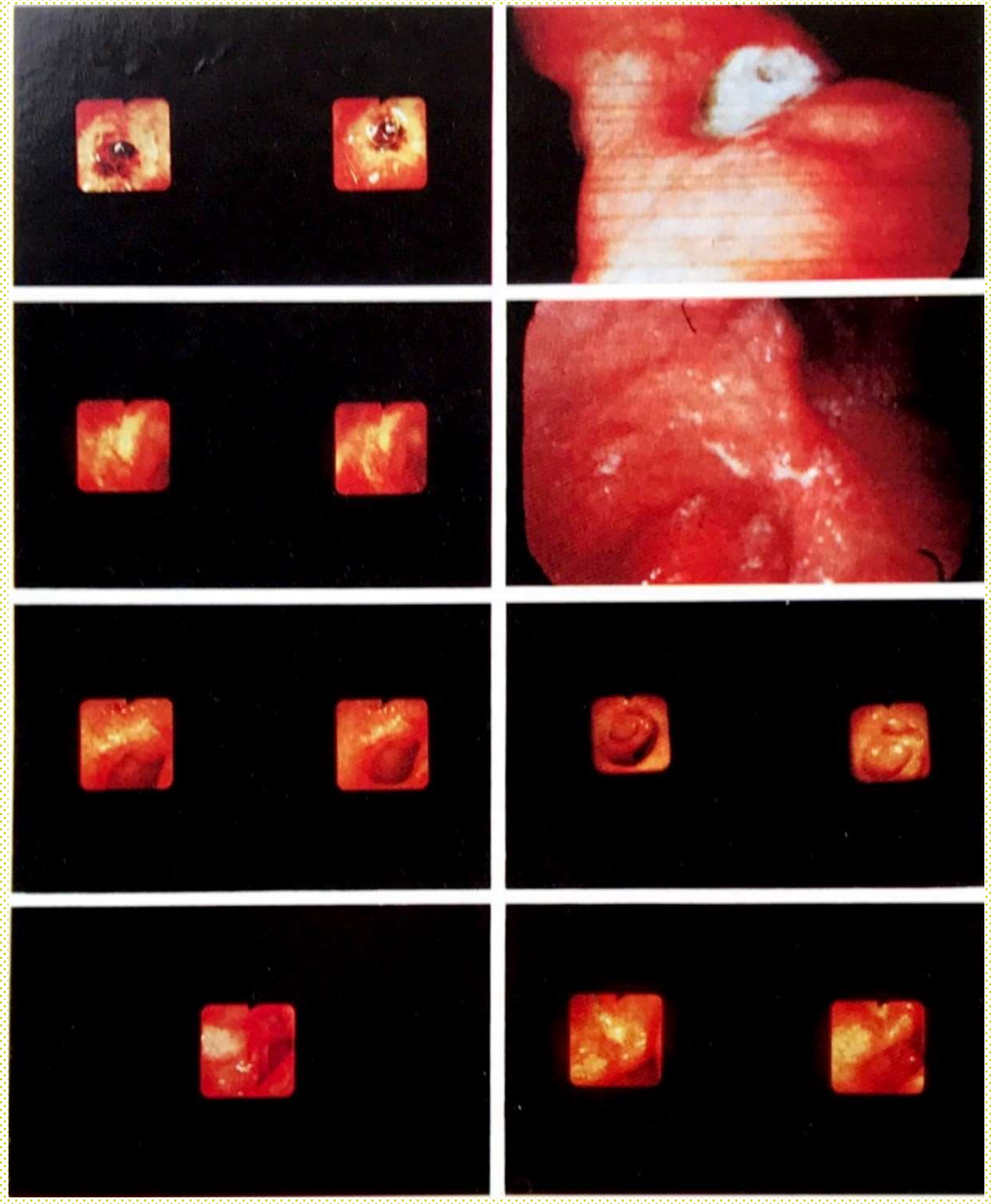
******

1980

«Osse[illegible]vazione a distanza delle U[illegible]cere Gastriche con iniziale [illegible]spetto di sospetta malignità». Tesi di Laurea 24.7.1980

IL CICLO DELL'ULCERA



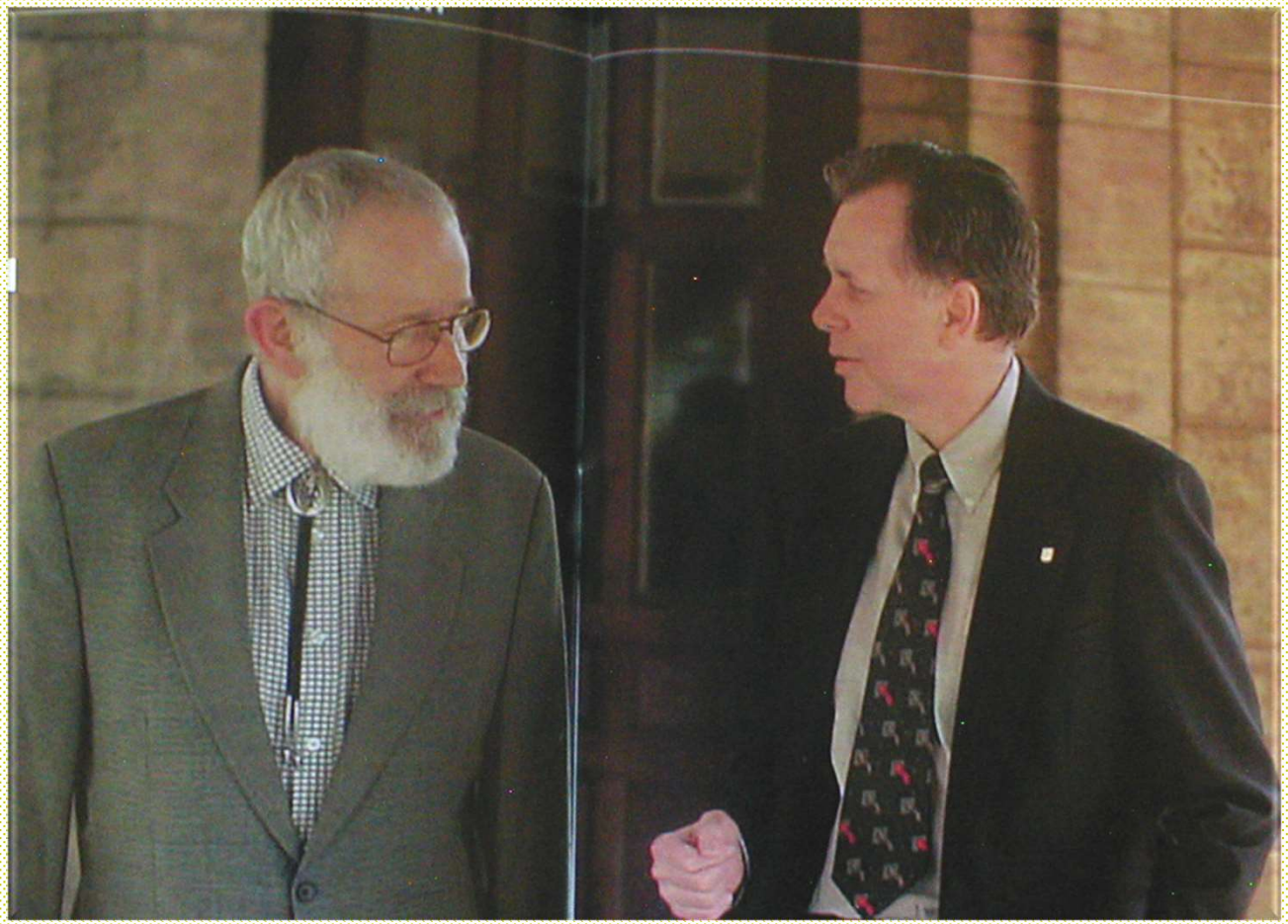


MALATTIA PEPTICA

+ FATTORI AGGRESSIVI
- FATTORI DIFENSIVI ?

INTERNATIONAL DUODENAL CLUB

Royal Perth Hospital



UNIDENTIFIED CURVED BACILLI ON GASTRIC EPITHELIUM IN ACTIVE CHRONIC GASTRITIS

Warren JR, Marshall BJ. *Lancet 1983;i:1273-5.*

INTERNATIONAL DUODENAL CLUB- ROMA
XI Meeting,24-25 May 1985. LECTURE
Micro-chromo-Endoscopy in duodenal disease
G.NAVA

MICRO-CHROMO-ENDOSCOPY IN DUODENAL DISEASES

G. NAVA
Gastroenterology & Digestive Endoscopy Service, S. Eugenio Hospital, 00142 Rome, ITALY

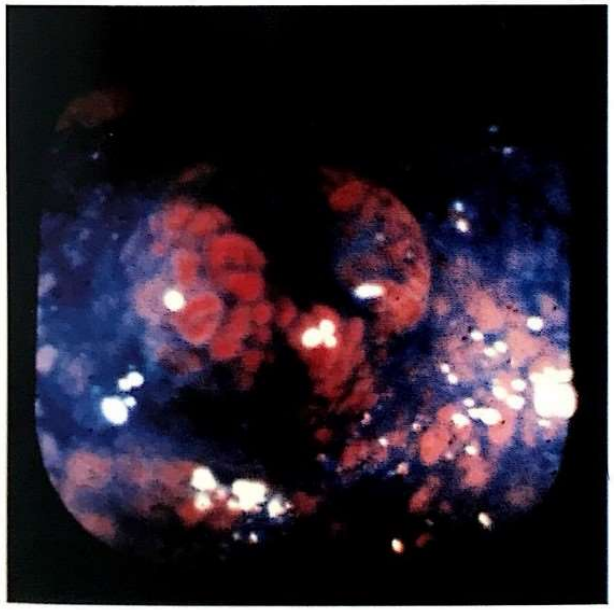


Fig. 7. Incomplete erosion (micro-chromo-endoscopy).

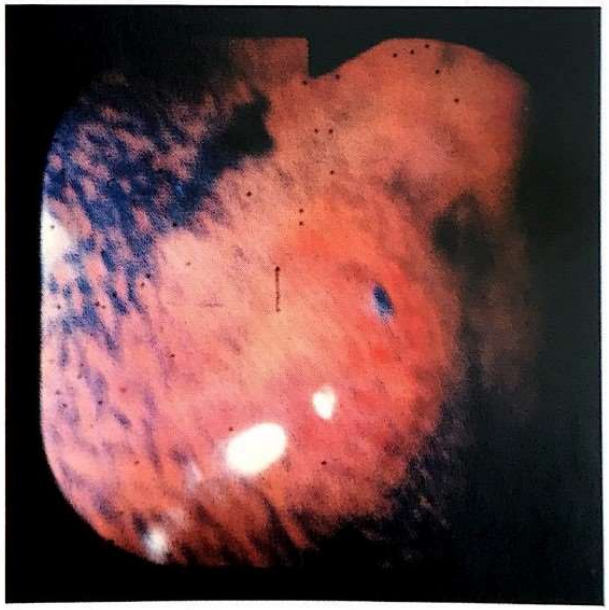


Fig. 8. Incomplete erosion (micro-chromo-endoscopy).

April 15,1985 Vol. 142 THE MEDICAL JOURNAL OF AUSTRALIA

ORIGINAL ARTICLES

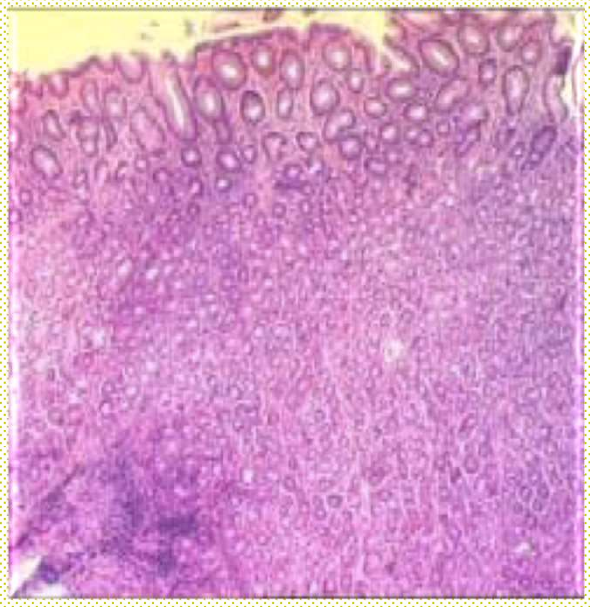
Attempt to fulfil Koch's postulates for pyloric campylobacter

Barry J. Marshall, John A. Armstrong, David B. McGechie and Ross J. Glancy

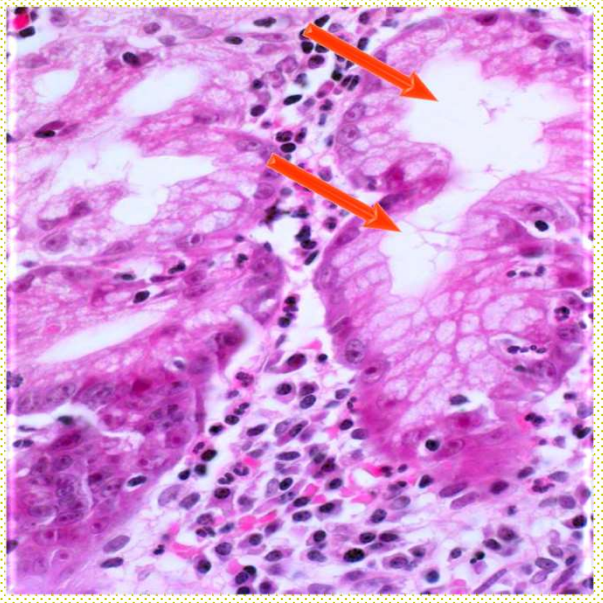
Abstract

A volunteer with histologically normal gastric mucosa received pyloric campylobacter by mouth. A mild illness developed, which lasted 14 days. Histologically proven gastritis was present on the tenth day after the ingestion of bacteria, but this had largely resolved by the fourteenth day. The syndrome of acute pyloric campylobacter gastritis is described. It is proposed that this disorder may progress to a chronic infection which predisposes to peptic ulceration.

Istologia di base



Istologia dopo 30 giorni



Campilobacter pylori: Facts or fantasy?

Prof Giorgio NAVA
Ospedale S.Eugenio
17 giugno 1986

Endoscopic characteristics of duodenal ulcers refractory to H2 receptors Blockers

G.Nava,G.Pippa,M.Apuzzo,M.E. Bazuro and GF. Tammaro
Gastrointestinal Unit,Ospedale S.Eugenio,Roma,Italy

Acta Gastroenterologica Latino Americana 13:236, 1983

…Colloidal Bismuth (De Nol) was quite effective in the healing of refractory duodenal ulcers…

INTERNATIONAL DUODENAL CLUB.XIII Meeting,Heidelberg October 1987

Refractory duodenal ulcers: Is there a role for colloidal bismuth?

GF Tammaro,M.Apuzzo,M.E. Bazuro,A Morace and G.Pippa.
Gastrointestinal Unit,Ospedale S.Eugenio,Roma,Italy

Refractory duodenal ulcers: Is there a role for colloidal bismuth? A Preliminary report from a randomized, single blind trial

G. F. Tammaro, M. Apuzzo, M. E. Bazuro, A. Morace and G. Pippa
Gastrointestinal Unit, Ospedale S. Eugenio, Rome, Italy

Refractory duodenal ulcers make up an unsettled problem from both a pathogenic and therapeutic point of view. It is also uncertain the definition itself, since it is termed as refractory both a duodenal ulcer (DU) which fails to heal in four weeks (Lam) and the one that is still active after twel… months (Pounder). Many… tions on the topic … rify the is… res…

…ckers
…sage
… with different H_2-re…
…blockers
— administration of both H_2-receptors-blockers and pirenzepine
— replacement with colloidal bismuth

The encouraging results achieved in the last study (1) have stimulated us to investigate on colloidal bismuth whose action on Campylobacter Pylo-ridis has flared new enthusiasm all over the scientific world.

Materials and methods

We selected 21 patients with refractoy DU (ulcers without reduction in size after 8 weeks and which fail to heal after 4 months of full dosage H_2-receptors-blockers therapy) (2) and randomized them to receive either collo… bismuth, 2 + 2 tablets 12… plus ranitidine 150… dine 150 …

…rmal
…had duodenal
…ion profile.

Results

In four out of ten patients in the Bismuth-Ranitidine group the ulcer was healed at 8 weeks compared with five out of eleven in the Ranitidine group. The majority of patients in both groups were asymptomatic or complained of mild epigastric pain. For this reason antacid consumption was low. One patient in the Bismuth-Ranitidine group felt as very disturbing his passing dark stools as he had experienced an episode of bleeding in the past. Patients who failed to heal, in both groups are being tested in a crossover manner.

Conclusions

Although the study has not been completed, we cannot demostrate any real

RISULTATI NON CONCLUSIVI!!!

The *Campylobacter pylori* Story

B. J. MARSHALL

Division of Gastroenterology, University of Virginia,
Charlottesville, Virginia, USA

Scandinavian Journal of Gastroenterology 1988; 23 (suppl 146), 58-66

Valutazione

a 48-72 ore

(circa 100 tentativi)

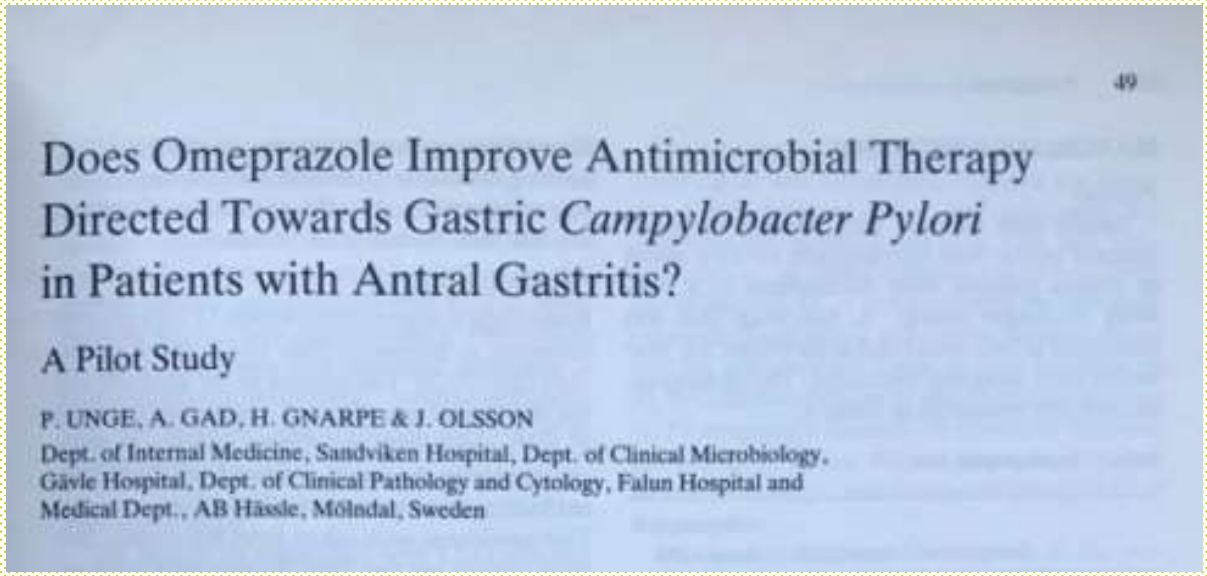
Valutazione
a 5 giorni

INTERNATIONAL DUODENAL CLUB

Does Omeprazol Improve Antimicrobial Therapy Directed towards Campylobacter Pylori in Patients with Antral Gastritis. A Pilot Study.

P.Unge.A. Gad, H.Gnarpe and J.Olsson
Medical Dept. and Clinical Pathogy Dept. Falun,Sweden

Proceedings from XIV International Duodenal Club.
Scandinavian Journal of Gastroenterology 1989; 24 (suppl 167, 49-54)



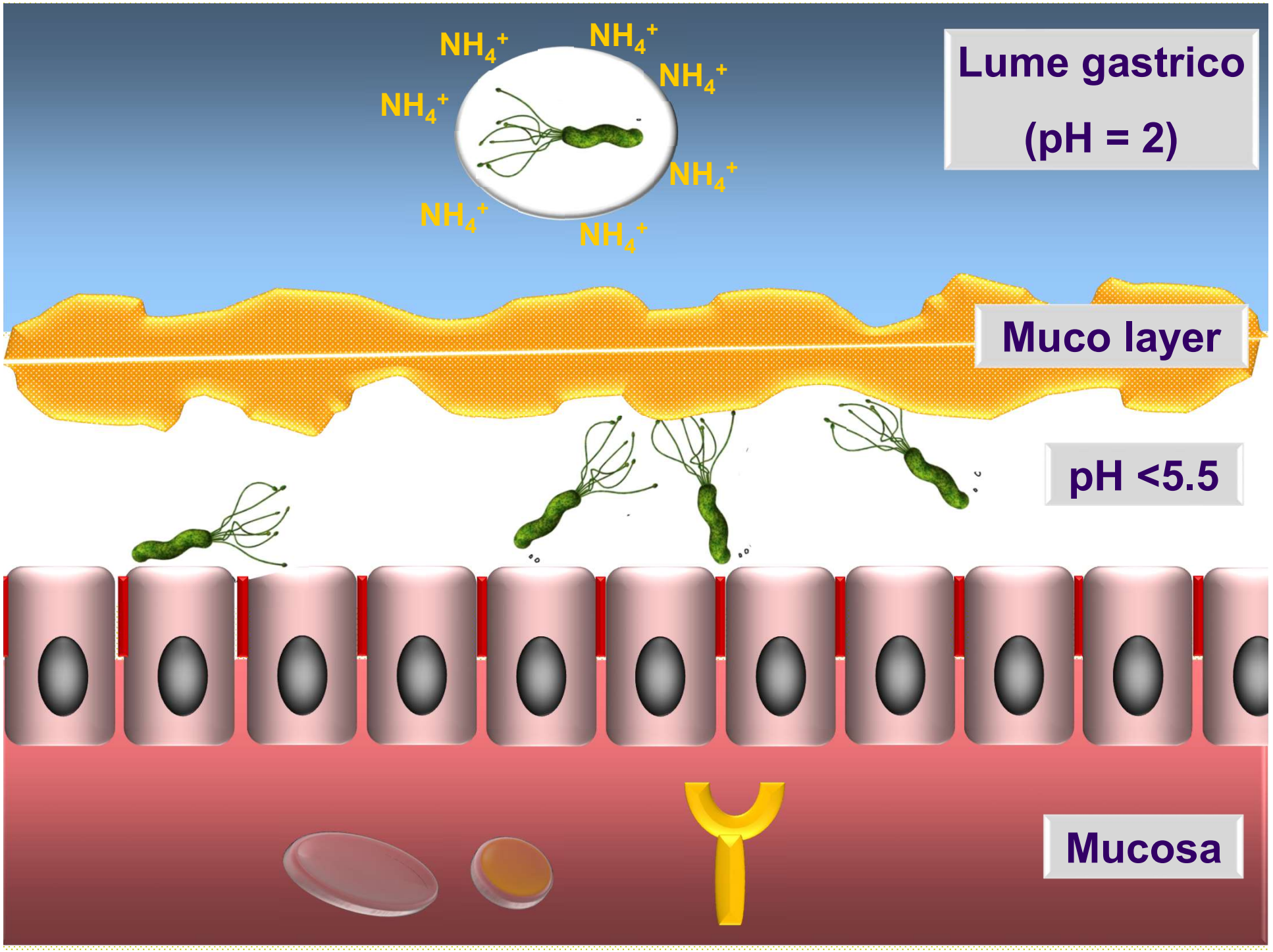
49

Does Omeprazole Improve Antimicrobial Therapy Directed Towards Gastric *Campylobacter Pylori* in Patients with Antral Gastritis?

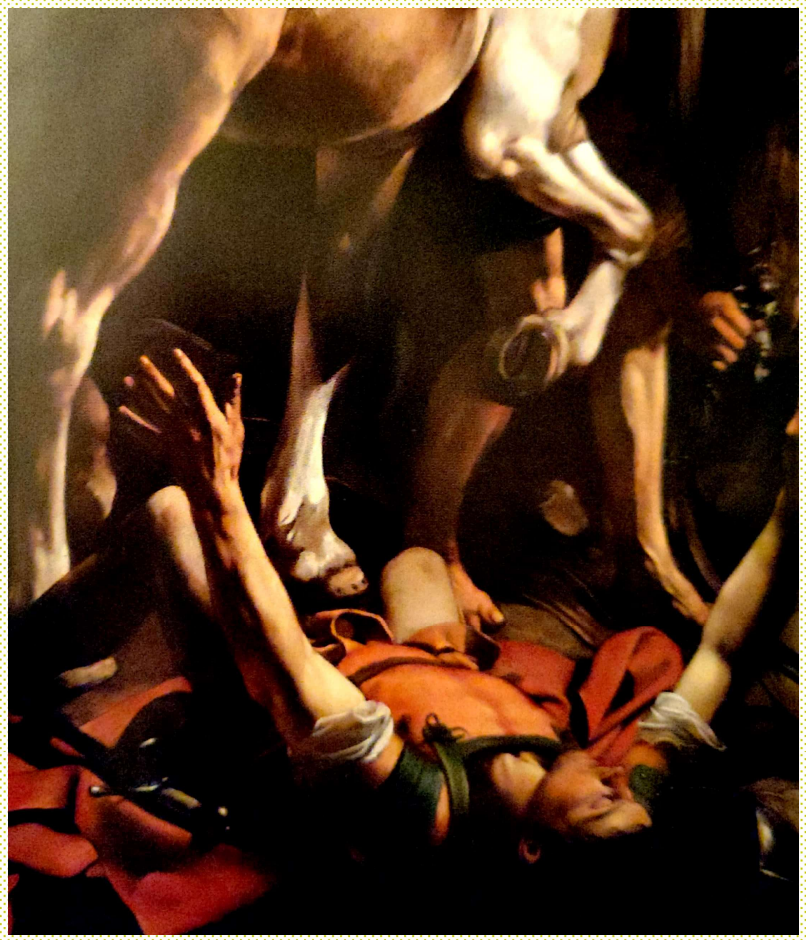
A Pilot Study

P. UNGE, A. GAD, H. GNARPE & J. OLSSON
Dept. of Internal Medicine, Sandviken Hospital, Dept. of Clinical Microbiology, Gävle Hospital, Dept. of Clinical Pathology and Cytology, Falun Hospital and Medical Dept., AB Hässle, Mölndal, Sweden

Nel gruppo di 8 pz trattati con
OMP 40 mg e AMX 750 mg x 2
5 pz su 8 erano negativi al CP dopo 4 settimane dalla terapia


NH_4^+
NH_4^+
NH_4^+
NH_4^+
NH_4^+
NH_4^+
NH_4^+
Lume gastrico
(pH = 2)
Muco layer
pH <5.5
Mucosa

LA CONVERSIONE



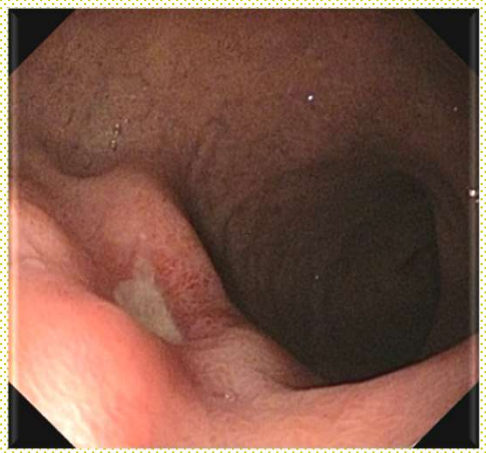
IL CAMMINO DELL'H. PYLORI

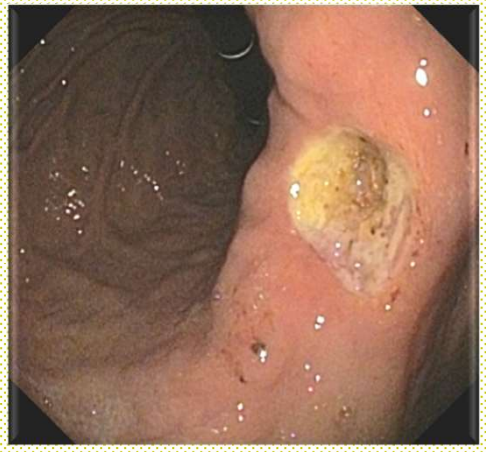
CLINICA
Quali malattie non causa…!

- *Cardiopatia ischemica*
- *Patologie autoimmuni (tiroidite, LES, ecc.)*
- *Allergie*
- *Cefalea*
- *Acne rosacea*
- *Encefalopatia epatica, Steatosi epatica*
- *Glaucoma*
- *Ipertensione*
- *Alzheimer, Parkinson…*
- *ecc…!*

Zullo A. *World J Gastroenterol 2013;19:786-9.*

CLINICA
Quali malattie causa?





BENIGNE

Digestive

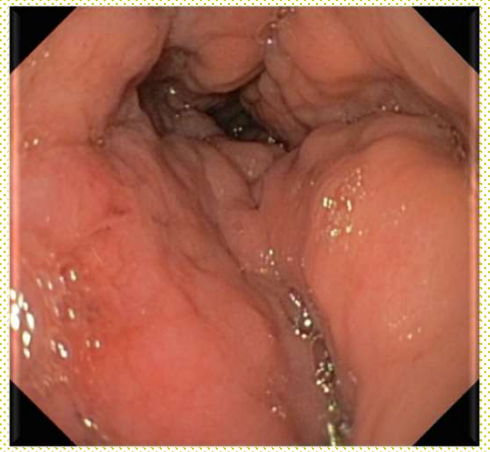
- Gastrite cronica attiva
- Dispepsia non ulcerosa
- Ulcera gastrica
- Ulcera duodenale

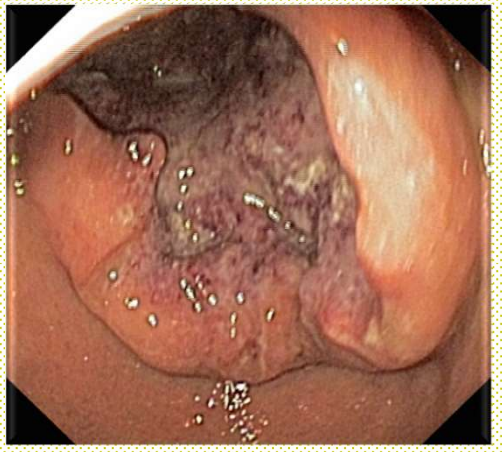
Extra-digestive

- Piastrinopenia autoimmune
- Anemia sideropenica

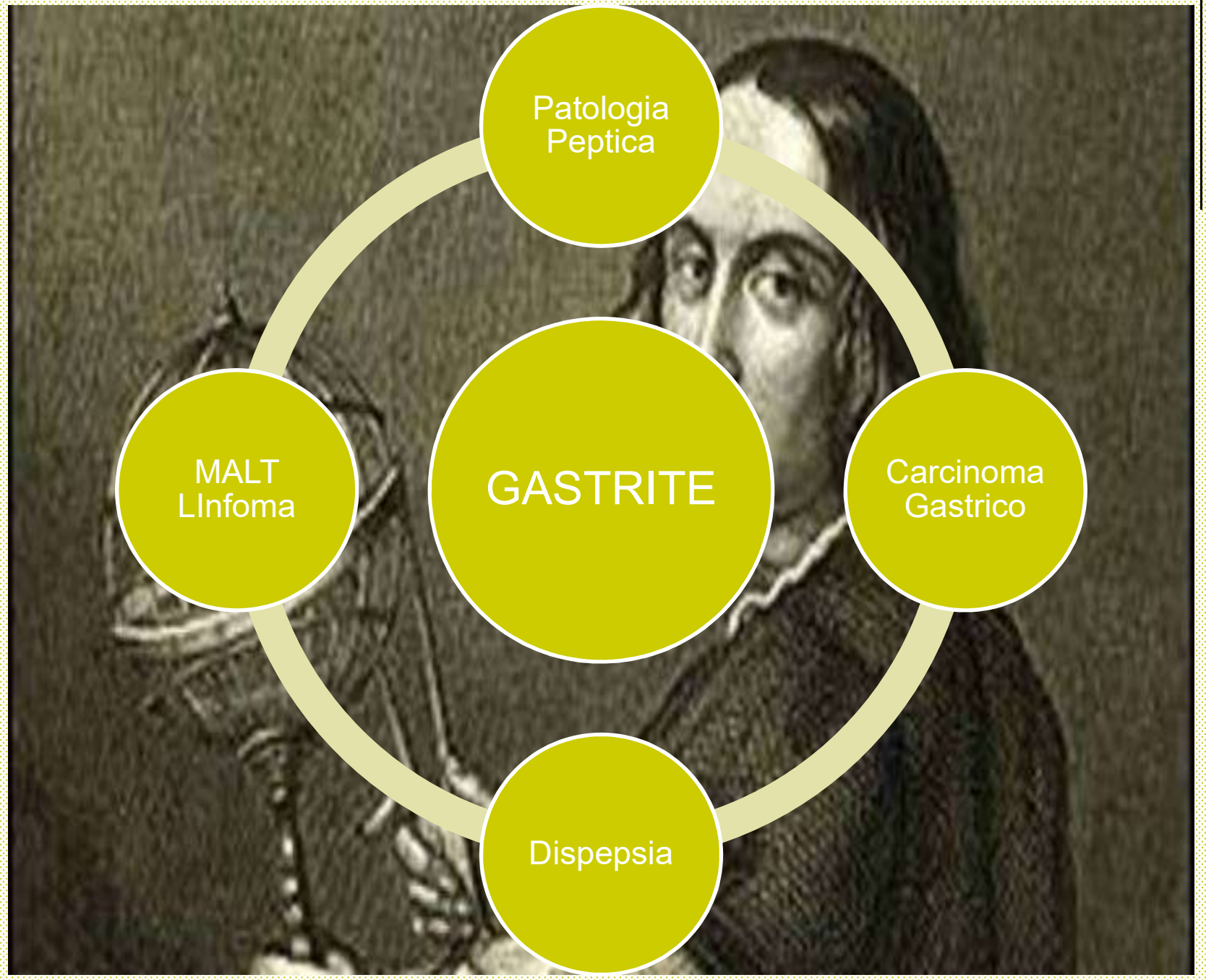
MALIGNE

- Linfoma-MALT
- Cancro gastrico

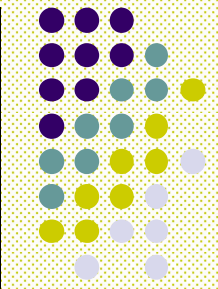




Zagari RM. *Dig Liver Dis 2015:47:903–912*


Patologia Peptica
MALT LInfoma
GASTRITE
Carcinoma Gastrico
Dispepsia

Le Gastriti da H.pylori



Fattori dell'ospite (familiarità,abitudini)

Fattori del batterio

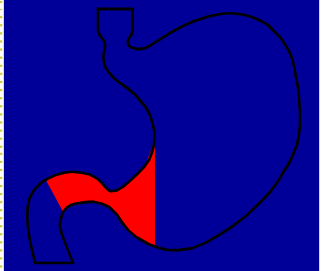
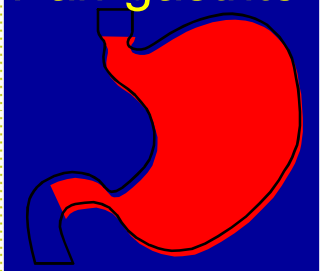
↓

pattern di virulenza (Cag A,Vac A)

↓

topografia della flogosi

H. Pylori e pH intragastrico: alterazioni fisiopatologiche e topografia della flogosi

Pattern di gastrici	*Quadri Gastrici*	*Acid Output*	*Quadri Duodenali*	*Rischio*
Antrum 	• Infiammazione cronica • Polimorfonucleati	Aumentato	• Metaplasia gastrica • Infiammazione cronica attiva	Ulcera duodenale
Pan-gastrite 	• Infiammazione cronica • Polimorfonucleati • Atrofia • Metaplasia intestinale	Ridotto	Normale	Ulcera gastrica e Carcinoma Gastrico

Dixon 1994

H. Pylori e ulcera peptica

Dopo l'eradicazione di *H. pylori*

La recidiva dell'ulcera peptica (gastrica e duodenale) è: ~0%

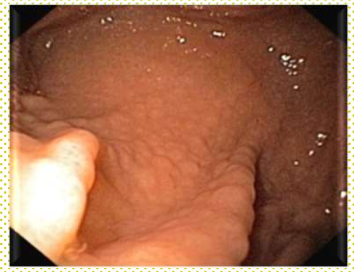
***Helicobacter pylori* and Nonmalignant Diseases**

Alaa Alakkari,* Angelo Zullo† and Humphrey J. O'Connor*

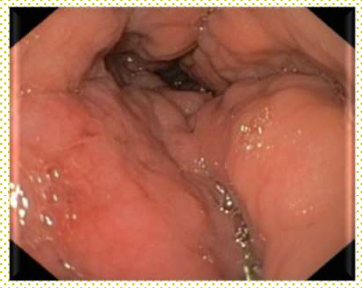
Effects of *Helicobacter pylori* Eradication on Early Stage Gastric Mucosa–Associated Lymphoid Tissue Lymphoma

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2010;8:105–110

ANGELO ZULLO,* CESARE HASSAN,* FRANCESCA CRISTOFARI,* ALESSANDRO ANDRIANI,‡ VINCENZO DE FRANCESCO,§ ENZO IERARDI,§ SILVERIO TOMAO,‖ MANFRED STOLTE,¶ SERGIO MORINI,* DINO VAIRA#



Gastrite follicolare



Linfoma MALT

32 trials
1.408 pz

77.5%

Stadio I
78.5%

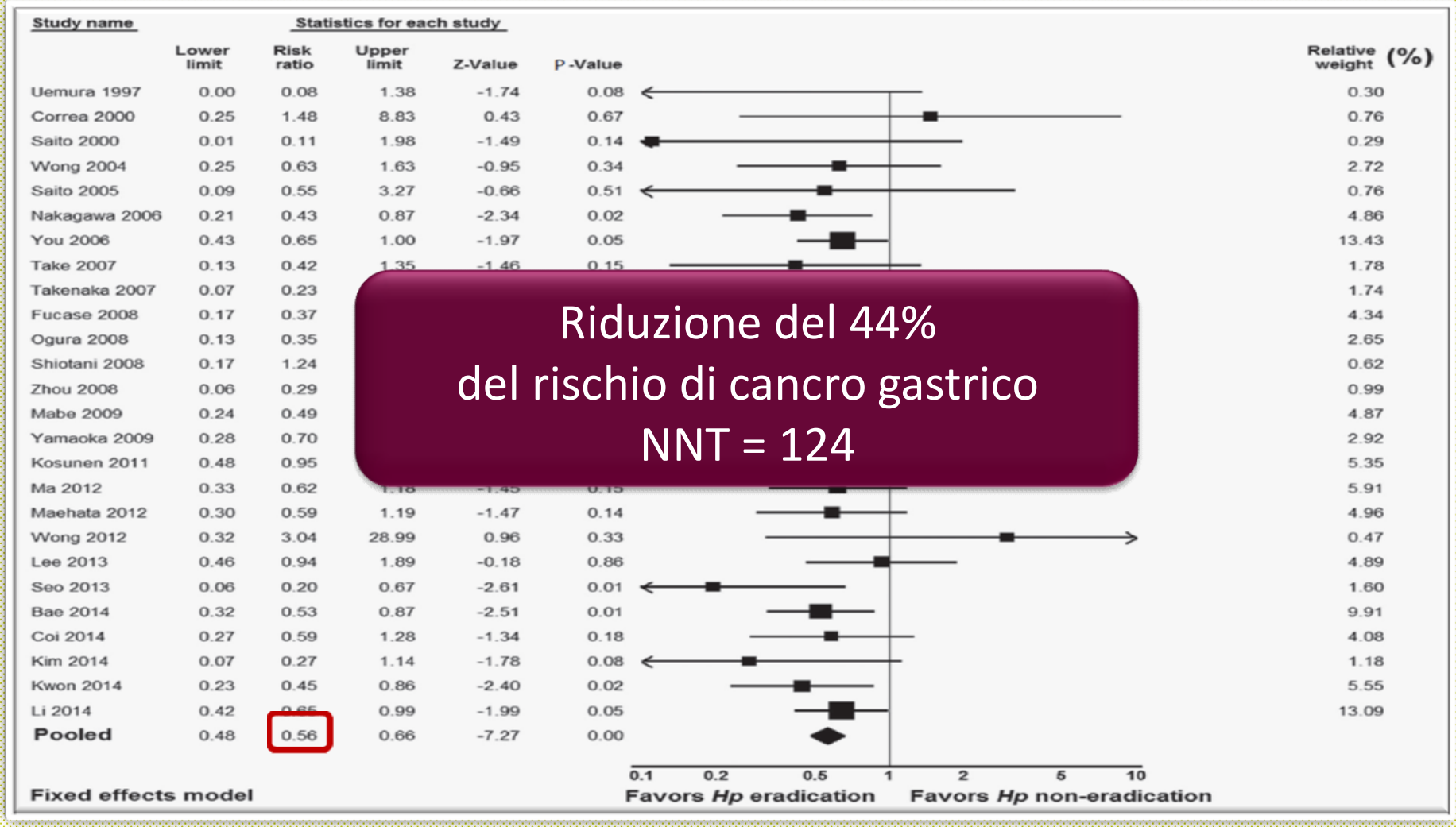
Stadio II
55.6%

A systematic review and meta-analysis of the role of *Helicobacter pylori* eradication in preventing gastric cancer

Annals of Gastroenterology (2017) **30,** 414-423

Theodore Rokkas[a], Androniki Rokka[b], Piero Portincasa[b]

Henry Dunant Hospital, Athens, Greece; Aldo Moro University, Bari Medical School, Bari, Italy



Riduzione del 44%
del rischio di cancro gastrico
NNT = 124

Digestive and Liver Disease 51 (2019) 471–483

Diagnosis of chronic anaemia in gastrointestinal disorders: A guideline by the Italian Association of Hospital Gastroenterologists and Endoscopists (AIGO) and the Italian Society of Paediatric Gastroenterology Hepatology and Nutrition (SIGENP)

Luca Elli[a,*], Lorenzo Norsa[b], Angelo Zullo[c], Antonio Carroccio[d,e], Carlo Girelli[f], Salvatore Oliva[g], Claudio Romano[h], Gioacchino Leandro[i], Massimo Bellini[j], Riccardo Marmo[k], Marco Soncini[l], Fabio Monica[m], Vincenzo De Francesco[n], Emma Paulon[m], Maria Domenica Cappellini[o,p], Irene Motta[o,p], Francesca Ferretti[a], Stefania Orlando[a], Pasquale Mansueto[e], Elisabetta Buscarini[q], Guido Manfredi[q], Carlo Agostoni[r,p], Carolina Tomba[s], Renato Cannizzaro[t]

- *H. pylori infection needs testing in adult patients with IDA (strong recommendation, high level of evidence).*

- *H. pylori eradication is a therapeutic option for patients with otherwise unexplained IDA (strong recommendation, low level of evidence).*

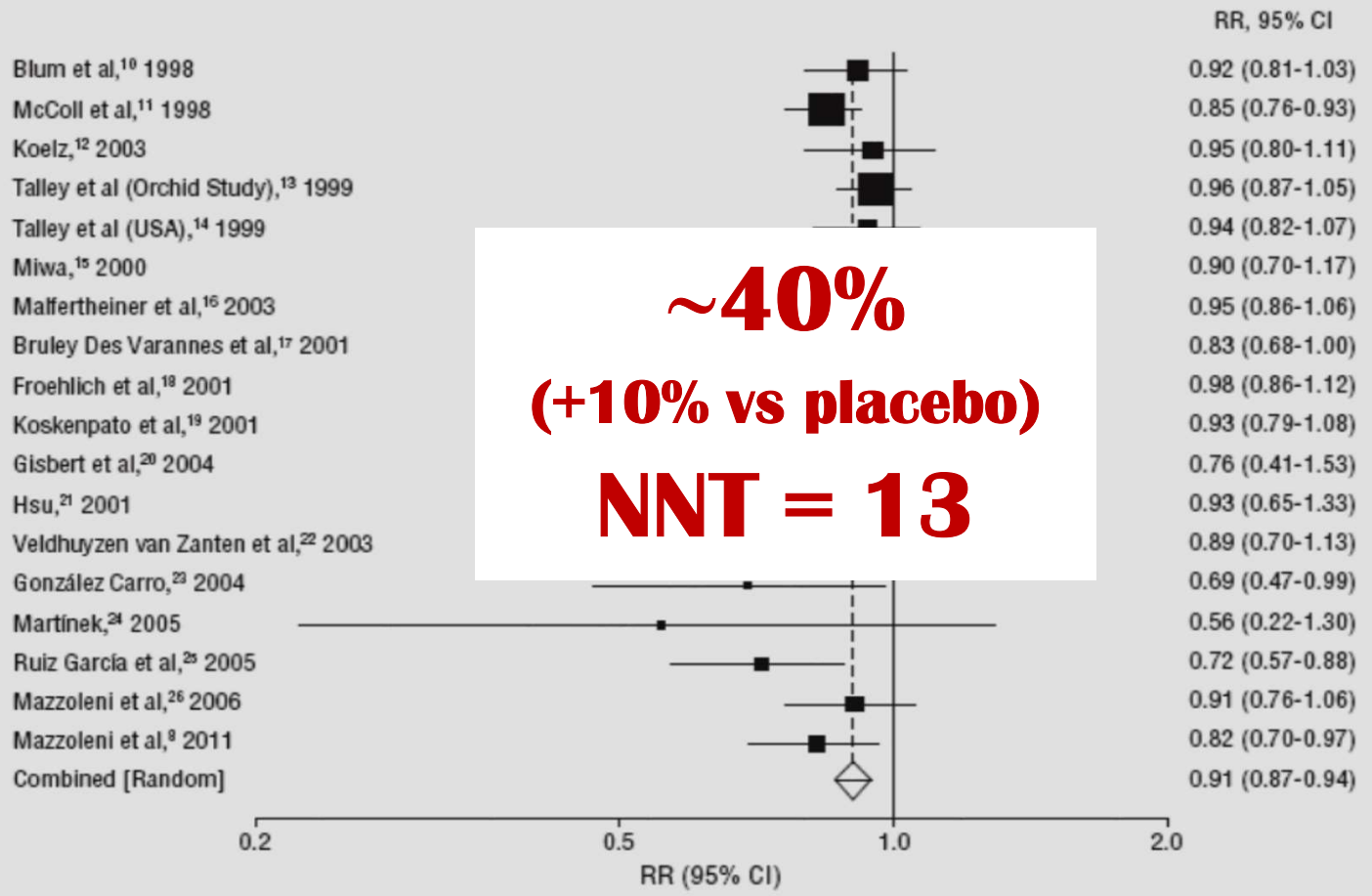
La Dispepsia

Fussli-1781: "l'Incubo"

Helicobacter pylori Eradication for Functional Dyspepsia

Paul Moayyedi

Arch Intern Med 2011;171(21):1936-1937



~40%

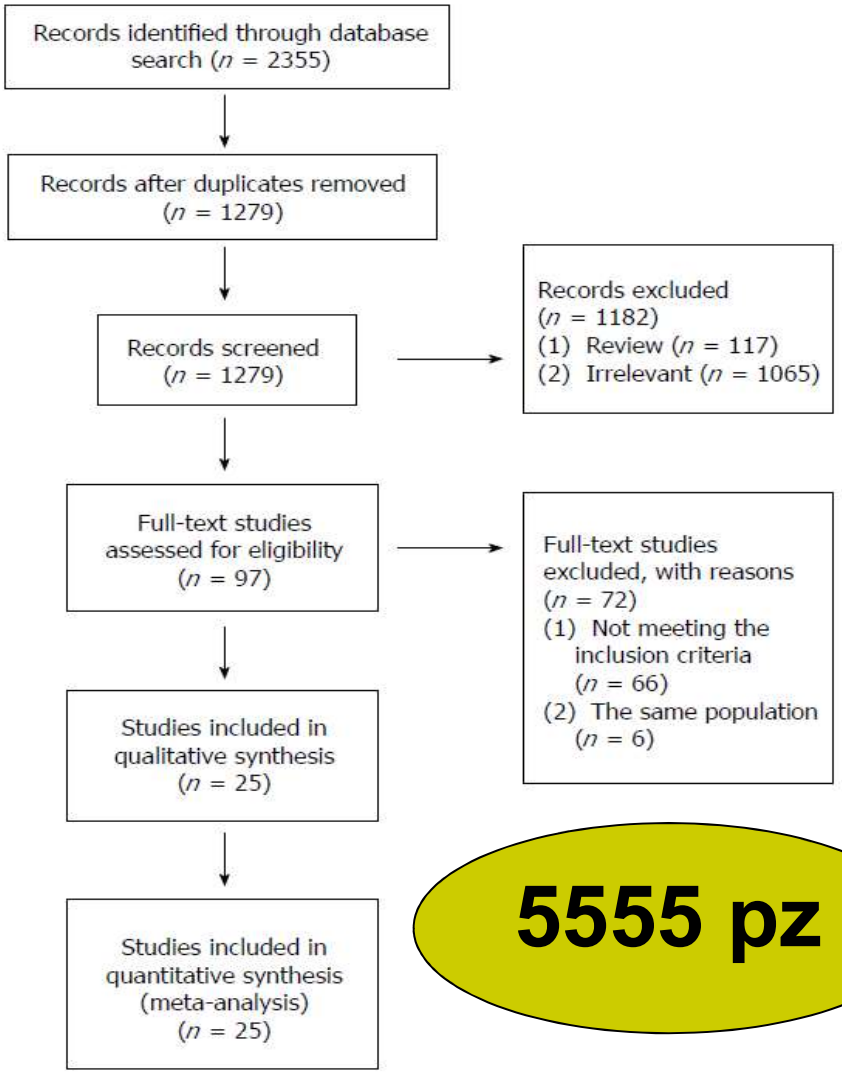
(+10% vs placebo)

NNT = 13

Helicobacter pylori eradication therapy for functional dyspepsia: Systematic review and meta-analysis

World J Gastroenterol 2016 March 28; 22(12): 3486-3495

Li-Jun Du, Bin-Rui Chen, John J Kim, Sarah Kim, Jin-Hua Shen, Ning Dai

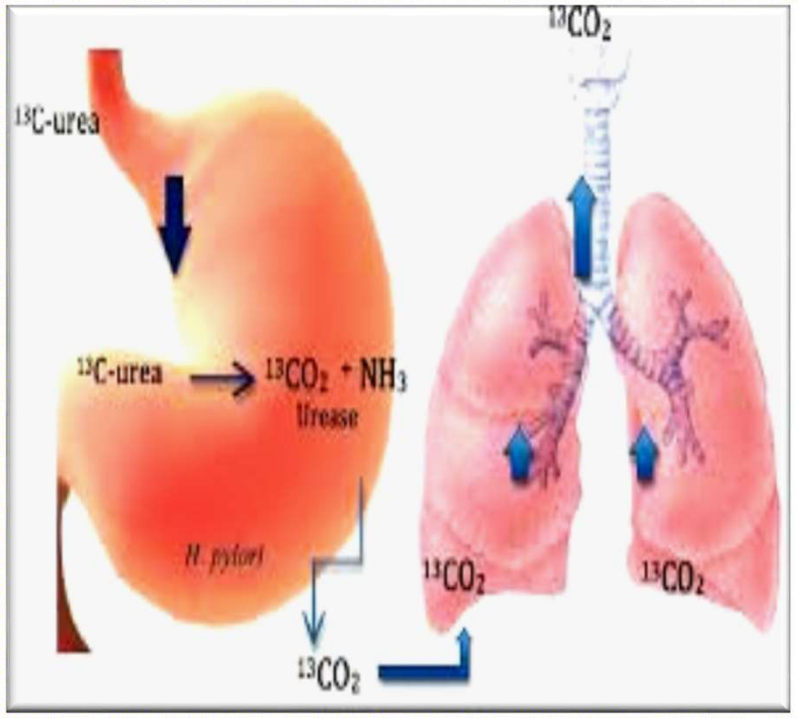


5555 pz

1. **Miglioramento della qualità della vita**
2. **Incidenza di effetti collaterali**
3. **Risoluzione dei sintomi**
4. **Riduzione del rischio di ulcera**
5. **Risoluzione del danno istologico**

DIAGNOSI

Urea Breath test



SENSIBILITA' E SPECIFICITA'

PRE-TRATTAMENTO = 98-100%

POST-TRATTAMENTO= 98-100%

Gisbert JP *Aliment Pharmacol Ther 2004;20:1001-17.*

DIAGNOSI

Test degli antigeni fecali

~~TEST POLIONALE~~

TEST MONOCLONALE

Pre-terapia

Sensitivity, %	96	76.8–100
Specificity, %	97	77.6–100

TEST MONOCLONALE

90.1% sensitivity

92.4% specificity

Post-terapia

Gisbert JP. *Helicobacter 2004;9:347-68*
Lee JY. *Ann Transl Med 2015;3:1-8*

Megraud F. *Helicobacter 2016;21:8-13*

DIAGNOSI

Quale test?

SINTOMI DI ALLARME:
- anemia
- ematemesi/melena
- vomito persistente
- disfagia
- calo ponderale

(familiarità per cancro gastrico)

Paziente dispeptico

Età <50 aa senza sintomi di allarme

UBT
Test antigeni fecali

Età >50 aa o con sintomi d'allarme

EGDS con biopsie standard

E' INDISPENSABILE INTERROMPERE IL TRATTAMENTO CON INIBITORI DELLA POMPA PROTONICA ALMENO 2 SETTIMANE PRIMA DI ESEGUIRE QUALSIASI TEST!

GLI INIBITORI DELLA POMPA PROTONICA (IPP)

- Omeprazolo 20 mg
- Lansoprazolo 30 mg
- Pantoprazolo 40 mg
- Rabeprazolo 20 mg
- Esomeprazolo 20 o 40 mg

½ h prima di colazione

½ h prima di cena

Terapia per *H. pylori:* dosaggio IPP

Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of *Helicobacter pylori* infection

Aliment Pharmacol Ther 2012; **36**: 414–425

A. G. McNicholl*,†, P. M. Linares*,†, O. P. Nyssen*, X. Calvet†,‡ & J. P. Gisbert*,†

20 mg bid

(b)

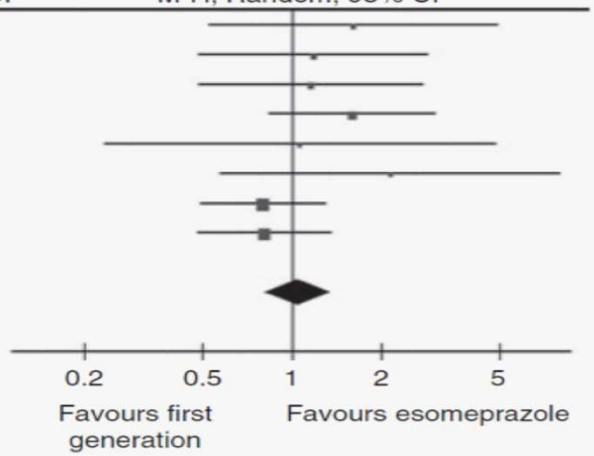
Study or Subgroup	Esomeprazole Events	Esomeprazole Total	First generation Events	First generation Total	Weight	Odds ratio M-H, Random, 95% CI
Chen 2005	46	52	43	52	5.4%	1.60 [0.53, 4.89]
De los Rios 2009	26	41	25	42	8.5%	1.18 [0.49, 2.86]
Huh 2004	44	57	41	55	8.9%	1.16 [0.49, 2.75]
kang 2008	121	137	157	190	16.2%	1.59 [0.84, 3.02]
Maev 2003	46	51	26	29	2.9%	1.06 [0.23, 4.81]
Miehlke 2003	38	42	31	38	3.8%	2.15 [0.57, 8.01]
Subei 2007 (1)	139	186	148	188	28.8%	0.80 [0.49, 1.29]
Tulassay 2001 (2)	184	222	192	224	25.5%	0.81 [0.48, 1.35]
Total (95% CI)		788		818	100.0%	1.04 [0.80, 1.35]
Total events	644		663			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.65$, df = 7 ($P = 0.58$); $I^2 = 0\%$

Test for overall effect: $Z = 0.30$ ($P = 0.77$)

(1) Omeprazole arm uses 3 extra weeks of PPI treatment

(2) Omeprazole arm uses 3 extra weeks of PPI treatment



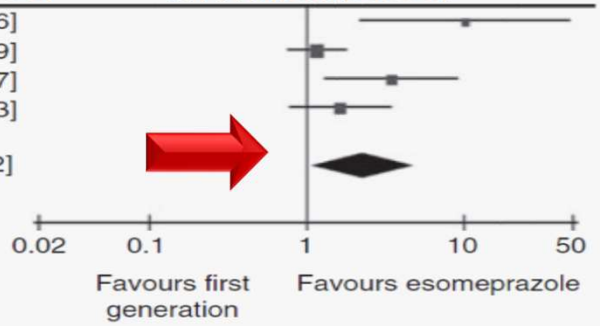
40 mg bid

(c)

Study or Subgroup	Esomeprazole Events	Esomeprazole Total	First generation Events	First generation Total	Weight	Odds ratio M-H, Random, 95% CI
Anagnostopoulos 2004	50	52	37	52	14.8%	10.14 [2.18, 47.06]
Choi 2007	104	148	193	288	34.0%	1.16 [0.76, 1.79]
Hsu 2005	94	100	82	100	23.4%	3.44 [1.30, 9.07]
Sheu 2005	86	100	79	100	27.9%	1.63 [0.78, 3.43]
Total (95% CI)		400		540	100.0%	2.27 [1.07, 4.82]
Total events	334		391			

Heterogeneity: $Tau^2 = 0.39$; $Chi^2 = 10.17$, df = 3 ($P = 0.02$); $I^2 = 71\%$

Test for overall effect: $Z = 2.13$ ($P = 0.03$)



GLI ANTIBIOTICI

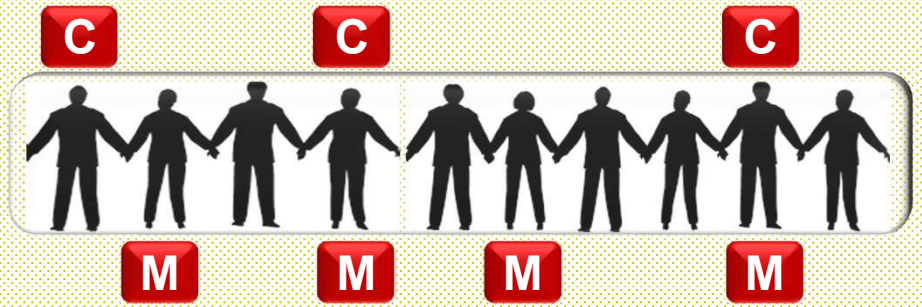
- Amoxicillina 1 g
- Claritromicina 500 mg
- Tinidazolo 500 mg
- Tetraciclina 125 mg
- Levofloxacina 250/500 mg
- Rifabutina 150/300 mg

Dopo colazione

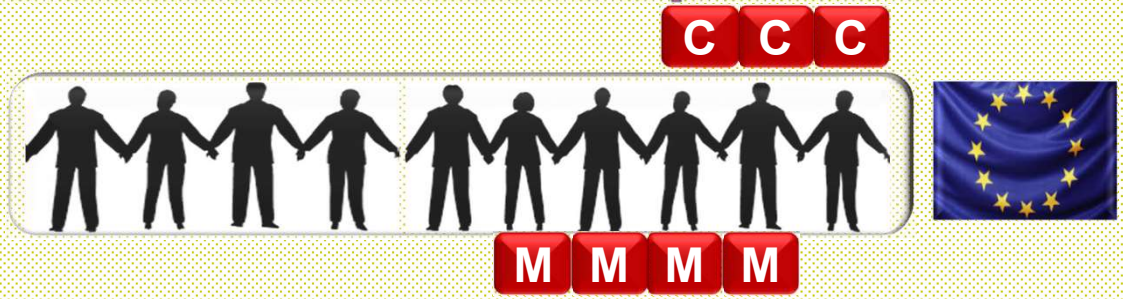
Dopo cena

La terapia per *H. pylori*

1 Basata sulla resistenza verificata



2 Basata sulla resistenza presunta



3 Terapia empirica

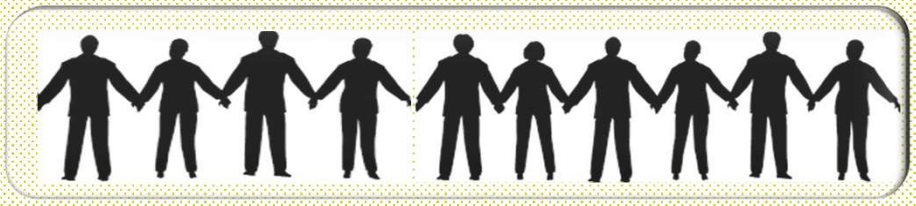
Terapia empirica

Special Article

Digestive and Liver Disease 47 (2015) 903–912

Guidelines for the management of *Helicobacter pylori* infection in Italy: The III Working Group Consensus Report 2015

Rocco Maurizio Zagari[a,*], Marco Romano[b], Veronica Ojetti[c], Reinhold Stockbrugger[d], Sergio Gullini[e], Bruno Annibale[f], Fabio Farinati[g], Enzo Ierardi[h], Giovanni Maconi[i], Massimo Rugge[j], Carlo Calabrese[a], Francesco Di Mario[k], Francesco Luzza[l], Stefano Pretolani[m], Antonella Savio[n], Giovanni Gasbarrini[c], Michele Caselli[e]



One of the following regimens should be used as first-line treatment in Italy:

- **standard 14-day PPI-based clarithromycin-containing triple therapy**
- **10-day sequential therapy**
- **10-day concomitant therapy (non-bismuth quadruple).**

Evidence level: 1a; Grade of recommendation: A

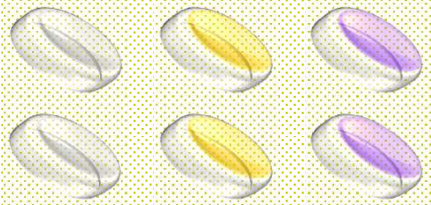
The "3-drug pill" (bismuth, metronidazole and tetracycline) may represent a valid alternative, when available.

Evidence level: 1b; Grade of recommendation: A

LE TRIPLICI TERAPIE

IPP Cla Amo

OPPURE



IPP Cla Tin

6 cpr al giorno

per 14 giorni

Tot: 84 cpr

Costo: 54,28 €

LE TRIPLICI TERAPIE

Annals of Internal Medicine | REVIEW

Meta-analysis: Duration of First-Line Proton-Pump Inhibitor–Based Triple Therapy for *Helicobacter pylori* Eradication

Lorenzo Fuccio, MD; Maria Eugenia Minardi, MD; Rocco Maurizio Zagari, MD; Diego Grilli, PhD; Nicola Magrini, MD; and Franco Bazzoli, MD

Ann Intern Med. 2007;147:553-562.

ERADICAZIONE

- **TRIPLICE TERAPIA PER 7 GIORNI** → **72%**
- **TRIPLICE TERAPIA PER 14 GIORNI** → **78%**

LA TERAPIA SEQUENZIALE“5+5”

A new highly effective short-term therapy schedule for Helicobacter pylori *eradication*

Aliment Pharmacol Ther 2000; 14: 715–718.

A. ZULLO, V. RINALDI, S. WINN, P. MEDDI, R. LIONETTI, C. HASSAN, C. RIPANI, G. TOMASELLI & A. F. ATTILI

IPP Amo + **IPP Cla Tin**

4 cpr al giorno per 5 giorni → **6 cpr al giorno per 5 giorni**

10 giorni

Tot: 50 cpr

Costo: 29,40 €

LA TERAPIA SEQUENZIALE "5+5"

The sequential therapy regimen for *Helicobacter pylori* eradication: a pooled-data analysis

Gut 2007;**56**:1353–1357.

Angelo Zullo, Vincenzo De Francesco, Cesare Hassan, Sergio Morini, Dino Vaira

Table 1 Overall eradication rate following sequential therapy at intention to treat (ITT) and per protocol (PP) analysis

Author (reference)	Year	Centres involved	Patients enrolled	Patients cured	ITT (%)
Zullo *et al*[32]	2000	1	52	51	98
De Francesco *et al*[32]	2001	2	63	61	93.8
Focareta *et al*[33]	2002	1	94	90	95.7
Zullo *et al*[34]	2003	8	522	481	92
Hassan *et al*[35]	2003	1	152	142	93.4
Focareta *et al*[36]	2003	1	174	166	95.4
De Francesco *et al*[37]	2004	1	162	151	93.2
De Francesco *et al*[38]	2004	2	45	43	95.5
De Francesco *et al*[39]	2004	2	116	110	94.8
Francavilla *et al*[40]	2005	1	38	36	94.7
Zullo *et al*[41]	2005	3	89	84	94.4
Zullo *et al*[42]	2005	1	40	38	95
Scaccianoce *et al*[43]	2005	2	72	68	94.4
Francavilla *et al*[40]	2006	1	40	33	82.5
Vaira *et al*[45]	2007	2	146	133	91.1
Total			1805	1687	93.5

Impact of primary antibiotic resistance on the effectiveness of sequential therapy for *Helicobacter pylori* infection: lessons from a 5-year study on a large number of strains

L. Gatta[1,2] | C. Scarpignato[2] | G. Fiorini[3] | J. Belsey[4] | I. M. Saracino[3]
C. Ricci[5] | D. Vaira[3]

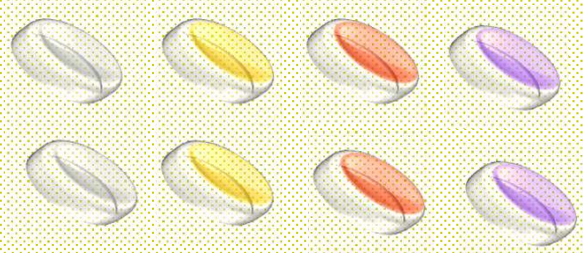
Aliment Pharmacol Ther 2018;47:1261-1269

1.120 pazienti

Tassi di eradicazione:

ITT: 91.1% (95% CI: 80.6 - 97.7)
PP: 93.7% (95% CI: 90.4 - 96.3)

LA TERAPIA CONCOMITANTE



IPP Cla Amo Tin

8 cpr al giorno

per 10 giorni

Tot: 80 cpr

Costo: 68,32 €

LA TERAPIA CONCOMITANTE

Sequential, concomitant and hybrid first-line therapies for *Helicobacter pylori* eradication: a prospective randomized study

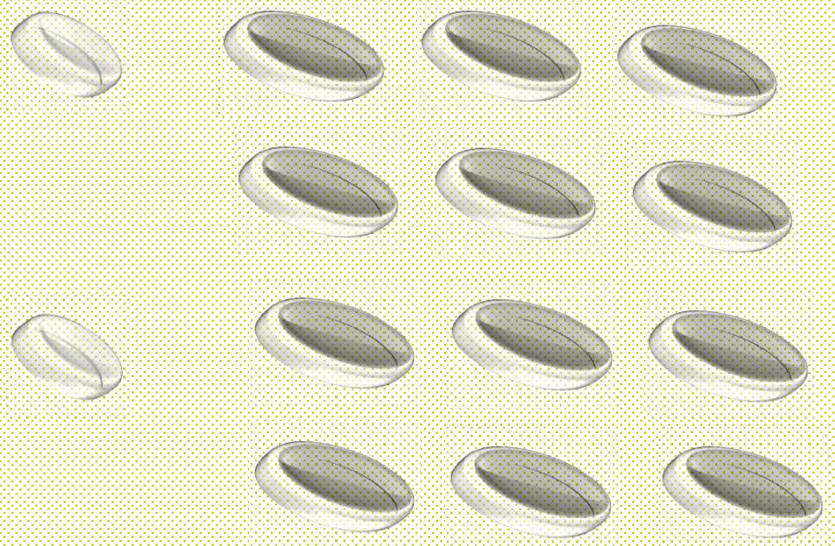
Journal of Medical Microbiology (2014), 63, 748–752

Vincenzo De Francesco,[1] Cesare Hassan,[2] Lorenzo Ridola,[2] Floriana Giorgio,[3] Enzo Ierardi[3] and Angelo Zullo[2]

Table 2. Results of the first-line therapies

	Sequential	Concomitant	
	10 day	5 day	14 day
ITT eradication rate			
Percentage (95% CI)	90% (84.3–95.6)*	78.1% (70.4–85.9)	86.3% (79.9–92.7)
No. of patients	99/110	86/110	95/110
PP eradication rate			
Percentage (95% CI)	94.2% (89.8–98.7)	85.1% (78.2–92)†	95% (90.7–99.2)
No. of patients	99/105	86/101	95/100

LA QUADRUPLICE CON PYLERA



Dopo colazione

Dopo pranzo

Dopo cena

Prima di coricarsi

IPP

Pylera

Bismuto = 140 mg
Tetraciclina = 125 mg
Metronidazolo = 125 mg

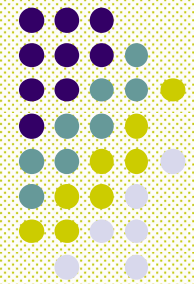
14 cpr al giorno

per 10 giorni

Tot: 140 cpr

Costo: 74,04 €

LA QUADRUPLICE CON PYLERA



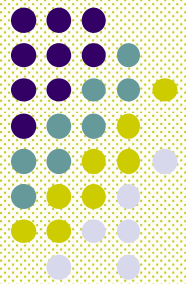
New bismuth-containing quadruple therapy in patients infected with *Helicobacter pylori*: A first Italian experience in clinical practice

Helicobacter. 2017;22:e12371.

Antonio Tursi[1] | Francesco Di Mario[2] | Marilisa Franceschi[3] | Rudi De Bastiani[4] | Walter Elisei[5] | Gianluca Baldassarre[3] | Antonio Ferronato[3] | Simone Grillo[2] | Stefano Landi[2] | Maria Zamparella[4] | Manuela De Polo[4] | Laura Boscariolo[4] | Marcello Picchio[6]

Setting	Eradicazione
Prima linea	51/55 (92.7%)

LA QUADRUPLICE CON PYLERA



Quadruple, sequential, and concomitant first-line therapies for *H. pylori* eradication: a prospective, randomized study

Vincenzo De Francesco[a,*], Stefano Pontone[b], Annamaria Bellesia[a], Gaetano Serviddio[c], Cristina Panetta[b], Rossella Palma[b], Angelo Zullo[d]

Digestive and Liver Disease 50 (2018) 139–141

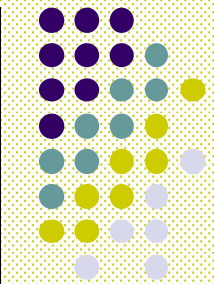
Eradication rates at intention-to-treat (ITT) and per protocol (PP) analyses.

	Pylera	Concomitant	Sequential
ITT eradication rate; N	52/61	60/63	59/63
% (95% CI)	85.2 (70.2–89.7)	95.2 (89.9–100)	93.6 (87.6–99.6)
PP eradication rate; N	52/55	60/62	59/62
% (95% CI)	94.5 (88.5–100)	96.7 (92.3–100)	95.1 (89.8–100)

First-line therapies for *Helicobacter pylori* eradication: a critical reappraisal of updated guidelines

Annals of Gastroenterology (2017) **30,** 373-379

Vincenzo De Francesco[a], Annamaria Bellesia[a], Lorenzo Ridola[b], Raffaele Manta[c], Angelo Zullo[d]



Therapy regimen	Duration (days)	Number of tablets	Cost in Italy (euros)	
Standard triple therapy				
- PPI* + clarithromycin 500 mg+amoxicillin 1000 mg	14	84	49.72	<80%
- PPI+clarithromycin 500 mg+tinidazole 500 mg	14	84	57.28	
Sequential				
PPI+amoxicillin 1000 mg (5 days) followed by PPI+clarithromycin 500 mg+tinidazole 500 mg (5 days)	10	50	29.40	>90%
Concomitant				
PPI+clarithromycin 500 mg+amoxicillin 1000 mg+tinidazole 500 mg	10	80	48.8	>85%
PPI+clarithromycin 500 mg+amoxicillin 1000 mg+tinidazole 500 mg	14	112	68.32	
Bismuth-based quadruple (three-in-one tablets; Pylera®)				
PPI+3 Pylera®	10	140	74.04	>90%
PPI+3 Pylera®	14	196	103.04	

Digestive and Liver Disease 47 (2015) 903–912

Special Article

Guidelines for the management of *Helicobacter pylori* infection in Italy: The III Working Group Consensus Report 2015

Rocco Maurizio Zagari[a,*], Marco Romano[b], Veronica Ojetti[c], Reinhold Stockbrugger[d], Sergio Gullini[e], Bruno Annibale[f], Fabio Farinati[g], Enzo Ierardi[h], Giovanni Maconi[i], Massimo Rugge[j], Carlo Calabrese[a], Francesco Di Mario[k], Francesco Luzza[l], Stefano Pretolani[m], Antonella Savio[n], Giovanni Gasbarrini[c], Michele Caselli[e]

Second-line therapy

Levofloxacin-containing triple therapy	10 days **(14 giorni)**
Bismuth-containing quadruple therapy (when bismuth is available)	7–14 days **(10 giorni)**

Systematic review with meta-analysis: the efficacy of levofloxacin triple therapy as the first- or second-line treatments of *Helicobacter pylori* infection

P.-Y. Chen*, M.-S. Wu†, C.-Y. Chen*, M.-J. Bair‡,§, C.-K. Chou*, J.-T. Lin†,¶ & J.-M. Liou† for the Taiwan Gastrointestinal Disease and Helicobacter Consortium

Aliment Pharmacol Ther 2016; 44: 427–437

Table 1 | Efficacy of levofloxacin triple therapy in the treatment of *Helicobacter pylori* infection and factors

	Eradication rate (%)	95% Confidence intervals	Heterogeneity I^2	Heterogeneity *P* value
Overall	77.3	74.7–79.6	67.6	<0.001
Duration (days)				
7	74.5	70.8–77.9	70.2	<0.001
10	80.4	76.5–83.8	64.3	<0.001
14	83.4	71.4–91.1	0	0.811

High dose dual therapy versus bismuth quadruple therapy for *Helicobacter pylori* eradication treatment

Medicine (2019) 98:7(e14396)

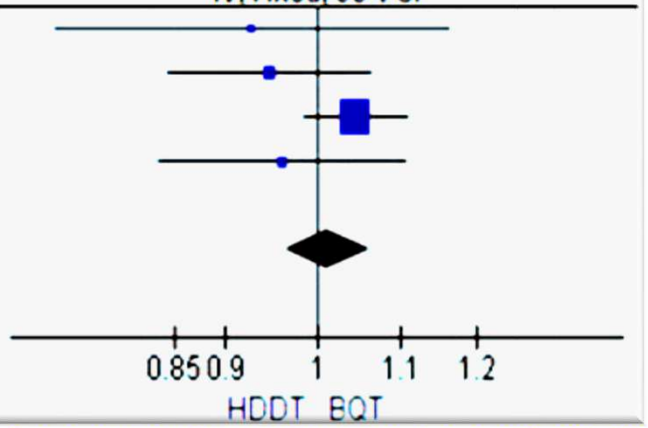
A systematic review and meta-analysis

Xue Yang, MD, Jin-Xia Wang, MD, Sheng-Xi Han, MD, Cai-Ping Gao, MD, PhD*

Study or Subgroup	HDDT Events	HDDT Total	BQT Events	BQT Total	Weight	Risk Ratio IV, Fixed, 95% CI
Miehlke 2003	31	41	35	43	4.7%	0.93 [0.74, 1.16]
Hu JL 2017	139	174	75	89	17.5%	0.95 [0.84, 1.07]
Hu CT 2017	161	170	154	170	65.9%	1.05 [0.98, 1.11]
Gao 2018	58	70	62	72	11.9%	0.96 [0.84, 1.11]
Total (95% CI)		**455**		**374**	**100.0%**	**1.01 [0.96, 1.06]**
Total events	389		326			

Heterogeneity: Chi² = 3.38, df = 3 (P = 0.34), I² = 11%

Test for overall effect: Z = 0.48 (P = 0.63)



Study or Subgroup	HDDT Events	HDDT Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
2015 Yang	50	56	44	56	21.2%	1.14 [0.96, 1.34]
2007 Shirai	60	66	61	66	53.9%	0.98 [0.89, 1.09]
2006 Miehlke	50	72	54	73	13.6%	0.94 [0.76, 1.15]
2003 Miehlke	31	41	35	43	11.3%	0.93 [0.74, 1.16]
Total (95% CI)		**235**		**238**	**100.0%**	**1.00 [0.93, 1.08]**
Total events	191		194			

Heterogeneity: Chi² = 3.21, df = 3 (P = 0.36); I² = 6%

Test for overall effect: Z = 0.03 (P = 0.97)

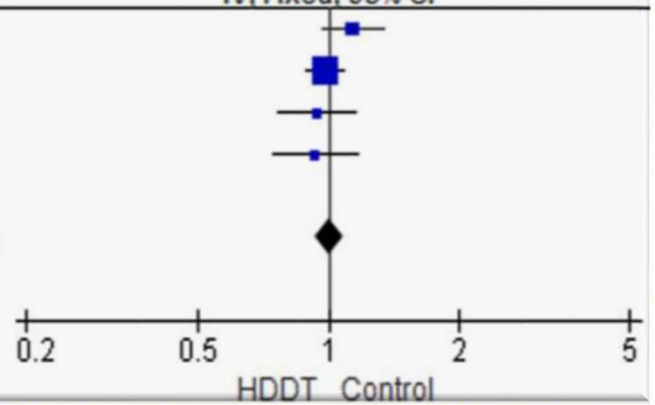


Table 1. Eradication rate with high-dose dual therapies as first-line treatment.

Study	Country	Therapy regimen	Pts	ITT cure (%)
Bayerdörffer E et al.	Germany	Ome 40 mg t.i.d	33	93.7
Lancet 1995;345:1591-4		Amox 750 mg t.i.d for 14 days		
Bayerdörffer E et al.	Germany	Ome 40 mg t.i.d	134	90.6
Gastroenterology 1995;108:1412-7		Amox 750 mg t.i.d for 14 days		
Incwe AT et al.	Turkey	Ome 20 mg q.i.d	74	81.1
Hepatogastroenterology 2014;61:1454-8		Amox 1 g b.i.d for 14 days		
Tai WC et al.	Taiwan	Eso 40 mg t.i.d	120	91.7
J Antimicrob Chemother 2019;74:1718-24		Amox 750 mg q.i.d for 14 days		
Yu L et al.	China	Eso 40 mg b.i.d	80	92.5
Helicobacter 2019 Aug;24(4):e12596		Amox 1 g t.i.d for 14 days		
Zullo A et al.	Italy	Eso 40 mg t.i.d	56	87.5
Ann Gastroenterol 2015;28:448-51		Amox 1 g t.i.d for 10 days		
Graham DY et al.	USA	Eso 40 mg t.i.d	36	72.2
J Gastroenterol 2010;45:816-20		Amox 750 mg b.i.d for 14 days		
Yang J et al.	China	Eso 20 mg q.i.d	116	87.9
Am J Gastroenterol 2019;114:437-45		Amox 750 mg q.i.d for 14 days		
Yang JC et al.	Taiwan	Rabe 20 mg q.i.d	150	95.3
Clin Gastroenterol Hepatol 2015;13:895-905		Amox 750 q.i.d for 14 days		
Hu JL et al.	China	Rabe 20 mg q.i.d	87	81.6
Saudi J Gastroenterol 2017;23:275-80		Amox 750 q.i.d for 14 days		
Sapmaz F et al.	Turkey	Rabe 20 mg t.i.d	98	84.7
Am J Ther 2017;24:e393-e398		Amox 750 t.i.d for 14 days		
Furuta T et al	Japan	Lanso 30 mg q.i.d	45	95.5
Clin Pharmacol Ter 2007;81:521-8		Amox 500 mg q.i.d for 14 days		
Attuni TA et al.	USA	Dexlansoprazole 120 mg b.i.d	13	53.8
Helicobacter 2014;19:319-22.		Amox 1 g b.i.d for 14 days		
Kwack W et al.	Korea	Ilaprazole 40 mg b.i.d	29	79.3
Gastroenterol Res Pract 2016;1648047		Amox 750 q.i.d for 14 days		

Ome: omeprazole; Eso: esomeprazole; Lanso: lansoprazole: Rabe: rabeprazole. Amox: amoxicillin;

PRIMA LINEA

ESO 40 mg t.i.d
+
AMOX 1 g t.i.d

(14 giorni)

Zullo A. *Eur J Gastr Hepatol 2019 (in press)*

J Clin Gastroenterol 2016

Rifabutin Triple Therapy is Effective in Patients With Multidrug-resistant Strains of *Helicobacter pylori*

Giulia Fiorini, MD, MSc, Angelo Zullo, MD,†*
Nimish Vakil, MD, FACP, FACG, AGAF, FASGE,‡
Ilaria M. Saracino, MD, PhD, Chiara Ricci, MD,§ Valentina Castelli, MD,**
*Luigi Gatta, MD,‖ and Dino Vaira, MD**

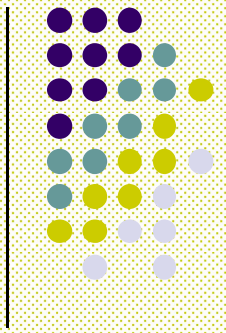
ESO 40 mg b.i.d + AMOX 1 g b.i.d + RIFAB 150 mg u.i.d (12 giorni)

TABLE 1. Clinical and Demographic Characteristics of all Enrolled Patients

	Numbers
Male/female	78/179
Age (mean ± SD) (y)	51.9 ± 13.3
Smokers/nonsmokers, ex-smokers	59/198
Peptic ulcer/nonulcer dyspepsia	23/234
Previous therapy failures	
1 attempt	55
2 attempts	70
3 attempts	73
4 attempts	39
> 4 attempts	20

ITT = 82.9%

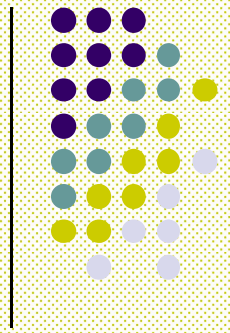
PP = 87.5%



Quale terapia di prima linea utilizzi nella tua pratica clinica per curare l'H. pylori:

1. La triplice terapia per 7-14 giorni
2. La terapia sequenziale di 10 giorni
3. La terapia concomitante per 10 giorni
4. La terapia con Pylera per 10 giorni

TEST



Nella pratica clinica ricerchi e curi l'infezione da H. pylori in:

1. Soggetti asintomatici
2. Soggetti con familiarità di primo grado per cancro dello stomaco
3. Soggetti con sintomi da reflusso gastro-esofageo
4. Soggetti con cardiopatia ischemica

Nella tua pratica clinica dopo aver praticato una terapia H. pylori eradicante valuti l'esito del trattamento:

1. In tutti i pazienti
2. In quelli in cui persistono i sintomi
3. In quelli con familiarità per cancro gastrico
4. In quelli non aderenti alla terapia

In un uomo dispeptico di età inferiore a 45 anni con anemia sideropenica :

1. Prescrivi terapia con inibitore della pompa protonica e ferro
2. Richiedi la ricerca del sangue occulto fecale
3. Richiedi Urea Breath Test e tratti l'infezione da H. pylori se presente
4. Richiedi una gastroscopia con biopsie multiple

In un uomo di >50 anni con sintomi dispeptici da oltre 3 mesi:

1. Prescrivi terapia con inibitore della pompa protonica
2. Richiedi Urea Breath Test e tratti l'infezione da H. pylori se presente
3. Richiedi una gastroscopia con biopsie multiple
4. Richiedi un'ecografia dell'addome superiore

Nella tua pratica per la ricerca di H. pylori scegli test invasivo o non invasivo in base a:

1. Gradimento del paziente ed età
2. Età e sesso
3. Presenza di sintomi di allarme
4. Età e presenza di sintomi di allarme

Dopo l'eradicazione di H. pylori consigli un controllo endoscopico-istologico in caso di gastrite atrofica o metaplasia intestinale:

1. Mai
2. Dopo 1-2 anni
3. A 3 anni
4. Dopo 6 mesi

Nella tua pratica clinica consigli di ripetere una gastroscopia in un paziente con ulcera duodenale dopo aver praticato una terapia H. pylori eradicante:

1. Sempre per controllare la cicatrizzazione dell'ulcera
2. Richiedi solo Urea Breath Test per testare l'avvenuta eradicazione
3. Non esegui alcun controllo
4. Prescrivi terapia con IPP ai cambi di stagione

Good night and good luck!