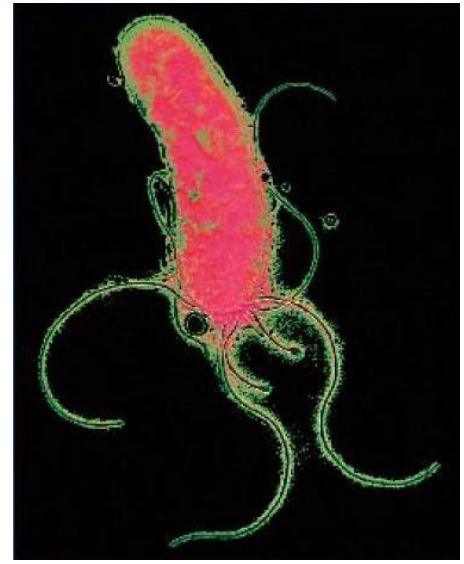
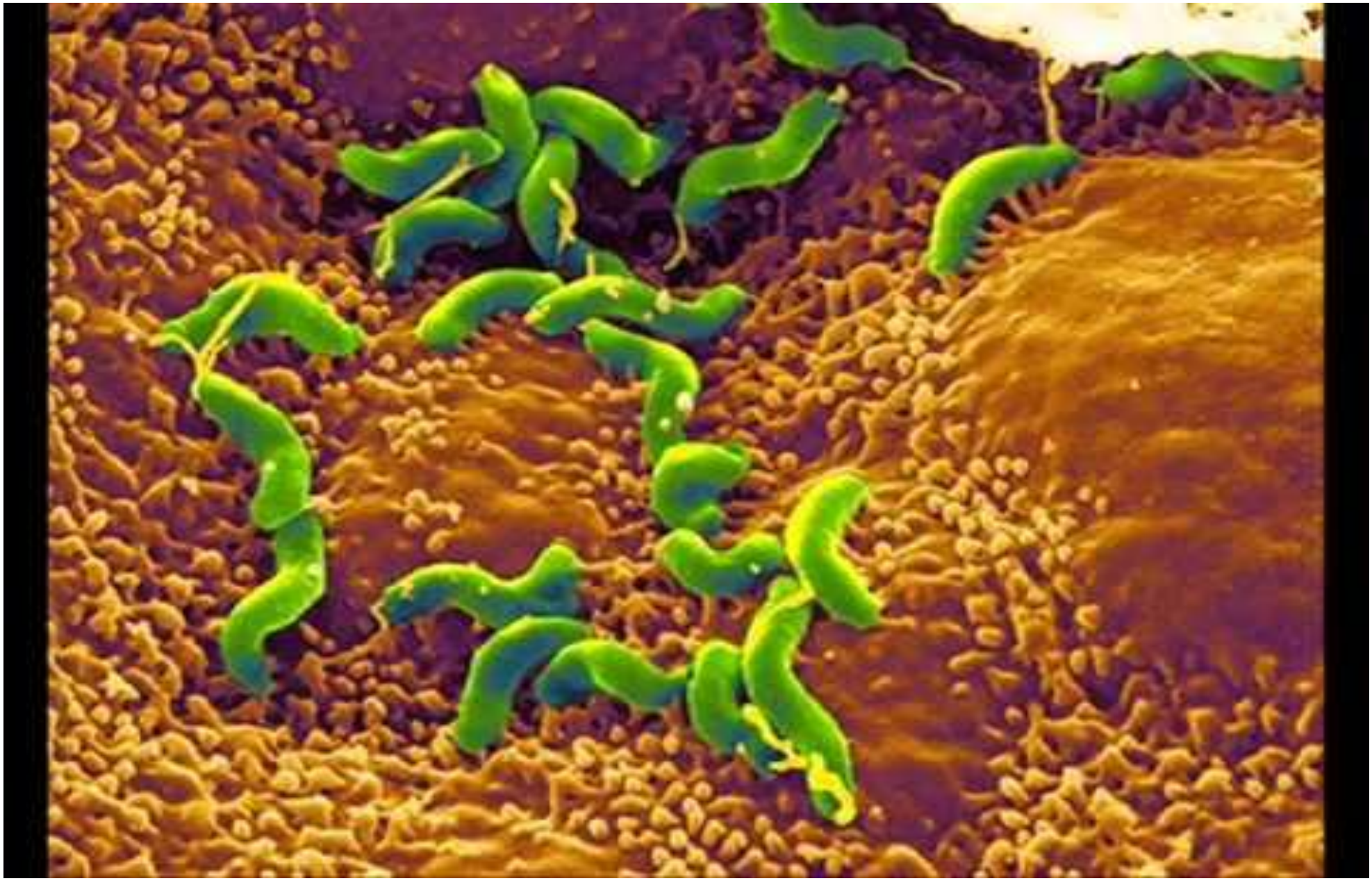
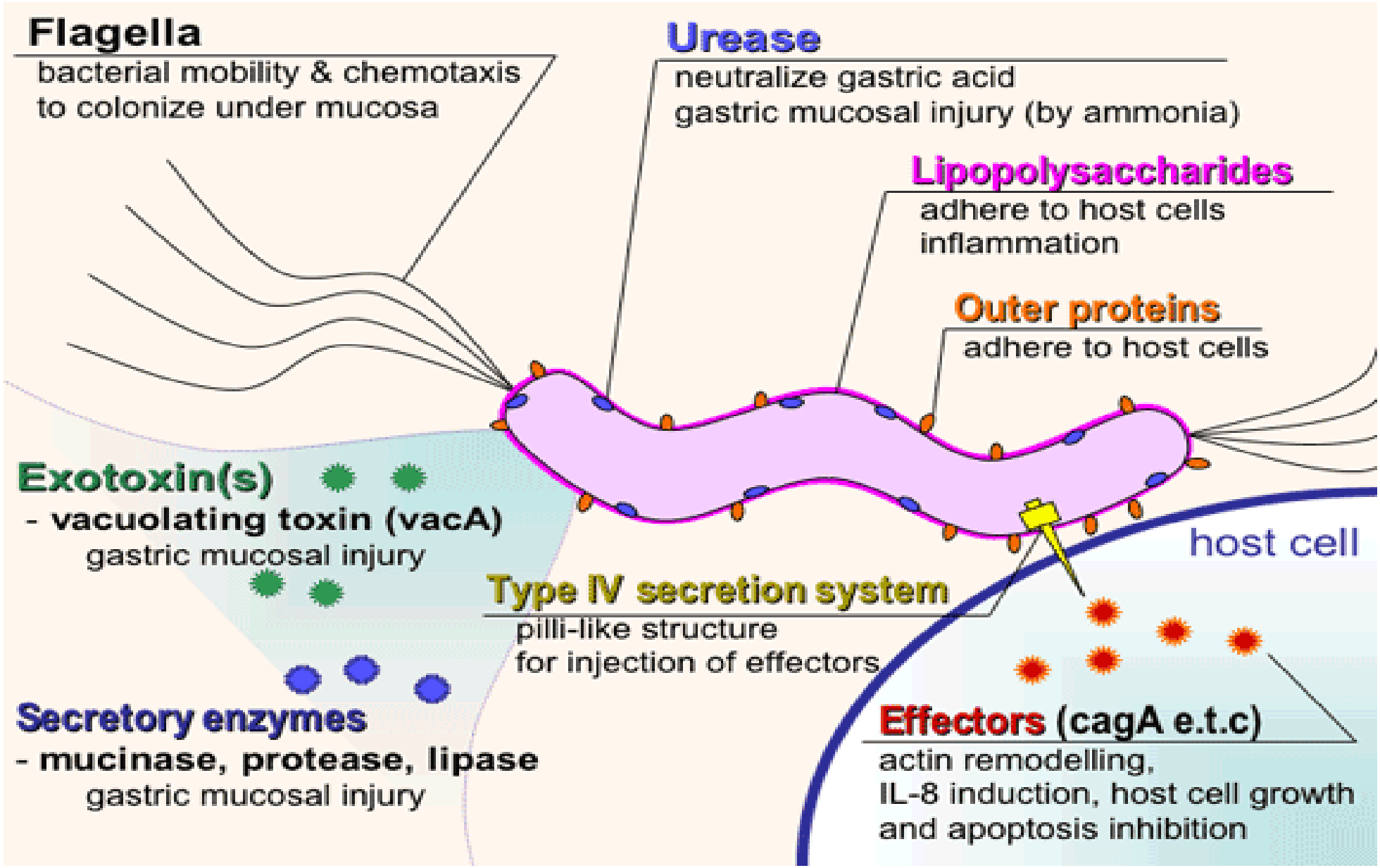
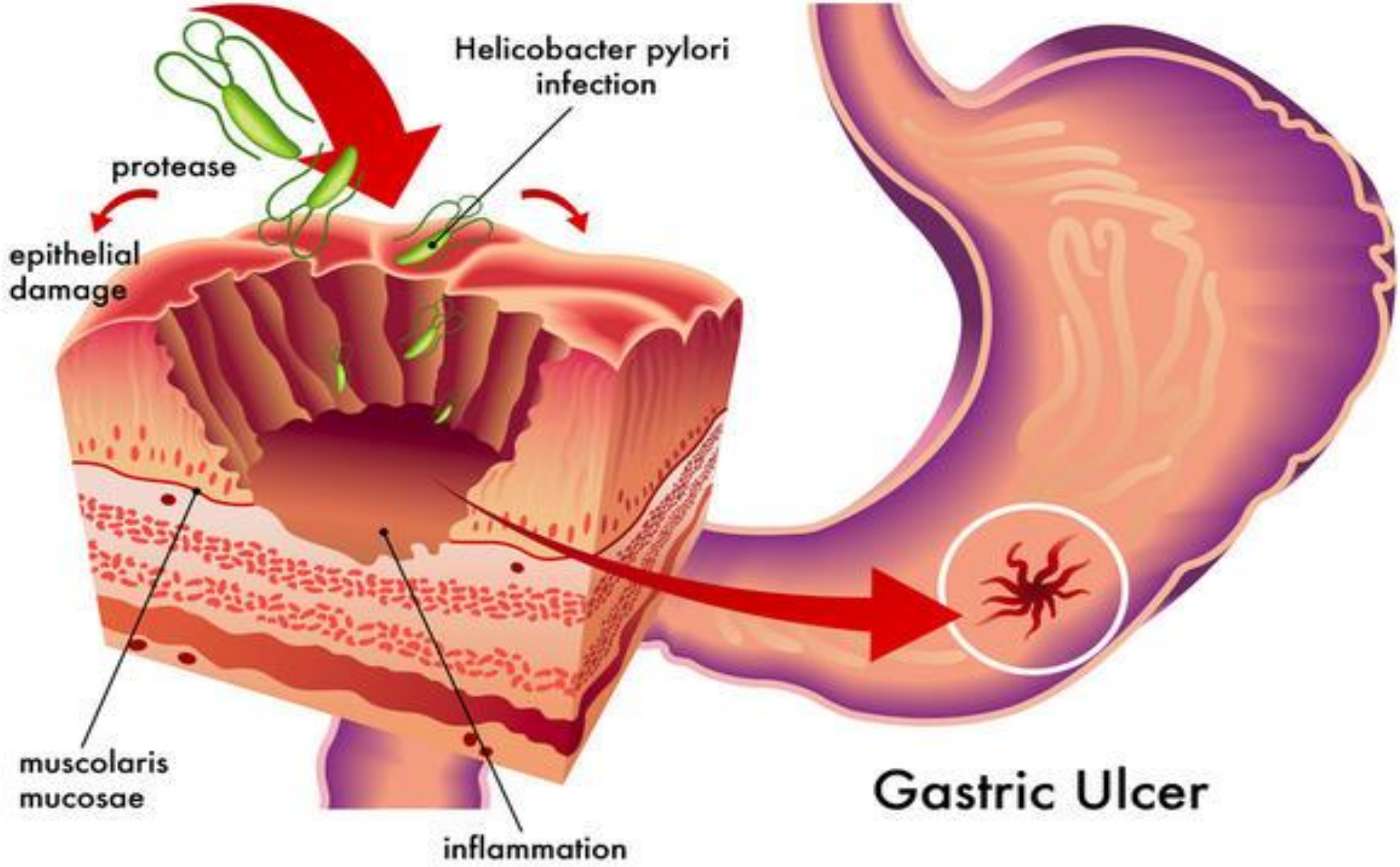
UPPER GI DISORDERS

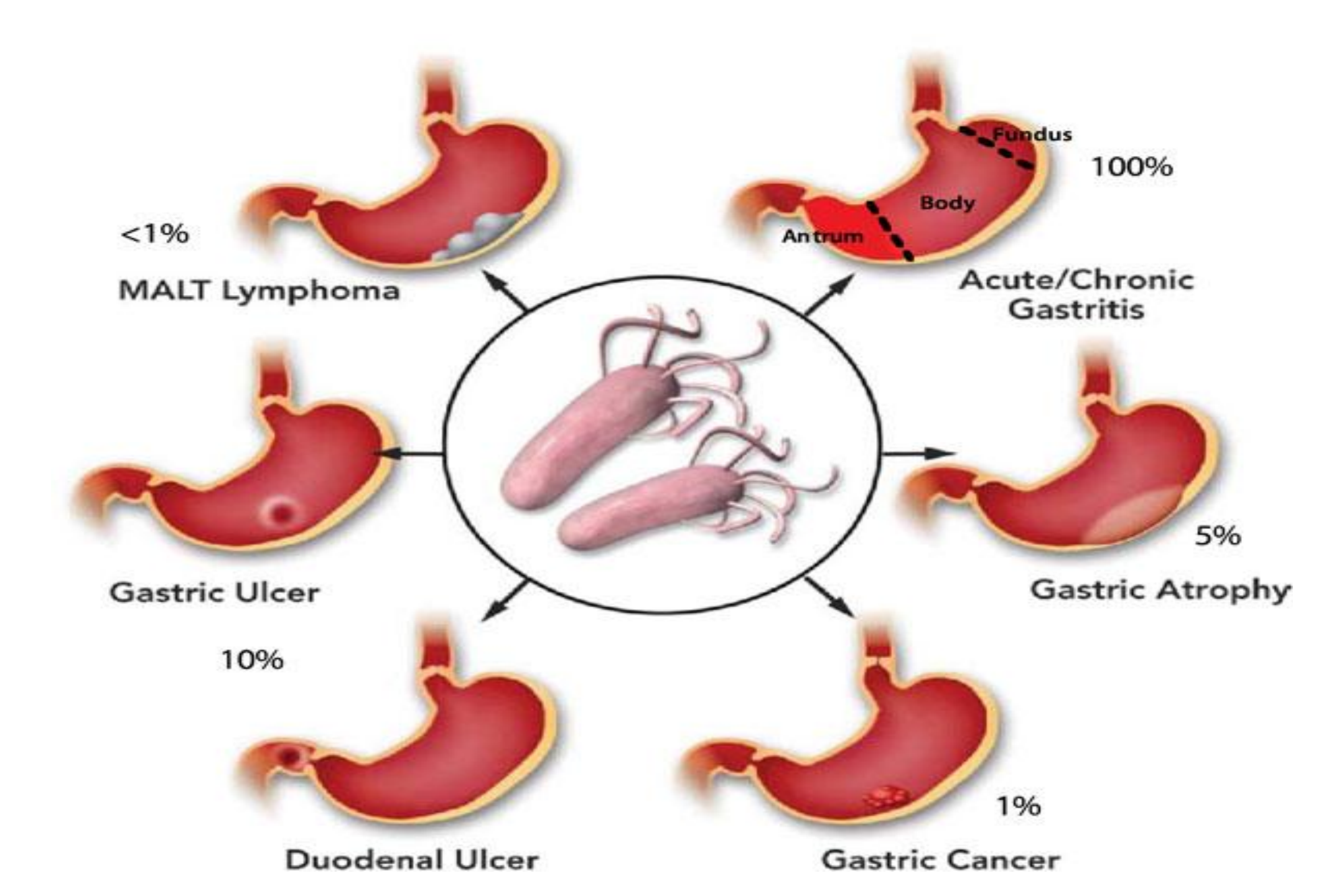
The role of Helicobacter pylori infection

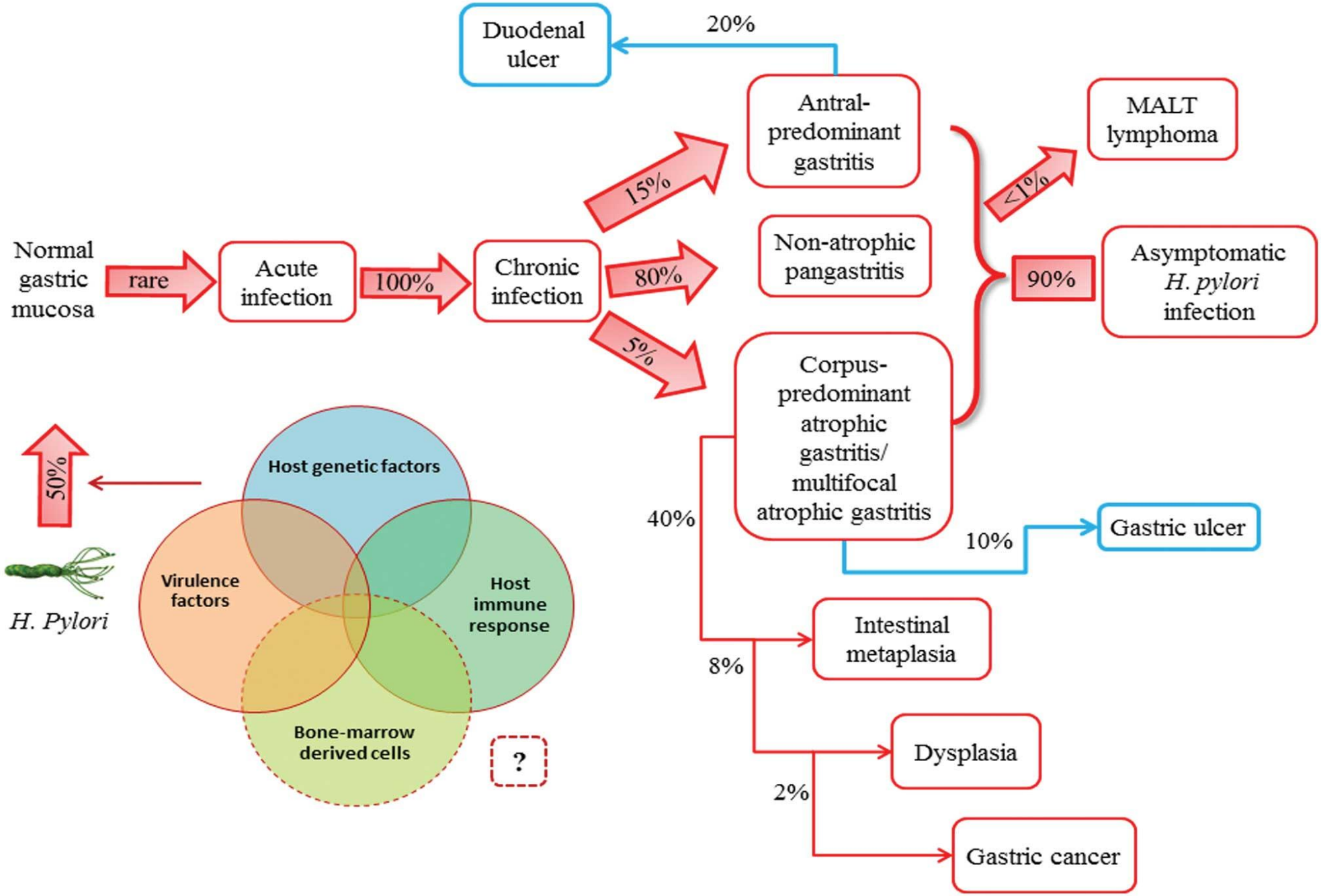


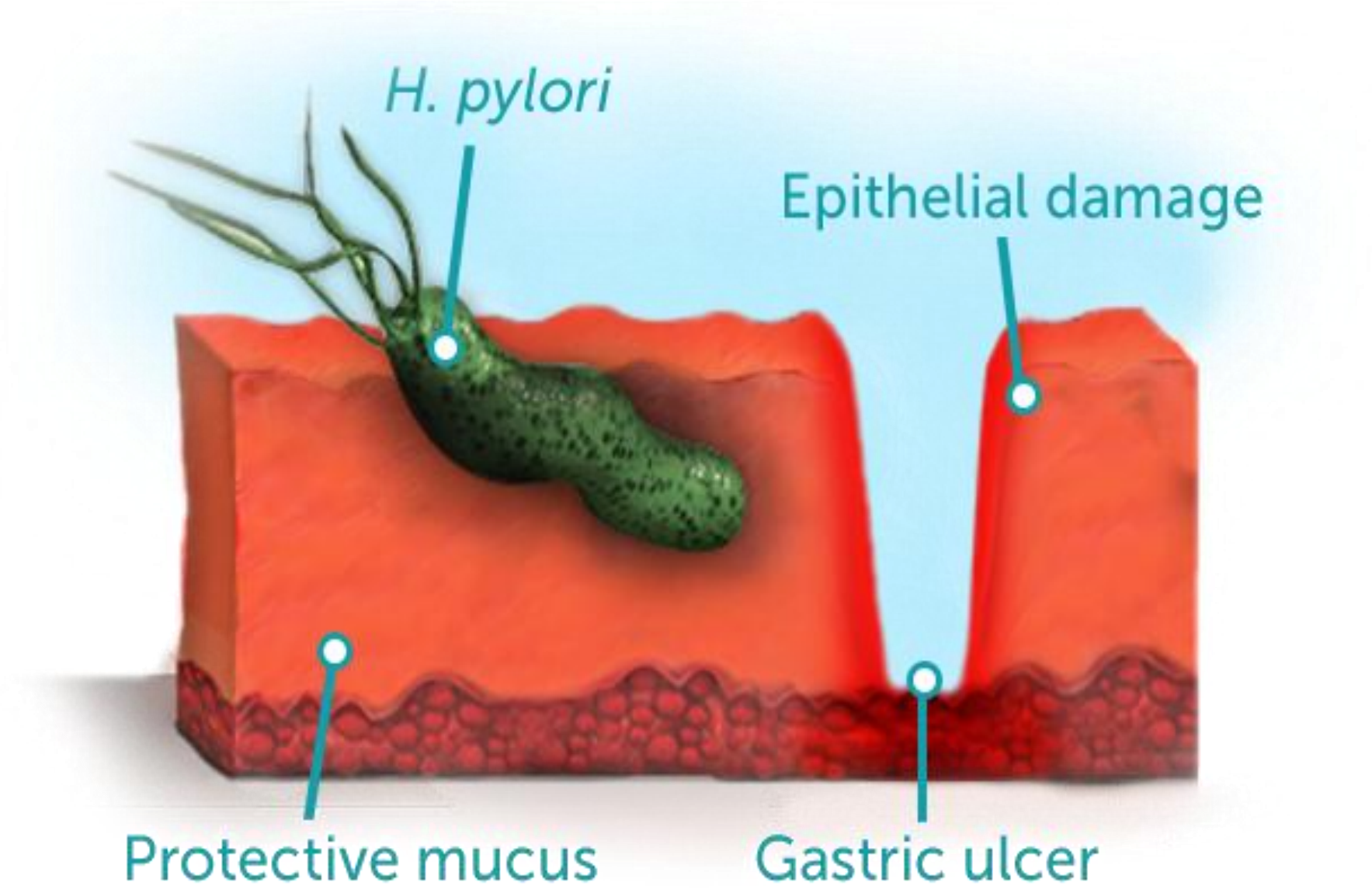


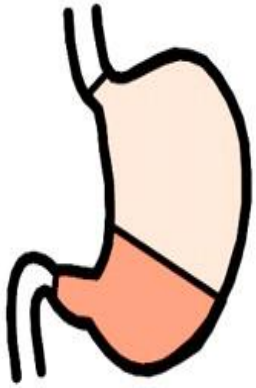

Flagella
bacterial mobility & chemotaxis
to colonize under mucosa
Urease
neutralize gastric acid
gastric mucosal injury (by ammonia)
Lipopolysaccharides
adhere to host cells
inflammation
Outer proteins
adhere to host cells
Exotoxin(s)
- vacuolating toxin (vacA)
gastric mucosal injury
host cell
Type IV secretion system
pilli-like structure
for injection of effectors
Secretory enzymes
- mucinase, protease, lipase
gastric mucosal injury
Effectors (cagA e.t.c)
actin remodelling,
IL-8 induction, host cell growth
and apoptosis inhibition


Helicobacter pylori
infection
protease
epithelial
damage
muscolaris
mucosae
inflammation
Gastric Ulcer

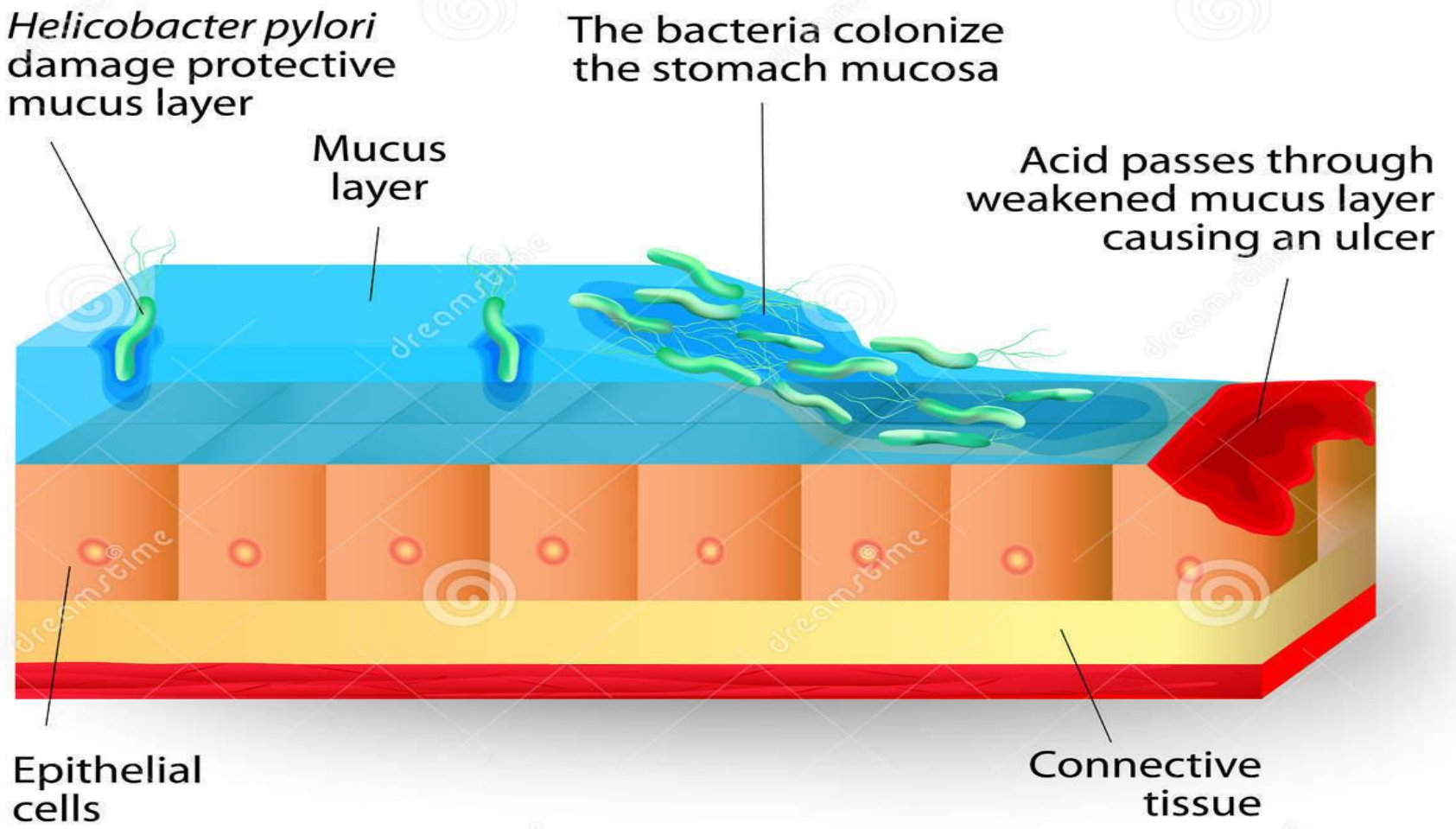

<1%
MALT Lymphoma
Fundus
Body
Antrum
100%
Acute/Chronic
Gastritis
Gastric Ulcer
10%
5%
Gastric Atrophy
Duodenal Ulcer
1%
Gastric Cancer


Duodenal ulcer
20%
Antral-predominant gastritis
MALT lymphoma
<1%
15%
Normal gastric mucosa
rare
Acute infection
100%
Chronic infection
80%
Non-atrophic pangastritis
90%
Asymptomatic H. pylori infection
5%
Corpus-predominant atrophic gastritis/ multifocal atrophic gastritis
40%
10%
Gastric ulcer
50%
Host genetic factors
Virulence factors
Host immune response
Bone-marrow derived cells
?
H. Pylori
Intestinal metaplasia
8%
Dysplasia
2%
Gastric cancer


H. pylori
Epithelial damage
Protective mucus
Gastric ulcer

Pattern of gastritis	Gastric histology	Duodenal histology	Acid secretion	Clinical condition
 Pan-gastritis	• Chronic inflammation • Atrophy • Intestinal metaplasia	• Normal	• Reduced	• Gastric ulcer • Gastric cancer
Antral-predominant	• Chronic inflammation • Polymorph activity	• Gastric metaplasia • Active chronic inflammation	• Increased	• Duodenal ulcer

PEPTIC ULCER



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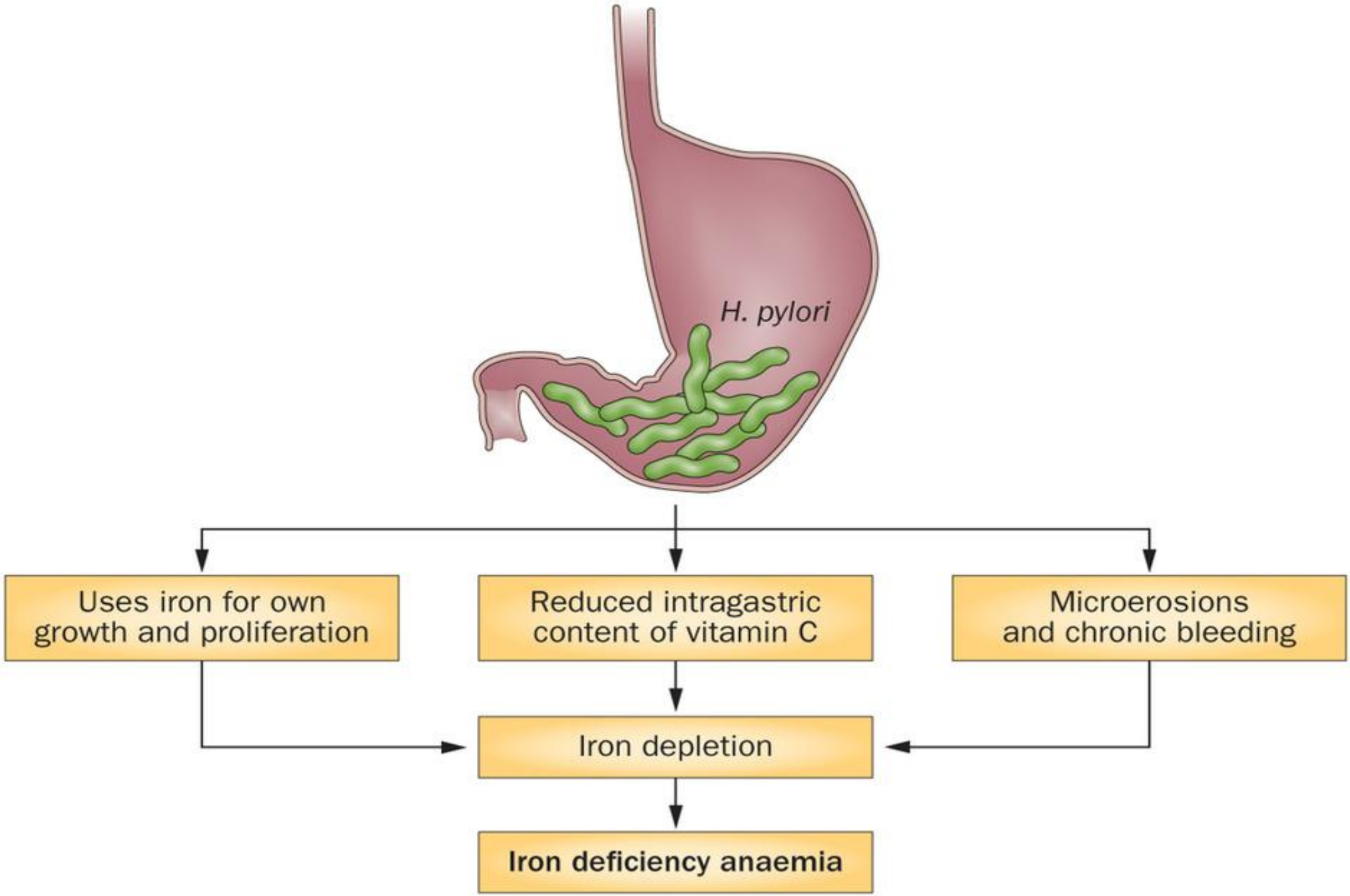
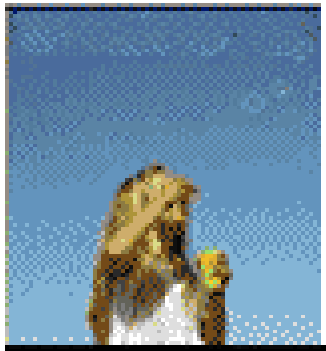
Designua | Dreamstime.com

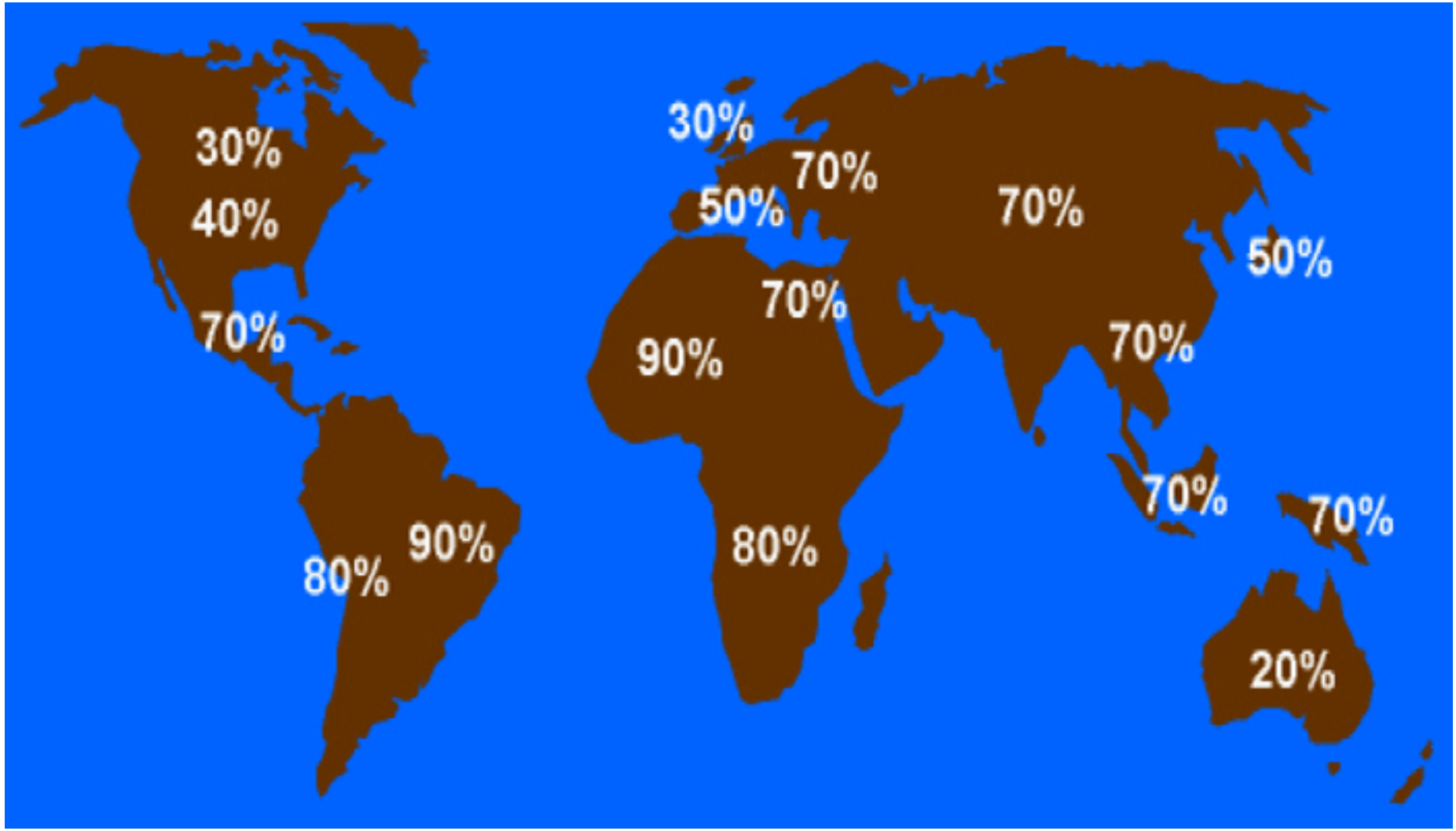

H. pylori
Uses iron for own growth and proliferation
Reduced intragastric content of vitamin C
Microerosions and chronic bleeding
Iron depletion
Iron deficiency anaemia



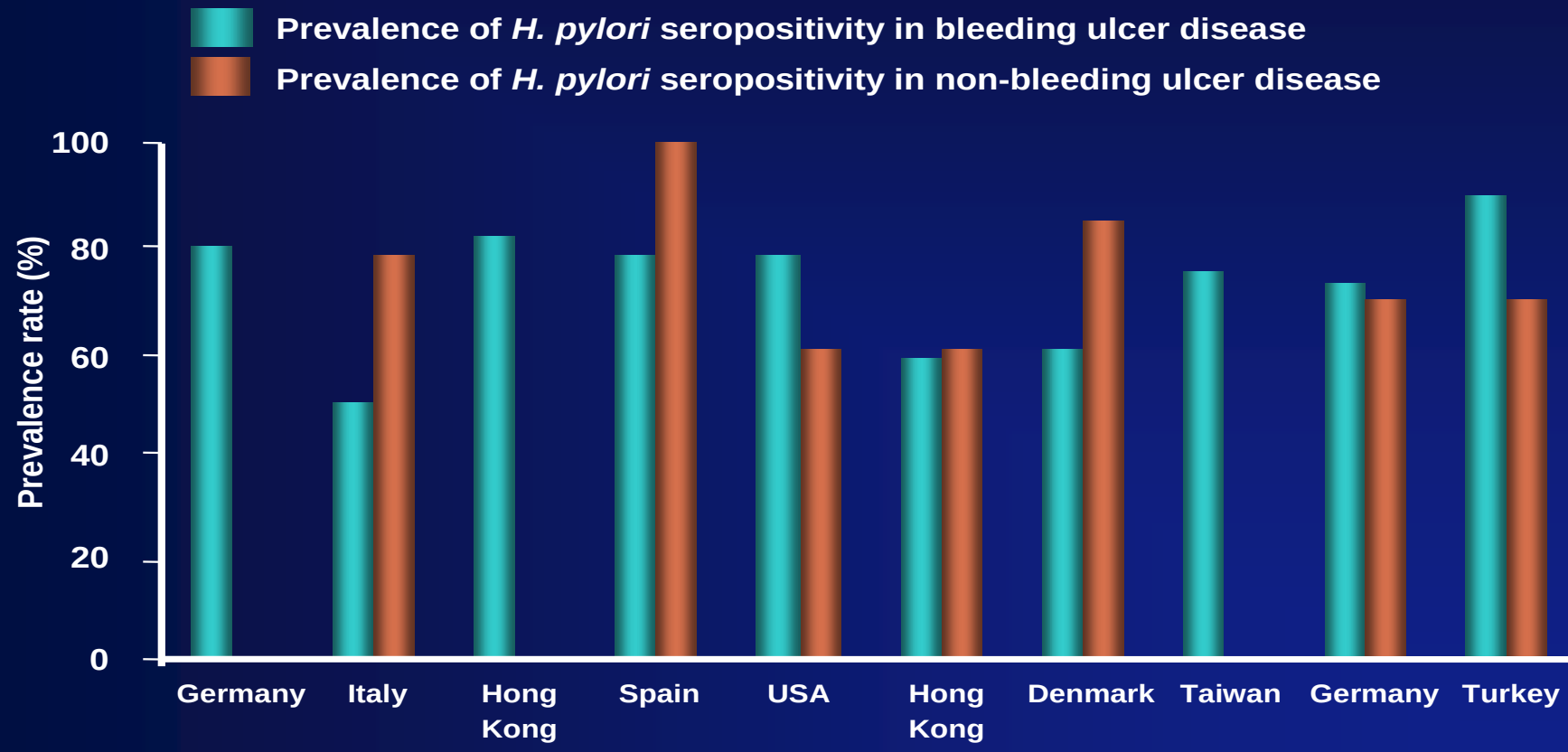
Transmission of *H. pylori* infection and risk factors for acquisition

- Transmission
  - fecal–oral, gastric–oral, oral–oral
  - water
  - zoonotic
- Risk factors
  - infected family members
  - number of siblings (≥2)
  - crowded living conditions
  - clustering in institutions, day care centers, health care workers
  - poor sanitation (fecal contamination of water supply)
  - poor hygiene

Logan et al, BMJ 2001; 323: 920
Go, Aliment Pharmacol Ther 2002; 16(S1): 3


30%
40%
70%
90%
80%
30%
70%
50%
70%
90%
80%
70%
50%
70%
70%
70%
70%
20%

Prevalence of *H. pylori* in PUD



Vaira *et al., Gastroenterol* 1997; **113**(Suppl 6): S78–84.

Possible risk factors for infection with *H. pylori*

- **Age**
  - Rapid acquisition in childhood in developing countries
- **Country of exposure**
  - Higher rates of seropositivity in developing countries
- **Income**
  - Income inversely related to seropositivity
- **Gender**
  - Similar incidence of infection
- **Family**
  - Intrafamilial clustering? Spouse–spouse/ gastro-oral transmission?
- **Alcohol**
  - No increased risk
- **Blood group**
  - Most studies indicate no association
- **Smoking**
  - No increased risk

Logan & Walker, *BMJ* 2001; **323**: 920–2.
Report of the Digestive Health Initiative, *Gastroenterol* 1997; **113**: S4–8.

Diagnostic tests for *H. pylori*

Diagnostic tests

- **Non-endoscopic**
  - Antibody detection
  - Urea breath test
  - Stool antigen detection
- **Endoscopic**
  - Biopsy urease test
  - Histology
  - Culture

Logan & Walker, *BMJ* 2001; **323**: 920–2.

H. pylori testing in clinical practice

Patient presenting	Test
Asymptomatic	Not recommended
Frequent dyspepsia <50 years, no alarm symptoms	Non-endoscopic diagnostic test
Persistent symptoms >50 years or alarm features	Endoscopy

Only test for *H. pylori* if you intend to treat!

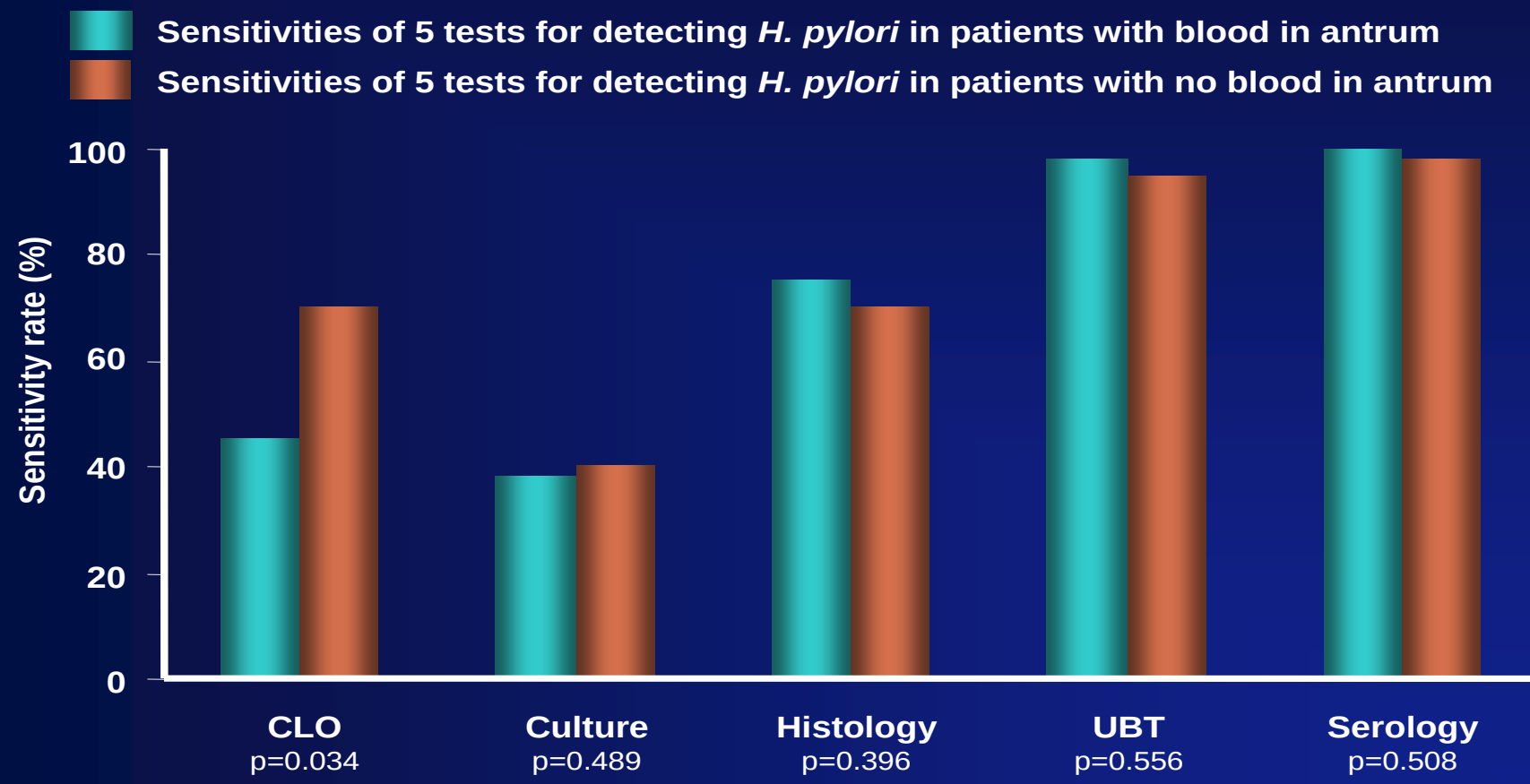
Report of Digestive Health Initiative, *Gastroenterol* 1997; **113**: S4–8.

Factors influencing *H. pylori* antibody testing

- Background prevalence of *H. pylori* infection
- Host/bacterial factors
- *H. pylori* antigen heterogeneity
- Previous antibiotic use

Leodolter & Mégraud, *Curr Opin Gastroenterol* 2001; **17**(Suppl 1): S19–23.
Logan & Walker, *BMJ* 2001; **323**: 920–2.

Comparative sensitivities of *H. pylori* detection tests



CLO = urea test UBT = urea breath test

Tu *et al.*, *Gastrointest Endosc* 1999; **49**: 302–6.

Treatment of *H. pylori*-positive ulcers

Most frequently used agents in anti-*H. pylori* regimens

- PPIs
- Ranitidine bismuth citrate (RBC)
- Amoxicillin
- Macrolides (e.g. clarithromycin)
- Nitroimidazoles (e.g. metronidazole)
- Tetracycline
- Bismuth

Gisbert *et al*., *Curr Opin Gastroenterol* 2001; **17**(Suppl 1): S47–54.

Sequence of anti-*H. pylori* therapies

Maastricht 2–2000

First-line therapy (triple therapy)			
PPI twice daily (or RBC)	+ clarithromycin 250 mg twice daily	+ metronidazole 500 mg twice daily	
Or			
PPI twice daily (or RBC)	+ clarithromycin 500 mg twice daily	+ amoxicillin 1 g twice daily	
Second-line therapy (quadruple therapy)			
PPI twice daily	+ bismuth 120 mg four times daily	+ metronidazole 500 mg twice daily	+ tetracycline 500 mg four times daily
Third-line therapy			
Given on a case-by-case basis			

RBC = ranitidine bismuth citrate

Pilotto & O'Morain, *Curr Opin Gastroenterol* 2000; **16**(Suppl 1): S44–51.
Bazzoli, *Eur J Gastroenterol Hepatol* 2001; **13**(Suppl 2): S3–7.

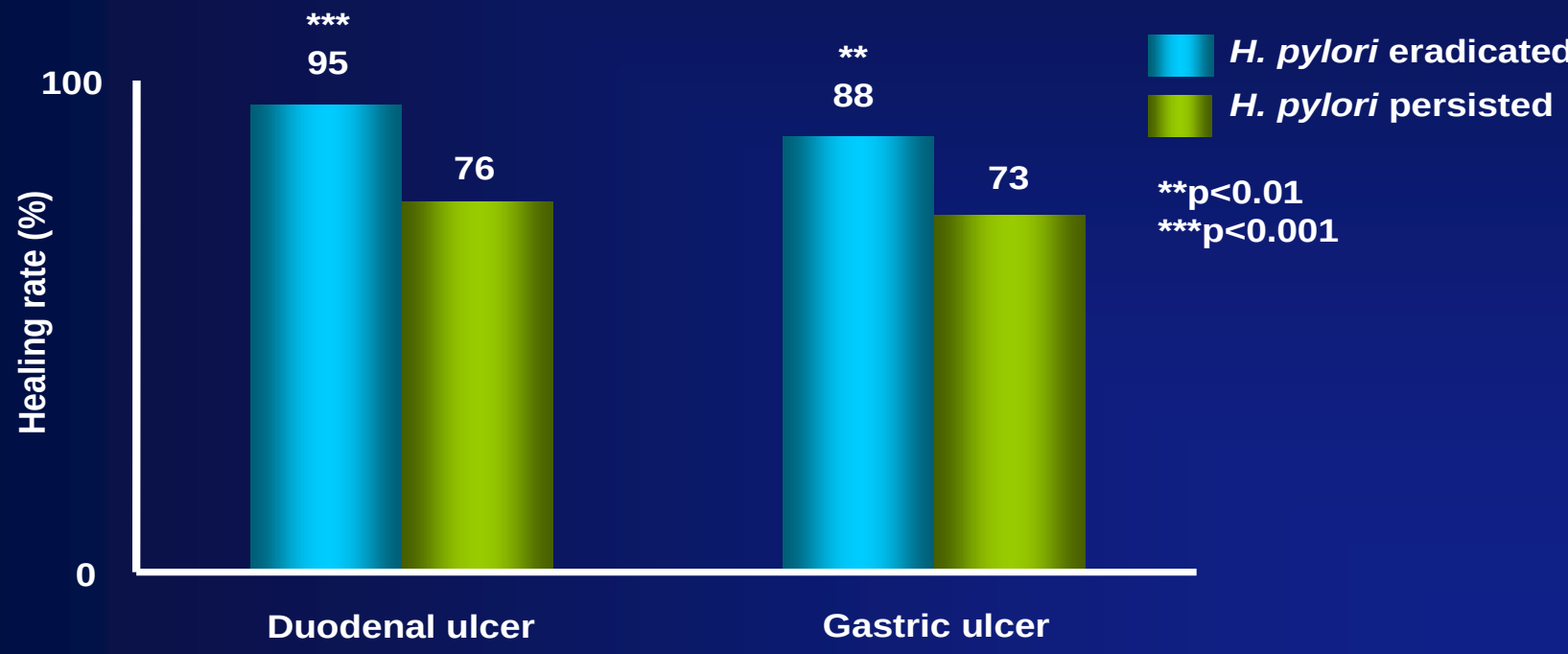
Success rates for the secondary eradication of *H. pylori*

Studies with quadruple therapy 1997–2000	n/n
Pieramico *et al.*	20/21
Choi *et al.*	6/21
Lee *et al.*	15/20
Peitz *et al.*	17/29
Neville *et al.*	16/32
Gisbert *et al.*	17/29
Chan *et al.*	5/7
Total	**106/160 (66%)**

Axon. In: *H. pylori* : Basic Mechanisms to Clinical Cure. Hunt & Tygat, eds. Dordrecht, The Netherlands, Kluwer Academic Publishers, 2000.

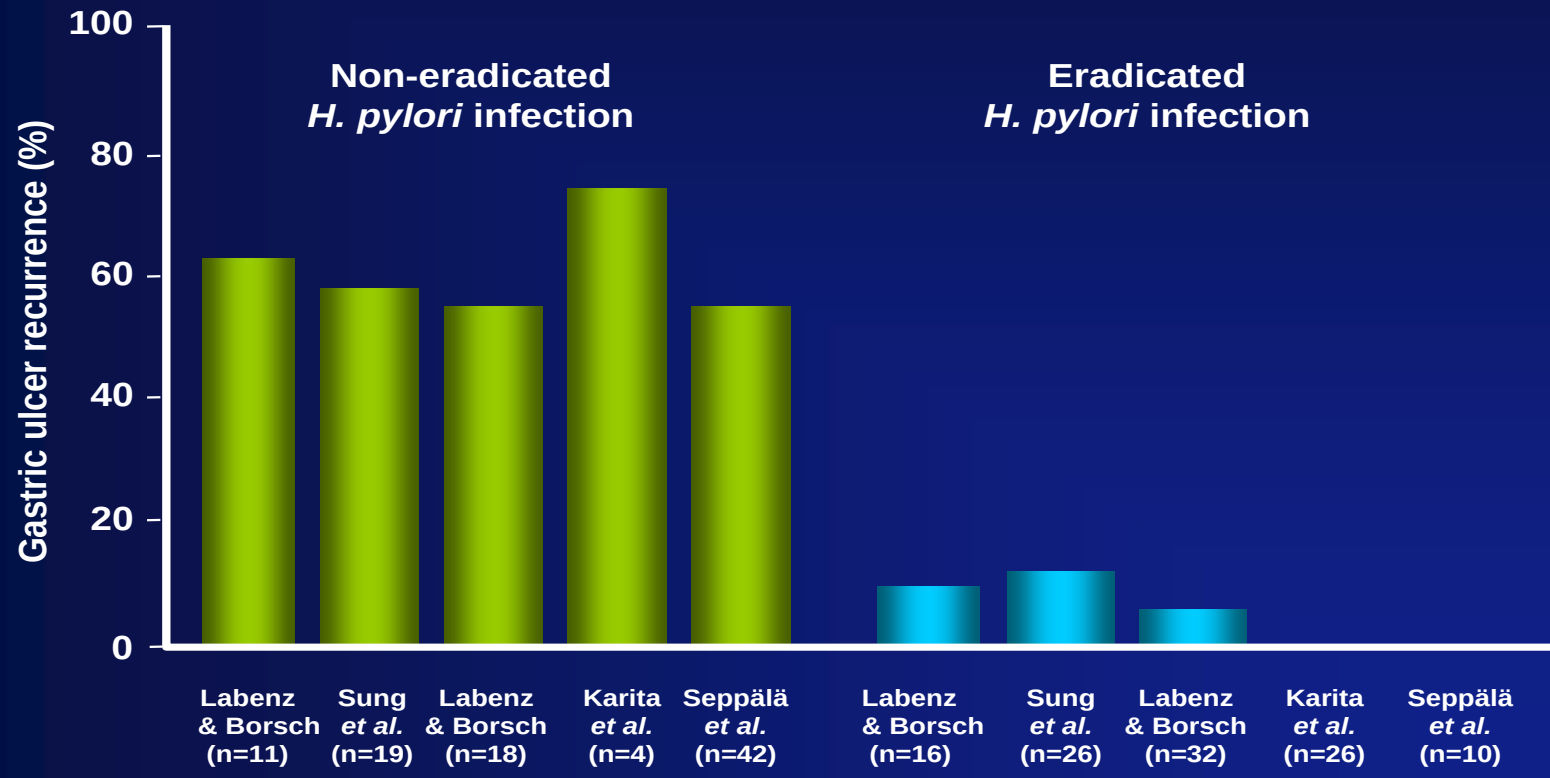
Influence of successful eradication of *H. pylori* on ulcer healing

Review of 60 trials; 4329 patients
Ulcer healing rate according to post-treatment *H. pylori* status



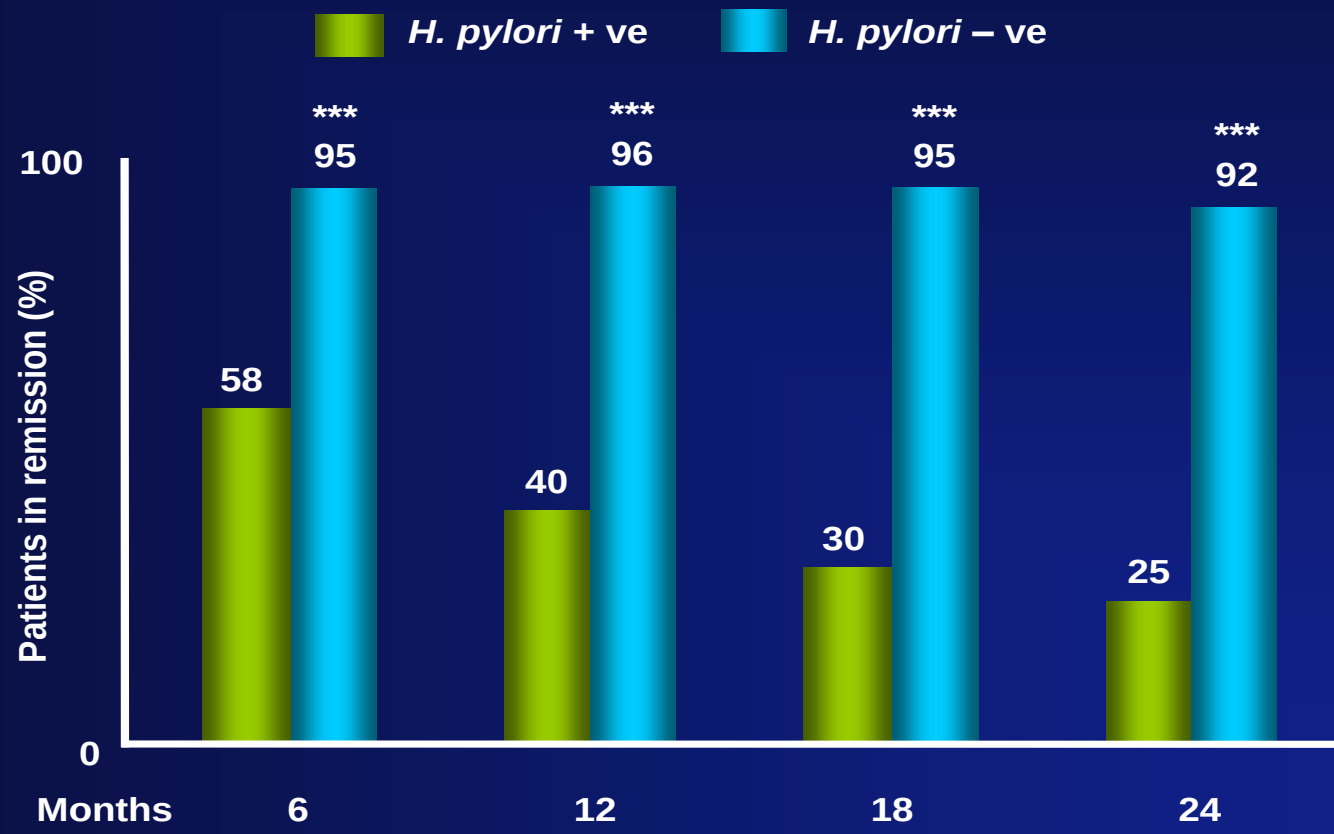
Treiber & Lambert, *Gastroenterol* 1998; **93**: 1080–4.

H. pylori eradication reduces recurrence in gastric ulcer



Hopkins *et al.*, *Gastroenterol* 1996; **110**: 1244–52.

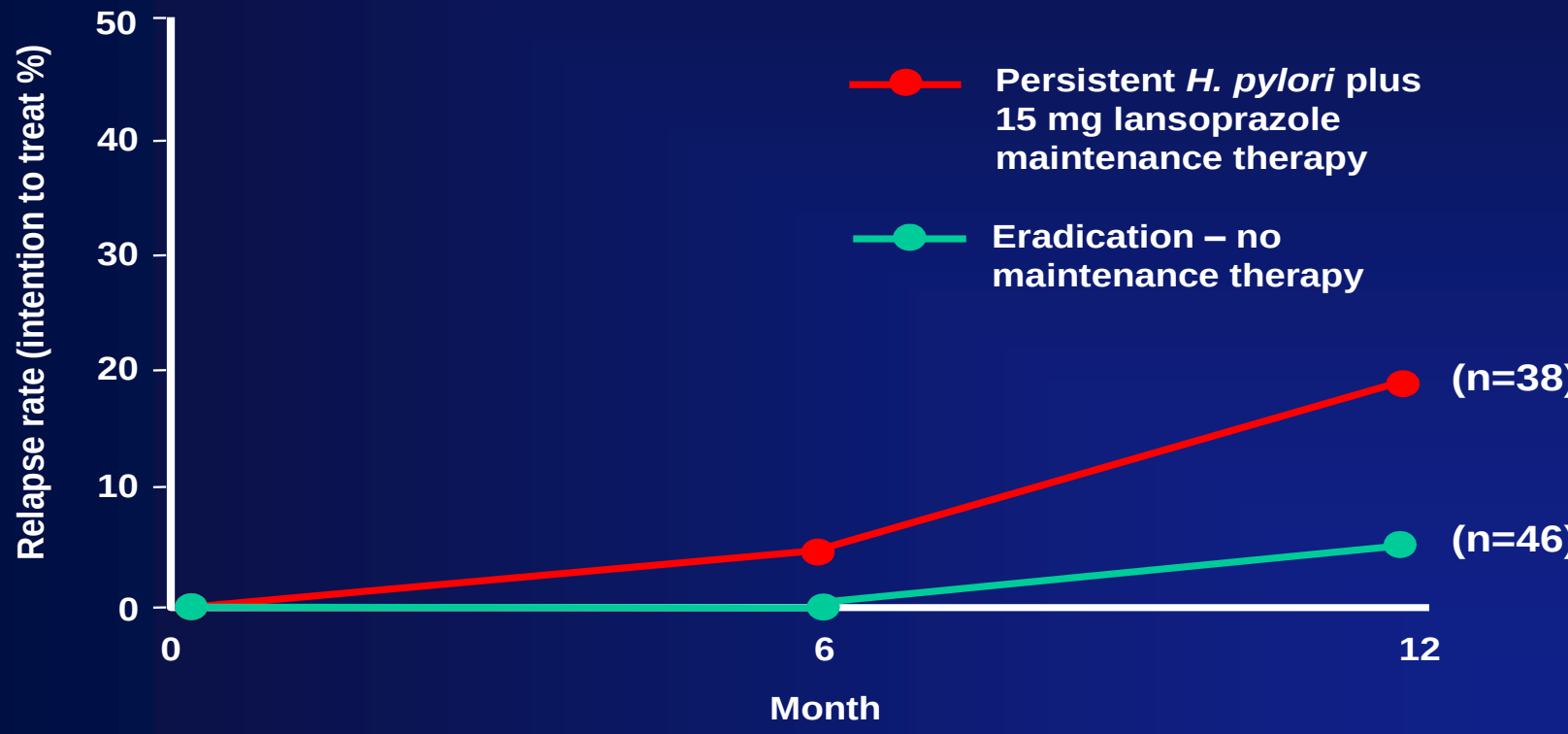
Eradication of *H. pylori* almost eliminates duodenal ulcer recurrence



***p<0.001

Huang *et al., Am J Gastroenterol* 1996, **91**: 1914.

Prevention of duodenal ulcer recurrence after *H. pylori* eradication



Parente et *al.*, *Hepatogastroenterol* 1998; **45**: 990–3.

Reinfection/recrudescence rates according to geographical area

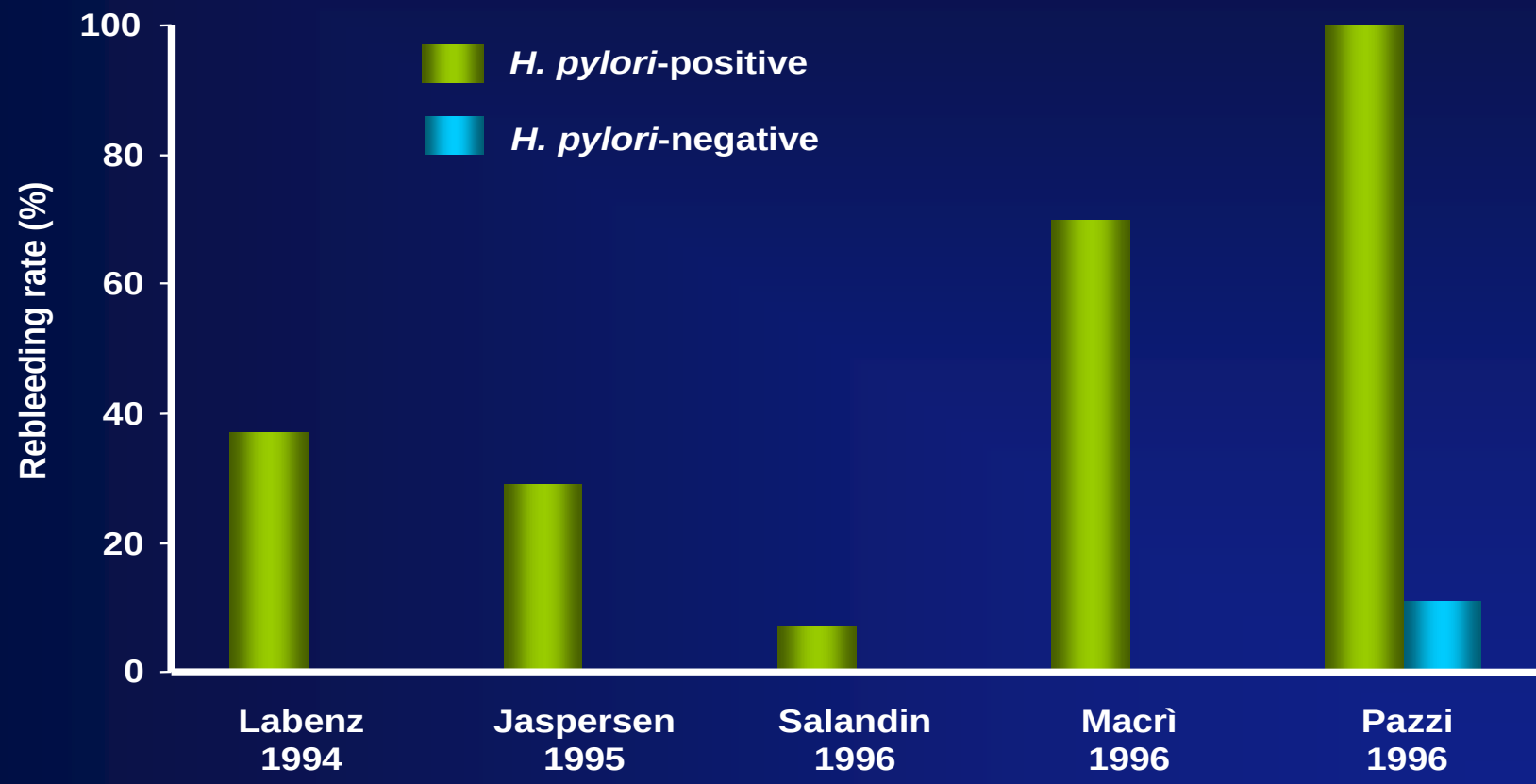
H. pylori assessment during follow-up and patient-years studied

Geographical area studied	*H. pylori* assessment during follow-up	Re-infection/ patient-year	Annual rate (%)	Strain comparison pre-/post-treatment
The Netherlands	Hist., cult.	7/605	1.2	Identical (six tested)
Austria	RUT, hist., cult.	2/65	3.1	Identical
Brazil	^{14}C-UBT	6/44	13.6	ND
Italy (children)	RUT, hist., cult.	5/37	13.5	ND

Hist: histology; RUT: rapid urease test; Cult: culture; ^{14}C-UBT: ^{14}C urea breath test; ND: not done
*In these studies *H. pylori* eradication was assessed 12 months after cessation of therapy

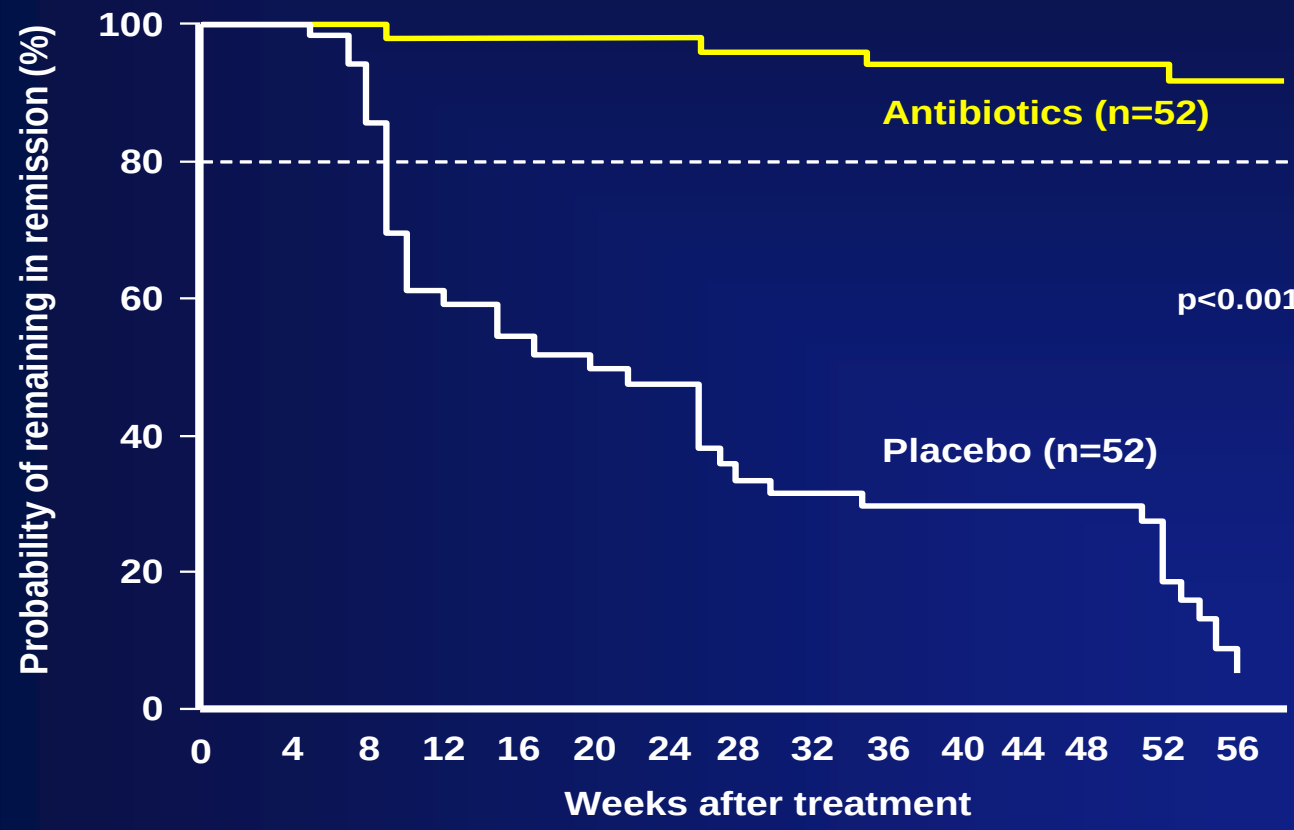
van der Ende *et al., Aliment Pharmacol Ther* 1997; **11**(Suppl 1): 55–61.

Rebleeding rates of peptic ulcer after treatment for *H. pylori*



Labenz *et al*., *Digestion* 1994; **55:** 19–23; Jaspersen *et al*., *Gastrointestinal Endosc* 1995; **41**: 5–7.; Salandin *et al*., *Gastroenterology* 1996; **110:** A248; Macri *et al*., *Gut* 1996; **39**(Suppl 3): A143; Pazzi *et al*., *Gastroenterology* 1996; **110**: A224.

Duodenal ulcer relapse by *H. pylori* status



Hentschel *et al*., *N Engl J Med* 1993; **328**: 308–12.

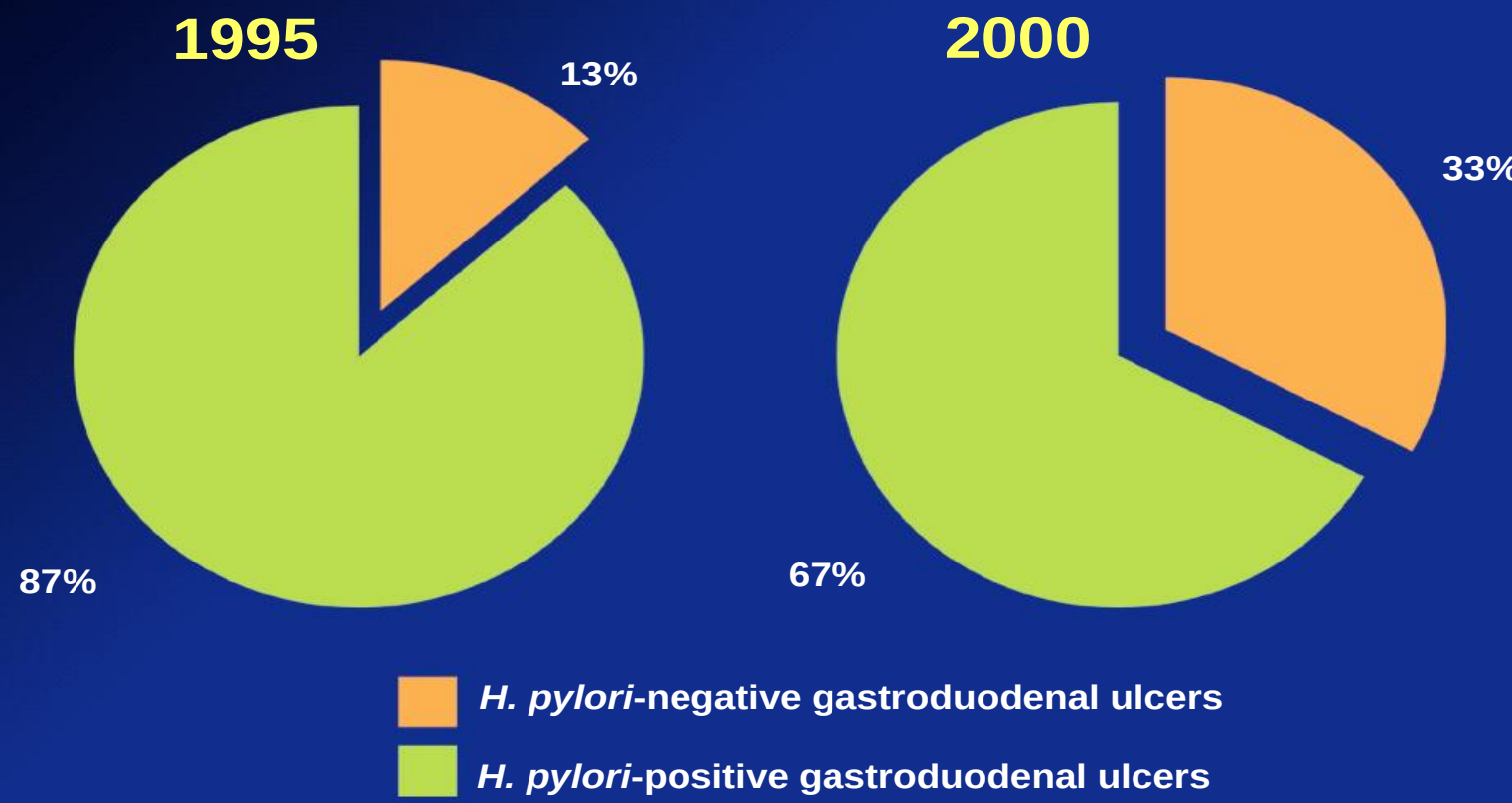
Causes of treatment failure

- Antibiotic resistance
- Lack of patient compliance
- Inadequate eradication regimen
- Disease entity
- Smoking
- Geographical area

Pilotto & O'Morain, *Curr Opin Gastroenterol* 2000; **16**(Suppl 1): S11–18.
Harris & Misiewicz, *BMJ* 2001; **323**: 1047–50.
Perri *et al.*, *Aliment Pharmacol Ther* 2001; **15**: 1023–9.
Pilotto, *Drugs Aging* 2001; **18**: 487–94.

H. pylori-negative PUD

Increasing proportion of *H. pylori*-negative ulcers 1995–2000



Juhasz, *Gut* 2001; **49**: A64.

Possible explanations for *H. pylori*-negative duodenal ulcer

- Non-steroidal anti-inflammatory drugs (NSAIDs) intake
  - The risk in NSAID users is increased by a factor of 3–5
- Changing background of *H. pylori* prevalence in the general population
- False-negative results due to diagnosis methods
- Prior antibiotic or antisecretory therapy
- Gastric acid hypersecretion
- Other infection
- Other

Freston, *Aliment Pharmacol Ther* 2001; **15**(Suppl 2): 2–5.
Harris & Misiewicz, *BMJ* 2001; **323**:1047–50.

H. pylori, NSAID use and risk of PUD: a meta-analysis

- Both *H. pylori* infection and NSAID use independently and significantly increase the risk of peptic ulcer and ulcer bleeding
- *H. pylori* infection and NSAID use are synergistic for peptic ulcer development and ulcer bleeding

Huang *et al*., *Lancet* 2002; **359**: 14–22.

Treatment summary for peptic ulcer: key points

- *H. pylori* eradication is essential in *H. pylori*-positive patients
- NSAIDs should be discontinued or reduced, if possible
- Otherwise, patients at risk should receive a gastro-protective agent (lansoprazole and omeprazole have evidence of efficacy)
- PPIs are the most effective agents for acid suppression and the most appropriate first-line therapy

Παράγοντες που επηρεάζουν την επιλογή της καταλληλότερης μεθόδου διάγνωσης της λοίμωξης

Επί λήψης αντιεκκριτκκών φαρμάκων ή πρόσφατης γαστρορραγίας

Ιστολογική διάγνωση (δοκιμασία ουρεάσης και δοκιμασία αναπνοής έχουν υψηλά ποσοστά ψευδώς αρνητικών απτελεσμάτων)

για τη δοκιμασία αναπνοής

απαιτείται διακοπή της θεραπείας επί λίγες εβδομάδες και νηστεία >10 ωρών

Απόλυτες ενδείξεις εφαρμογής θεραπείας εκρίζωσης H. *pylori*

1. πεπτικό έλκος (δωδεκαδακτυλικό ή γαστρικό)
2. MALT λέμφωμα
3. ατροφική γαστρίτιδα
4. μετεγχειρητικά σε καρκίνο στομάχου
5. σε ασθενείς που έχουν πρώτου βαθμού συγγένεια με ασθενείς που ανέπτυξαν καρκίνο στομάχου
6. σε περίπτωση επιθυμίας του ίδιου ασθενούς (αφού γίνει πλήρης ενημέρωση από το γιατρό του)

Malfertheiner et al., Aliment Pharmacol Ther 2002;16 :167-80

θεραπεία εκρίζωσης H. pylori

για 7-10 ημέρες

αλκαλοποίηση του γαστρικού pH

+

αντιβιοτικά

σημαντική μείωση της γαστρικής έκκρισης με PPI X2

+

συνδυασμός δύο αντιβιοτικών

Ευχαριστώ