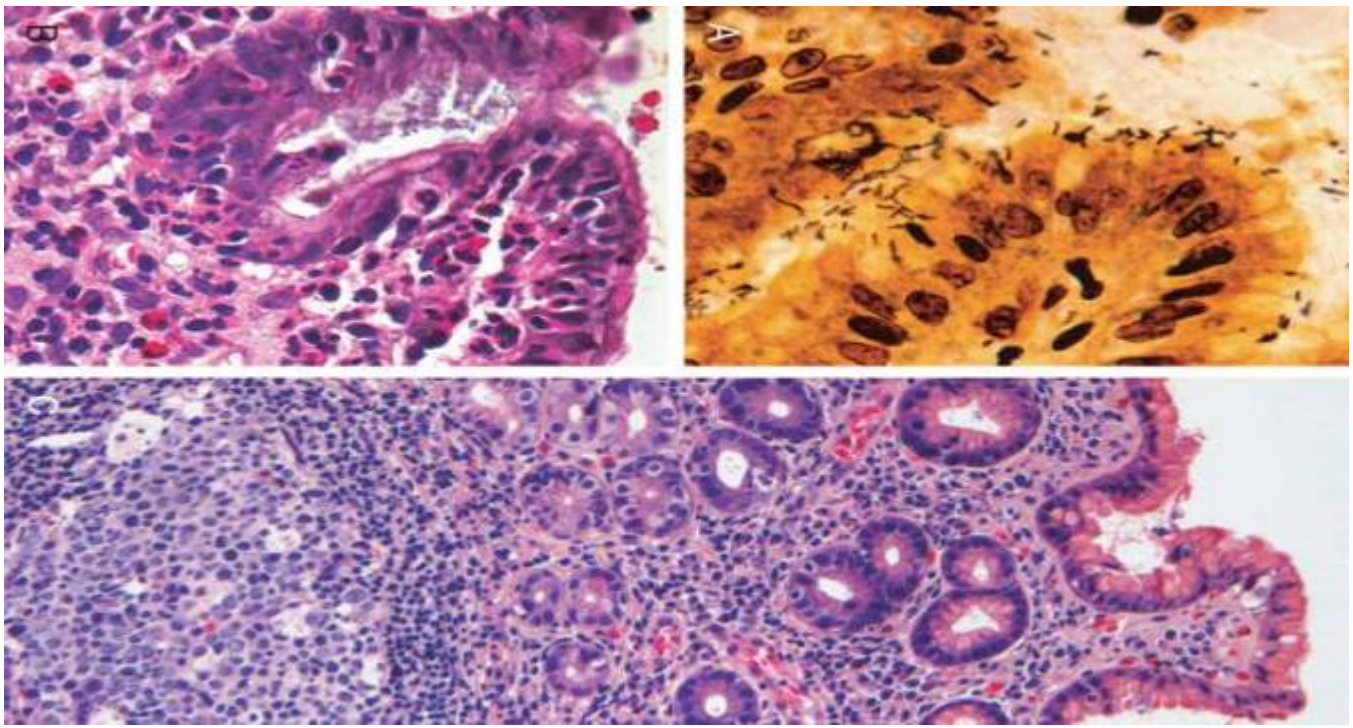
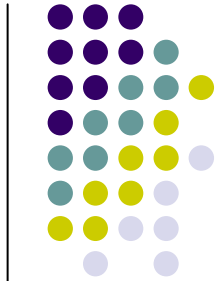
Frazier's Top Ten Things to Know About H. Pylori

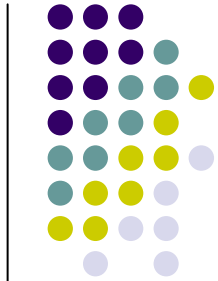


Why I Became Interested



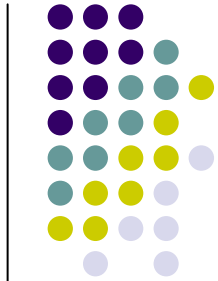
- DDSEP…
- H.Pylori is inversely associated with EAC
- In patients who will need long term PPI therapy, H.Pylori should be eradicated
- MAKES NO SENSE!

Changing The Way We Think About HP



- We should differentiate HP
  - Antral vs Corpus
  - PUD vs nonPUD associated
  - Cag A (+) vs Cag A (-)
  - Acute vs Chronic Infection
  - EAC vs Gastric CA

Frazier's Top Ten

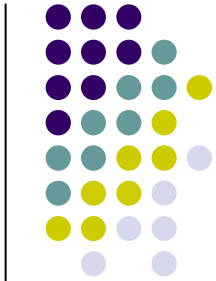


1. Pathogenesis
2. Prevalence
3. Diagnosis
4. Treatment
5. Gastric Acid/PUD
6. Cancer
7. Dyspepsia
8. GERD
9. EAC
10. Non-GI Associations

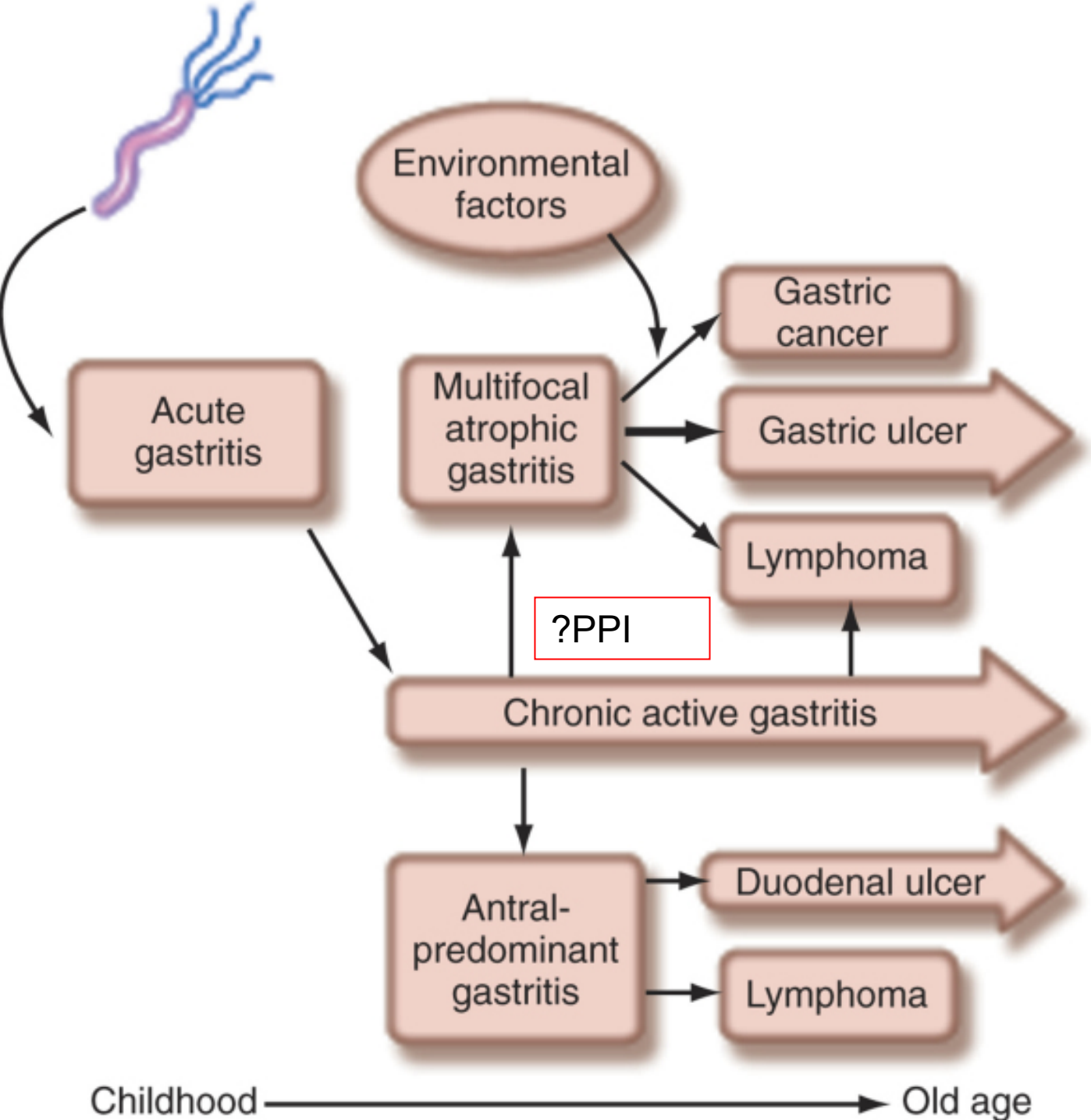
Pathogenesis: Colonization versus Infection

- Present exclusively in humans since the beginning
- Roughly 50% of the world's population has HP
- Only 20% of this 50% will ever have any HP associated condition
- Linked to several disease processes
- Also inversely associated with some disease processes
- Is/was there some evolutionary advantage to our relationship?

Pattern of Chronic Gastritis

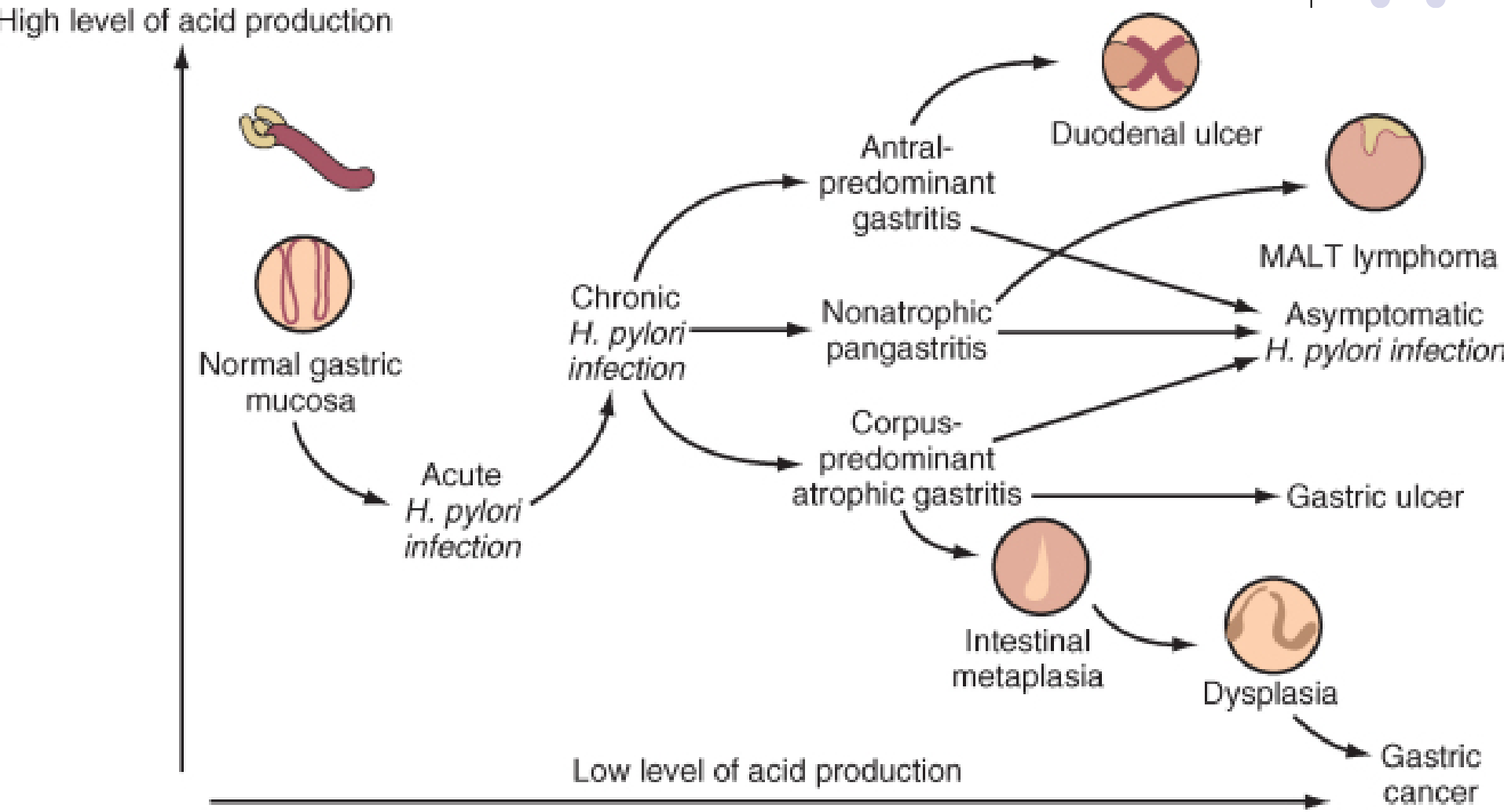


- Superficial
- Multifocal Atrophic (Corpus Predominant)
- Antral Predominant
- The outcome of both infection and eradication depends on the pattern of gastritis

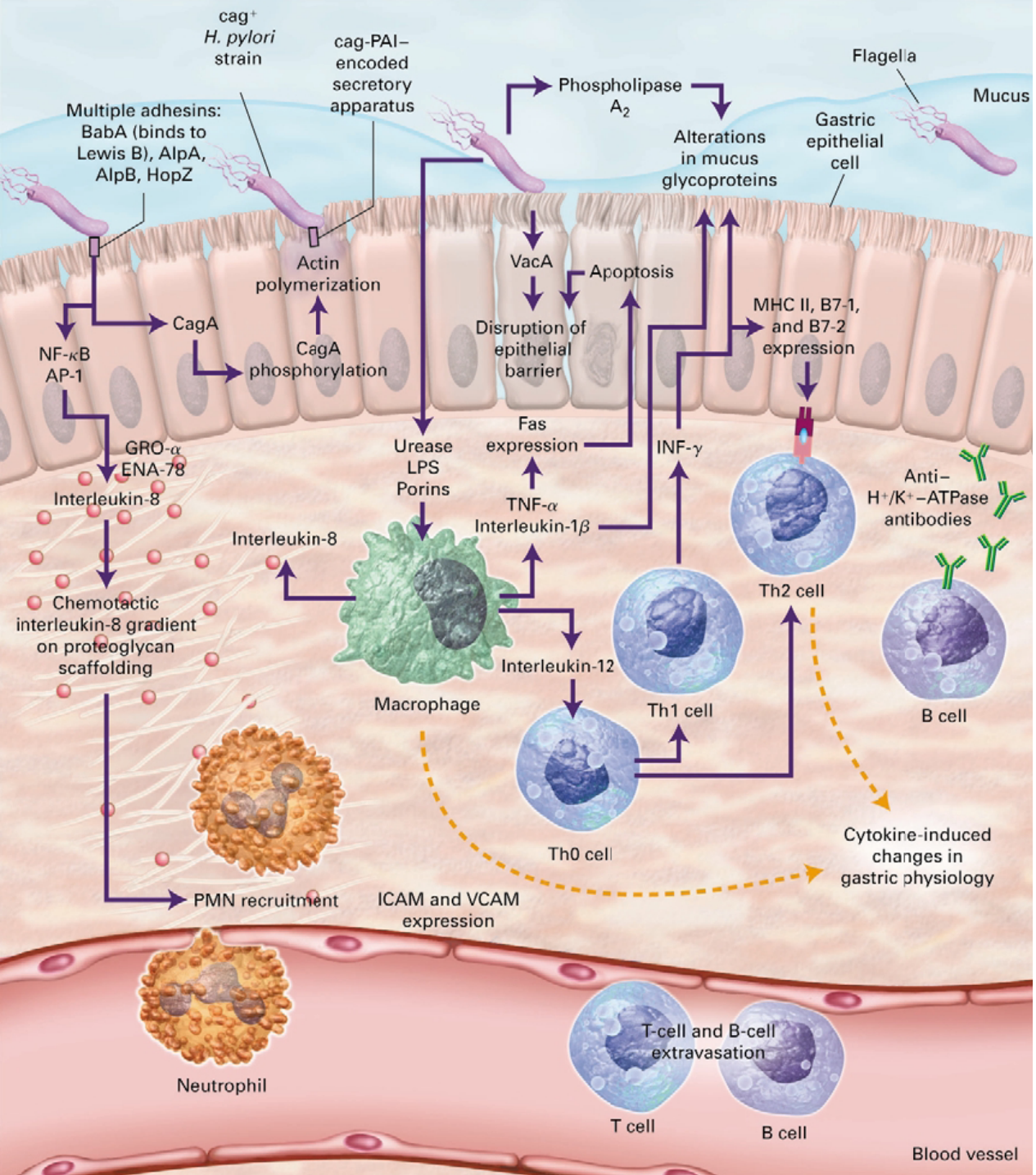


Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease

Pathogenesis

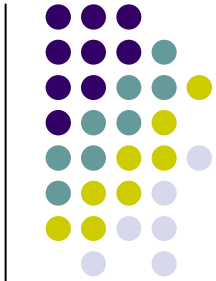


Long: Principles and Practice of Pediatric Infectious Diseases, 3rd ed.



Lancet 2003; 362: 1231–33

Cytotoxin-associated antigen (CagA)



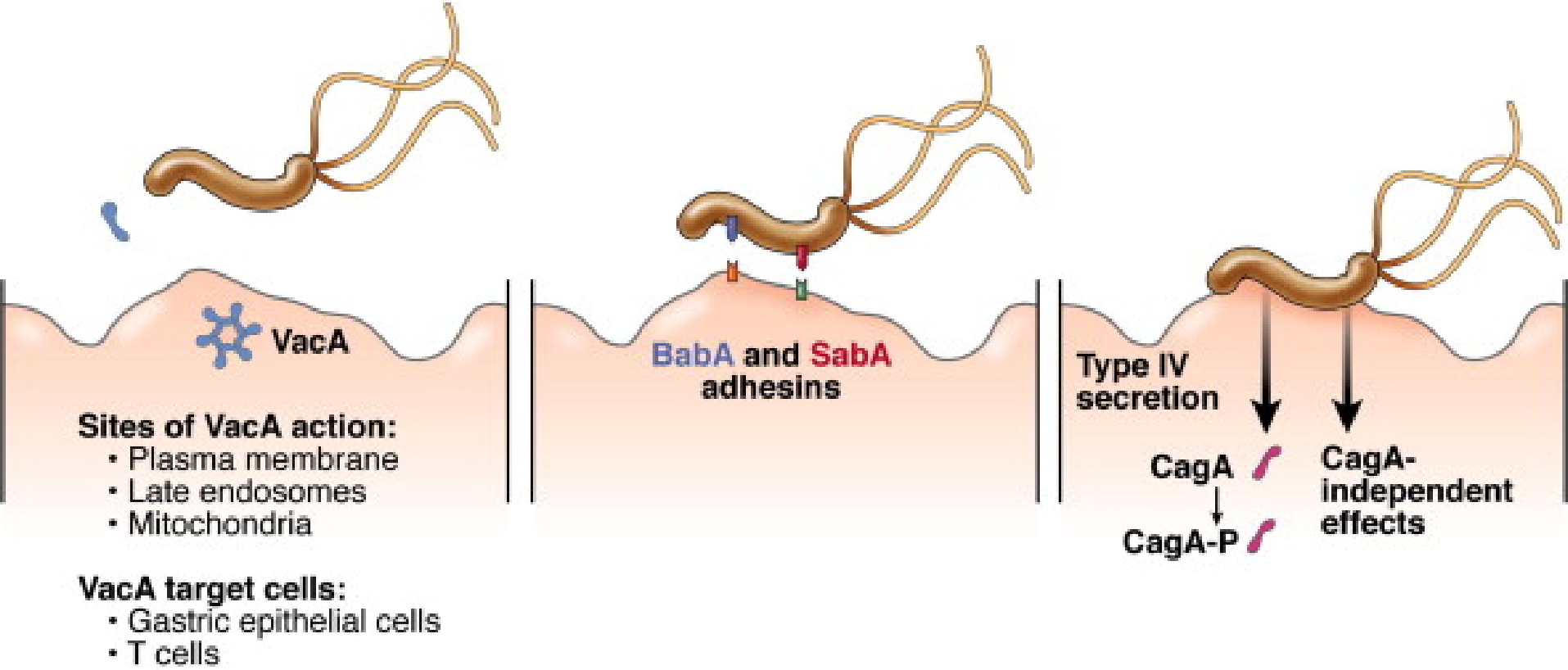
- There are different strains of H. pylori.
- Cag PAI includes approximately 31 putative genes, including cagA—the gene that encodes the CagA protein.
- CagA protein can be delivered into gastric epithelial cells
  - alterations in cell structure and cell motility
  - alterations of tight junctions,
  - Alterations in cell scattering and proliferation
  - perturbation of epithelial cell differentiation and polarity
  - increases the turnover of the gastric epithelium

Cag A

- Western countries = 60% to 80%
- Asia= > 90% of isolates express CagA
- Results in more corpus inflammation
  - Decrease in gastric acidity
  - Increase in proinflammatory cytokines (IL-8, IL-1, TGF-β, TNF-α, leptin, ↓ghrelin)
  - ↓ Histamine and somatostatin
  - ↑ Gastrin (basal and meal stimulated)
- Increase risk of Gastric Ca
- Decrease risk of EAC, Barrett's and GERD

Vac A

- Effects of active VacA
  - alterations of late endocytic compartments
  - increased plasma membrane permeability,
  - increased mitochondrial membrane permeability,
  - apoptosis



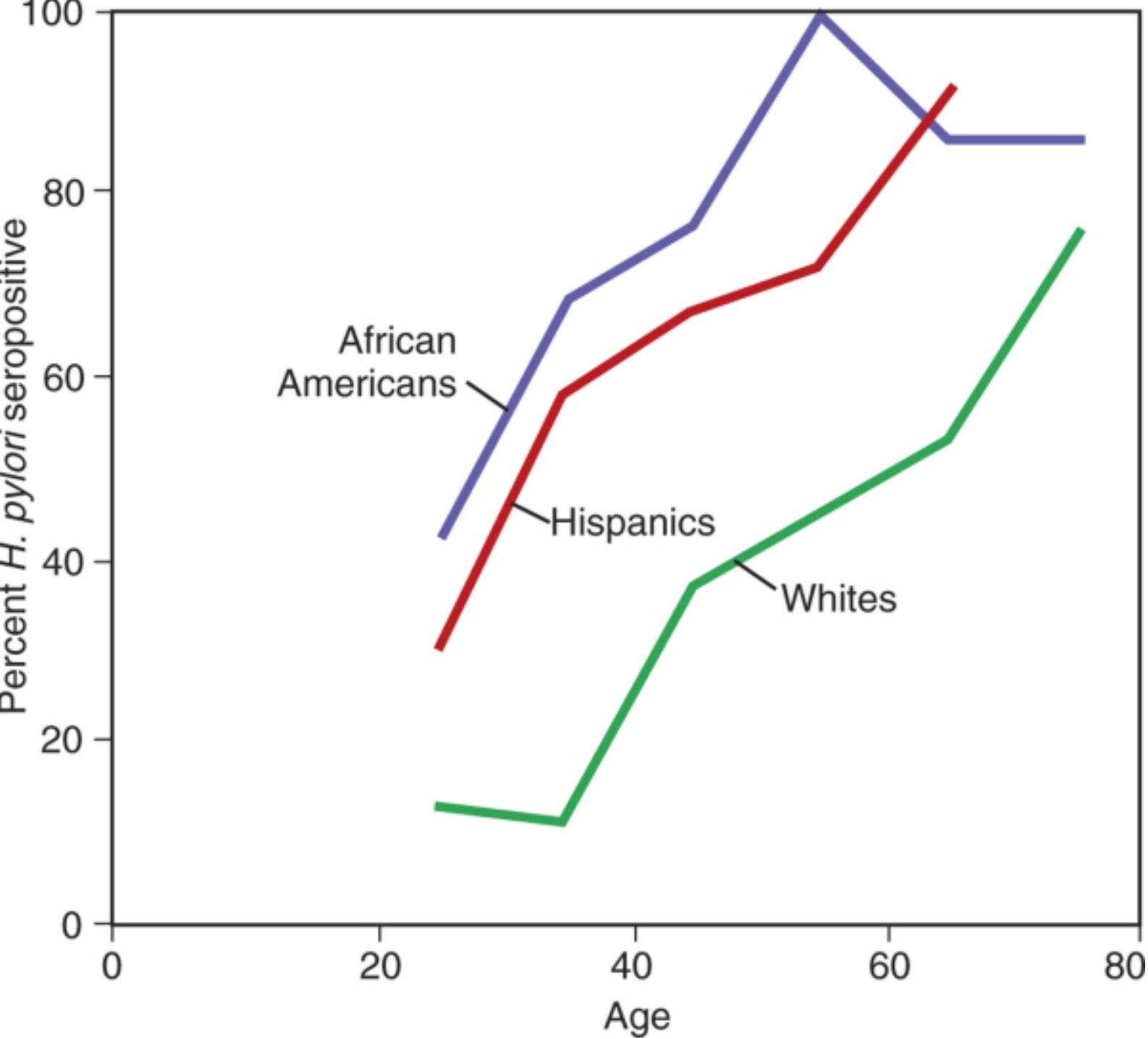
Helicobacter pylori in Health and Disease
Gastroenterology, Volume 136, Issue 6, Pages 1863-1873
T. Cover, M. Blaser

Prevalence of HP

A

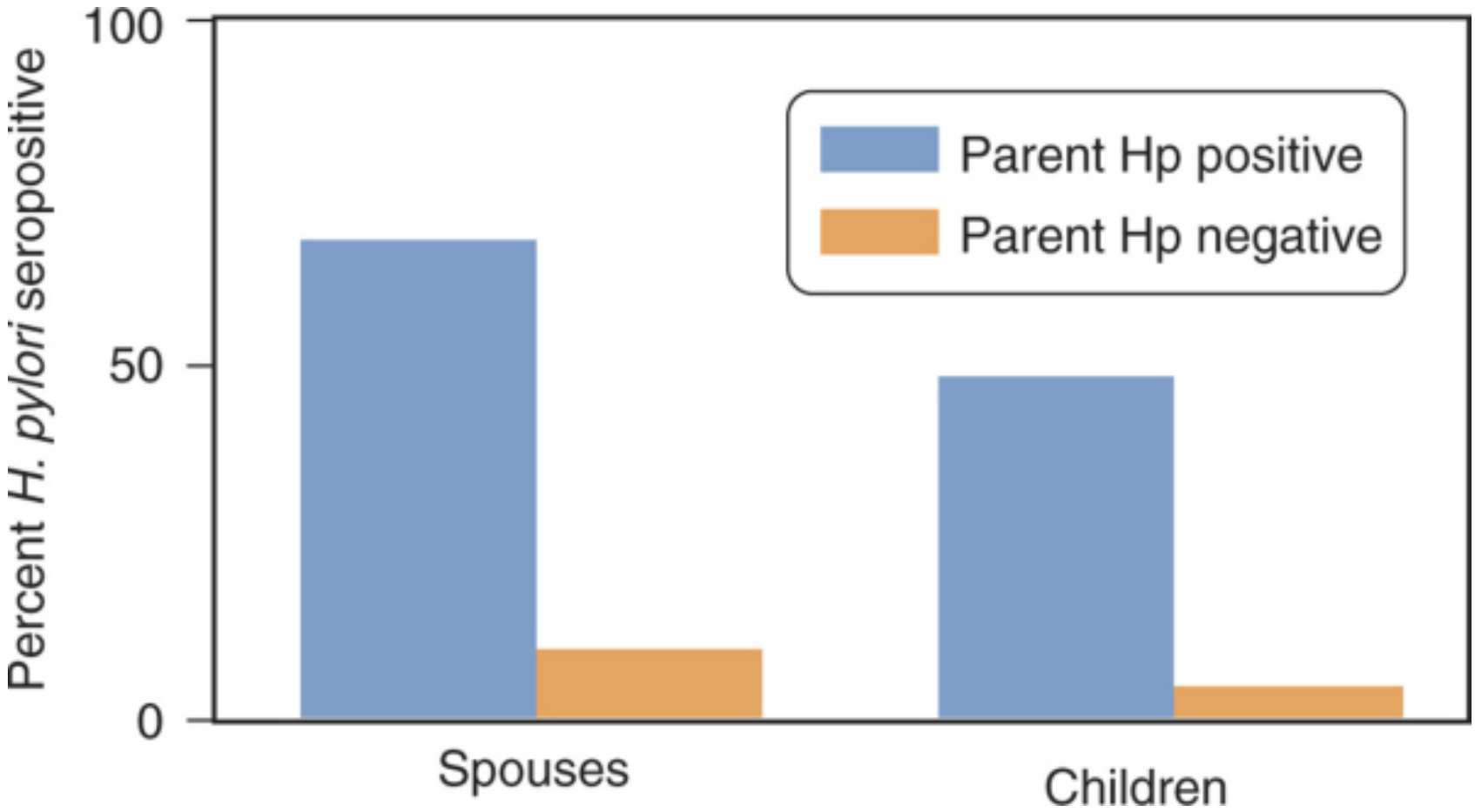
B

Mandell, Bennett, & Dolin: Principles and Practice of Infectious Diseases

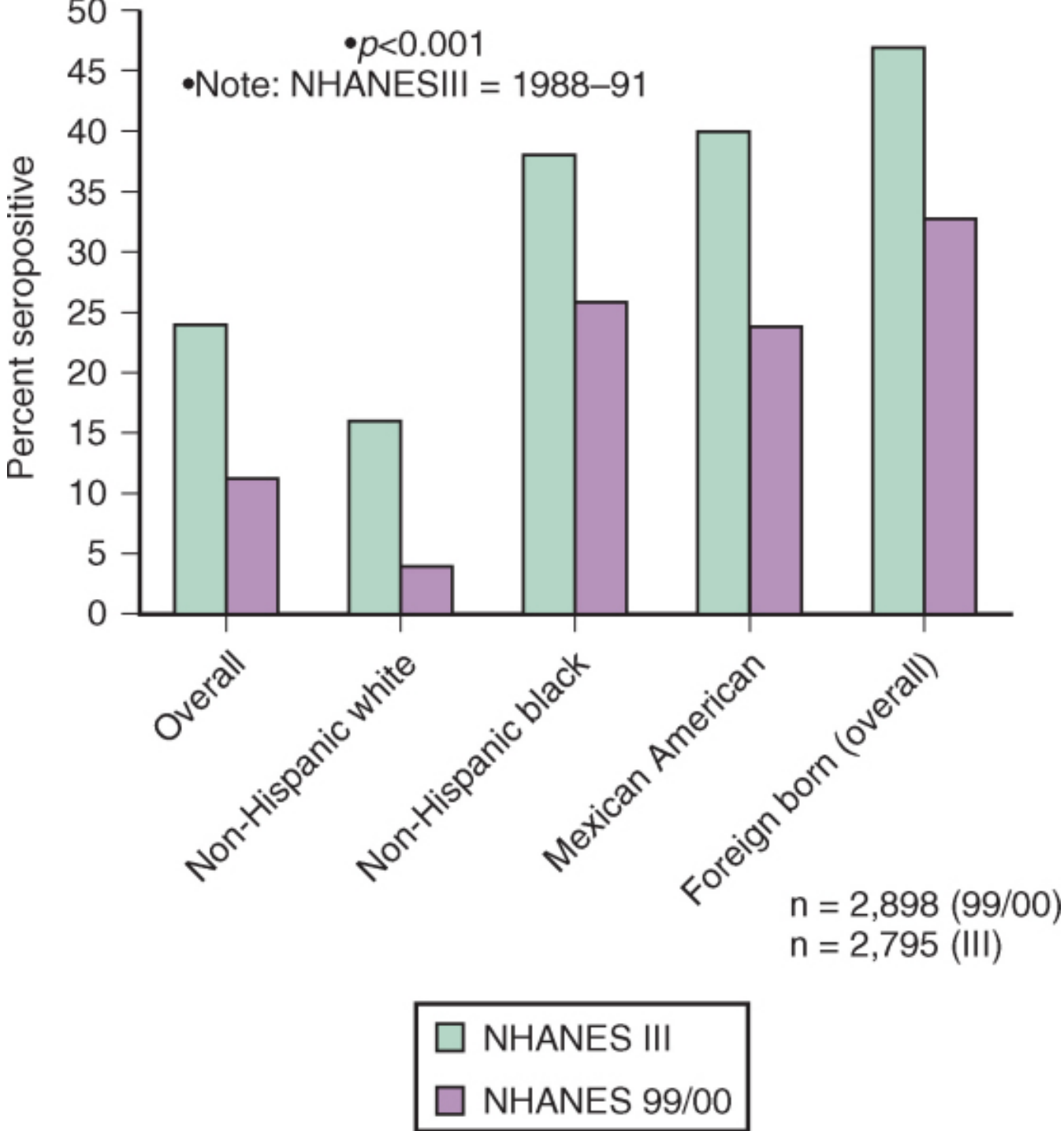


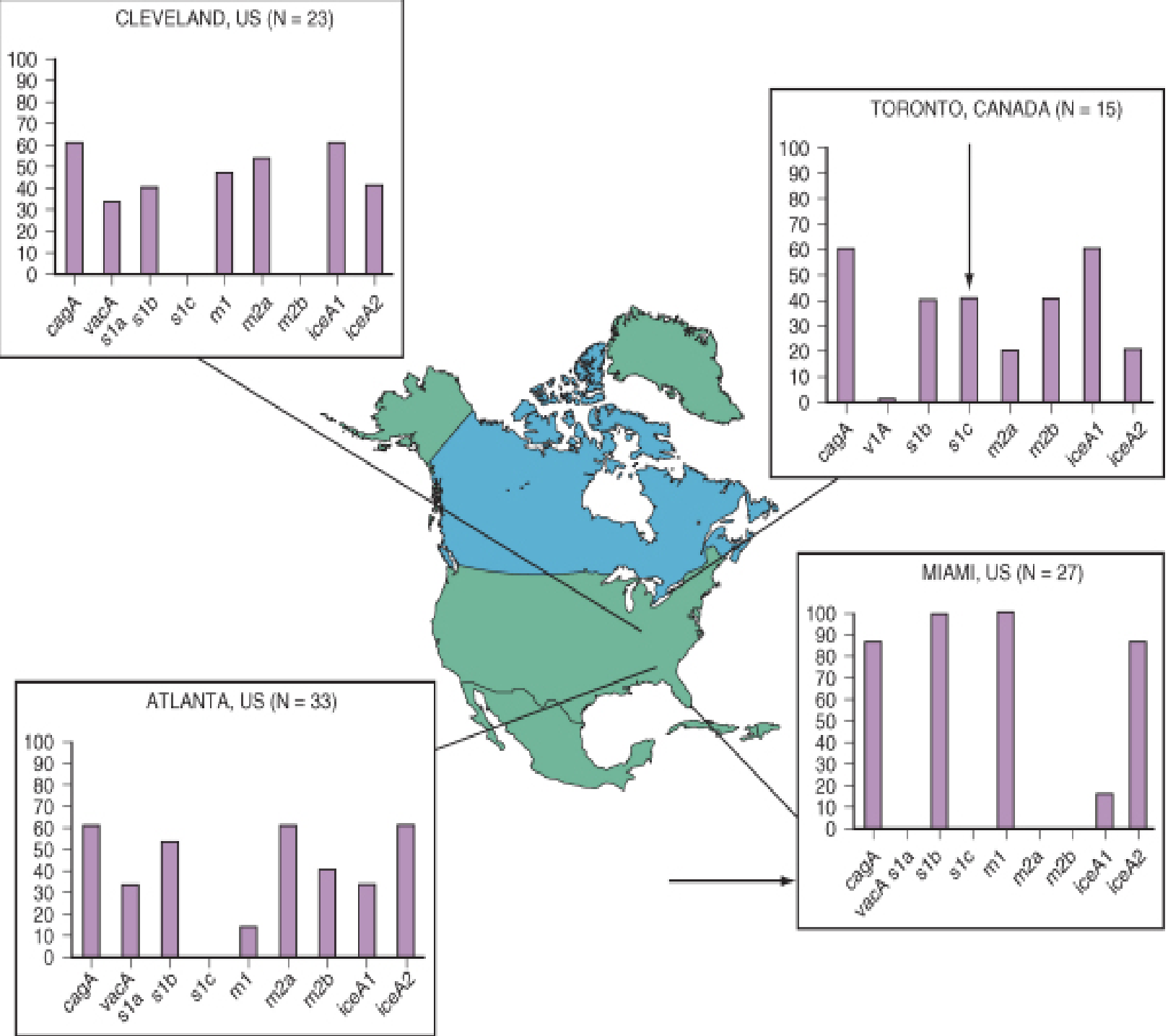
Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease

HP prevalence



Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease


•p<0.001
•Note: NHANESIII = 1988–91
Percent seropositive
50
45
40
35
30
25
20
15
10
5
0
Overall
Non-Hispanic white
Non-Hispanic black
Mexican American
Foreign born (overall)
n = 2,898 (99/00)
n = 2,795 (III)
NHANES III
NHANES 99/00



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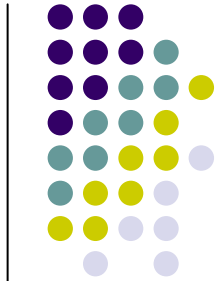
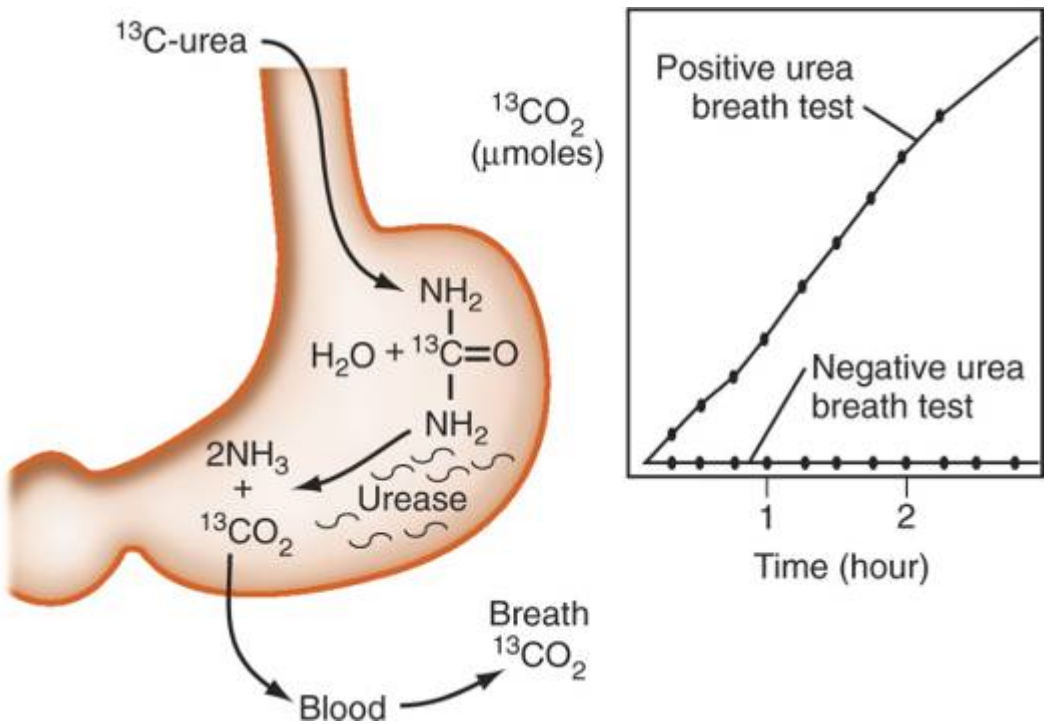
HP Prevalence Key Points



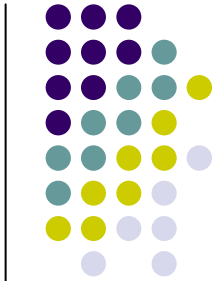
- High risk gastric Ca areas (mostly Cag A +) vs other (mixed)
- Cag A+
  - More intense corpus inflammation
  - More gastric Ca
  - Less GERD, Barrett's and EAC
- Prevalence is decreasing (sanitation + abx)

Diagnosis

- Who to Test and How to test em…



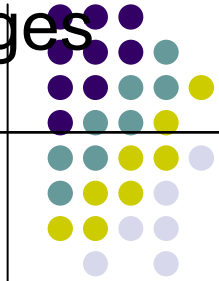
Who to test?



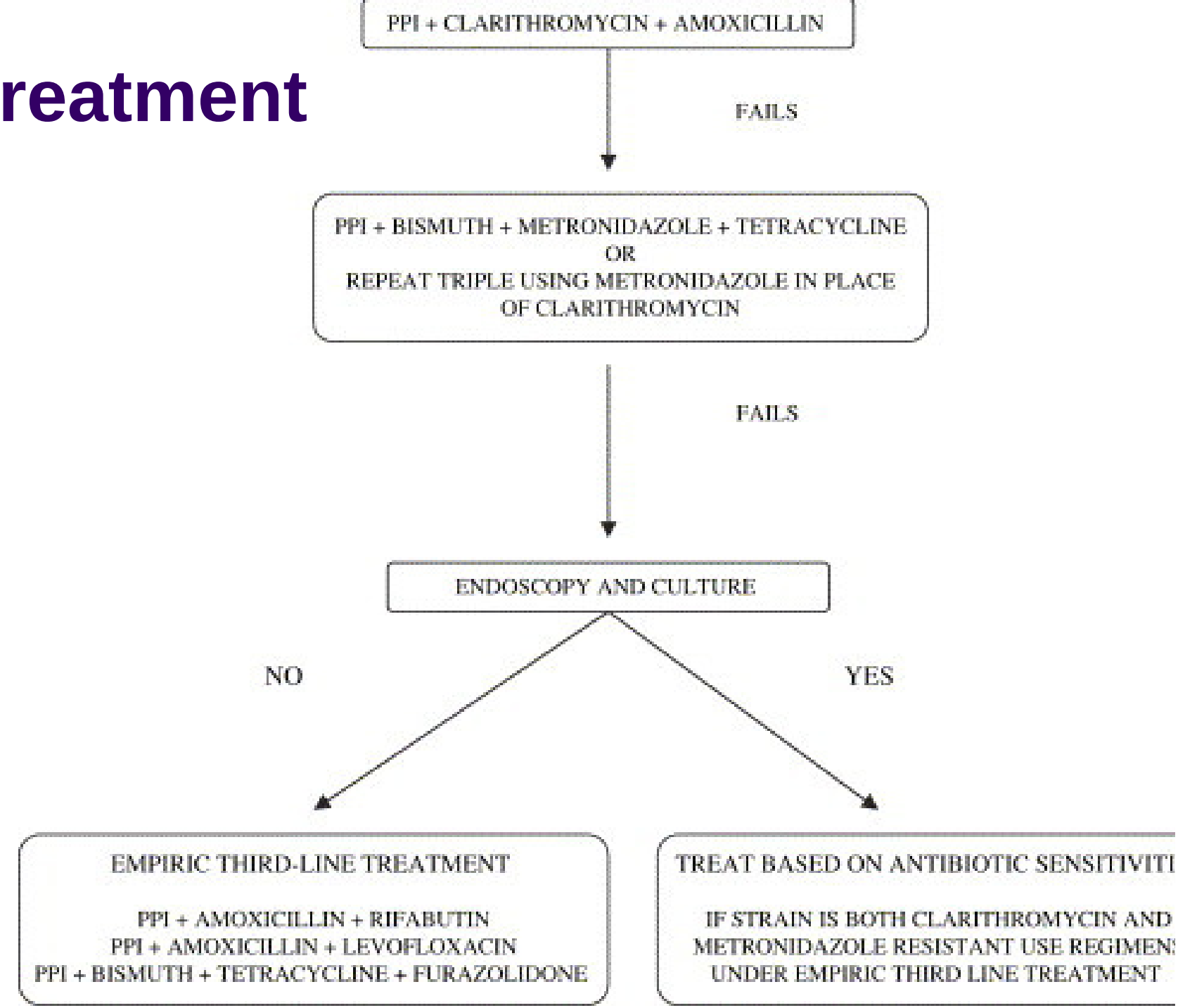
- **Established**
  - PUD
  - Gastric low-grade MALT lymphoma
  - Univestigated dyspepsia
  - After endoscopic resection of early cancer
  - Evaluate success of eradication therapy

- **Controversial**
  - High Risk for Gastric Ca (e.g. relatives of patients who have gastric cancer)
  - Unexplained Iron Deficiency anemia
  - Nonulcer dyspepsia
  - Chronic nonsteroidal anti-inflammatory drug/aspirin therapy a
  - Chronic antisecretory drug therapy (eg, gastroesophageal reflux disease) b
  - Relatives of patients who have ***H pylori*** infection
  - Patient desires to be tested
- a When planning long-term therapy and NAIVE.
- b When planning long-term antisecretory therapy.

	Advantages	Disadvantages
Histology*	**Allows assesment of presence/severity/distribution of gastritis**	**Time**
Rapid Urease*	**Its rapid**	**PPI, abx, and bismuth cause false (-)**
Culture*	**Allows assesment of abx resistence**	**Time/not always available/not sesitive**
PCR*	**100% sensitive, can identify drug resistence**	**Restricted to research**
Serology	**90% sensitivity and specificity**	**False - in atrophic gastritis and cancer** **this test cannot be used to assess eradication after therapy.**
Urea Breath Test	**sensitivity and specificity are > than 95%.**	**Eradication: must wait 4 weeks after therapy is finished.** **PPI, abx, and bismuth cause false (-)**
Stool Antigen Test	**Sensitive and specific means of assesing presence and eradication**	**Poop test**

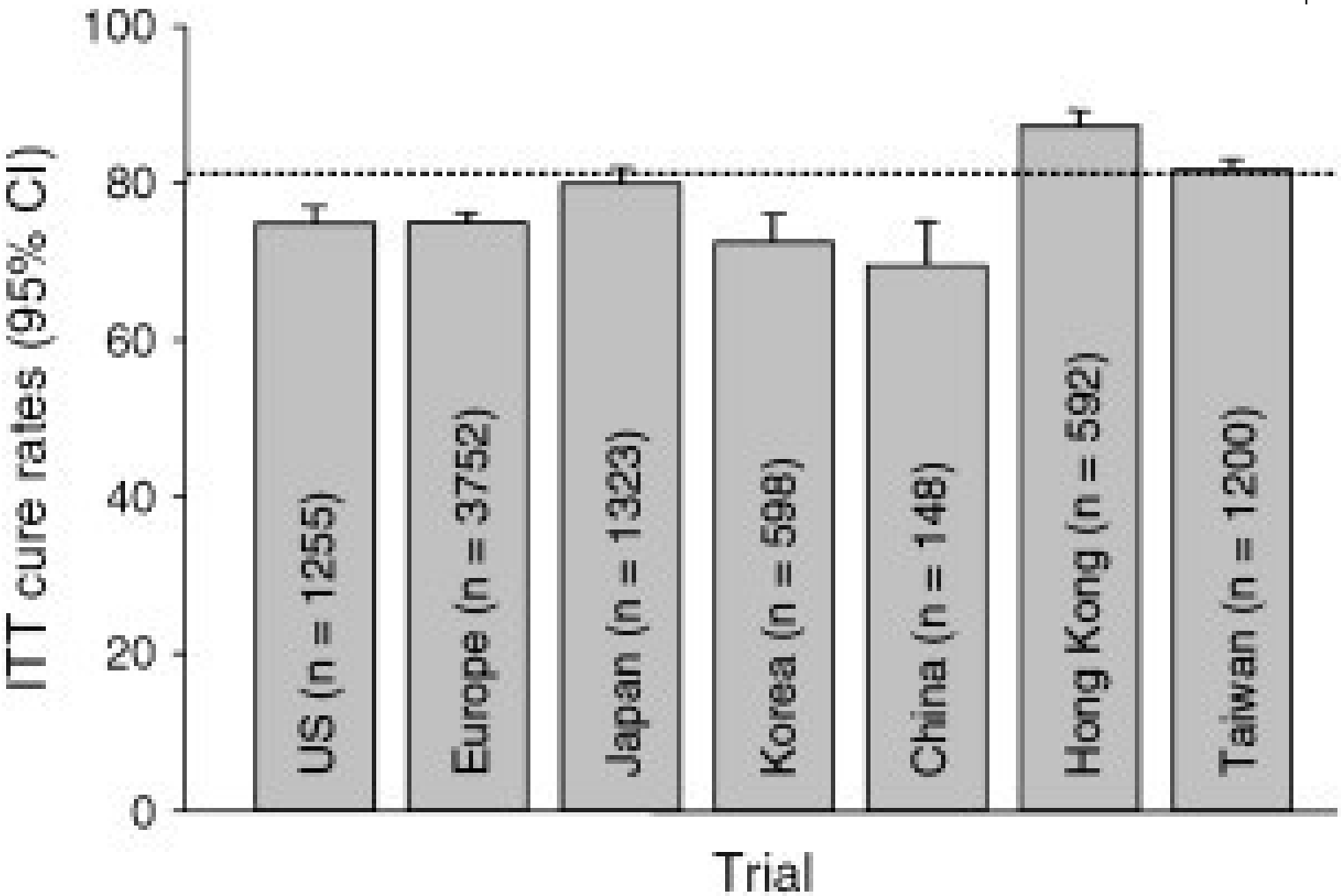


Treatment



Medical Clinics of North America - Volume 90, Issue 6 (November 2006)

Standard Therapy



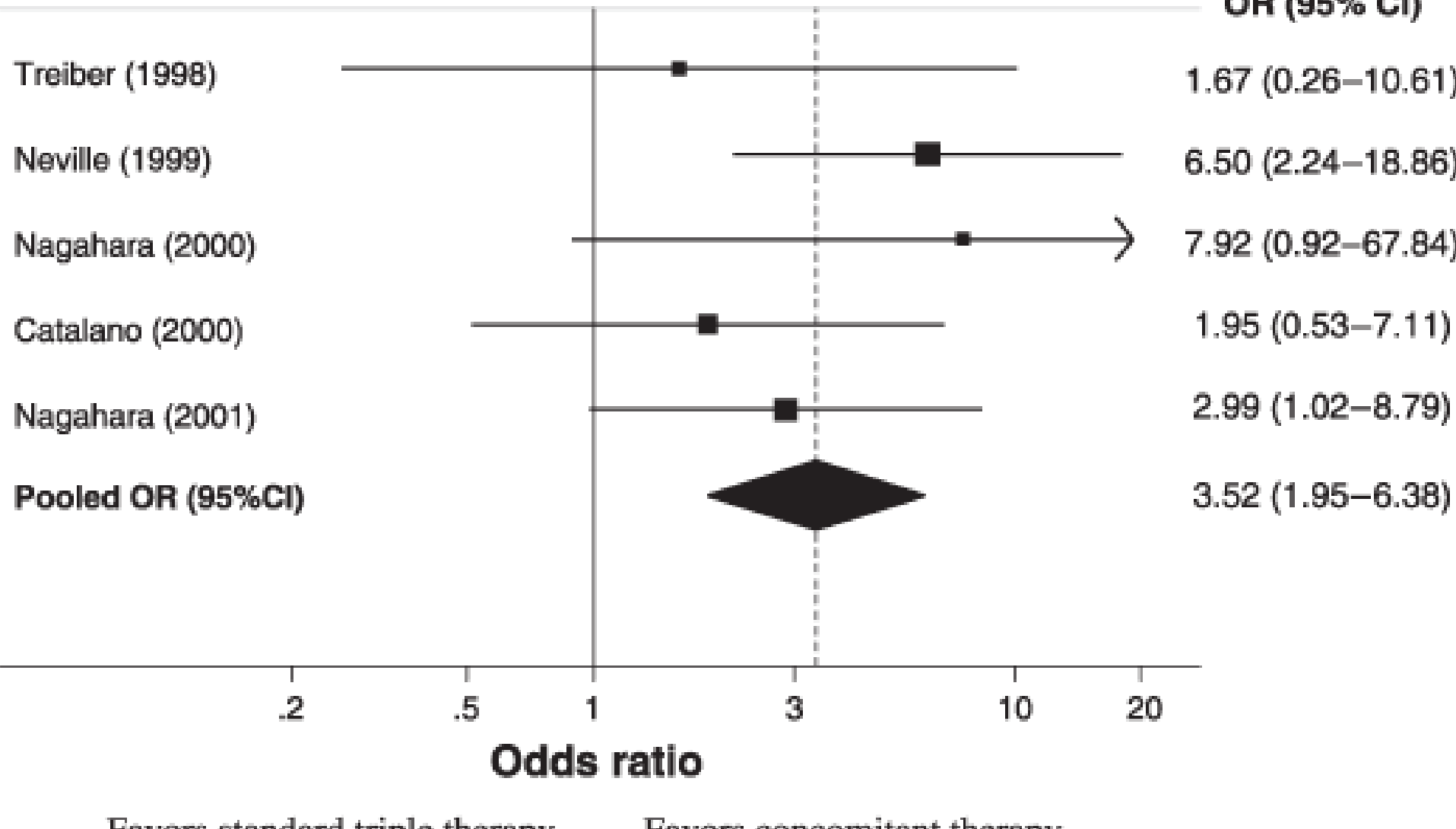
Gastroenterology Clinics - Volume 38, Issue 2 (June 2009)

H. Pylori Eradication

- **Legacy therapies**
  - Triple therapy: A PPI plus amoxicillin, 1 g, plus clarithromycin, 500 mg, or metronidazole/tinidazole, 500 mg, bid for 14 days
  - Quadruple therapy: Bismuth, metronidazole, 500 mg, tetracycline, 500 mg, three times a day plus a PPI twice a day for 14 days
- **Concomitant triple therapies**
  - A PPI plus amoxicillin, 1 g, plus clarithromycin, 500 mg, and metronidazole/tinidazole, 500 mg, bid for 14 days
- **Sequential therapy**
  - A PPI plus 1 g amoxicillin, twice a day for 5 days. On day 6 stop amoxicillin and add clarithromycin, 250 or 500 mg and metronidazole/tinidazole, 500 mg, bid to complete the 10-day course.
- **Salvage therapy**
  - Best if based on the results of susceptibility testing

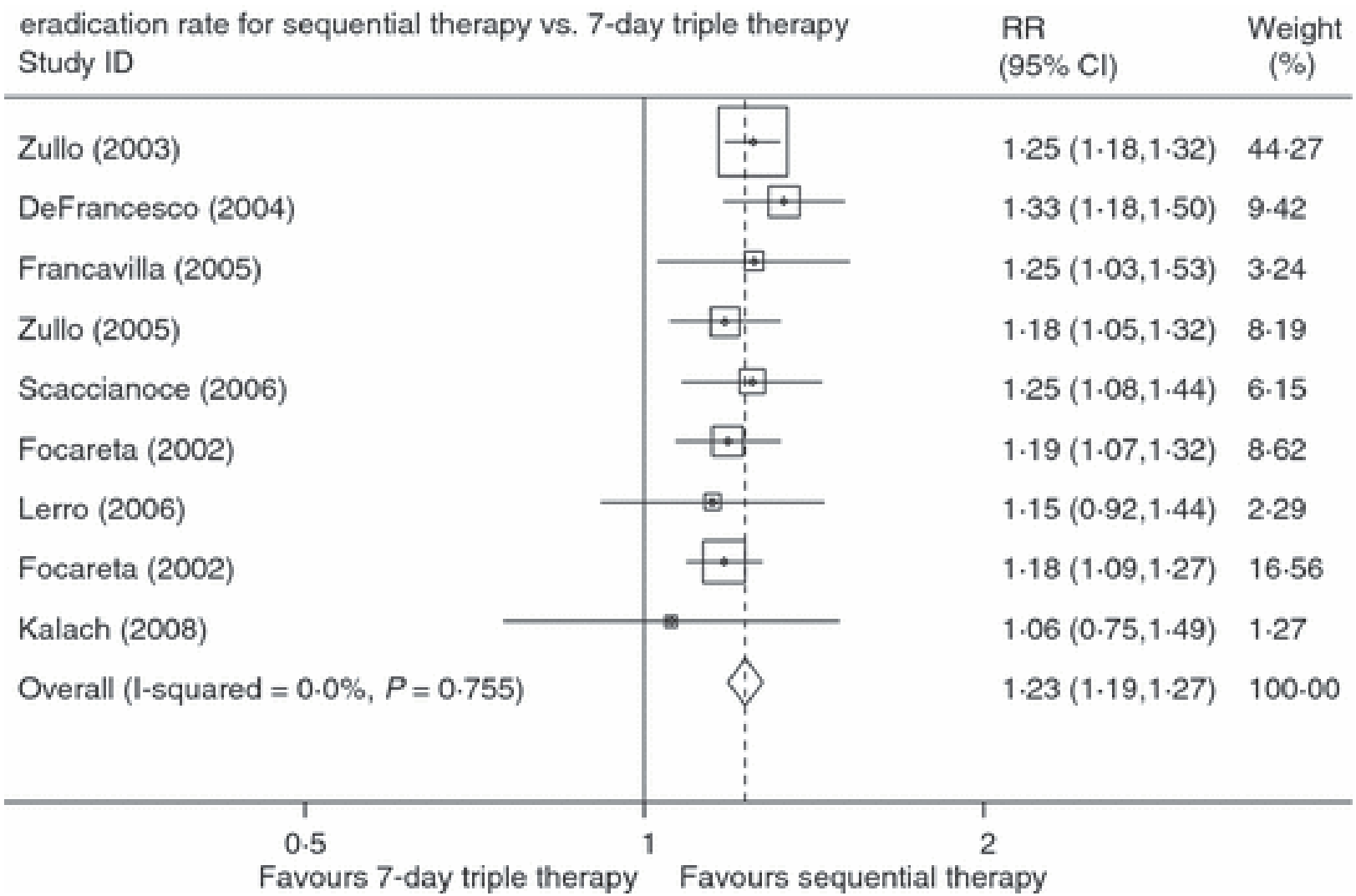
American College of Gastroenterology Guideline on the Management of *Helicobacter pylori* Infection 2007

Concominant Therapy



Sequential Therapy

	Pantoprazole (40 mg twice daily) +amoxicillin (1 g twice daily)				
Day	1	2	3	4	5
	Pantoprazole (40 mg twice daily) +clarithromycin (500 mg twice daily) +tinidazole (500 mg twice daily)				
Day	6	7	8	9	10



Journal of Clinical Pharmacy and Therapeutics Vol. 34, 1 Pages: 41-53

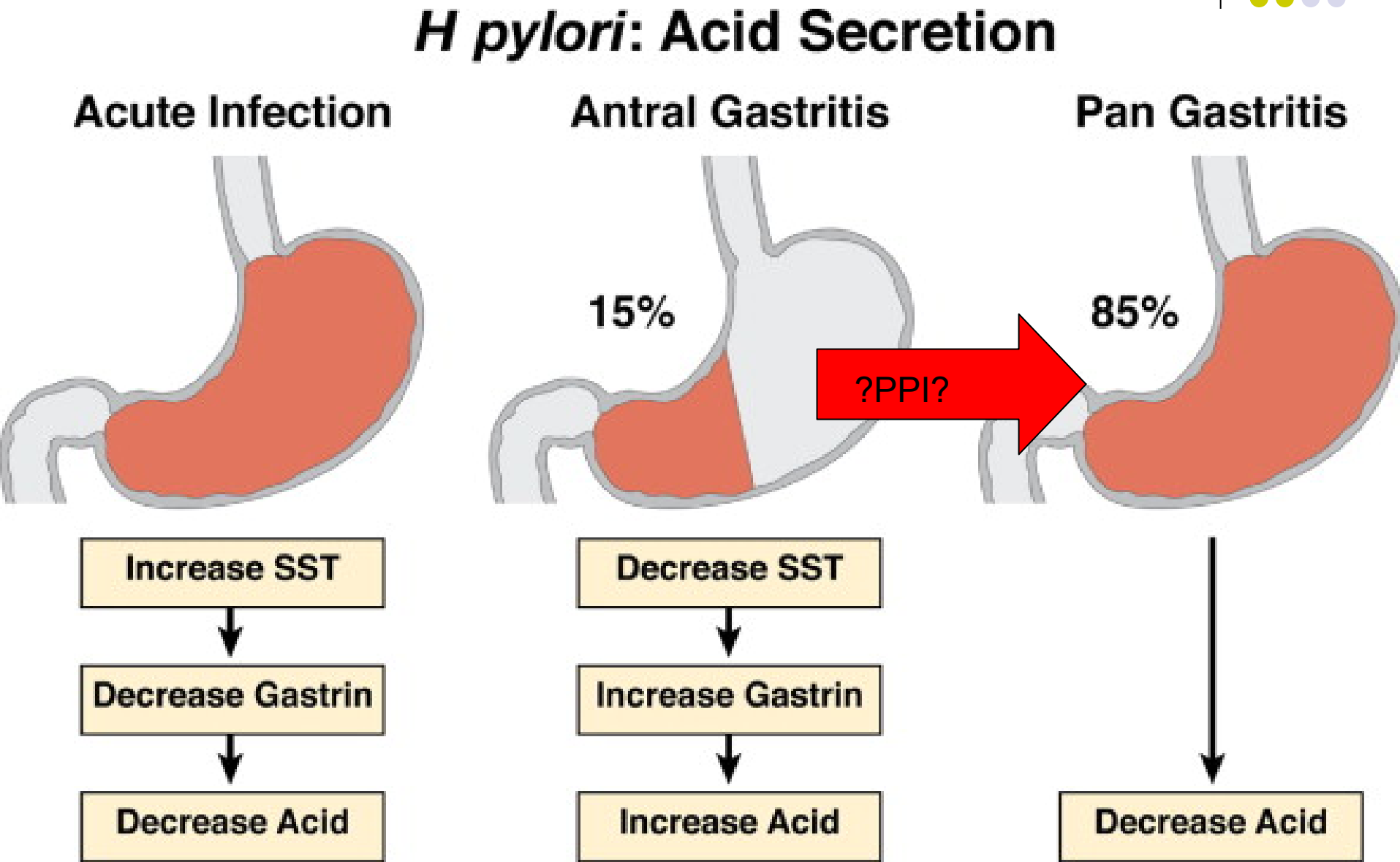
When to Confirm Eradication

- Any patient with an *H. pylori*-associated ulcer.
- Individuals with persistent dyspeptic symptoms despite the test-and-treat strategy.
- Those with *H. pylori*-associated MALT lymphoma.
- Individuals who have undergone resection of early gastric cancer.

American College of Gastroenterology Guideline on the Management of *Helicobacter pylori* Infection 2007

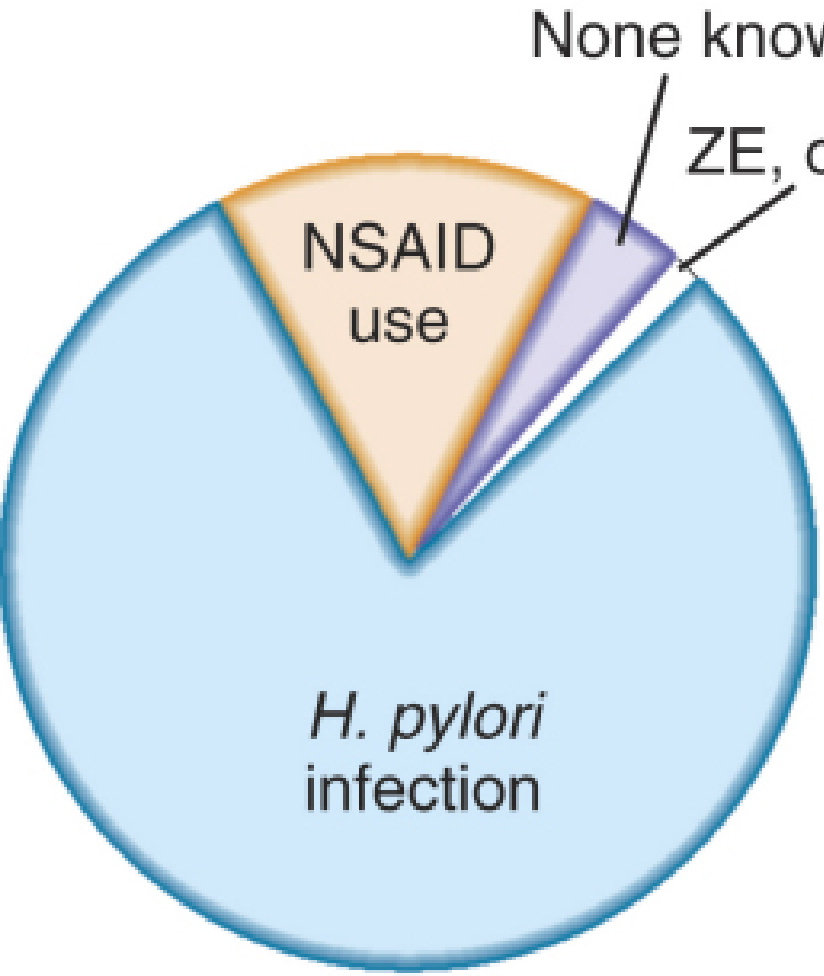
HP and Acid

GASTROENTEROLOGY
2008;134:1842–1860

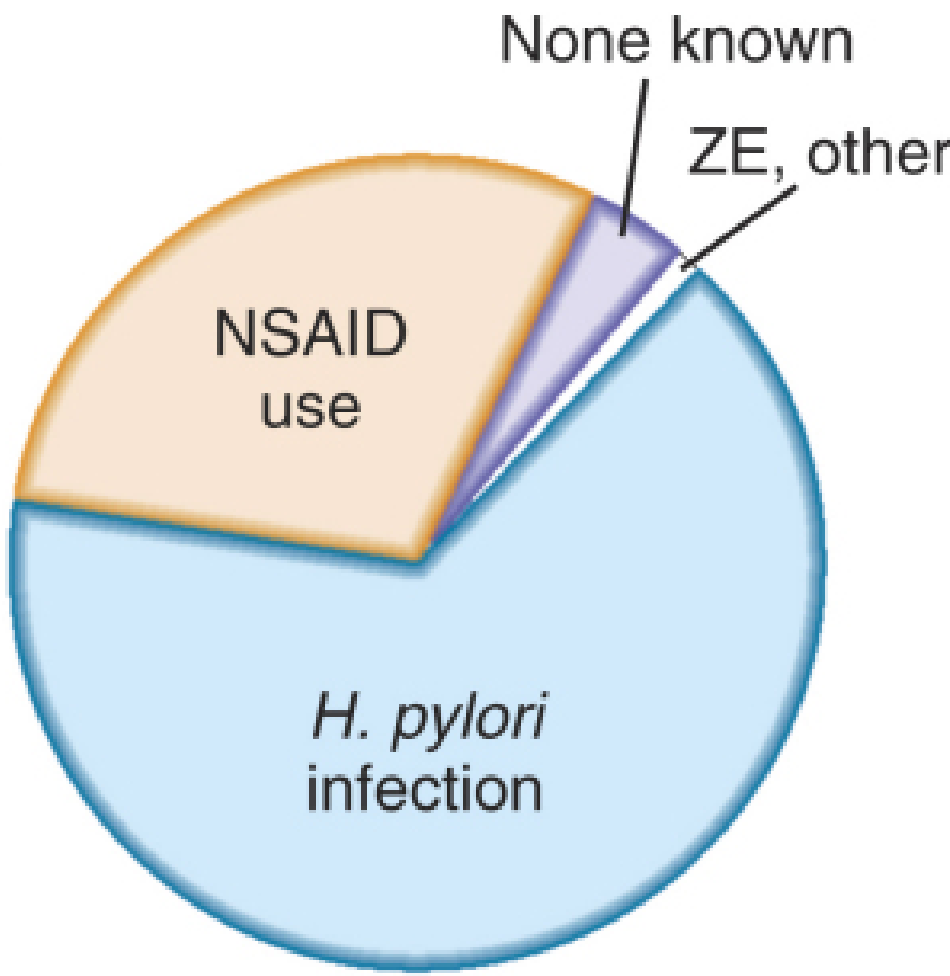


Diseases of the Esophagus (2009) **22**, 256–263

CONDITIONS ASSOCIATED WITH PEPTIC ULCER

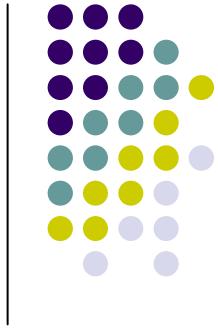


Duodenal



Gastric

H. Pylori and PUD

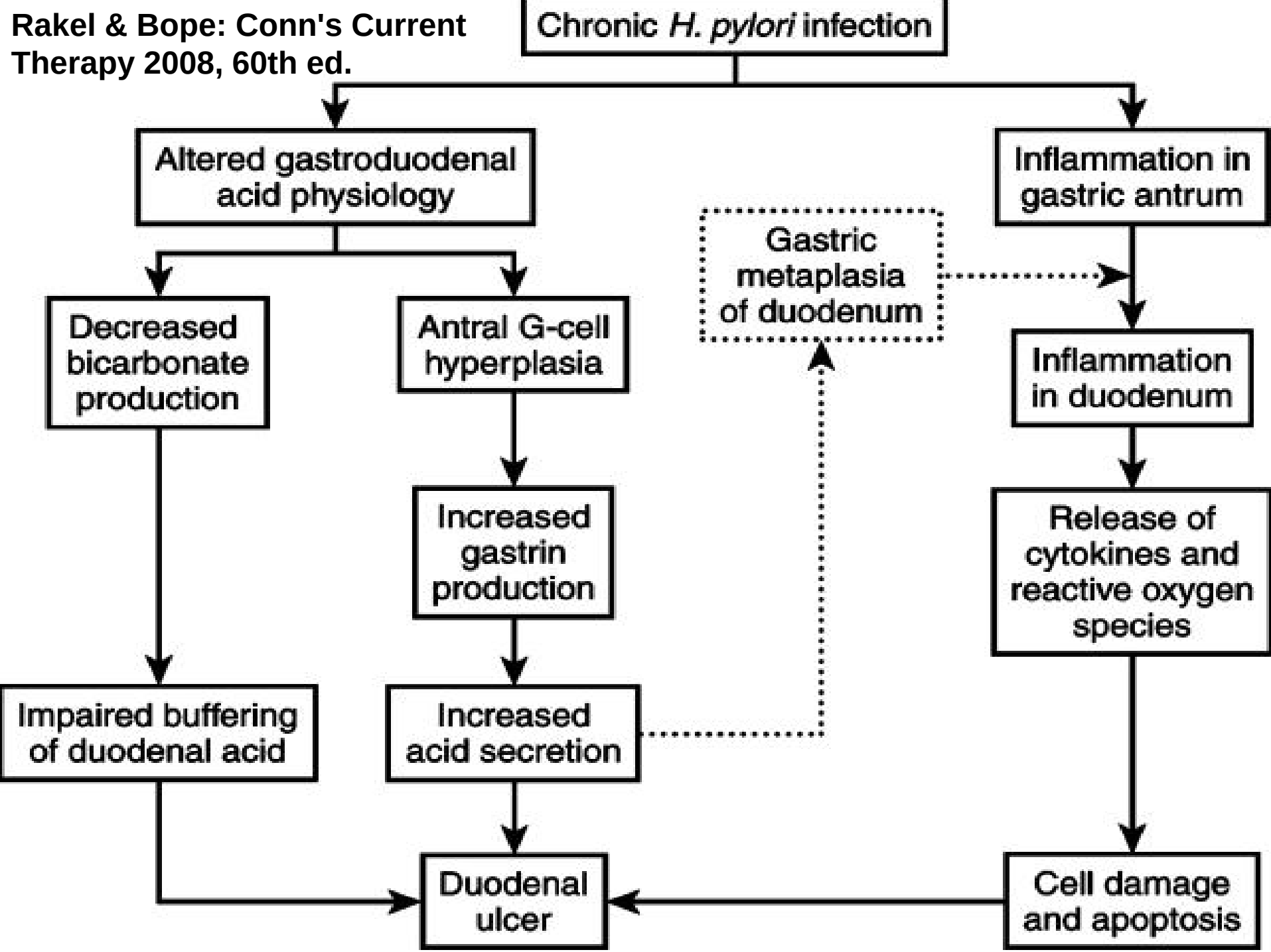


- 90% of duodenal ulcers and roughly 75% of gastric ulcers are associated with ***H. pylori***
- Treat…NSAIDs or not
- Antral predominant HP = High Gastrin = High gastric acid = PUD
- Eradication reduces recurrence and rebleeding rates

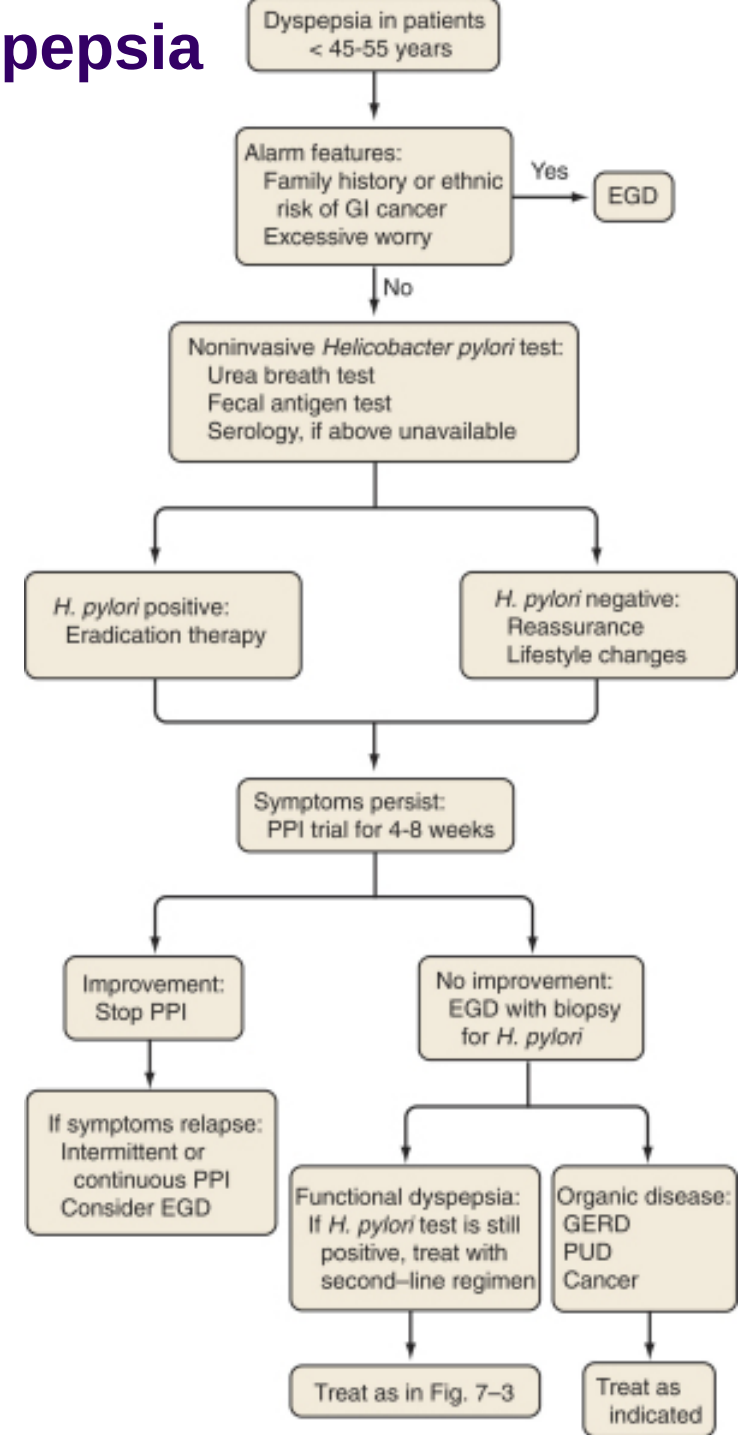
Mechanisms responsible for *H. pylori*–induced GI injury

1. Production of toxic products to cause local tissue injury
2. Induction of a local mucosal immune response
3. Increased gastrin levels with a resultant increase in acid secretion

Rakel & Bope: Conn's Current Therapy 2008, 60th ed.



H.Pylori and Dyspepsia

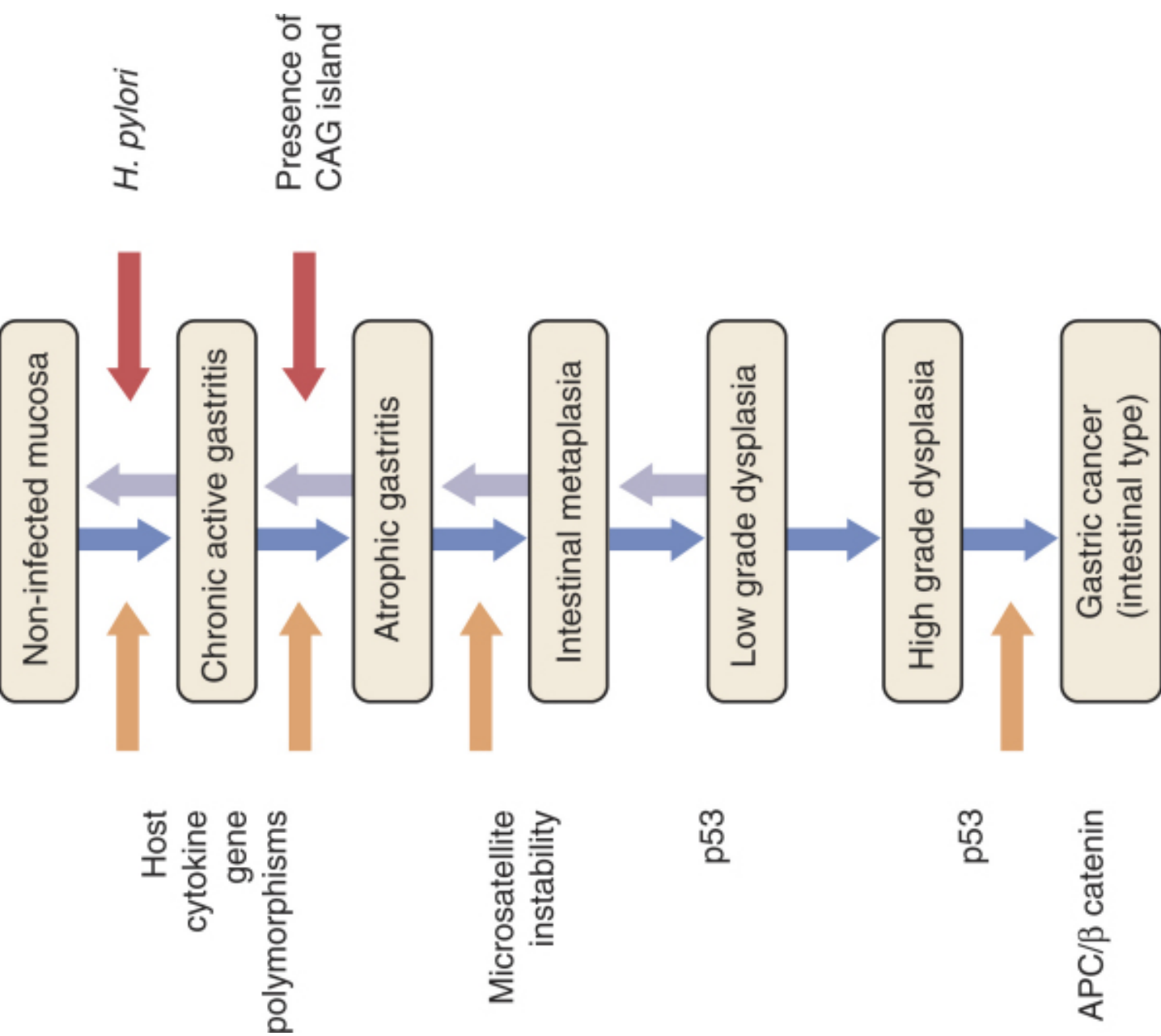


Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th ed.

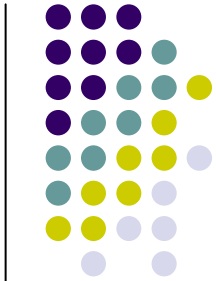
H.Pylori and Gastric Cancer

- Cag A positive strains confer a higher risk of noncardia gastric cancer than CagA-negative strains.
- Surrogate end-points suggest a benefit from HP eradication ((severity and distribution of gastritis and gastric preneoplastic lesions (multifocal atrophic gastritis,intestinal metaplasia, or dysplasia))
- “there is no definitive population-based data to suggest that H. pylori eradication reduces the incidence of gastric adenocarcinoma”

Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th ed.

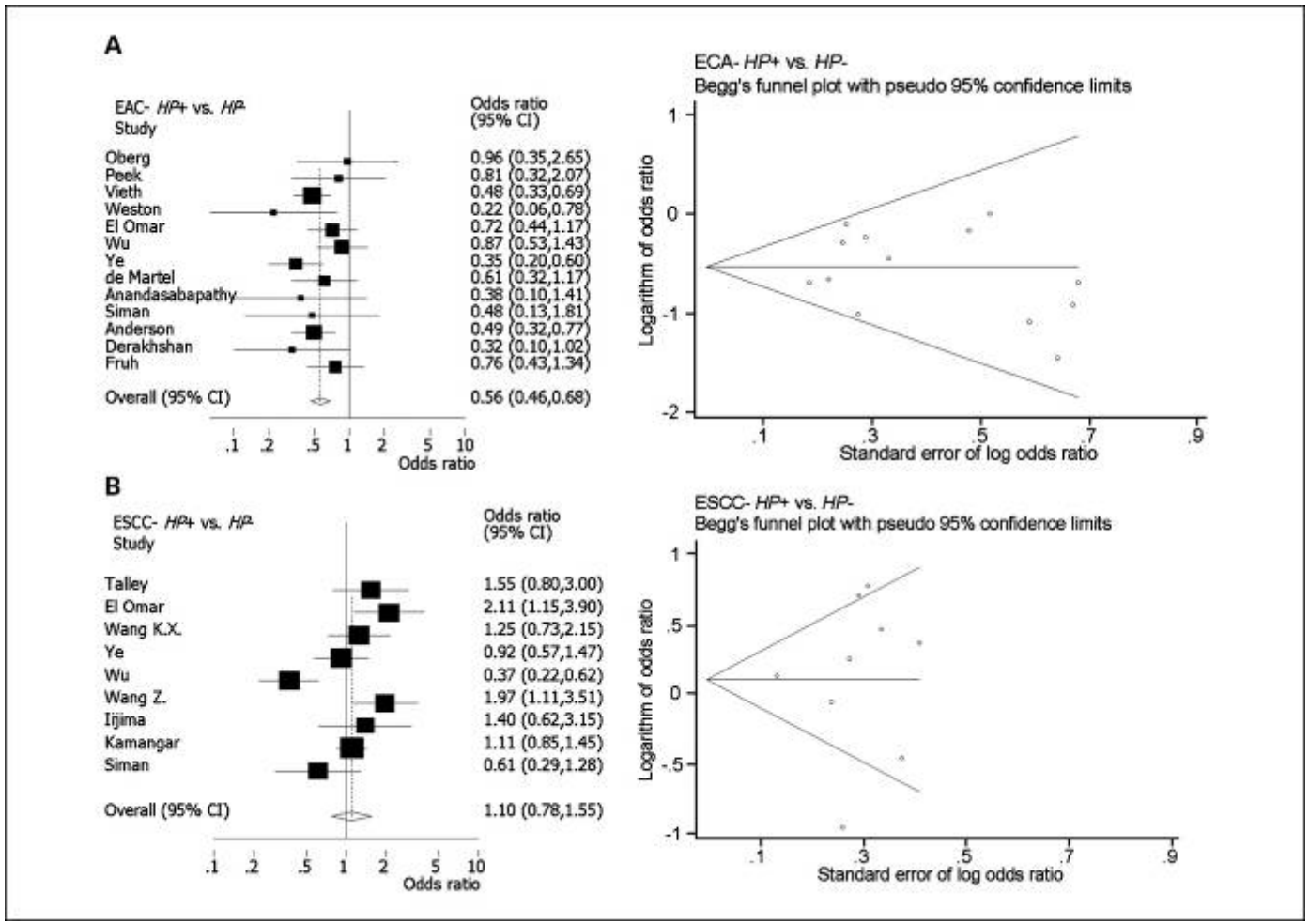


H.Pylori and EAC/Gastric Ca (cardia)



- EAC= ↑ incidence
  - 450,000 new cases annually,
  - 8th most common incident cancer in the world
- H. pylori (CagA, corpus predominant) may ↓ risk of EAC by ↓ acid production in the stomach and ↓ acid reflux to the esophagus
- It may also reduce EAC risk by decreasing the production of the hormone ghrelin
- HP eradication alone does not explain the increasing incidence (obesity, smoking, etc)

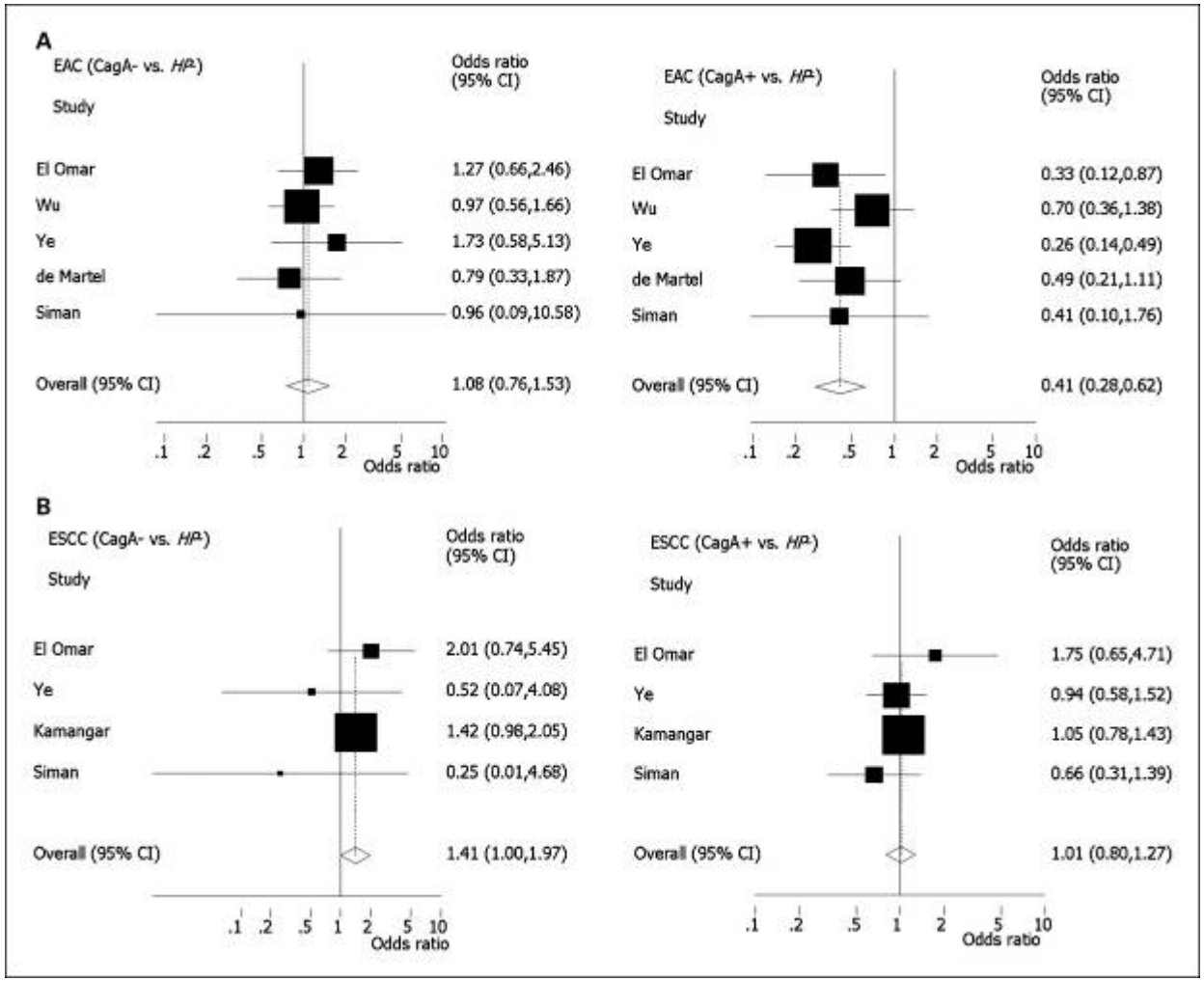
Fig. 1 Forest plot and Begg's funnel for the association between H. pylori and esophageal cancer



Islami, F. et al. Cancer Prev Res 2008;1:329-338

AACR American Association for Cancer Research
Cancer Prevention Research

Fig. 2 The association between CagA-positive and CagA-negative strains and esophageal cancer



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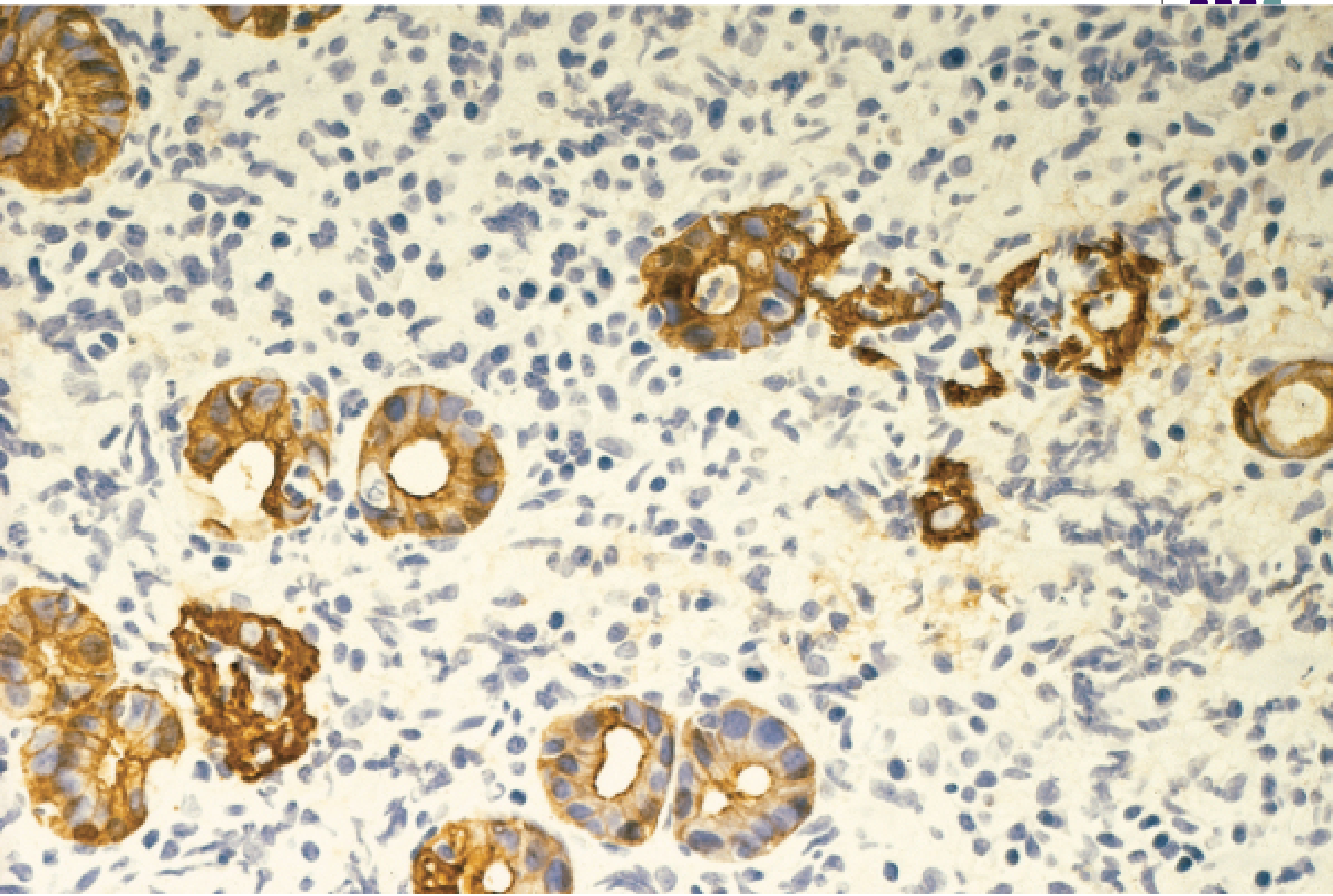
MALT-lymphoma

- For localized gastric MALT lymphoma, *H. pylori* treatment = tumor regression in 60–90% of patients
- *H. pylori* eradication in patients with low-grade MALT lymphoma = recurrence rates of 3–13% over 5 yr
- Recent Study
  - High grade MALT lymphoma
  - HP eradication = complete remission in 64%
  - Of these, relapse rate = 0% @ 5yrs

American College of Gastroenterology Guideline on the Management of *Helicobacter pylori* Infection (2007)



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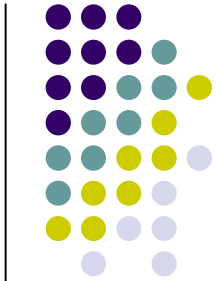
Nongastrointestinal Tract Diseases Possibly Associated with *Helicobacter pylori* Infection



- Iron deficiency anemia
- Asthma (↓)
- Coronary artery disease
- Cerebrovascular disease
- Hypertension
- Raynaud's phenomenon
- Migraine headaches
- Vomiting of pregnancy
- Immune thrombocytopenic purpura
- PSE
- Sudden infant death syndrome
- Growth retardation
- Anorexia of aging
- Rosacea
- Chronic urticaria

Iron Deficiency Anemia

- Independent risk factor for iron deficiency anemia
- Mechanism
  - chronic pangastritis
    - achlorhydria
    - reduced ascorbic acid secretion
    - reduced intestinal iron absorption.
  - Occult blood loss from erosive gastritis and sequestration
  - utilization of iron by the organism
- There is emerging evidence to suggest that eradication of *H. pylori* can improve iron deficiency anemia

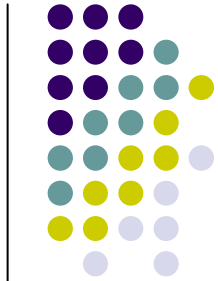
American College of Gastroenterology Guideline on the Management of *Helicobacter pylori* Infection (2007)

ITP

- Molecular Mimicry?
  - Platelets eluated from patients with chronic **ITP** recognize the CagA protein of *H. pylori*
- Treatment of HP results in 50% successful treatment of patients with ITP and CagA + HP
- Expected to be highest in Asia, where the majority of infections are with CagA-positive infections.

Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th ed.

Changing The Way We Think About HP



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