

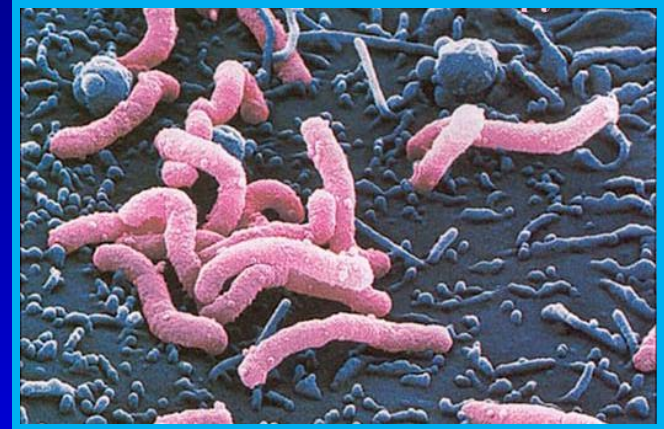
Update on Helicobacter Pylori

Thomas Hargrave M.D.

November 19, 2010

What Is *Helicobacter pylori*?

- Gram-negative, curved or spiral bacterium
- Flagellated – highly motile
- Ideally adapted to survive in the human stomach
 - Potent producer of urease, which breaks down urea in gastric juice
 - Protected from highly acidic environment
- The most common single chronic bacterial infection, affecting 50% of humans.



Historical Time Points of *H. pylori* Infection



1983

Barry Marshall develops gastritis after self-inoculation²

1982

Barry Marshall and Robin Warren isolate curved bacillus from patients with gastritis or ulcer disease¹

1994

NIH Consensus Guidelines for *H. pylori* published⁴

2005

Nobel Prize for Medicine⁵



1980



1990

1990

Duodenal ulcer cured by *H. pylori* eradication³

2000

H. pylori accepted as a major causal factor in peptic ulcer disease, gastric cancer, and gastric MALT lymphoma⁶

2010

1. Warren JR, Marshall BJ. *Lancet*. 1983;1(8336):1273-1275; 2. Gustafson J, Welling D. *J Am Coll Surg*. 2010;210(1):110-116; 3. Rauws EA, Tytgat GN. *Lancet*. 1990;335(8700):1233-1235; 4. NIH Consensus Development Panel. *JAMA*. 1994;272(1):65-69; 5. Press release. http://nobelprize.org/nobel_prizes/medicine/laureates/2005/press.html. Accessed August 25, 2010; 6. Go MF. *Aliment Pharmacol Ther*. 2002;16(suppl 1):3-15.

Ulcer Dogma: Pre-1983

- Duodenal ulcer disease is caused by idiopathic hypersecretion of gastric acid.
“No Acid, No Ulcer”
- Peptic ulcer disease is a recurrent life-long illness.
- No long-term cure
- Acid suppression results in healing of duodenal ulcers, but recurrence was common within one year.

Helicobacter-Era Dogma:1990-1999

- Up to 90-100% of duodenal ulcers, and 70-80% of gastric ulcers, not due to NSAID usage, are caused by *Helicobacter pylori*.
- Eradication of *Helicobacter* results in a life-long cure of duodenal ulcer disease.
- *H. Pylori* is a class 1 gastric carcinogen.
- All chronic human diseases are in some way related to HP
- The only good *H. pylori* is a dead *H. pylori*!!

HP 2010: Benefits of Identification and Eradication Less Clear

- **Helicobacter now account for < 80% of non-NSAID duodenal ulcers**
 - 20-45% of duodenal may ulcers recur despite successful eradication of HP
- **HP infection may reduce the severity and prevalence of GERD, Barrett's esophagus, and GERD-associated esophageal adenocarcinoma.**
- **Helicobacter gastritis potentiates the efficacy of both H2 receptor antagonists and PPI's**
- **HP infection may reduce the risk of childhood allergies, asthma, and modulate the gut-associated immune system**

Epidemiology

H. pylori Infection: Epidemiology

Routes of Transmission

- Usually acquired in childhood; chronic if not cleared or treated¹
- Fecal-oral, gastric-oral, oral-oral²

Risk Factors

- Infected family members, increased number of siblings³
- Crowded living conditions²
- Poor sanitation and hygiene²

Relationship With Socioeconomic Status

- More common in developing than developed countries⁴
- Decreasing prevalence in US and some world regions⁴

1. Logan RP, Walker MM. *BMJ*. 2001;323(7318):920-922; 2. Vale FF, Vitor JM. *Int J Food Microbiol*. 2010;138(1-2):1-12; 3. Garg PK, et al. *Epidemiol Infect*. 2006;134(3):450-459; 4. Chey WD, Wong BC. *Am J Gastroenterol*. 2007;102(8):1808-1825.

H. pylori Infection in the United States

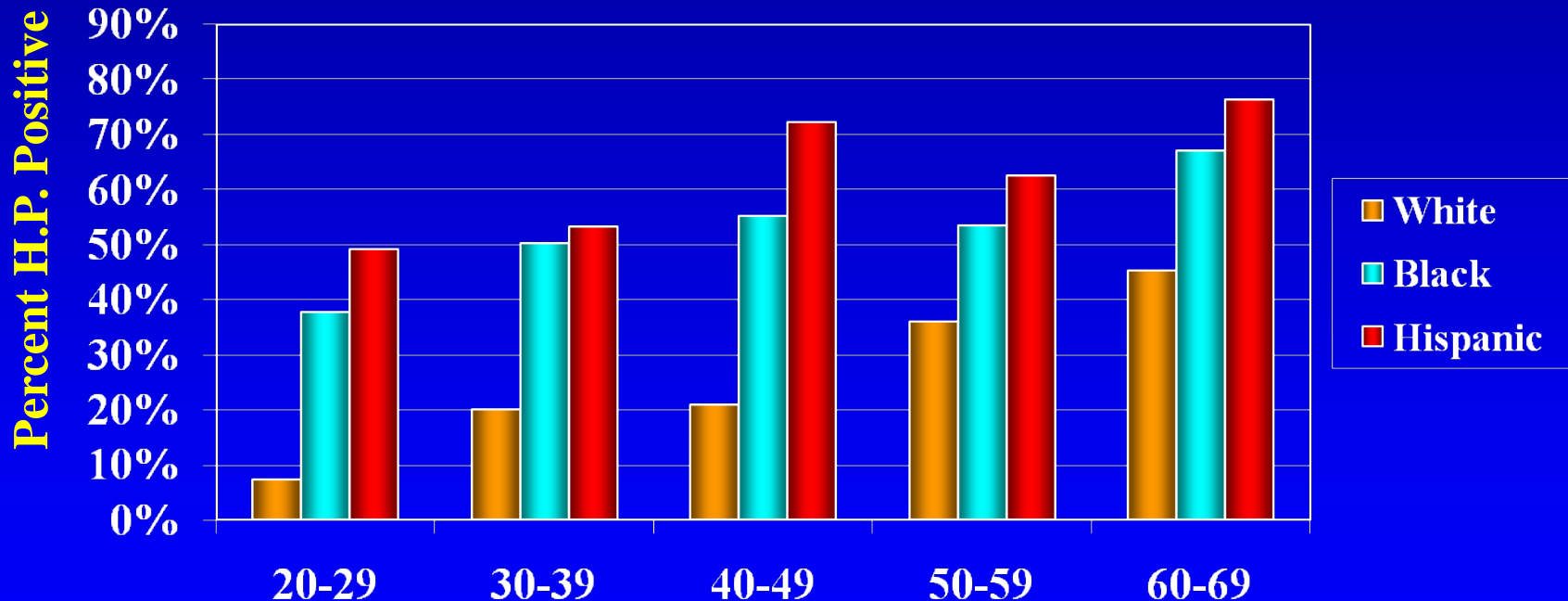
Race/Ethnicity	H. pylori Seropositivity (%)
Non-Hispanic white	18.4
Non-Hispanic black	46.2
Mexican-American	49.1
Other Hispanic	47.1
Other	34.5
Place of Birth	
Outside United States	56.3
United States	21.9

Data based on 7462 participants aged ≥ 3 years, National Health and Nutrition Examination Survey, United States, 1999–2000.

Cardenas VM, et al. *Am J Epidemiol.* 2006;163(2):127-134.

Helicobacter Prevalence Rates in USA: 1988-1991

7465 Patients tested for positive HP serology



Diseases Associated with Helicobacter Pylori Infection

- **Established Associations**
 - Duodenal Ulcer
 - Gastric Ulcer
 - Chronic Gastritis
 - Gastric MALT Lymphoma
 - Corpus and Antral Adenocarcinoma (achlorhydria)
- **Probable Associations**
 - Idiopathic thrombocytopenic purpura
 - Iron deficiency anemia
 - Uninvestigated dyspepsia

Pathophysiology

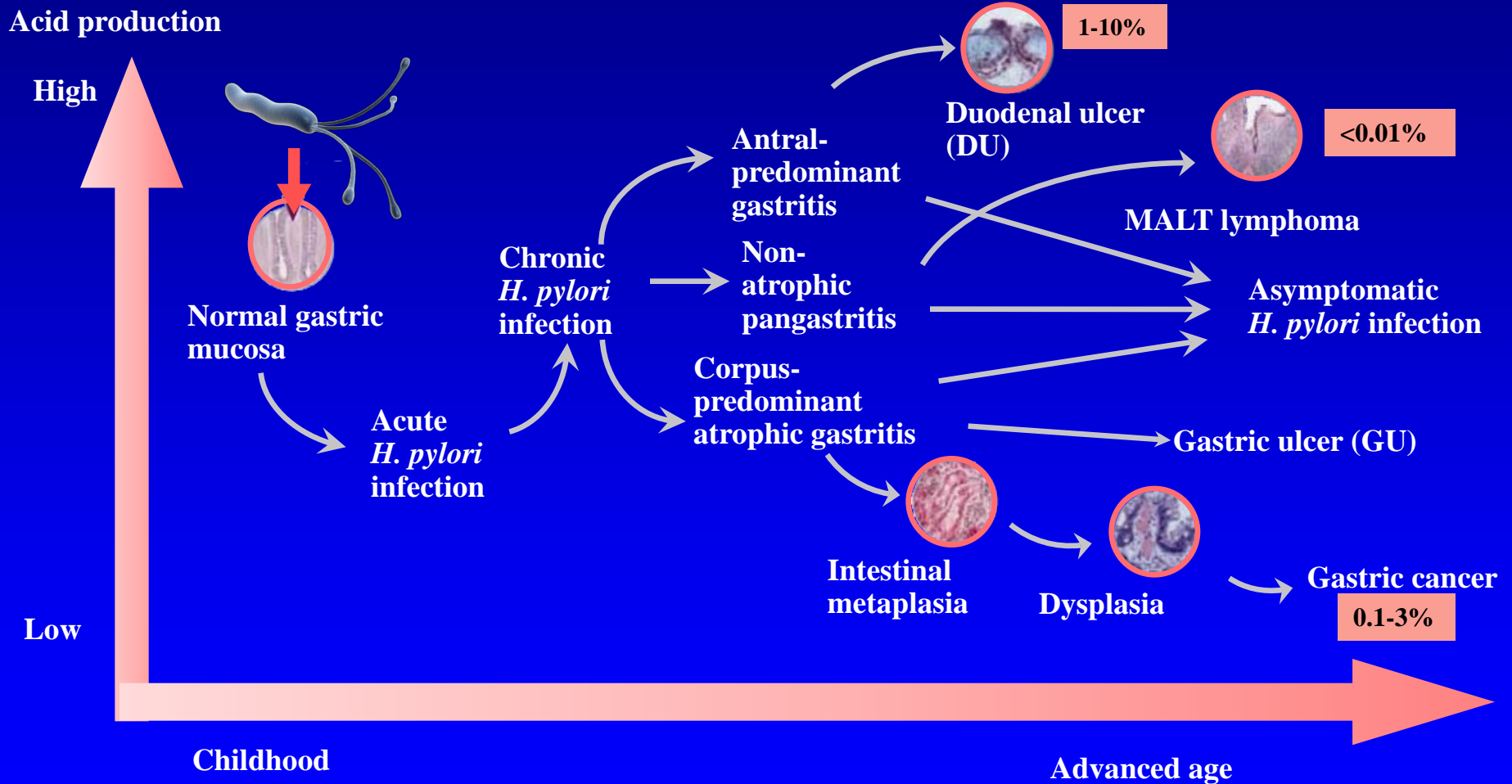
Helicobacter Infection Produces Both Hyperacidity and Hypochlorhydria

- Population studies indicate that gastric cancer and duodenal ulcers are essentially mutually exclusive phenomena even though *H. pylori* infection causes both.
- The acid profile of H.P. infection is determined by the distribution of the infection within the stomach and virulence factors in the HP genome

Possible Outcomes of Helicobacter Infection

- **Chronic mild pan-gastritis without atrophy/metaplasia and +/- normal gastric physiology**
 - Not associated with significant disease
- **Chronic, predominantly antral, gastritis with high acid secretion**
 - Up to 15% of patients with develop duodenal ulcers
- **Chronic diffuse gastritis with gastric atrophy and multifocal atrophic gastritis and intestinal metaplasia:**
 - At risk for gastric ulcer and gastric cancer

Natural History of *H. pylori* Infection



Diagnosis

Indications for *H. pylori* Testing

Established¹


- Peptic ulcer disease (PUD)
 - DU or GU
 - Recent or previous diagnosis
- Gastric MALT (B-cell) lymphoma (low and high grade)

Probable²⁻⁴

- Dyspepsia
 - Uninvestigated²
 - Functional³
- Prior to long-term use of NSAIDs⁴

NSAID = non-steroidal anti-inflammatory drug.

1. Chey WD, Wong BC. *Am J Gastroenterol.* 2007;102(8):1808-1825; 2. Talley NJ, Vakil N. *Am J Gastroenterol.* 2005;100(10):2324-2337; 3. Moayyedi P, et al. *Cochrane Database Syst Rev.* 2006;(2):CD002096; 4. Lanza FL, et al. *Am J Gastroenterol.* 2009;104(3):728-738.

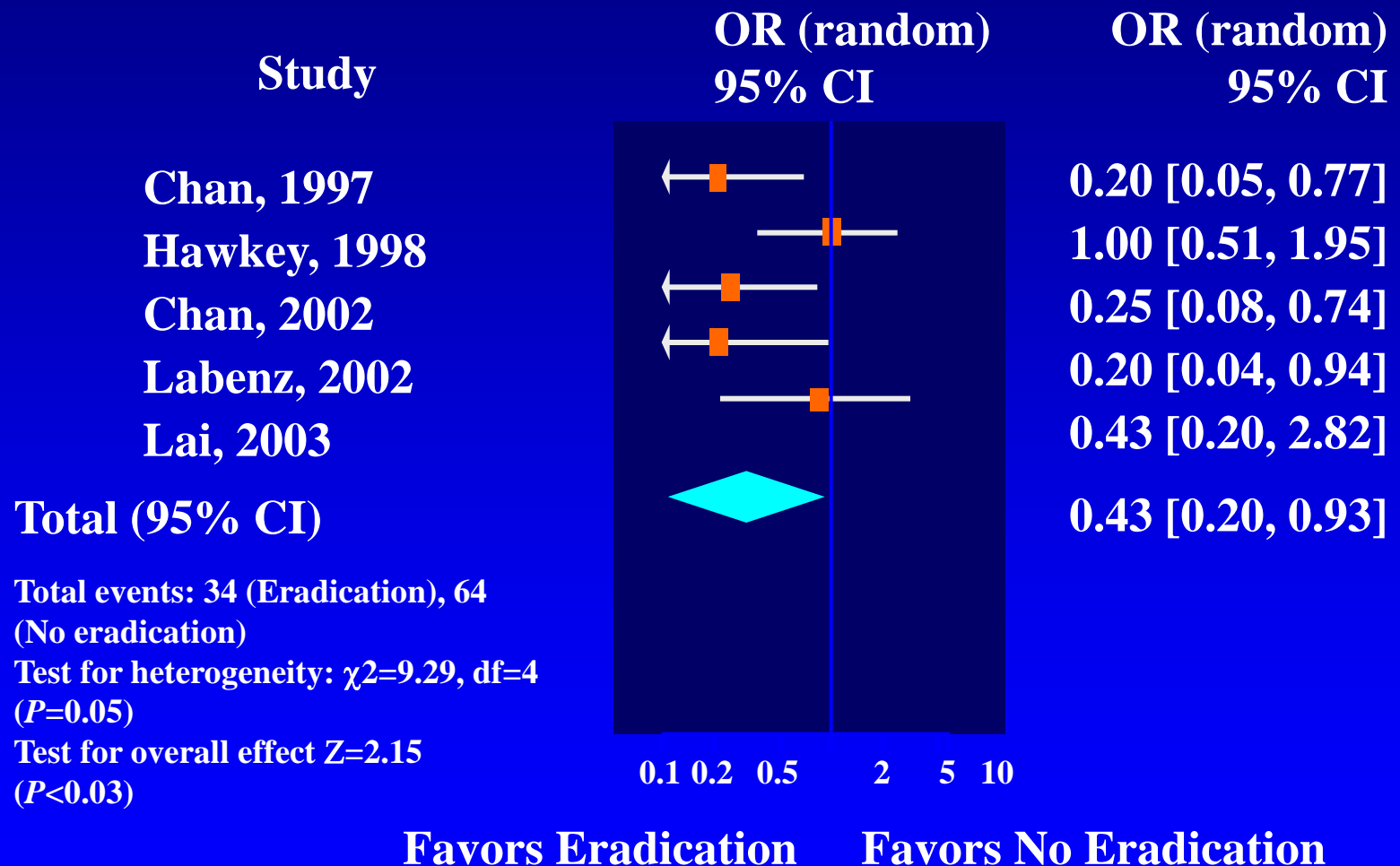


ACG Practice Guidelines on Preventing NSAID-related Ulcer Complications

- “*H. pylori* infection increases the risk of NSAID-related gastrointestinal (GI) complications”
- “There is potential advantage of testing for *H. pylori* infection and eradicating the infection if positive in patients requiring long-term NSAID therapy”
- “All patients regardless of risk status who are about to start long-term traditional NSAID therapy should be considered for testing for *H. pylori* and treated, if positive*”

* Level of evidence = 2 (Favors recommendation); Strength of recommendation = A (Strong evidence for multiple published, well-controlled randomized trials or a well-designed meta-analysis)

H. pylori Eradication Reduces Risk of Ulcers in NSAID Users



Other Reasons to Consider Testing for *H. pylori* Infection

- Family history or ethnicity with high risk of gastric cancer¹
- Otherwise unexplained iron deficiency anemia¹
- Idiopathic thrombocytopenic purpura¹
- Prior to bariatric surgery³
- Prior to long-term proton pump inhibitor (PPI) use for non-GERD dyspepsia¹

1. Malfertheiner P, et al. *Gut*. 2007;56(6):772-781; 2. Axon AT. *Aliment Pharmacol Ther*. 2000;14(suppl 3):1-6; 3. Ramaswamy A, et al. *Arch Surg*. 2004;139(10):1094-1096.

Diagnosis of HP Infection

- Testing for HP should only be performed if the clinician plans to offer treatment for a positive results.
- The choice of tests relies heavily upon whether upper endoscopy is required

Methods of Testing for *H. pylori* Infection

	Active Infection	History of Exposure
Endoscopic	<ul style="list-style-type: none"> • Biopsy urease test • Histology • Culture 	—
Non-endoscopic	<ul style="list-style-type: none"> • Urea breath test (UBT) <ul style="list-style-type: none"> — ^{13}C — non-radioactive 	

ACG Practice Guidelines

- In populations with a low pretest probability of *H. pylori* infection, non-endoscopic tests such as the UBT and stool antigen test offer superior positive predictive value compared with antibody tests.

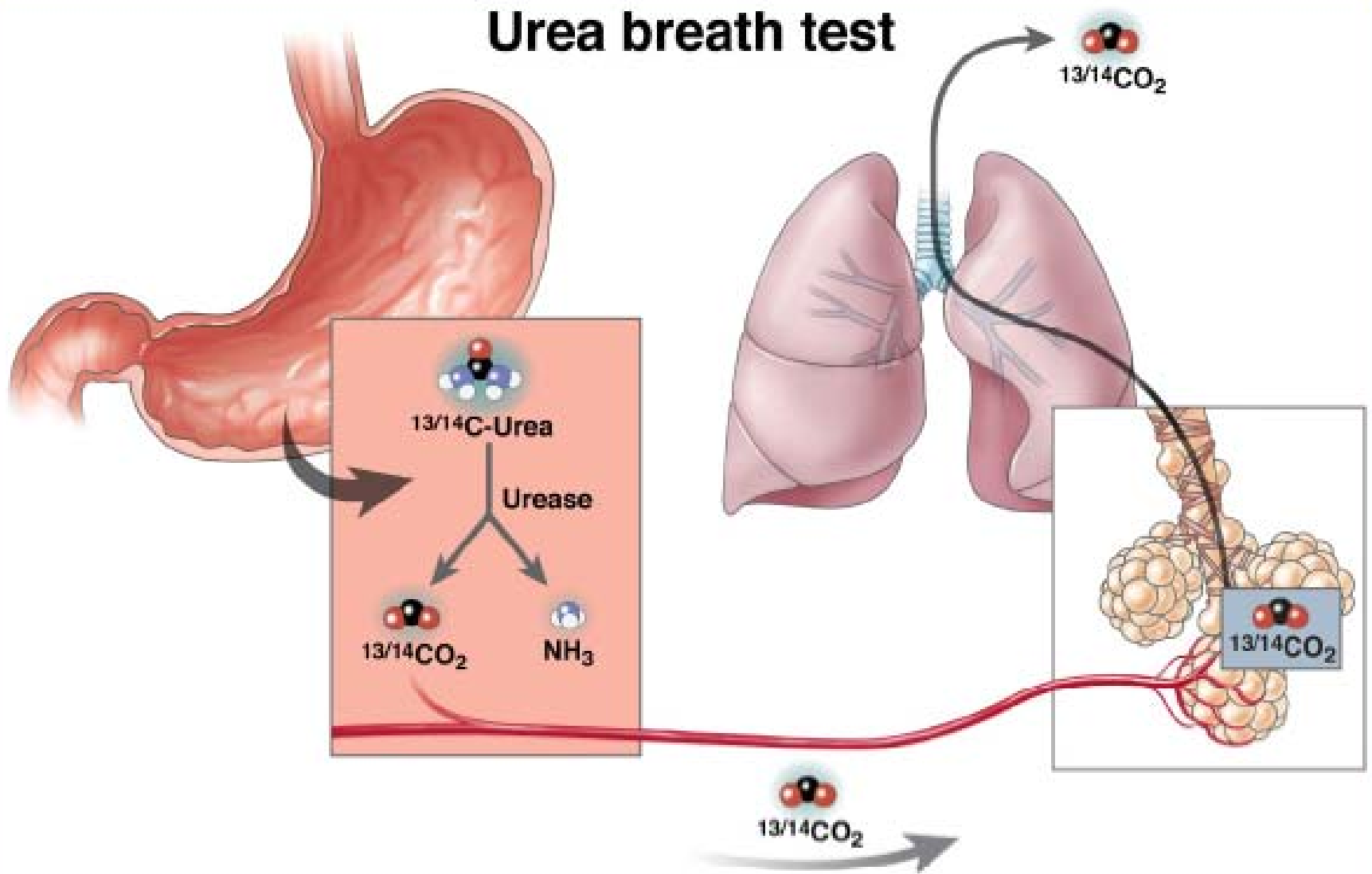
Diagnosis of HP Infection

- Serology: Whole blood or serum ELISA to detect Iga or IgG antibodies
 - Relatively Inexpensive (\$90 per correct diagnosis)
 - Sensitivity 85-90% Specificity 79%
 - Overall accuracy only 80-84%
 - The PPV varies significance with HP prevalence
 - **Impractical test for documenting eradication:**
 - Titers drop by 50% at three month and undetectable at 18 months after eradication in 60-100%

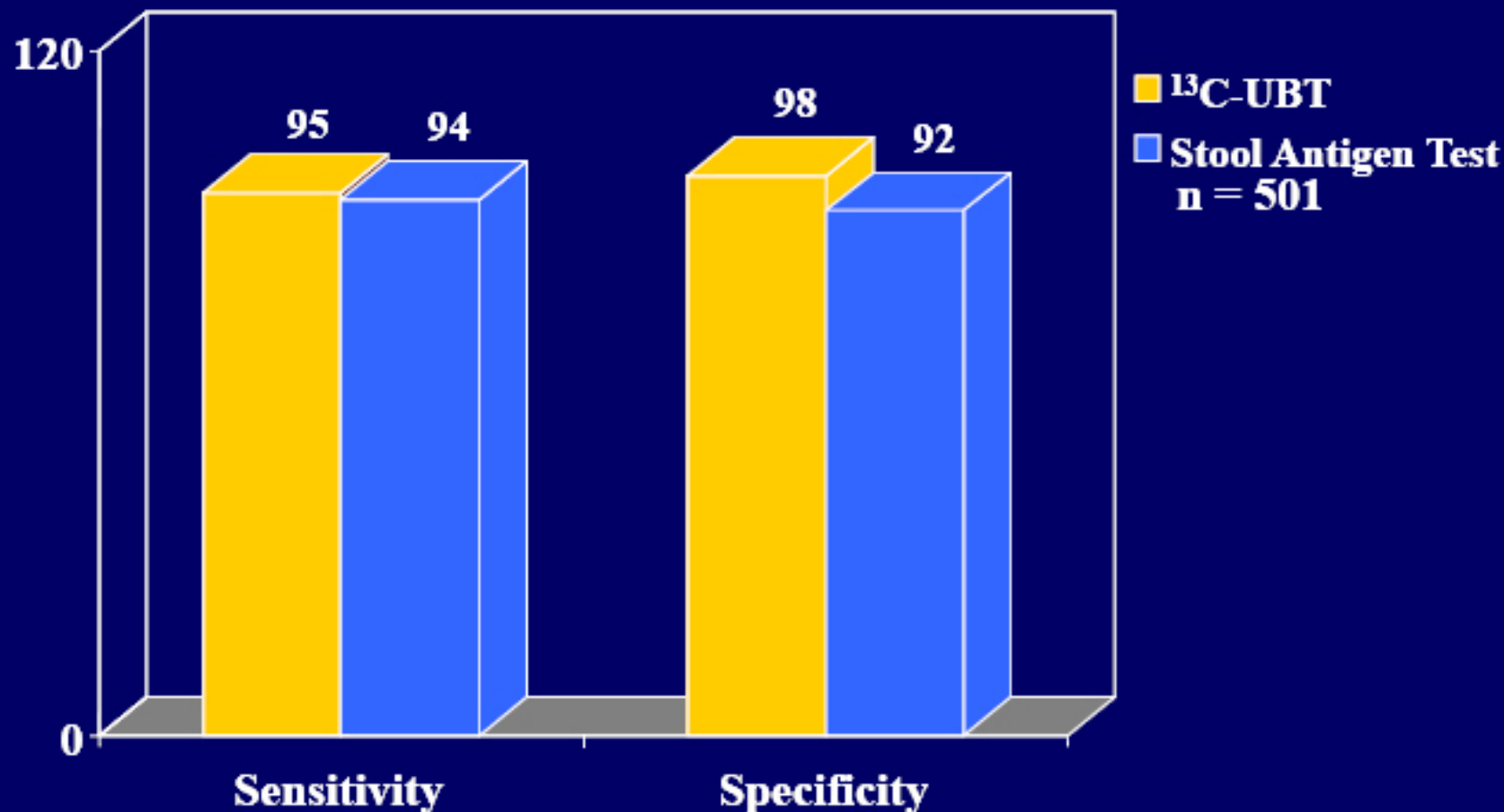
Diagnosis of HP Infection

- C-14 or C-13 Urea Breath Test
 - Sensitivity 88-98%
 - Specificity 95-100%
 - False negatives with bismuth, PPI, antibiotics
 - No antibiotics 4 weeks, no PPI for 2 weeks
- Stool Antigen (enzyme immunoassay)
 - Sensitivity 94%
 - Specificity 89-92% Accuracy 93%
 - Most useful in documenting eradication
 - Similar false negatives to UBT

Urea breath test



Urea Breath Test or Stool Antigen Test for *H. pylori* Infection



Vaira D, et al. *Gut*. 1999;45(supp1):I23-I27

Sensitivity and Specificity of Tests for *H. pylori*

	UBT (BreathTek®) ^{1,2}	Stool (HpSA™) ¹	Endoscopic Biopsy ³ (routine histology)	Serology (ELISA) ¹
Sensitivity	95%	93%	93%	85%
Specificity	90%	93%	90%	79%

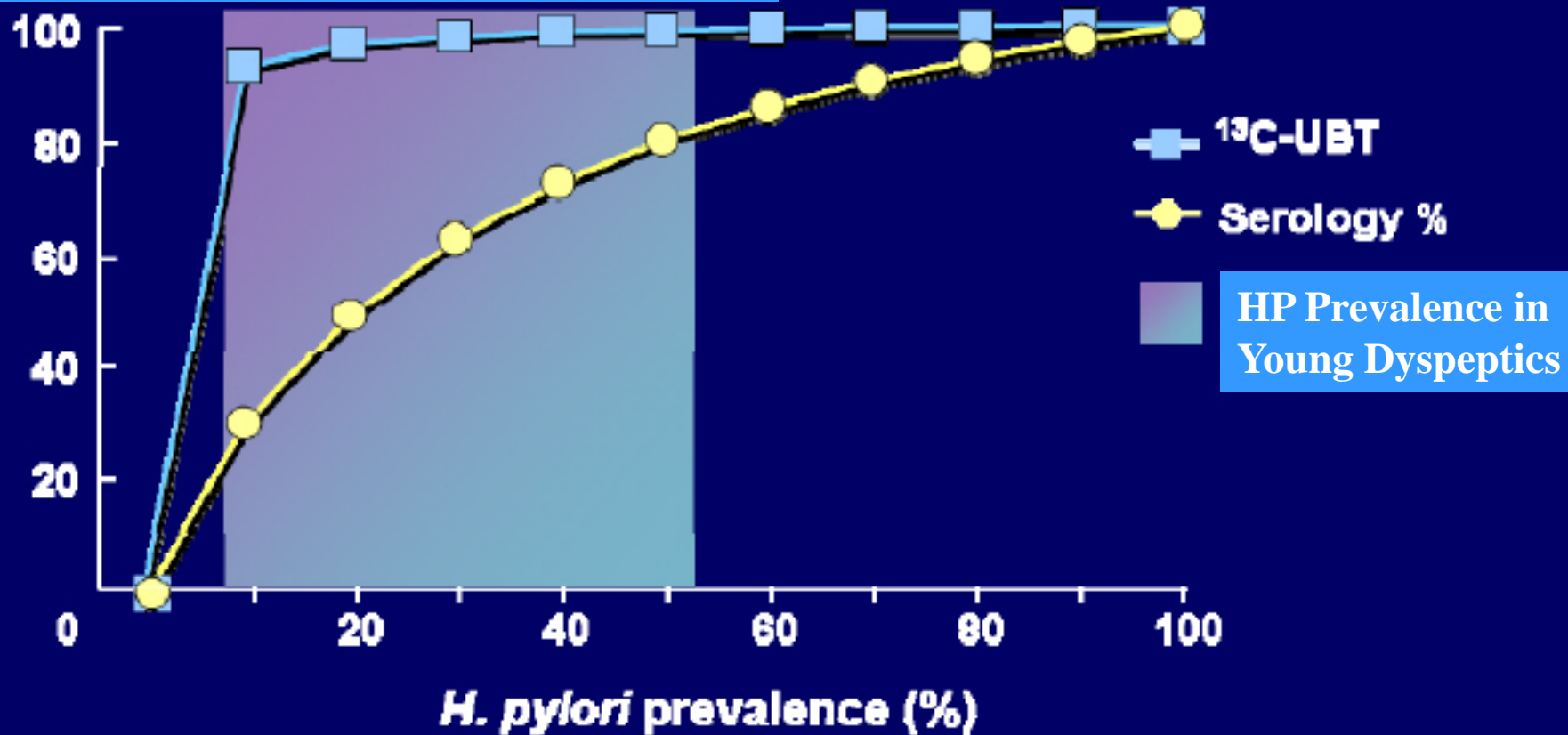
Compilation of data is not the result of a comparative study.

ELISA = enzyme-linked immunosorbent assay.

Vaira D, Vakil N. *Gut*. 2001;48(3):287-289 ; 2. BreathTek® UBT Package Insert; 3. Maconi G, et al. *Aliment Pharmacol Ther*. 1999;13(3):327-331.

Positive predictive value of test *vs H. pylori* prevalence

Positive Predictive Value (%)



Non-endoscopic Tests for *H. pylori*: Summary

Test	Advantages	Disadvantages
Serology	<ul style="list-style-type: none">• Widely available• Least expensive of available tests	<ul style="list-style-type: none">• Positive results may reflect previous rather than current infection• Not recommended for confirming eradication
Urea breath test	<ul style="list-style-type: none">• High negative and positive predictive values• Useful before and after treatment	<ul style="list-style-type: none">• False negative results possible in the presence of PPIs or with recent use of antibiotics or bismuth preparations• Considerable resources and personnel required to perform test
Stool antigen test	<ul style="list-style-type: none">• High negative and positive predictive values with monoclonal-antibody test• Useful before and after treatment	<ul style="list-style-type: none">• Process of stool collection may be distasteful to patient• False negative results possible in the presence of PPIs or with recent use of antibiotics or bismuth preparation

Treatment

FDA-approved PPI-containing Triple Regimens for *H. pylori* Infection

PPI	Antibiotics	Duration (days)
Omeprazole 20 mg bid	Clarithromycin 500 mg bid Amoxicillin 1000 mg bid	14
Lansoprazole 30 mg bid	Clarithromycin 500 mg bid Amoxicillin 1000 mg bid	10 or 14
Rabeprazole 20 mg bid	Clarithromycin 500 mg bid Amoxicillin 1000 mg bid	7
Esomeprazole 40 mg qd	Clarithromycin 500 mg bid Amoxicillin 1000 mg bid	10

Treatment Regimens

- **First-line, treatment of choice: Triple Rx**
 - PPI bid for 10-14 days
 - Clarithromycin 500 bid for 10-14 days
 - Amoxicillin 1000 mg bid for 10-14 days
- For penicillin-allergic patients substitute metronidazole 500 mg for amoxicillin
- **Quadruple Therapy**
 - Bismuth subcitrate 525 mg qid,
 - Metronidazole 500 qid,
 - Tetracycline 500 qid,
 - PPI bid for 14 days (94-98%)

HP Therapies Failure Rate 20-25%

Author/ reference/ year	Regimen										Duration of therapy (days)	Intent to treat Eradication Rate	95% CI
	A	C	T	B	M	E	O	L	P	R			
Laine 15/1998	●	●					●				10	75%*	(70 - 81)
Fennerty 16/1998	●	●						●			10	81%	(74 - 88)
	●	●						●			14	82%	(74 - 88)
Laine 13/2000	●	●				●					10	78%*	(70 - 85)
Laine 14/2003			●	●	●		●				10	88%	(82 - 93)
	●	●					●				10	83%	(77 - 90)
Bochenek 17/2003	●	●							●		7	65%*	(57 - 73)
		●			●				●		7	77%*	(69 - 84)
Vakil 18/2004	●	●								●	7	77%	(71 - 83)
	●	●								●	10	78%	(72 - 84)
	●	●					●				10	73%	(67 - 79)

General Principles for *H. pylori* Eradication in the Era of Resistance

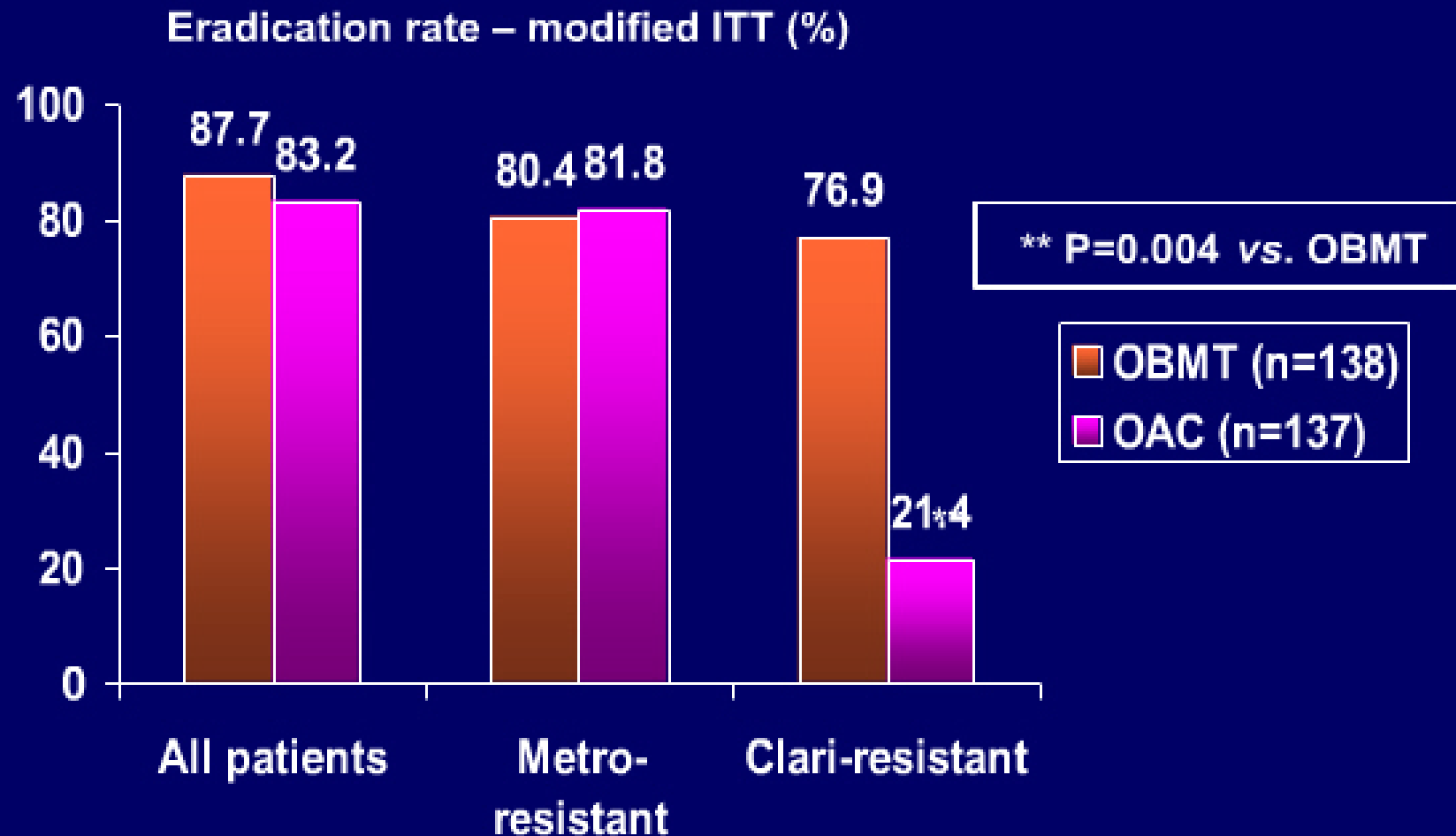
- Antibiotic resistance is thought to be the cause of failure in 20%–50% of 1st attempts to eradicate *H.P.*
- Clari-R is absolute: Clari-R rates rising: up to 20%
 - Cannot be overcome with increasing dose or duration
- Because Clari-R is absolute, avoid using clarithromycin in patients with any prior macrolide exposure (azithromycin, erythromycin, clarithromycin)
Graham DY, Fischbach L. *Gut*. 2010;59(8):1143-1153.
- Metronidazole-R as high as 66% but does not appear to significantly impact efficacy of triple therapy

Clarithromycin and Metronidazole:

Any previous exposure increases resistance

- 125 pts infected with *Hp* from Alaska
 - 30% Clari-R, 66% Metro-R, 29% Dual-R
 - Clarithromycin resistance
 - » Previous macrolide 92% in those with Clari-R vs. 57% in those with Clari-S ($p < 0.001$)
 - » Likelihood of resistance related to number of courses of macrolide
 - » Rx failed in 77% with Clari-R vs 13% with Clari-S strains
 - Metronidazole resistance
 - » Previous Rx 60% vs. no previous Rx 10% ($p < 0.001$)
 - » Rx failed in 11% with Met-R vs 38% with Met-S strains

“Single-triple” capsule & PPI or triple therapy for *H. pylori* infection



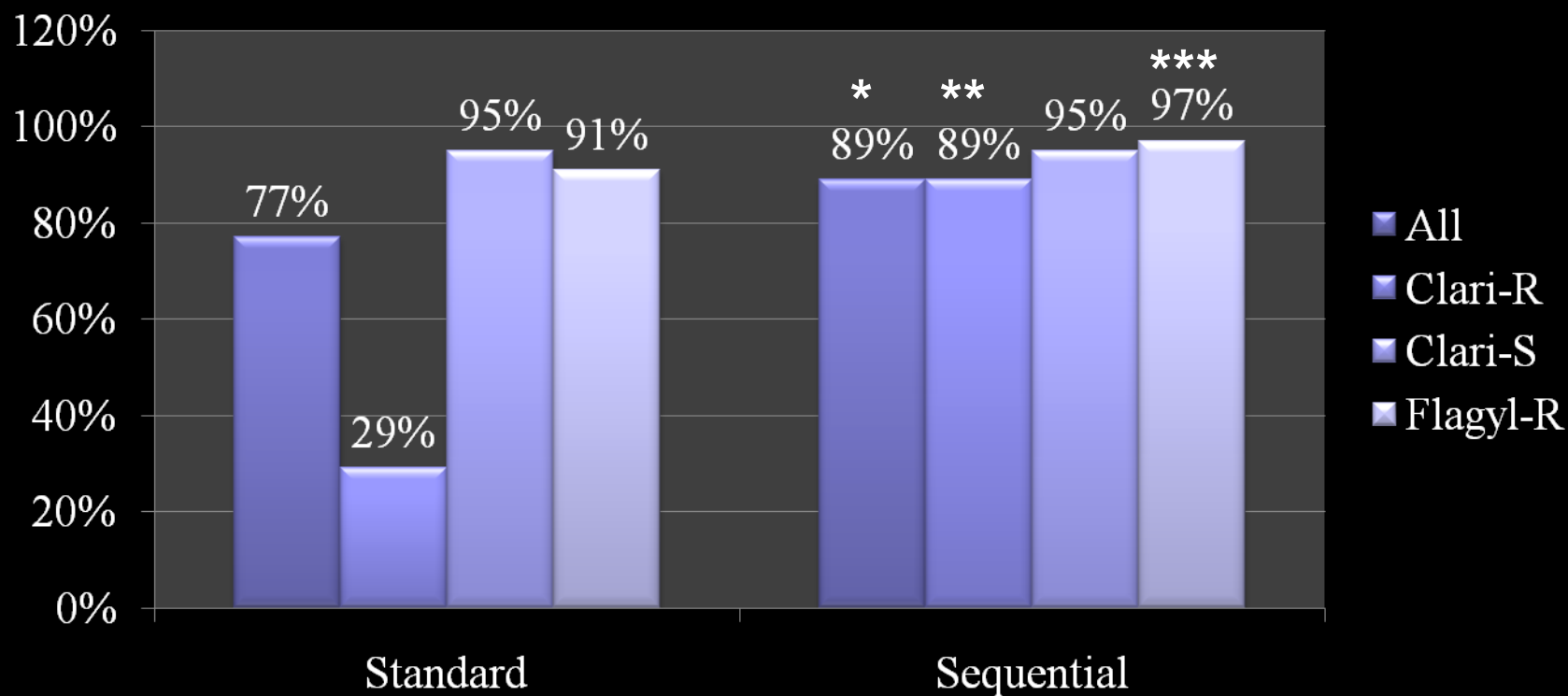
Sequential Therapy

- Randomized trial of pantoprazole 40 bid with amoxicillin 500 bid for 5 days followed by pantoprazole 40 bid/ clarithromycin 500 bid/ tinadazole 500 bid for 5 days vs standard 10 day PPI/ clarithromycin/ amoxicillin
- 16.9% clarithromycin resistant
- 28% metronidazole resistant 4% Clari/Metro Resistant

	<u>Sequential</u>	<u>Standard</u>
• Eradication	91%	78%
• Clarithromycin-resistant	88.9%	28.6%
• Flagyl-resistant	97%	90.9%

Sequential vs Triple Therapy

Successful Eradication of Helicobacter Pylori



* All pt $p=0.013$

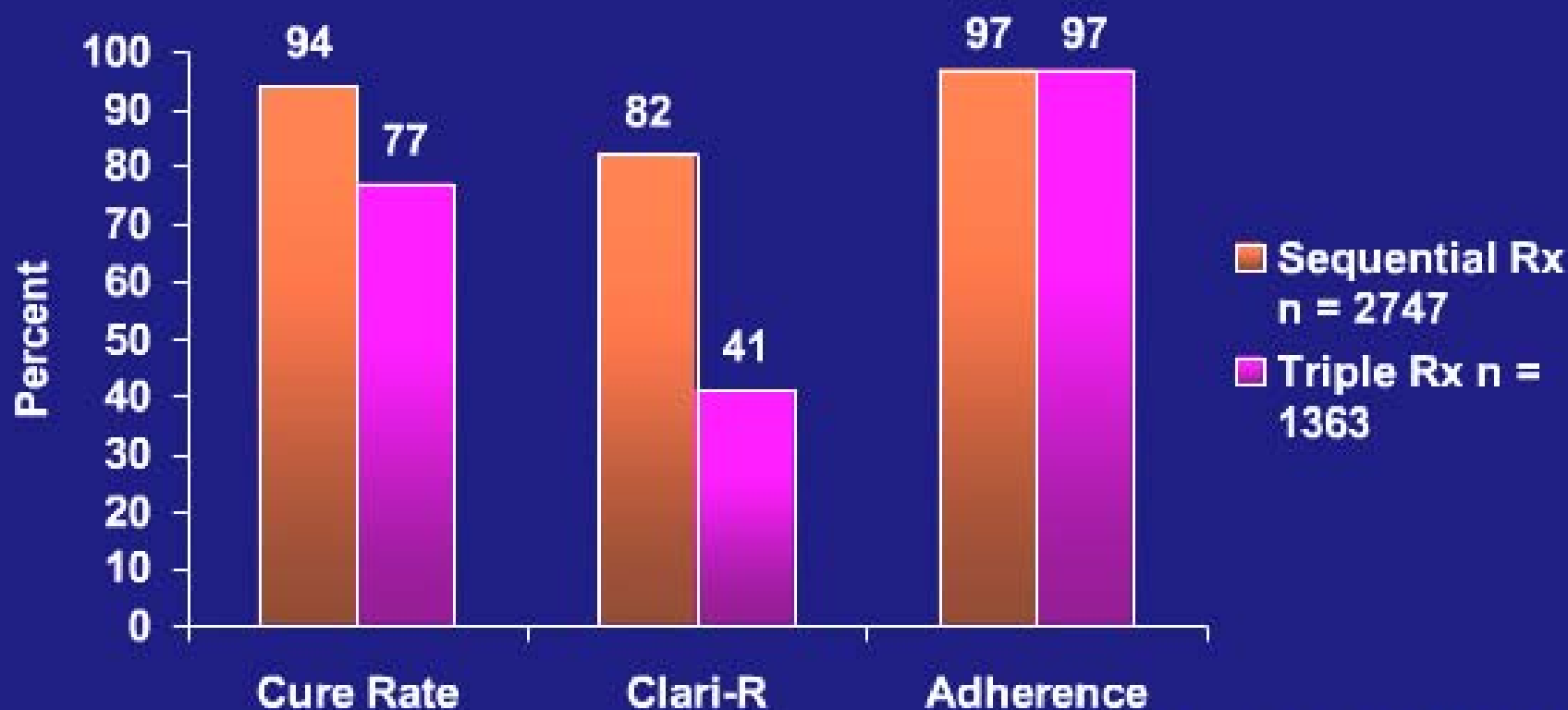
** Clari-R $p=0.003$

** Flagyl-R $p=0.557$

Ann. Int Medicine 2007;146:556

Meta-analysis of Sequential vs. Triple therapy for *H. pylori*

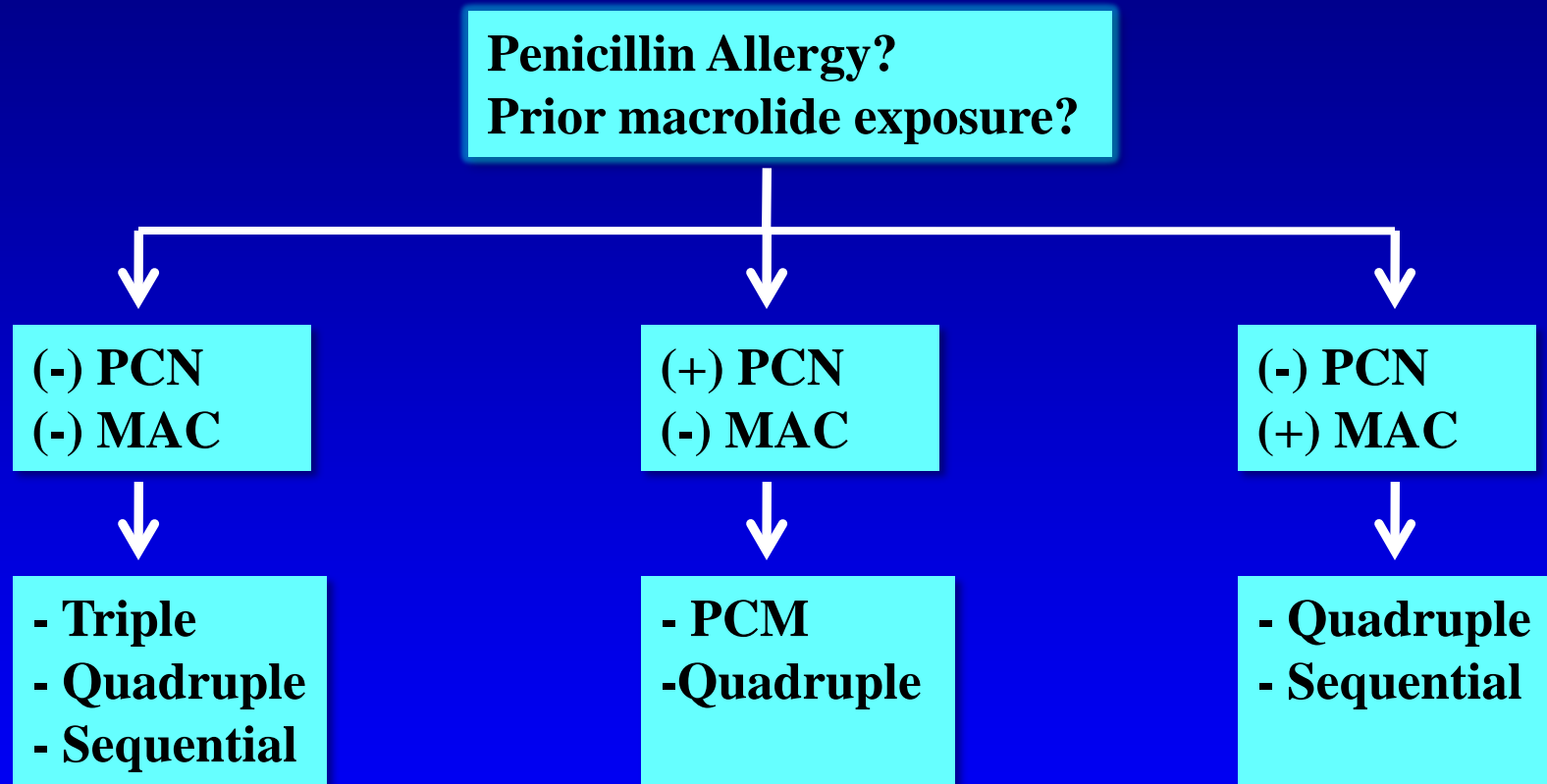
- 10 RCTs
- Publication bias, only 1 DB, most Italian



Sequential Therapy for *Helicobacter pylori*

- Bottom line: Sequential therapy is at least as good and may be superior to triple therapy.
- Greatest benefit appears to be in those with Clari-R *Hp*
- Not clear if drugs need to be given sequentially
- Complexity is a concern
- Sequential therapy requires validation in the US before it can be recommended as standard first-line therapy

Choosing First-line Therapy of HP



Importance of Post-treatment Testing for *H. pylori* Eradication

- ACG recommends routine post-treatment testing in patients with
 - *H. pylori*-associated ulcers
 - Persistent dyspepsia
 - Gastric MALT lymphoma
 - Post resection of early gastric cancer
- Perform testing ≥ 4 weeks after treatment completion
- Test of active infection is preferred when endoscopic follow-up is unnecessary (Breath test or fecal antigen)
- Avoid serologic testing in the post-treatment setting
 - Results can remain positive for years after successful eradication

Salvage Treatments for Persistent HP

Salvage Therapies for Persistent *H. pylori* infection

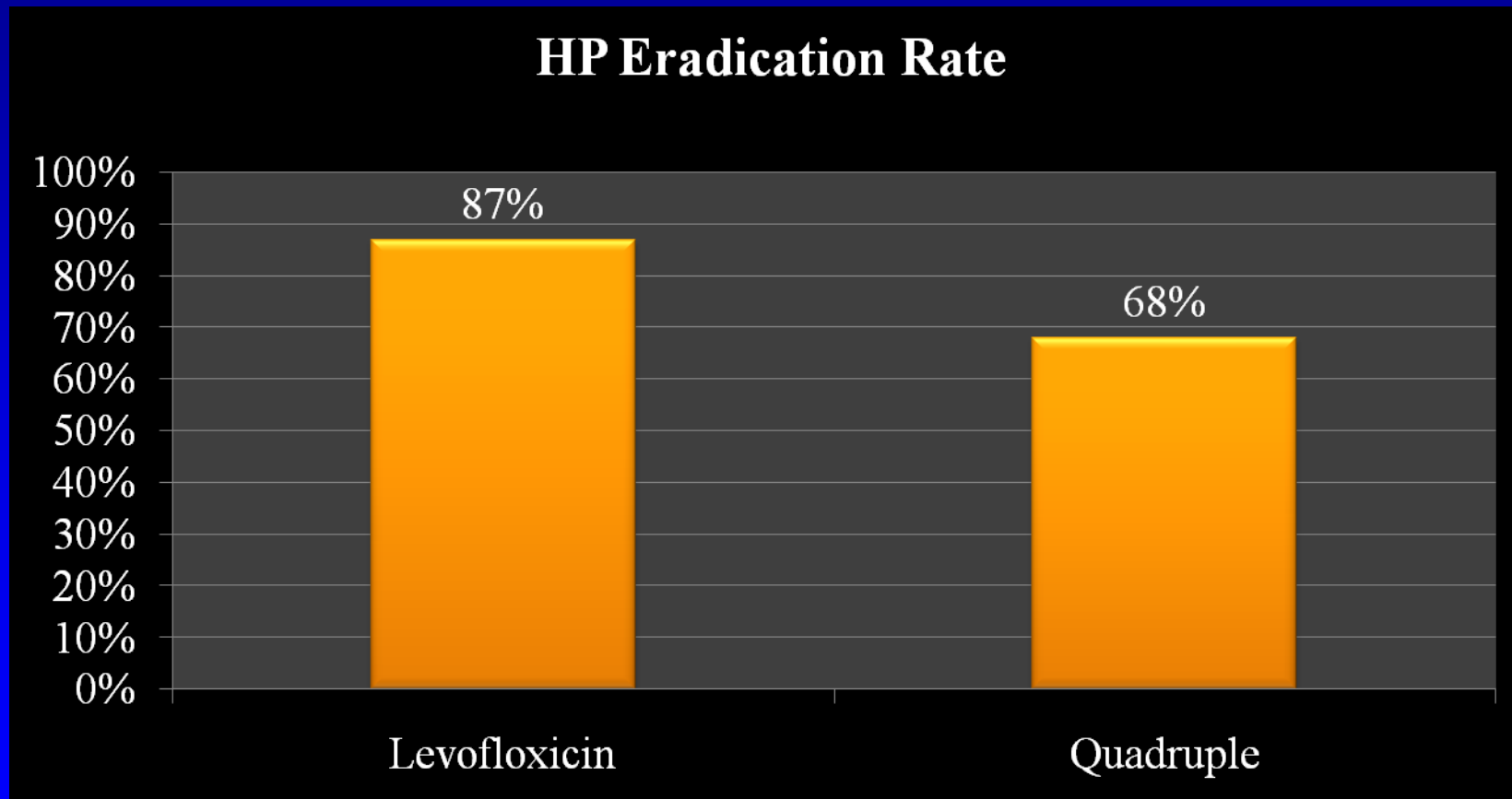
Bismuth Quadruple Therapy	Frequency	Duration
PPI	QD	7-14 d.
Tcn, bismuth subsalicylate, metronidazole	QID	

Levofloxacin Triple Therapy		
PPI, Amoxicillin 1 gm	BID	10-14 d.
Levofloxacin 500 mg	QD	

Salvage Treatments for Persistent HP

- Meta-analysis of RCTs comparing levofloxacin-based triple salvage therapy (levofloxacin + amoxicillin + PPI) to bismuth-based quadruple salvage therapy
- Levofloxacin-based triple therapy was better tolerated than quadruple therapy with a lower incidence of side effects
- Levofloxacin-based triple therapy demonstrated higher eradication rates with 10-day *versus* 7-day regimen (87% *vs* 68%)
- Eight trials (n = 477 patients) demonstrated no difference with 500 mg daily *versus* 250 mg b.i.d. dosing of levofloxacin

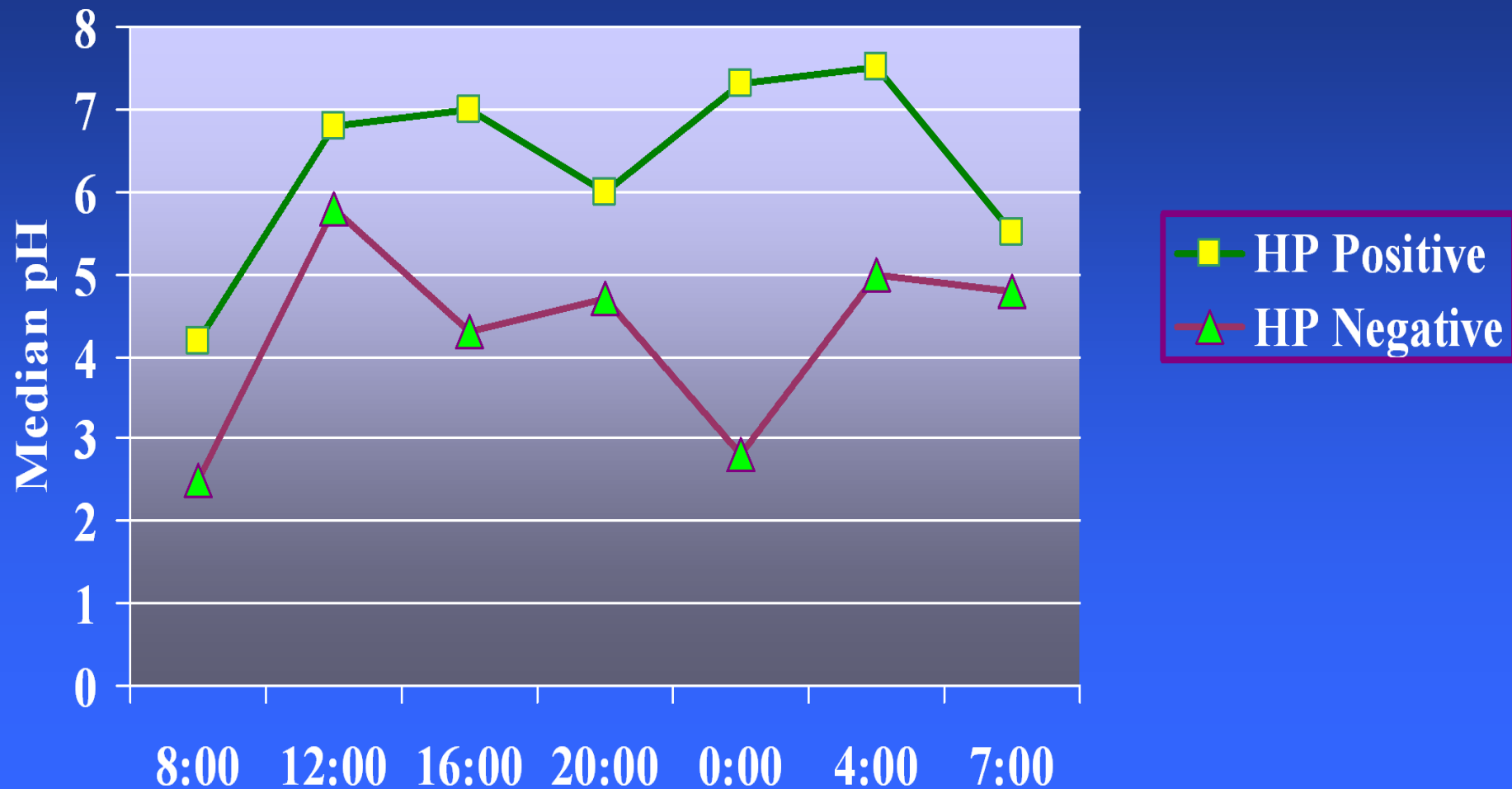
Salvage Rx: Levofloxacin Triple vs Quadruple Therapy



Effect of H.P. Status on Efficacy of Acid Suppression Medications

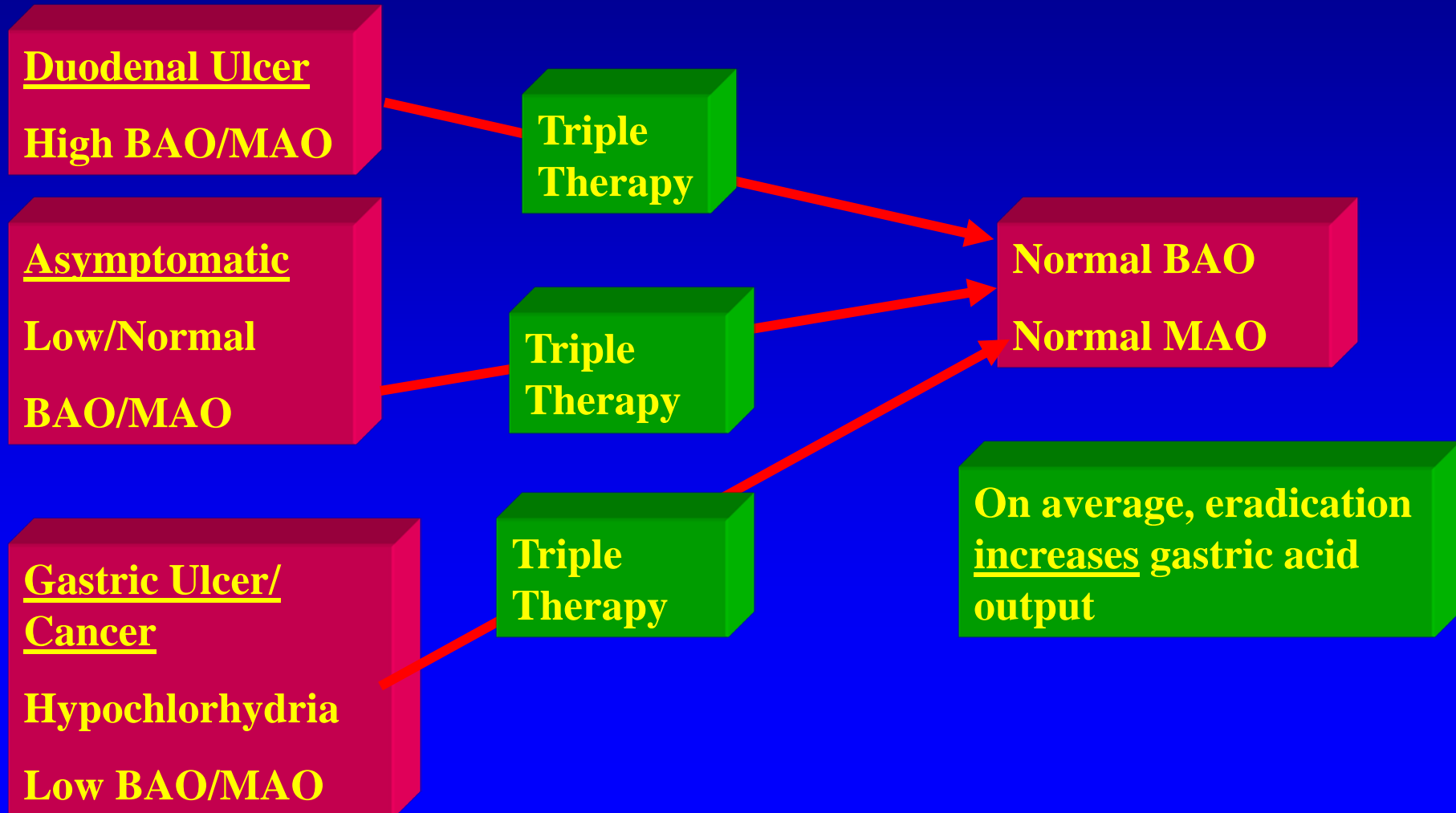
- Proton pump inhibitors produce significantly higher intra-gastric pH in H.P. positive patients vs. H.P. negative patients.
- Similar, but less pronounced, results also observed with H₂ receptor antagonists.
- The mechanisms responsible are partially understood.

Effect of HP Status on 24-Hour pH on Rabeprazole 20 mg./day



(Alim. Pharm. Therapeutics 2000; 14:1049-1056)

Effect of Helicobacter Eradication on Acid secretion

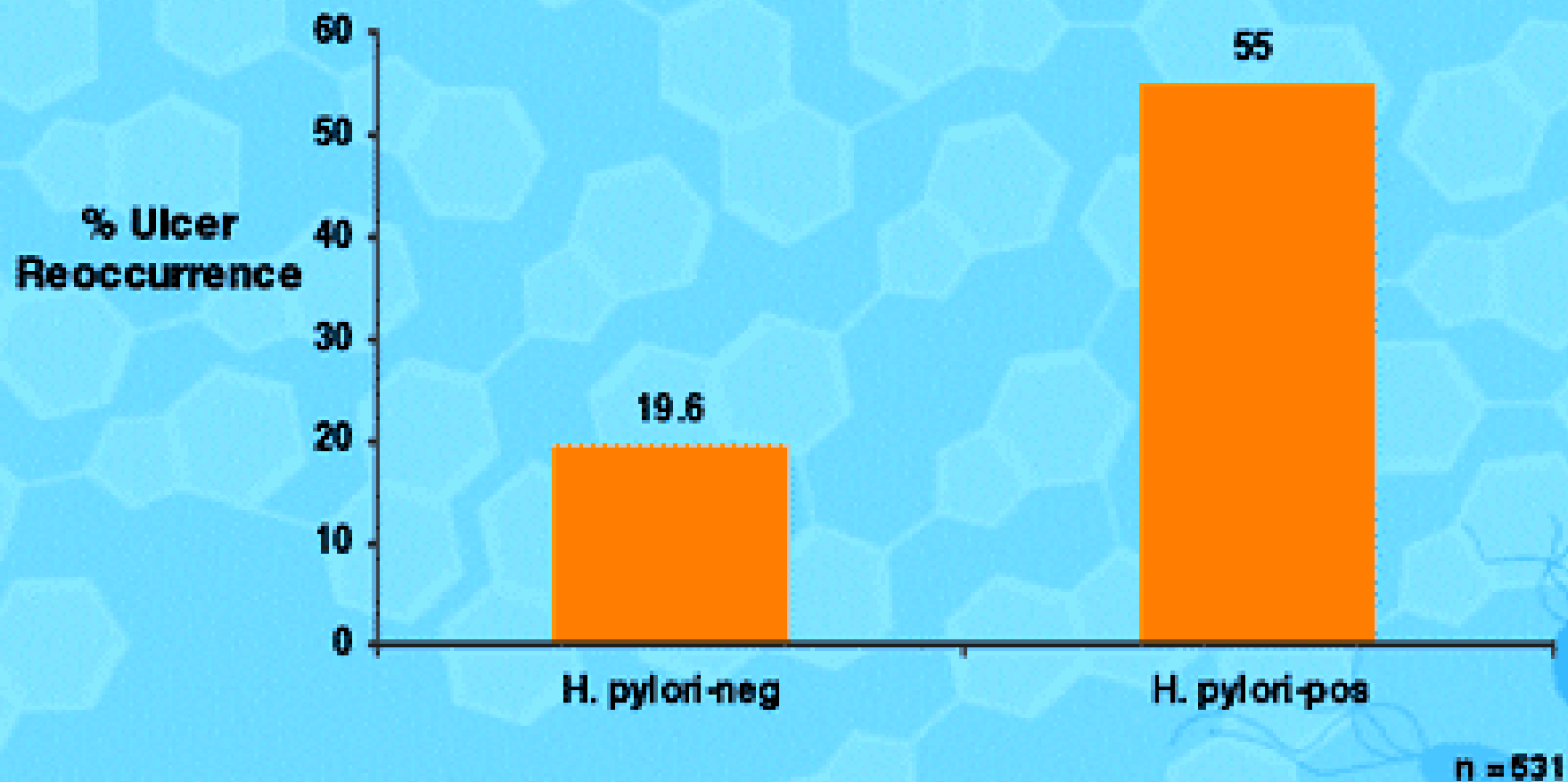


HP- Negative Duodenal Ulcers

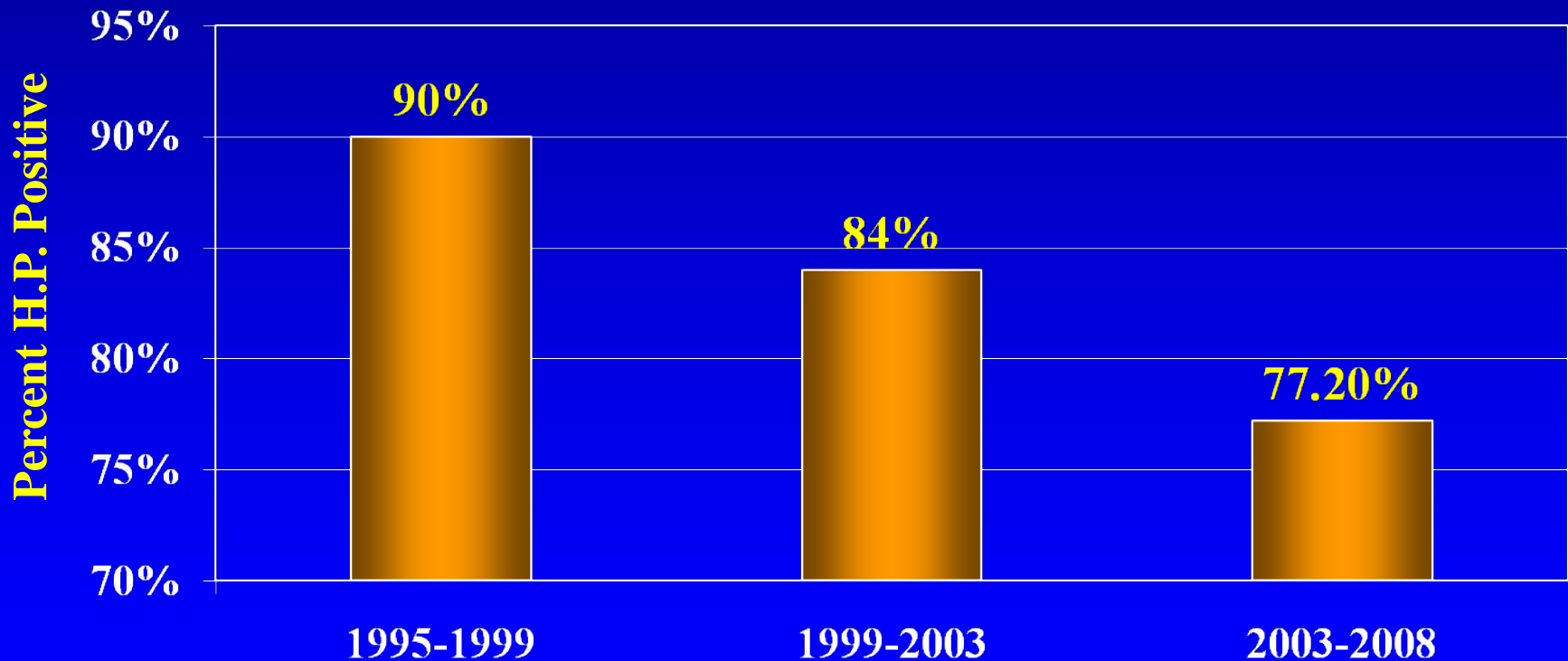
Declining Role of Helicobacter Pylori in Duodenal Ulcer

- The population prevalence of H. pylori is rapidly declining, 10% in US adults 18-30 years old, and it's role in ulcer disease also appears to be diminishing .
- In a recent multi-center study of 2900 duodenal ulcer subjects, 27% were “idiopathic”, i.e. not due to NSAIDS or H. Pylori. *Am. J Gastro.* 1999; 94:1834-40
- Several studies in the USA of patients with HP-positive duodenal ulcers demonstrate **19-45% ulcer recurrence despite successful eradication**

Ulcer Recurrence in the US After *H. pylori* Eradication: 6-Month Follow-up



Decreasing Helicobacter Prevalence in Duodenal Ulcers:1995-2008



Alimentary Pharmacology & Therapeutics. 2009;30(8):791-815.

Helicobacter Pylori-Negative Ulcers

- Characteristics of patients with HP-negative ulcers are incompletely understood
- Higher rates of ulcer complications occur in HP-negative ulcers even after adjusting for NSAID use
- These patients may represent non-ZE acid hypersecretors
- Long-term acid suppression may be indicated to prevent recurrence and complications

Helicobacter Pylori: 2004

- Diagnostic Tests
- HP and Duodenal Ulcer
- Treatment Regiments
- HP and functional dyspepsia
- HP and NSAID/ aspirin toxicity
- HP and gastric cancer

Dyspepsia

- **Uninvestigated dyspepsia**
 - Abdominal pain in which no objective test to identify etiology has been performed
- **Non-ulcer dyspepsia**
 - Ulcer-like symptoms in which testing has excluded peptic ulcer disease

Helicobacter and Functional Dyspepsia

- The issue of eradication of HP in functional dyspepsia remains an important controversy in GI
- 5 large well-designed prospective studies have been published; 3 showing no benefit and 2 showing benefit
- 2 recent meta-analyses published with discordant results

BMJ 2000; 321:659

Annals Int. Med 2001; 134:361

American Gastroenterological Association (AGA) Algorithm for the Management of Dyspepsia

Dyspepsia without GERD or NSAIDs

Age >55 or *alarm symptoms present*

EGD

EGD = esophagogastroduodenoscopy

Age ≤55 and
no alarm symptoms

Test for *Hp*

Negative

PPI trial 4–6 weeks

If fails

Reassurance,
reassess diagnosis

Consider EGD

Positive

Treat for *Hp*

If fails

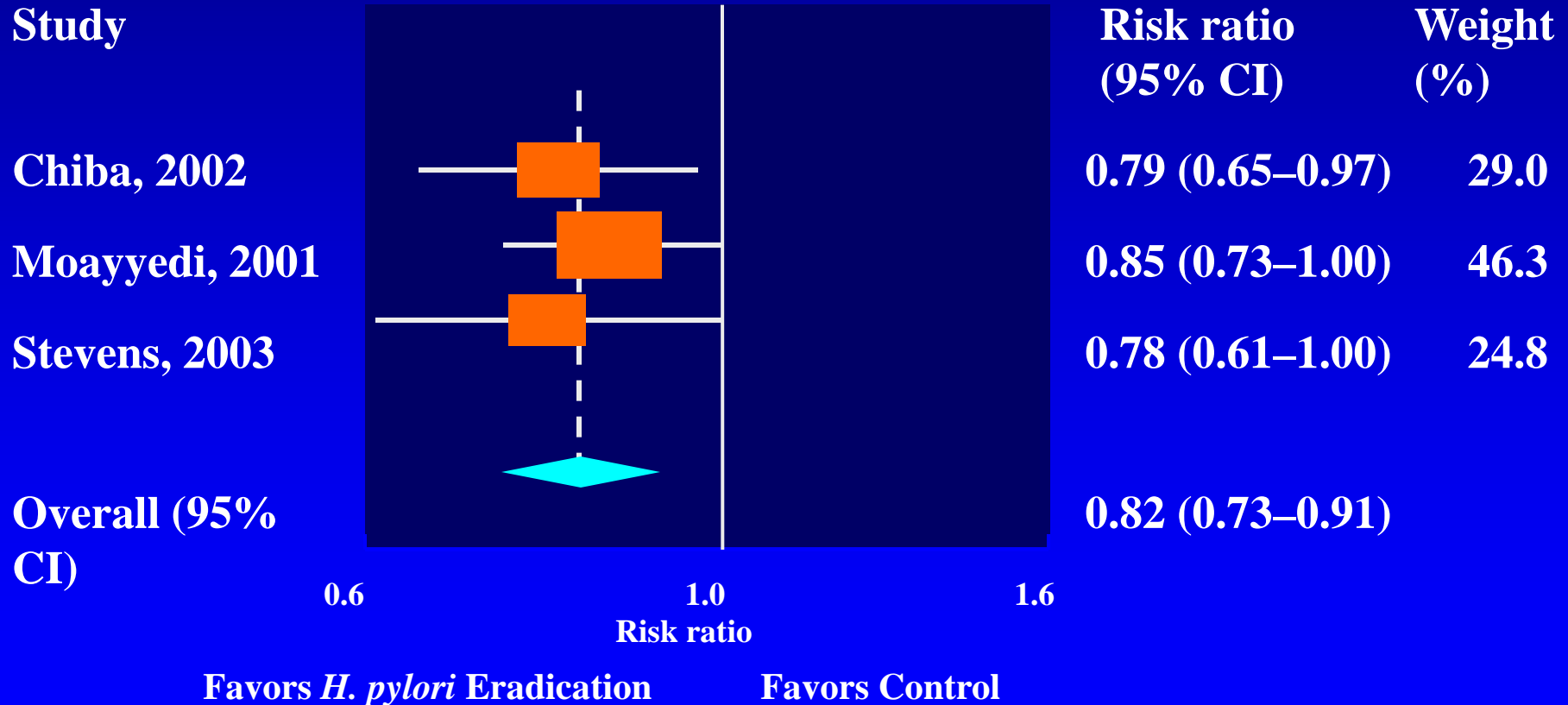
PPI trial 4 weeks

If fails

H. pylori testing should
be performed by a
¹³C-urea breath test
or stool antigen test

H. pylori Eradication Superior to Short-term Acid Suppression in Patients With Dyspepsia

Meta-analysis of RCTs



Helicobacter and Functional Dyspepsia

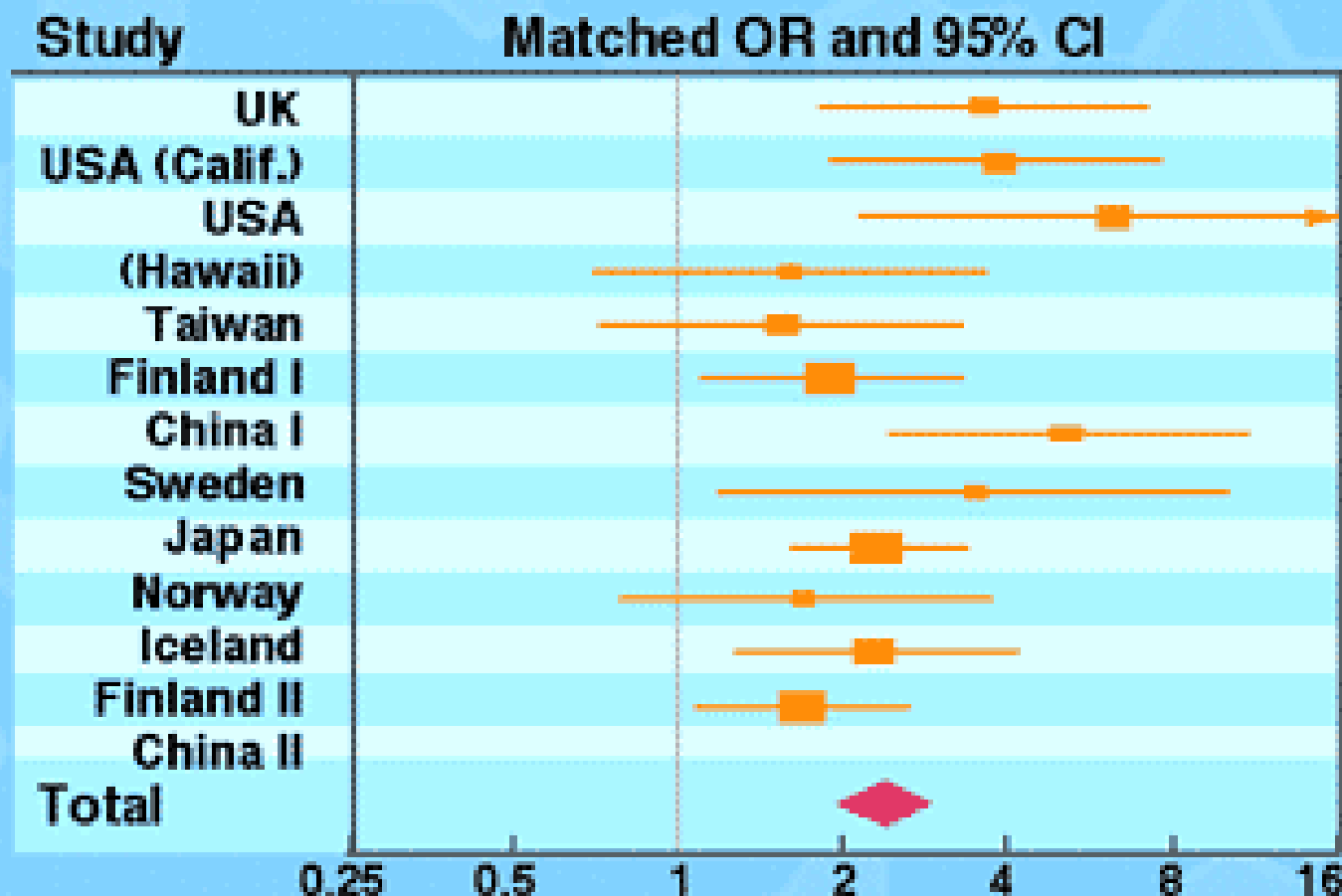
- Review of all well-designed studies indicates a statistically significant benefit in the successful eradication of HP in uninvestigated dyspepsia
- Unfortunately the magnitude of the benefit is small: 5-10% reduction in dyspepsia vs placebo
- The critical and unresolved issue is whether the marginal benefit of eradication of HP for dyspepsia is sufficient to justify therapy in all patients

Helicobacter Pylori: 2004

- Diagnostic Tests
- HP and Duodenal Ulcer
- Treatment Regimens
- HP and functional dyspepsia
- HP and Gastric Cancer
- HP and NSAID/ aspirin toxicity

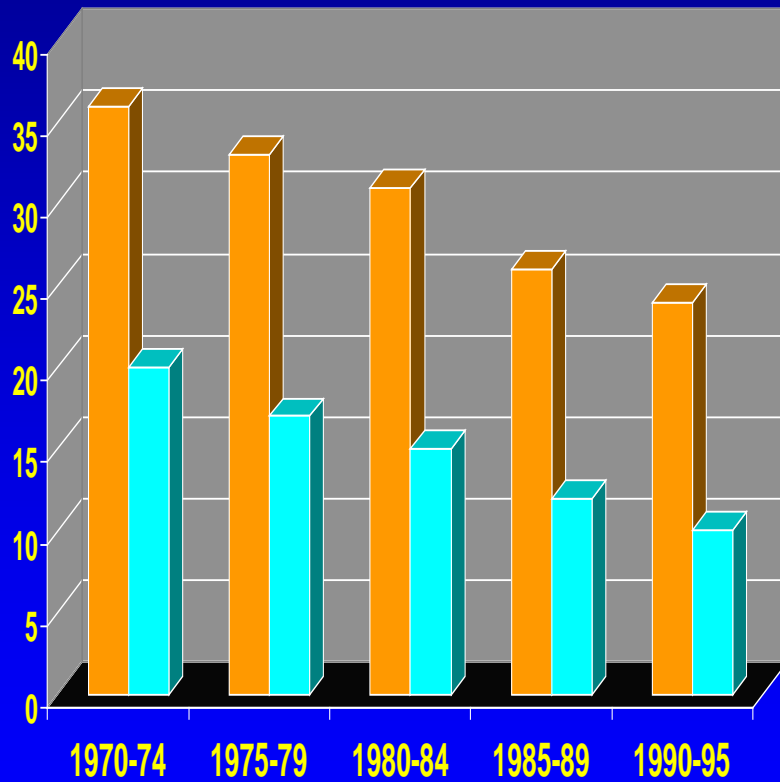
What Is the Relationship Between H. Pylori and Gastric Cancer?

H. pylori and Risk of Gastric Cancer



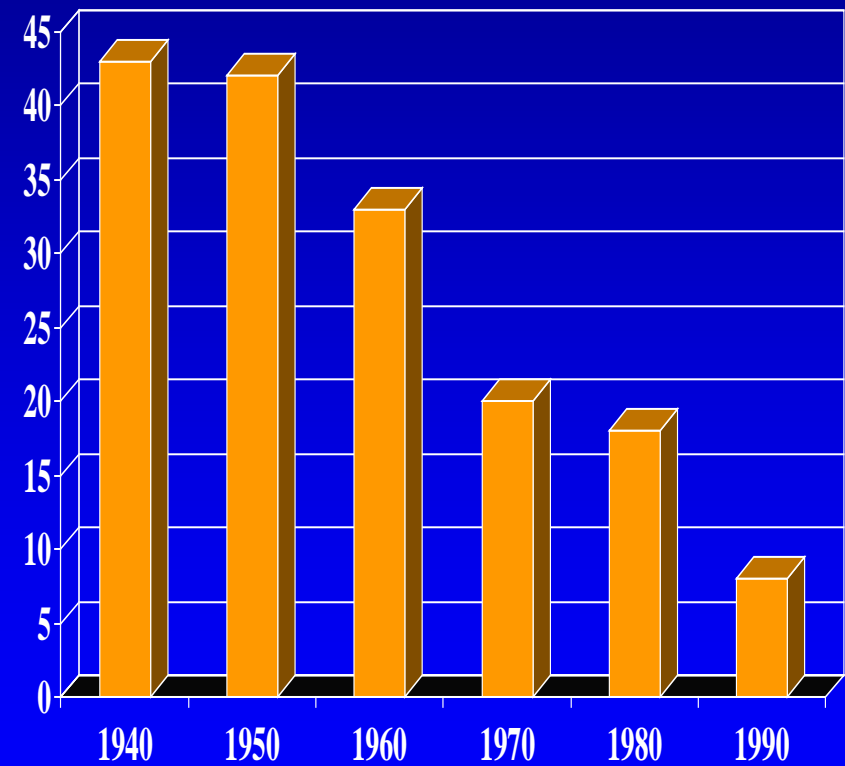
Distal Gastric Cancer

Incidence 1970-1995



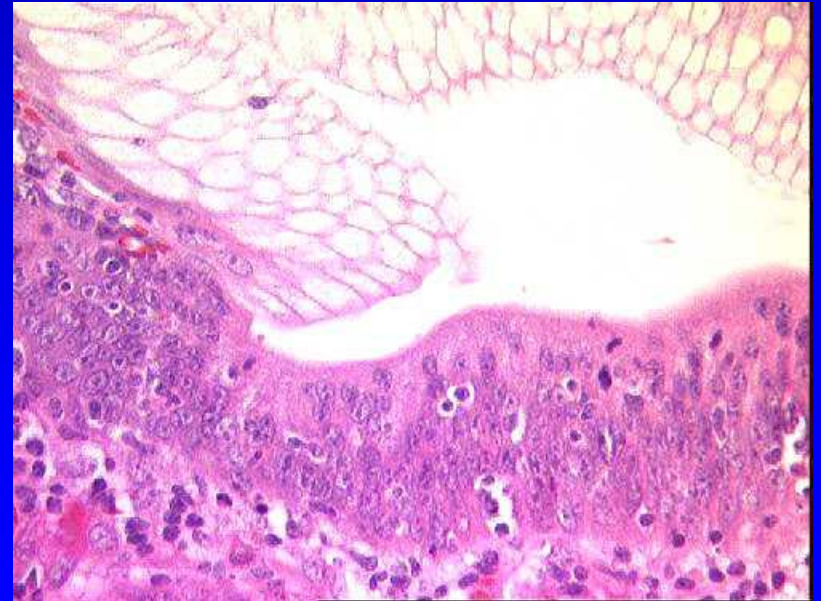
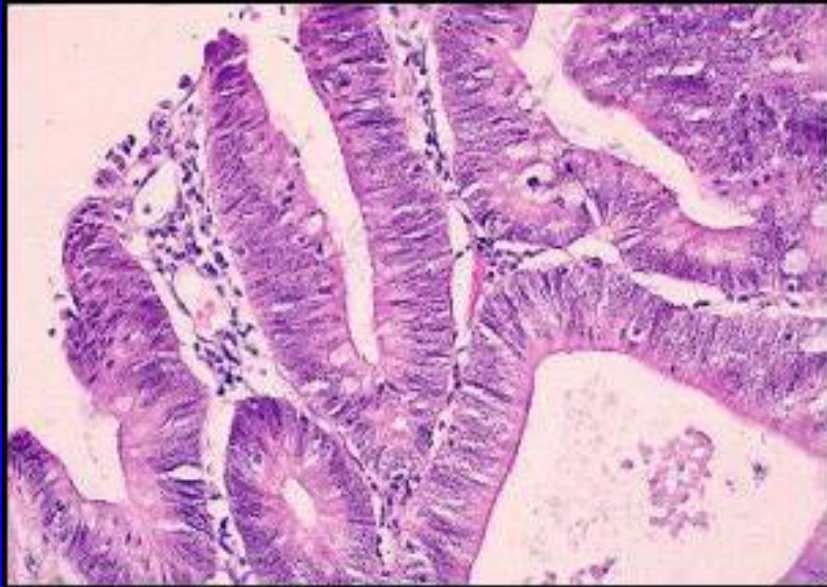
Helicobacter Prevalence

1940-1990



Helicobacter and Intestinal Metaplasia

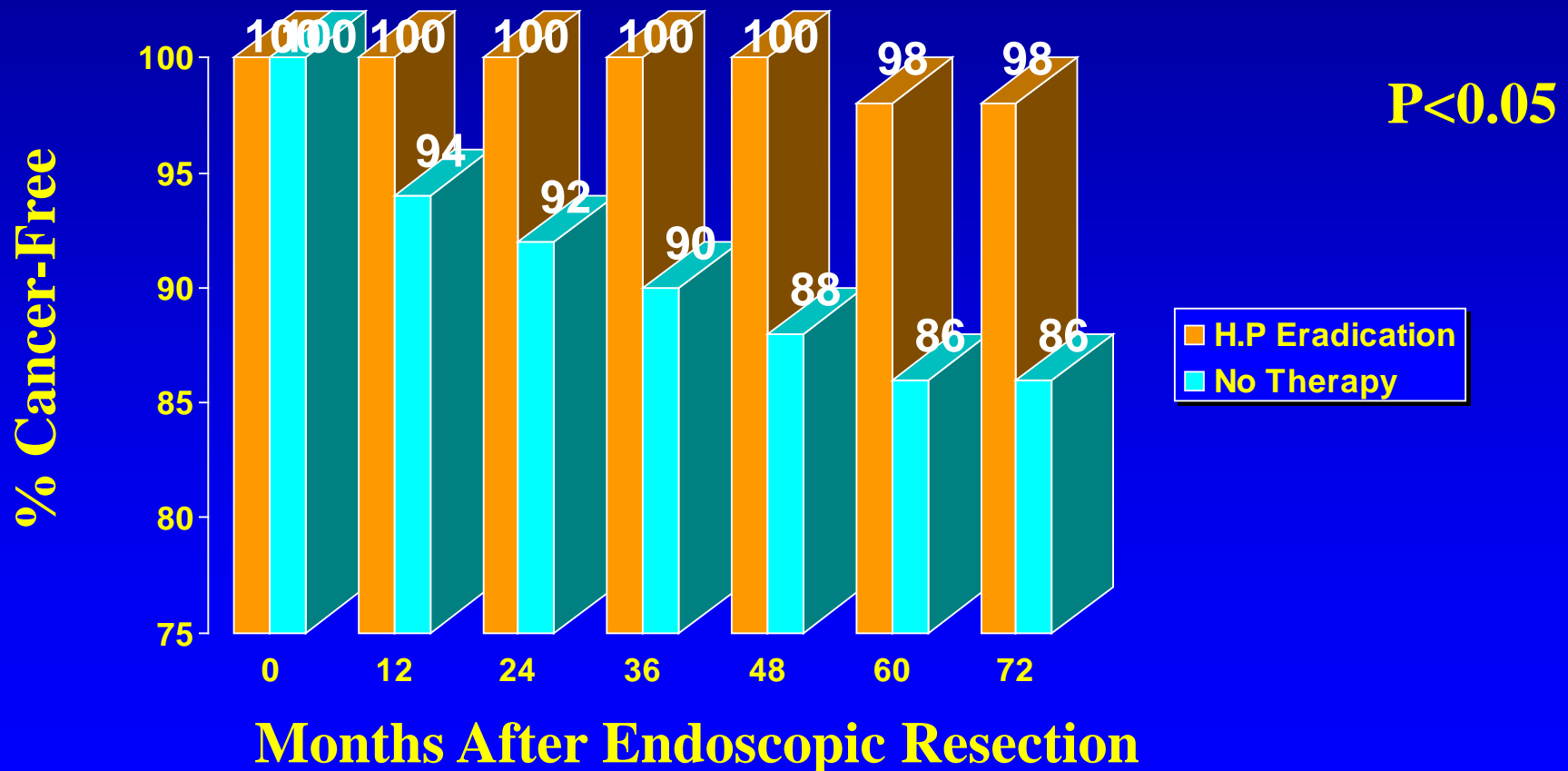
- Approximately 50% of H.P-infected patients over the age of 65 have intestinal metaplasia
- Intestinal metaplasia is the primary risk factor for gastric adenocarcinoma
- Advanced gastric intestinal metaplasia, like Barrett's esophagus, does not appear to be a reversible process



Helicobacter Controversies

- Does eradication of HP infection prevent progression of intestinal metaplasia to gastric cancer?
- At least 10 international gastric cancer prevention studies underway in Europe, Japan, China and South America

Effect of H.P Eradication on the Incidence of Second Gastric Cancer After Resection of Early Gastric CA.



Will Cure of *H. pylori* Infection Reverse Pre-cancerous Gastric Lesions?

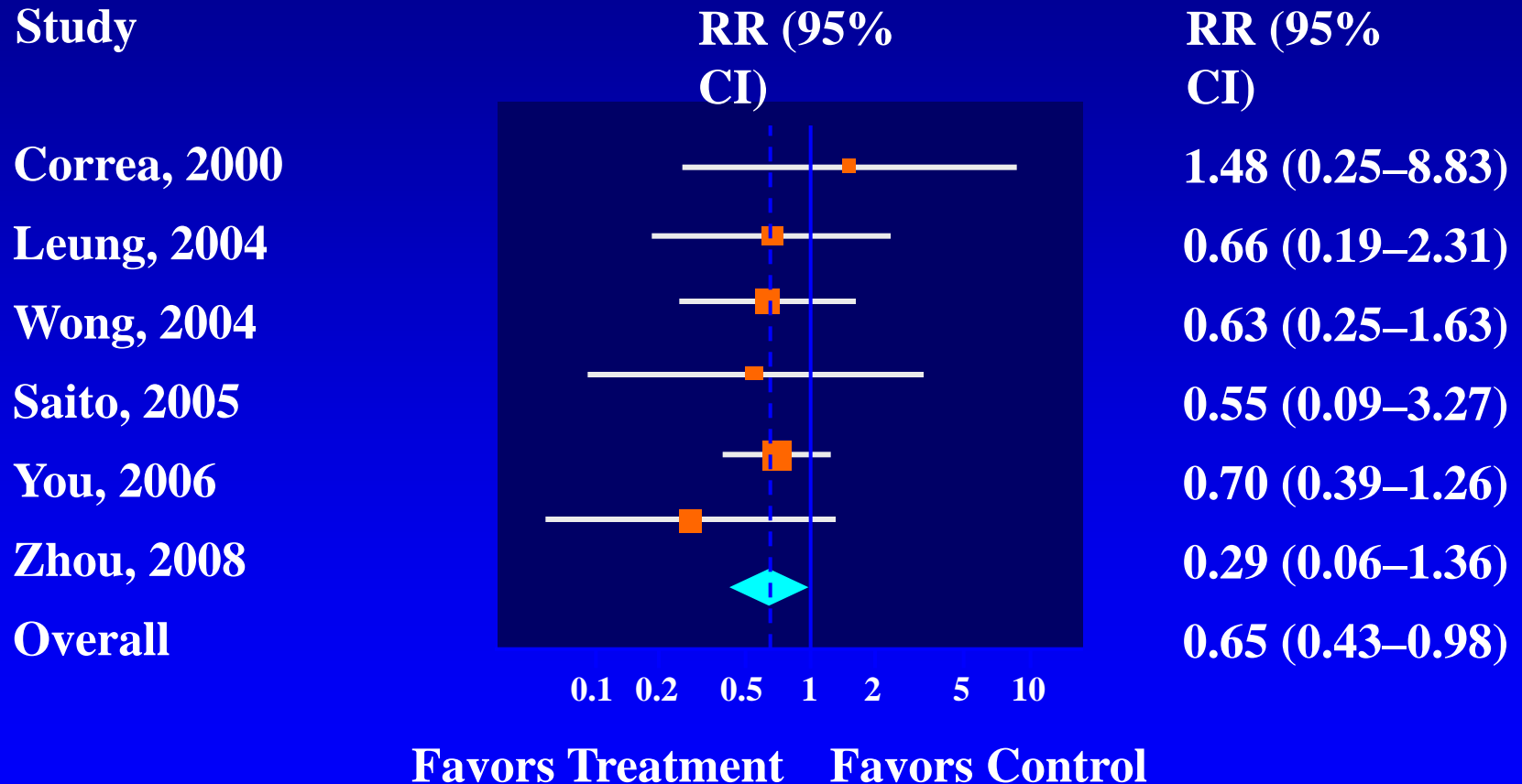
- Prospective, randomized, placebo-controlled population-based prevention study in China
- 1630 healthy carriers of *H. pylori* randomized to:
 - *H. pylori* eradication treatment (n = 817)
 - placebo (n = 813)
- 18 new cases of gastric cancers after 7.5 years of follow-up
 - 7 = *H. pylori* eradication treatment
 - 11 = placebo

} $P = 0.33$
- Subgroup of participants with no pre-cancerous lesions* (n = 998 on study entry)
 - 0 = *H. pylori* eradication treatment
 - 6 = placebo

$P = 0.02$

*Gastric atrophy, intestinal metaplasia, gastric dysplasia.

Effect of *H. pylori* Eradication on Risk of Gastric Cancer: Meta-analysis of RTCs



Helicobacter and Gastric Cancer:

Conclusions

- Eradication of *Helicobacter pylori* may reduce the risk of progression of intestinal metaplasia to gastric adenocarcinoma.
- The lifetime risk of gastric cancer is estimated at less than 1%, so the absolute benefit is small.
- Despite the decline in gastric cancer incidence, it is still 20-30 fold more common than esophageal adenocarcinoma.
- Medical-legal considerations demand treatment once H.P. infection is established.

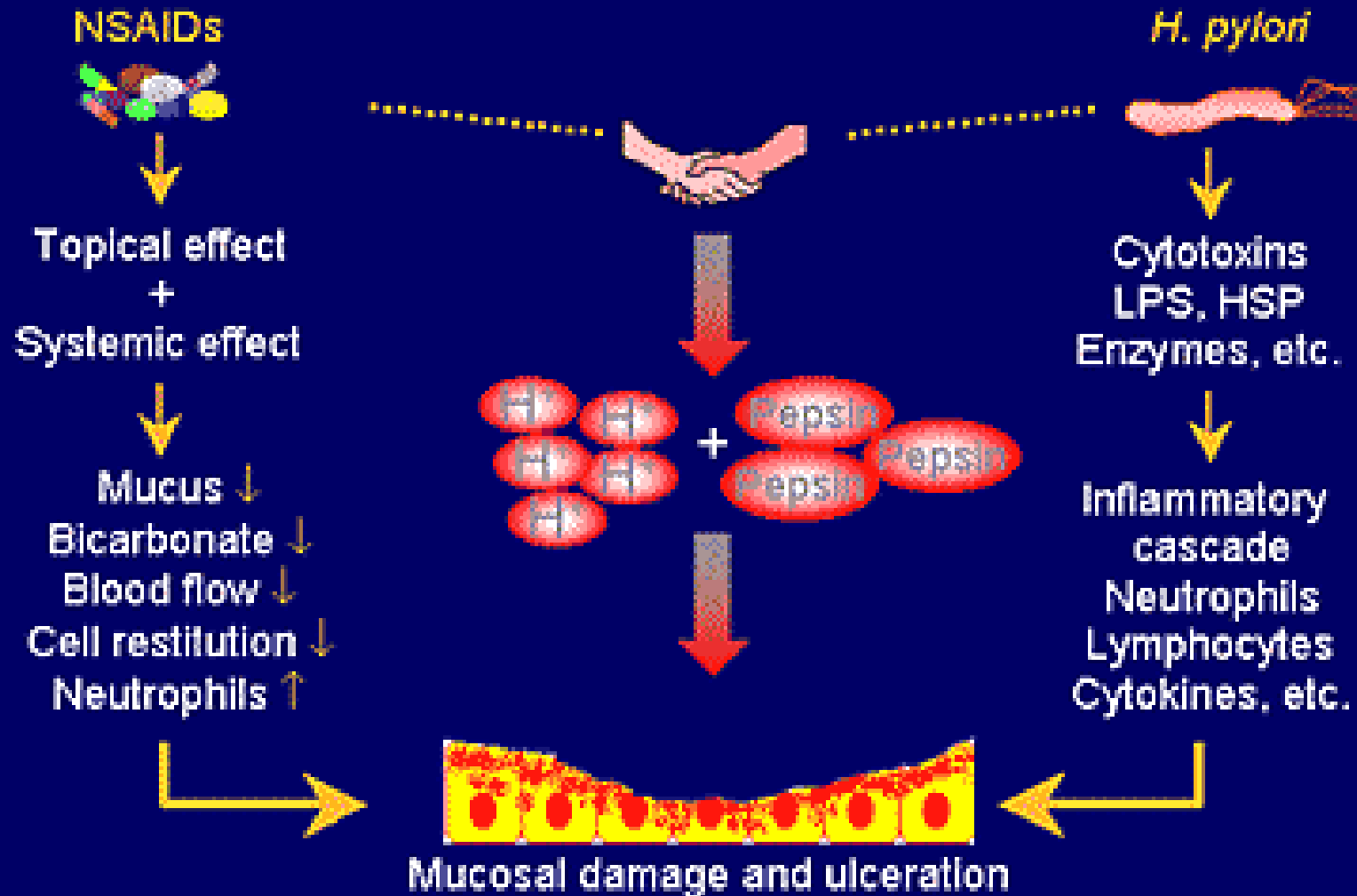
Helicobacter Pylori: 2004

- Diagnostic Tests
- HP and Duodenal Ulcer
- Treatment Regimens
- HP and functional dyspepsia
- HP and Gastric Cancer
- HP and NSAID/ aspirin toxicity

HP and NSAID GI Toxicity

- A great debate has raged as to whether HP should be tested for and eradicated in patients on NSAIDs to reduce complications.
- Discrepant results in epidemiologic studies are due to three factors:
 - Are subjects on low-dose aspirin
 - Initiating NSAID or chronic NSAID users
 - High risk vs low risk for ulcer complications

H. pylori and NSAIDs: Additive or Synergistic Effect on Gastric Mucosal Damage?



HP and NSAID GI Toxicity

- **HP and NSAIDs are the most important pathogenic agents in the development of peptic ulcers**
- **Each causes ulcer by different mechanisms**
- **The interaction between HP and aspirin and non-aspirin NSAIDs is extremely controversial**
- **Different studies have show that HP increases, decreases, and has no effect on the likelihood of NSAID or aspirin-related ulcer complications**

HP and NSAID GI Toxicity

- **International endoscopic study of 200 patients on stable doses of low-dose ASA (80-325 mg) for at least 28 days (no other NSAID or acid suppression allowed)**
- **Prevalence of DU 5.3% and GU 5.9%**
- **HP infection increased the odds ratio for ulcer by 5.7**

**Gastroenterology 2002;
122:A104 abstract**

HP and NSAID GI Toxicity

- In case-controlled studies of patients on low-dose ASA admitted with UGIB, HP was an independent risk factor for bleeding (OR 4.7)
- Study of HP-positive patients on ASA or NSAIDs randomized to eradication of HP vs long-term omeprazole to determine risk of rebleeding
- Among high-risk users, eradication of HP was equivalent to chronic PPI treatment

400 HP-Positive Patients With UGI Bleed Due To NSAID or Aspirin-Induced Ulcer

**NSAID/ HP (+)
150 patients**

**Aspirin/ HP (+)
250 patients**

**No Eradication
+ Omeprazole**

**Eradication HP
75**

**Eradication HP
(125)**

**No Eradication +
omeprazole (125)**

6 mo. Naprosyn 500 bid

6 mo. Aspirin 81 mg/day

**Rebleed
4.4%**

**Rebleed
18.8%**

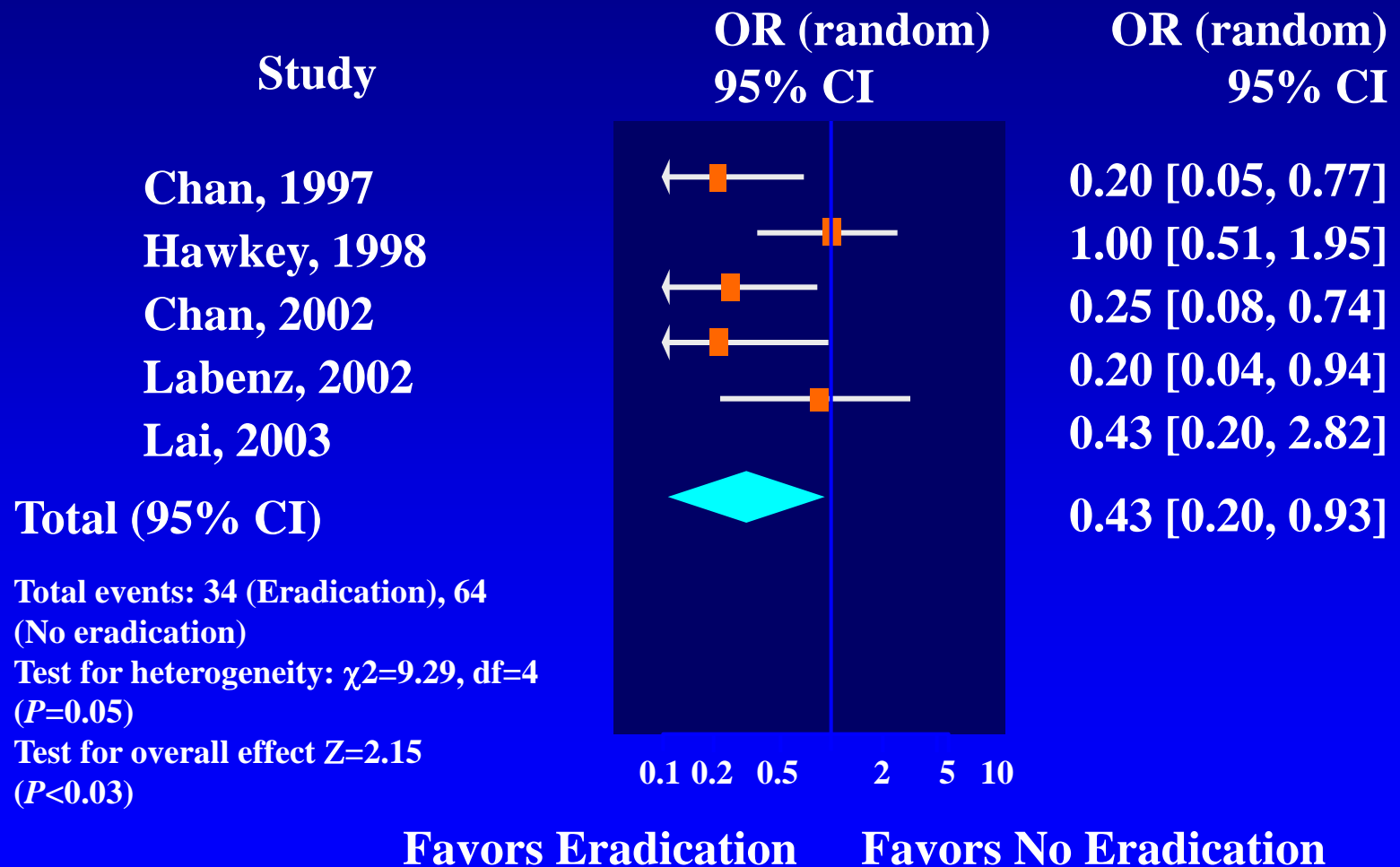
**Rebleed
1.9%**

**Rebleed
0.9%**

(Ulcers healed prior to randomization)

NEMJ 2001;433:967

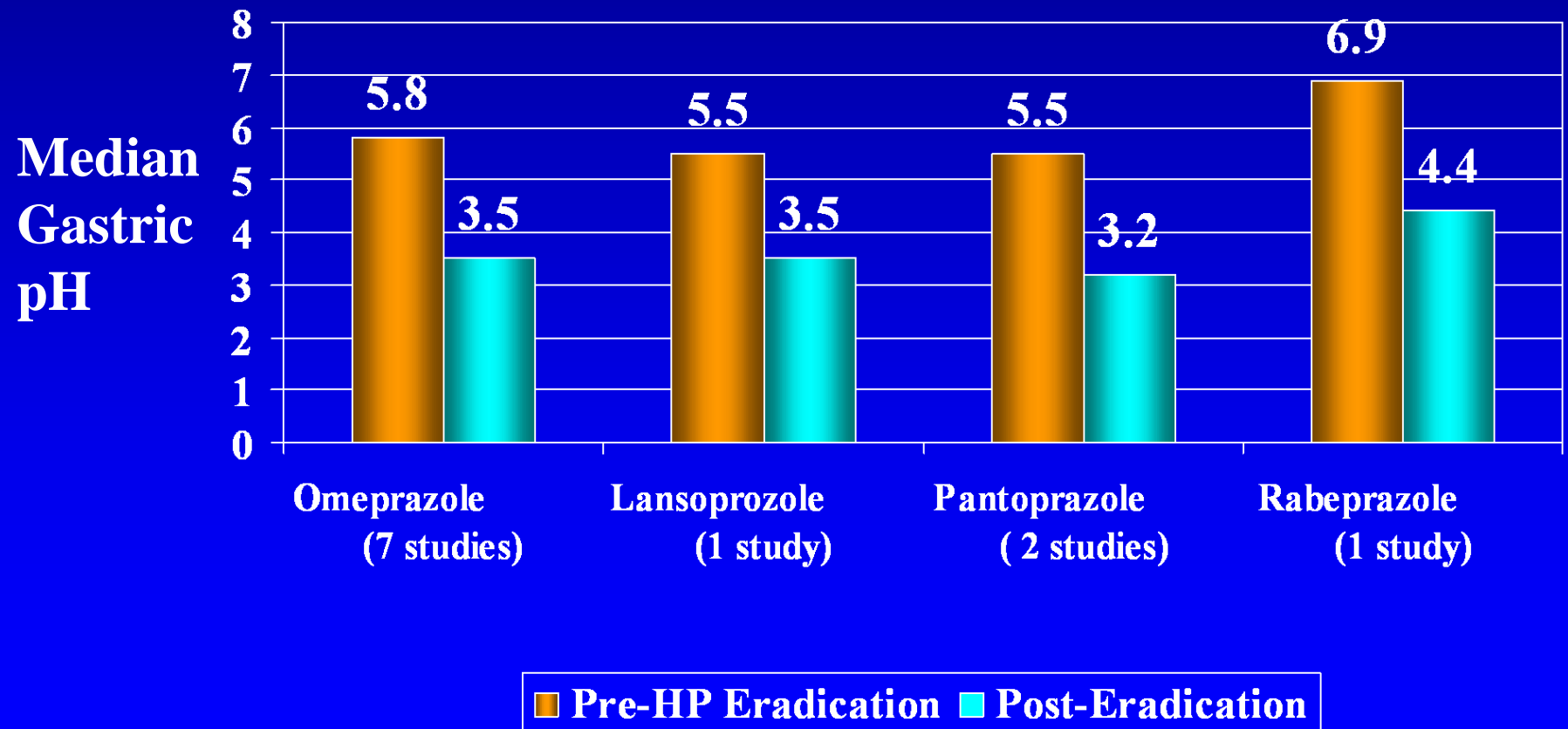
H. pylori Eradication Reduces Risk of Ulcers in NSAID Users



HP and NSAIDs: Key Points

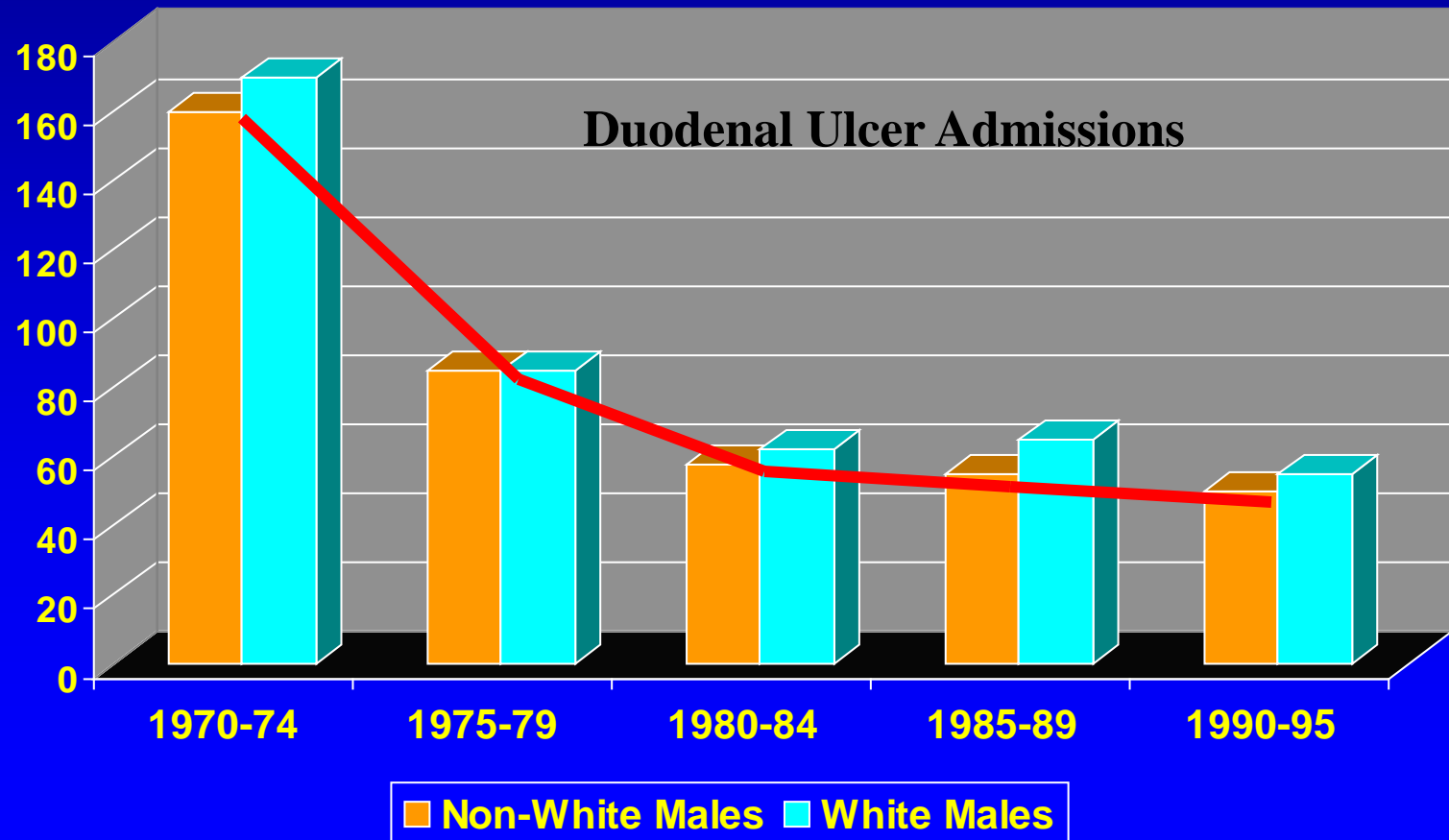
- HP and NSAID are additive risk factors for ulcers and ulcer bleeding
- HP infection significantly increases the risk of ulcer and ulcer complications of low-dose aspirin
- In patients already on NSAIDs, HP testing is recommended if there is a history of ulcer with or without complications
- All high-risk patients (prior ulcers, age >70) should be tested for HP prior to starting on low-dose aspirin
- Routine testing for HP is not currently recommended for NSAID users with no risk factors

Effect of Eradication of Helicobacter on Median Gastric pH



VA Hospital Duodenal Ulcer Admissions 1970-1995

Hospitalizations per 100,000 veterans at VA Hospitals 1970-1995



Should We Eradicate All *Helicobacter Pylori* ?

PRO

- Class 1 Carcinogen
- Duodenal Ulcer Cure
- Gastric Ulcer Cure

CON

- PPI's more effective
- H2-RA more effective
- May reduce severity of GERD
- Possible protection from esophageal adenocarcinoma
- Modulation of GALT

Helicobacter and Gastric Cancer

- In 1994, the world health organization designated *H. pylori* as a class 1 carcinogen in humans.
- The dramatic decline in gastric cancer rates in the west over the last century has coincided with a parallel decline in the prevalence of *H. pylori*.

Helicobacter Pylori and Gastric Cancer

- Before 1940 gastric cancer was the leading cause of cancer-related death in American males and third in females
- Since 1950 there has been a progressive decline in the incidence of gastric cancer in the US and other developed countries.
- Between 1950 and 1980, gastric cancer mortality rates fell 67% in the US

Helicobacter and Gastric Cancer

- Gastric cancer rates vary widely between geographic regions
- $>35/100,000$ in Southeast Asia
- $<15/100,000$ in North America, Western Europe, and most African countries.
- H.P. infection increases gastric cancer relative risk 2-8 fold over controls without infection.

Risk Factors for Gastric Cancer

- Chronic Helicobacter Atrophic/Pan-gastritis
- High Salt Intake
- Lack of Fresh Fruits and Vegetables
- High N-Nitroso Compound Consumption
- Smoking
- Alcohol Consumption

Helicobacter and Gastric Cancer

- Gastric carcinogenesis is a multistep process with progressive evolution from:
 - **Chronic Gastritis**
 - **Gastric Atrophy**
 - **Intestinal Metaplasia**
 - **Dysplasia**
 - **Carcinoma**
- No difference in incidence of intestinal metaplasia between males and females.

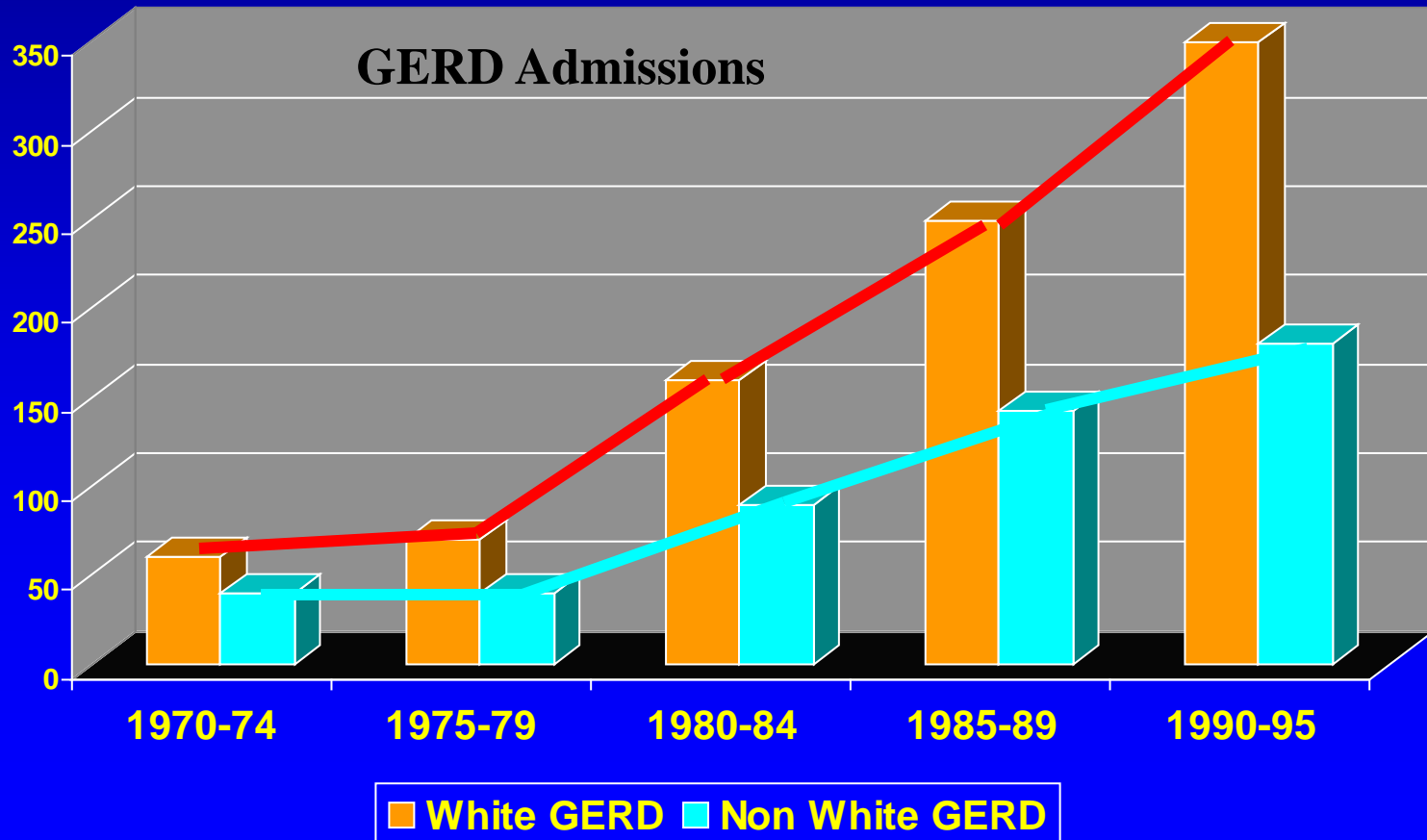
Does Infection With Helicobacter Pylori Reduce the Incidence of GERD and Esophageal Adenocarcinoma?

Helicobacter Pylori and GERD

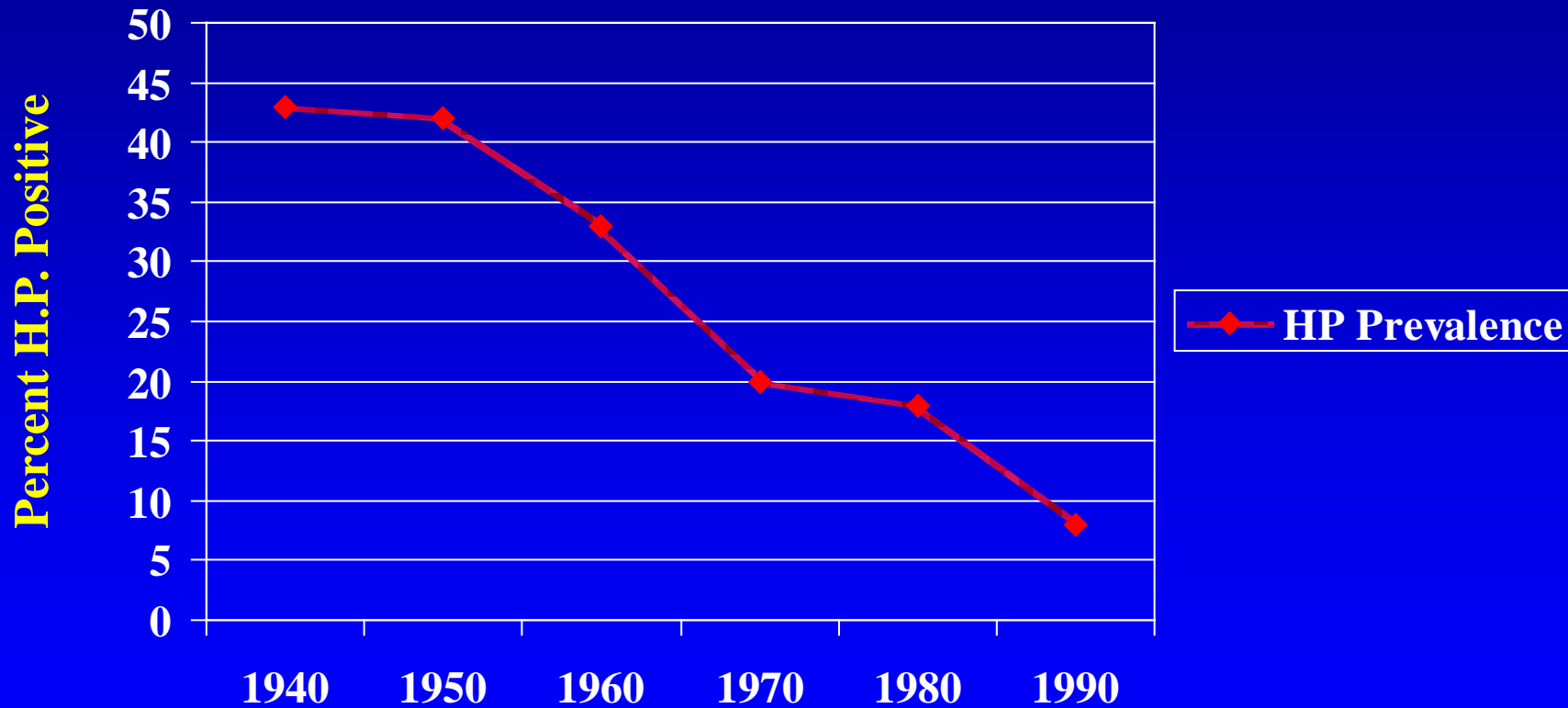
- There is growing interest in the relationship between H.P. and GERD.
- The relationship is complex and probably based on multiple unknown variables.
- There appears to be a statistical negative correlation between H.P. infection and GERD, but the data are conflicting.

VA Hospital GERD Admissions 1970-1995

Hospitalizations per 100,000 veterans at VA Hospitals 1970-1995



Helicobacter Prevalence Rates in U.K. for 15 Year-Olds by Decade



Helicobacter Pylori and GERD: Mechanism of Beneficial Effects

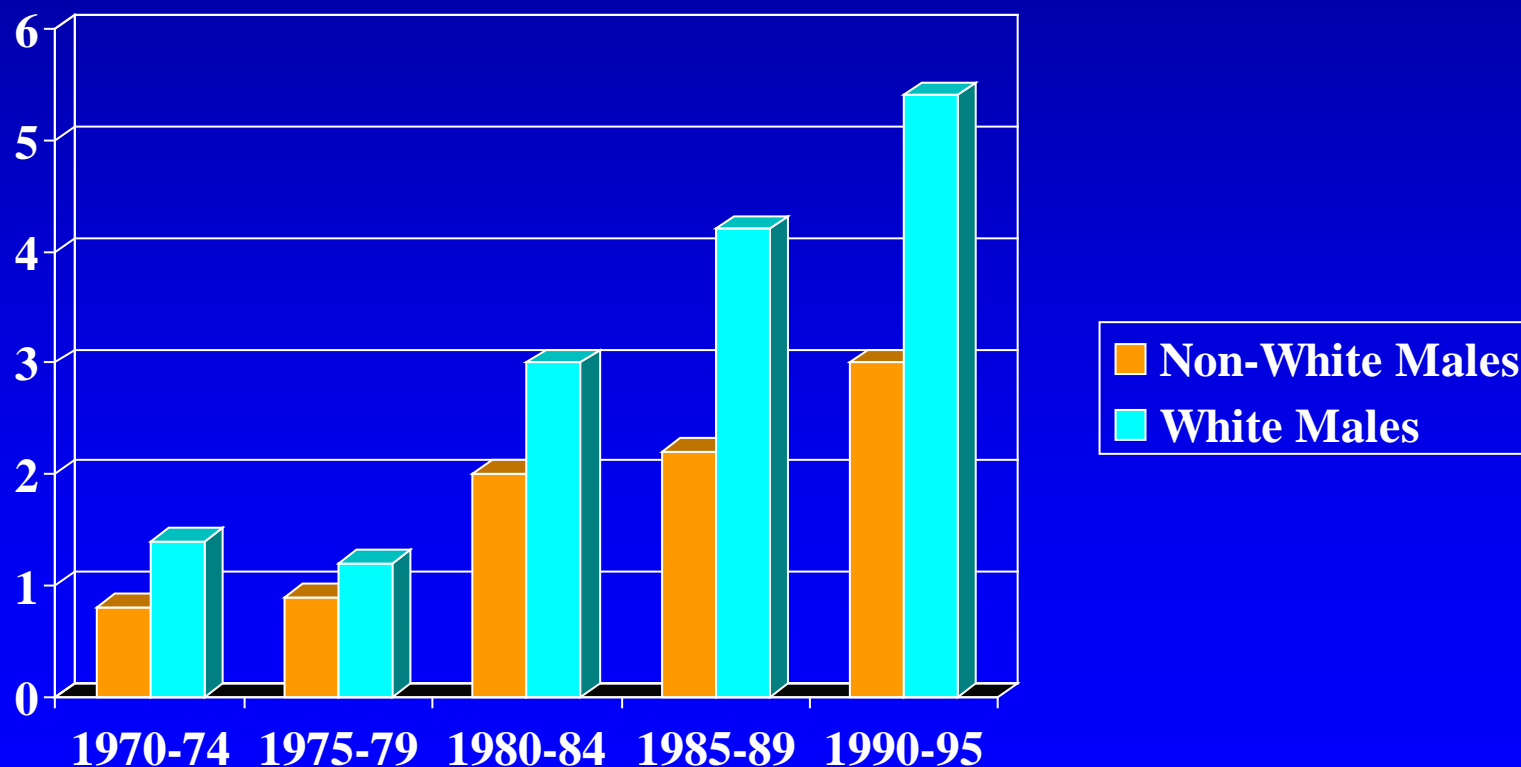
- H.P. does not affect gastric emptying. or the frequency of transient LES relaxations.
- Ammonia produced by the organism may serve as a buffer in the relatively higher pH of the esophagus.
- Atrophic gastritis, especially associated with virulent strains, may result in relative hypochlorhydria.

Helicobacter and Esophageal Cancer

- There is a strong causal relationship between GE reflux and esophageal adenocarcinoma.
- The more frequent, more severe, and long-lasting the symptoms of reflux, the greater the risk, regardless of the presence of Barrett's esophagus.

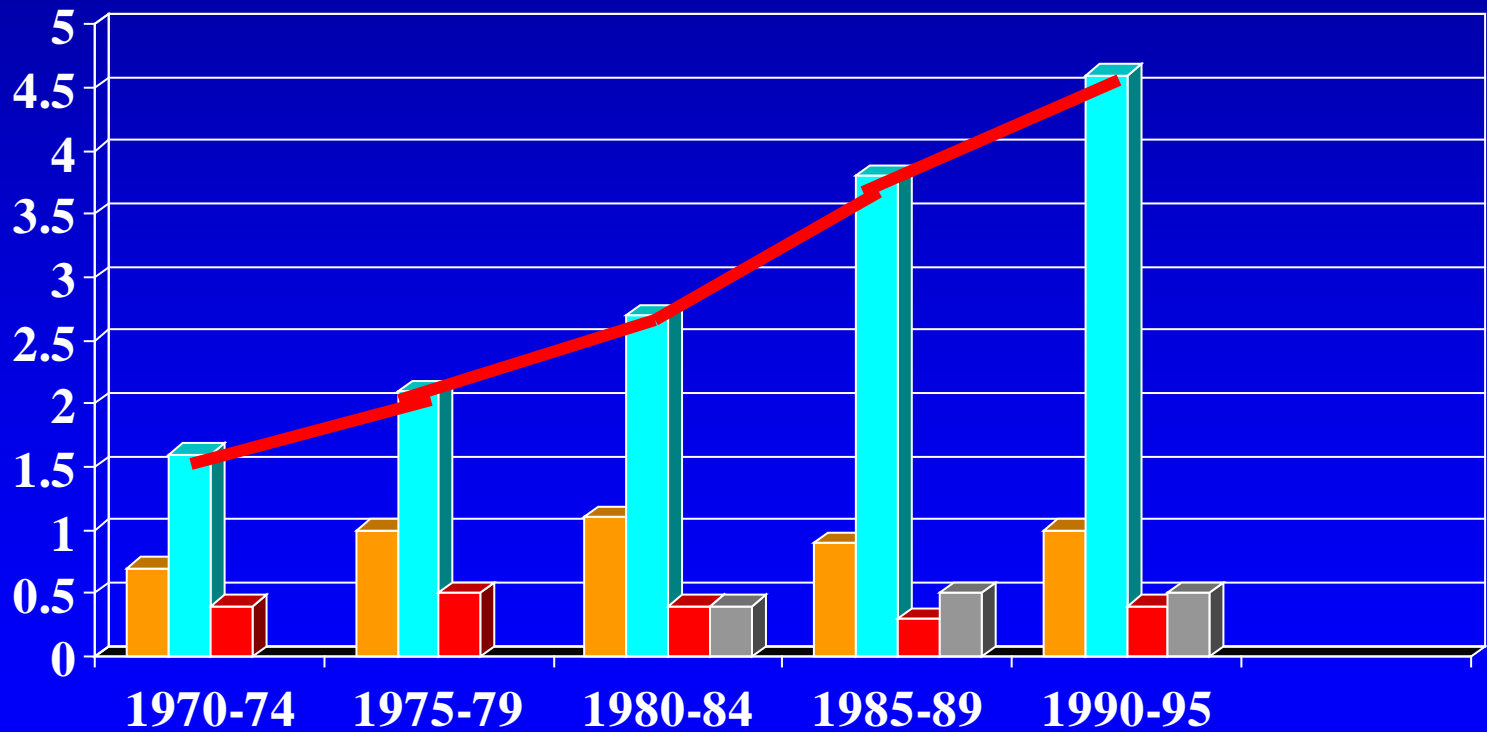
Cancer of the Gastric Cardia/Distal Esophagus 1970-1995

Hospitalizations per 100,000 veterans at VA Hospitals 1970-1995



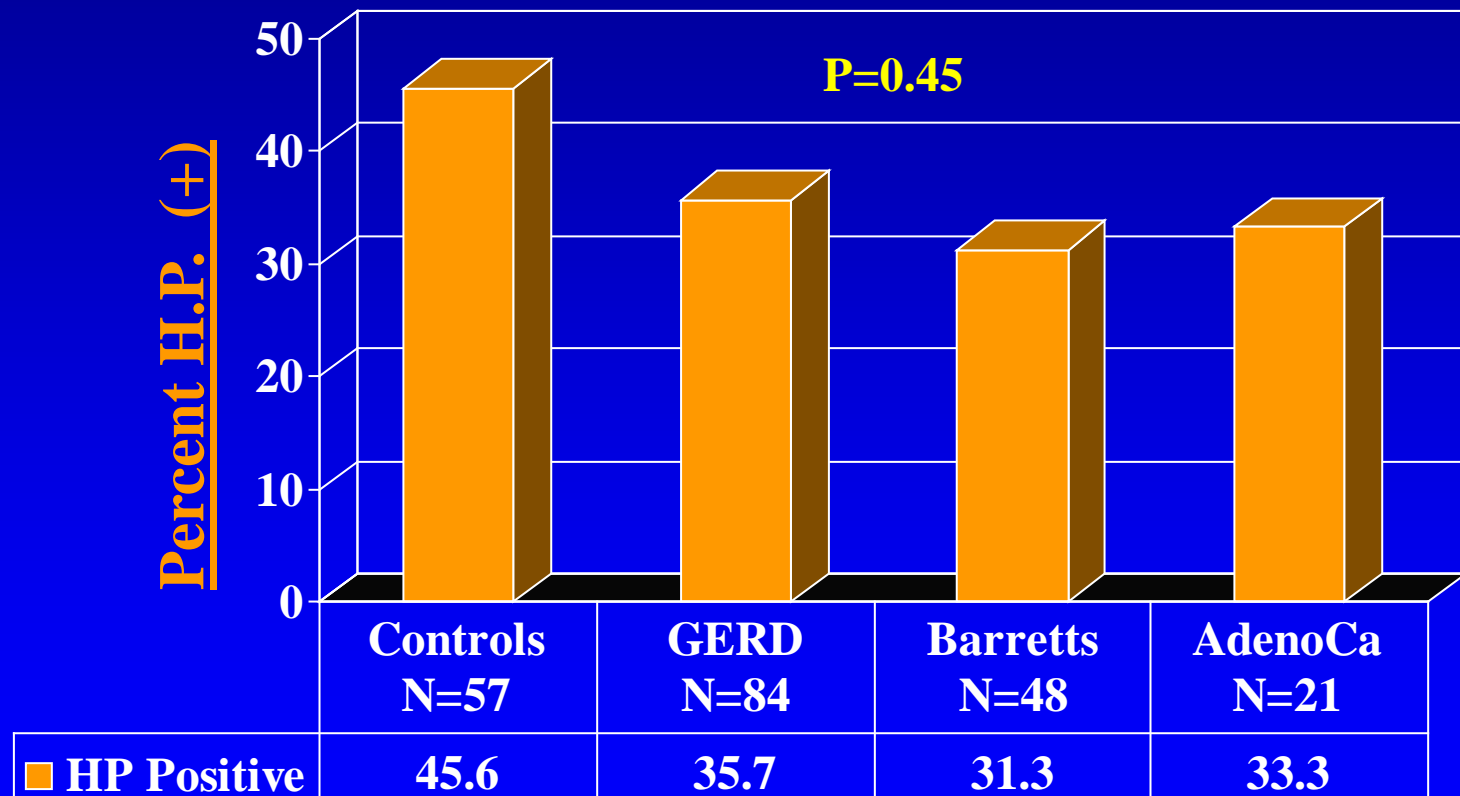
Deaths from Cancer of the Cardia/Distal Esophagus 1970-1995

Age-adjusted Deaths per Million Population

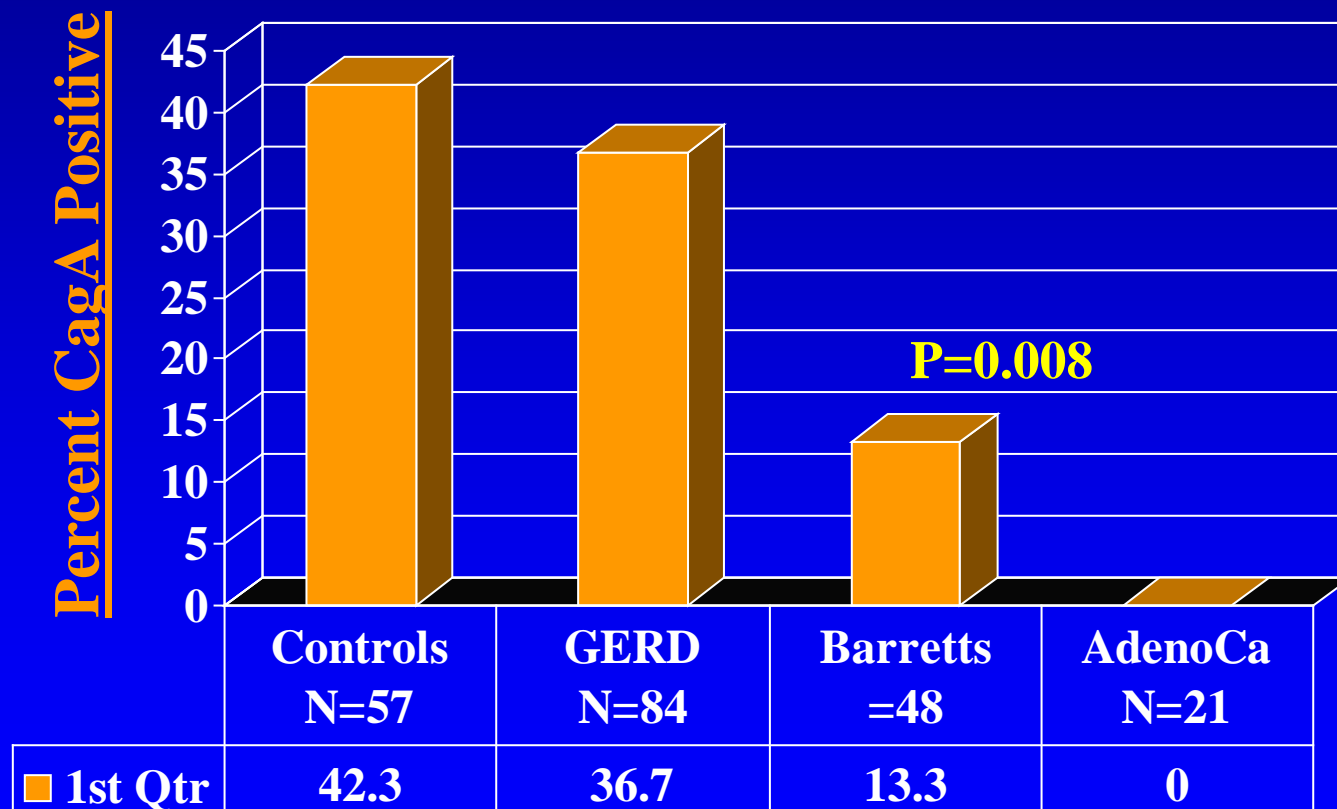


■ Non-White Males ■ White Males ■ Non White Female ■ White Female

Seroprevalence of Helicobacter Pylori in GERD



Seroprevalence of CagA-Positive Helicobacter in GERD

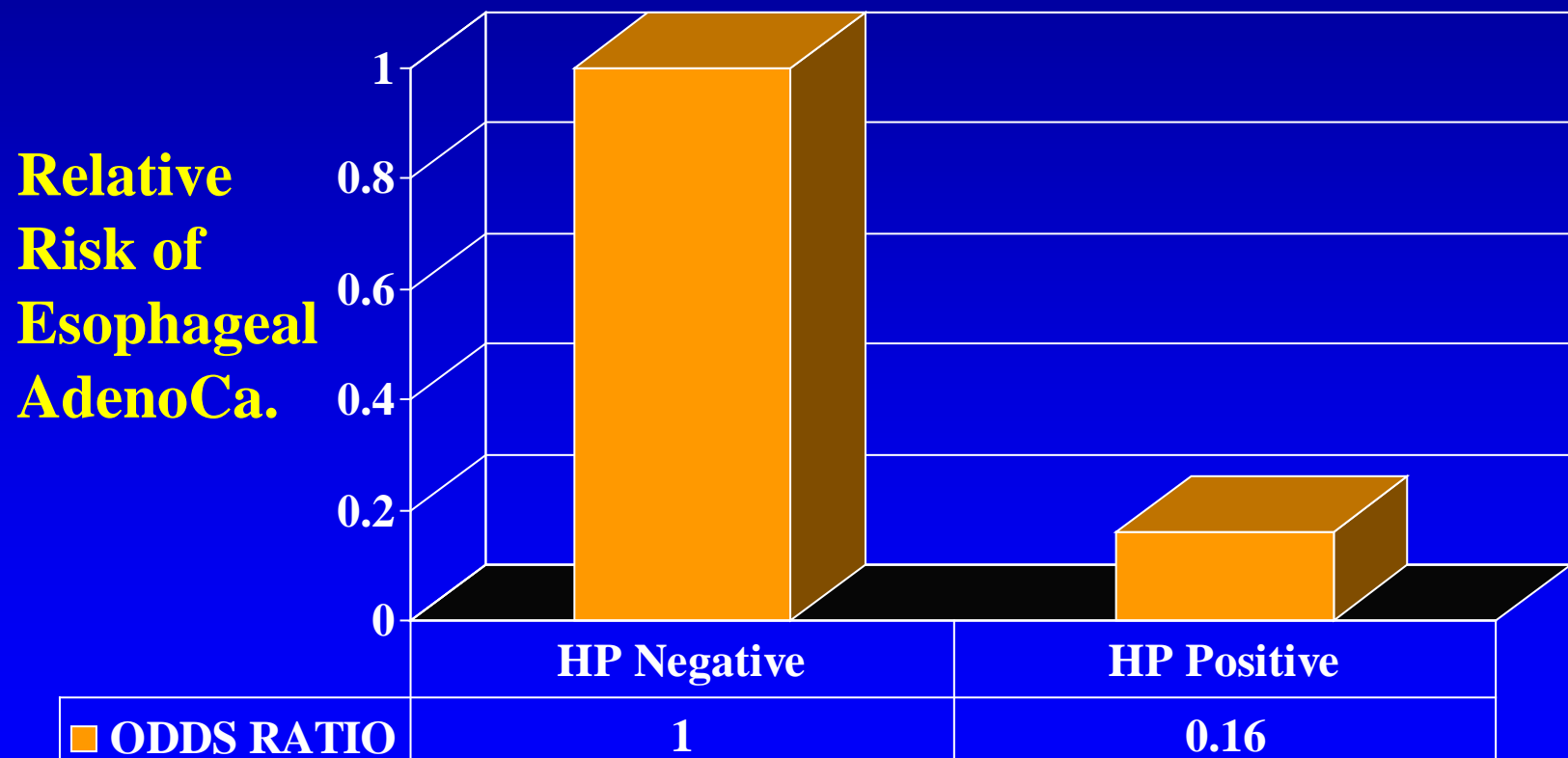


Cytotoxin-Associated Antigen (cagA)

- CagA is a virulence factor for H. P. infection associated with more aggressive disease and higher rates of duodenal ulcer and antral cancer.
- CagA-positive strains cause more intense mucosal inflammation and colonize the gastric mucosa more densely.
- When pan-gastritis is present, the intense inflammation of the corpus produces more extensive multifocal atrophic gastritis and secondary hypochlorhydria.

Helicobacter Pylori Infection Decreases Risk of Esophageal Cancer

44 cases of esophageal Ca, Malmo, Sweden, (pop. 32,906, 1974-1994)



(Multivariate analysis: controlled for occupation, smoking, alcohol)

Helicobacter, GERD, and Esophageal Cancer: Conclusions

- The incidence of esophageal adenocarcinoma has been increasing exponentially over the last 30-40 years.
- Acid reflux is also increasing rapidly.
- Both phenomena are inversely correlated with Helicobacter prevalence.
- The interrelationships are, however, complex and incompletely understood.

Helicobacter, GERD, and Esophageal Cancer: Conclusions

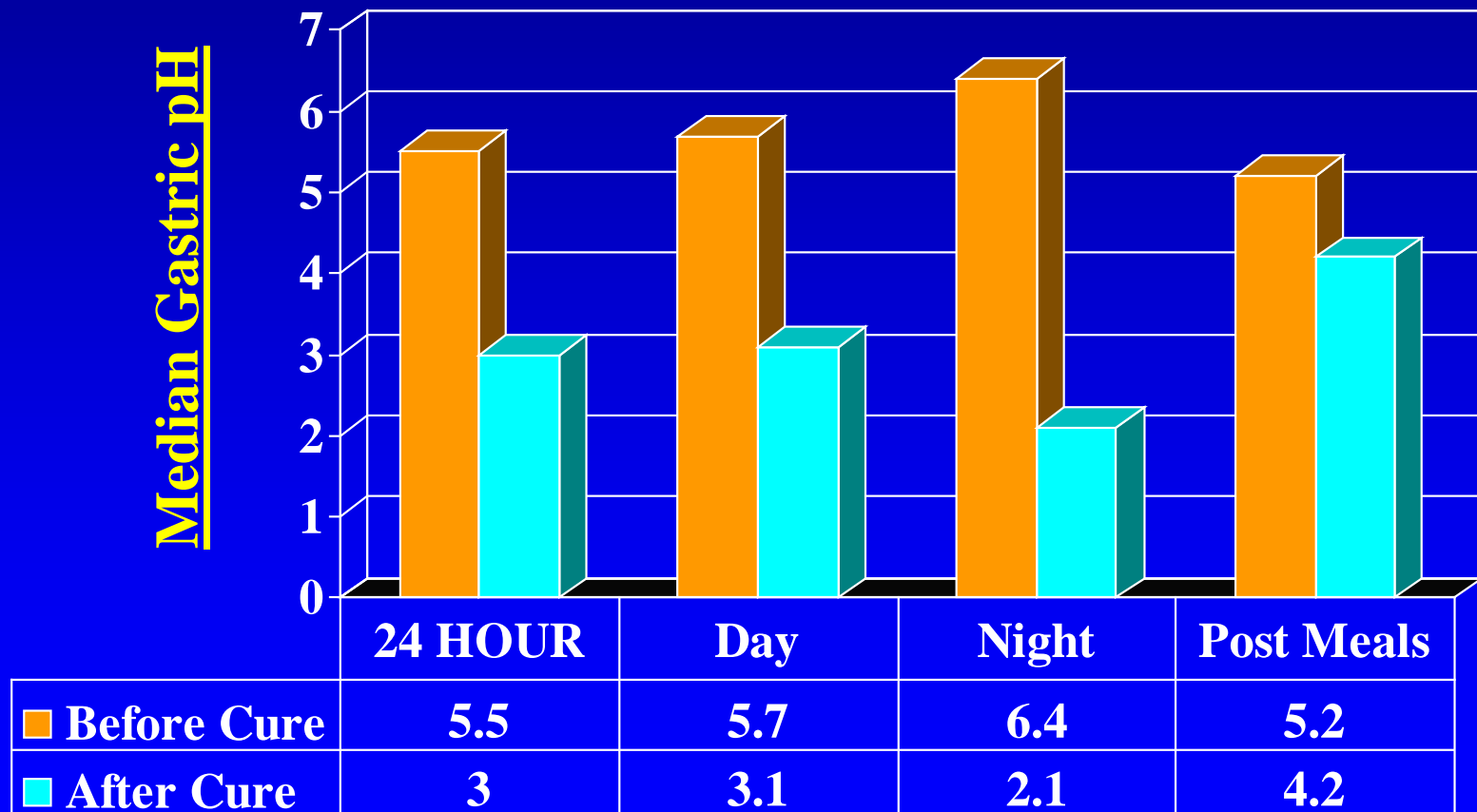
- If GERD symptoms predominate, it is probably not indicated to check for and eradicate H.P.
- Despite the potential benefits of H.P. infection in preventing Barrett's esophagus and adenocarcinoma, the absolute risk of gastric cancer still dwarfs that of esophageal cancer by a factor of 20-30 fold.
- Treatment of known infection is, therefore, indicated

Helicobacter Pylori Gastritis Enhances the Activity of Acid- Suppressing Drugs

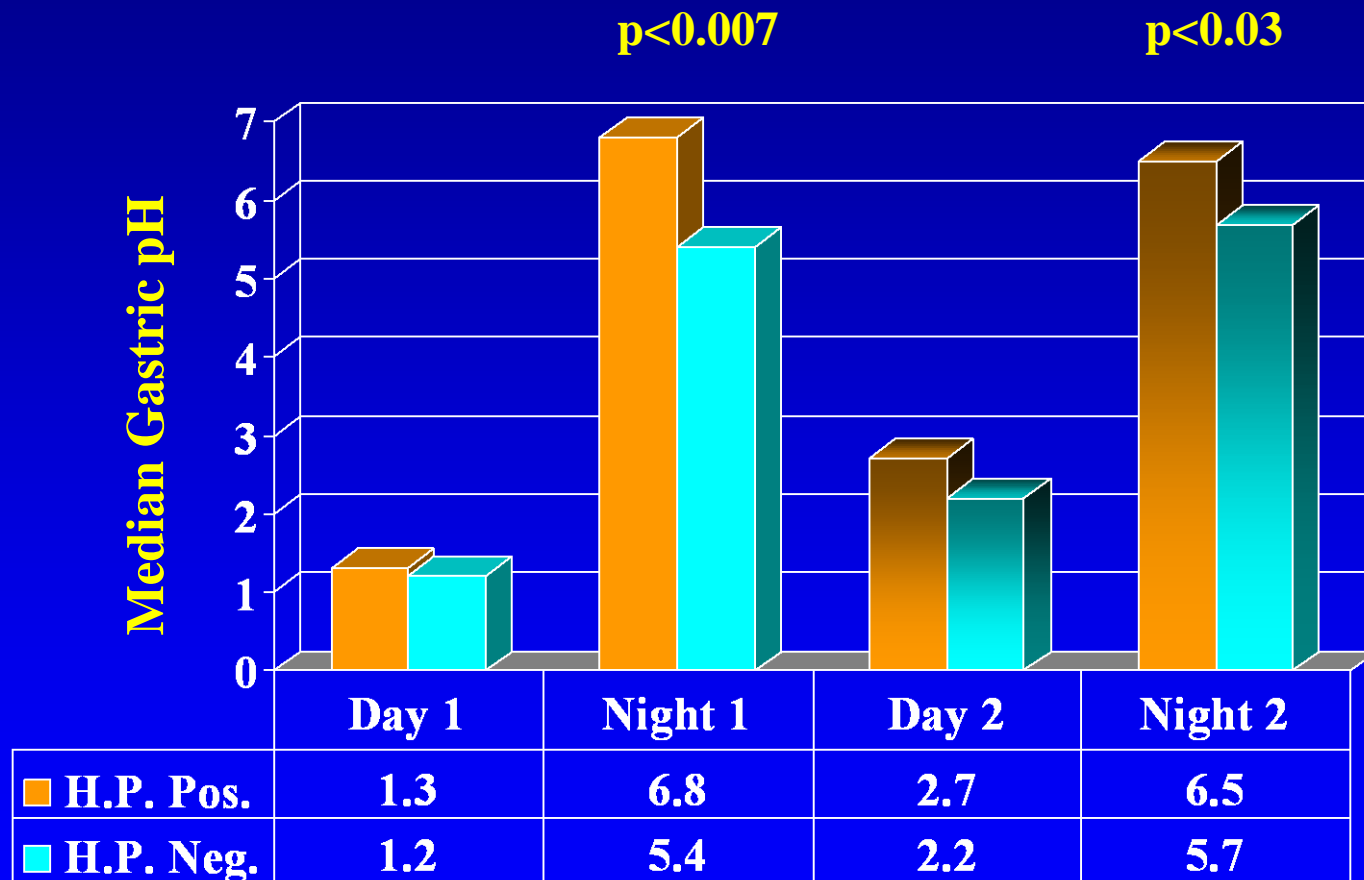
Effect of H.P. Status on Efficacy of Acid Suppression Medications

- Proton pump inhibitors produce significantly higher intra-gastric pH in H.P. positive patients vs. H.P. negative patients.
- Similar, but less pronounced, results also observed with H₂ receptor antagonists.
- The mechanisms responsible are not fully understood.

Effect of H. Pylori Eradication on Median Gastric pH with Omeprazole



Effect of H.P. Status on Acid Suppression by Ranitidine

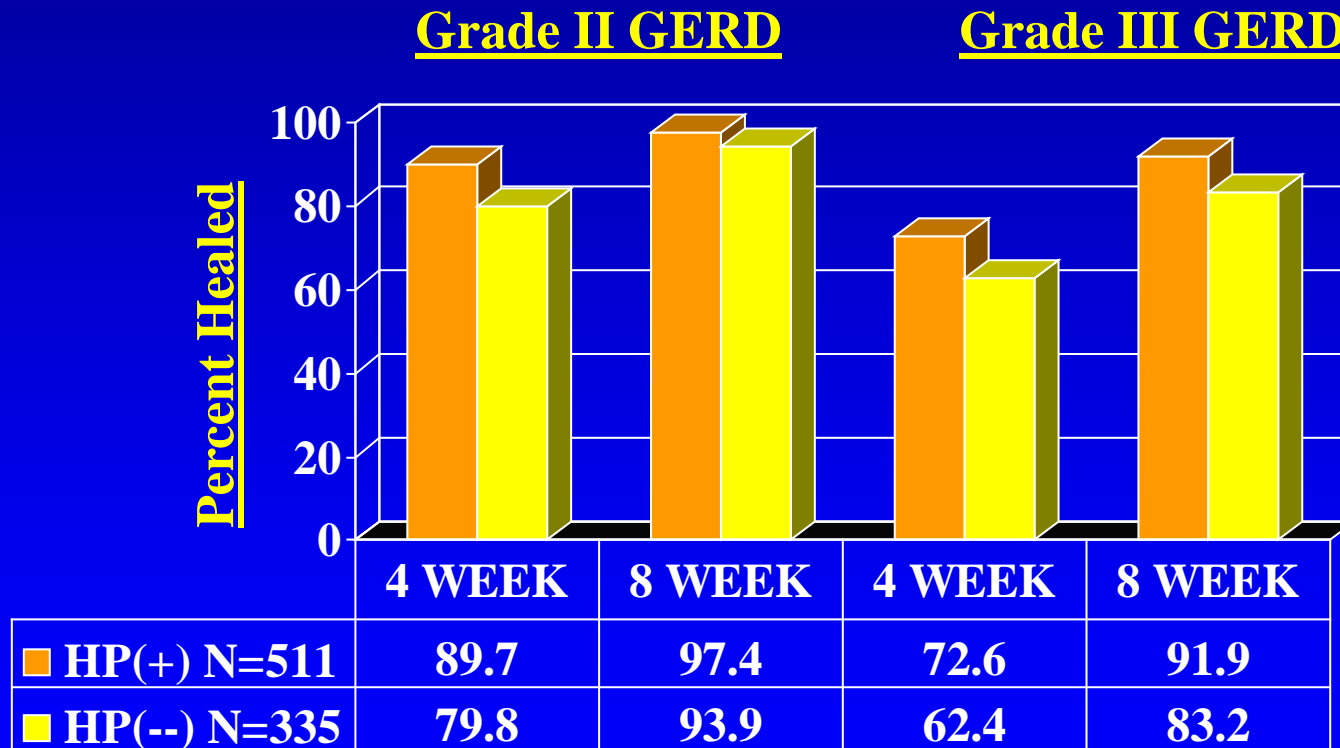


(Ref 1: Gut 1997; 41:33-6)

(Ref 2: Alim. Pharm Ther 1999; 13:731-40)

Effect of H.P. Status on Healing of Grade II/III Esophagitis

Pantoprazole 40 mg/day for eight weeks/ Endoscopy at 4 and 8 weeks



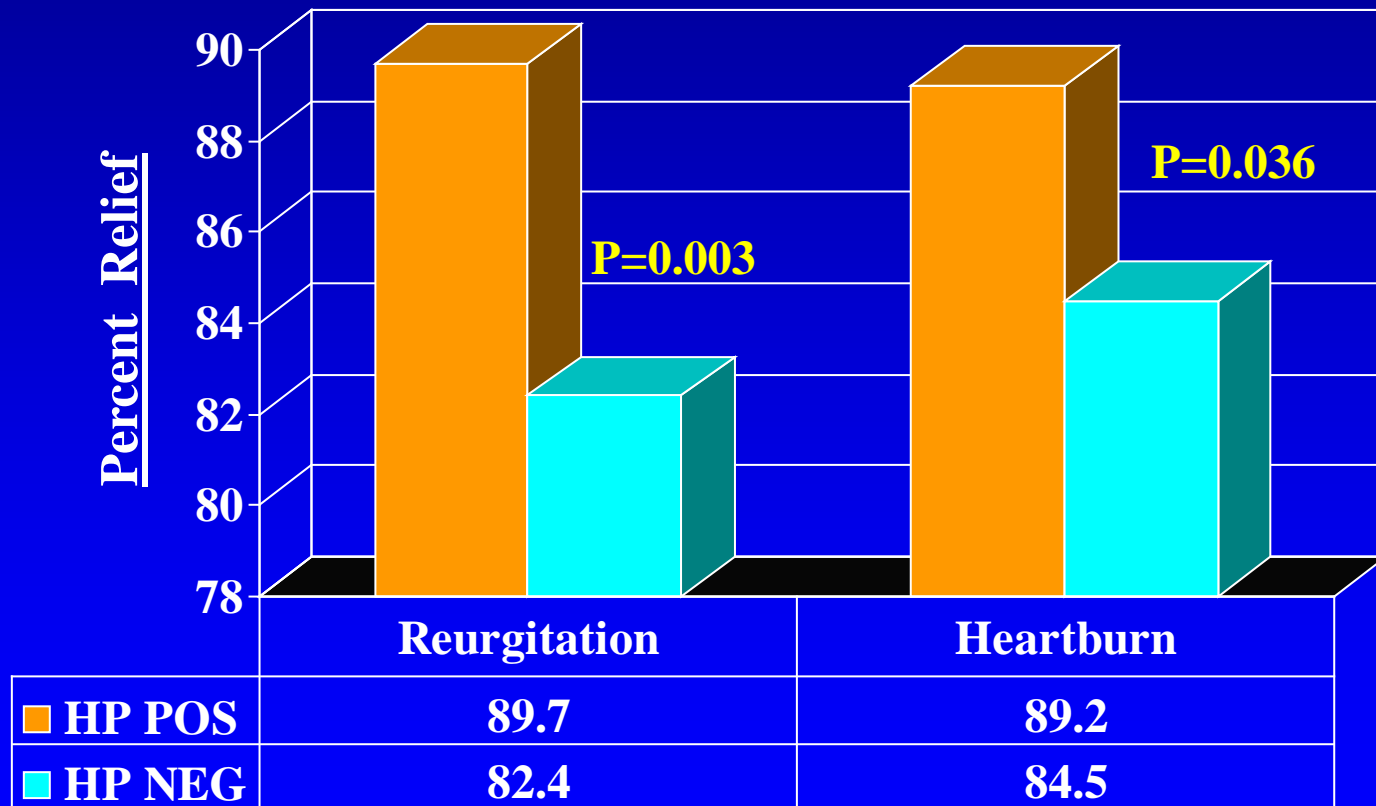
(P=0.0005)

(P=0.004)

(Gastroenterology. 1999; 117:11-16)

Relief of Main GERD Symptom After 4 Weeks of Treatment

Pantoprazole 40 mg/day for eight weeks



(Gastroenterology. 1999; 117:11-16)

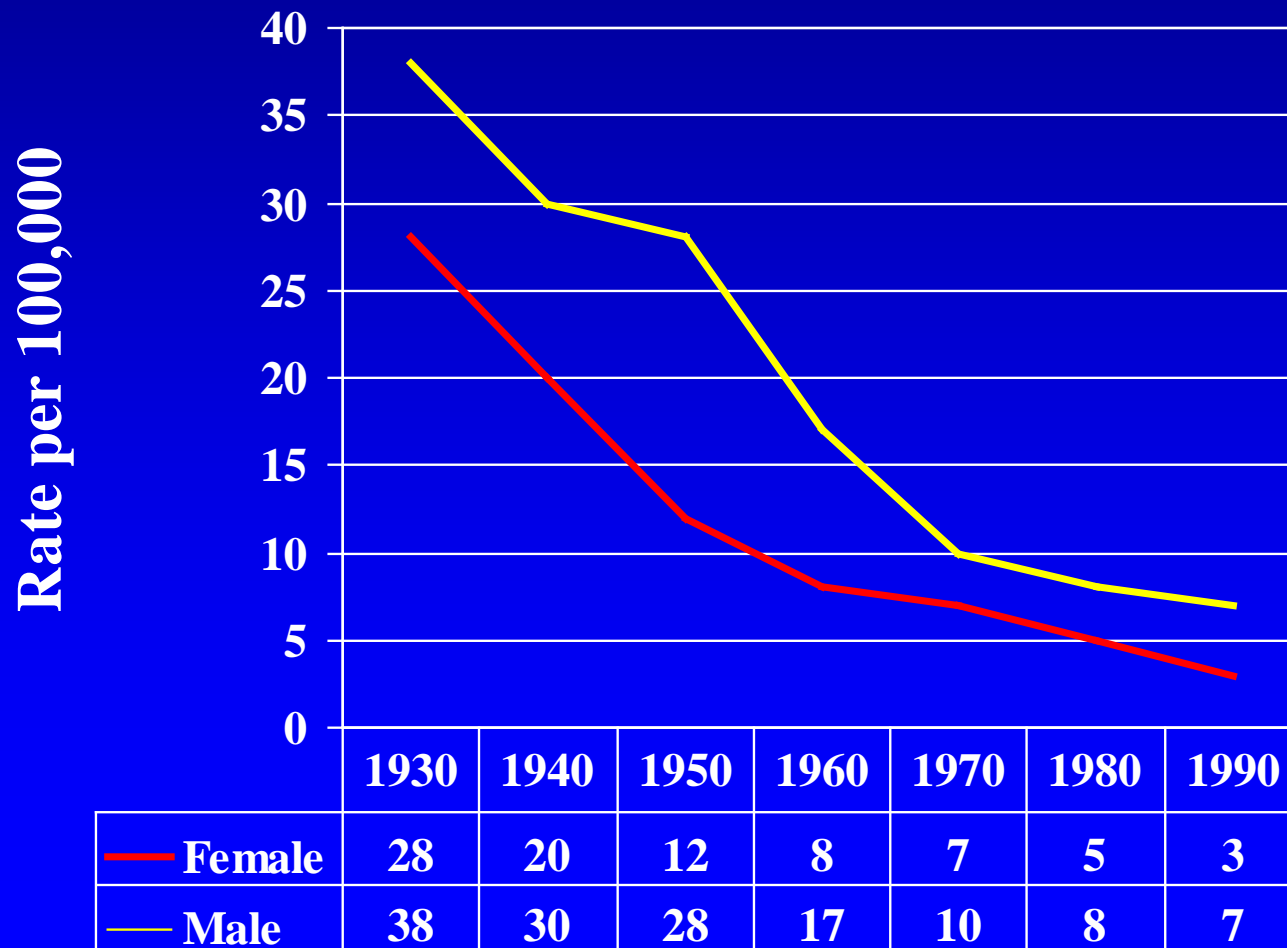
Helicobacter and Acid Suppression Medications

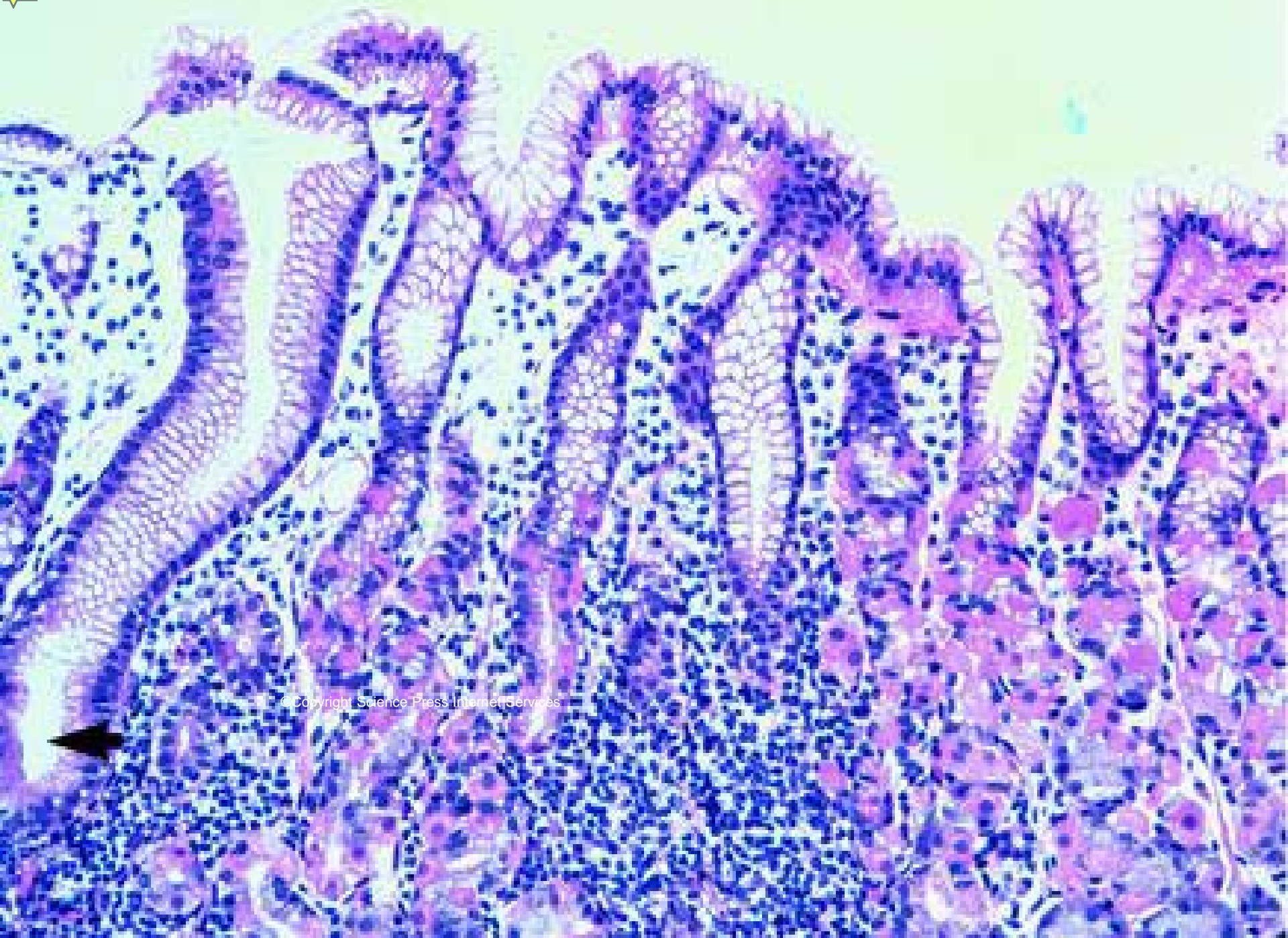
- H.P. Infection enhances the acid suppression produced by PPI's and H2-RA.
- In the short term, H.P. infection speeds healing of esophagitis and relief of symptoms.
- If symptoms suggest GERD rather than ulcer disease, empiric treatment for H.P. not recommended.

Management Strategies for Uninvestigated Dyspepsia

- Early Endoscopy with Diagnosis-Driven Therapy
- H. Pylori Test and Treat
- Empiric therapy with acid suppression, prokinetic agents, anticholinergics based on the predominant symptoms.
- Scope those who fail to respond to treatment

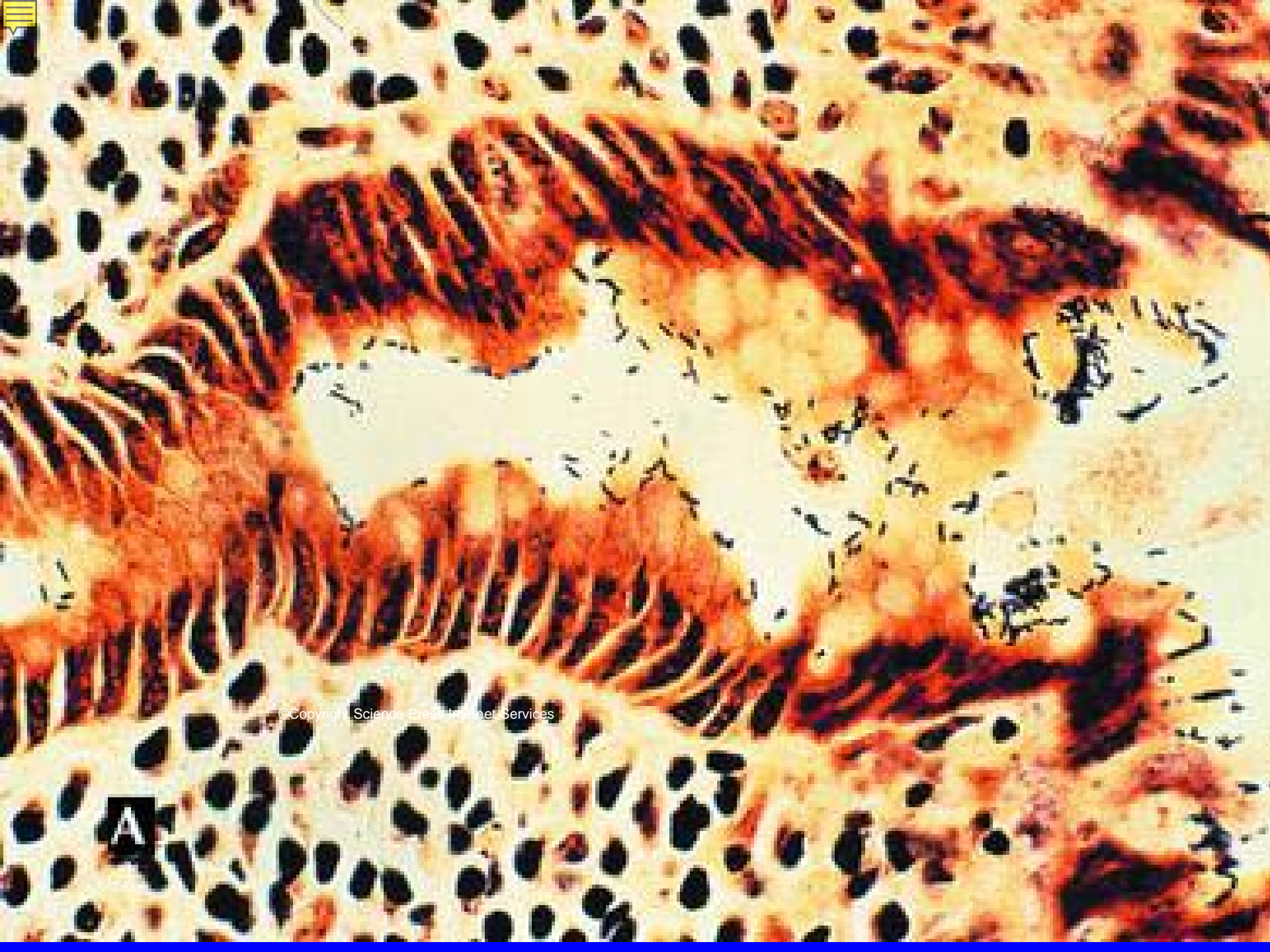
Age-adjusted USA Death Rates for Stomach Cancer 1930-1990





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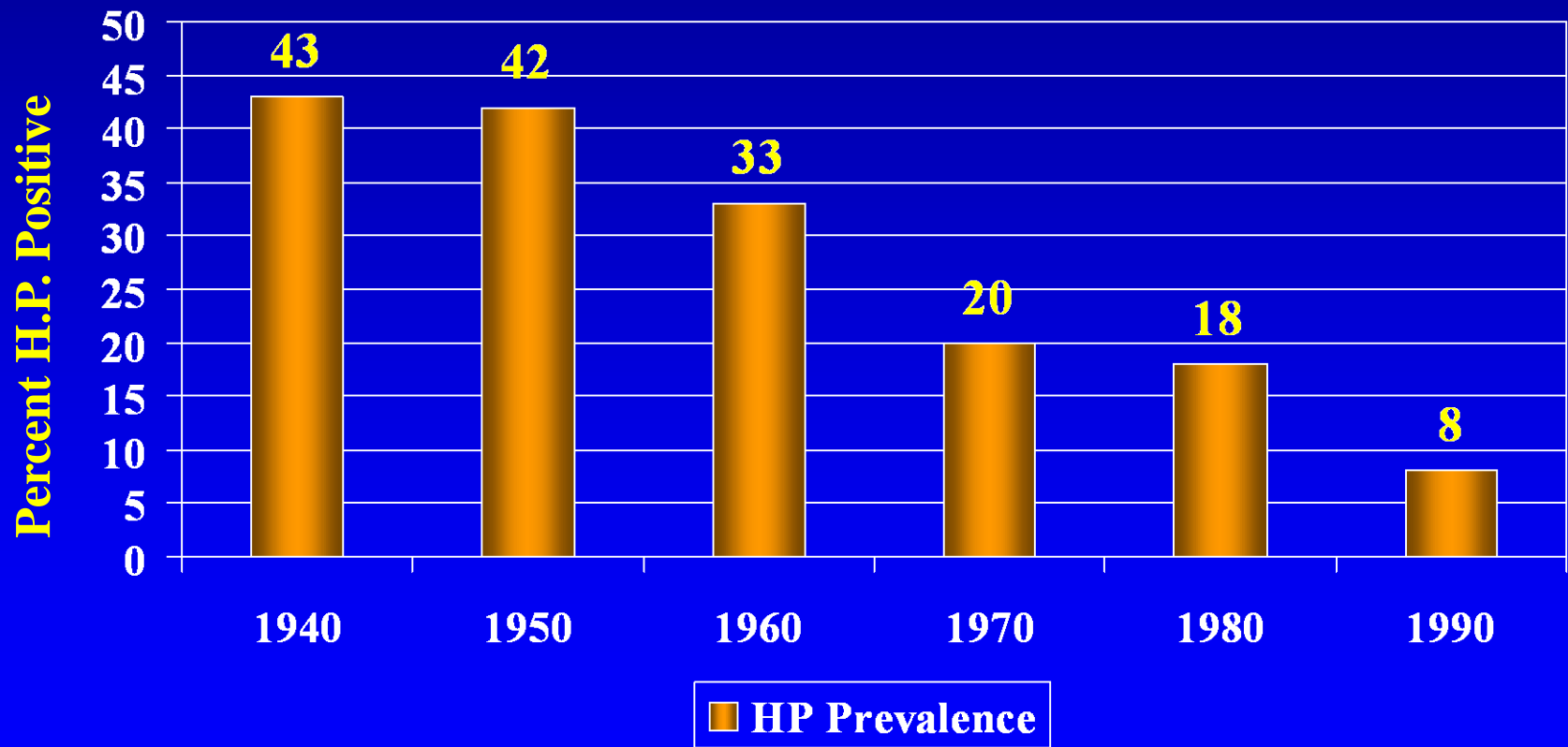




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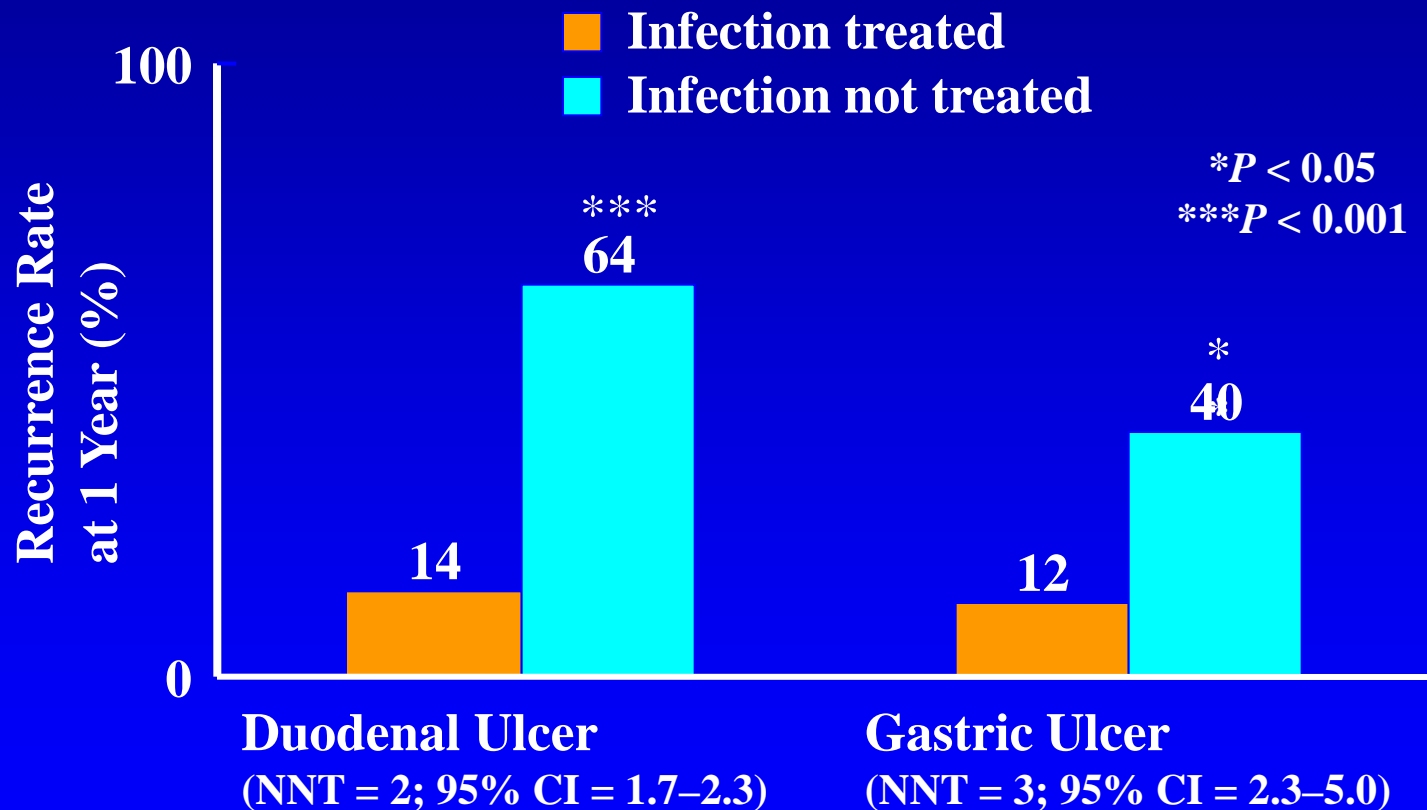
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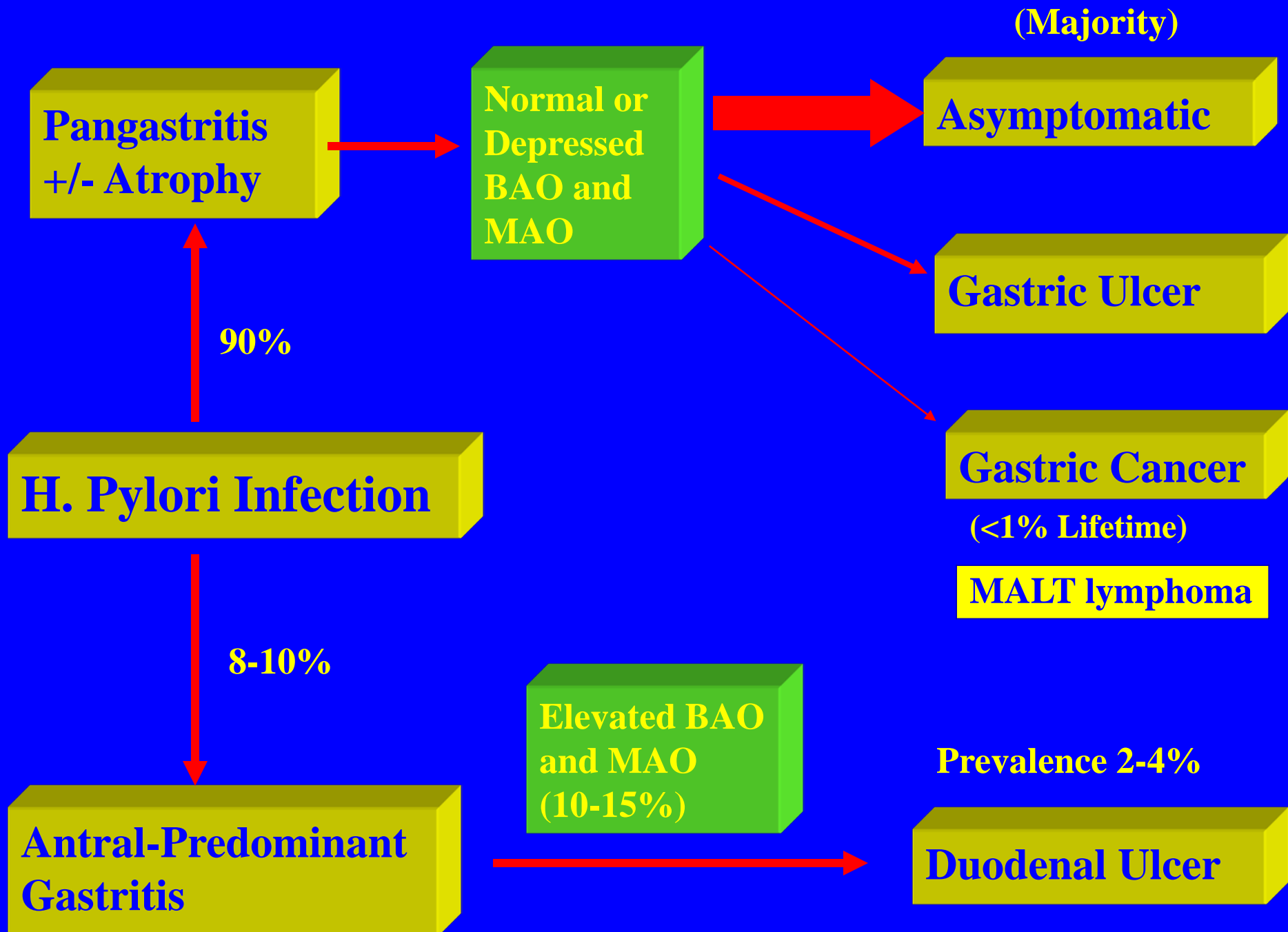
Helicobacter Prevalence Rates in 15 Year-Olds by Decade (UK)



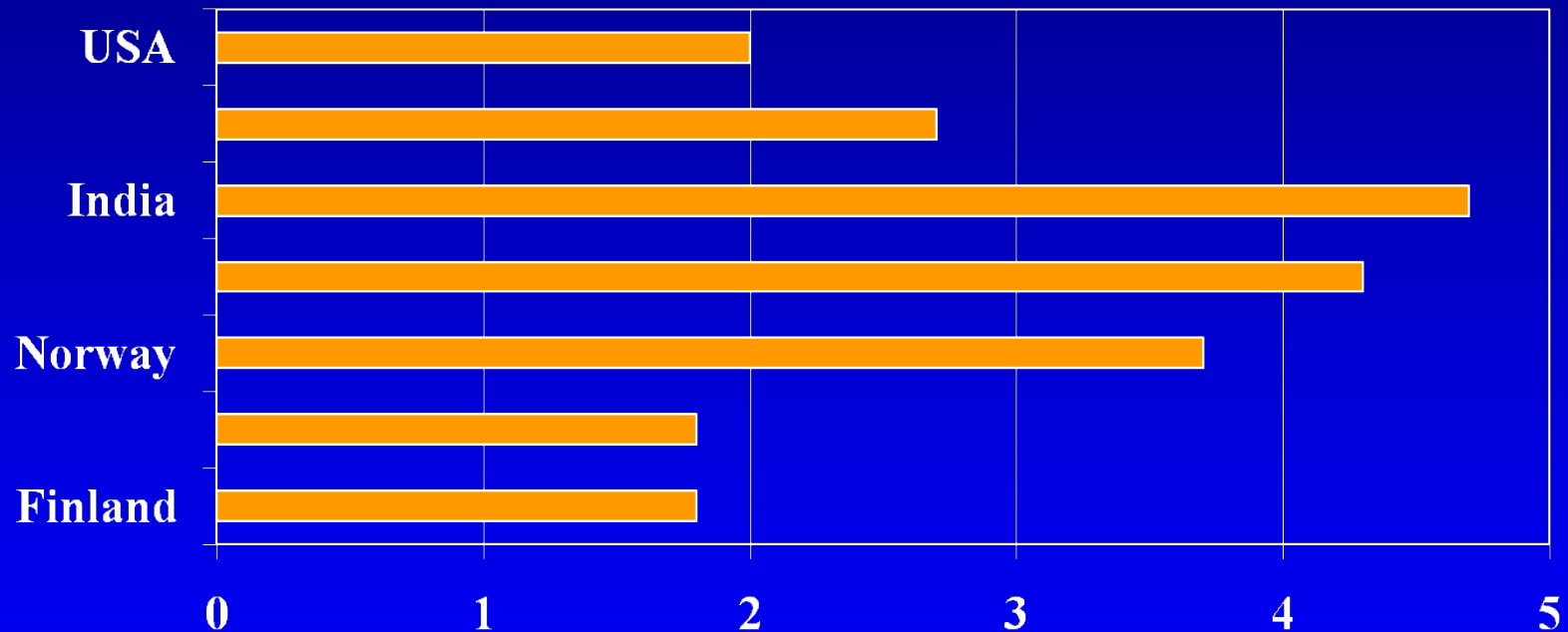
Decreased Ulcer Recurrence After Treatment of *H. pylori* Infection

Fifty-two trial meta-analysis in which ulcer recurrence rates were assessed after treatment for *H. pylori* infection or control treatment





Percent of Asymptomatic H.P Positive Patients with Active Ulcers



	Finland	USA	Norway	Japan	India	USA	USA
■ Finland	1.8	1.8	3.7	4.3	4.7	2.7	2