A Guide to *Helicobacter pylori* Disease, Diagnostics, and Treatment

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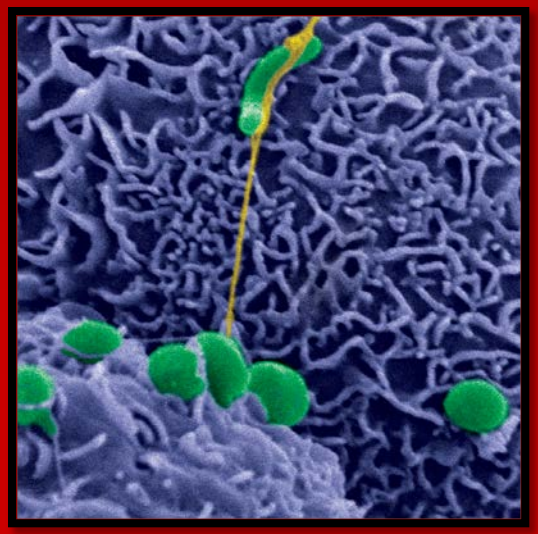
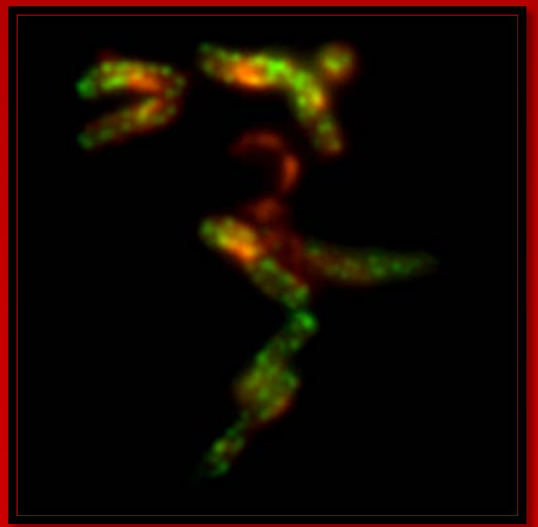
June 4, 2012





Objectives

1. Explore the pathogenesis, epidemiology, and diseases associated with *H. pylori*
2. Review the available and recommended testing strategies for diagnosing disease
3. Gain an appreciation for the challenges regarding: proper ordering practices, treatment failure, and retreatment

J.R. Warren

THE LANCET, JUNE 4, 1983

UNIDENTIFIED CURVED BACILLI ON GASTRIC EPITHELIUM IN ACTIVE CHRONIC GASTRITIS

J. ROBIN WARREN

UNIDENTIFIED CURVED BACILLI IN THE STOMACH OF PATIENTS WITH GASTRITIS AND PEPTIC ULCERATION*

BARRY J. MARSHALL J. ROBIN WARREN

Departments of Gastroenterology and Pathology, Royal Perth Hospital, Perth, Western Australia

The Lancet · Saturday 16 June 1984

B.J. Marshall

2005 Nobel Prize in Medicine & Physiology

“I preferred to believe my eyes, not the medical textbooks of the medical fraternity.”

Dr. Robin Warren

Excerpt from Barry Marshall's Nobel Lecture

- ✓ Koch's 3rd Postulate
- ✓ Koch's 4th Postulate

"Barry J. Marshall - Nobel Lecture". Nobelprize.org. 5 Mar 2012
http://www.nobelprize.org/nobel_prizes/medicine/laureates/2005/marshall-lecture.html

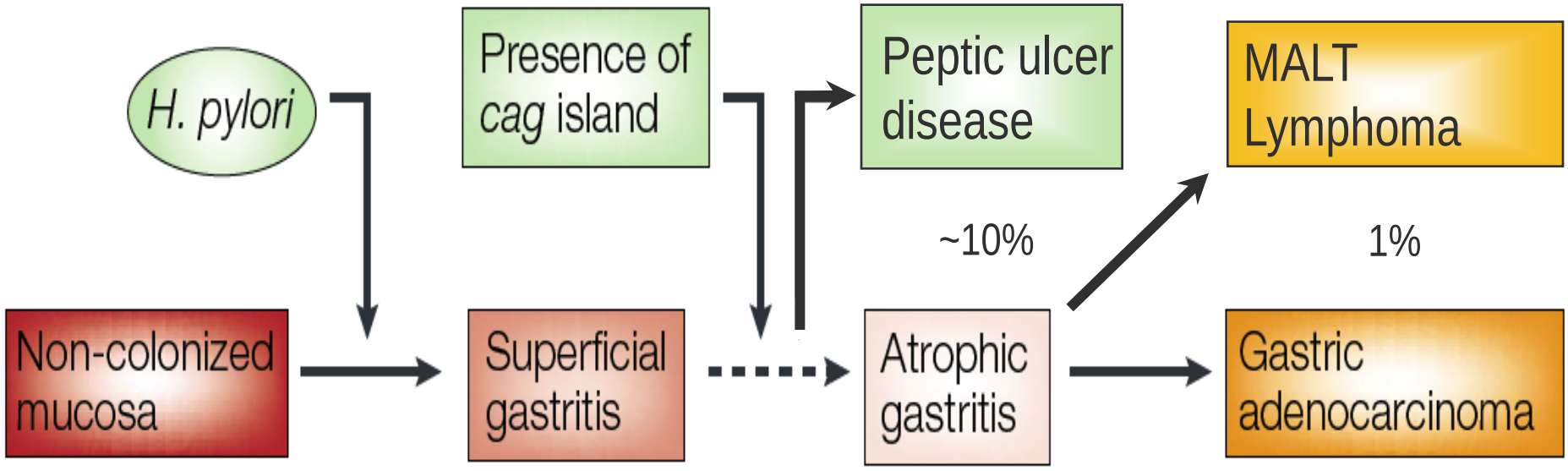
Helicobacter pylori

- Gram negative microaerophile
- Lophotrichous flagella
- Human 1^{o} host
- Gastric pathogen

H. pylori Disease Associations

- Established:
  - Peptic Ulcer Disease (PUD)
  - Dyspepsia
  - Non-ulcer dyspepsia (NUD)
  - Gastric adenocarcinoma
  - MALT lymphoma
- Possible:
  - Iron deficiency
- Not associated:
  - Gastroesophageal reflux disease (GERD)
  - Coronary artery disease (CAD)

Disease progression



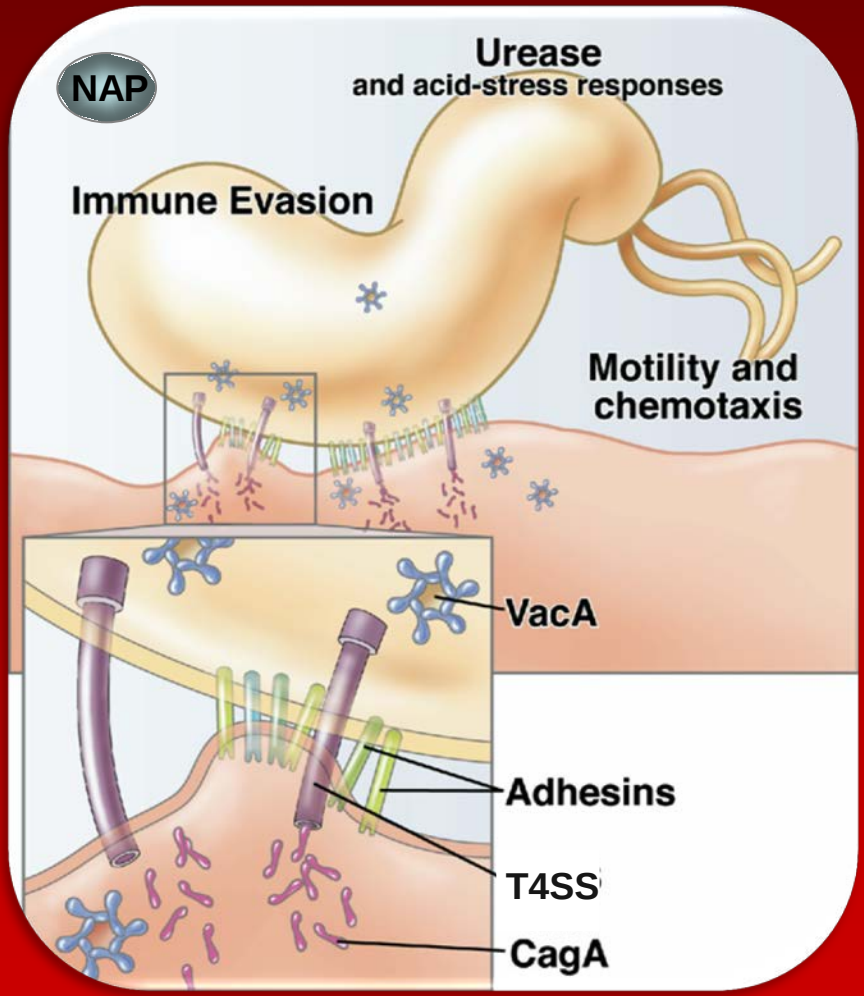
Adapted from: Peek and Blaser, Nature Rev. Cancer, 2002

None → Mild → Severe

WHO classifies *H. pylori* as the only bacterial Class 1 Carcinogen

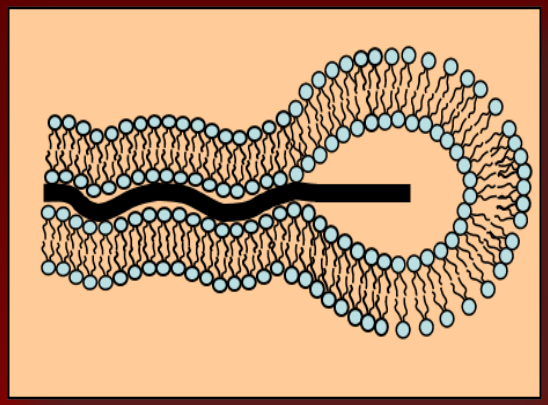
Virulence factors

- Urease and Flagella
- Multiple adhesins
- NAP (Neutrophil Activating Protein)
- VacA (Vacuolating Cytotoxin)
- CagA (Cytotoxin associated gene) & Cag T4SS



Adapted from Amieva and El-Omar, *Gastroenterology*, 2008

Flagella



- Provide motility through harsh stomach environment
- Corkscrew shape of *H. pylori* + flagella allows for penetration of mucus in stomach

- Possess a sheath that masks the flagellin subunit normally recognized by Toll-like receptor 5 (TLR5)[1]
  - Paddle-like structure[2]

[1] Andersen-Nissen *et al*. *PNAS*, 2005

[2] O'Toole *et al.* *Mircobed Infect*, 2000

Urease

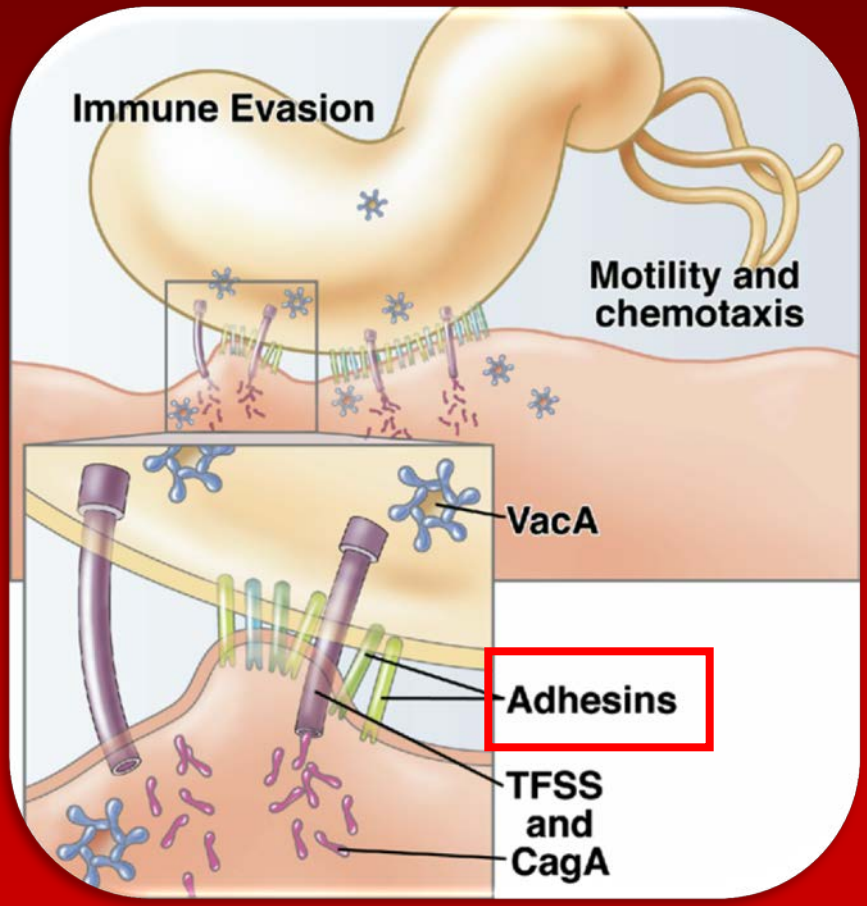
- Highly expressed by all known gastric *Helicobacter* spp.[1]
- Indirectly neutralizes the HCl in the stomach
- Breakdown of urea into CO_2 and ammonia[2]
  - Urea breath test exploits CO_2 production
  - Ammonia neutralizes HCl
- Localized neutralization of the stomach allows for colonization[2]

[1] Solnick, J. Clinical Infectious Diseases, 2003

[2] Kusters *et al. Clin Microbiol Rev*, 2006

Adhesins

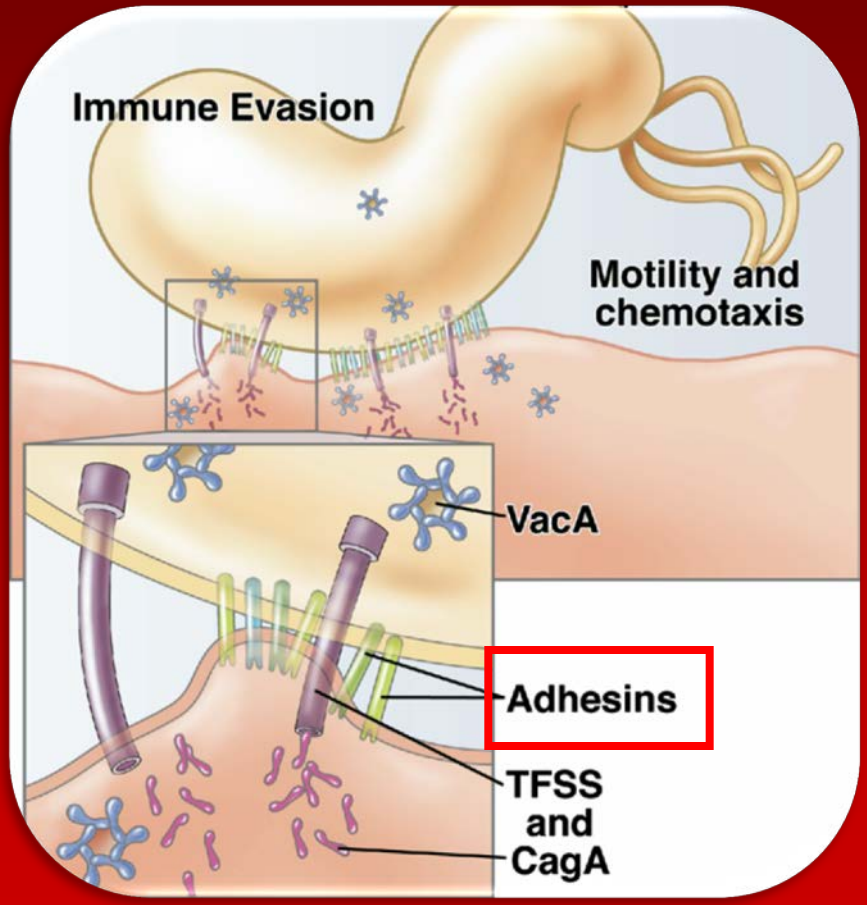
- Surface exposed molecules
  - Haemagglutinin
  - Blood antigen binding protein
  - Lewis antigens
- Initial attachment to the host gastric epithelium
- Facilitate intimate contact



Adapted from Amieva and El-Omar, *Gastroenterology*, 2008

Lewis Antigens

- *H. pylori* Lewis antigens are analogous to Human Lewis blood group antigens
- Bind cell surface and reduce localized inflammation[1]
  - Temporarily inactivates T and B cells
  - Temporary anti-inflammatory effect

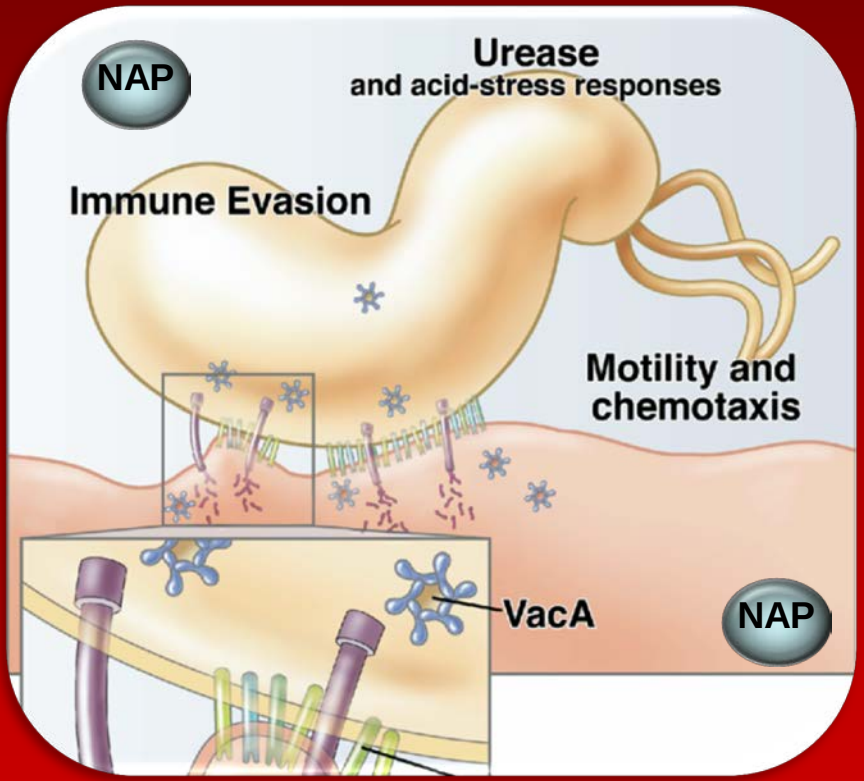


Adapted from Amieva and El-Omar, *Gastroenterology*, 2008

[1]Kusters *et al. Clin Microbiol Rev*, 2006

HP-NAP: Neutrophil Activating Protein[1]

- Attracts/activates neutrophils, monocytes, & dendritic cells
- Leads to a proinflammatory T_h1 polarized response
- MAJOR inflammatory modulator
  - Compounded by host polymorphisms & bacterial factors



Adapted from Amieva and El-Omar, *Gastroenterology*, 2008

[1]D'Elios *et al. FEMS Immunol Med Microbiol*, 2007

VacA: Vacuolating Cytotoxin A

- Gene present in nearly all cultured strains[1]
  - Protein expressed in almost all isolates
  - Active protein produced by 40% of isolates
- Implicated in peptic ulceration[2]
- Forms channels that allow release of nutrients to extracellular space
- Pro-apoptotic & initiates proinflammatory response in conjunction with HP-NAP

[1] Atherton & Blaser, *Journal of Clinical Investigation,* 2009

[2] Atherton *et al. J Biol Chem*, 1995

CagA: Cytotoxicity Associated Gene

- Associated with severe disease state
  - "Oncoprotein"
- Injected into gastric cell by a Type 4 Secretion System
- Tyrosine phosphorylated on multiple repetitive conserved motifs
  - Degree of phosphorylation predicts disease severity

CagA (unphosphorylated)

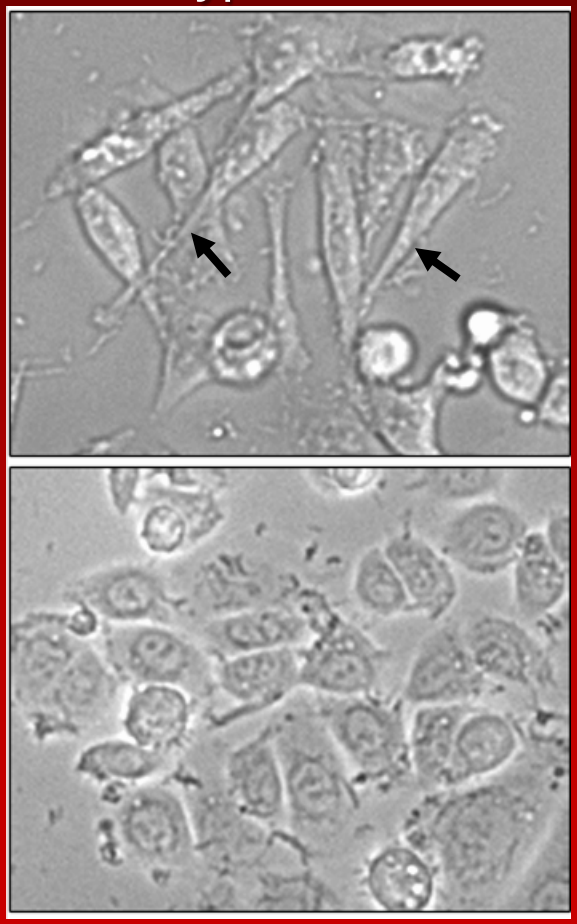
- CagA targets to host membrane
  - Interrupts gastric cellular junctions
  - Disrupts the integrity of cell layers
- Alters cell cycle progression[1]
  - Prolongs cell life
- Upregulates mitogenic genes implicated in carcinogenesis[2]

[1]Chang *et al. Cell Microbiol*, 2006 [2] Franco *et al. PNAS*, 2005

CagA^{PY} (phosphorylated)

- Interacts with phosphotyrosine binding proteins involved in:
  - cytoskeletal rearrangement
  - cell scattering
  - cell elongation
- Cell morphology termed "hummingbird phenotype"
- Triggered by interaction with a cellular oncogene[1]

Wild-type Infected



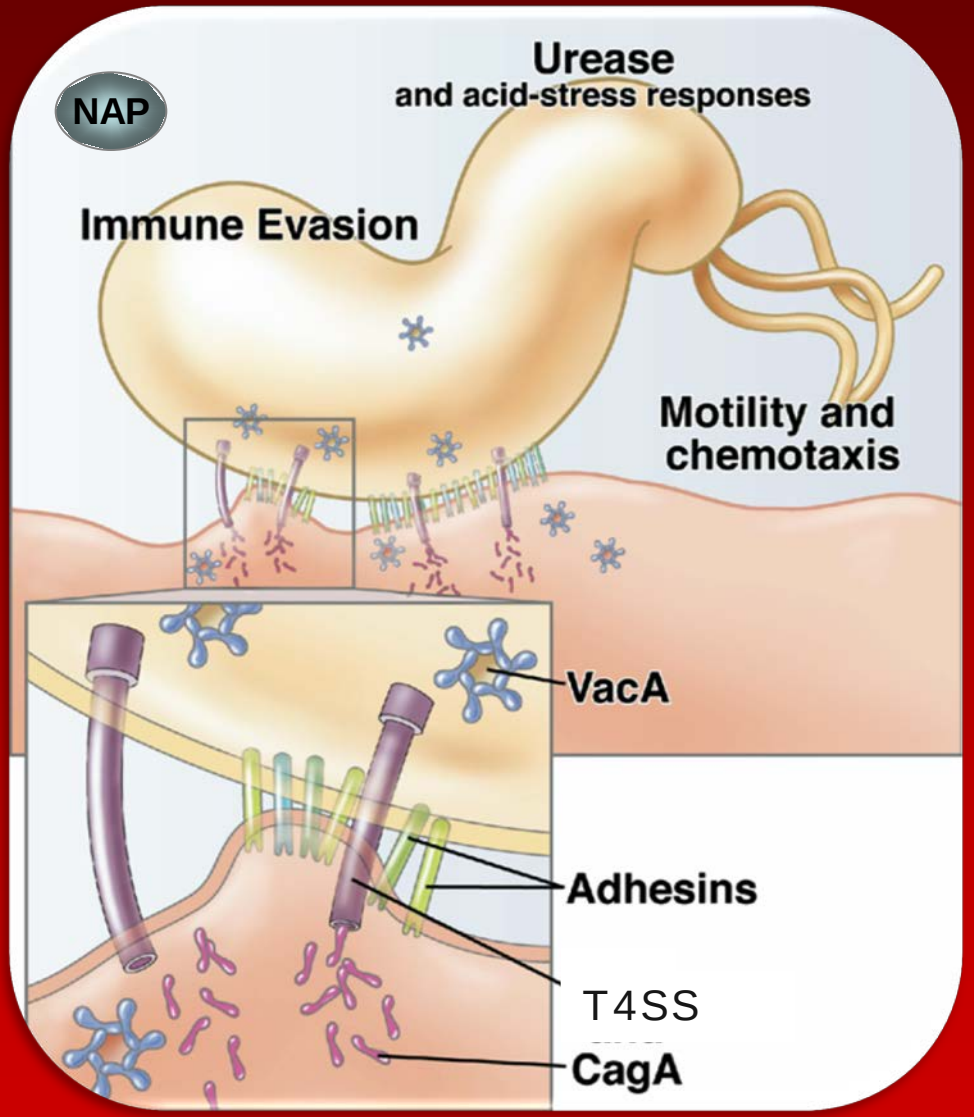
ΔCag Infected

[1]Rieder *et al. Current Opinion in Microbiology*, 2005

Couturier *et al. Infect & Immun*, 2006

Summary of Virulence

- Motility
- Colonization
- Immune evasion
- Immune stimulation
- Cellular damage

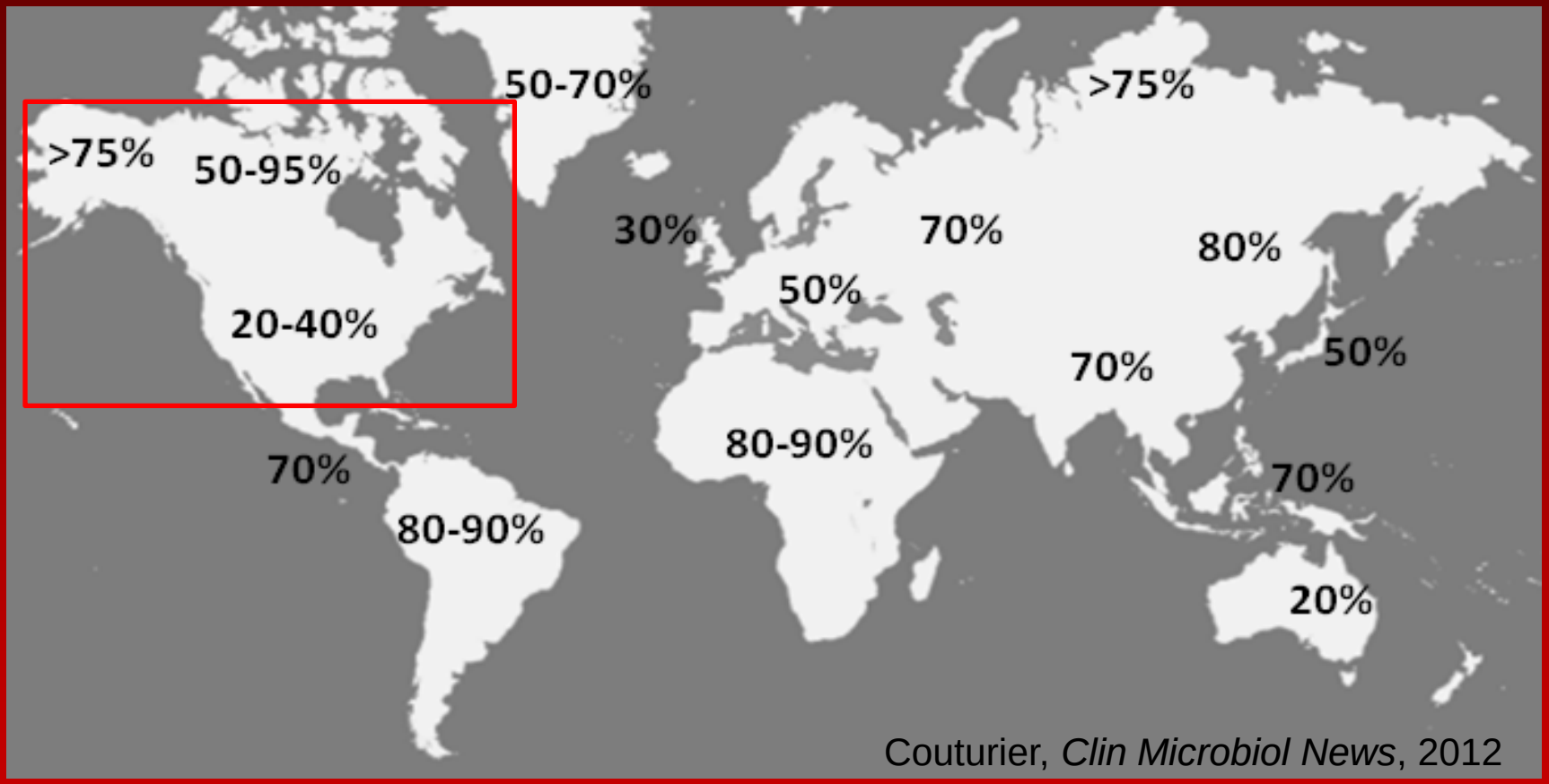


Adapted from Amieva and El-Omar, *Gastroenterology,* 2008

Global epidemiology

Why are we concerned about *H. pylori?*

Worldwide epidemiology



Couturier, *Clin Microbiol News*, 2012

- ~ 50% of the world infected
  - Developing world/impoverished areas primarily
  - Transmission mode still unclear (familial, fecal/oral?)

Epidemiological Trends

- Male skew in *H. pylori* infections (adulthood not childhood)
  - Males have higher PUD & gastric cancer rates (1.5 - 3.0 times more common)[1]
- Infected mothers typically have infected children[2]
- People of low socioeconomic standing are more likely to be infected[3]
- In developed countries infection rates are higher in non-Caucasian individuals[3]
- Occupational exposure to feces linked to increased infection rates[2]

[1]Replogle *et al. Am J Epidemiol*. 1995 [2]Covacci *et al.* 1999 *Science* [3]Azevedo *et al.* 2009 *Helicobacter*

H. pylori in Northern-California

IgG based study of Northern California adults age 20-39

- Ethnic groups chosen based on different gastric cancer risks
- Confirmed sex skew in males for seropositivity
- Strong disparity between Caucasian-Americans and African & Hispanic Americans
- Increasing age also identified as a risk factor

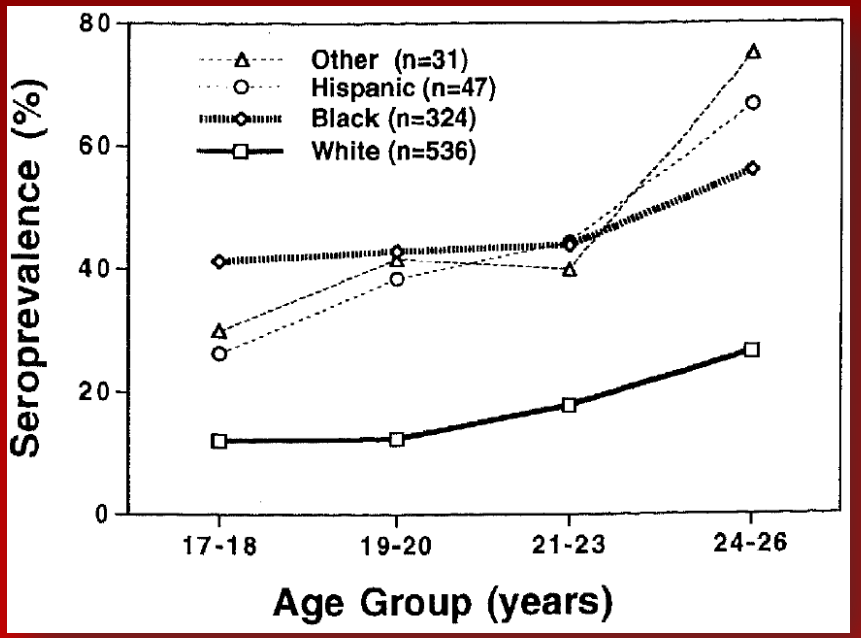
TABLE 1. Characteristics of participants in a study of sex and *Helicobacter pylori* infection and their prevalence of immunoglobulin G antibodies to *H. pylori*: Kaiser Permanente Medical Care Program, 1992–1993

	No.	% of total	No. with *H. pylori*	%	RR* for *H. pylori*	95% CI*
Sex						
Female	300	52.9	63	21.0	1.0	
Male	267	47.1	91	34.1	1.6	1.2–2.1
Race/ethnicity†						
White	201	35.4	20	9.9	1.0	
African-American	198	34.9	64	32.3	3.3	2.1–5.2
Hispanic	157	27.7	69	43.9	4.4	2.8–6.9
Japanese	11	1.9	1	9.1	0.9	0.1–6.2
Age (years)						
20–24	114	20.1	19	16.7	1.0	
25–29	142	25.0	37	26.1	1.6	1.0–2.6
30–34	156	27.5	50	32.1	1.9	1.2–3.1
35–39	155	27.3	48	30.9	1.9‡	1.2–3.0

Replogle *et al. Am J Epidemiol*. 1995

H. pylori seroprevalence in US Army recruits

- Male & Female recruits age 17-26 (Ft. Jackson, SC)
  - No geographic or ethnic restrictions
- Age and race were strongest predictors of “infection”
- Median income is predictive for seropositivity (↓ = ↑)



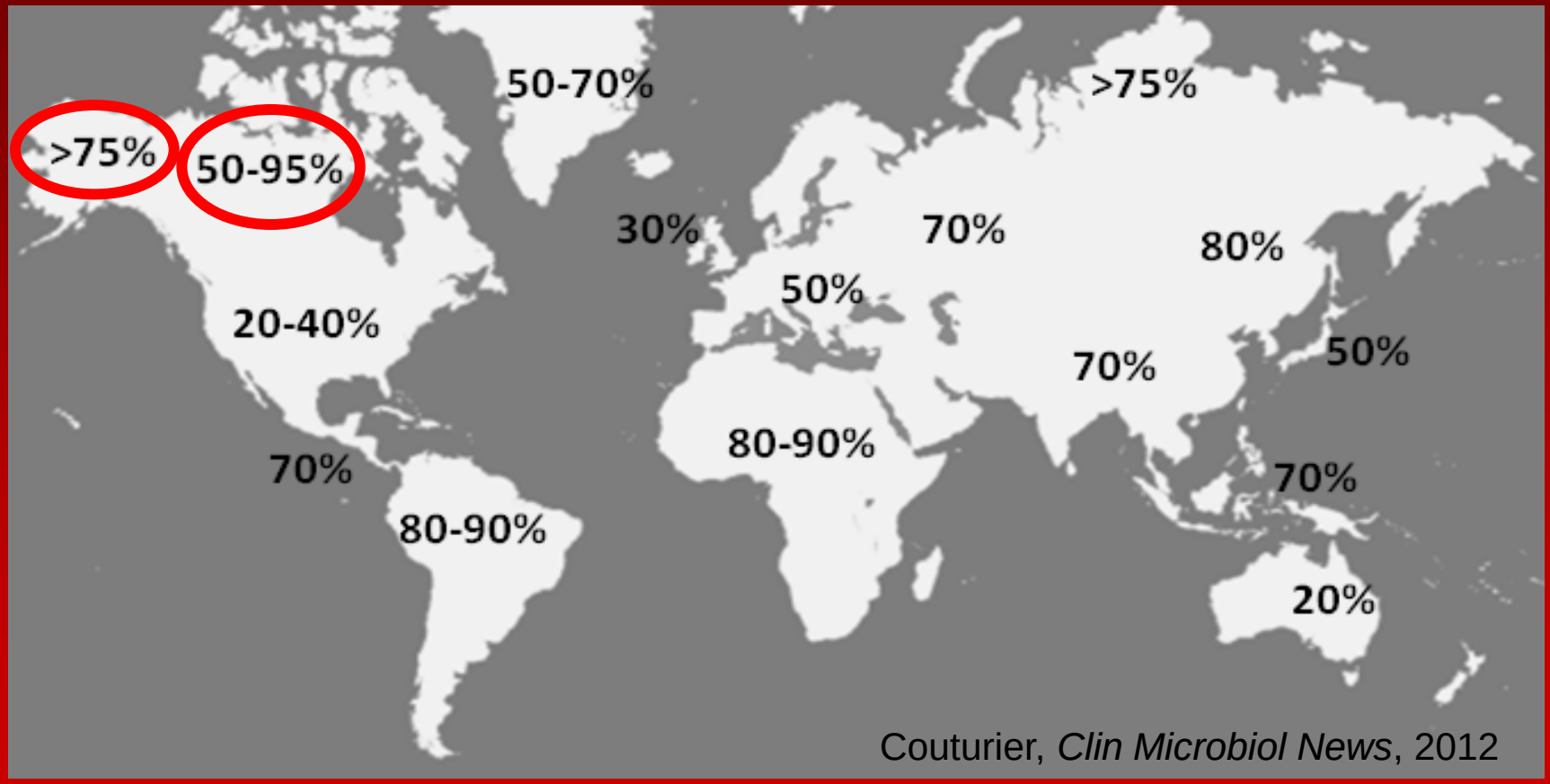
Smoak *et al.* Am J Epidemiol. 1994

H. pylori in low income African Americans from 13 southern states

- Patients self-identified as “white” or “African American”
  - Degree of African ancestry determined by genetic markers as “low, medium, and high”
- Seropositivity of low-income African-Americans and Caucasian:
  - 89% African Americans
  - 69% Caucasians
- African American race 2- to 6-fold increase odds of seropositivity for $VacA^{+}/CagA^{+}$ *H. pylori*
- ↑ odds of *H. pylori*-positivity with increased African ancestry
  - Medium and high ancestry carries 2.5- and 3.4-fold increase in *H. pylori* seropositivity
  - 3.5- and 4.9-fold increase in CagA seropositivity

Epplein *et al. Cancer Epidemiol Biomarkers Prev*. 2011

Arctic Epidemiology



Couturier, *Clin Microbiol News*, 2012

Chesterfield Inlet/Repulse Bay

- Arctic towns share risk factors for *H. pylori* prevalence
  - Overcrowding
  - Inadequate drinking water
  - Poor sewage disposal
- 130 of 256 adults from communities tested
- 51 % *H. pylori* IgG seropositive
  - 62 % CagA seropositive
  - 35 % of *H. pylori* ELISA negative patients were CagA seropositive

McKeown et al. 1999 Am J Gastro.

Aklavik, Northwest Territory

CANHelp project: Aklavik

- Population of 600
  - 60% Inuit, 25% Dene, 15% Alaskan
- Prevalence unknown
- 313 patients screened by UBT
  - 58% positive
- Old Crow,Yukon Ter. project now underway

Cheung *et al*. *Can J Gastroenterol* , 2008

Cancer in Arctic First Nations

- Gastric cancer is 10th most common cancer in Canadian men[1,2]
  - 5th most common cancer in NWT men[1]
  - 2 X more gastric cancer in NWT[1]
  - 3rd leading cause of cancer-related death in NWT vs 9th for all of Canada[2]

Top Three Cancer Diagnoses in Males by Ethnic Group

		Male		
		Dene (n=109)	Inuit (n=32)	Other (n=193)
Rank	1	Colorectal (35%)	Trachea, Bronchus and Lung (25%)	Trachea, Bronchus and Lung (19%)
	2	Trachea, Bronchus and Lung (19%)	Stomach (16%)	Colorectal (17%)
	3	Prostate (7%) Stomach (7%)	x	Prostate (14%)

"Other" includes Non-Aboriginals and Métis. X = cells with less than five cases are suppressed. N values represent the number and % values represent the proportion of cases in each gender-specific ethnic group.
Source: NWT Cancer Registry (1992-2000)

Gastric cancer not in top 6 cancers for Females in NWT

- Alaska natives have 3X more gastric cancer than Caucasian Americans[2]

[1]Cancer in the Northwest Territories, 1990-2000. A descriptive report. 2003. <www.hlthss.gov.nt.ca>

[2]Goodman *et al.* . *Can J Gastroenterol, 2008*

H. pylori antibiotic resistance in Canada

- Canada-wide resistance rates for *H. pylori* (*ca.* 2000)
  - Clarithromycin ~4%
  - Metronidazole 18-22%
- Unknown in first nations people of Canada

CBC**news**

Aklavik residents, scientists hopeful antibiotics curb cancer-causing bacteria
Tuesday, May 26, 2009 | 3:10 PM ET

Fallone CA. Can J Gastroenterol 2000

A prediction of antibiotic resistance

2003 study of Alaska Natives in Anchorage[1]

- 30% of *H. pylori* isolates resistant to clarithromycin
  - 13% w/clari^{S} *H. pylori* failed clari-based treatment
- 66% resistant to metronidazole
  - 50% w/metro^{S} *H. pylori* failed therapy
- Resistance linked to previous macrolide or metronidazole use
- Reinfection rates[2]
  - 7% at six months
  - 10% at one year
  - 15% at two years

[1]McMahon BJ et al. *Ann Intern Med,* 2003

[2]McMahon BJ *et al. Aliment Pharmacol Ther,* 2006

Impact of Therapy

Hospitalization rates between 1998 and 2005 for PUD & related complications w/ special focus on *H. pylori* diagnosis in the USA

- 21% Decrease (Age adjusted)
- Decline in most ethnic groups
  - Lowest rates in whites & decrease in African Americans
  - No decline in Hispanics
  - Many native American tribes declined, others increased dramatically
- Hospitalization for PUD highest for ≥65 years old
  - Higher for men than women
- Age adjusted *H. pylori* hospitalization rates also declined overall

Feinstein *et al*. *Emerg Infect Dis,* 2010

Zhu *et al*. *Clinical Microbiol Infect*, 2006

What effect will treatment have?

Condition	*H. pylori* causation	Effect of *H. pylori* eradication
PUD	Yes	Reduces recurrence
Dyspepsia	Yes in some	Symptom improvement in some
NUD	Possibly in few	Improvement in some
Gastric Cancer	Yes	Little effect if any
MALT lymphoma	Yes	Remission in ≥ 50%
Iron Deficiency	Likely in some	Improvement in some
NSAID ulcers	Naïve users?	May reduce incidence
GERD	No	None
CAD	No	None

Fennerty, *Cleveland Clin J Med,* 2005

To Treat or Not to Treat

…and how to treat

First we must decide whether to test

New Dyspepsia Guidelines

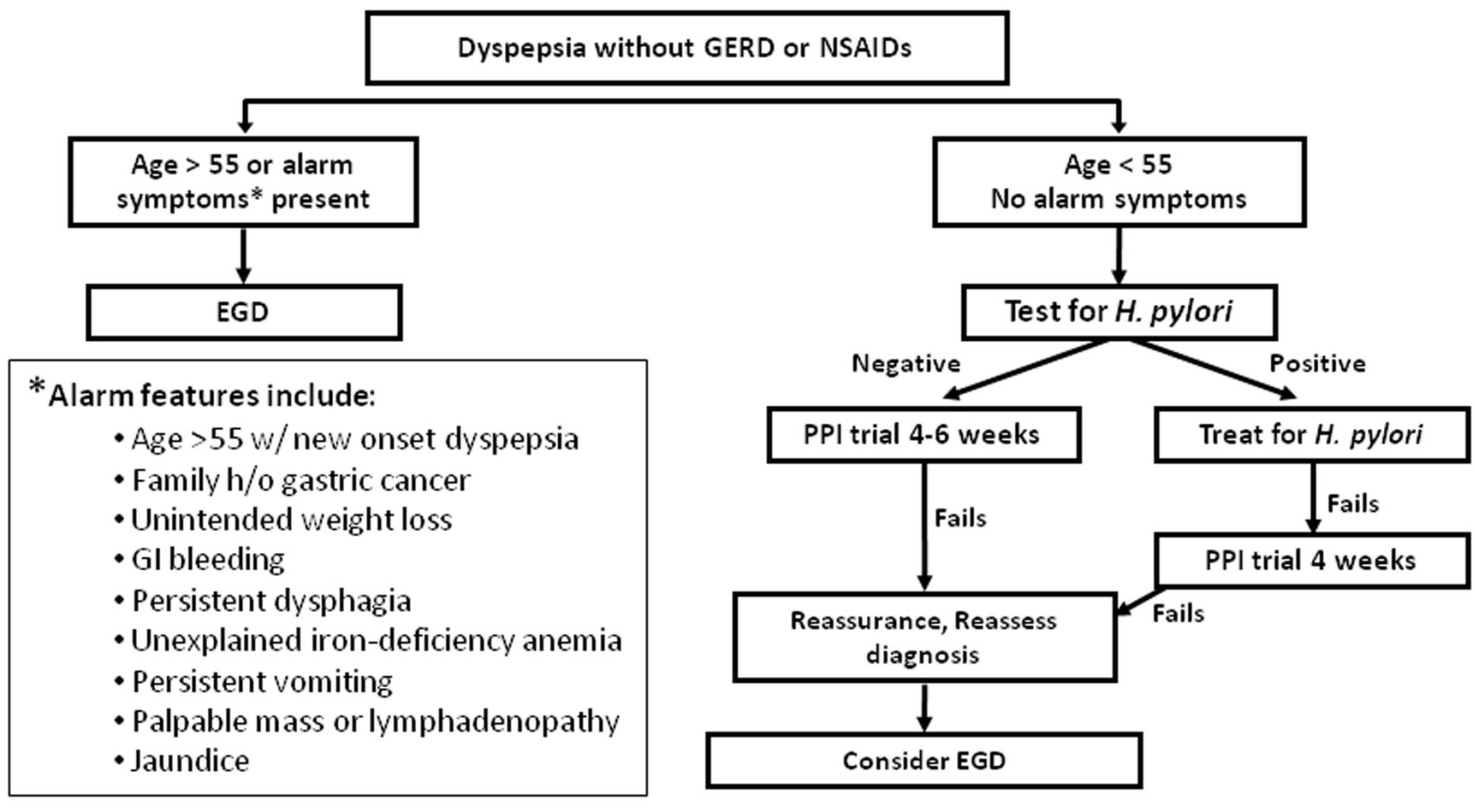
- "Chronic or recurrent pain or discomfort centered in the upper abdomen"
- The AGA recommends that:

  "Patients 55 years of age or younger without alarm features should receive *H. pylori* test and treat followed by acid suppression if symptoms remain."

- Despite this clear mandate…
  this is not happening!

Talley et al. *Gastroenterology*, 2005

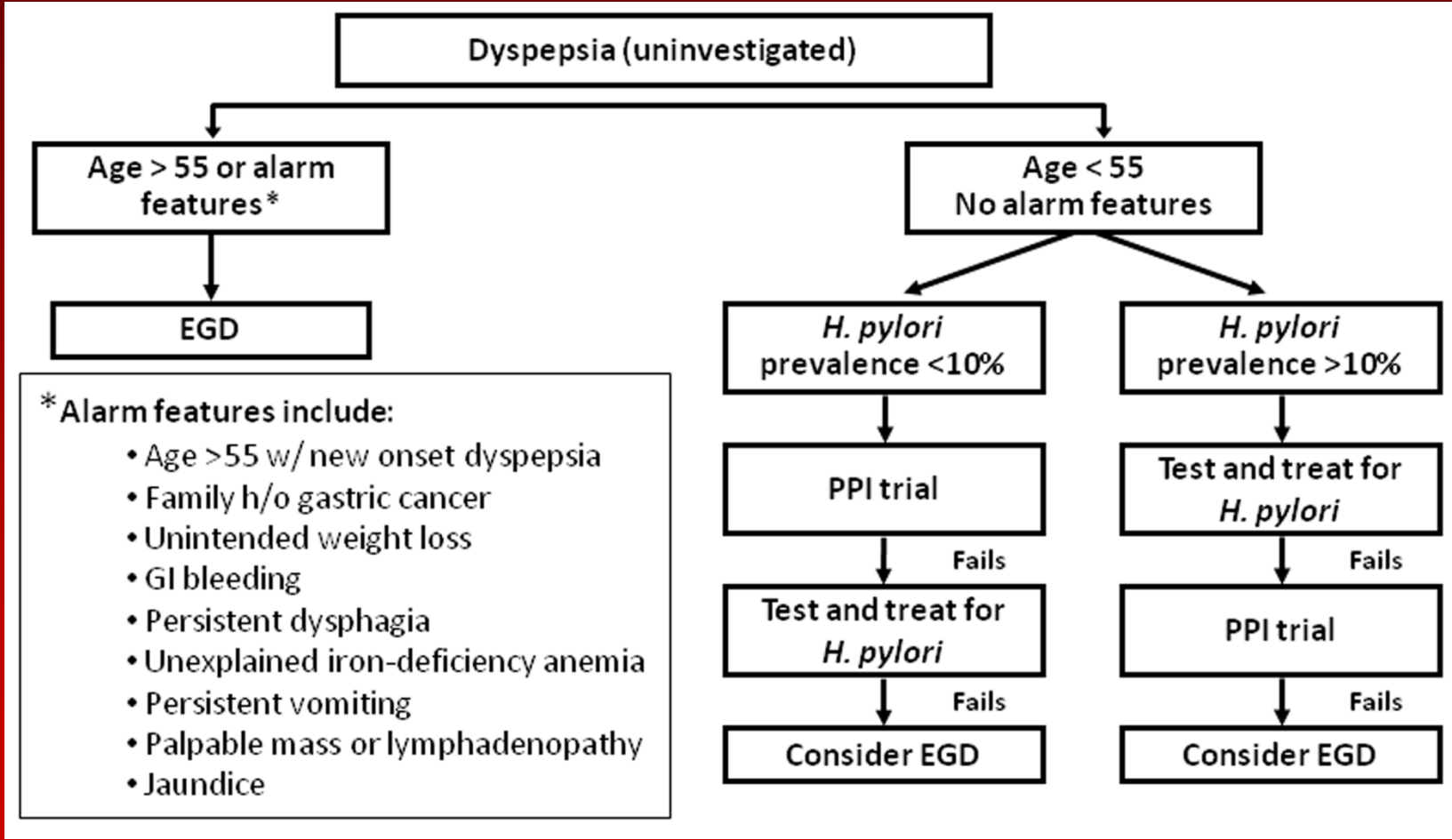
New AGA Dyspepsia Guidelines



EGD: esophagogastroduodenoscopy

Couturier. *Clin Micro News* 2012 (adapted from Talley et al. *Gastroenterology*, 2005)

Not only the AGA…
New ACG Dyspepsia Guidelines



EGD: esophagogastroduodenoscopy

Couturier. *Clin Micro News* 2012 (Adapted from Talley and Vakal *Am J of Gastroenterology*, 2005)

Testing Methods

Laboratory testing

Endoscopy-based (Invasive)

- Culture from biopsy & susceptibility
- Rapid urease from biopsy (CLO)
- Immunohistochemistry

Non-endoscopy (Non-invasive)

- Serology (IgA, IgM, IgG)
  - No longer recommended!
- ^{13}C or ^{14}C-urea breath test
- Stool antigen test

Endoscopy-based: Culture

Advantages:

- Provides clinical isolate for susceptibility testing
- Direct evidence of infection

Disadvantages:

- Limited sensitivity
- Demands highly experienced microbiologists
- Invasive procedure

Endoscopy-based: Rapid Urease (CLO)

Advantages:

- Direct evidence of infection with CLO
- Rapid turn around time
- Limited technical expertise required

Disadvantages:

- Non-specific
- Invasive procedure

Non-Endoscopy: Urea Breath Test

^{13}C or ^{14}C-urea ingested by patient; test for isotopic CO_2 in patient breath

Advantages:

- Rapid result: can be performed in the doctors office (if available)
- Direct measure of CLO infection
- Test post treatment (confirm eradication)
- High sensitivity
- FDA approved for pediatric use

Disadvantages:

- ^{14}C involves exposure to radiation
- PPIs & antibiotics must be stopped 2 weeks prior
- Requires technical demands from physician office
- Not specific for *H. pylori*
- Limited availability & expensive

Non-Endoscopy: Stool Antigen Test

Immunoassay detection of *H. pylori* antigen in the stool

Advantages:

- Detect active infection/monitor therapy
- Least invasive
- Excellent for pre- and post-treatment
- Readily available
- High specificity and sensitivity
- FDA approved for pediatric use

Disadvantages:

- Stigma in sample type
- PPIs & antibiotics should be stopped
- Variable performance across vendors
  - Poly vs monoclonal

Vaira and Vakil, *Gut* 2001

Non-Endoscopy: Serology

Includes IgA, IgM, and IgG testing

Advantages:

- Easily establish prevalence in research studies
- Non-invasive and inexpensive
- Not directly affected by antibiotic or PPI use

Disadvantages:

- Does NOT diagnose an active infection
- CANNOT be used as test-of-cure
- Limited sensitivity; negative result does not rule out
- Can lead to clinical confusion
- May NOT reimburse in some states/insurance carriers

Test Performance of Non-Invasive Testing

	Percentages (%)	
Test	Sensitivity	Specificity
Stool antigen test	90-95%	90-95%
Urea breath test	95-100%	90-95% ??
Serum IgG antibody*	80-85%	75-80%

*Does NOT test for active infection

“We must to it right at UUHC”

January 2011 – December 2011

	UBT	SAT	IgG	IgG & IgA	IgA	IgM
UU Hospital	104	319	290	384	12	360

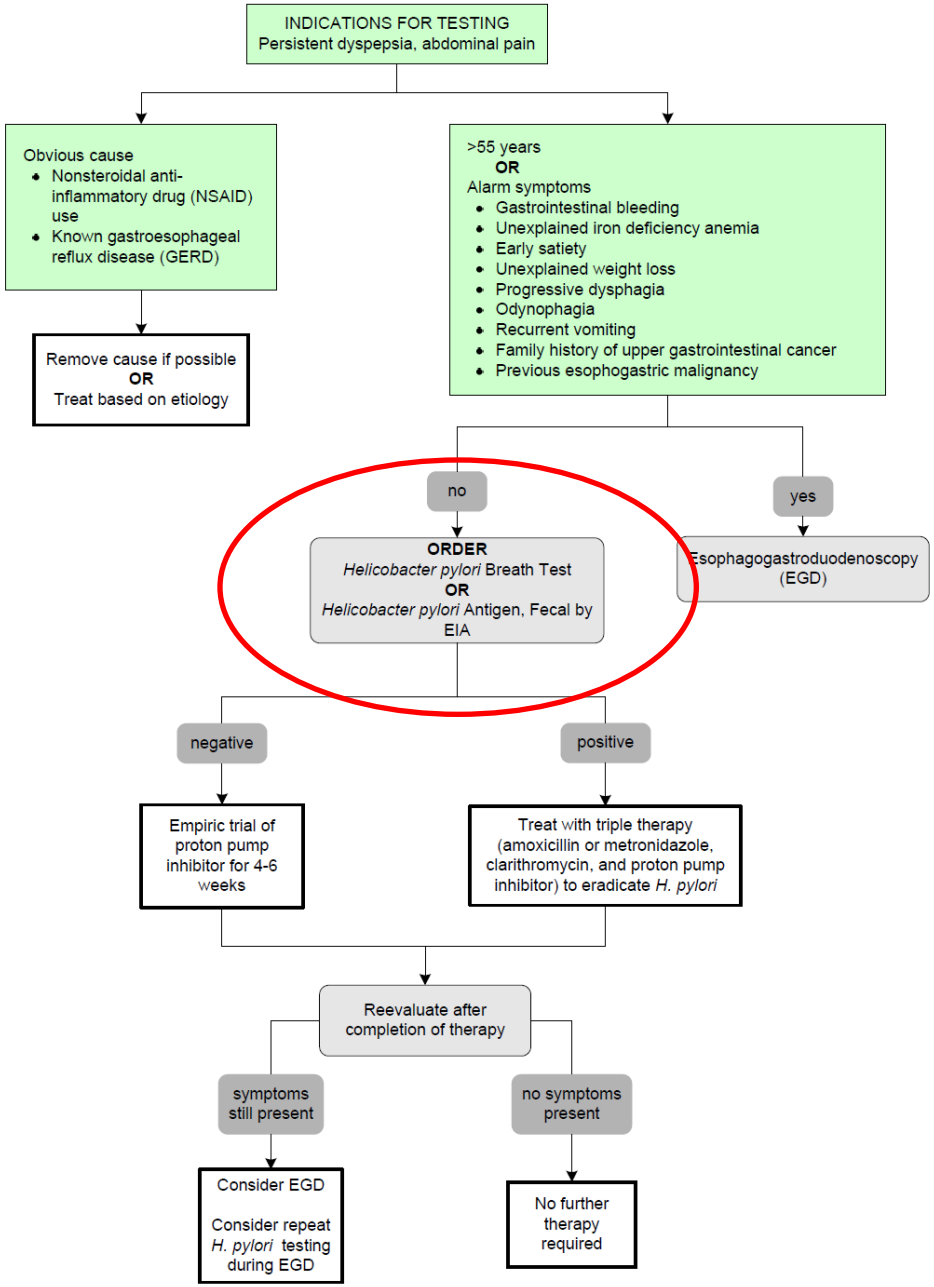
- UUH – 423 active tests / 1046 serology

  ~1 active : 3 passive

ARUP Consult

Helicobacter pylori Testing

Click here for topics associated with this algorithm



		administration not followed correctly • Presence of other gastric spiral organisms such as *H. heilmannii* ^{13}C and ^{14}C breath tests are noninvasive, but expensive due to need for special equipment	
Helicobacter pylori Antigen, Fecal by EIA 0065147 Method: Qualitative Enzyme Immunoassay	Determine if *H. pylori* has been eradicated or just temporarily suppressed, especially in adult patients with complicated, recurrent or refractory peptic ulcers Antigen testing should be performed no sooner than 1 month after therapy concluded	Less accurate in pediatric patients (low sensitivity)	
Helicobacter pylori Antibodies, IgG & IgA 0050994 Method: Semi-Quantitative Enzyme Immunoassay	Determine if *H. pylori* is causing active infection Not recommended for primary diagnosis	May require repeat testing if results are equivocal and clinical suspicion present	
Helicobacter pylori by Immunohistochemistry 2003941 Method: Immunohistochemistry	Aid in histologic diagnosis of *H. pylori* Stained and returned to client pathologist; consultation available if needed		

Additional Tests Available

Click the plus sign to expand the table of additional tests.

Ordering Rules for CPOE

- WARNING FLAG for IgG, IgA, IgM:
- “Do not use to diagnose *H. pylori;* order *H. pylori* urea breath test or fecal antigen by EIA”
- Active in March, will re-evaluate efficacy at 6 months.

Evolving Issues with *H. pylori* testing

- Many major insurance carriers no longer reimbursing for certain *H. pylori* testing
- Serology rapidly viewed as "medically unnecessary testing"
- SAT & UBT on a single patient in non-reimbursable

Serology non-reimbursement

- Major insurance plans NOT reimbursing for serology
  - Aetna, Cigna, BC/BS, & Geisinger
    - Likely many others
- States affected:
  - NY, CA, PA, FL, WV, KY, IN, MO, OH, WI, others?
- Specific CPT codes defined as: "medically unnecessary"

So we've correctly diagnosed

Now how do we treat???

Helicobacter pylori treatment

Therapy	Regimen	Duration (Days)	Cure Rate	Indications
Triple (clarithromycin)	PPI, clarithromycin, amoxicillin	10-14	70-85%	Primary therapy for patients with no macrolide exposure or penicillin allergies
	PPI or H_2RA, clarithromycin, metronidazole	10-14	70-85%	Primary therapy for penicillin allergic patients with no macrolide exposure or patients unable to tolerate bismuth quadruple therapy
Quadruple	Bismuth subsalicylate, metronidazole, tetracycline, PPI	10-14	75-90%	Primary therapy for patients with macrolide exposure or patients with penicillin allergies
Sequential	PPI, amoxicillin	5	>90%	Consider as alternative primary therapy to triple therapy (not validated in USA). May be effective in patients with macrolide resistant strains
	PPI, clarithromycin, tinidazole	5		

H. pylori re-treatment

- Salvage therapy indicated on treatment failures

Therapy	Regimen	Duration (Days)	Cure Rate	Indications
Quadruple	Bismuth subsalicylate, metronidazole, tetracycline, PPI	7	68%	Salvage therapy after triple therapy failure
Triple (levofloxacin)	PPI, amoxicillin, levofloxacin	10	87%	Patients who failed triple and/or quadruple therapy. May not be effective in patients with prior quinolone exposure

- Alternative salvage therapies include:
  - Fluoroquinolones
  - Rifabutin (TB drug) 40-90% effective

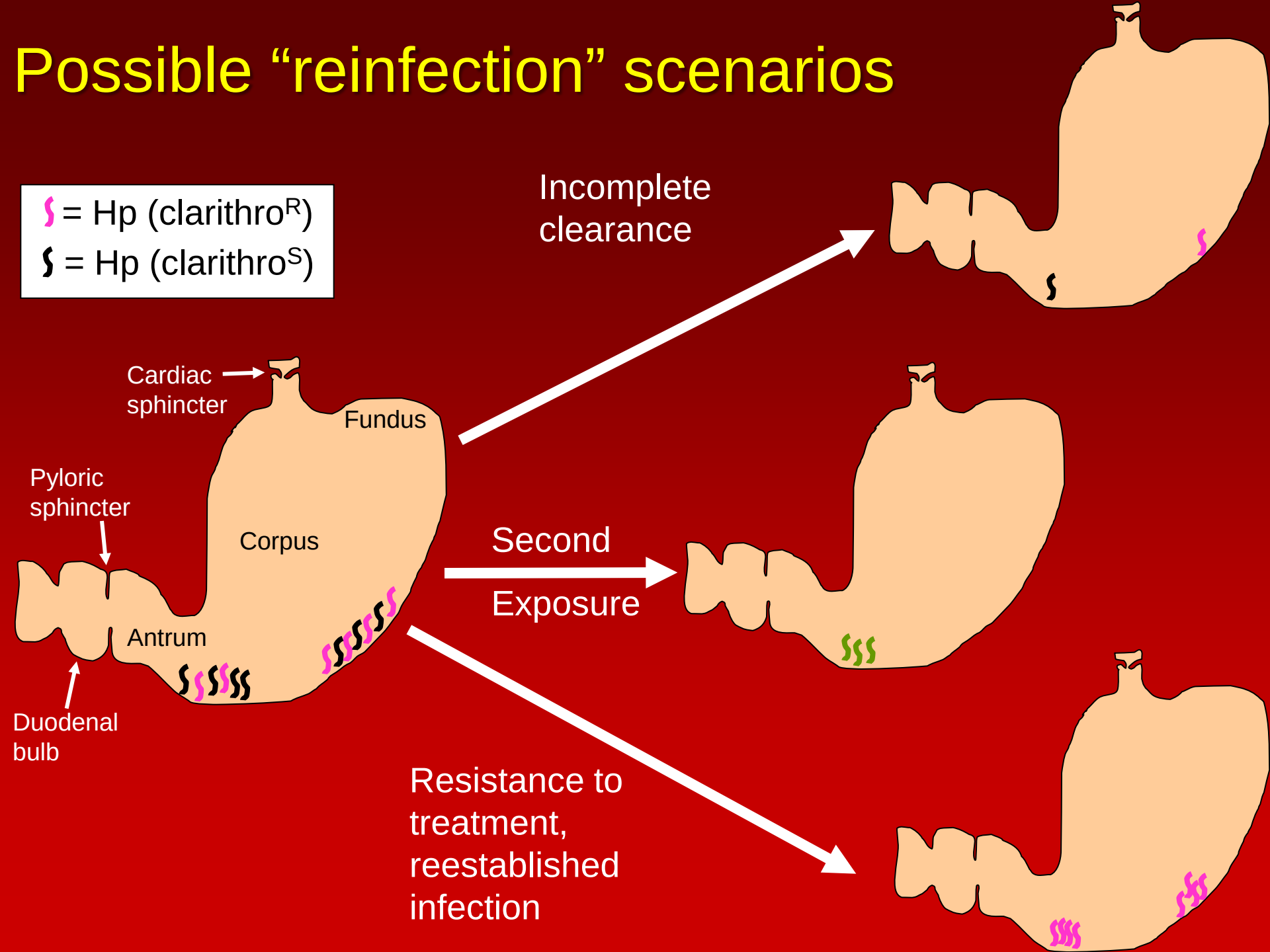
Helicobacter pylori treatment

- Recommended to not repeat the same therapy after initial failure
  - Avoid using therapy consisting of previously used antibiotics

- Re-infection:
  - 5% in developed countries[1]
  - Re-infection may be a result of incomplete clearance *i.e.* relapse

[1] Azevado *et al.* 2009 *Helicobacter*

Possible “reinfection” scenarios



Summary

- *H. pylori* infections remain a global health issue
- Pathogenesis is complex and involves multiple unique virulence factors
- Genetic/ethnic/geographic/socioeconomic disparities exist
- Proper patient management: testing for active infection and appropriate antimicrobial therapy
- Antibiotic resistance and treatment failures are an ongoing challenge


Questions?