

Helicobacter pylori Infections

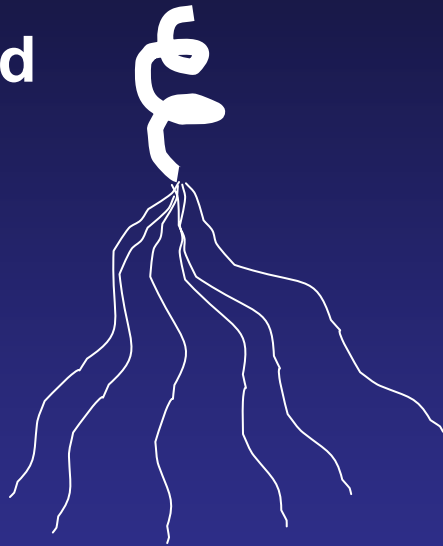
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2005 Nobel Laureates Marshall & Warren

Microbiology: *Helicobacter pylori*

Gastric mucosa

Spiral-shaped
Flagellated



Agar



Slow-growing (3-7 days)
Gram negative rod
Microaerophilic (5% O₂)

Catalase +

Oxidase +

Urease + →

Urea → CO₂ + NH₃ → ↑ pH

Survival

Colonization

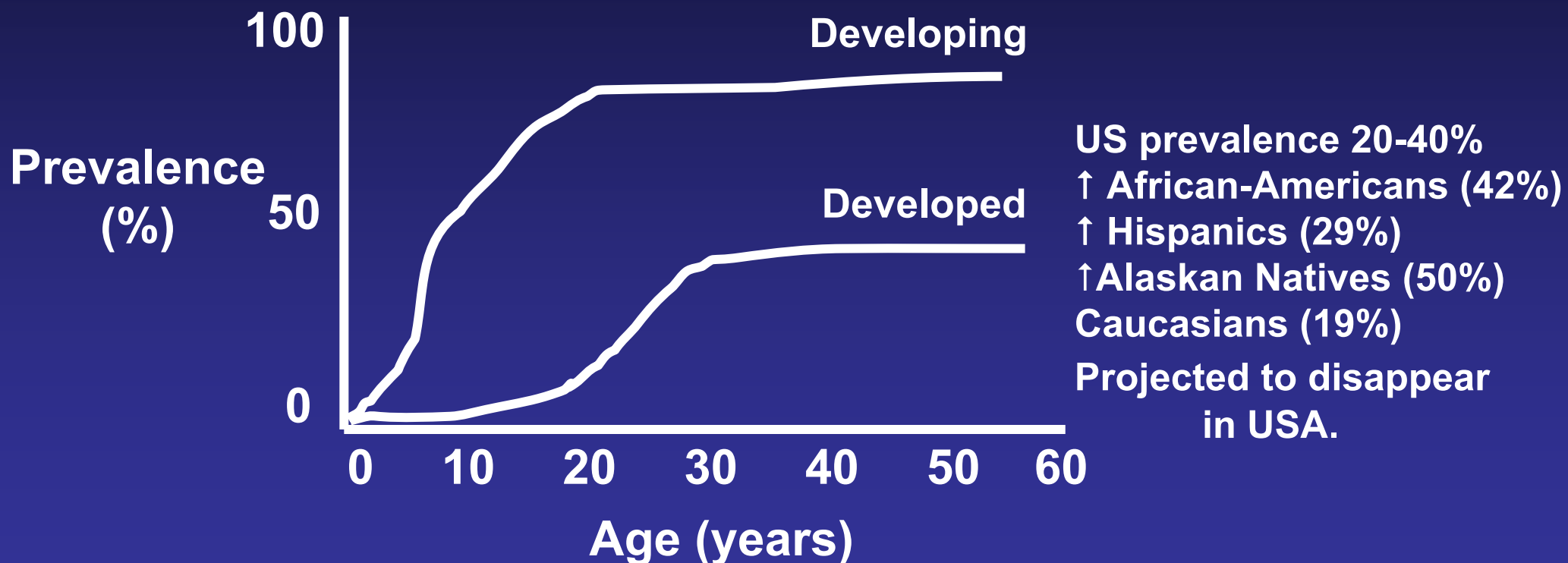
Diagnostic testing

Marked genetic diversity

Helicobacter pylori: Key Points

- Only colonizes humans and primates
- Infects $\geq 50\%$ of the world's population
- A leading chronic infection in humans, similar to dental caries
- Majority are asymptomatic but **all** have gastritis

Prevalence of *H. pylori* among populations in developing and developed countries



Dig Dis Sci 51:1801, 2006; Helicobacter 11:581, 2006.

Transmission of *H. pylori*

Gastric-oral	Vomit [*] 100% +, 10 ⁶ CFU/ml
Saliva	19% +
Fecal-oral	Formed stools 100% negative
	Persons with diarrhea 50% +

*Culture positive rates, N=16
JAMA 282:2240, 1999.

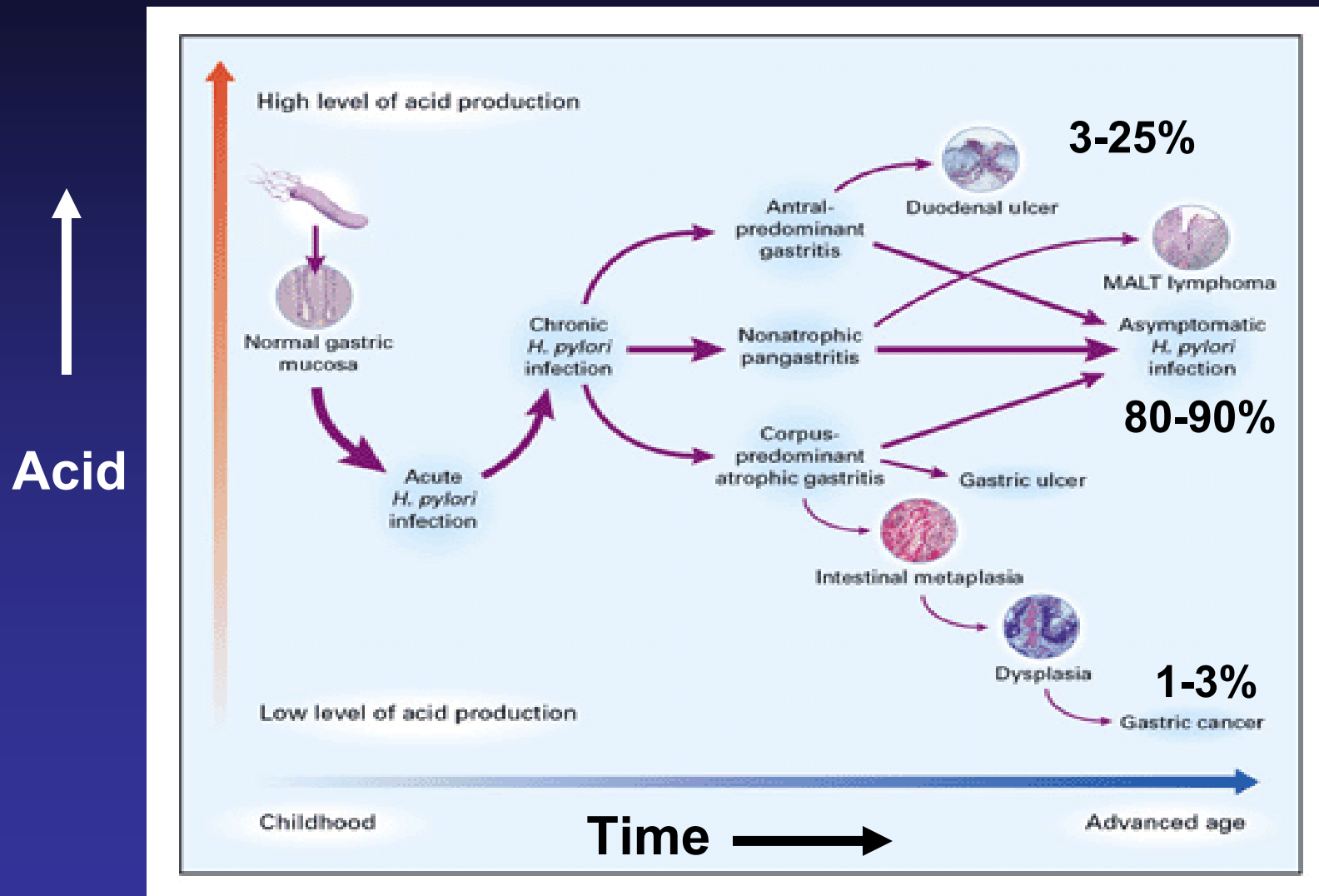
Intrafamilial spread (person-to-person, esp. mother to child)
Low SE status, poor sanitation, crowding
associated with ↑ transmission.

***H. pylori*: Disease Associations**

- **PUD: 95% DU, 70% GU**
- **MALT lymphomas (72-98%)**
- **Gastric Cancer (60-90%)**
- **Iron deficiency anemia, ITP**
- **Not associated with GERD**

Hp is classified by WHO as a Class 1 carcinogen.
MALT = mucosal-associated lymphoid tissue

Helicobacter pylori: Disease Pathogenesis



All Hp not equal
CagPAI +
>disease risk
(*cagA* gene)

Vacuolating cytotoxin
(*vacA*)

NEJM
Vol. 347
Page 1175
Oct, 2002

Clinical outcome of *H. pylori* infection varies by:

Age of acquisition

Host gene polymorphisms

CYP2C19

IL-1 β , *IL-1R*, *IL2*, *IL6*, *IL8*, *IL-10*, *IL12*

H. pylori strain (Cag PAI & CagA+)

Organism load

Site of pathology

Extent of inflammation

Smoking

**CYP2C19* genotypes influence the rate of PPI metabolism (pharmacogenomics); *IL-1 β* , *IL-1R* and other IL alleles correlate with gastric atrophy/Ca risk.

Diagnosis of *H. pylori* Infection: Tests with Sampling Errors

Culture 100% specific but challenging (Hp is fragile)
Not routine at present.

Invasive Test

Endoscopy with biopsy

- Histology (90-95%/95-98%)*
- Rapid urease test (80-95%/92-100%)

Issues with Histology/RUT: minimum 10^4 organisms
false negatives: bleeding,
PPI/H₂ blockers, abx

* sensitivity/specificity

Diagnosis of *H. pylori* Infection: 'Global' Non-invasive Tests

Serology detects Hp exposure, not active infection
 can not be used for TOC
 low sensitivity & specificity (85%/79%)

Urea Breath Test* C^{13/14} technology
(live Hp) > 90% sensitivity/specificity
 availability variable

Stool Antigen Test* (EIA, immunochromatography)
(live & dead Hp) >90% sensitivity/specificity
 stool handling impt (freeze -20°C)
 less expensive
 monitor therapy & TOC (FDA-approved)

* False negatives with bismuth, abx, PPI use

Approach to Initial Diagnosis of *H. pylori*

- **Stool antigen test or Urea Breath Test**
 - ‘Test and Treat’ in younger population (< 45 yo)
 - No PPI or Abx for at least 2-4 wks prior to testing
- **Endoscopy mandatory if ‘alarm symptoms or signs’:**
 - Age > 45-50
 - Anemia
 - GI bleeding
 - Weight Loss
 - Palpable mass

Who should be treated for *H. pylori* infection?

Established Indications

PUD (active/prior hx)
MALT lymphoma
Atrophic gastritis
After gastric Ca resection
1st degree relative/gastric Ca

Controversial

Non-ulcer dyspepsia*
Use of NSAIDs/ASA
Long term PPI use
Fe deficiency anemia**
Desire of the patient

Maastricht III. Gut 56:772-781, 2007
Am J GE 102:1808, 2007 (USA)

* 'test and treat' if ↑ Hp prevalence

** unexplained

Stratified Approach to *H. pylori* Therapy (PUD, MALT lymphoma)

**PPI BID + Clarithromycin 500 BID +
Amoxicillin 1 gm BID for 7-14 days**

PPI + Clarithro +
Metro 500 mg BID

(1st line therapy, 'Triple')



**PPI BID + Bismuth subsalicylate/subcitrate 525 mg +
Metronidazole 1-2 gms/d* + Tetracycline 500 QID
for 7-14 days**

*Metro 250 mg QID/500 mg TID/
500 mg QID

(2nd line therapy, 'Quadruple')



Case-by-case management, culture & sensitivity

Management Issue: Timing and reliability of test of cure for *H. pylori* Infection

- **Stool antigen test** Perform > 6-8 weeks post-rx*
 - positive test , day 7 post-rx or later → likely treatment failure
 - predictive value for cure of a negative test increases with time post-rx.
- **Urea Breath Test** Perform > 4 weeks post-rx.

* FDA-approved.

However, Maastricht-3
Consensus Report (2005)
states UBT is preferred test
for TOC.

AIM 136:280, 2002
Am J GE 96:2829, 2001
The Medical Letter 6:55, 2008

Stratified Approach to *H. pylori* Therapy (PUD, MALT lymphoma)

**PPI BID + Clarithromycin 500 BID +
Amoxicillin 1 gm BID for 7-14 days**

PPI + Clarithro +
Metro 500 mg BID

(1st line therapy, 'Triple')

Eradication Rates: 50-75%*

**PPI BID + Bismuth subsalicylate/subcitrate 525 mg +
Metronidazole 1-2 gms/d* + Tetracycline 500 QID
for 7-14 days**

*Metro 250 mg QID/500 mg TID/
500 mg QID

(2nd line therapy, 'Quadruple')

Eradication Rate: ~80%

Case-by-case management, culture & sensitivity

***Eradication rate for std. triple rx 10 years ago: > 90%**

***H. pylori* & Antimicrobial Resistance**

- Amoxicillin Rare
- Tetracycline Rare
- Clarithromycin 10-15%

If local resistance is 15-20%, do susceptibility testing or use another treatment regimen.

- Metronidazole 20-30%*

Query abx history: clarithromycin & metronidazole

* nearly 100% in developing countries.

Rates of resistance show substantial **geographic** differences.

Prior, even distant, **Abx hx** can inform likelihood of Hp Abx resistance.

NOTE: Rx with amoxicillin & tetracycline yields low response rates.

AIM 139:463, 2003; CID 44:e5-8, 2007.

Meta-analysis of Sequential Therapy for Hp (N=10 RCTs*, 5 high quality)

	<u>Hp eradication % (95% CI)</u>	<u>N</u>
Sequential Therapy	93.4 (91.3-95.5)	1363
-5d PPI + amox then 5d PPI + clarithro + tinidazole		
Std. Triple Therapy	76.9 (71-82.8)	1384
-PPI + clarithro + amox or imidazole X 7-10 d		

Limitations: only pts naïve to Hp rx (& no PPI/H2B/Abx in 30d)
predominantly Italy **
unable to assess dual clarithro + imidazole R
publication bias?
no RCT to compare to quadruple rx or 14 d triple rx
if fails, limited options

*RCT = randomized controlled trial, only 1 double-blinded **Am J GE 103:2220, 2008 (Spain)
All subgroup analyses favor sequential rx; no triple rx study with higher eradication rate
than sequential rx. AIM 148:923, 2008; 148:962, 2008.

References

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3. Impact of Resistance on *H. pylori* Therapy.

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Annals Internal Medicine 139:463-469, 2003. Impact of prior Abx history on Hp sensitivity.

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