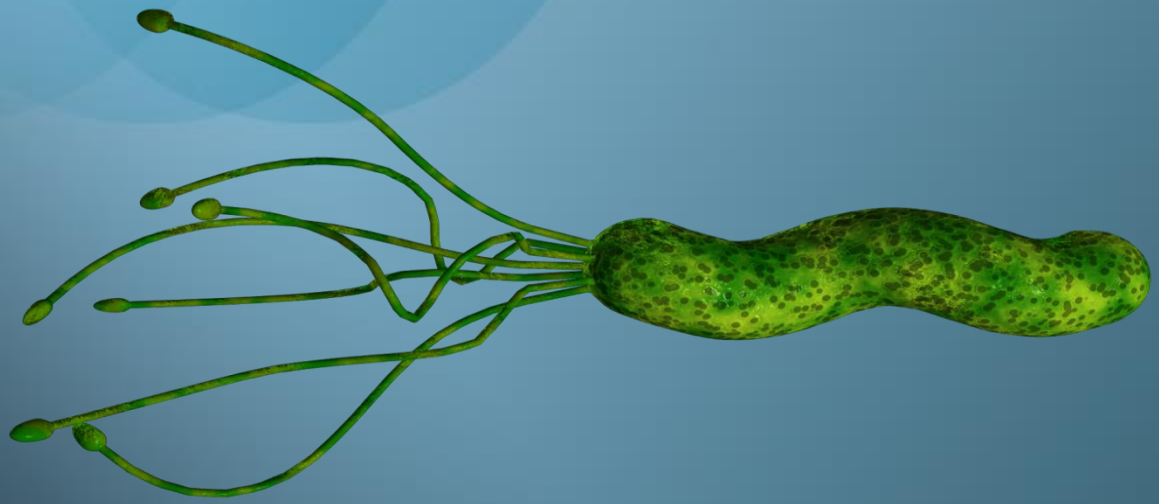
HELICOBACTER PYLORI



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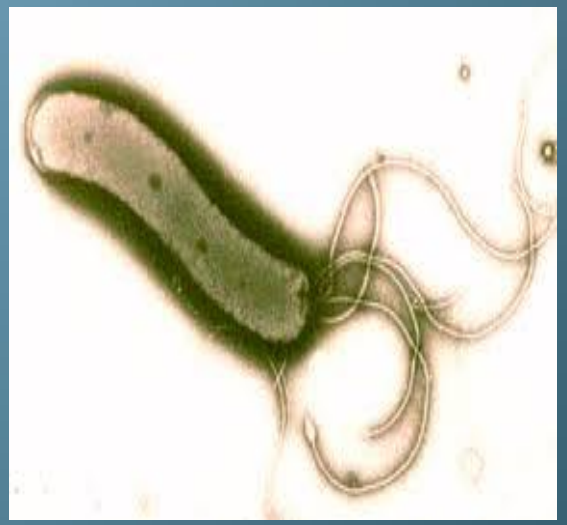
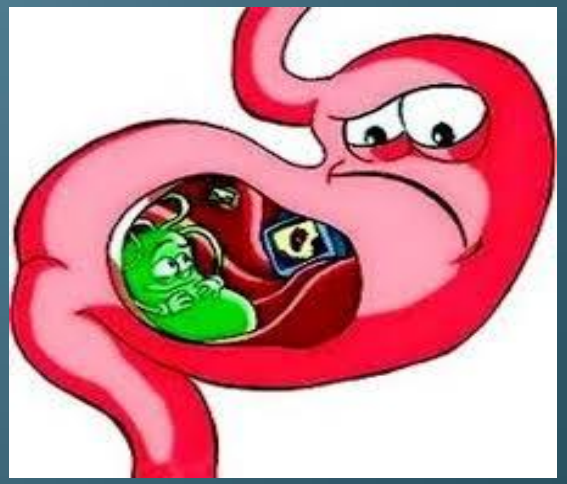
HELICOBACTER PYLORI



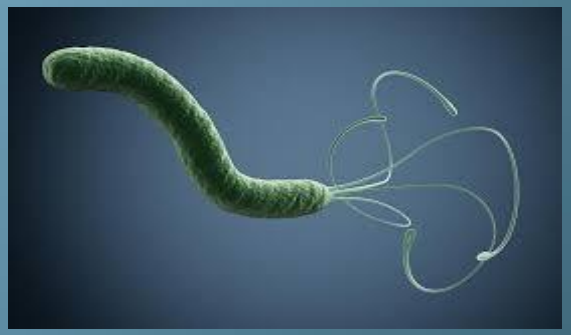
- *H pylori* is a spiral-shaped
- gram-negative.
- It has multiple flagella at one pole
- actively motile
- *H pylori* is oxidase positive and catalase
- positive
- is a strong producer of urease.



- ***H pylori* is associated with**

1. antral gastritis
2. duodenal (peptic) ulcer disease
3. gastric ulcers
4. gastric adenocarcinoma
5. gastric mucosa-associated lymphoid tissue (MALT) lymphomas.

H. pylori



H. pylori verulence factors

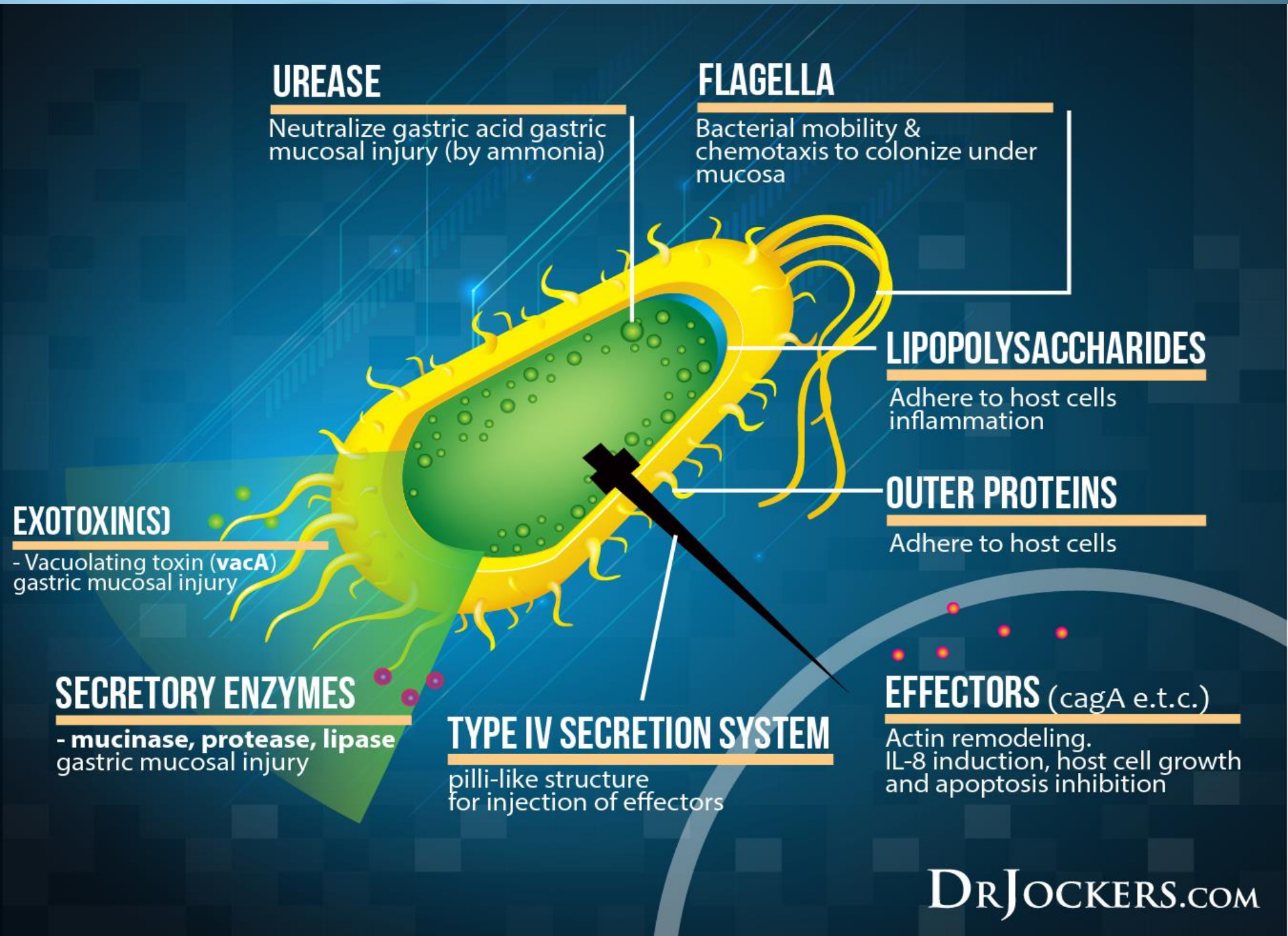
1. Outer membrane proteins:
a. The adhesions: adhesion to host cell
b. Porin proteins, iron transport and flagella proteins

2. The lipopolysuccharide (LPS)

3. The exotoxins: The vaculating (Vac A) toxin (gastric mucosal enjury)
4. The secretory enzymes:
a. The urease : Neutralize gastric acid
b. The mucinase, lipase and protease (mucosal injury)

5. The flagella (motility)

6. The effector cytotoxin: The cytotoxin associated gene A (Cag A).


UREASE
Neutralize gastric acid gastric mucosal injury (by ammonia)
FLAGELLA
Bacterial mobility & chemotaxis to colonize under mucosa
LIPOPOLYSACCHARIDES
Adhere to host cells inflammation
OUTER PROTEINS
Adhere to host cells
EXOTOXIN(S)
- Vacuolating toxin (vacA) gastric mucosal injury
SECRETORY ENZYMES
- mucinase, protease, lipase gastric mucosal injury
TYPE IV SECRETION SYSTEM
pilli-like structure for injection of effectors
EFFECTORS (cagA e.t.c.)
Actin remodeling. IL-8 induction, host cell growth and apoptosis inhibition
DrJockers.com

H. pylori

Pathogenesis

H pylori grows optimally at a pH of 6.0–7.0 and would be killed or not grow at the pH within the gastric lumen.

Gastric mucus is impermeable to acid and has a strong buffering capacity.

On the lumen side of the mucus, the pH is low (1.0–2.0); on the epithelial side, the pH is about 7.4. *H pylori* is found deep in the mucous layer near the epithelial surface where physiologic pH is present.

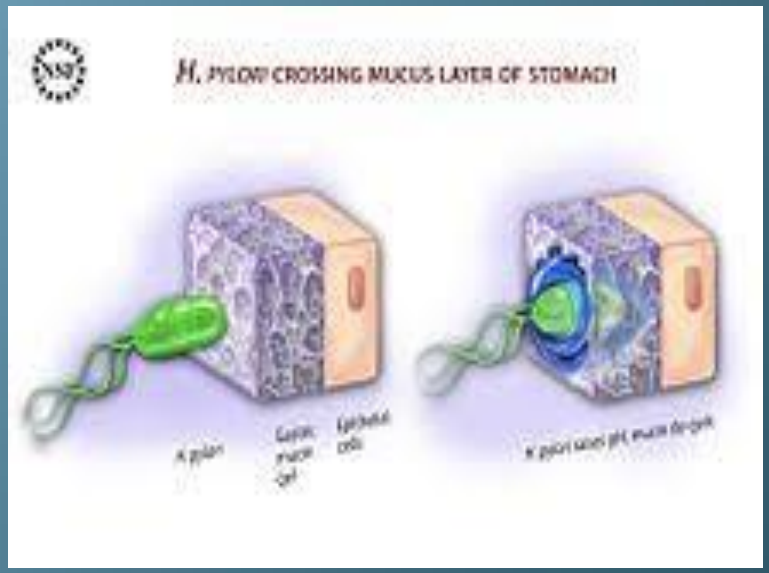
H pylori produces a protease that modifies the gastric mucus and reduces the ability of acid to diffuse through the mucus.

H pylori produces potent urease activity, which yields production of ammonia and further buffering of acid.

H. pylori

H pylori is quite motile, even in mucus, and is able to find its way to the epithelial surface. *H pylori* overlies gastric-type but not intestinal-type epithelial cells.

With its flagella and its spiral shape, the bacterium drills into the mucus layer of the stomach, and can either be found suspended in the gastric mucosa or attached to epithelial cells.



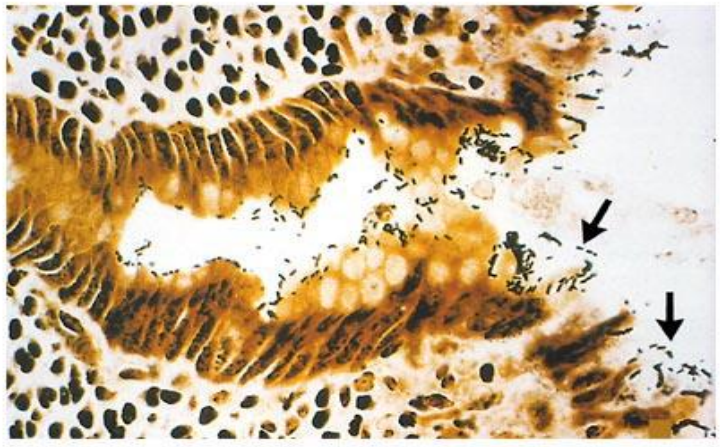
H. pylori

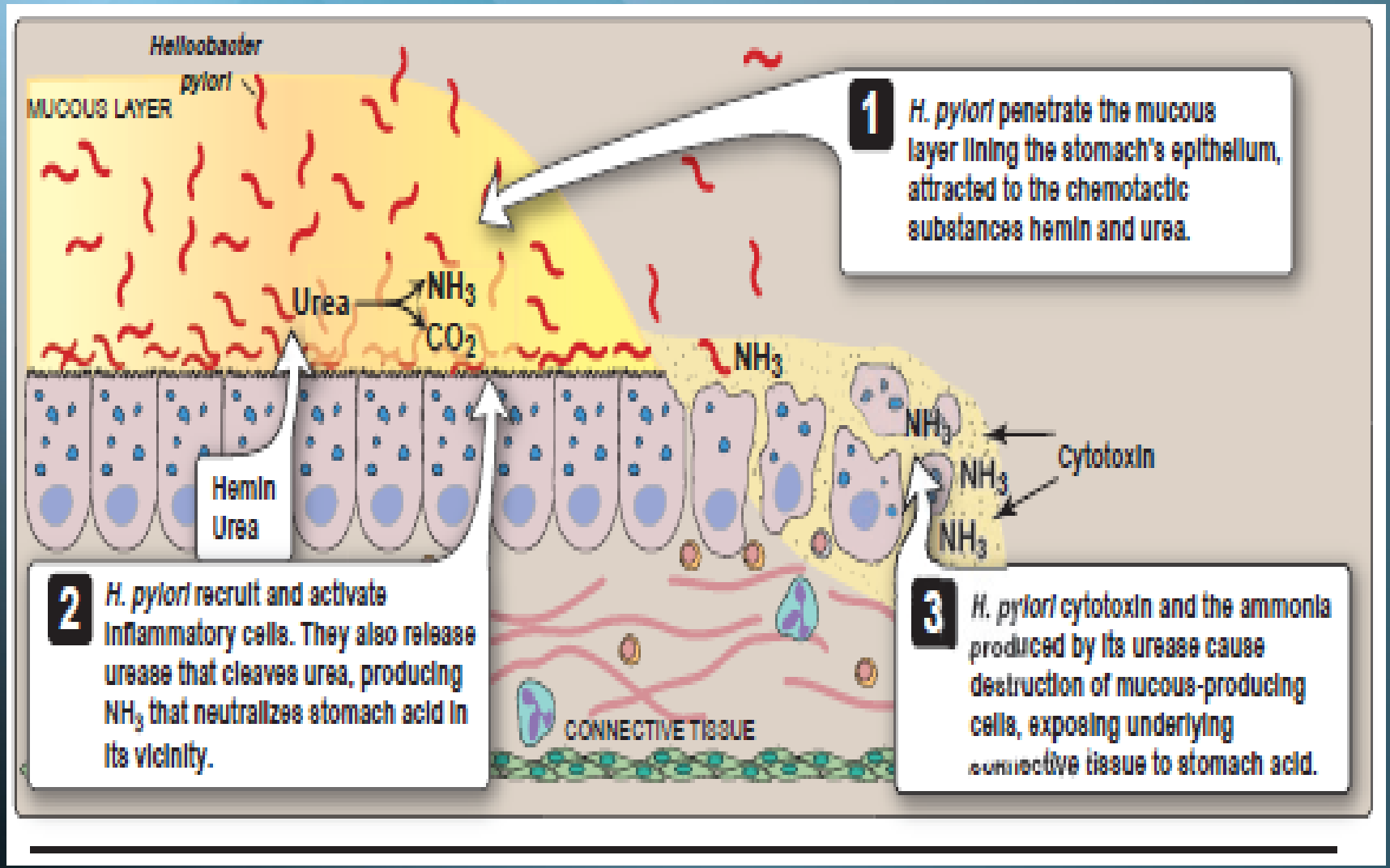
In human, ingestion of *H pylori* resulted in development of gastritis and hypochlorhydria. There is a strong association between the presence of *H pylori* infection and duodenal ulceration.

Antimicrobial therapy results in clearing of *H pylori* and improvement of gastritis and duodenal ulcer disease.

Toxins and lipopolysaccharide may damage the mucosal cells, and the ammonia produced by the urease activity may also directly damage the cells.

Gastric-biopsy specimen showing *Helicobacter pylori* adhering to gastric epithelium and underlying inflammation





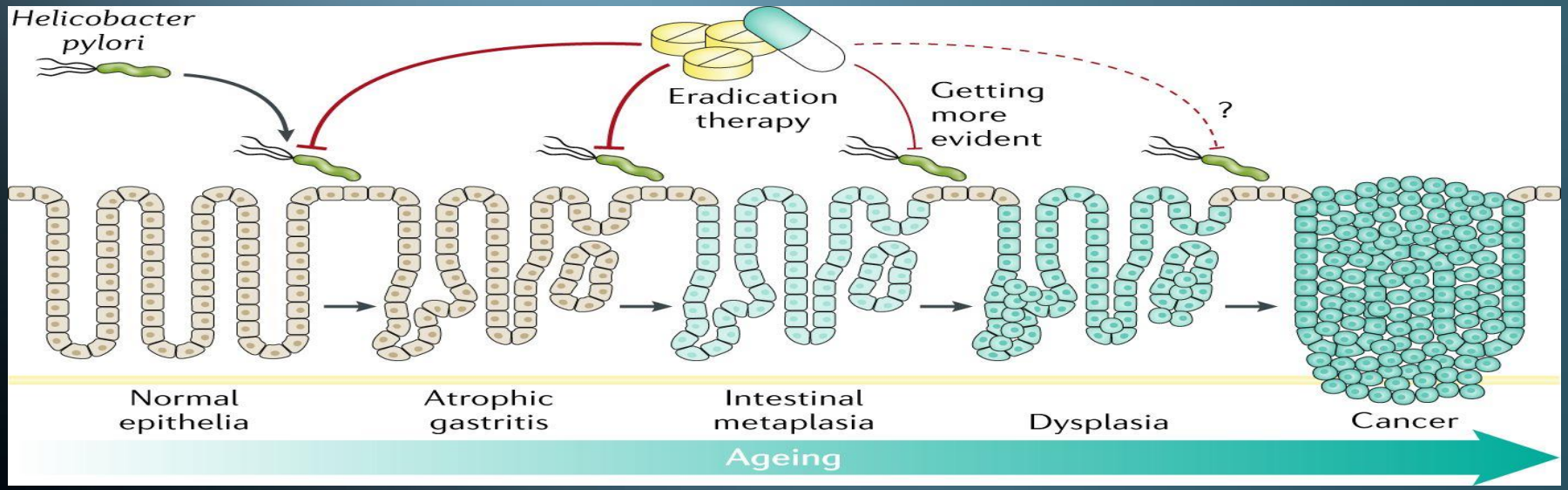
H. pylori infection, resulting in ulceration of the stomach.

H. pylori

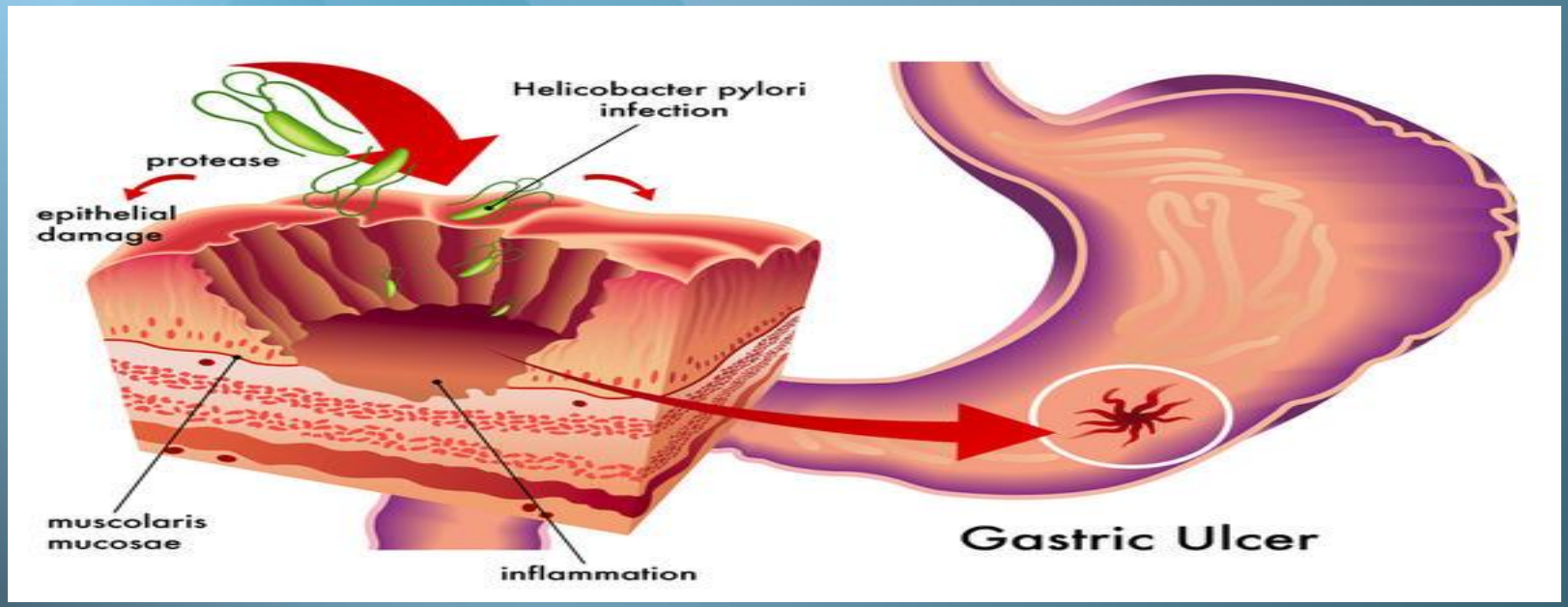
Histologically, gastritis is characterized by acute and chronic inflammation.

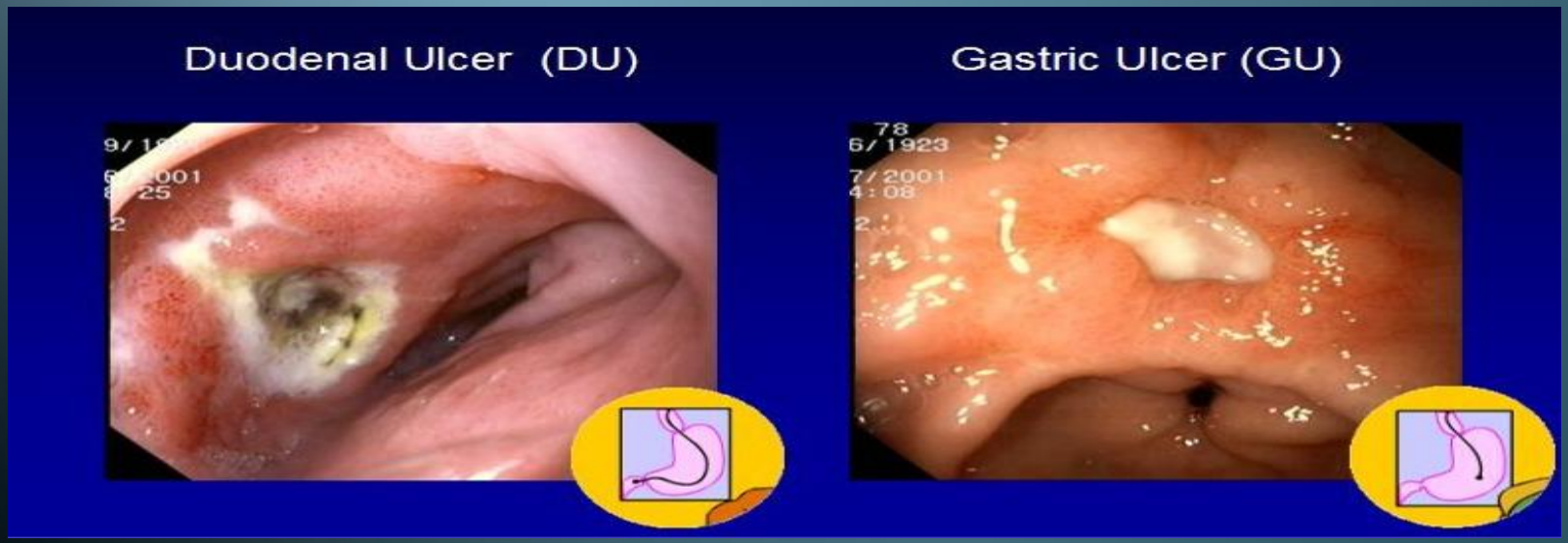
Polymorphonuclear and mononuclear cell infiltrates within the epithelium and lamina propria.

Destruction of the epithelium is common, and glandular atrophy may occur. *H pylori* thus is a major risk factor for gastric cancer.



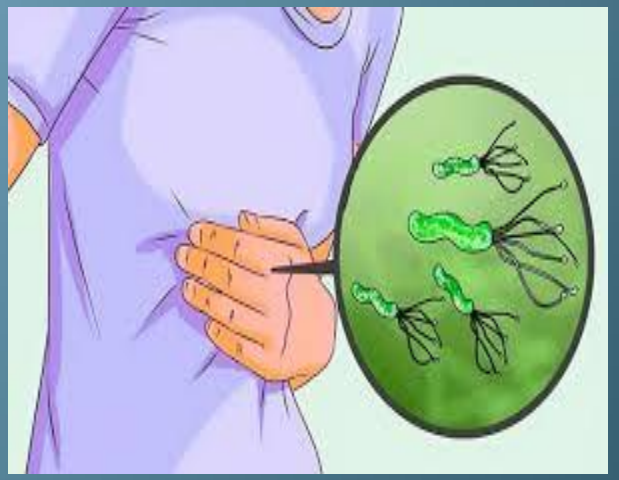
H. pylori


Helicobacter pylori infection
protease
epithelial damage
muscolaris mucosae
inflammation
Gastric Ulcer


Duodenal Ulcer (DU)
Gastric Ulcer (GU)

H. pylori

Clinical Findings



Acute infection can yield an

- upper gastrointestinal illness with
- nausea and pain
- vomiting
- Fever
- Poor appetite
- Weight loss
- Heart burn
- Dyspepsia

After colonization, the *H pylori* infection persists for years and perhaps decades or even a lifetime.

About 90% of patients with duodenal ulcers and 50–80% of those with gastric ulcers have *H pylori* infection.

Recent studies confirm that *H pylori* also is a risk factor for gastric carcinoma and lymphoma.

H. pylori

Diagnostic Laboratory Tests

- Diagnostic test are of two kinds:

A. Invasive test

Endoscopy guided multiple biopsies can be taken from gastric mucosa and are subjected to:

a. Histopathology

b. Microbiological methods

. Gram staining

. Culture media

. Biochemical tests

B. Biopsy urease test (Rapid urease test)

B. Noninvasive test

a. Urea breath test

b. Stool antigen assay

c. Antibody detection

d. Polymerase chain reaction (PCR)

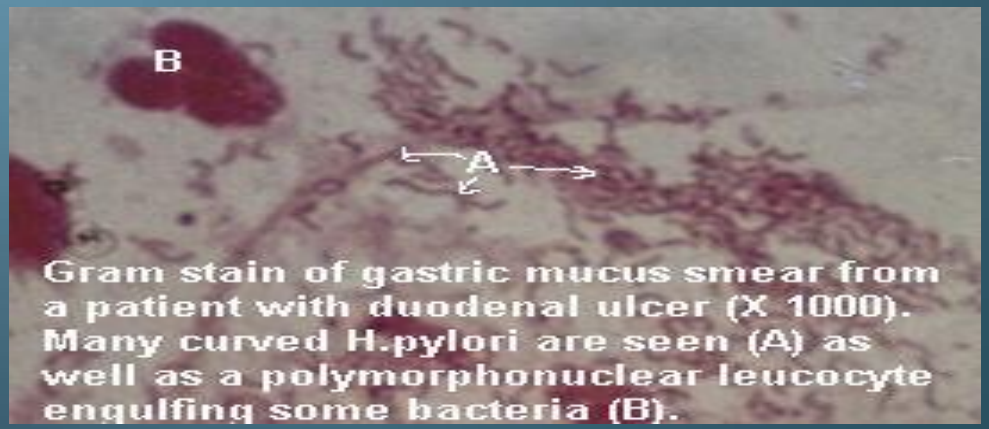
H. pylori

Laboratory Diagnosis

A. Invasive test

1. Histopathology

The diagnosis of gastritis and *H pylori* infection can be made histologically. A gastroscopy procedure with biopsy is required. Routine stains demonstrate gastritis, and Giemsa or special silver stains can show the curved or spiral-shaped organisms.

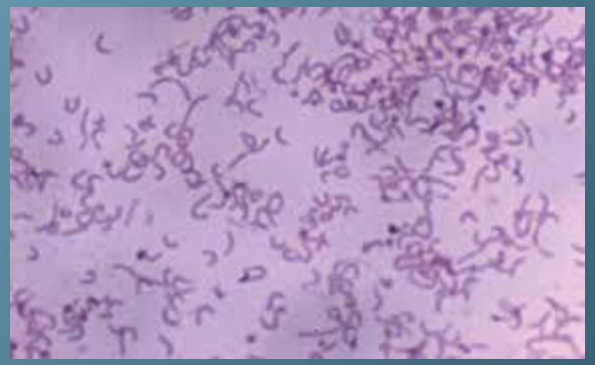


Gram stain of gastric mucus smear from a patient with duodenal ulcer (X 1000). Many curved H.pylori are seen (A) as well as a polymorphonuclear leucocyte engulfing some bacteria (B).

2. Microbiological methods

a. Gram stain:

Curved gram – negative bacilli with gull-wing shaped morphology.



b. Culture

H.pylori grows in 3–6 days when incubated at 37°C in a microaerophilic environment.

The media for primary isolation include Skirrow's medium with vancomycin, polymyxin B, and trimethoprim, chocolate medium, and other selective media with antibiotics (eg, vancomycin, nalidixic acid, amphotericin). The colonies are translucent and 1–2 mm in diameter.

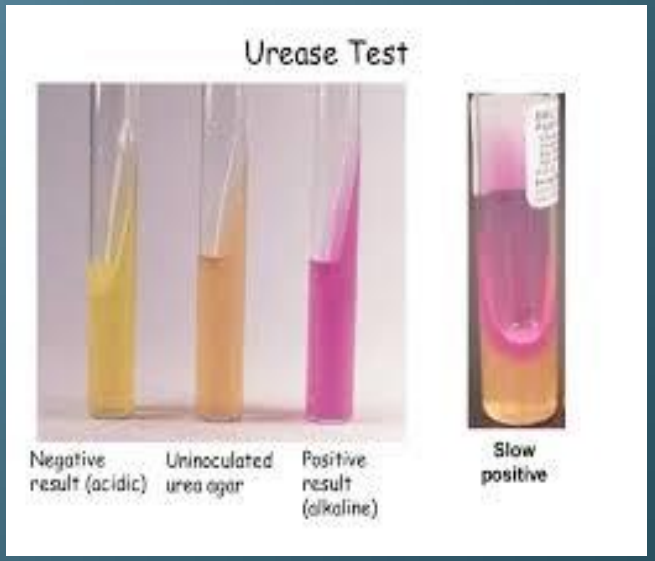
c. Biochemical tests

Oxidase and catalase are positive

3. Biopsy urease test (rapid urease test)

Detects urease activity in gastric biopsies. It is rapid, sensitive and cheap.

Gastric biopsy material can be placed onto a urea-containing medium (urease test) with a color indicator. If *H pylori* is present, the urease rapidly splits the urea, and the resulting shift in pH yields a color change in the medium.



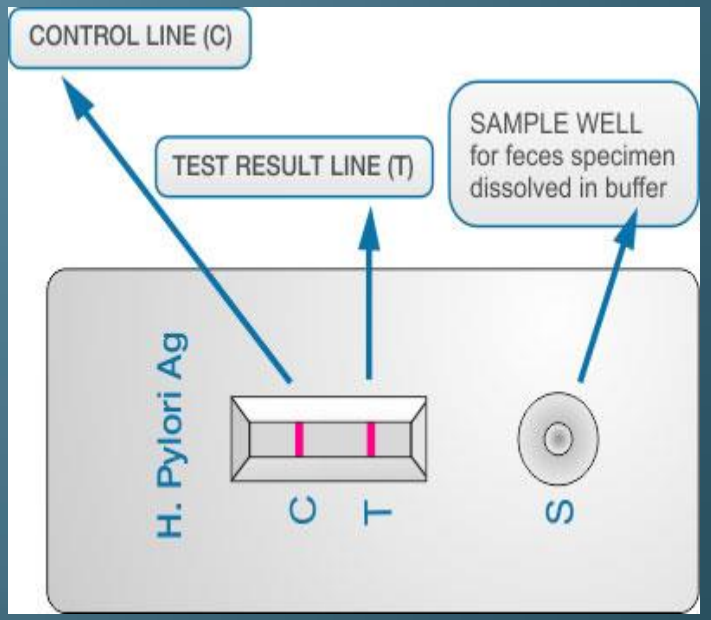
H. pylori

B. Noninvasive test

1. Urea breath tests

In vivo tests for urease activity can be done also. In urea breath tests, 13C- or 14C-labeled urea is ingested by the patient.

If *H pylori* is present, the urease activity generates labeled CO2 that can be detected in the patient's exhaled breath.



2. Stool antigen assay

specimens is appropriate as a test of cure for patients with known *H pylori* infection who have been treated.

H. pylori

3. Antibody (IgG) detection

Antibodies to *H. pylori* can be detected in the patients serum by ELISA test.

The serum antibodies persist even if the *H pylori* infection is eradicated, and the role of antibody tests in diagnosing active infection or after therapy is therefore limited.

4. Polymerase chain reaction (PCR)

H. pylori

Treatment

1st line triple drug therapy

Omeprazole + Clarithromycin + Metronidazole or Amoxicillin
given for 7 -14 dayes

↓

Urea breath test is done
If the 1st line regimen fails (Urea breath test +ve)

↓

2nd line quadruple drug therapy

Omeprazole + Bismuth subsalicylate + Metronidazole + Tetracycline
Given for 14 dayes

↓

If 2nd line quadruple drug therapy fails then –
Culture of endoscopic guided biopsy is done and treatment is
Given based on antimicrobial susceptibility test

Control

H pylori is present on the gastric mucosa of fewer than 20% of persons younger than years 30 but increases in prevalence to 40–60% of persons age 60 years, including persons who are asymptomatic.

In developing countries, the prevalence of infection may be 80% or higher in adults.

Person-to-person transmission of *H pylori* is likely because intrafamilial clustering of infection occurs. Acute epidemics of gastritis suggest a common source for *H pylori*.

There is no vaccine or other specific preventive measure.

Helicobacter Pylori Treatment

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Indications

- Peptic Ulcer Disease
- Gastric MALT lymphoma
- First degree relatives of patients with gastric adenocarcinoma
- Non Ulcer Dyspepsia
- GERD requiring long-term acid suppression?

- Community screening for treatment of *H. pylori* as primary prophylaxis for gastric cancer and PUD are not currently recommended.

- No single agent is effective.
- Combination therapy for 14/d provides the greatest efficacy.
- Shorter course administration (7–10/d), although attractive, has not proved as successful as the 14/d.

Goals in treating PUD:

- To provide relief of symptoms (pain or dyspepsia)
- Promote ulcer healing
- Prevent ulcer recurrence and complications.

- Documented eradication of *H. pylori in PUD is associated with a dramatic decrease in ulcer* recurrence to <10–20% as compared to 59% in GU and 67% in DU when the organism is not eliminated.
- Eradication of the organism may lead to diminished recurrent ulcer bleeding.
- The impact of its eradication on ulcer perforation is unclear.

- Choice of a particular regimen will be influenced by:
- Patient tolerance
- Existing antibiotic resistance
- Cost of the drugs

- The aim for initial eradication rates should be 85–90%.
- Dual therapy are not recommended in view of studies demonstrating eradication rates of <80–85%.

- The combination of bismuth, metronidazole, and tetracycline was the first triple regimen found effective against *H. pylori.*
- Addition of acid suppression assists in providing early symptom relief and may enhance bacterial eradication.

Important factors in H. pylori treatment

- Patient's close compliance
- Ease of administration
- Use of drugs to which *H. pylori* has not acquired resistance.
- Cost
- Side effects

First line therapy
Triple Therapy

1. Bismuth subsalicylate *plus*	2 tablets qid
Metronidazole *plus*	250 mg qid
Tetracycline[a]	500 mg qid
2. Ranitidine bismuth citrate *plus*	400 mg bid
Tetracycline *plus*	500 mg bid
Clarithromycin or metronidazole	500 mg bid
3. Omeprazole (lansoprazole) *plus*	20 mg bid (30 mg bid)
Clarithromycin *plus*	250 or 500 mg bid
Metronidazole[b] *or*	500 mg bid
Amoxicillin[c]	1 g bid

- In penicillin-allergic: MetronidazoleIn penicillin-allergic: Metronidazole (500 mg twice daily) can be substituted for amoxicillin

American College of Gastroenterology first-line H. pylori regimens (Adult dosing, oral administration)

Patients who are **not** allergic to penicillin and have not previously received a macrolide	Standard dose PPI* twice daily (or esomeprazole 40 mg once daily) plus clarithromycin 500 mg twice daily, and amoxicillin 1000 mg twice daily for 10-14 days*
Patients who are allergic to penicillin, and who have not previously received a macrolide or metronidazole or are unable to tolerate bismuth quadruple therapy	Standard dose PPI twice daily, clarithromycin 500 mg twice daily, metronidazole 500 mg twice daily for 10-14 days•
Patients who are allergic to penicillin	Bismuth subsalicylate 525 mg four times daily, metronidazole 250 mg four times daily, tetracycline 500 mg four times daily, standard dose PPI* twice daily for 10-14 daysΔ **OR** Bismuth subcitrate 420 mg four times daily, metronidazole 375 mg four times daily, tetracycline 375 mg four times daily, standard dose PPI* twice daily for 10-14 daysΔ

*Lansoprazole 30 mg twice daily, omeprazole 20 mg twice daily, pantoprazole 40 mg twice daily, or rabeprazole 20 mg twice daily.
•Eradication rates of 70-85 percent.
ΔEradication rates of 75-90 percent.

Table adapted from data published in: Chey, WD, Wong, BCY. American College of Gastroenterology Guideline on the Management of Helicobacter pylori Infection. Am J Gastroenterol 2007; 102:1808-25.

- Triple therapy has several drawbacks:
- Poor patient compliance
- Drug-induced side effects

- Compliance is being addressed by simplifying the regimens (medications twice a day)
- Written instructions should be given
- Minor side effects should be explained

- Simpler (dual therapy) and shorter regimens (10 d) are not as effective as triple therapy for 14 d.

- Prevpac (lansoprazole, clarithromycin, and amoxicillin)
- Helidac (bismuth subsalicylate, tetracycline, and metronidazole)

- Prevpac are to be taken BD for 14 d.
- Helidac constituents are taken QID with an antisecretory agent (PPI or H_2 blocker), for at least 14 d.

Side effects

- In up to 20–30% of triple therapy.
- Bismuth: black stools, constipation, or darkening of the tongue.
- Amoxicillin: pseudomembranous colitis(<1–2%), antibiotic-associated diarrhea, nausea, vomiting, skin rash, and allergic reaction.
- Tetracycline: rashes and, hepatotoxicity and anaphylaxis (rarely)

- Metallic taste due to metronidazoleMetallic taste due to metronidazole or clarithromycin.
- Metronidazole : peripheral neuropathy, seizures, and a disulfuram-like reaction
- Clarithromycin : taste alteration, nausea, vomiting, abdominal pain, and rarely QT prolongation.
- Tetracycline can induce a photosensitivity reaction in some cases. It should also not be administered to pregnant women or young children.

Antibiotic Resistant

- The incidence strains vary worldwide.
- Strains resistant to metronidazole, clarithromycin, amoxicillin, and tetracycline have been described.
- The latter two being uncommon.

- Antibiotic-resistant strains are the most common cause for treatment failure in compliant patients.

- In vitro resistance does not predict outcome in patients.
- Culture and sensitivity testing of *H. pylori* is not performed routinely.
- Although resistance to metronidazole has been found in 80% in developing countries, triple therapy is effective in >50% of patients infected with a resistant strain.

- Clarithromycin resistance in 13%.
- Clarithromycin resistance was associated with:
- *Geographic region*
- *Older age*
- *Female sex*
- *The presence of inactive ulcer disease.*

- Metronidazole resistance was associated with:
- *Female sex*
- *Asian ethnicity,*

- Resistance to Amoxicillin & Tetracycline being <1%
- Resistance to both metronidazole and clarithromycin in 5%

Antibiotic susceptibilities

- Is not usually undertaken because endoscopy and mucosal biopsy are necessary to obtain *H. pylori* for culture and because most microbiology laboratories are inexperienced in *H. pylori* culture.
- In the absence of susceptibility information, a ***history of the patient's antibiotic use*** should be obtained, and if distant exposure is identified, use of the agent should be avoided.

Treatment Failures

- We recommend quadruple therapy.
- If this one is also failed then endoscopy, biopsy, and culture plus treatment based on documented antibiotic sensitivities

Second line therapy

Omeprazole (lansoprazole)	20 mg (30 mg) daily
Bismuth subsalicylate	2 tablets qid
Metronidazole	250 mg qid
Tetracycline	500 mg qid

- A proton pump inhibitor (PPI) can be combined with bismuthA proton pump inhibitor (PPI) can be combined with bismuth and two antibiotics (eg, metronidazoleA proton pump inhibitor (PPI) can be combined with bismuth and two

Suggested treatments for H. pylori

Regimen	Comment
PPI, amoxicillin 1 gm, clarithromycin 500 mg all twice daily for 7-14 days	1st line treatment regimen of choice (can substitute metronidazole 500 mg twice daily for amoxicillin but only in penicillin allergic patients)
Bismuth 525 mg, metronidazole 500 mg, tetracycline 500 mg all four times daily with a PPI twice daily for 7-14 days	Can be used as 1st line treatment (7-14 days) but generally reserved for retreatment (14 days)
PPI, amoxicillin 1 gm, metronidazole 500 mg all twice daily for 14 days	1st line treatment in macrolide allergic patients and retreatment if failed 1st line treatment of choice
PPI, levofloxacin 250 mg, amoxicillin 1 gm all twice daily for 14 days	"Rescue" therapy for those failing two course of above treatments
PPI, rifabutin 150 mg, amoxicillin 1 gm all twice daily for 14 days	Alternative "rescue" therapy
PPI twice daily plus amoxicillin 1 three times daily for 14 days	Alternative "rescue" therapy

PPI: proton pump inhibitor.

Courtesy of David Peura, MD.
http://www.elsevier.com/locate/jacc;
http://www.sciencedirect.com

Second-line (Rescue-Salvage) therapy

- Pantoprazole, amoxicillin, and rifabutin for 10/d (86% cure rate)
- Levofloxin, amoxicillin and PPI for 10/d
- Furazolidone, amoxicillin and PPI for 14/d.

- There is no universally accepted treatment regimen recommended for patients who have failed two courses of antibiotics.
- Patients in whom second-line therapy fails should undergo endoscopy for *H. pylori* culture and antibiotic susceptibility testing.

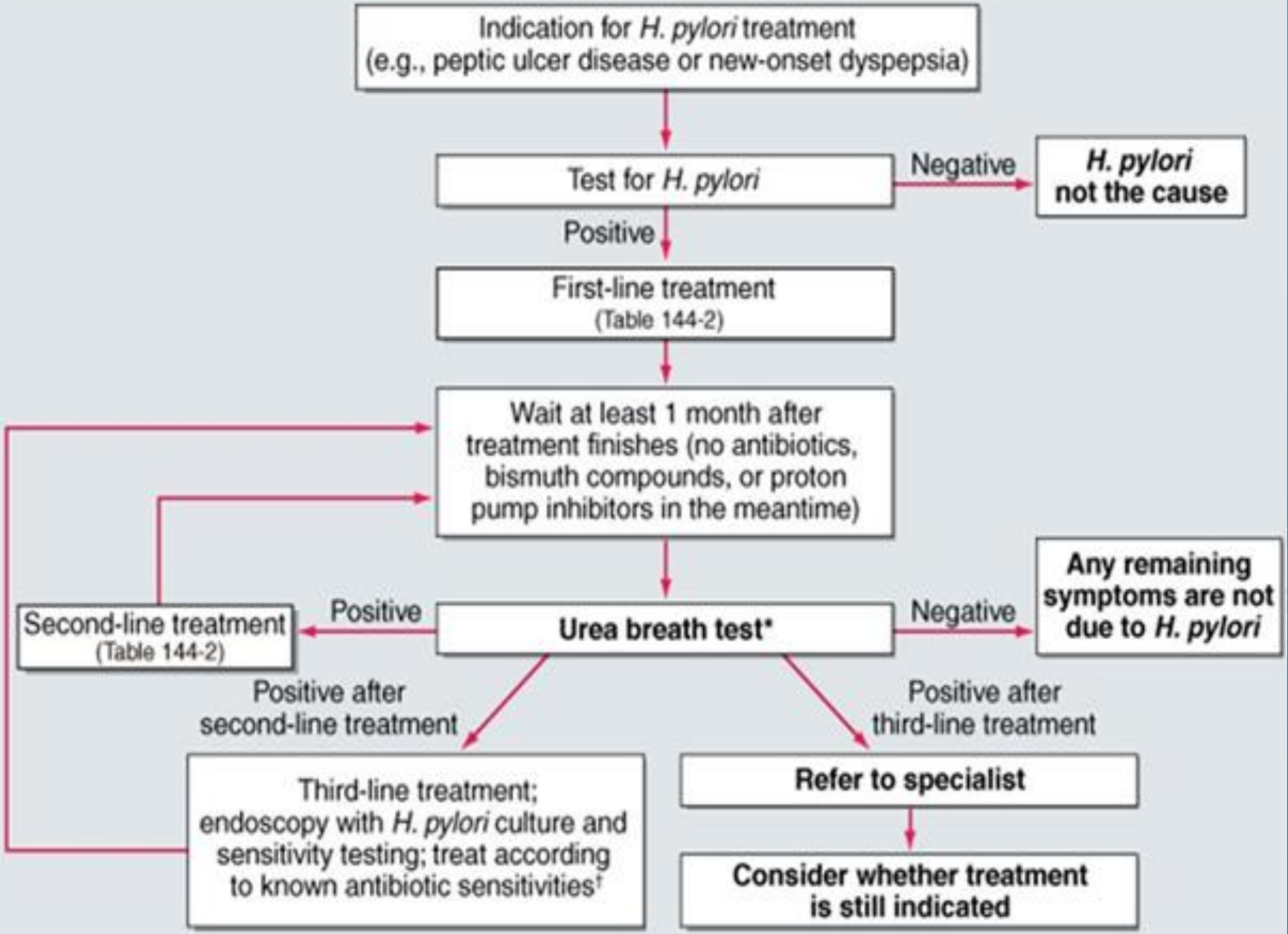
- Factors that may lower eradication rates:
- patient's country of origin (Northeast Asia > other parts of Asia or Europe)
- cigarette smoking.

Sequential therapy

- In clarithromycin resistant stains
- 5 days of amoxicillin and a PPI, followed by an additional 5 days of PPI plus tinidazole and clarithromycin. (eradication rates of >90%)
- Good patient tolerance.

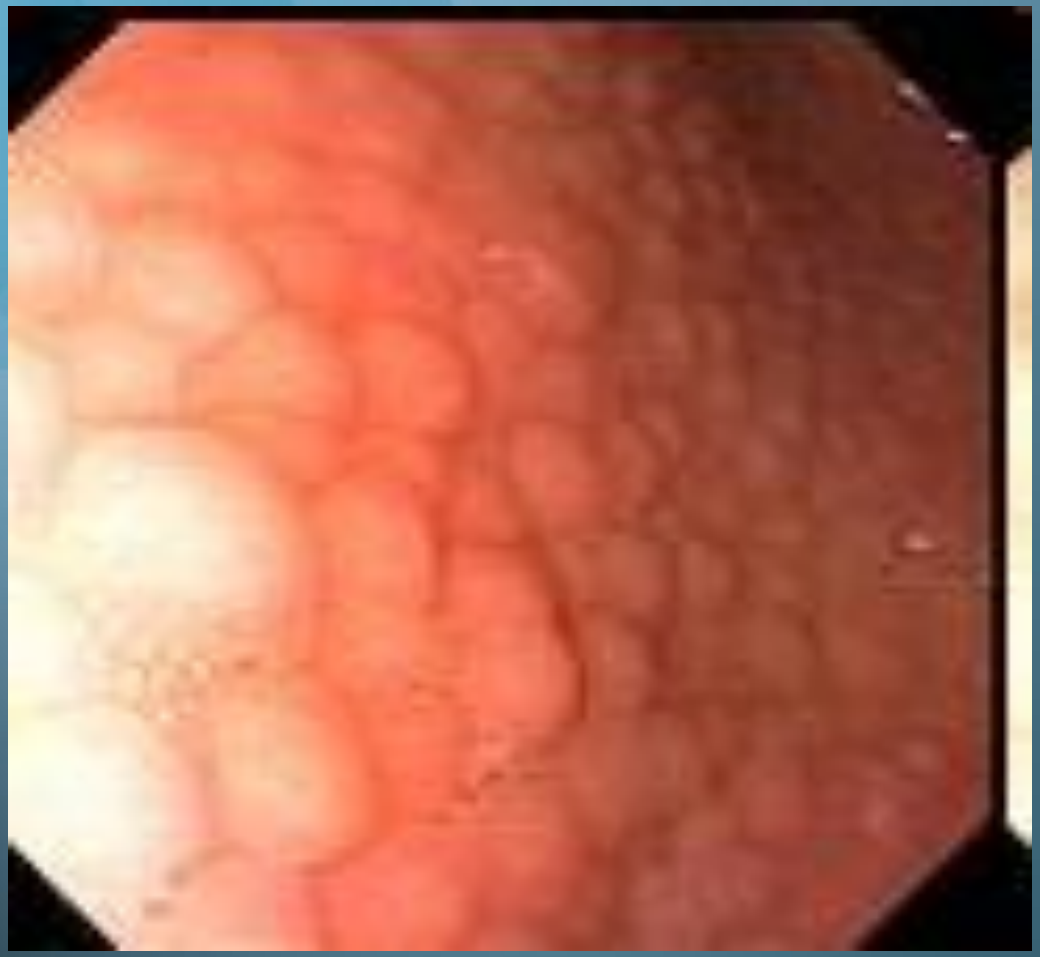
Probiotics

- Probiotics are live, nonpathogenic bacteria that benefit a host through altering gut microfloral composition.
- Because some probiotics have antimicrobial effects, they have been proposed as treatment for H. pylori infection but they should not be considered a substitute for standard antibiotic treatments.
- Probiotics may reduce side effects of standard H. pylori treatments, especially diarrhea.
- As a result, they may be useful adjuncts to improve tolerability and compliance with more traditional antibiotic regimens


Indication for H. pylori treatment (e.g., peptic ulcer disease or new-onset dyspepsia)
Test for H. pylori
Negative
H. pylori not the cause
Positive
First-line treatment (Table 144-2)
Wait at least 1 month after treatment finishes (no antibiotics, bismuth compounds, or proton pump inhibitors in the meantime)
Second-line treatment (Table 144-2)
Positive
Urea breath test*
Negative
Any remaining symptoms are not due to H. pylori
Positive after second-line treatment
Positive after third-line treatment
Third-line treatment; endoscopy with H. pylori culture and sensitivity testing; treat according to known antibiotic sensitivities†
Refer to specialist
Consider whether treatment is still indicated

Reinfection

- After successful eradication of *H. pylori* is rare in the United States (<1%/year).
- If recurrent infection occurs within the first 6 months after completing therapy, the most likely explanation is ***recrudescence*** as opposed to ***reinfection***.



Thank you