Peptic Ulcer Diseases: Treatment

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Introduction

- Peptic ulcer disease (PUD) is a common disorder that affects millions of individuals worldwide
- It is accounting for roughly 10% of medical costs for digestive diseases

Introduction

- Major advances have been made in the understanding PUD pathophysiology, particularly the role of *Helicobacter pylori* infection & NSAIDs
- This has led to important changes in diagnostic & treatment strategies, with potential for improving clinical outcome & decreasing health care costs

NSAIDs= nonsteroidal anti-inflammatory drugs

Definitions

- **Ulcer:**

  A lesion on an epithelial surface (skin or mucous membrane) caused by superficial loss of tissue

- **Erosion:**

  A lesion on an epithelial surface (skin or mucous membrane) caused by superficial loss of tissue, limited to the mucosa

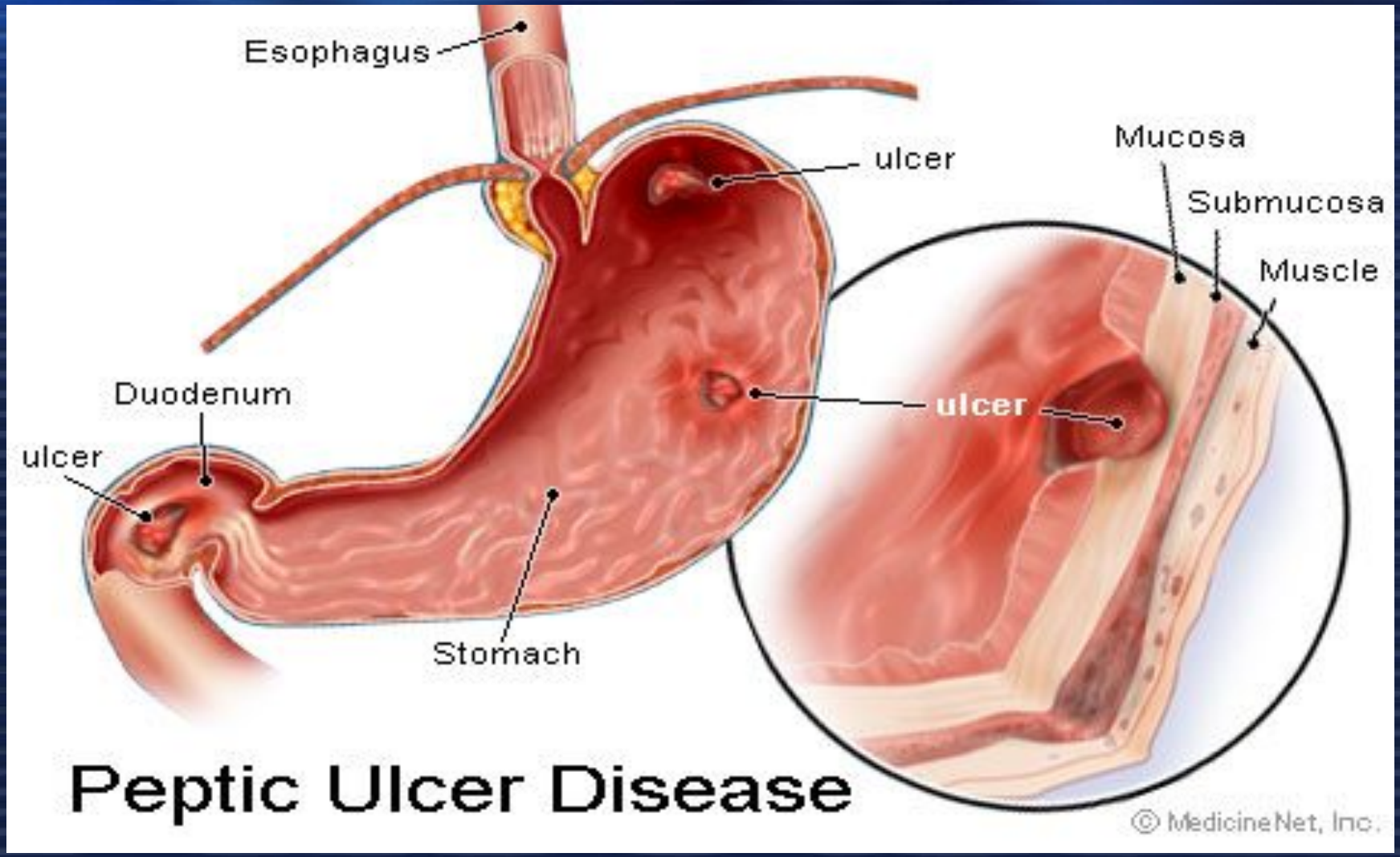
Definitions

- **Peptic Ulcer**

  An ulcer of the alimentary tract mucosa, usually in the stomach or duodenum, & rarely in the lower esophagus, where the mucosa is exposed to the acid gastric secretion

- *It has to be deep enough to penetrate the muscularis mucosa*

Peptic Ulcer Disease



Gastric Mucosa & Secretions

The gastroduodenal mucosal integrity is determined by protective (defensive) & damaging (aggressive) factors

Gastric Mucosa & Secretions

When the aggressive factors increase or the defensive factors decrease, mucosal damage will result, leading to erosions & ulcerations

Negative Feedback Regulation of Acid Secretion

Antral distention
Protein content

↑ intragastric PH

↓ Gastrin release

↑ somatostatin secretion

Increased gastric acid secretion

↑ CGPR release

↓ Intragastric PH

CGPR= calcitonin gene related peptide

Pathophysiology

- A peptic ulcer is a mucosal break, 3 mm or greater in size with depth, that can involve mainly the stomach or duodenum.

Pathophysiology

Two major variants in peptic ulcers are commonly encountered in the clinical practice:

1) *Duodenal Ulcer* (DU)
2) *Gastric Ulcer* (GU)

Pathophysiology

DU result from *increased acid load to the duodenum* due to:

1) Increased acid secretion because of:

   A. Increased parietal cell mass

   B. Increased gastrin secretion (e.g. Zollinger-Ellison syndrome, alcohol & spicy food)

2) Decreased inhibition of acid secretion, possibly by *H. pylori* damaging somatostatin-producing cells in the antrum

Pathophysiology

DU result from *increased acid load to the duodenum* due to:

3) Smoking impairing gastric mucosal healing

4) Genetic susceptibility may play a role (more in blood gp. O)

5) HCO3 secretion is decreased in the duodenum by *H. pylori* inflammation

Pathophysiology

GU results from the *break down* of gastric mucosa:

1) Associated with gastritis affecting the body & the antrum
2) The local epithelial damage occurs because of cytokines released from *H. pylori* & because of abnormal mucus production
3) Parietal cell damage occur so that acid production is normal or low

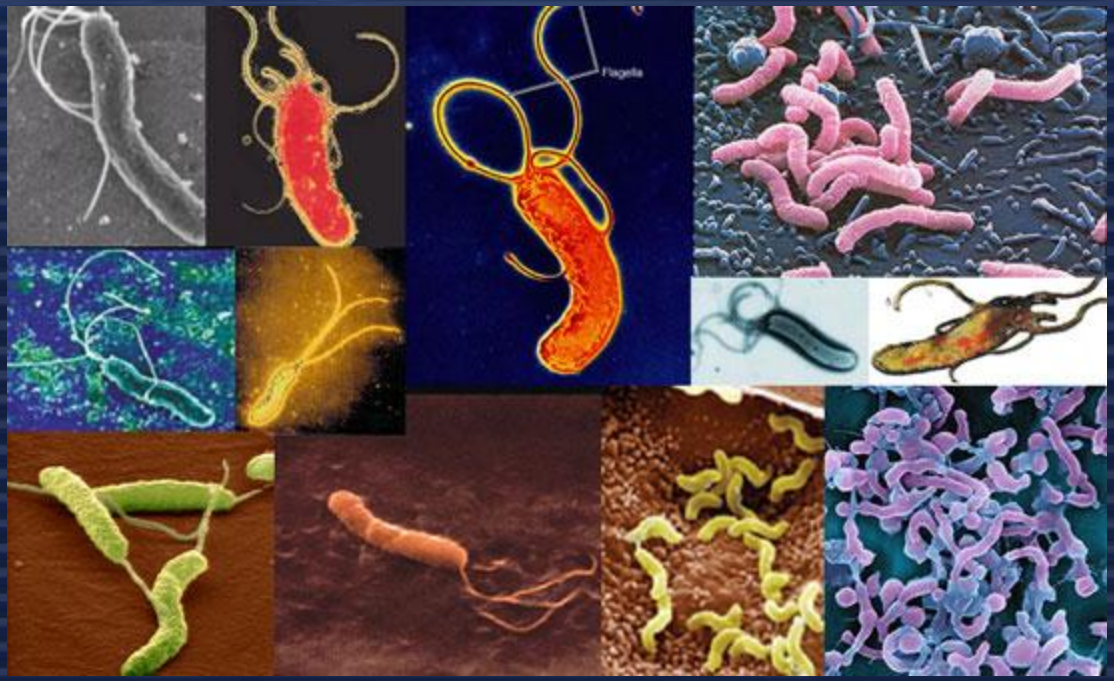
Etiology

- The two most common causes of PUD are:
  - *Helicobacter pylori* infection (70-80%)
  - Non-steroidal anti-inflammatory drugs (NSAIDS)

Etiology

- Other uncommon causes include:
  - Gastrinoma (Gastrin secreting tumor)
  - Stress ulceration (trauma, burns, critical illness)
  - Viral infections
  - Vascular insufficiency

1. Etiology – *Helicobacter pylori*



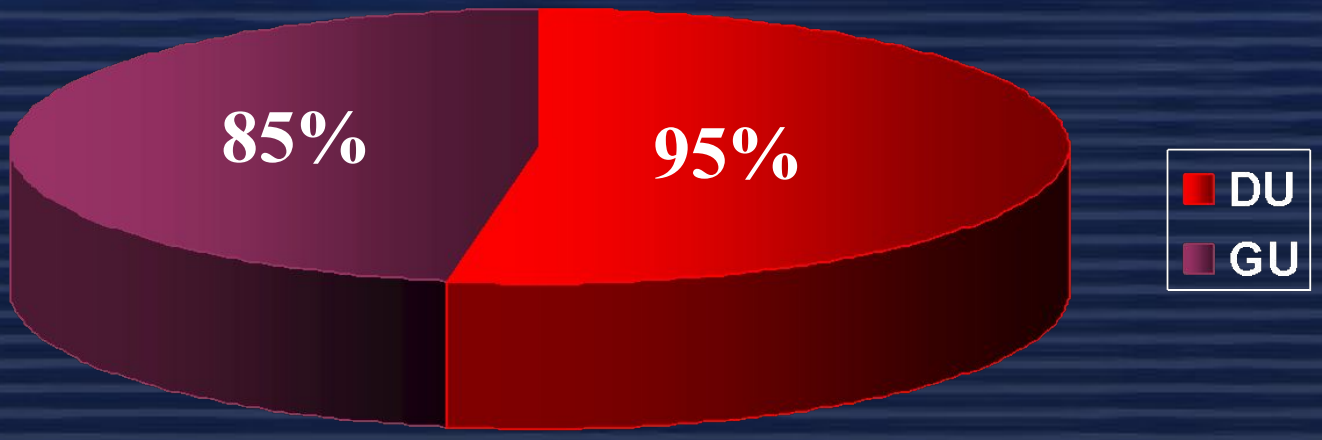
H.pylori Epidemiology

- One half of world's population has *H.pylori* infection, with an estimated prevalence of 80-90 % in the developing world
- The annual incidence of new *H. pylori* infections in industrialized countries is 0.5% of the susceptible population compared with ≥ 3% in developing countries

H.pylori as a cause of PUD

The majority of PUD patients are *H. pylori* infected

H.pylori as a cause of PUD

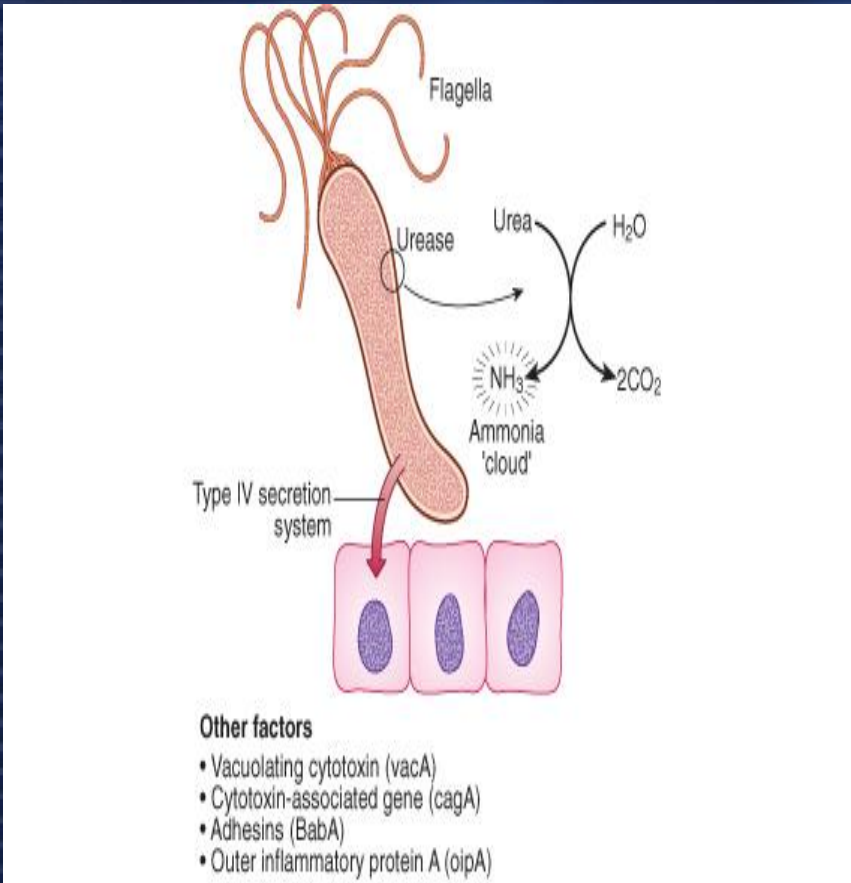


Pathogenesis of *H. pylori* infection

- *H. pylori* is Gram-negative, spiral & has multiple flagella at one end
- Transmitted from person-to-person by Oro–oral or feco-oral spread
- No reservoir in animal or water supply

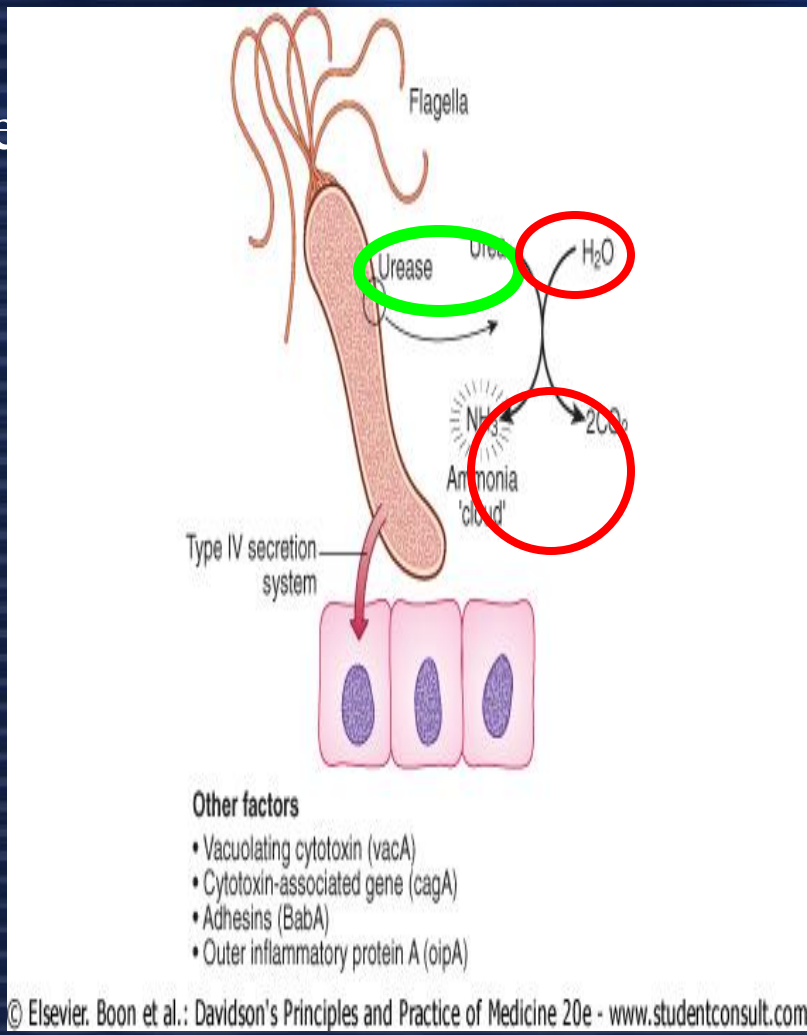
Pathogenesis of *H. pylori* infection

- The Flagellae make it motile, allowing it to live deep beneath the mucus layer
- It uses an adhesin molecule to bind to epithelial cells Where the pH there is close to neutral



Pathogenesis of *H. pylori* infection

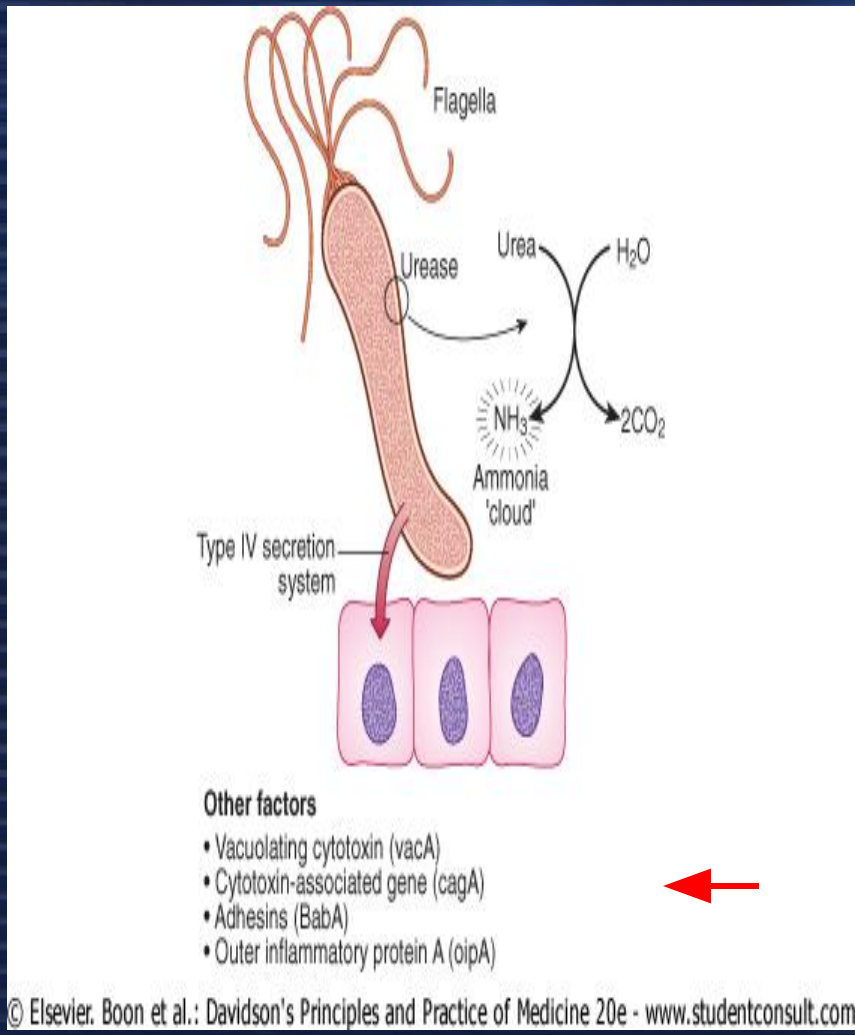
- Any acidity is buffered by the organism's production of the enzyme urease, which catalyzes the production of ammonia (NH_3) from urea & raises the pH there
- The bacterium stimulates chronic gastritis by provoking a local inflammatory response.



Pathogenesis of *H. pylori* infection

In the cellular level:

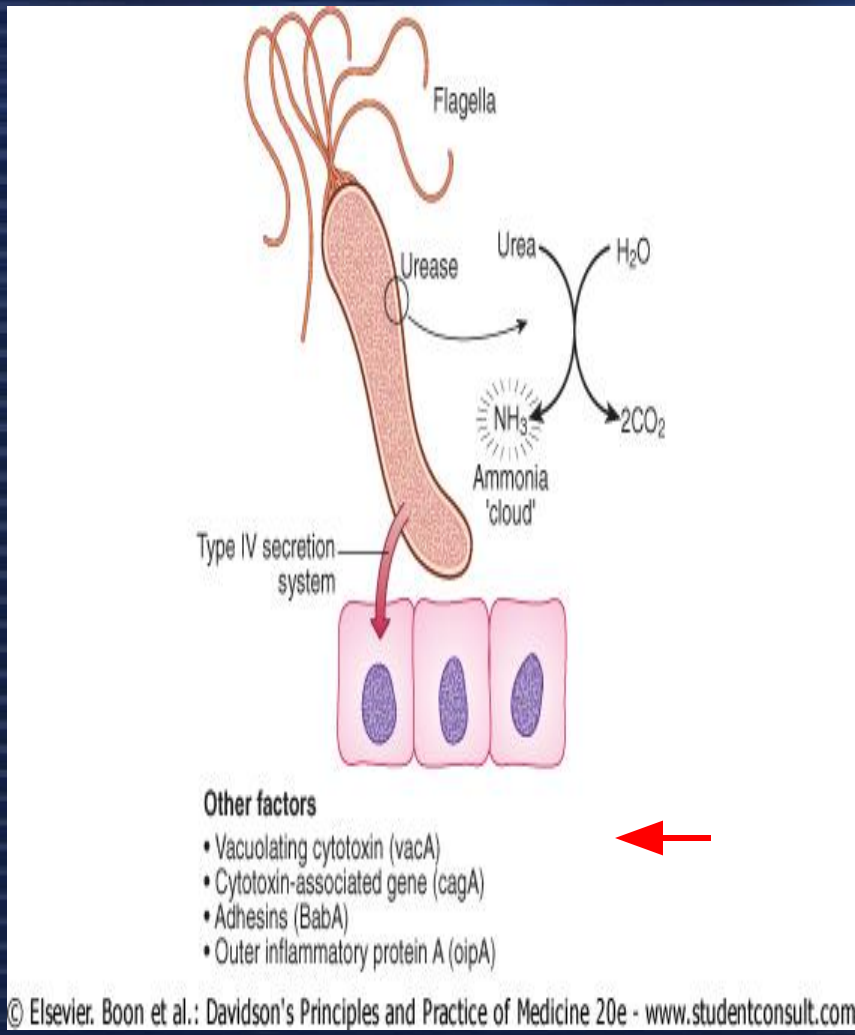
- *H. pylori* express **cagA** & **vacA** genes
- **cagA** gene signals to the epithelial cells involving:
  - Cell replication,
  - Apoptosis, &
  - Morphology



Pathogenesis of *H. pylori* infection

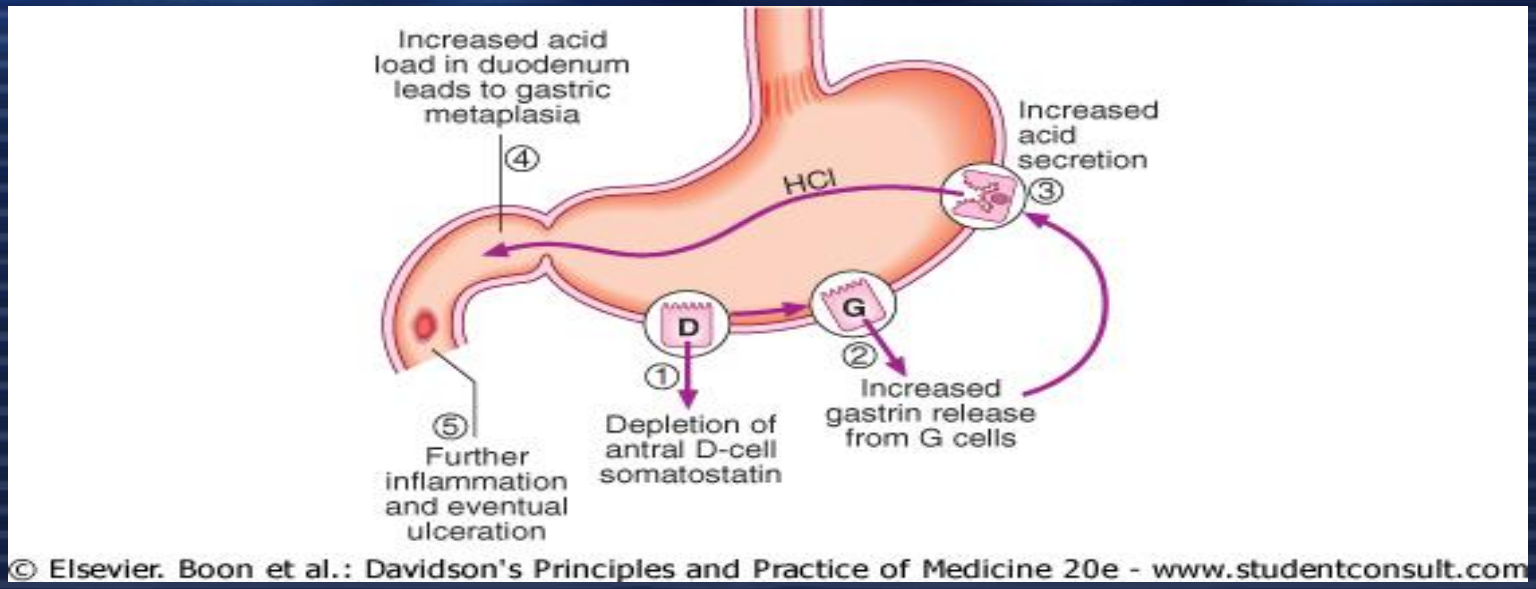
In the cellular level:

- **vacA** gene producing a pore-forming protein, which has many destructing effect to the epithelium like:
  -↑Cell permeability & efflux of micronutrients,
  - Induction of apoptosis, &
  - Suppression of local cell immunity



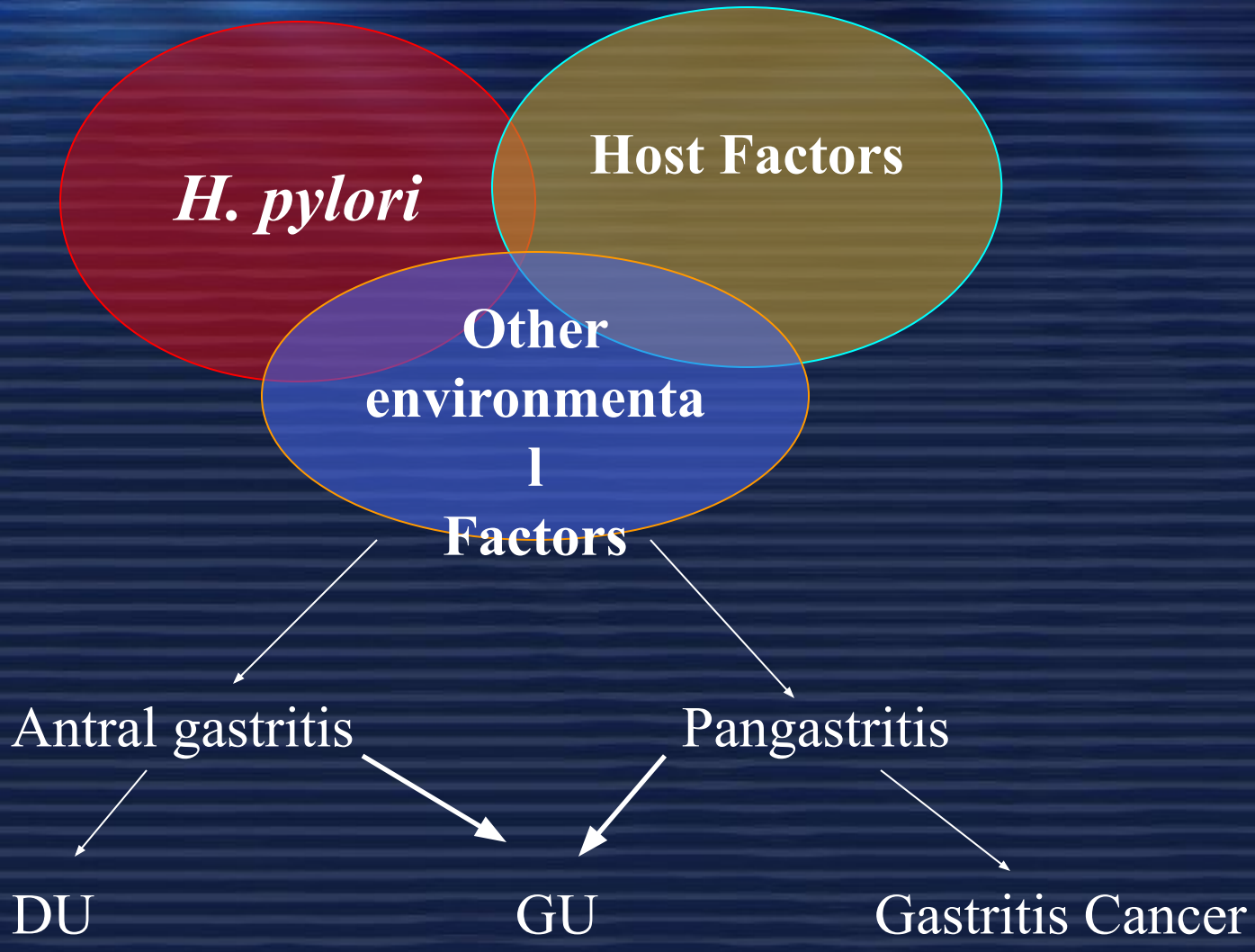
Pathogenesis of *H. pylori* infection

Effects of *H. pylori* on gastric Hormones



This effect is <u>exaggerated</u> among smokers!

Carcinogenic effect of *H. pylori*



Carcinogenic effect of *H. pylori*

- Epidemiologic evidence suggests that infection with HP is associated with >2 fold increase risk of gastric cancer
- However due to uncertainty regarding the benefit of HP eradication on reducing cancer risk, wide-spread screening for HP in asymptomatic individuals cannot be recommended at this time

For persons at high risk for gastric cancer (e.g., first degree relatives) screening can be considered on a case by case basis

ABLES A Z et al. *American Family Physician. 2007*

2. Etiology -Non-Steroidal Anti-inflammatory Drugs (NSAIDS)

NSAIDS

- Symptomatic GI ulceration occurs in 2% - 4% of patients treated with NSAIDs for 1 year
- In view of the million of people who take NSAIDs annually, these small percentages translate into a large number of symptomatic ulcers
- The effects of aspirin & NSAIDs on the gastric mucosa ranges from mucosal hemorrhages to erosions & acute ulcers

NSAIDS

- Inhibits the production of prostaglandins precursor from membrane fatty acids resulting in:

1. Decrease mucus & HCO3 production
2. Decrease mucosal blood flow
3. Reduce cell renewal

- The drugs also generate oxygen-free radicals & products of the lipoxygenase pathway that may contribute to ulceration

NSAIDS

- Gastric acid probably aggravates NSAID-induce mucosal injury by

- Converting superficial injury to deeper mucosal necrosis,

- Interfering with haemostasis & platelet aggregation

- Impairing ulcer healing

NSAIDS

- Users of NSAIDs are at approximately 3 times greater relative risk of serious adverse gastrointestinal events than nonusers

NSAIDS

- **Identify risk factors:**
  - Age > 65 years (3.5-fold increased risk)
  - Smoking
  - Previous history of GI event (e.g. ulcer bleeding 4-fold increase risk)
  - Concomitant drug use
    - Anticoagulants (eg, warfarin; 3-fold increase)
    - Corticosteroid (2-fold increase)
    - Low dose aspirin alone (2.5-fold increase)
    - Aspirin + NSAIDS (4-fold increase vs aspirin alone)

Type of NSAID & Risk of Ulcer

Risk Group	Drug	Relative Risk
Low	Ibuprofen	2.0
	Diclofenac	4.2
Medium	Naproxen	9.1
	Indomethacin	11.3
	Piroxicam	13.7
High	Ketoprofen	23.7
	Azapropazone	31.5

Does *H. pylori* Influence the Ulcer Risk in NSAID Users?

Does H. pylori Influence the Ulcer Risk in NSAID Users?

- Many investigators had attempted to address this question using case-control or observational studies
- To date, there are studies showing that the interaction between *H. pylori* and NSAIDs in ulcer development is synergistic, additive, independent or antagonistic

Does H. pylori Influence the Ulcer Risk in NSAID Users?

- These conflicting results can be largely accounted for by methodological heterogeneity and diversified host response to *H. pylori* infection.

Recommendations for *H.pylori* Testing & Eradication in NSAID Users

1- Patients who have a history of ulcer complication should undergo *H. pylori* testing. *H. pylori* should be eradicated in all infected patients because it is not plausible to determine whether the ulcer complications were caused by NSAIDs or both

Recommendations for *H.pylori* Testing & Eradication in NSAID Users

3- Patients who are about to start receiving NSAIDs, *H. pylori* testing & treatment reduces the ulcer risk at an affordable incremental cost

4- Since treatment with PPIs aggravate *H. pylori* corpus gastritis, it is advisable to test for *H. pylori* & eradicate if present before starting long term therapy with PPI as prophylaxis against NSAID-induced ulcers

Clinical Presentation

- Recurrent epigastric pain (the most common symptom)
  - Burning
  - Occurs 1-3 hours after meals
  - Relieved by food □ DU
  - Precipitated by food □ GU
  - Relieved by antacids
  - Radiate to back (consider penetration)
  - Pain may be absent or less characteristic in one-third of patients especially in elderly patients on NSAIDs

Clinical Presentation

- Nausea, Vomiting
- Dyspepsia, fatty food intolerance
- Chest discomfort
- Anorexia, weight loss especially in GU
- Hematemesis or melena resulting from gastrointestinal bleeding

Diagnosis of PUD

Peptic Ulcer Disease

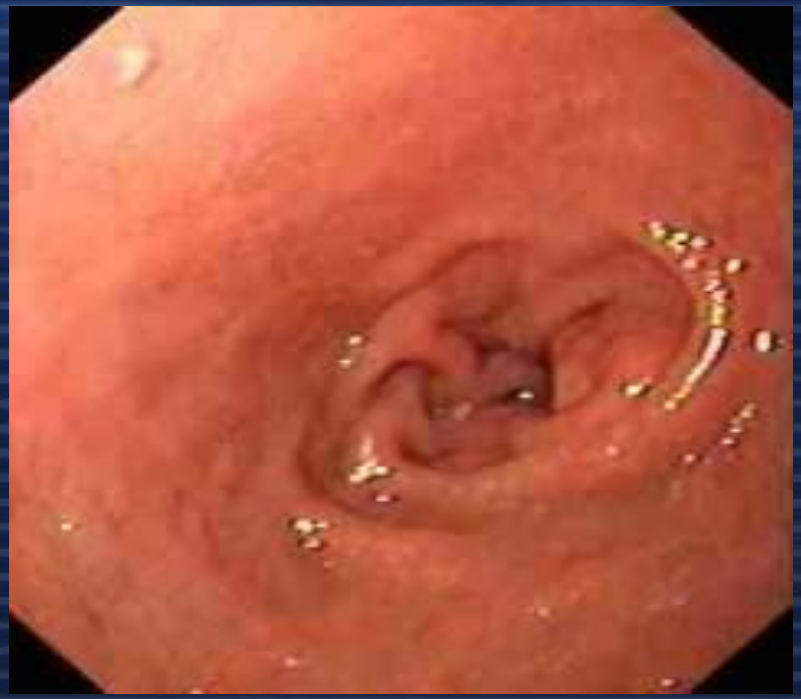
Diagnosis:

1) Diagnosis of ulcer
2) Diagnosis of H. pylori

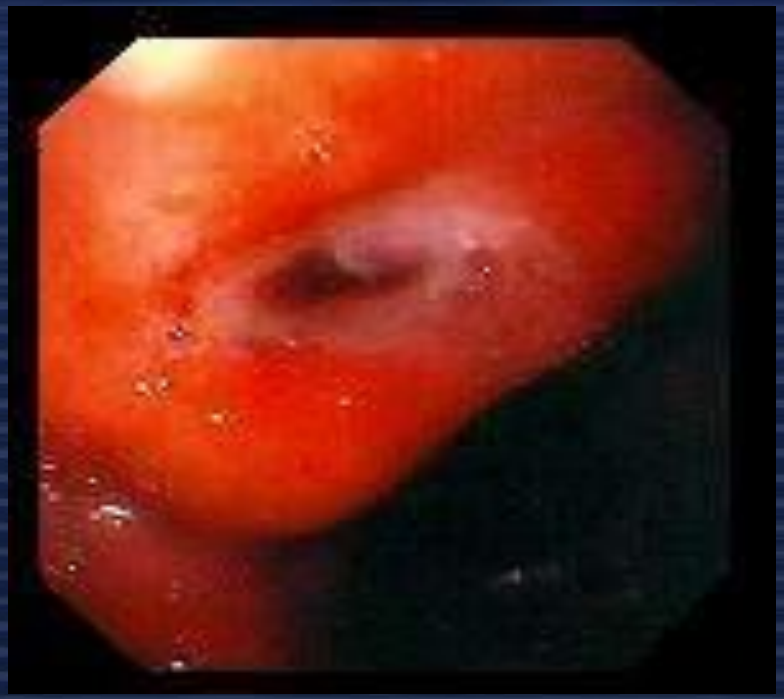
Diagnosis of PUD

Diagnosis of PUD depends mainly on endoscopic and radiographic confirmation

Doudenal Ulcer on Endoscopy

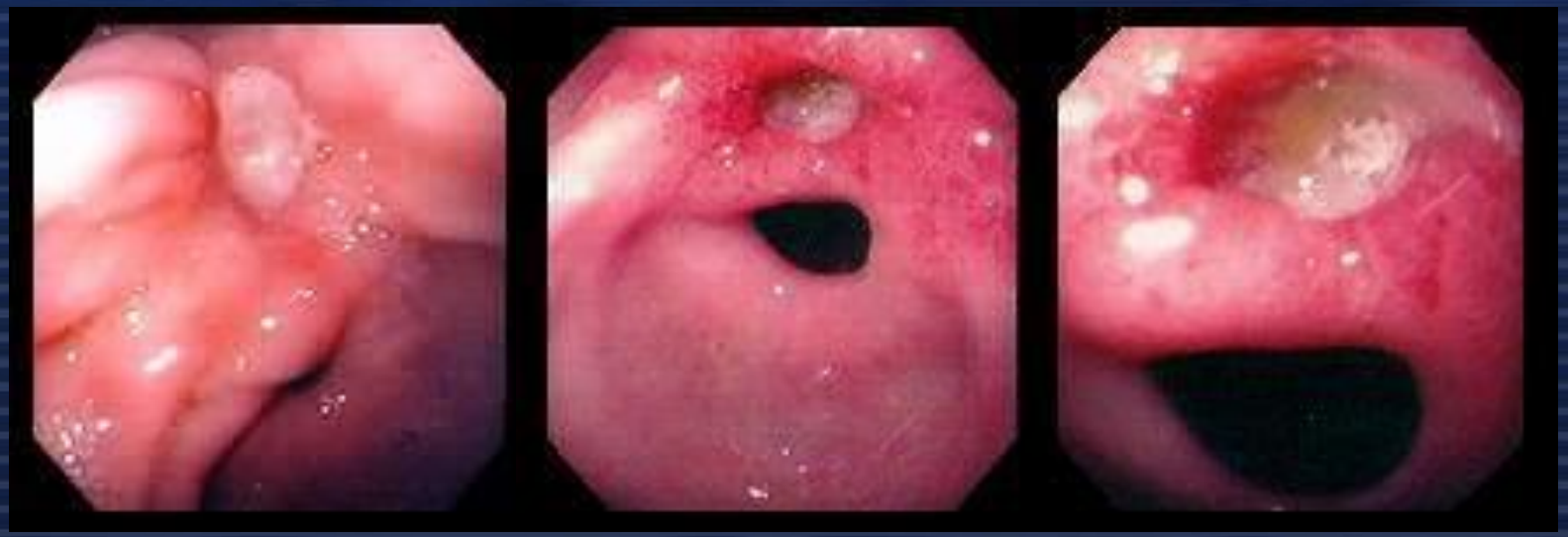


Normal doudenal bulb



Doudenal Ulcer

Gastric Ulcer on Endoscopy



Chronic Gastric Ulcers

Diagnosis of *H. pylori*

- **Non-invasive**
  - C^{13} or C^{14} Urea Breath Test
  - Stool antigen test
  - H. pylori IgG titer (serology)
- **Invasive**
  - Gastric mucosal biopsy
  - Rapid Urease test

Diagnosis of *H. pylori*

Non-invasive

1. C13 or C14 Urea Breath Test

The best test for the detection of an active infection

Diagnosis of *H. pylori*

Non-invasive

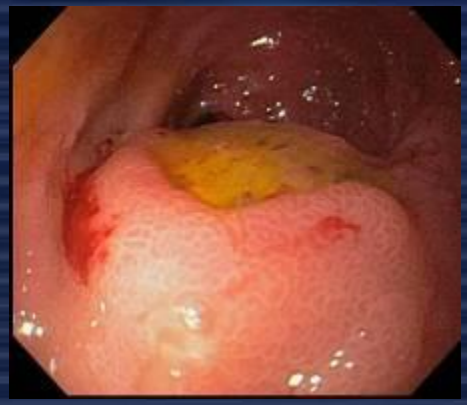
1) Serology for *H pylori*

   a. Serum Antibodies (IgG) to *H pylori* (Not for active infection)

   b. Fecal antigen testing (Test for active HP)

Diagnosis of *H. pylori*

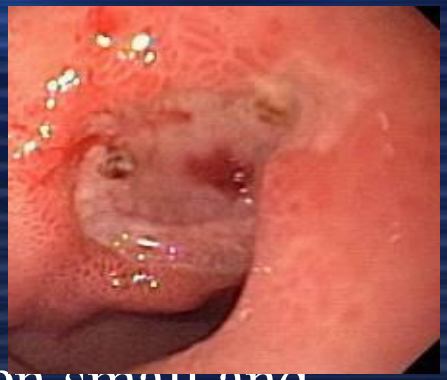
Invasive



- Upper GI endoscopy
  - Highly sensitive test
  - Patient needs sedation
  - Has both diagnostic & therapeutic role

Diagnosis of *H. pylori*

Invasive (endoscopy)



- Diagnostic:
- Detect the site and the size of the ulcer, even small and superficial ulcer can be detected
- Detect source of bleeding
- Biopsies can be taken for rapid urease test, histopathology & culture

Diagnosis of *H. pylori*

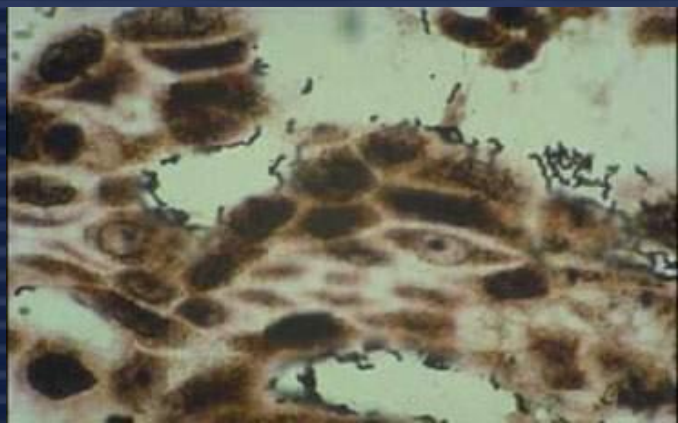
Invasive (endoscopy)

- **Rapid urease test (RUT)**
  - Considered the endoscopic diagnostic test of choice
  - Gastric biopsy specimens are placed in the rapid urease test kit. If *H pylori* are present, bacterial urease converts urea to ammonia, which changes pH and produces a **COLOR** change

Diagnosis of *H. pylori*

Invasive (endoscopy)

* Histopathology
  - Done if the rapid urease test result is negative
* Culture
  - Used in research studies and is not available routinely for clinical use



Diagnostic Tests for *Helicobacter pylori*

Invasive

Test	Sensitivity (%)	Specificity (%)	Usefulness
Endoscopy with biopsy			Diagnostic strategy of choice in children with persistent or severe upper abdominal symptoms
Histology	> 95	100	Sensitivity reduced by PPIs, antibiotics, & bismuth-containing compounds
Urease activity	93 to 97	> 95	Sensitivity reduced by PPIs, antibiotics, bismuth-containing compounds, & active bleeding
Culture	70 to 80	100	Technically demanding

ABLES A Z et al. *American Family Physician*. 2007

Diagnostic Tests for *Helicobacter pylori*

Noninvasive

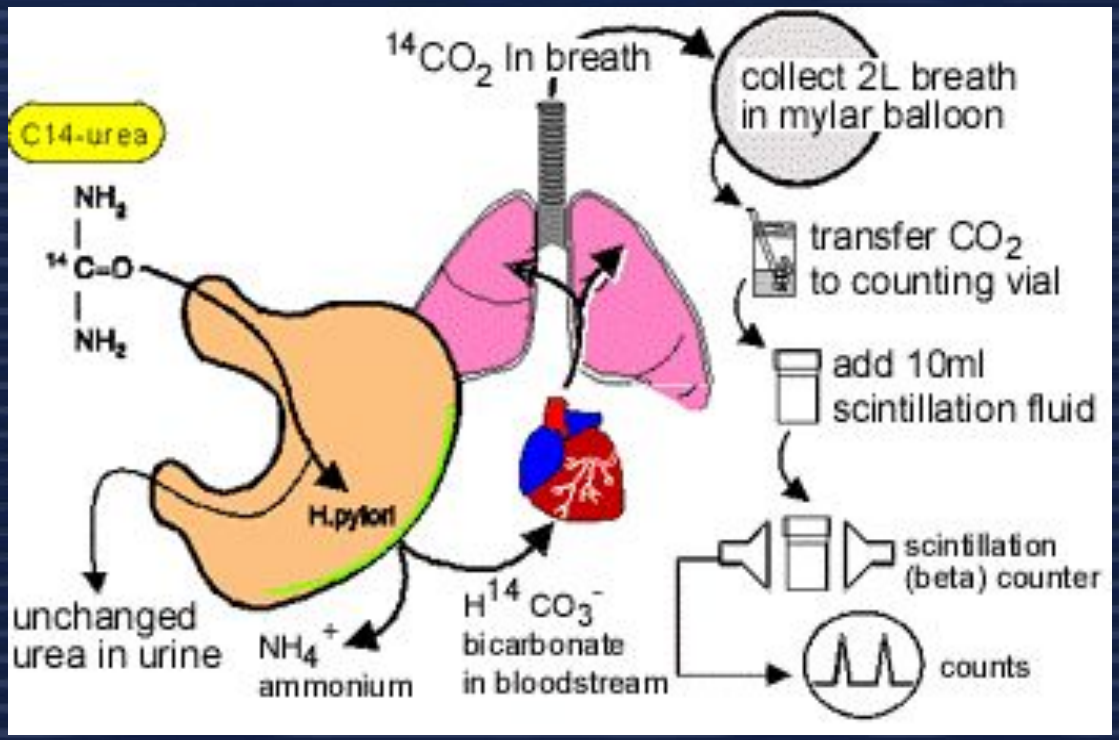
Test	Sensitivity (%)	Specificity (%)	Usefulness
Serology for IgG	85	79	Sensitivity & specificity vary widely; positive result may persist for months after eradication. Reliability in children not adequately validated; not recommended

ABLES A Z et al. *American Family Physician. 2007*

Diagnostic Tests for *Helicobacter pylori*

Noninvasive

Test	Sensitivity (%)	Specificity (%)	Usefulness
Urea breath test	95 to 100	91 to 98	Requires separate appointments; sensitivity reduced by PPIs, antibiotics, & bismuth-containing compounds; reliable test for cure.



Best available noninvasive test in children but higher false +ve rates in infants & children younger than six years compared with school-age children & adolescents

ABLES A Z et al. *American Family Physician. 2007*

Diagnostic Tests for *Helicobacter pylori*

Noninvasive

Test	Sensitivity (%)	Specificity (%)	Usefulness
H. pylori stool antigen	91 to 98	94 to 99	Test for cure 7 days after therapy is accurate; sensitivity reduced by PPIs, antibiotics, & bismuth-containing compounds. Easy to perform independent of age; possible alternative to urea test; monoclonal antibody-based test most reliable

ABLES A Z *et al. American Family Physician. 2007*

Testing to Document HP Eradication

- Since treatment is not effective is some cases (> 20%), individuals at high risk for HP-associated complications (e.g., prior bleeding ulcer) should undergo confirmatory testing with either

  - Stool antigen test or

  - Urea breath test to confirm HP cure

  (Serology has no role in confirmatory testing)

Testing to Document HP Eradication

- Should be confirmed after end of therapy; *noninvasive* testing with *UBT* is preferred, *4-8 weeks* after completion of therapy
- If ulcer recurs after eradication therapy, a more careful search for reinfection or eradication failure should be carried out by testing for presence of active infection (e.g. by *histologic* examination & *culture*, together with *antibiotic-sensitivity test*)

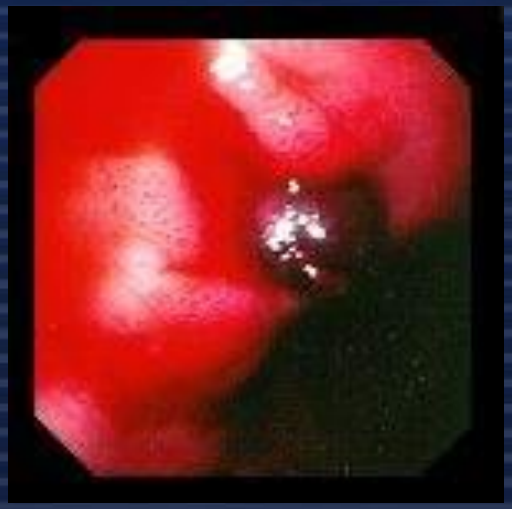
Diagnosis of *H. pylori* in patients with bleeding PU

- It is limited by the decreased sensitivity of standard invasive tests; usually, both the *RUT & histologic* testing should be performed & then combined with the *UBT* test
- Infection should be considered as present when any test is positive, whereas both the invasive tests & the breath test should be *negative* to establish the absence of infection

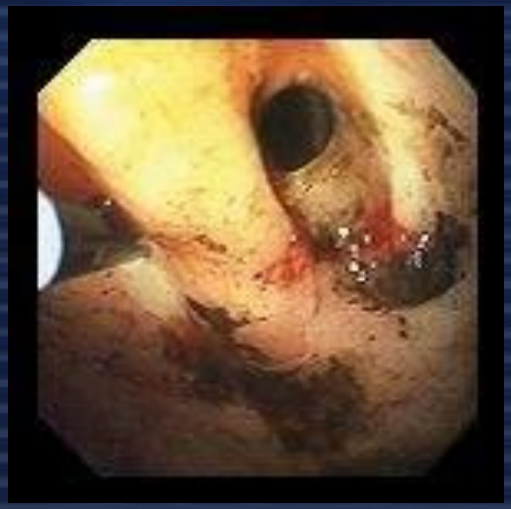
PUD – Complications

- Bleeding
- Perforation
- Gastric outlet or duodenal obstruction
- Chronic anemia

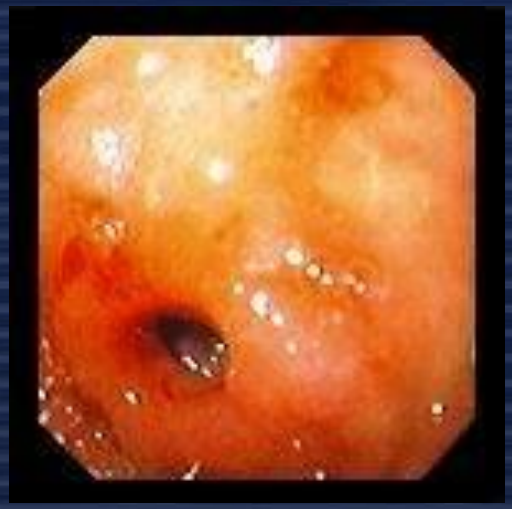
Complications of PUD on Endoscopy



Bleeding DU



Perforated GU



Duodenal stricture

PUD Treatment

Treatment Goals

- Rapid relief of symptoms
- Healing of ulcer
- Preventing ulcer recurrences
- Reducing ulcer-related complications
- Reduce the morbidity (including the need for endoscopic therapy or surgery)
- Reduce the mortality

General Strategy

- Treat complications aggressively if present
- Determine the etiology of ulcer
- Discontinue NSAID use if possible
- Eradicate *H. pylori* infection if present or strongly suspected, even if other risk factors (e.g., NSAID use) are also present;
- Use antisecretory therapy to heal the ulcer if *H. pylori* infection is not present

General Strategy

- Smoking cessation should be encouraged
- If DU is diagnosed by endoscopy, RU testing of endoscopically obtained gastric biopsy sample, with or without histologic examination should establish presence or absence of *H. pylori*
- If DU is diagnosed by x-ray , then a serologic , UBT, or fecal antigen test to diagnose *H. pylori* infection is recommended before treating the patient for *H. pylori*

Drugs Therapy

- H2-Receptors antagonists
- Proton pump inhibitors
- Cyto-protective agents
- Prostaglandin agonists
- Antacids
- Antibiotics for *H. pylori* eradication

Management of NSAIDs Ulcers

Management of NSAIDs Ulcers

- **This can be considered under two headings:**

1. The healing of an ulcer that has developed during NSAID or COX-2 inhibitor treatment; &
2. Strategies for preventing NSAID ulcers in patients who currently are ulcer free

Healing the Established NSAIDs-Associated Ulcer

- If possible, NSAID should be stopped, as healing with a histamine H2-receptor antagonist (H2-RA) will be faster than if the NSAID is continued
- PPI have been shown in 3 randomized controlled trials to be more effective than ranitidine or misoprostol for healing NSAID ulcers when the NSAID is continued

Best Prevention & Treatment for Upper GI Lesions Induced by NSAIDs

- There is conclusive evidence that PPIs decrease the incidence of ulcers & erosions, & heal them when they have occurred, even when NSAIDs administration is continued

Mearin & Ponce. Drugs, 2005

The Astronaut Study

- *Ranitidine* 150 mg twice daily ***Vs.*** *Omeprazole* 20 or 40 mg daily
- Gastroduodenal ulcer healing rates at 8weeks

Ranitidine 87% & Omeprazole 20 mg 71%

Are Better Results Obtained if Additional Inhibition of Gastric Acid Secretion is Achieved?

The healing rate of *H.pylori* eradication, peptic ulcer healing, or the extent of mucosal damage induced by NSAIDs are **clearly related to the acid inhibition level achieved with the corresponding treatment**

Reducing Risk of NSAIDs Ulcers by Choice of Agent

- Choose, where possible, an NSAID from the less damaging end of the spectrum,
- Use it in the lowest dose that is effective

Reducing Risk of NSAIDs Ulcers by Choice of Agent

- Use highly selective COX-2 inhibitors (whether to use them instead of a largely non-selective NSAID such as diclofenac or ibuprofen requires judgments about cost vs. benefit for the individual patient

Reducing Risk of NSAIDs Ulcers by Choice of Agent

- In low-risk patients such as young - middle age individuals without past history of ulcer & with no hazard-increasing cotherapies (e.g warfarin or steroids), the risk of using a non-selective NSAID is very small

Preventing NSAIDs Ulcers with Co-Prescribed Gastric Protectants

- Patients who continue to require NSAIDs should receive either a PPI or misoprostol to prevent ulcer recurrence

Drugs Therapy for Treatment of PUD

1- H2-Receptors antagonists

2- H^+, K^+ ATPase: Proton pump inhibitors (PPIs)

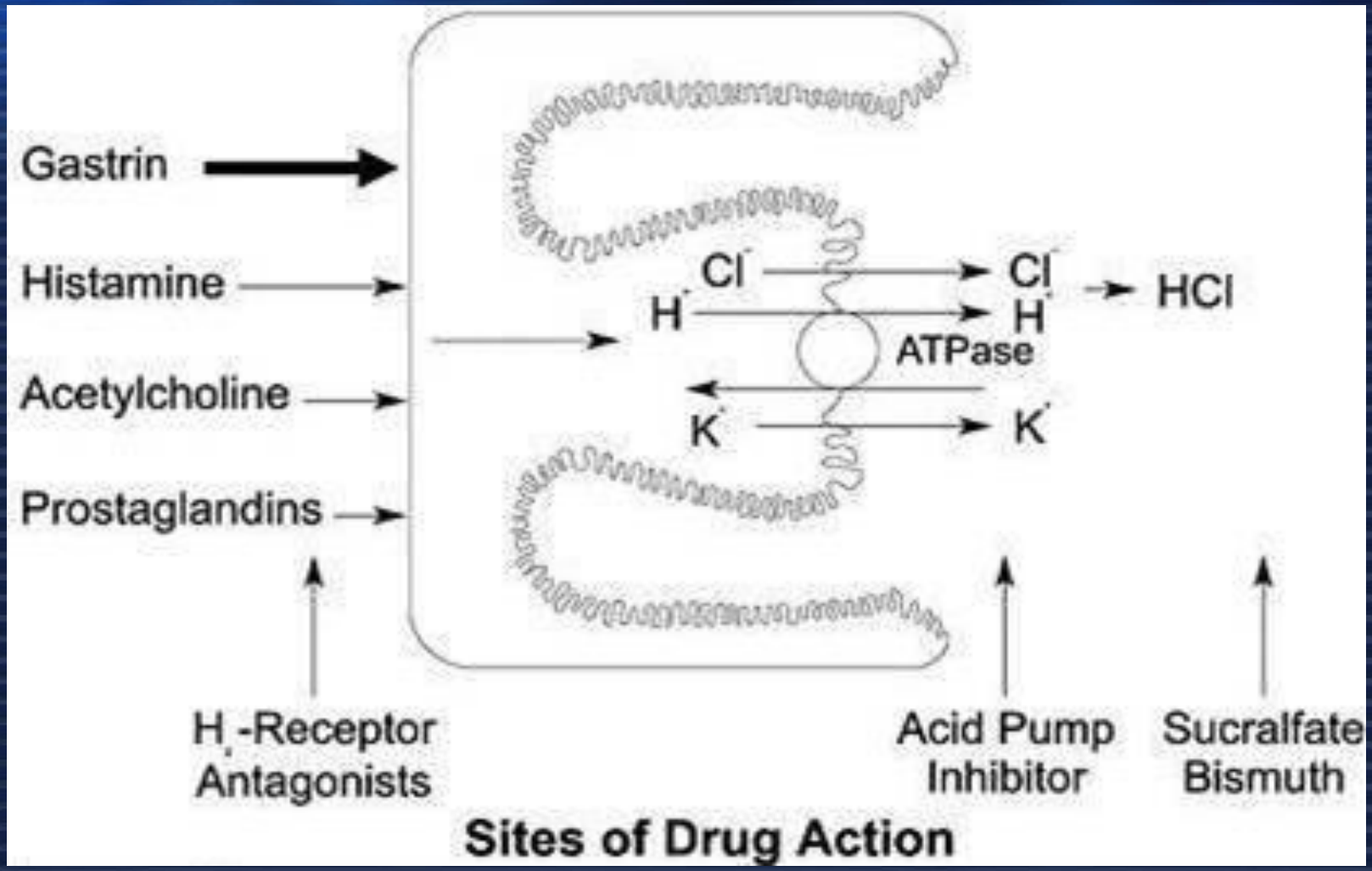
3- Cyto-protective agent (Sucalfate)

4- Prostaglandin agonists

5- Antacids

6- Antibiotics for *H. pylori* eradication

Peptic Ulcer Disease - Treatment



Degree of Acid Inhibition to Heal an Ulcer

- It has been reported that a sustained increase in pH > 3 would be sufficient to heal an ulcer
- However, one of the risk factors for refractory gastric ulcer appears to be the impossibility of maintaining gastric pH > 4 for a minimum daily period of 16 hr

Mearin & Ponce. Drugs, 2005

The Purpose of Inhibiting Gastric Acid Secretion in cases of Upper GI Bleeding

- In upper GI bleeding, the aim is to achieve the least acid gastric pH possible in order to prevent acid degradation of the clot & accelerate healing as much as possible
- Both clinical & experimental studies suggest that extremely potent inhibition is required to achieve the intended efficacy

Mearin & Ponce. Drugs, 2005

The Ideal Drug to Achieve Potent Acid inhibition

- Ideal drug should be able to maintain pH > 4 for ≥ 16 hr/day
- Such level guarantee a consistent response to treatment, & sufficient for most refractory cases of peptic acid disease
- Efficacy of the drug would also have to be consistent, so that such potent acid inhibition levels might be achieved in all patients, regardless of their basal acid secretion, metabolic capacity, or the presence or absence of H. pylori infection

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

1- H2-Receptors Antagonists

- These agents are capable of 90% reduction in basal & food-stimulated secretion of gastric acid after single dose. they are somewhat less effective in reducing nocturnal secretion
- Studies have demonstrated their effectiveness in promoting the healing of DU & GU, & preventing their recurrence
- These meds are equally effective in treating these conditions

Drugs Therapy for Treatment of PUD

1- H2-Receptors Antagonists

- Previous recommendations were to administer these agents at least twice a day, a single bedtime dose may be just as effective & may elicit better compliance
- If administered for 6-8 weeks, can heal DU 75% & 90% respectively

Drugs Therapy for Treatment of PUD

1- H2-Receptors Antagonists

Agents

- Cimetidine 800mg OD or 400mg BID
- Ranitidine 300mg OD or 150mg BID
- Famotidine 40mg OD or 20mg BID
- Nizatidine 300mg OD or 150mg BID
- Should by taken for 6-8 weeks

Drugs Therapy for Treatment of PUD

1- H2-Receptors Antagonists

Pharmacokinetics

- Rapidly absorbed 1-3 hrs to peak
- Ranitidine & Cimetidine hepatically metabolized whereas Famotidine & Nizatidine are renally excreted
- Dose adjustment is needed in some renal & hepatic failure patients

Drugs Therapy for Treatment of PUD

1- H2-Receptors Antagonists

Side Effects

- Usually minor; include headache, dizziness, diarrhea, & muscular pain
- Hallucinations & confusion in elderly patients;
- Hepatotoxicity with Ranitidine
- Cimetidine elevates serum prolactin & alters estrogen metabolism in men
- Gynecomastia, Galactorrhea and reduced sperm count

Drugs Therapy for Treatment of PUD

1- H2-Receptors Antagonists

Drug Interactions

- Cimetidine slows microsomal metabolism of some drugs
- Cimetidine causes these in a dose-dependent but reversible manner
- Inhibits the metabolism of warfarin, theophylline, diazepam & phenytoin
- Ranitidine has less effect on hepatic enzymes

Drugs Therapy for Treatment of PUD

1- H2-Receptors Antagonists

Drug Interactions

- Famotidine & Nizatidine has no effect on hepatic drug metabolism
- Combining H2 inhibitor with antacid has little rationale although is done. H2 antagonist + PPI inhibits efficacy of PPI
- Over the counter H2 blockers now available, labeled for short-term use in heartburn & dyspepsia

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

Same Acid Inhibition as Anti-H2??

- No
- Among anti-secretory drugs, PPIs can inhibit gastric acid secretion with a greater efficacy than anti-H2

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

Same Acid Inhibition as Anti-H2??

- They are potent acid inhibitors
- Potent acid inhibition is arbitrarily defined as inhibition that achieves maintenance of an intragastric pH > 4 for ≥ 16 hr out of 24 hr

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

Agents

- Omeprazole
- Lansoprazole
- Pantoprazole

1st Generation

- Rabeprazole
- Esomeprazole

2nd Generation

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

Pharmacological Effect

- PPIs dose-dependently inhibit basal & food acid secretion
- Decreases pepsinogen secretion &, due to the increase in intragastric pH, inhibit the proteolytic activity of pepsin

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

Comparative Anti-secretory Efficacy of the Different PPIs

- Among different PPIs administered at standard doses, esomeprazole 40 mg/day has a greater anti-secretory potency
- Rabeprazole 20 mg/day & lansoprazole 30 mg/day show a faster action, & slightly greater acid inhibition capacity than omeprazole 20 mg/day & pantoprazole 40 mg/day

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

Side Effects

- No evidence that they cause direct toxic effects.
- Most common adverse reactions include episodes of diarrhea, nausea, abdominal pain, dizziness, headache, or skin rash
- These manifestations are most often transient & moderate in severity, not requiring reductions in compound dosage

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

PPIs & Vitamin B12 Deficiency

- In some patients continuously taking PPIs, a mild vitamin B12 deficiency has been seen as the result of decreased vitamin absorption
- This is due to impaired release of the vitamin from food, because this is a process enhanced by the presence of an intragastric acid environment

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

Time of Administration

- Should by administered while fasting & before a meal so that at the time the peak plasma concentration is reached, there is also a maximum of proton pumps activated (i.e. secreting acid)
- For treatment of DU & GU should be used for 4-6 weeks

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

Pharmacokinetics

How can PPIs have a Short Half-life & a Long-lasting Effect?

- Despite their short plasma half-life, PPIs exert a persistent pharmacological action because by irreversibly binding to the proton pump they render necessary the synthesis of new enzymes to re-establish gastric acid secretion

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

Pharmacokinetics

Metabolism

- PPIs undergo extensive first-pass metabolism in the liver, resulting in various inactive metabolites that are excreted in the urine or bile
- Metabolized by the cytochrome P450 system (mainly by isoenzymes CYP2C19 & CYP3A4)

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

Pharmacokinetics

What is Esomeprazoie?

- It is the S isomer of omeprazole
- Pharmacokinetic & pharmacodynamic studies suggest that this isomer undergoes less first-pass metabolism in the liver & has a lower plasma clearance as compared with omeprazole

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

Dose Adjustment in Liver Failure

- In patients with severe liver failure, the area under the plasma curve for PPIs increases 7-9 fold, & their half-life is prolonged to 4-8 hr. A decrease in the usual dose of these drugs is recommended in this group of patients

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

Drug Interactions

- Theoretically, their influence on phenytoin, carbamazepine, warfarin, & diazepam should be monitored
- However, as confirmed by a recent analysis of cases recorded by (FDA), the clinical impact of these interactions is very low (rates lower than 0.1 -0.2 per 1,000,000 prescriptions), with no differences between the different PPIs

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

Presence of H. Pylori influence Degree of Acid inhibition ??

- PPIs show a decreased efficacy in patients not infected by *H. pylori*. This often requires the use of higher doses of the PPI

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

Do PPIs Have Direct Action on H.Pylori??

- Yes, PPIs inhibit the urease protecting *H. pylori* from acid & are effective on this microorganism *in vitro,* although *in vivo* they only achieve eradication in 10-15% of cases

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

2- Proton Pump Inhibitors (PPIs)

Do PPI Promote Actions of Antibiotics in H. Pylori Eradication?

- In vitro, PPIs have additive even synergistic effect with several antimicrobial agents
- Studies suggest that high dose omeprazole increase amoxycillin level in gastric juice, & high dose of PPIs improve *H.pylori* cure rate when given with amoxycillin
- Clarithromycin activity against *H. pylori* is enhanced as gastric pH increases

Mearin & Ponce. Drugs, 2005

Drugs Therapy for Treatment of PUD

3- Cyto-Protective Agent (Sucalfate)

- **Sucralfate** = complex of Aluminum Hydroxide & Sulfated Sucrose
- Binds to positively charged groups in proteins, glycoproteins of necrotic tissue **(coat ulcerated mucosa)**
- Not absorbed systemically
- Require acidic media to dissolve & coates the ulcerative tissue so, it can not be given with H2-antagonist, PPIs, & antacids

Drugs Therapy for Treatment of PUD

3- Cyto-Protective Agent (Sucalfate)

Administration

- Should not be given with food, give 1hr before or 3hr after meal
- **Dose:** 1gm/ 4times daily or 2 gm/ 2times daily
- Must be given for 6-8 weeks
- Large tablet & difficult to swallow

Drugs Therapy for Treatment of PUD

3- Cyto-Protective Agent (Sucalfate)

Side Effects

- Constipation; black stool & dry mouth
- **It is very safe in pregnancy**

Drugs Therapy for Treatment of PUD

4- Prostaglandin Agonists (PGE1) Misoprostol

- Inhibits secretion of HCl & stimulates secretion of mucus & bicarbonatemis
- It is a methyl analog of PGE1
- It is approved for prevention of ulcer induced by NSAIDs

Drugs Therapy for Treatment of PUD

4- Prostaglandin Agonists (PGE1) Misoprostol

- Optimal role in ulcer treatment is difficult to define
- PPIs may be as effective as misoprostol for this indication
- Routine clinical prophylaxis of NSAIDs-induced ulcers may not be justified
- However, in patients with rheumatoid arthritis requiring NSAIDs therapy, prophylaxis with Misoprostol or a PPI may be cost-effective

Drugs Therapy for Treatment of PUD

4- Prostaglandin Agonists (PGE1) Misoprostol

Administration

- Should be given 4 time/ day (inconvenient)

Side effects

- Up to 20% develop diarrhea & cramps
- Category X

Drugs Therapy for Treatment of PUD

5- Antacids

- Weak bases that react with gastric acid to form water & salt (Neutralize acid)
- Studies indicate mucosal protection either through stimulation of prostaglandin production or binding of unidentified injurious substance
- Antacids vary in palatability & price

Drugs Therapy for Treatment of PUD

5- Antacids

- Antacids contain either Sodium-bicarbonate, Aluminum-hydroxide, magnesium-hydroxide & calcium carbonate
- Require large neutralizing capacity (a single dose of 156 meq antacid given 1 hr after meal effectively neutralize gastric acid for 2 hr, a second dose given 3 hr after eating maintains the effect for over 4 hr after the meal)

Drugs Therapy for Treatment of PUD

5- Antacids

- Very inconvenient to administer
- Tablet antacids are generally weak in their neutralizing capability, & a large number of tablets would be required for this high-dose regimen

Drugs Therapy for Treatment of PUD

5- Antacids

Side Effects

- Cation absorption (sodium, magnesium, aluminum, calcium) leads to systemic alkalosis (concern with renal impairment)
- Sodium content an issue with congestive heart failure

Drugs Therapy for Treatment of PUD

5- Antacids

Side Effects

- Aluminum hydroxide may be constipating, Magnesium hydroxide may produce diarrhea so, they used in combination
- Calcium-carbonate containing antacids work rapidly & very effective but large dose may cause calciuria

The Mechanism & Side Effects of Various Acid Suppressive Medications

Drug	Mechanism	Common side effect
Antacid	Neutralize acid	Mg - diarrhea Al - constipation Ca – constipation
H2 receptor antagonists	Block histamine receptor	Cytochrome 450 altered metabolism of drugs
Prostaglandins	Agonist	Diarrhea, cramps, abortion
H+/K+ ATPase inhibitors	Block acid pump	Hypergastrinemia enterochromaffin cell (ECL) hyperplasia
Sucrafate	Coat ulcerated mucosa	Constipation

Drugs Therapy for Treatment of PUD

6- Antibiotics for H. Pylori Eradication

- *H. pylori* eradication significantly reduce the risk of ulcer recurrence & re-bleeding & less expensive than chronic antisecretory therapy
- Continuing antisecretory therapy for > 2 weeks following antibiotic treatment is unnecessary after *H.pylori* eradication

ABLES A Z et al. *American Family Physician. 2007*

Duration of treatment & adverse effects should be considered

Duration of *H. Pylori* Eradication Therapy

- Until recently, the recommended duration of therapy for *H.pylori* eradication was 10 -14 days
- There are number of recent studies evaluated one-, five-, & seven-day regimens
- Although not proven, potential benefits of shorter regimens include better compliance, fewer adverse drug effects, & reduced cost to the patient

ABLES A Z et al. *American Family Physician. 2007*

Adverse Effects

- The most commonly reported adverse events were nausea, vomiting, & diarrhea
- A bitter or metallic taste in the mouth is associated with eradication regimens containing clarithromycin
- Bismuth subsalicylate may cause a temporary grayish-black discoloration of the stool

ABLES A Z et al. *American Family Physician. 2007*

Selected Long-Duration Regimens for H. pylori Eradication

Treatment regimen	Duration (days)	Eradication Rate (%)
Omeprazole 20mg BID + Amoxicillin 1g BID + Clarithromycin500 mg BID	14	80-86
Lansoprazole 30mg BID + Amoxicillin 1g BID + Clarithromycin500 mg BID	10-14	86
Bismuth subsalicylate 525mg QID + Metronidazole 250mg QID + Tetracycline 500mg + Histamine H2 blocker	14 days (H2 blocker alone for an additional 14 days taken once or twice daily)	80

ABLES A Z et al. *American Family Physician. 2007*

Short-Course Therapy for Eradication of Helicobacter pylori

Treatment regimen	Duration (days)	Population studied	Eradication Rate(%)
Bismuth subsalicylate 524mg QID + amoxicillin 2g QID + metronidazole 500mg QID + lansoprazole 60mg once	1	H. Pylori (+) patients with dyspepsia	95
Lansoprazole 30mg BID + Amoxicillin 1g BID + Clarithromycin500 mg BID	7	H. Pylori (+) patients with dyspepsia	90

ABLES A Z et al. *American Family Physician. 2007*

Short-Course Therapy for Eradication of Helicobacter pylori

Treatment regimen	Duration (days)	Population studied	Eradication Rate(%)
Clarithromycin250 mg BID + amoxicillin 1g BID + metronidazole 400mg BID + lansoprazole 30mg BID	5	H. pylori (+) patients with dyspepsia for 3 months or endoscopically confirmed ulcers	89
Clarithromycin250 mg BID + amoxicillin 1g BID + metronidazole 400mg BID + ranitidine300mg BID	5	H. Pylori (+) patients with dyspepsia for 3 months or endoscopically confirmed ulcers	89

ABLES A Z et al. *American Family Physician. 2007*

Short-Course Therapy for Eradication of Helicobacter pylori

Treatment regimen	Duration (days)	Population studied	Eradication Rate(%)
[Lansoprazole 30 mg BID for 2 days (pretreatment)] + amoxicillin 1g BID + metronidazole 400mg BID + clarithromycin 250mg BID + lansoprazole 30mg BID	5	H. Pylori (+) patients with dyspepsia for 3 months or endoscopically confirmed ulcers	81

ABLES A Z et al. *American Family Physician. 2007*

Resistance

- Resistant *H. pylori* has been documented in cases of failed eradication therapy based on biopsy & culture results & is of great concern in patients at high risk for complications of *H.pylori* infection

ABLES A Z et al. *American Family Physician. 2007*

Resistance

- Resistance rate to clarithromycin is currently 2-30% & to metronidazole 15-66%
- Primary resistance to clarithromycin is a strong predictive risk factor for treatment failure, whereas primary resistance to metronidazole does not always lead to treatment failure

ABLES A Z et al. *American Family Physician. 2007*

Resistance

- 70 % of patients failing one or more regimens responded well to **triple-drug therapy** that included:

  Pantoprazole, amoxicillin, & levofloxacin for 10 days

ABLES A Z et al. *American Family Physician. 2007*

Resistance

- A meta-analysis of current literature on treatment of resistant *H. pylori* showed benefit in using **quadruple drug therapy, including:**

  - ✔ Clarithromycin + ranitidine + bismuth + amoxicillin (1 g twice daily) therapy, as well as a combination of
  - ✔ PPIs (standard dosage for 10 days) + bismuth + metronidazole + tetracycline

ABLES A Z et al. *American Family Physician. 2007*

Recurrence

- Recurrence of *H. pylori* infection is defined by:

  A positive result on urea breath or stool antigen testing six or more months after documented successful

ABLES A Z et al. *American Family Physician. 2007*

Recurrence

Risk factors for recurrence include:

- Non-ulcer dyspepsia
- Persistence of chronic gastritis after eradication therapy
- Female gender
- Intellectual disability
- Younger age
- High rates of primary infection
- Higher urea breath test values

ABLES A Z et al. *American Family Physician. 2007*

Recurrence

- Recurrence rates worldwide vary but lower in developed countries
- In the primary care setting, physicians may choose to treat recurrences with an alternative eradication regimen, depending on symptoms & risk factors for complications of infection
- It is too early to know whether shorter courses of eradication therapy will be associated with a higher resistance rate

ABLES A Z et al. *American Family Physician. 2007*

Thank U