UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA
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Patologia Sistemica VI (M-Z)
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# Diseases of the stomach and duodenum

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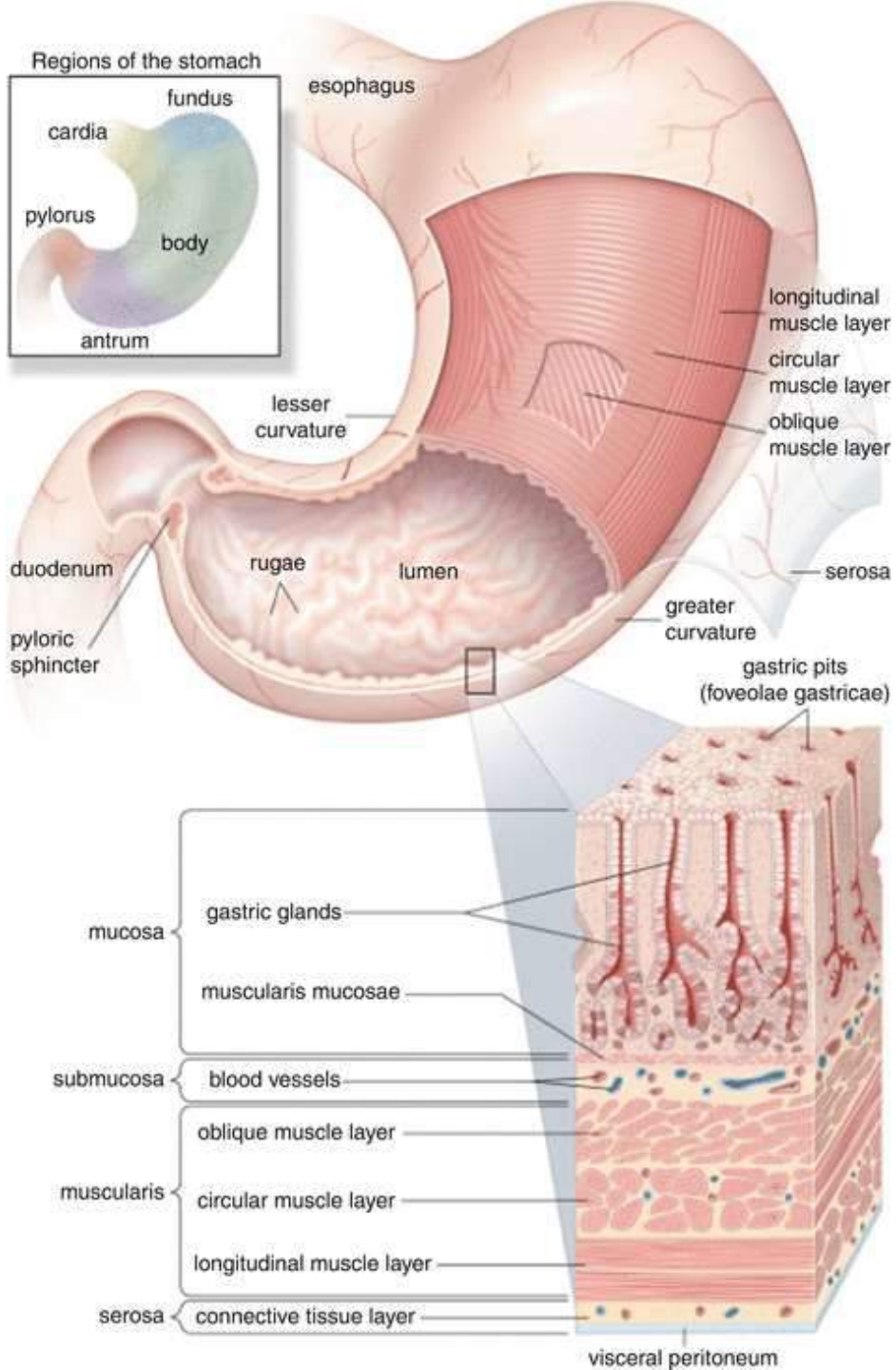
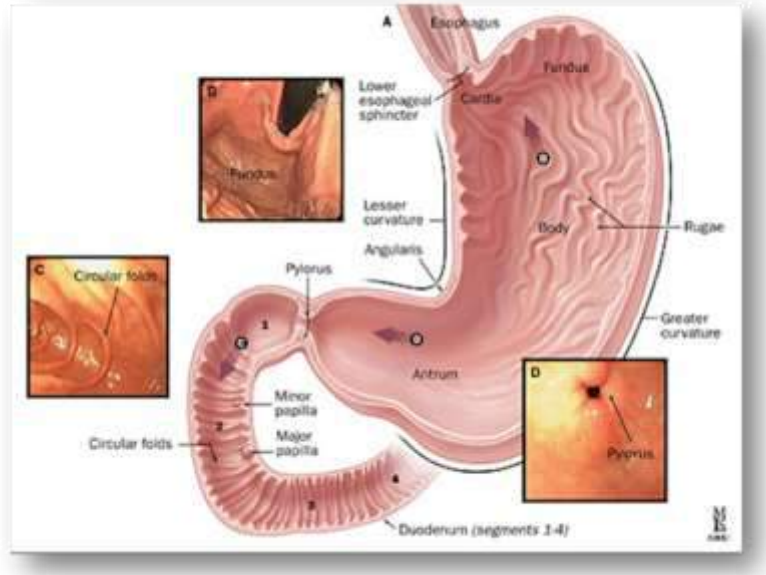
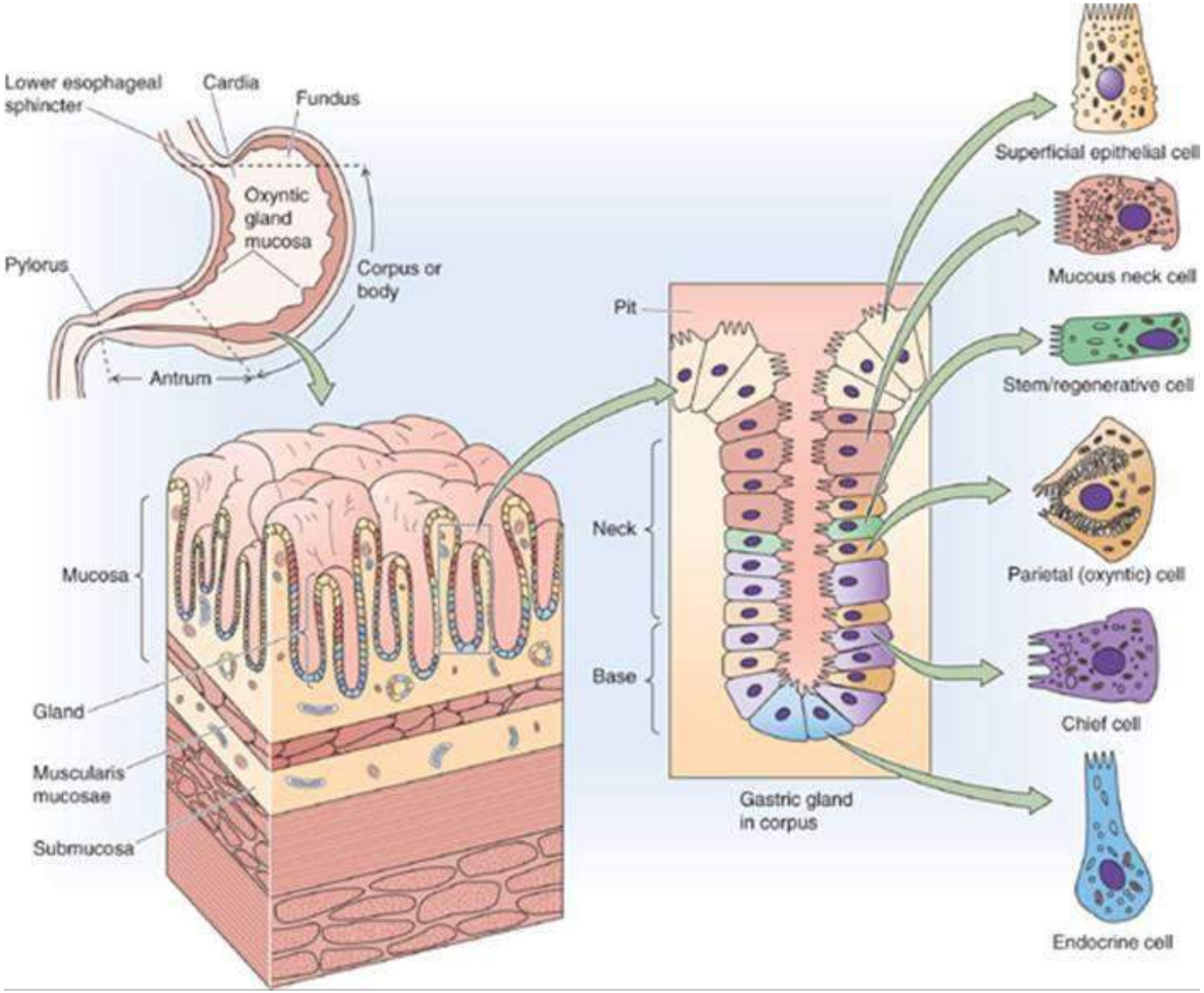
Testo consigliato Harrison's Principles of Internal Medicine – 19-20° Ed.


Regions of the stomach
fundus
cardia
pylorus
body
antrum
esophagus
longitudinal muscle layer
circular muscle layer
oblique muscle layer
lesser curvature
duodenum
rugae
lumen
serosa
greater curvature
pyloric sphincter
gastric pits (foveolae gastricae)
mucosa
gastric glands
muscularis mucosae
submucosa
blood vessels
muscularis
oblique muscle layer
circular muscle layer
longitudinal muscle layer
serosa
connective tissue layer
visceral peritoneum


A
Esophagus
Fundus
Lower esophageal sphincter
Cardia
B
Fundus
Lesser curvature
Angularis
Body
Rugae
C
Circular folds
Pylorus
Greater curvature
Antrum
D
Minor papilla
Major papilla
Circular folds
Pylorus
Duodenum (segments 1-4)

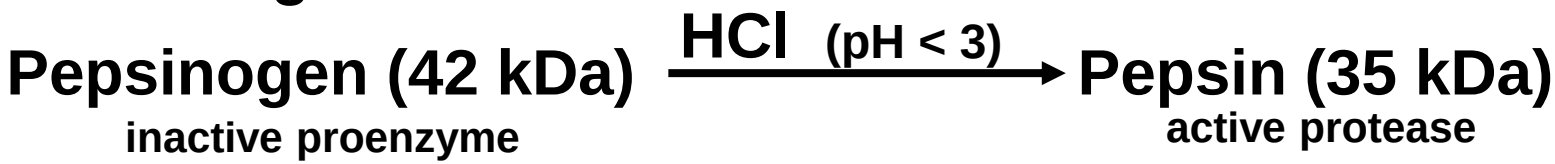
# Gastric glands and cells



# Secretions of the stomach

1. **Mucus:** Glycoprotein products found throughout entire GI tract. Primary function as lubricant, but can also have many other regionally specialized functions

2. **Pepsinogen:** Proenzyme made by chief cells. In gastric lumen:




3. **Hydrochloric Acid**: denature food; activate pepsinogen; dissolve bone; bacteriocidal

4. **Intrinsic Factor**: Essential for the absorption of Vit $B_{12}$

# Parietal cells and acid secretion: pharmaacology

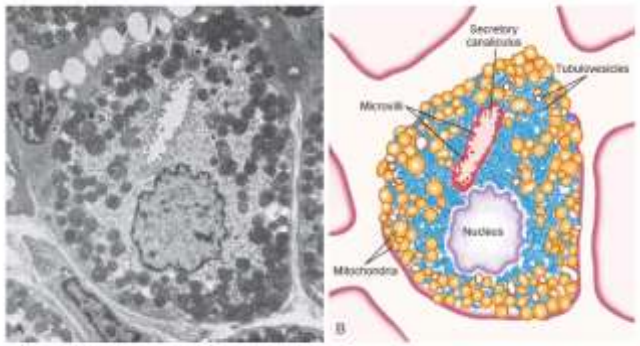
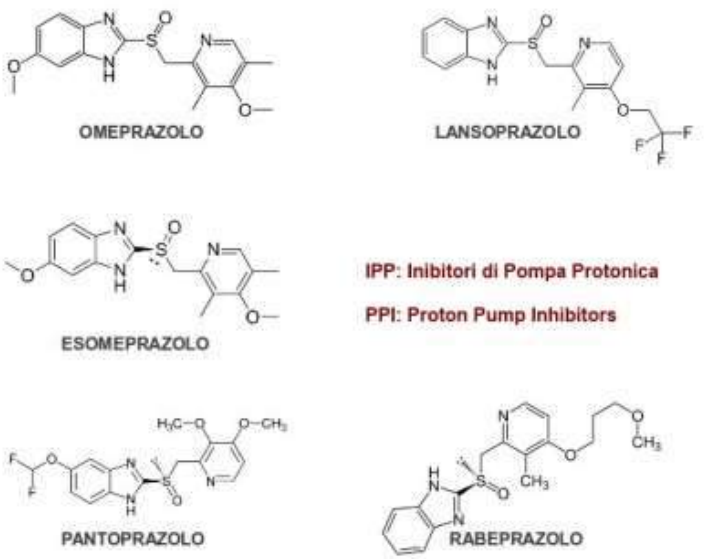
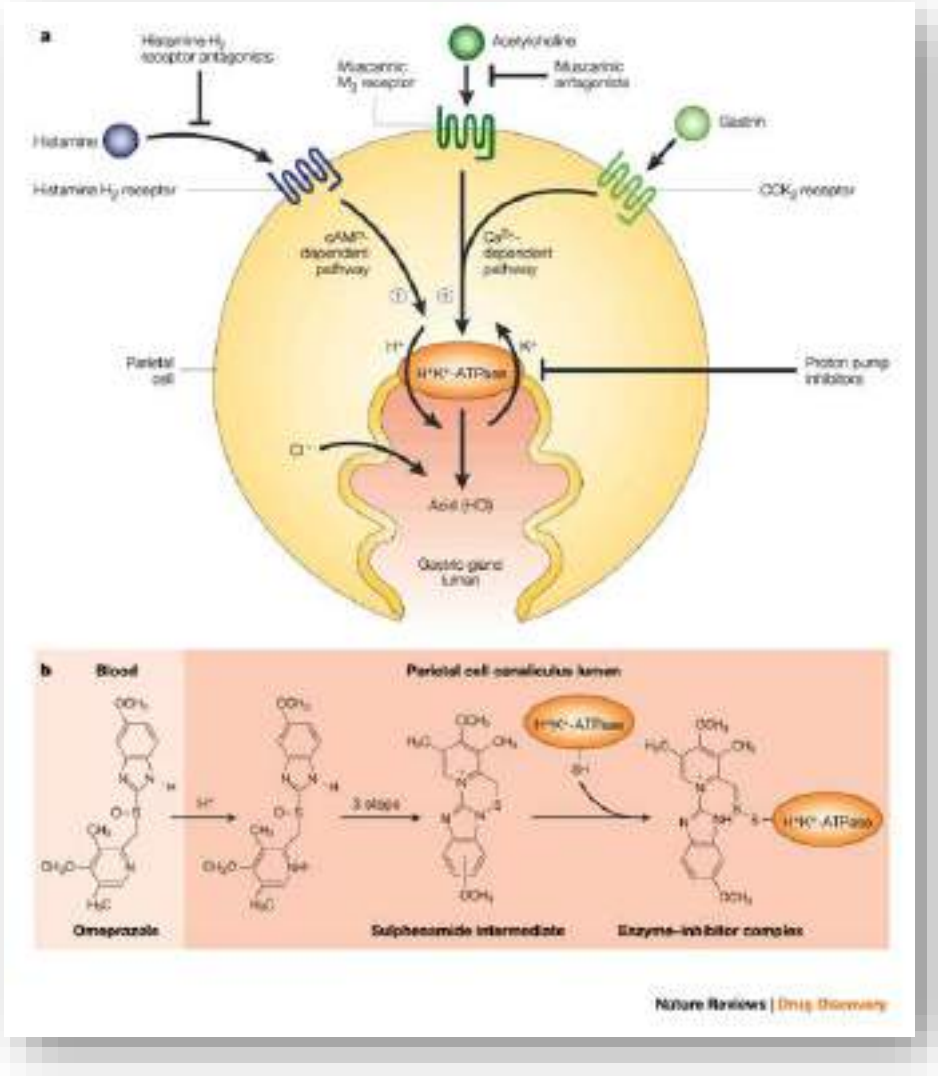
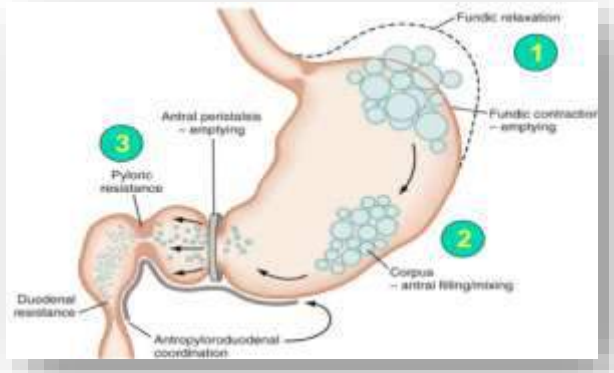


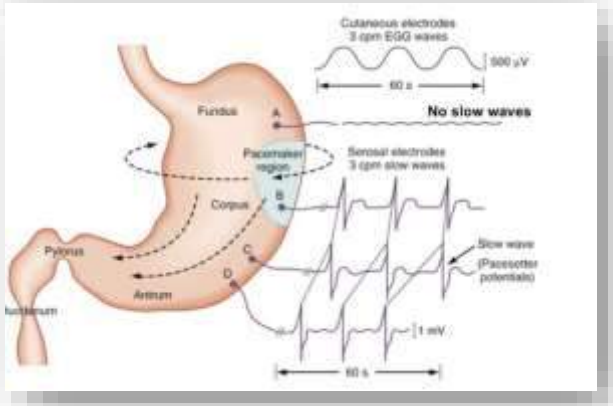

FIGURE 48-6. Parietal cell. A, Electron photomicrograph. B, Schematic representation. (From Johnson LR. Gastrointestinal physiology. 6th ed. St Louis: Mosby; 2001. pp 78-9.)



# Gastric emptying



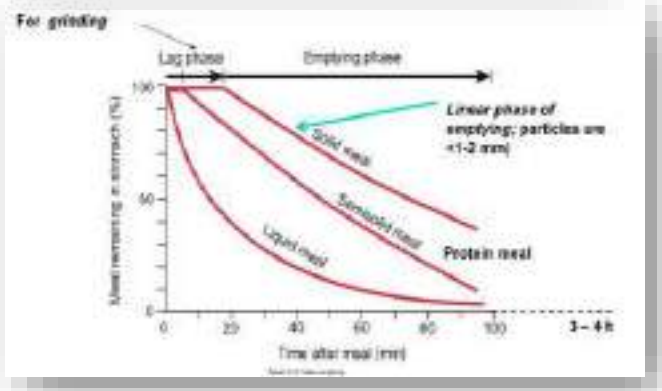
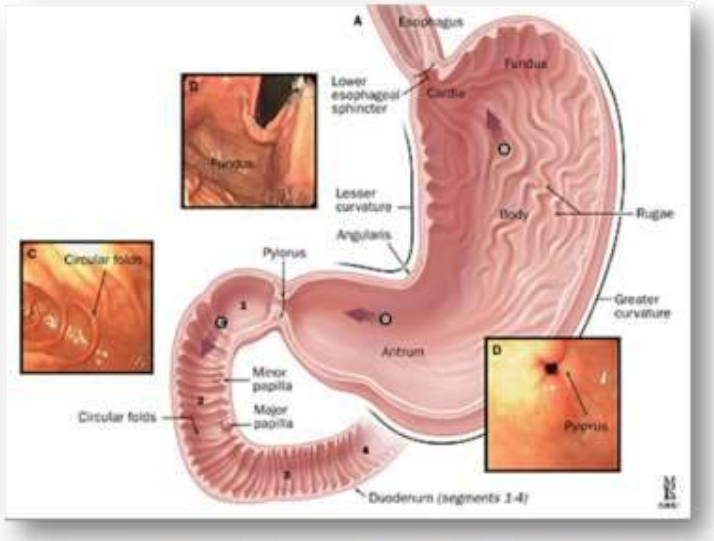




**TABLE 49-3** Causes of Gastroparesis

| Diagnosis | Incidence (%) |
|---|---|
| Idiopathic gastroparesis* | 40% |
| Diabetic gastroparesis (type 1 and 2 diabetes mellitus) | 30% |
| Postsurgical gastroparesis (antrectomy, vagotomy, fundectomy, fundoplication) | 20% |
| Obstructive gastroparesis (mechanical/spasm) | 5%-10% |
| Ischemic gastroparesis | <1% |
| Miscellaneous causes | <1% |

# Diagnostic procedure for gastric disorders

- Endoscopy
- Ecoendoscopy
- Radiology (CT and  RM)
- Functional tests (breath test, gastric acid measurement,..)


A
Esophagus
Fundus
Lower esophageal sphincter
Cardia
B
Fundus
Lesser curvature
Body
Rugae
Angularis
C
Circular folds
Pylorus
Greater curvature
Antrum
D
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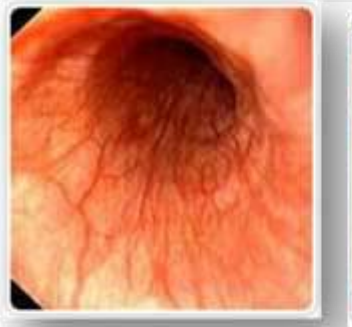
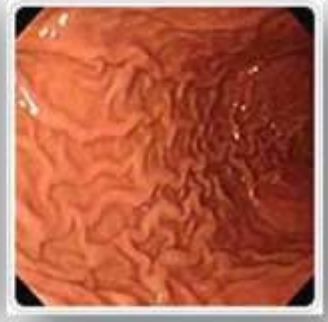
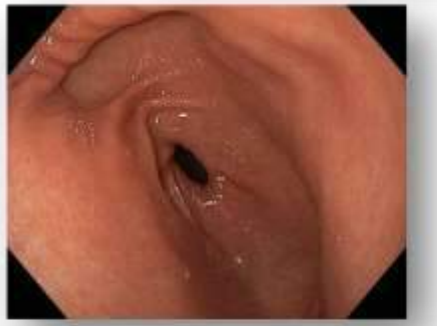
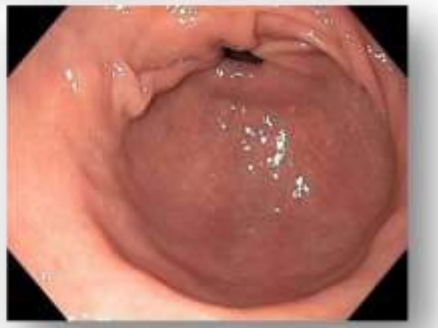
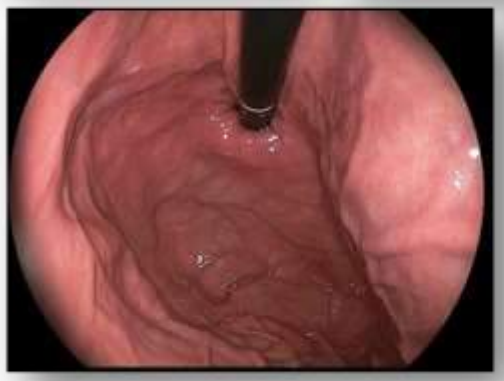
Circular folds
Pylorus
Duodenum (segments 1-4)



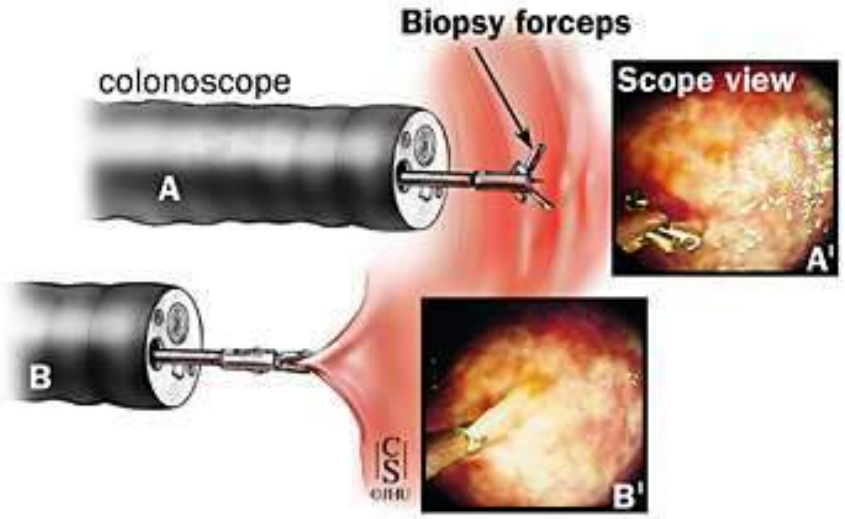


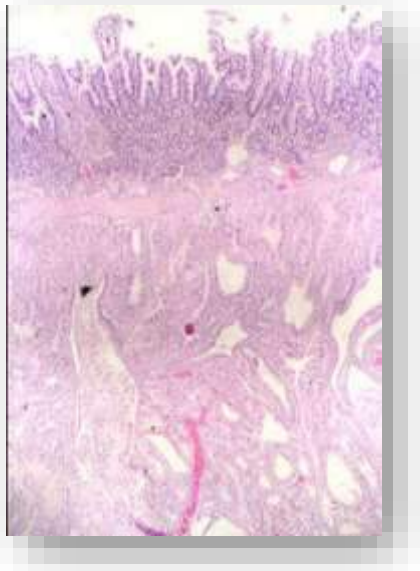


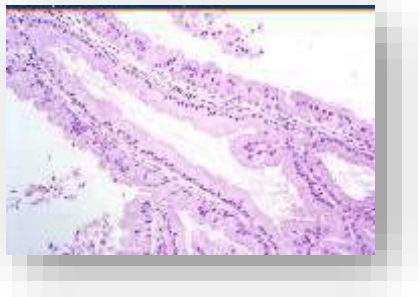




# Biopsy and histology

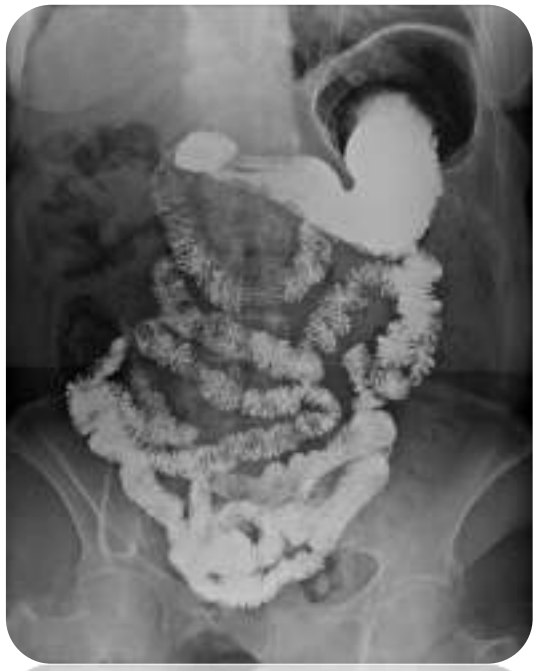


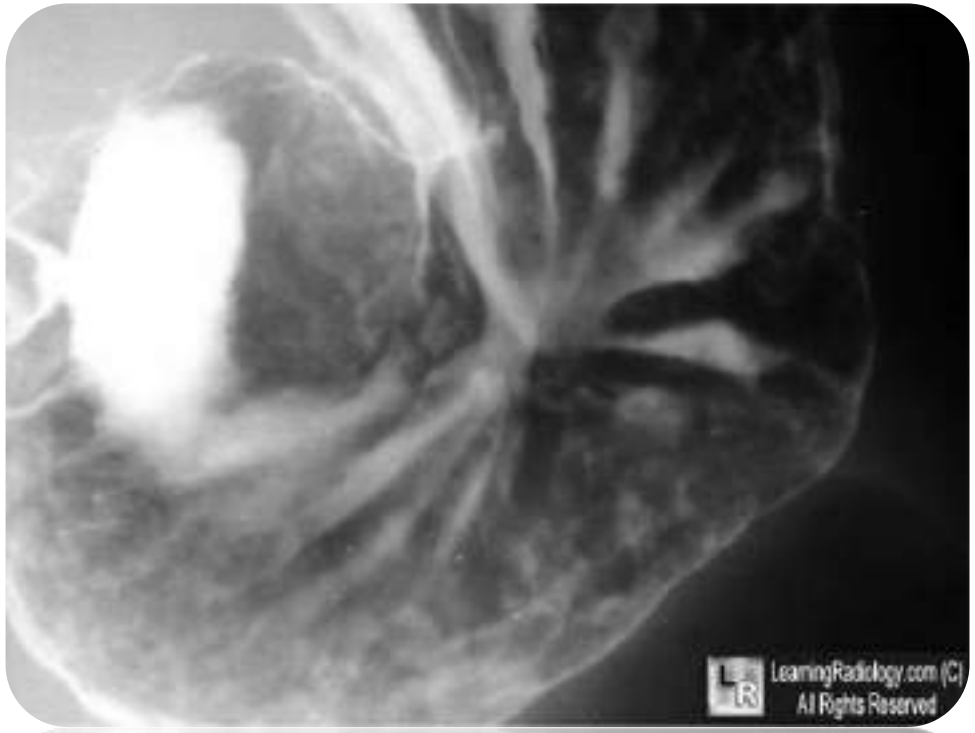





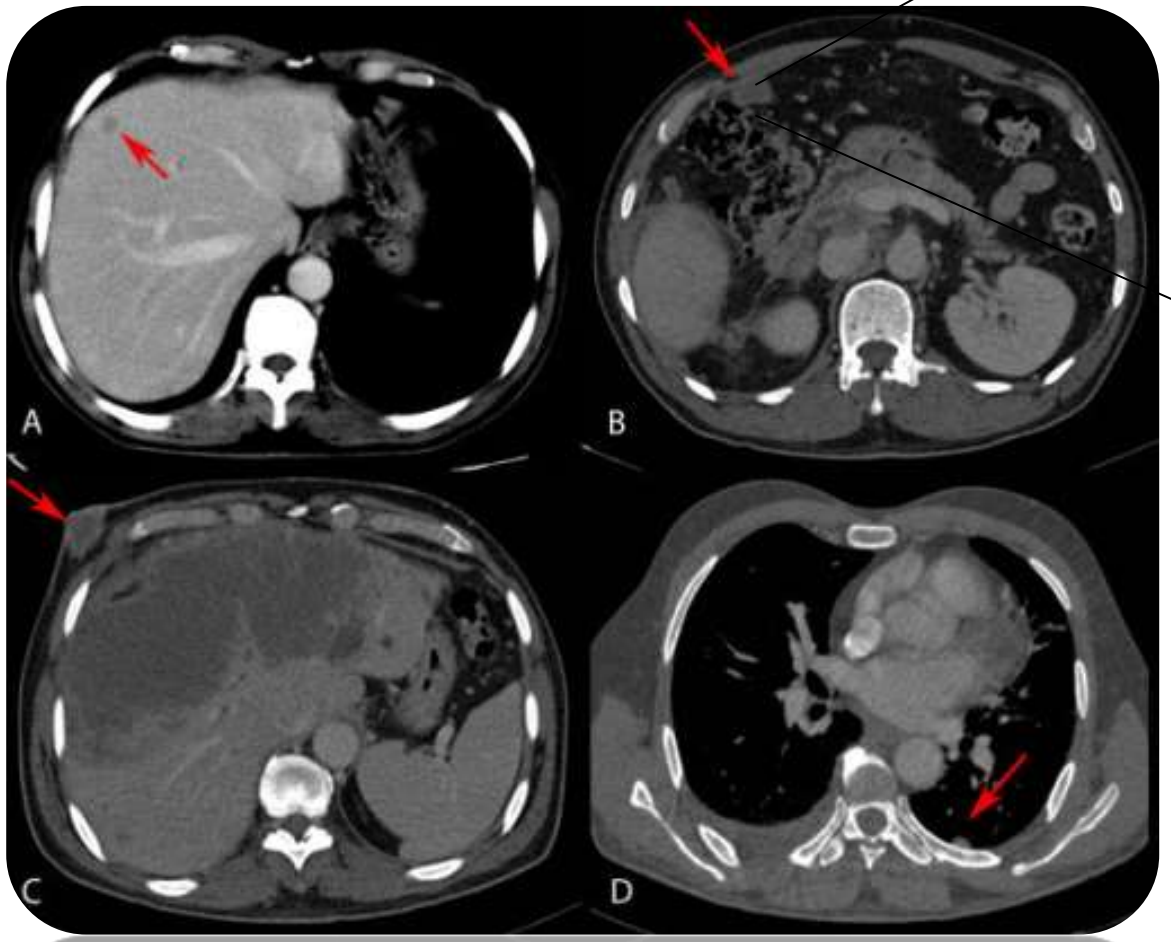
https://www.youtube.com/watch?v=DUVDKoKSEkU

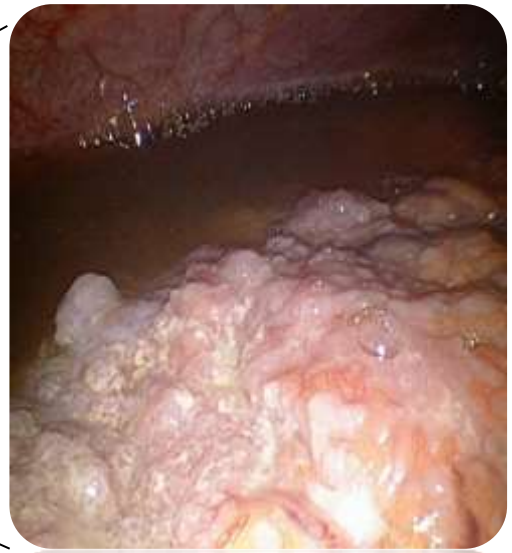
# Radiology



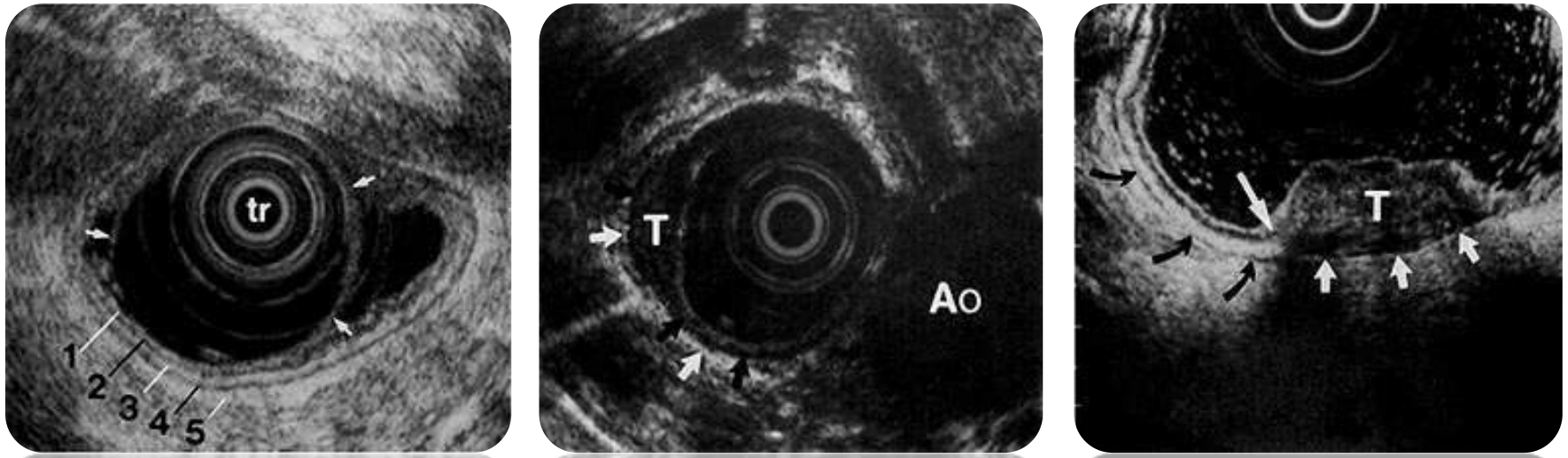


# Radiology



# Ecoendoscopy (EUS)




EUS image showing 5 layers of the gastric wall. 1, 3, and 5 = first, third, and fifth layers are hyperechoic (white); 2 and 4 = second and fourth layers are hypoechoic (black). Transducer (*tr*) is surrounded by a water-filled balloon (*arrows*). (EUS magnification range scale = 6 cm.)

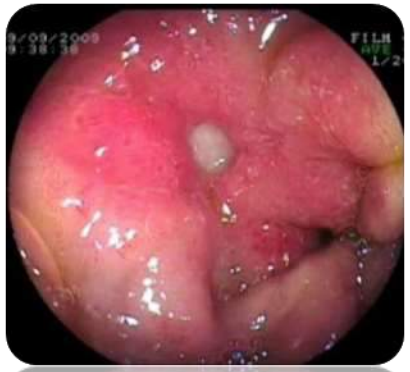
# Peptic ulcer disease (PUD)

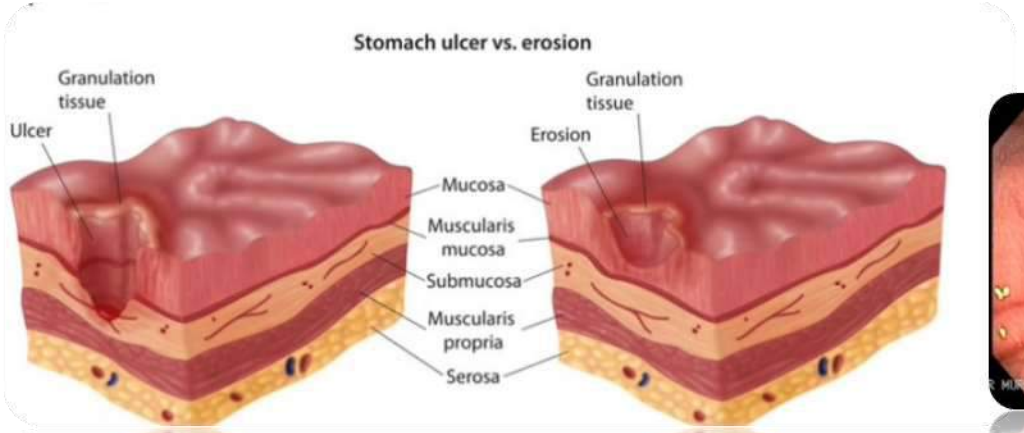
The term of peptic ulcer disease encompasses

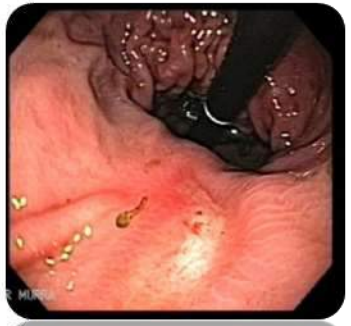
**both gastric and duodenal ulcers**.

**Ulcers are defined as breaks in the mucosal surface >5 mm in size, with depth to the submucosa.**

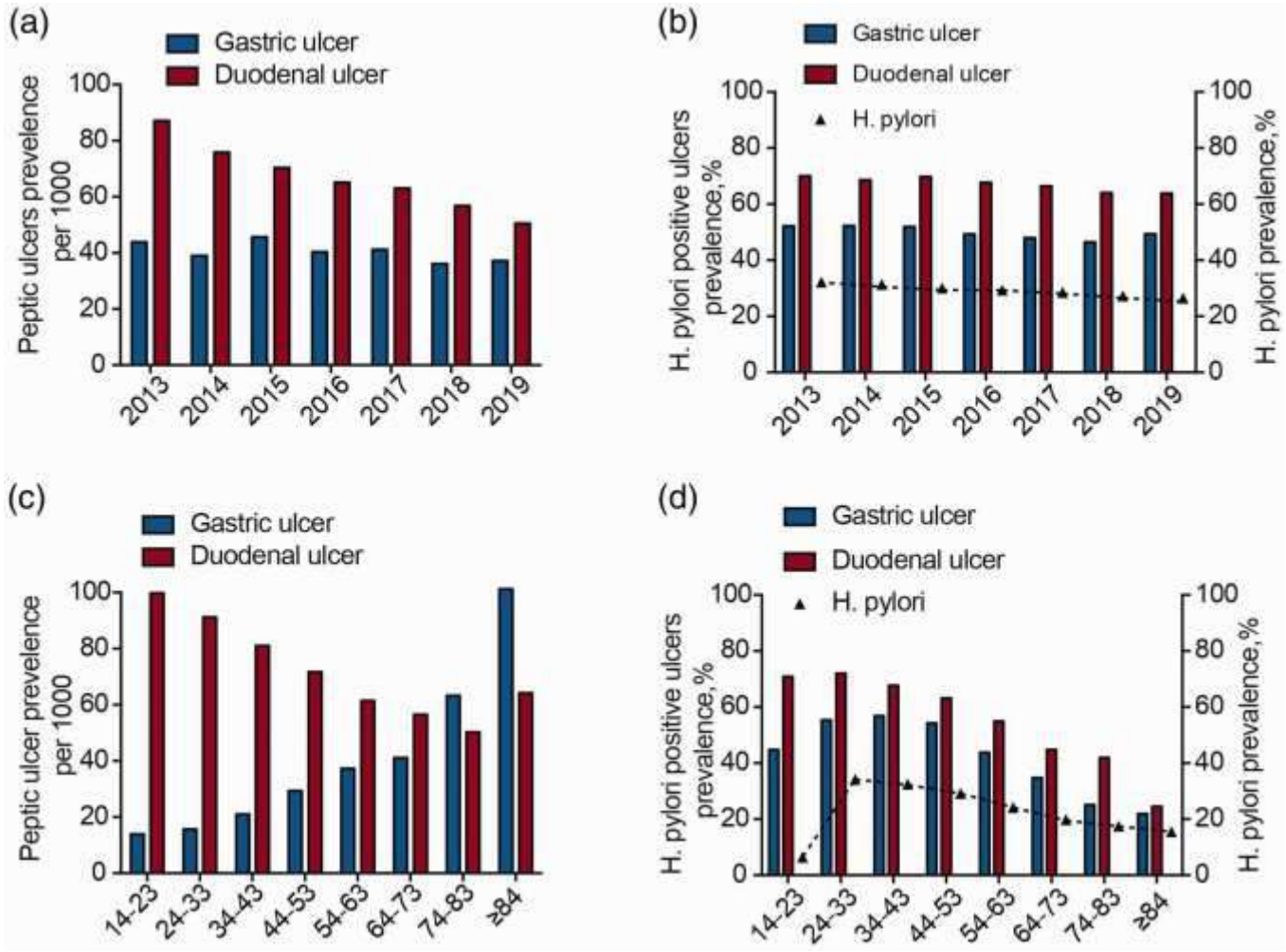
Duodenal ulcers (DUs) and gastric ulcers (GUs) share many common features in terms of pathogenesis, diagnosis, and treatment, but several factors distinguish them from one another





# Peptic ulcer disease: epidemiology




**GUs tend to occur later in life than duodenal lesions, with a peak incidence reported in the sixth decade**.

More than half of GUs occur in males and are less common than DUs, perhaps due to the higher likelihood of GUs being silent and presenting only after a complication develops.

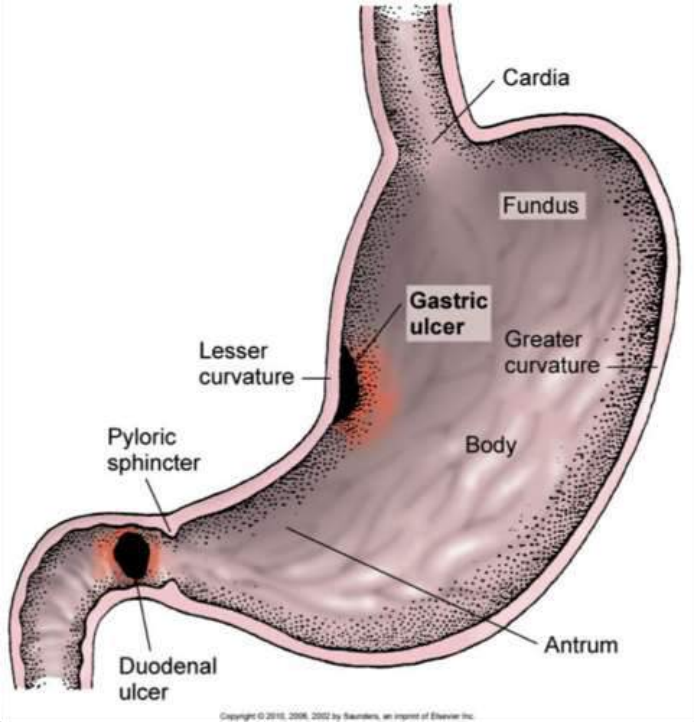
# Peptic ulcer disease: epidemiology

The reason for the reduction in the frequency of GU and DUs **is likely related to the decreasing frequency of *Helicobacter pylori*.**

Before the discovery of *H. pylori*, the natural history of DUs was typified by frequent recurrences after initial therapy.

**Eradication of *H. pylori* has greatly reduced these recurrence rates.**

# Gastric ulcers: pathology

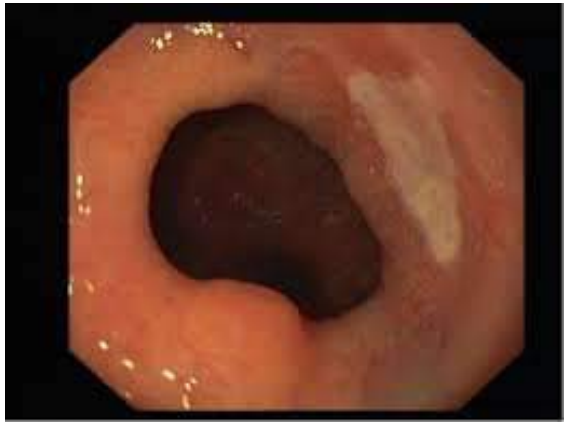


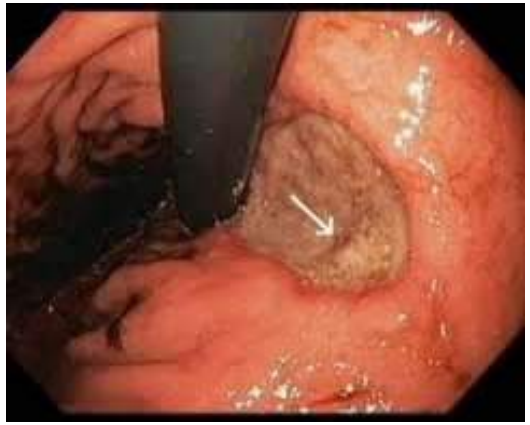

In contrast to DUs, GUs can represent a malignancy.

Benign GUs are **most often found distal to the junction between the antrum and the acid secretory mucosa**. Benign GUs are quite rare in the gastric fundus and are histologically similar to DUs.

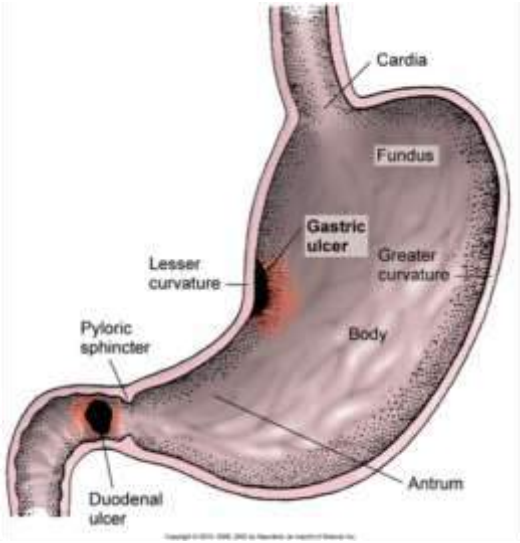
**Benign GUs associated with *H. pylori*** are also associated with antral gastritis.

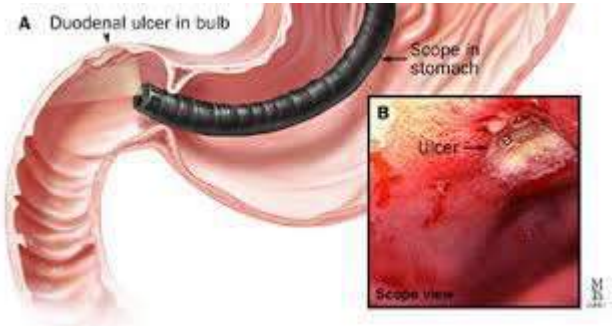
In contrast, NSAID-related GUs are not accompanied by chronic active gastritis

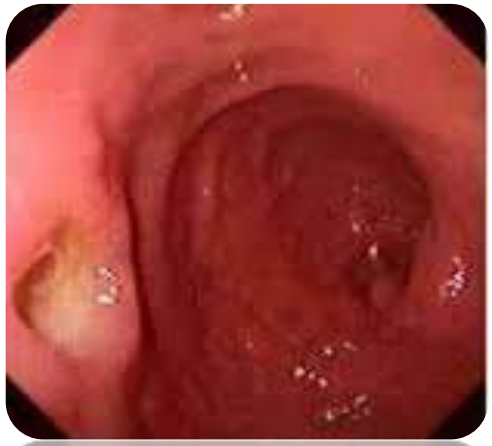


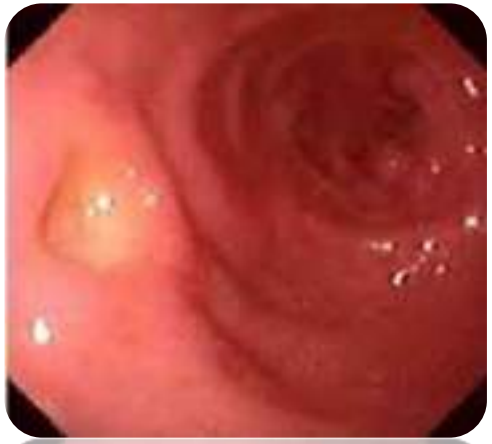


# Duodenal ulcers:pathology





DUs occur most often in the first portion of duodenum (>95%), **with ~90% located within 3 cm of the pylorus.**

They are usually 1 cm in diameter but can occasionally reach 3–6 cm (giant ulcer).

Malignant DUs are extremely rare.

# Peptic ulcers:pathophysiology

The majority of GUs and DUs can be attributed to either

***H. pylori* or NSAID-induced mucosal damage.**

**GASTRIC ACID SECRETION**

**Gastric acid output (basal and stimulated) tends to be normal or decreased in GU patients.**

**Basal and nocturnal gastric acid secretion appears to be increased in DU patients as compared to control**

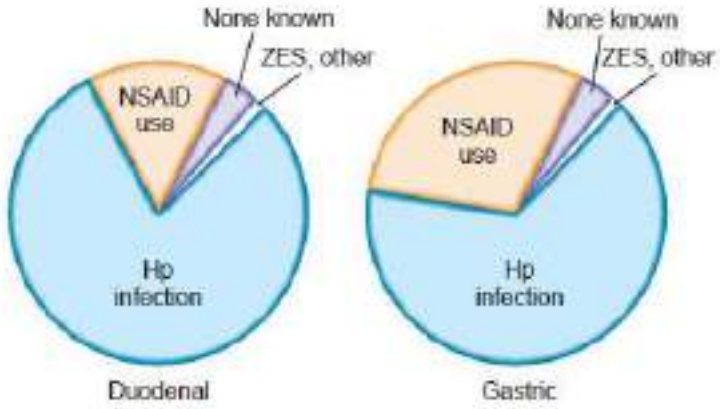
When GUs develop in the presence of minimal acid levels, impairment of mucosal defense factors may be present.

# Peptic ulcers: etiology

- *Helicobacter pylori* infection
- Drug (i.e., NSAIDs, ASS, SSRI)
- *H. pylori* and NSAIDs positive
- *H. pylori* and NSAIDs negative*
- Acid hypersecretory state (i.e., Zollinger-Ellison syndrome)
- Anastomosis ulcer after subtotal gastric resection
- Tumors (i.e., cancer, lymphoma)

* Requires search for other specific causes.

NSAID, nonsteroidal antiinflammatory drug; ASS, Acetylsalycilic acid; SSRI, Serotonin reuptake inhibitor.




Malfertheiner P, Schulz C. Peptic Ulcer: Chapter Closed? Dig Dis. 2020 Jan 6:1-5. doi: 10.1159/000505367. Epub ahead of print. PMID: 31905355.

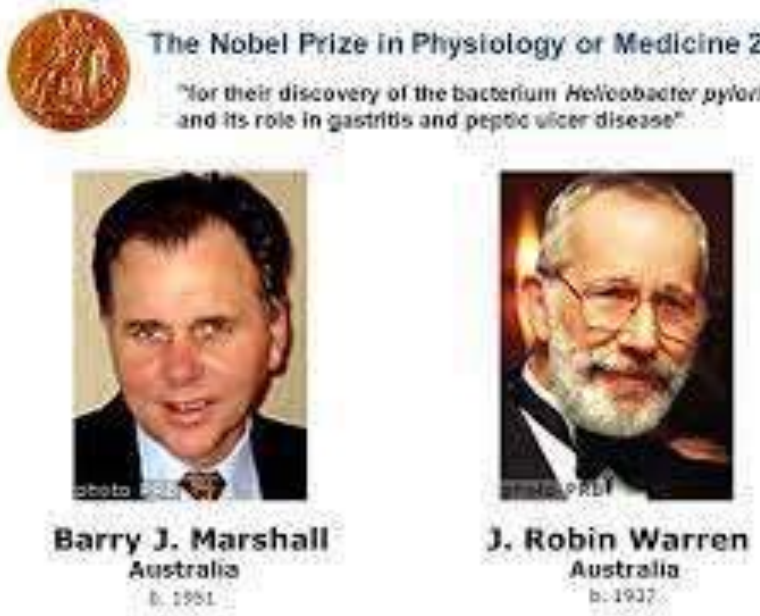
# Duodenal ulcer and H. Pylori

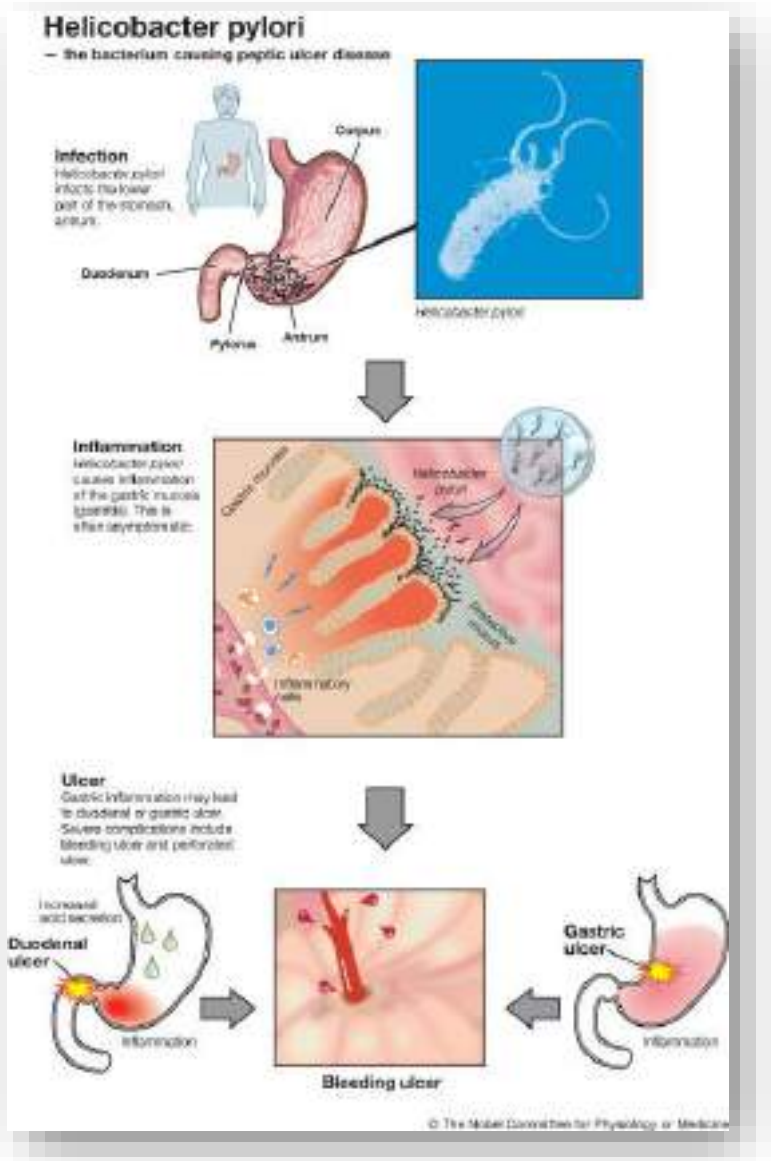
**How does gastric colonization by H.pylori causes duodenal ulceration?.**

***H. pylori*–induced gastritis diminishes the number of somatostatin-producing D cells. Since somatostatin inhibits gastrin release, gastrin levels are higher than in *H. pylori*–negative persons**.

These increased gastrin levels lead to **increased meal-stimulated acid secretion** in the gastric corpus, which is only mildly inflamed in antral-predominant gastritis. In turn, increased acid secretion eventually induces protective gastric metaplasia in the duodenum; the duodenum can then become colonized by *H. pylori*, inflamed, and ulcerated.

# H. pylori

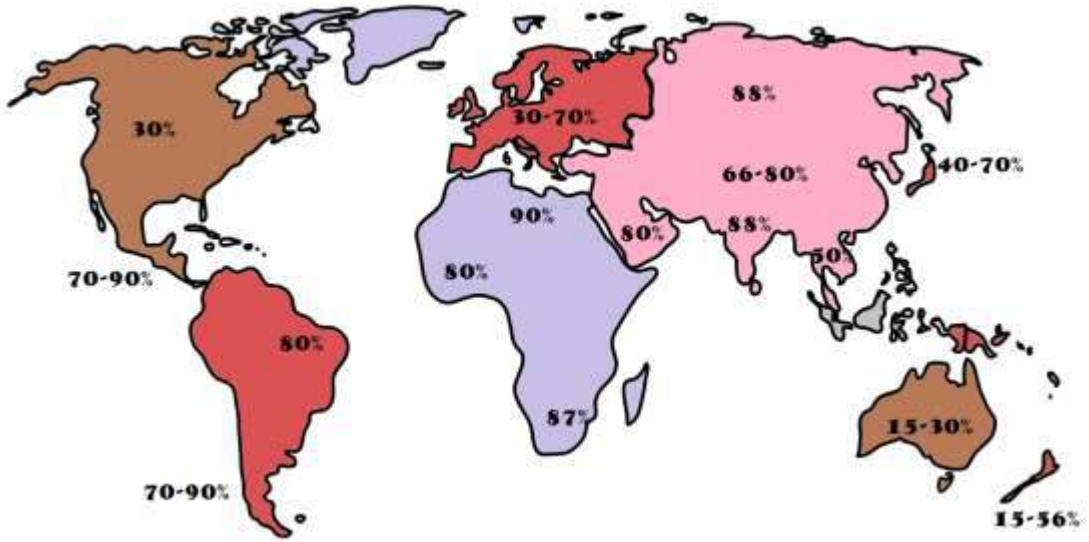



The Nobel Prize in Physiology or Medicine 2005 Barry J. Marshall, J. Robin Warren

# H. pylori-Epidemiology

- The prevalence of *H. **pylori*** **among adults is ~30% in the United States and Europe as opposed to >80% in most developing countries.**
- In the United States and Europe prevalence varies with age: ~50% of 60-year-old persons and ~20% of 30-year-old persons are colonized. *H. **pylori*** **is usually acquired in childhood.**

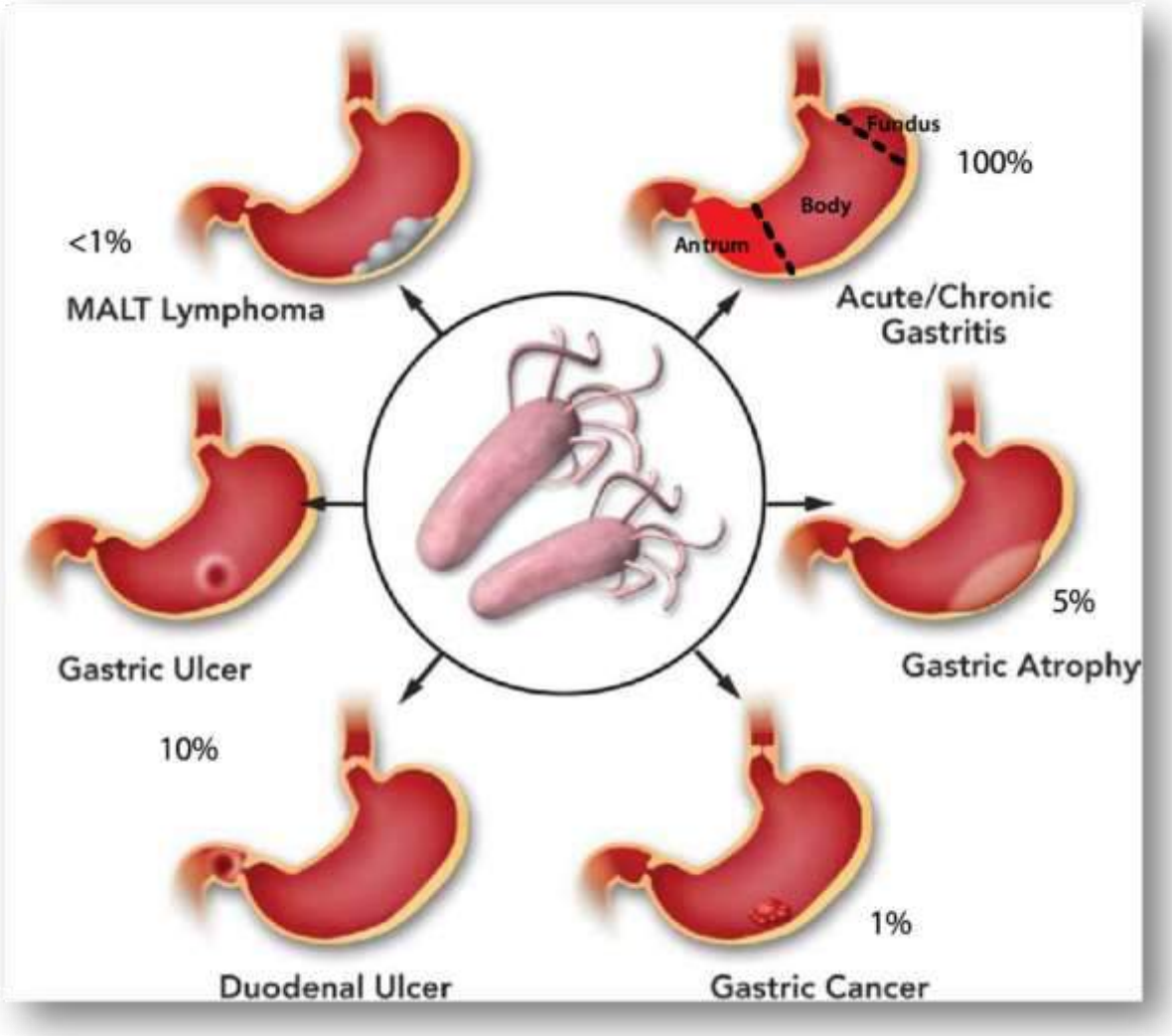


# H. pylori-Epidemiology

- The age association is due mostly **to a birth-cohort effect** whereby current 60-year-olds were more commonly colonized as children than current 30-year-olds.
- Children may acquire the organism from their parents (more often from the mother) or from other children.
- **Spontaneous acquisition or loss of *H. pylori* in adulthood is uncommon**.

# Natural history of H. Pylori infection (1)

The particular end result of *H. pylori* infection (**gastritis, PUD, gastric MALT lymphoma, gastric cancer)** is determined by a complex interplay between bacterial and host factors

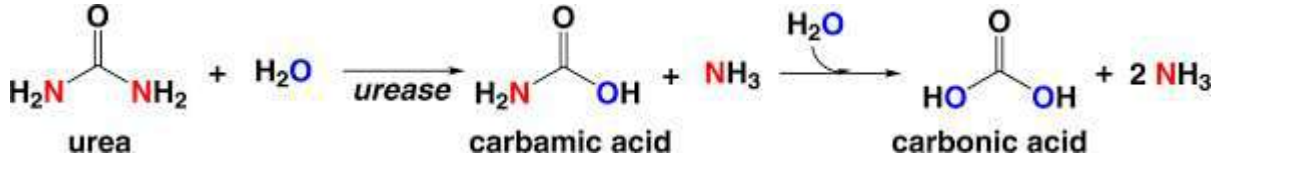


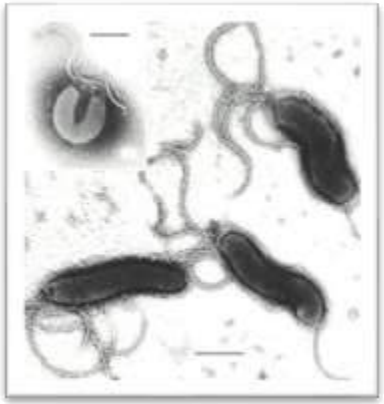
# H. Pylori

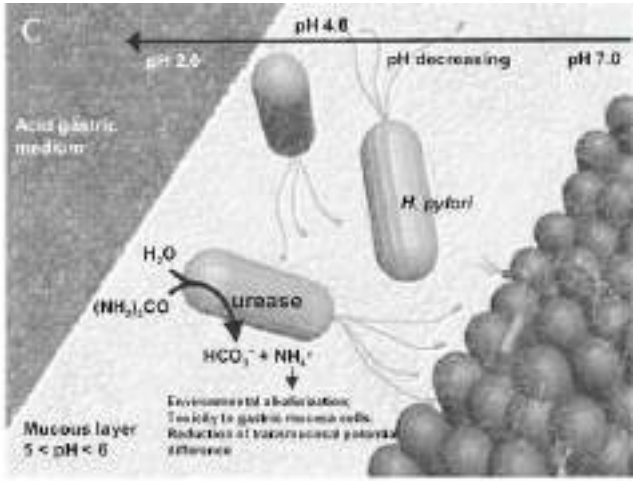
**H.p. is a gram-negative** microaerophilic rod found most commonly in the deeper portions of the mucous gel coating the gastric mucosa or between the mucous layer and the gastric epithelium. It may attach to gastric epithelium but under normal circumstances does not appear to invade cells.

It is S-shaped (~0.5 x 3 m in size) and contains multiple sheathed flagella.

Initially, ***H. pylori*** **resides in the antrum but, over time, migrates toward the more proximal segments of the stomach.**






The organism is capable of transforming into a **coccoid** form, which represents a dormant state that may facilitate survival in adverse conditions.

# H. Pylori  Genomic

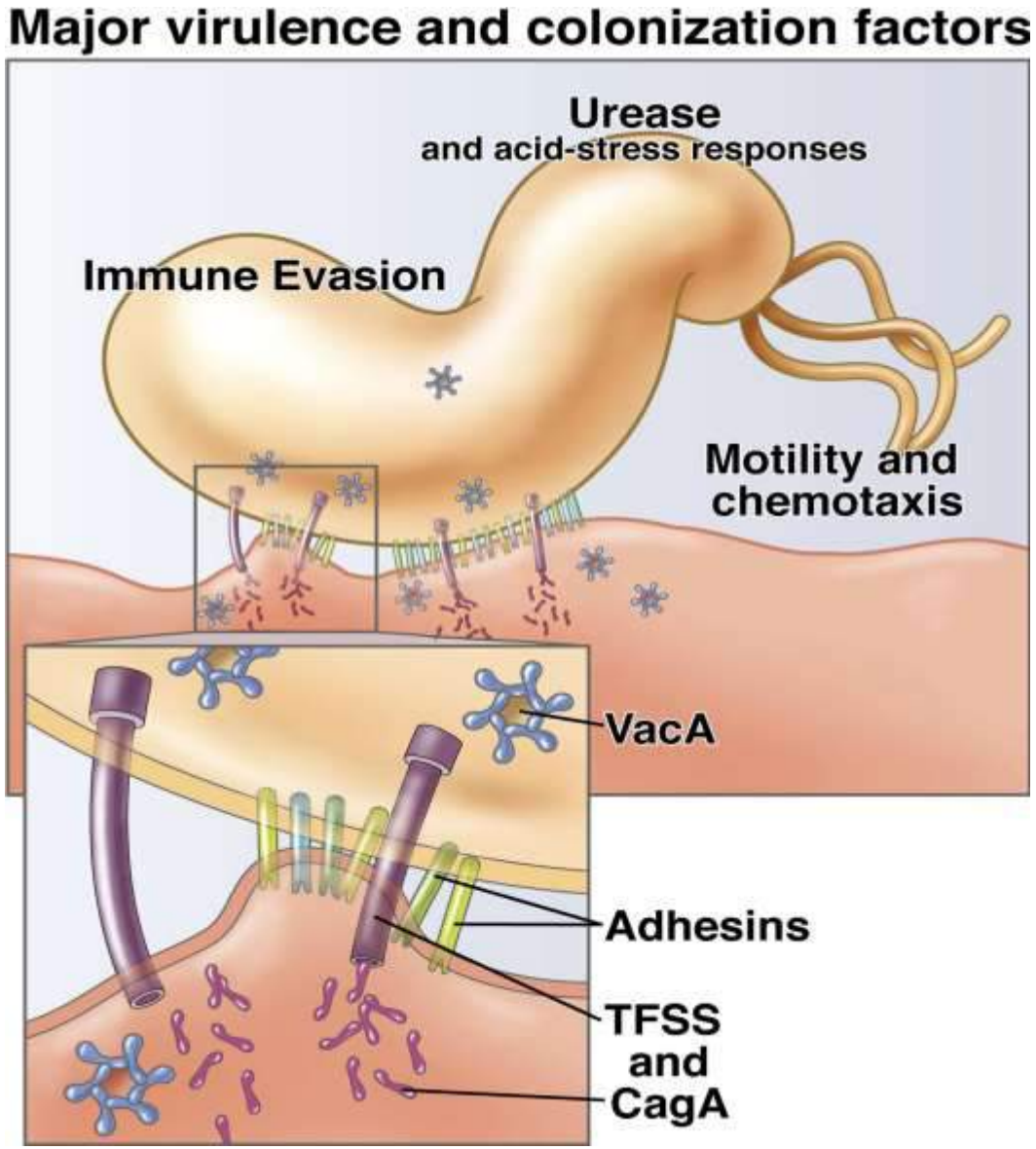
- The genome of *H. pylori* (1.65 million base pairs) encodes ~1500 proteins. Among this multitude of proteins there are factors that are essential determinants of *H. pylori*–mediated pathogenesis and colonization, such as the outer membrane protein (Hop proteins), **urease**, and the **vacuolating cytotoxin (Vac A).**

- **Moreover, the majority of *H. pylori* strains contain a genomic fragment that encodes the cag pathogenicity island (cag-PAI) and Cag A. Due to its association with gastric cancer, CagA is classified as oncogenic protein**

- Several of the genes that make up cag-PAI encode components of a **type IV secretion island that translocates Cag A into host cells.** Once in the cell, Cag A activates a series of cellular events important in cell growth and

## H. Pylori Secretory apparatus

Some H pylori actively adhere to the cell surface using a variety of specific OMP adhesins that recognize glycoproteins on the host cell surface



Cag A

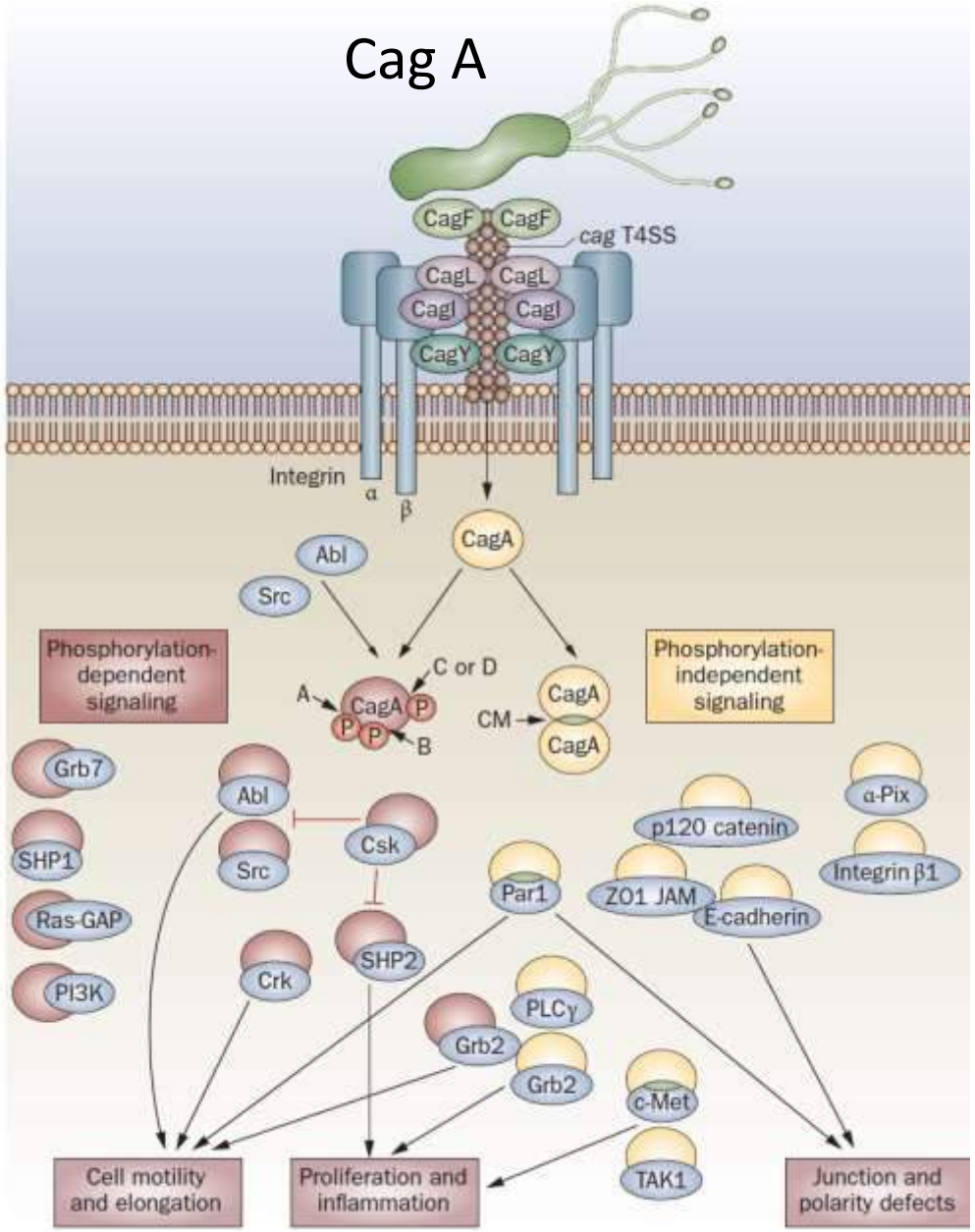
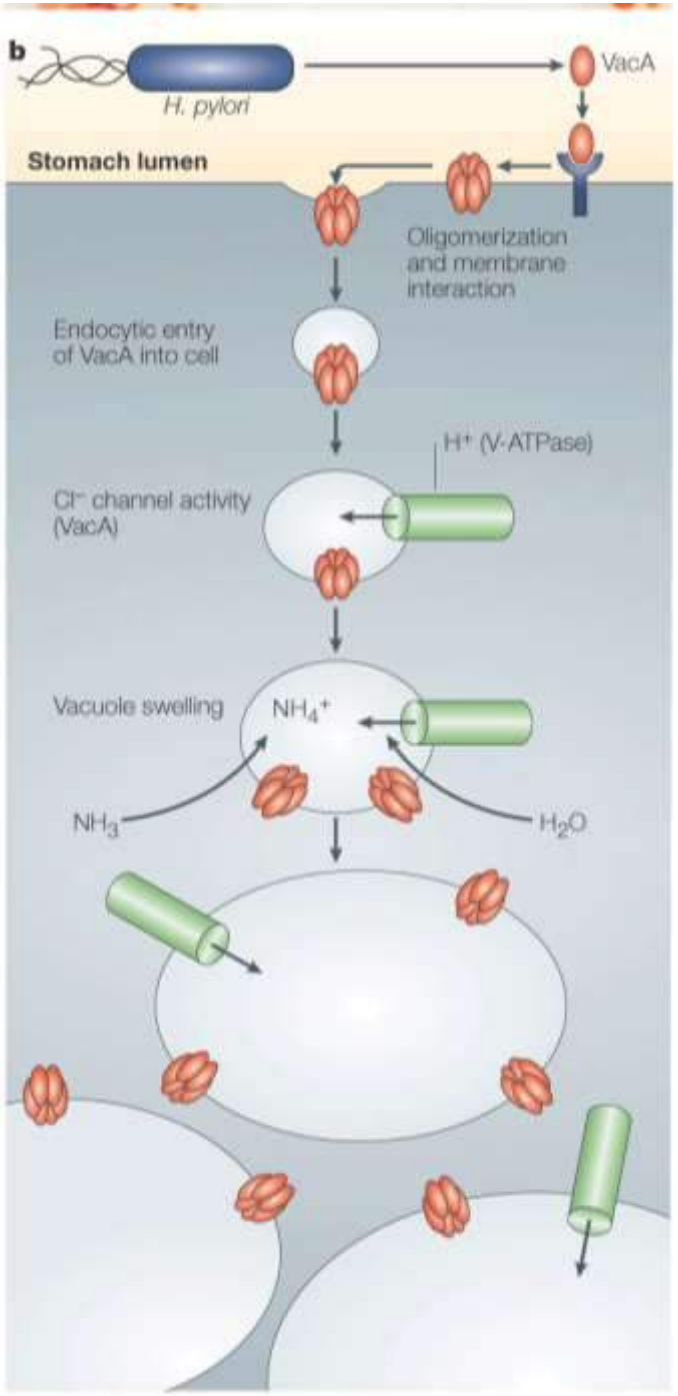
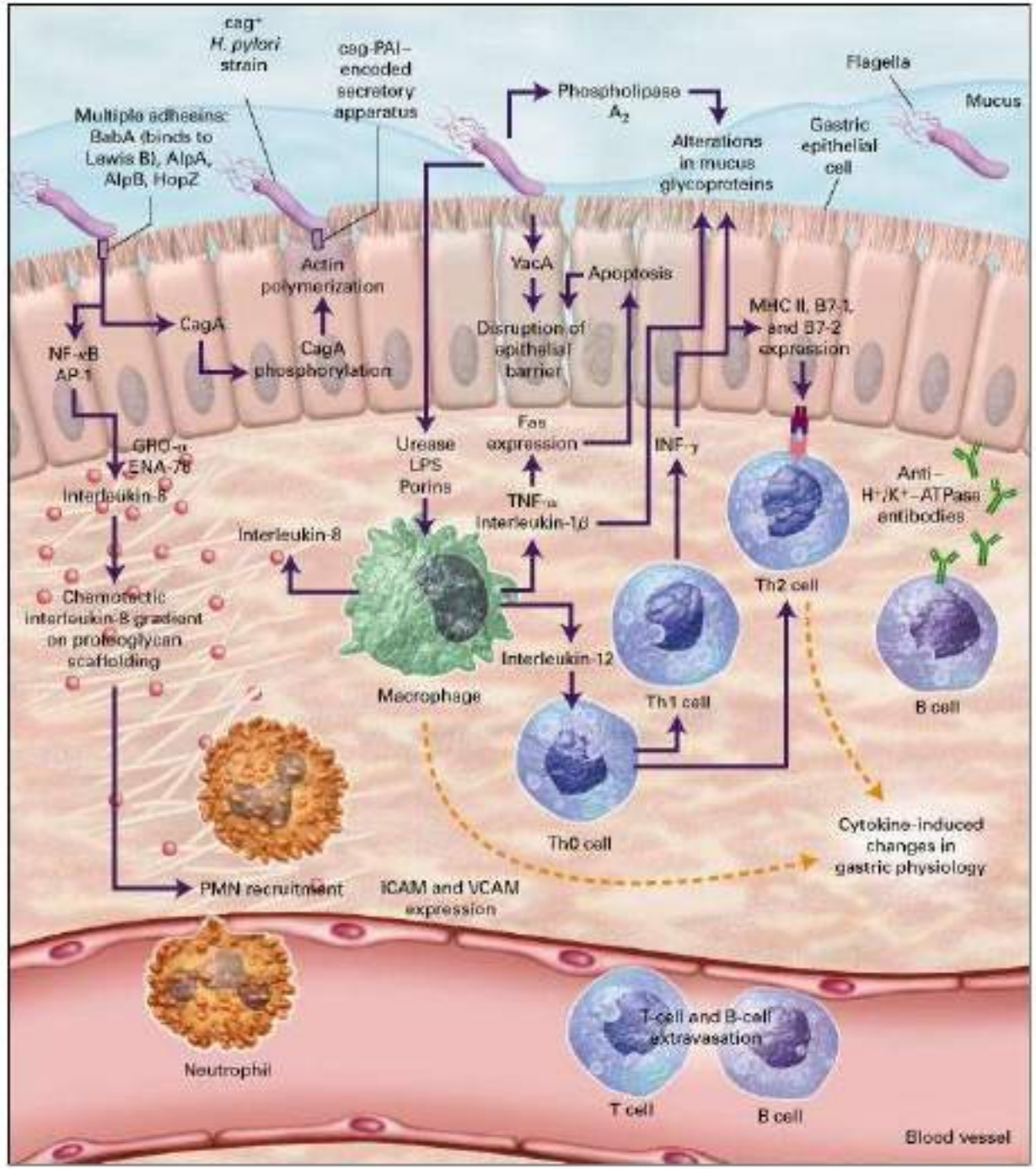



**Figure 3** | The pathogenesis of CagA-related signaling. In the early steps of CagA recognition, CagF binds CagA.[117,118] CagL, CagY and probably CagI utilize host integrin β1 as a cell-surface receptor, which triggers delivery of CagA into target

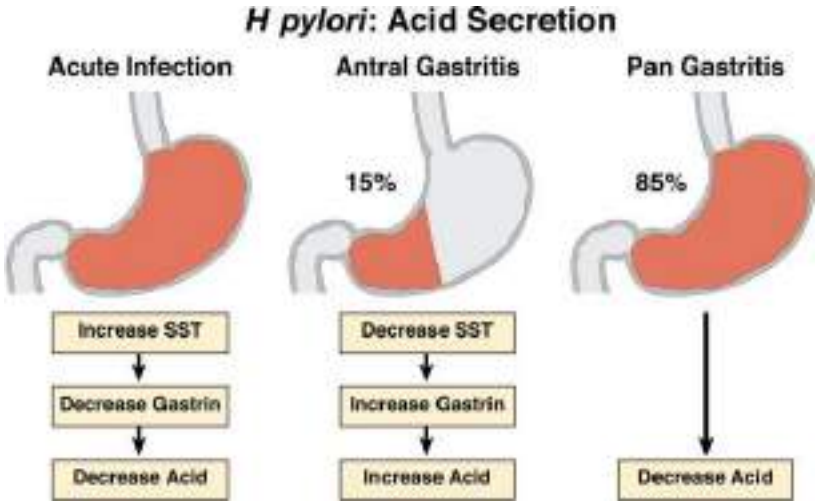
Vac A

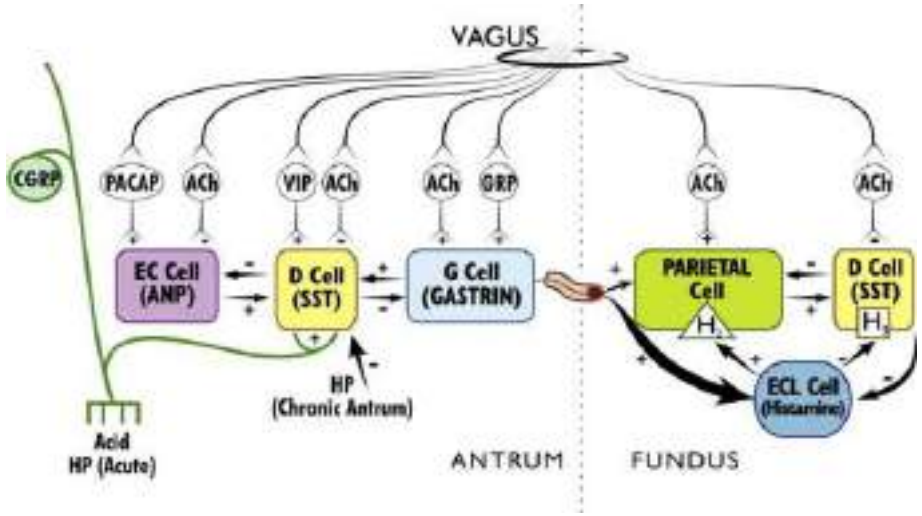


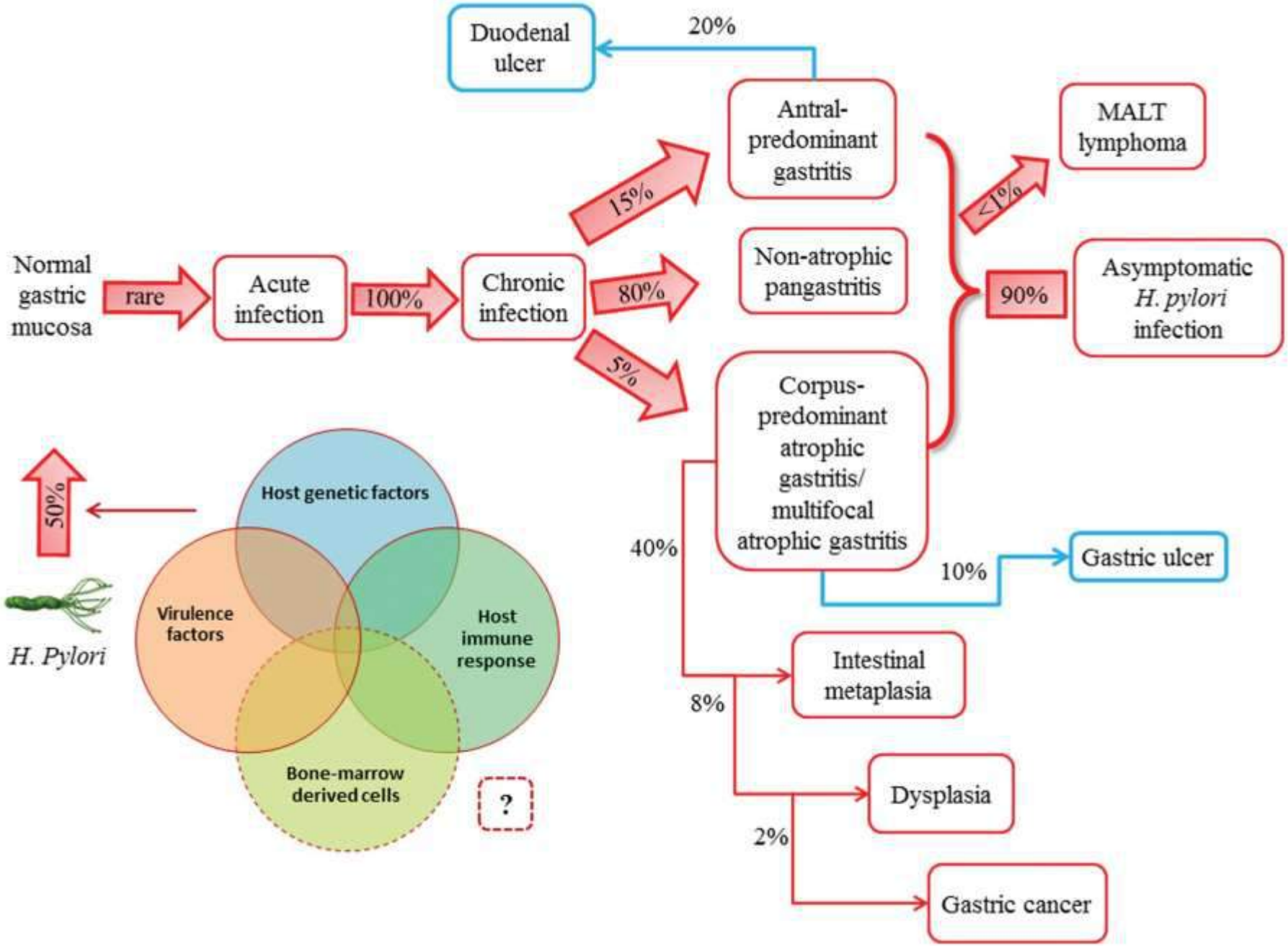

cag+
H. pylori
strain
cag-PAI–
encoded
secretory
apparatus
Phospholipase
A2
Flagella
Mucus
Multiple adhesins:
BabA (binds to
Lewis B), AlpA,
AlpB, HopZ
Alterations
in mucus
glycoproteins
Gastric
epithelial
cell
Actin
polymerization
VacA
Apoptosis
CagA
Disruption of
epithelial
barrier
MHC II, B7-1,
and B7-2
expression
NF-κB
AP-1
CagA
phosphorylation
Fas
expression
INF-γ
GRO-α
ENA-78
Interleukin-8
Urease
LPS
Porins
TNF-α
Interleukin-1β
Anti–
H+/K+–ATPase
antibodies
Interleukin-8
Th2 cell
Chemotactic
interleukin-8 gradient
on proteoglycan
scaffolding
Macrophage
Interleukin-12
Th1 cell
B cell
Th0 cell
Cytokine-induced
changes in
gastric physiology
PMN recruitment
ICAM and VCAM
expression
Neutrophil
T-cell and B-cell
extravasation
T cell
B cell
Blood vessel

# Progression to H. Pylori infection and gastric acid secretion

**H. *pylori*** infection leads to superficial gastritis over a period of weeks. The presence of proinflammatory host polymorphisms and the *H. pylori cag* pathogenicity island increase the risk of developing gastric atrophy, intestinal metaplasia that impact on gastric acid secretion

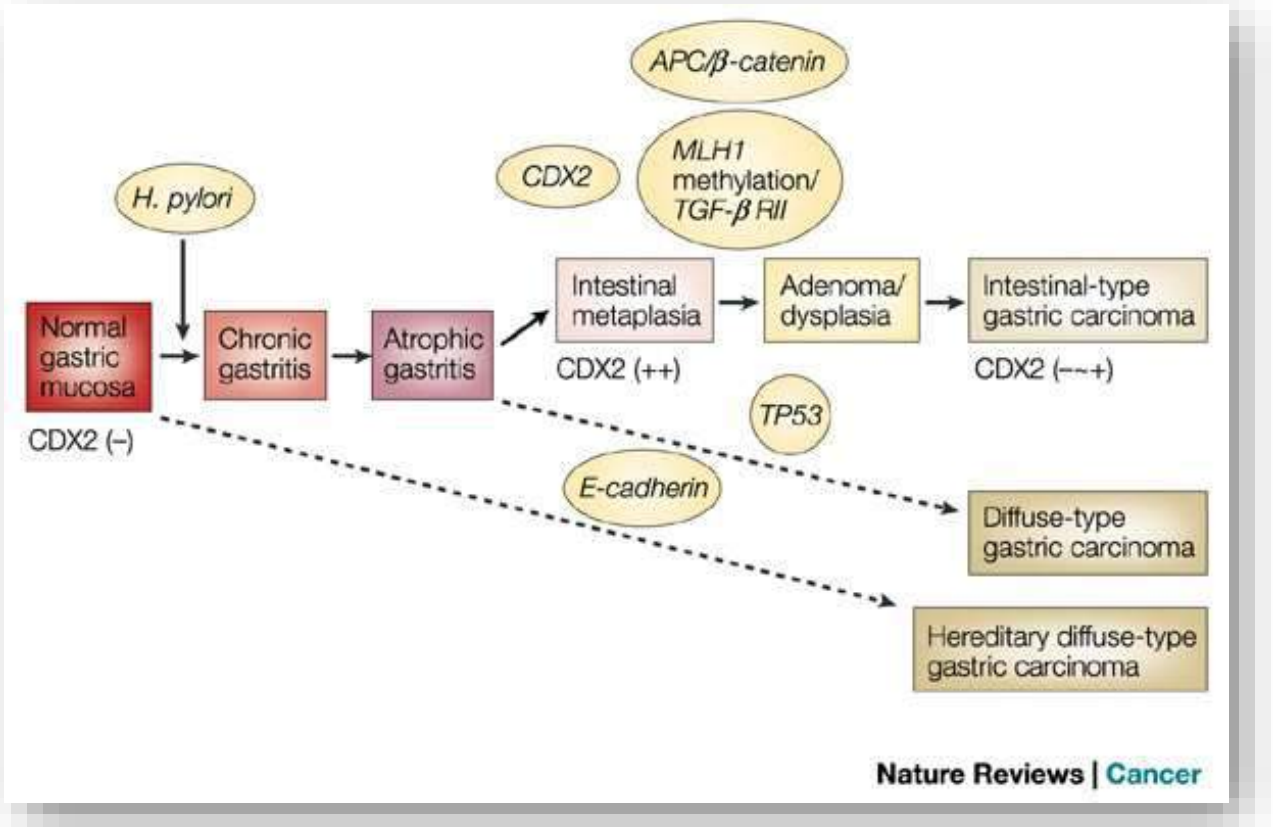



Duodenal ulcer
20%
Antral-predominant gastritis
MALT lymphoma
15%
<1%
Normal gastric mucosa
rare
Acute infection
100%
Chronic infection
80%
Non-atrophic pangastritis
90%
Asymptomatic H. pylori infection
5%
Corpus-predominant atrophic gastritis/ multifocal atrophic gastritis
40%
10%
Gastric ulcer
50%
Host genetic factors
Virulence factors
Host immune response
Bone-marrow derived cells
?
H. Pylori
Intestinal metaplasia
8%
Dysplasia
2%
Gastric cancer

# Progression to intestinal-type gastric cancer

***H. pylori*** infection leads to superficial gastritis over a period of weeks.
The presence of proinflammatory host polymorphisms and the *H. pylori cag* pathogenicity island increase the risk of developing gastric atrophy, intestinal metaplasia, and gastric adenocarcinoma.
Epigenetic inactivation of *E-cadherin* via promoter hypermethylation may also contribute to intestinal-type gastric cancer.



# H. Pylori eradication prevents peptic ulcer relapse

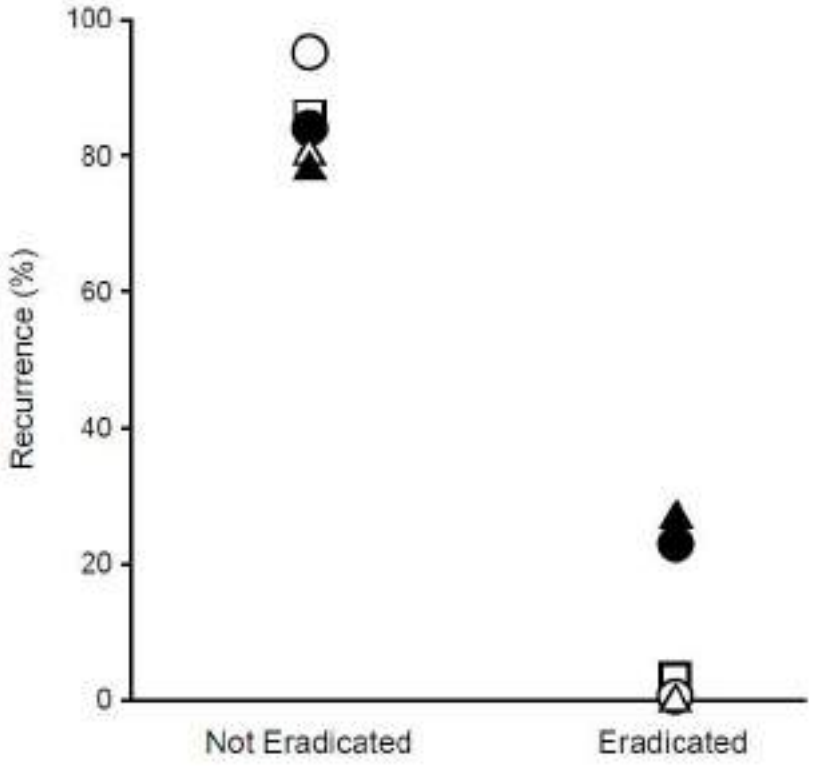



Figure 1. Twelve-Month Rates of Recurrence of Duodenal Ulcer in Patients in Whom *H. pylori* Was Eradicated and in Those in Whom It Was Not.

Data are from Marshall et al.[14] (solid circles), Hentschel et al.[15] (squares), Rauws and Tytgat[16] (open triangles), Coghlan et al.[17] (solid triangles), and Graham et al.[18] (open circles).

**THE TREATMENT OF *HELICOBACTER PYLORI* INFECTION IN THE MANAGEMENT OF PEPTIC ULCER DISEASE**
J OHN H. W ALSH , M.D., AND W ALTER L. P ETERSON , M.D. N Eengl J Med 1995

**Table 1** Diagnostic tests for the detection of *H. pylori* infection (2,15-17)

| Test | Sensitivity | Specificity | Advantages | Disadvantages |
|---|---|---|---|---|
| Noninvasive | | | | |
| Serology | 76-84 | 79-90 | Widely available, inexpensive | Positive result may reflect previous rather than current infection, not useful after treatment |
| Urea breath test | >95 | >95 | High negative and positive predictive values, useful before and after treatment | False-negative results possible in the presence of PPIs or with recent use of antibiotics of bismuth preparations, considerable resources and personnel required to perform test |
| Stool antigen test | 96 | 97 | High negative and positive predictive values, useful before and after treatment | Process of stool collection may be distasteful to patient, false-negative results possible in the presence of PPIs or with recent use of antibiotics or bismuth preparations |
| Invasive | | | | |
| Histology | 95 | 99 | Excellent sensitivity and specificity, especially with special and immune stains, provides additional information about gastric mucosa | Expensive (endoscopy and histopathology costs), interobserver variability, accuracy affected by PPI and antibiotics use, requires trained personnel |
| Rapid urease test | 90 | 93 | Rapid results, accurate in patients not using PPIs or antibiotics, no added histopathology cost | Requires endoscopy, less accurate after treatment or in patients using PPIs |
| Culture | 58.1 | 100 | Specificity 100%, allows antibiotics sensitivity testing | Variable sensitivity; requires trained staff and properly equipped facilities, expensive |

PPI, proton pump inhibitor; *H. pylori*, *Helicobacter pylori*.

# H. pylori- Diagnosis

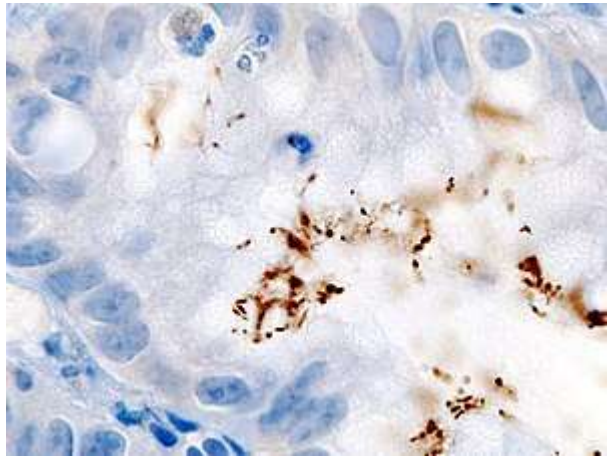
- **Endoscopic tests *H. pylori* testing**

**Rapid urease** test in gastric biopsy. Sensitivity/specificity >90%

**Histopathology.** Sensitivity/specificity >90%

**Biopsy culture.** Sensitivity/specificity >90%

**PCR**



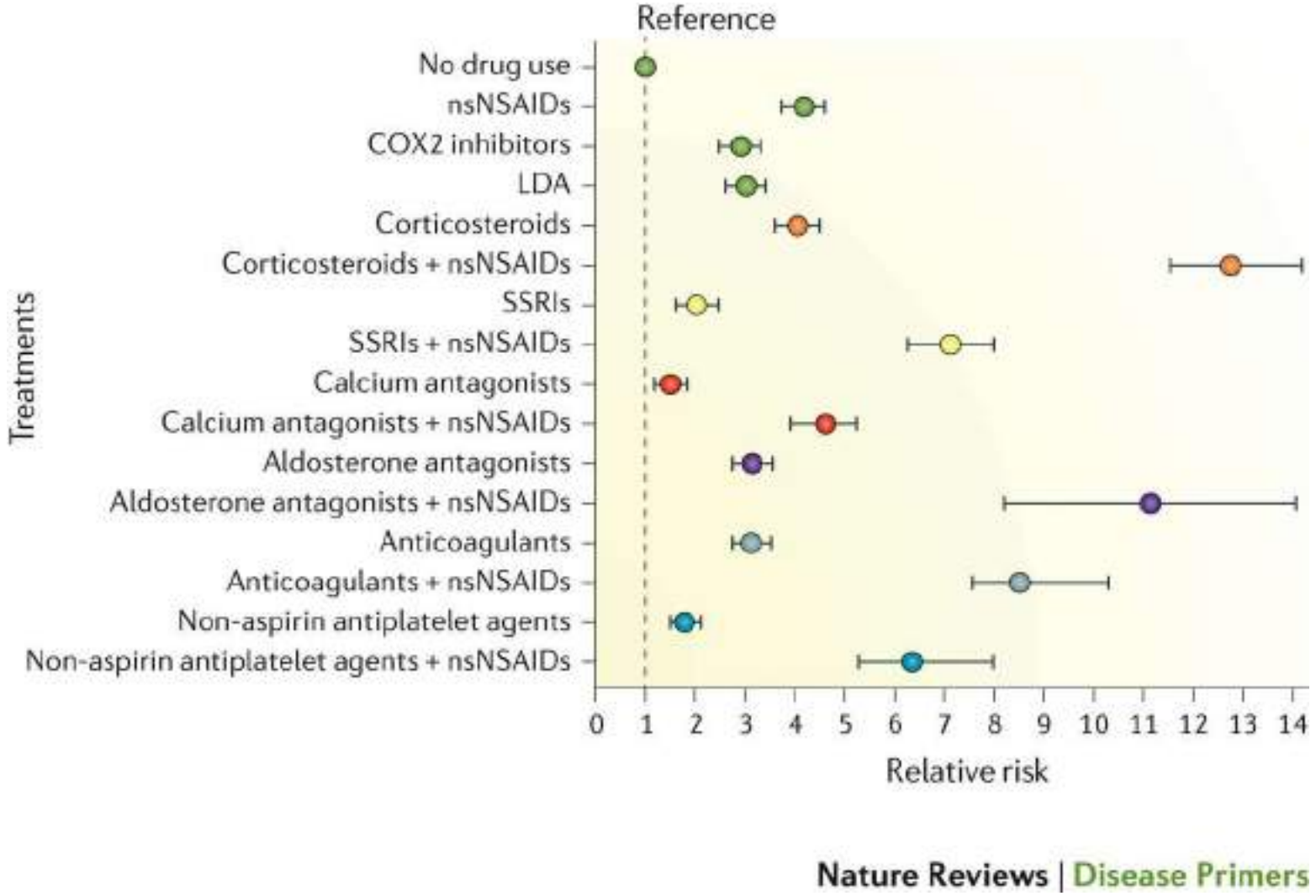
# H. pylori- Diagnosis

- **The urea breath test, the stool antigen test, and biopsy-based tests** can all be used **to assess the success of treatment.**
- However, because these tests are dependent on H. pylori load, their use <4 weeks after treatment may lead to false-negative results. Furthermore, these tests are unreliable if performed within 4 weeks of intercurrent treatment with antibiotics or bismuth compounds or within 2 weeks of the discontinuation of proton pump inhibitor (PPI) treatment.
- **Serologic tests are not used to monitor treatment success,** as the gradual drop in titer of H. pylori–specific antibodies is too slow to be of practical use.

# NSAIDS and ASA

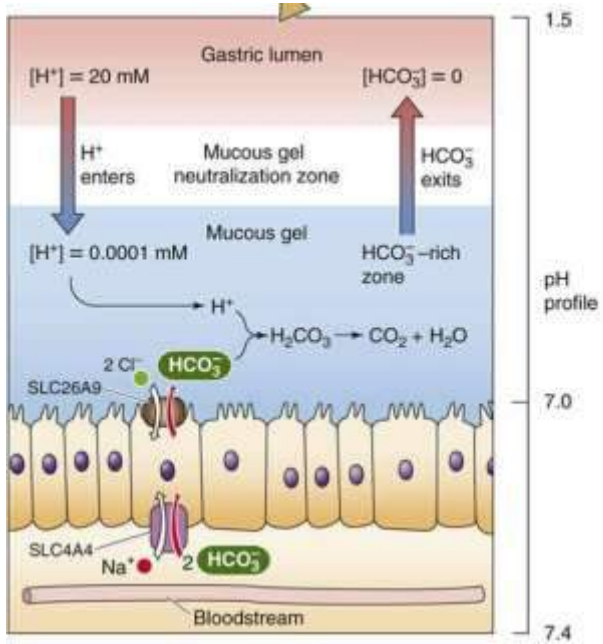
- NSAIDs represent a group of  commonly used medications. More than 30 billion over-the-counter tablets and over 100 million prescriptions are sold yearly in the United States alone. In fact, after the introduction of COX-2 inhibitors in the year 2000, the number of prescriptions written for NSAIDs was >111 million at a cost of $4.8 billion.
- Side effects and complications due to NSAIDs are considered the most common drug-related toxicities in the United States.
- The spectrum of NSAID-induced morbidity ranges from nausea and dyspepsia (prevalence reported as high as 50–60%) to a serious gastrointestinal complication such as endoscopy-documented peptic ulceration (15–30% of individuals taking NSAIDs regularly) complicated by bleeding or perforation in as many as 1.5% of users per year.

**Figure 5** Risk of developing GI upper bleding associated with certain drugs

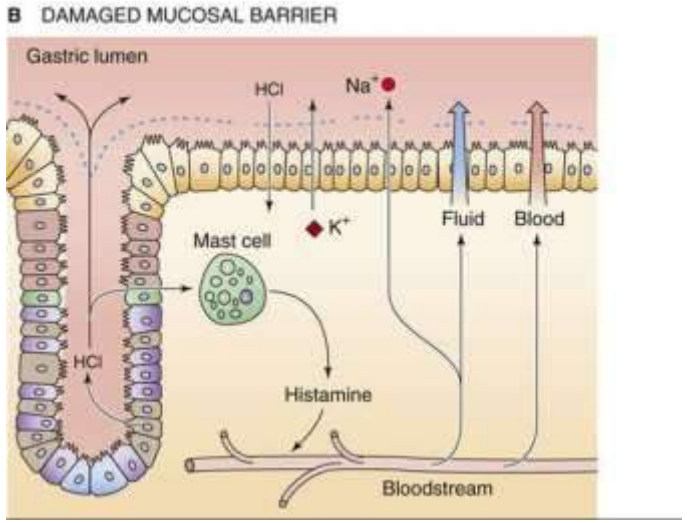



Lanas, A. et al. (2018) Non-variceal upper gastrointestinal bleeding
*Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2018.20

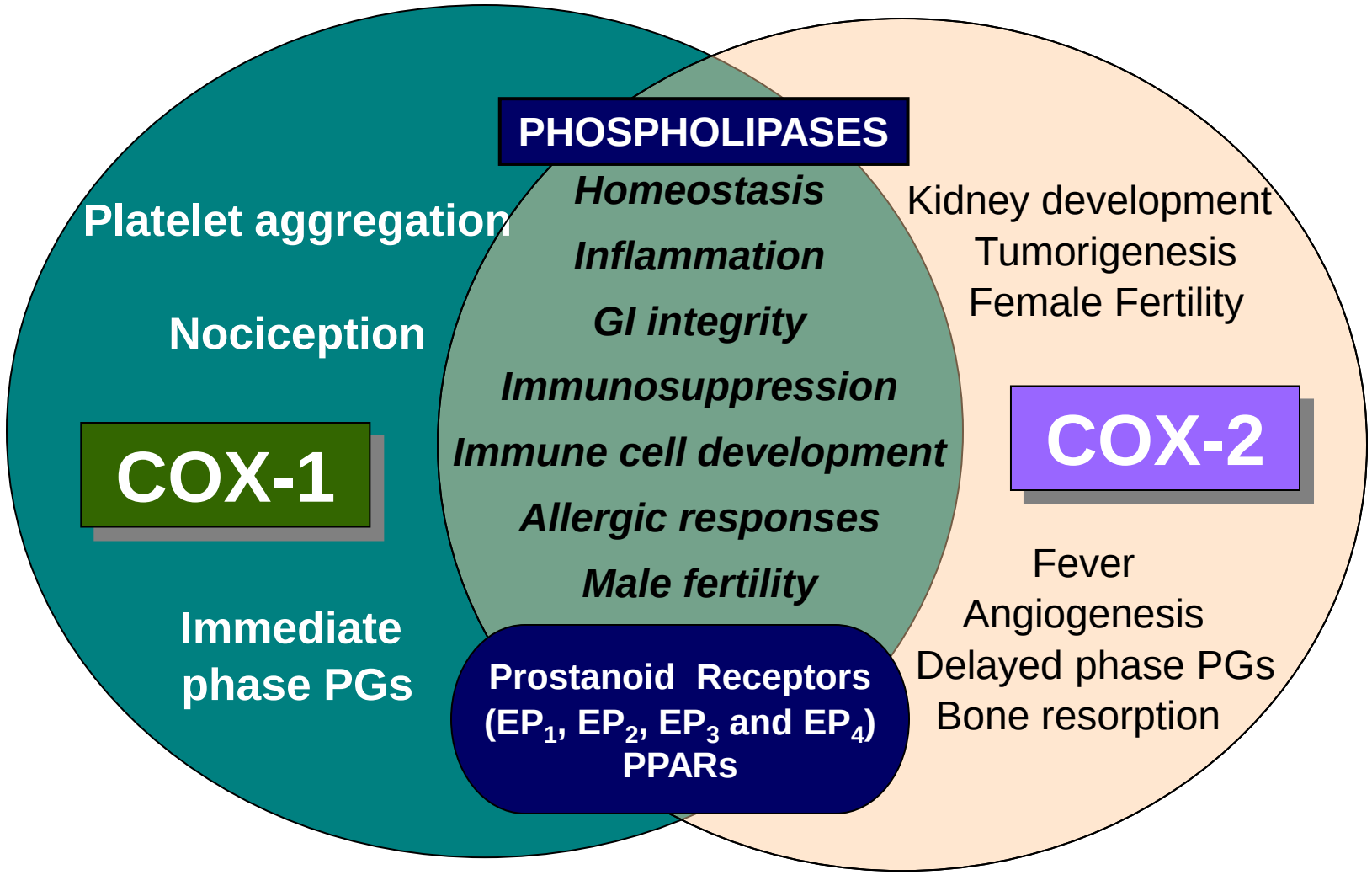
# Gastric mucosal barrier: Role of prostaglandins



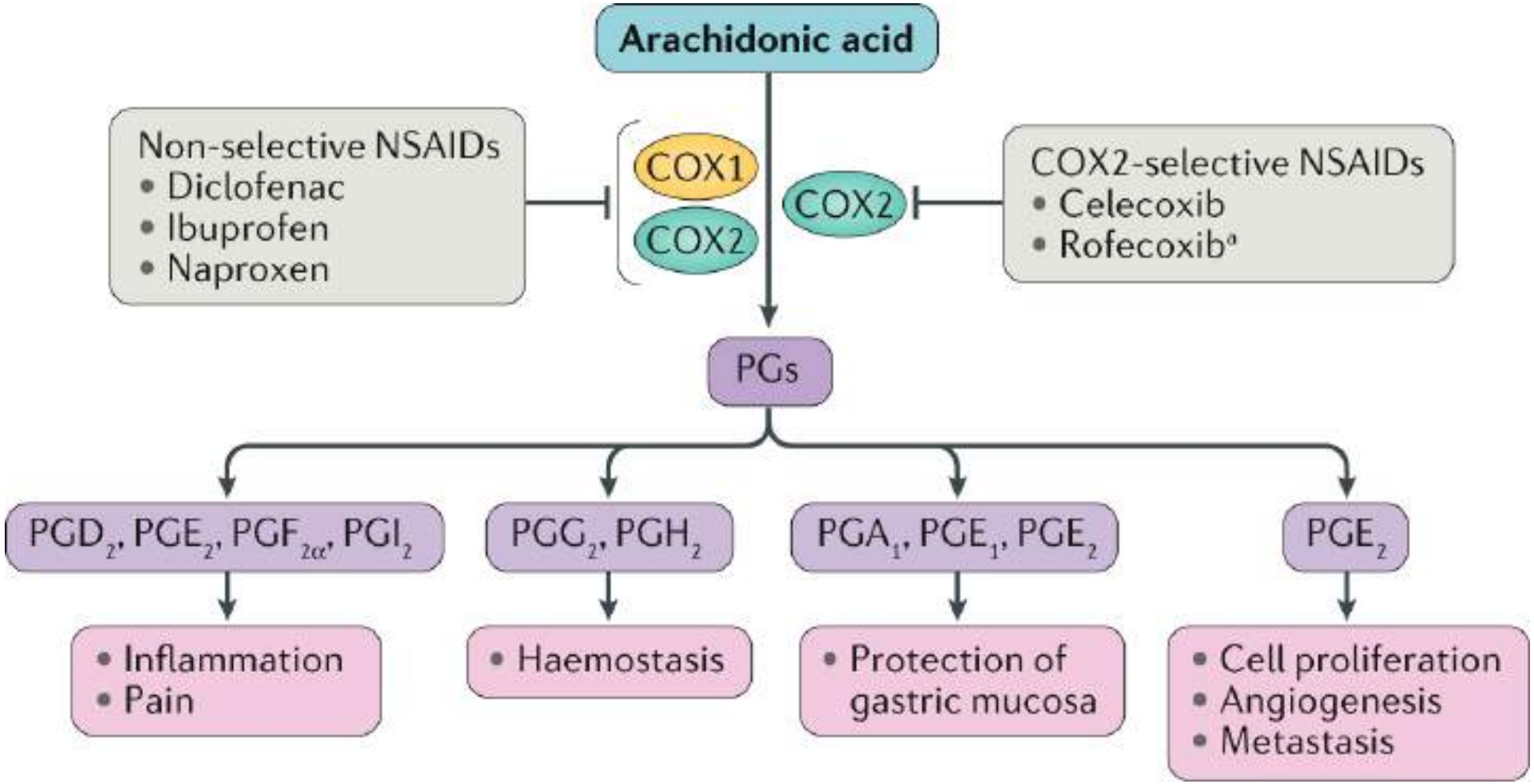




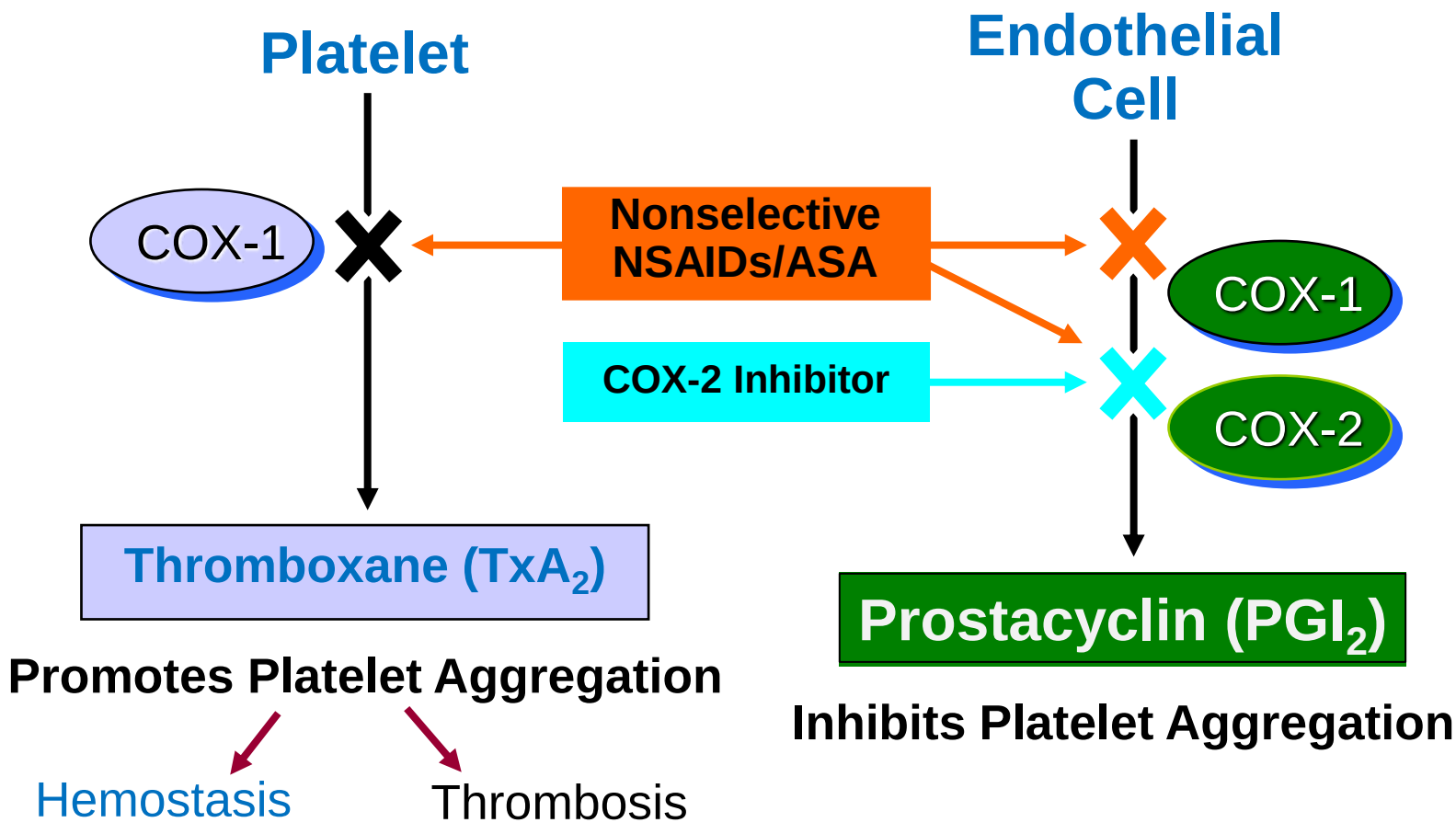
# Cyclooxygenase 1 and 2




Fiorucci S. Prevention of nonsteroidal anti-inflammatory drug-induced ulcer: looking to the future. Gastroenterol Clin North Am. 2009 Jun;38(2):315-32. doi: 10.1016/j.gtc.2009.03.001


Arachidonic acid
Non-selective NSAIDs
• Diclofenac
• Ibuprofen
• Naproxen
COX1
COX2
COX2
COX2-selective NSAIDs
• Celecoxib
• Rofecoxib[a]
PGs
$PGD_2$, $PGE_2$, $PGF_{2\alpha}$, $PGI_2$
$PGG_2$, $PGH_2$
$PGA_1$, $PGE_1$, $PGE_2$
$PGE_2$
• Inflammation
• Pain
• Haemostasis
• Protection of gastric mucosa
• Cell proliferation
• Angiogenesis
• Metastasis

# Effects of NSAIDs on Thromboxane and Prostacyclin




*McAdam et al. Proc. Natl. Acad Sci. USA . 1999;96:272.*

# Causes of Non-Hp and Non-NSAID Ulcer Disease

## Infection

Cytomegalovirus

Herpes simplex virus

*Helicobacter heilmanni*

## Drug/Toxin

Bisphosphonates

Chemotherapy

Clopidogrel

Crack cocaine

Glucocorticoids (when combined with NSAIDs)

Mycophenolate mofetil

Potassium chloride

## Miscellaneous

Basophilia in myeloproliferative disease

Duodenal obstruction (e.g., annular pancreas)

Infiltrating disease

Ischemia

Radiation therapy

Sarcoidosis

Crohn's disease

Idiopathic hypersecretory state

# PU- Clinical features

- **Abdominal pain** is common to many gastrointestinal disorders, including DU and GU, but has a poor predictive value for the presence of either DU or GU.
- Up to 10% of patients with NSAID-induced mucosal disease can present with a complication (bleeding, perforation, and obstruction) without antecedent symptoms.
- **Epigastric pain described** as a burning or gnawing discomfort can be present in both DU and GU.
- The discomfort is also described as an ill-defined, aching sensation or as **hunger pain.**
- The typical **pain pattern in DU occurs 90 min** to 3 h after a meal and is frequently relieved by antacids or food. Pain that awakes the patient from sleep (between midnight and 3 A.M.) is the most discriminating symptom, with two-thirds of DU patients describing this complaint. Unfortunately, this symptom is also present in one-third of patients with NUD.

# PU- Clinical features

- **The pain pattern in GU** patients may be different from that in DU patients, where discomfort may **actually be precipitated by food**. Nausea and weight loss occur more commonly in GU patients. Endoscopy detects ulcers in <30% of patients who have dyspepsia.
- The mechanism for development of abdominal pain in ulcer patients is unknown.
- Dyspepsia that becomes constant, is no longer relieved by food or antacids, or radiates to the back may indicate a penetrating ulcer (pancreas).
- Sudden onset of severe, generalized abdominal pain may indicate perforation.
- Pain worsening with meals, nausea, and vomiting of undigested food suggest gastric outlet obstruction.

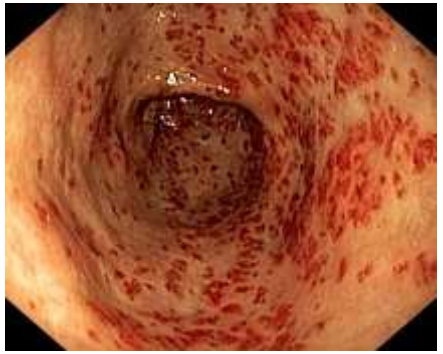
# PU- Clinical features

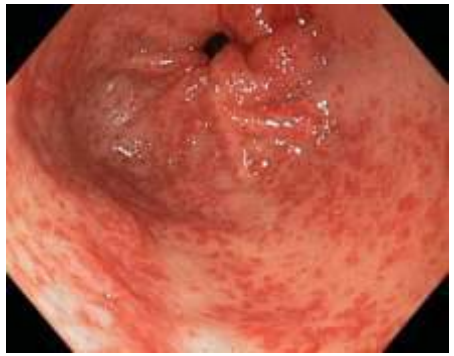
- **Physical Examination**
- Epigastric tenderness is the most frequent finding in patients with GU or DU.
- Pain may be found to the right of the midline in 20% of patients. Unfortunately, the predictive value of this finding is rather low. Physical examination is critically important for discovering evidence of ulcer complication.
- Tachycardia and orthostasis suggest dehydration secondary to vomiting or active gastrointestinal blood loss.
- A severely pain suggests a perforation. Presence of a succussion splash indicates retained fluid in the stomach, suggesting gastric outlet obstruction.

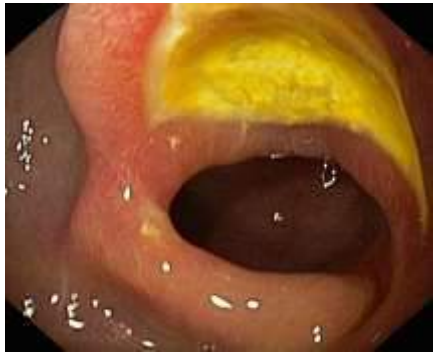
# Diagnosis

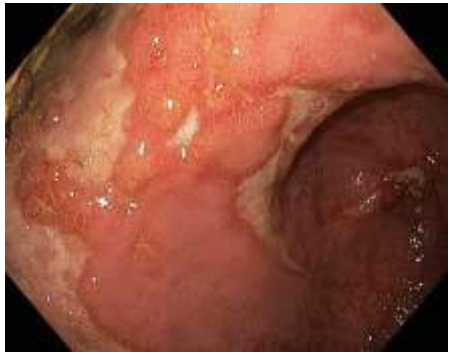
**Endoscopy provides the most sensitive and specific approach for examining the upper gastrointestinal tract**

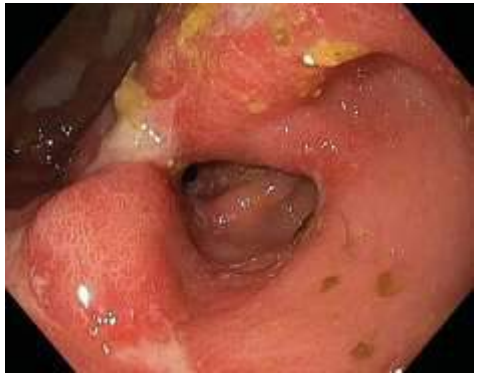
# Upper GI endoscopy

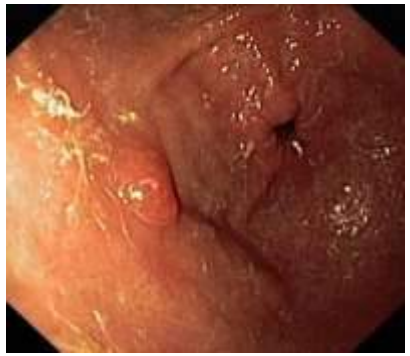


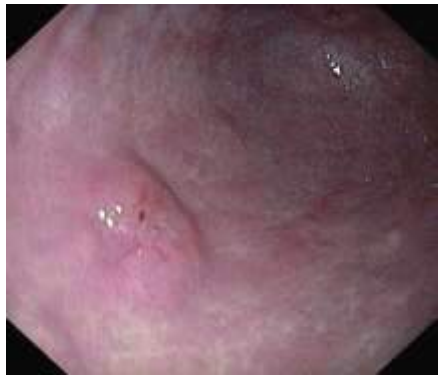












# PUB- Differential diagnosis

The most commonly encountered diagnosis among patients seen for upper abdominal discomfort **is NUD (non ulcer dyspepsia).**

**NUD, also known as *functional dyspepsia* or *essential dyspepsia*, refers to a group of heterogeneous disorders typified by upper abdominal pain without the presence of an ulcer.**

**Dyspepsia is common in the general population and up to 60% of patients seeking medical care for dyspepsia have a negative diagnostic evaluation**. The etiology of NUD is not established, and the potential role of *H. pylori* in NUD remains controversial.

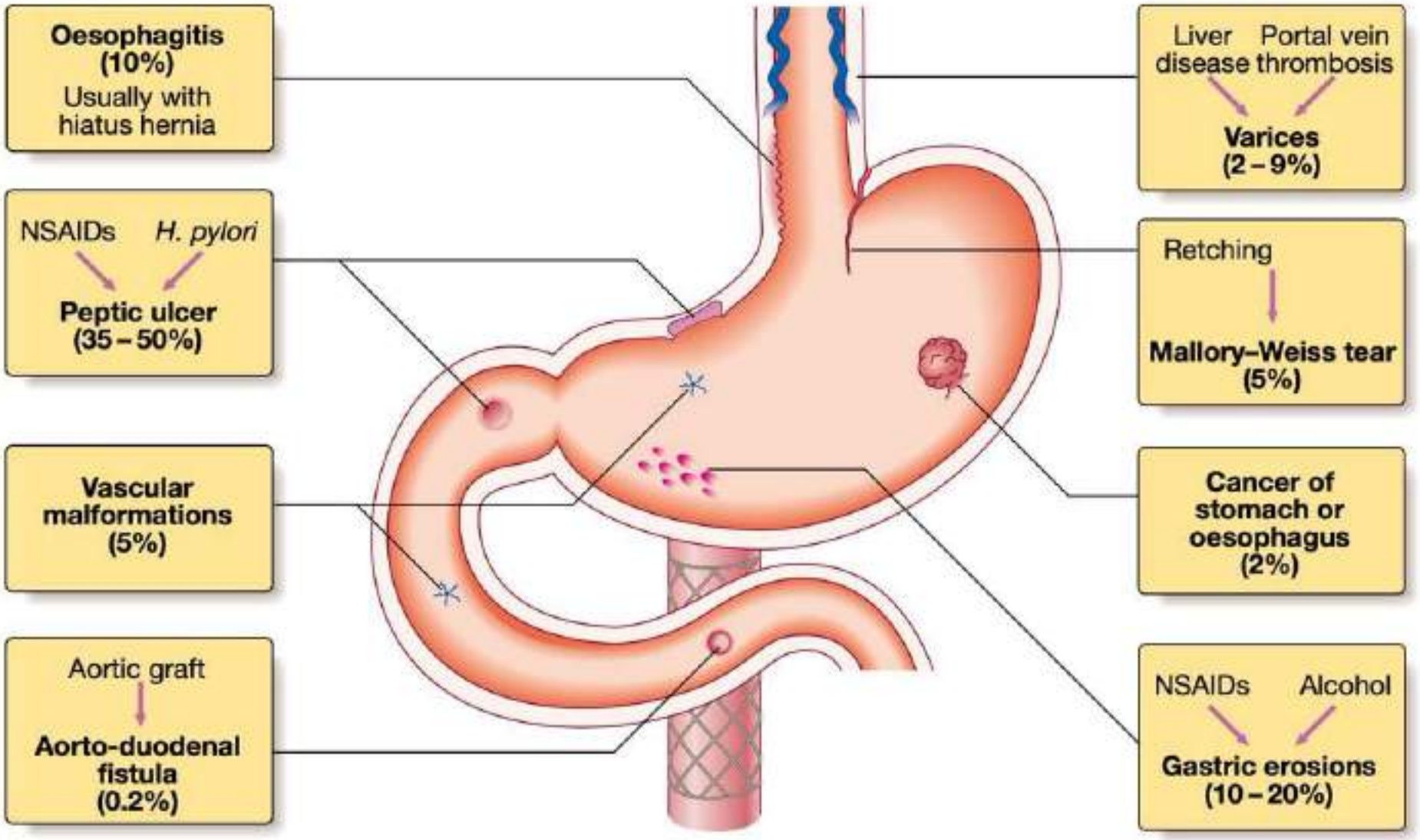
Several additional disease processes that may present with "ulcer-like" symptoms include proximal gastrointestinal tumors, gastroesophageal reflux, vascular disease, pancreaticobiliary disease (biliary colic, chronic pancreatitis), and gastroduodenal Crohn's disease.

# PUD-Related Complications

**Gastrointestinal Bleeding**

- Gastrointestinal bleeding is the most common complication observed in PUD.
- It occurs in ~15% of patients and more often in individuals >60 years old. The higher incidence in the elderly is likely due to the **increased use of NSAIDs in this group**.
- Up to 20% of patients with ulcer-related hemorrhage bleed without any preceding warning signs or symptoms.

# Causes of Upper GI bleedings

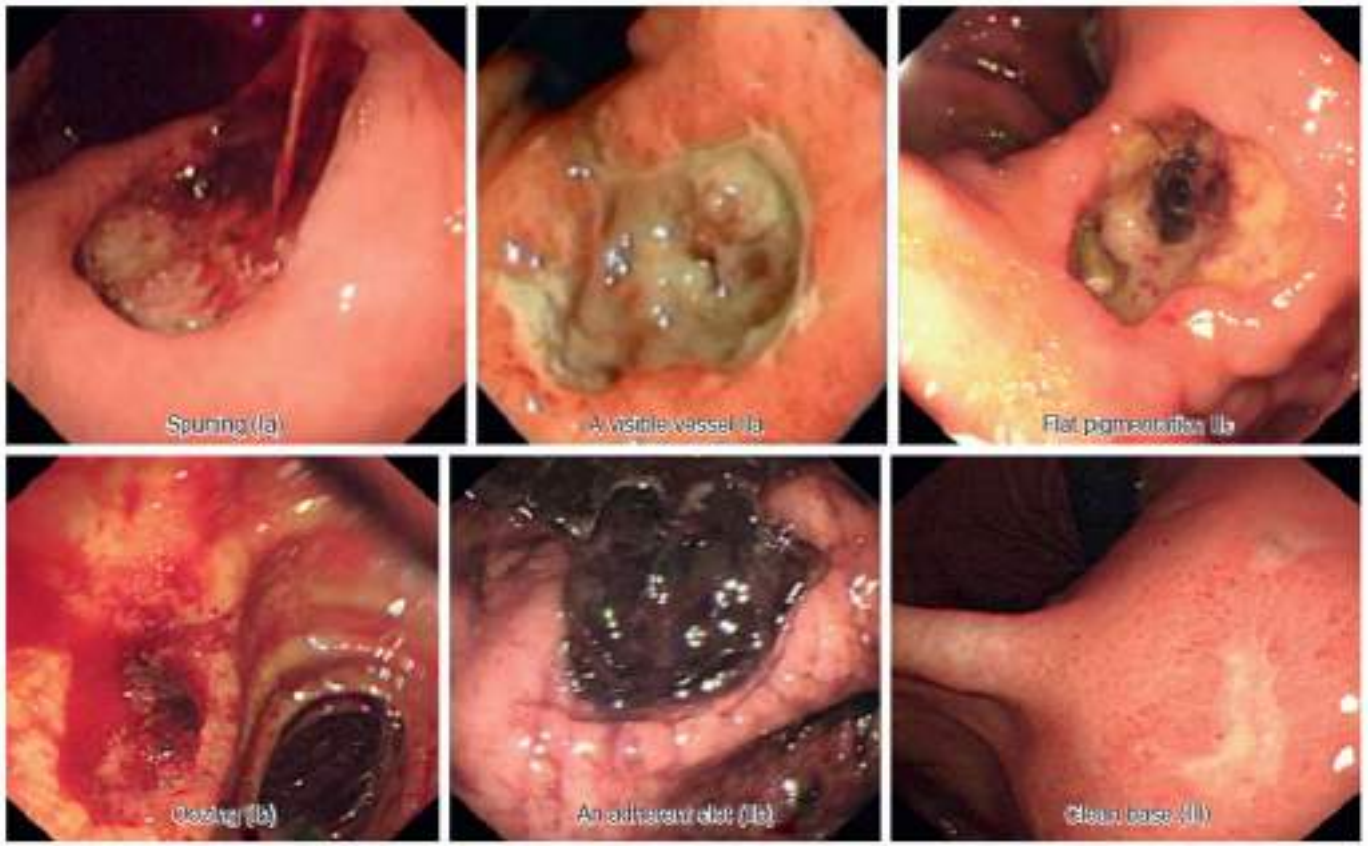


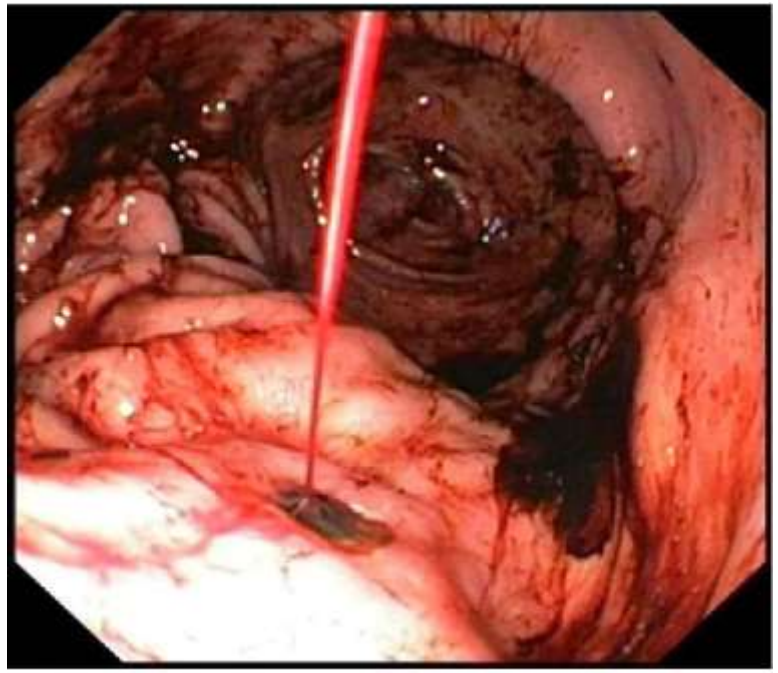
# Forrest classification system with predictive prognosis

| Forrest Classification | Rebleeding Incidence | Surgical Requirement | Incidence of Death |
|---|---|---|---|
| ***Type I: Active Bleed*** | 55-100% | 35% | 11% |
| Ia: Spurting Bleed | | | |
| Ib: Oozing Bleed | | | |
| ***Type II: Recent Bleed*** | 40-50% | 34% | 11% |
| IIa: Non-Bleeding Visible Vessel (NBVV) | 20-30% | 10% | 7% |
| IIb: Adherent Clot | | | |
| ***Type III: Lesion without Bleeding*** | 10% | 6% | 3% |
| Flat Spot | 5% | 0.5% | 2% |
| Clean Base | | | |

https://www.youtube.com/watch?v=Wo90bqiI5BQ

# Forrest classification





| Author, year | No. trials included | No. patients included | Compared techniques | Conclusion |
|---|---|---|---|---|
| Marmo 2007 [23] | 20 | 2472 | Epinephrine injection +other injection or thermal or mechanical method vs. monotherapy with one of these methods | Dual endoscopic therapy is superior to epinephrine injection alone, but not to thermal or mechanical monotherapy |
| Sung 2007 [24] | 15 | 1156 | Hemoclips vs. injection/thermocoagulation | Hemoclip placement is superior to injection alone but comparable to thermocoagulation |
| Yuan 2008 [26] | 12 | 699 | Hemoclips vs. other endoscopic techniques | Hemoclip placement is not superior to other endoscopic modalities |
| Laine 2009 [19] | 65 | 6237 | Thermal devices, sclerosant, hemoclips, fibrin glue and epinephrine | Thermal devices, sclerosant, clips and fibrin glue are comparable. Epinephrine monotherapy is inferior to other interventions. |
| Barkun 2009 [25] | 41 | 4261 | Pharmacotherapy, injection, thermocoagulation, clips or combinations | All endoscopic therapies are superior to pharmacotherapy alone. Thermal therapy or clips alone or in combination with injection are comparable |

# PUD-Related Complications

## Perforation

- The second most common ulcer-related complication is perforation, being reported in as many as 6–7% of PUD patients. As in the case of bleeding, the incidence of perforation in the elderly appears to be increasing secondary to increased use of NSAIDs. *Penetration* is a form of perforation in which the ulcer bed tunnels into an adjacent organ. DUs tend to penetrate posteriorly into the pancreas, leading to pancreatitis, whereas GUs tend to penetrate into the left hepatic lobe. Gastrocolic fistulas associated with GUs have also been described.

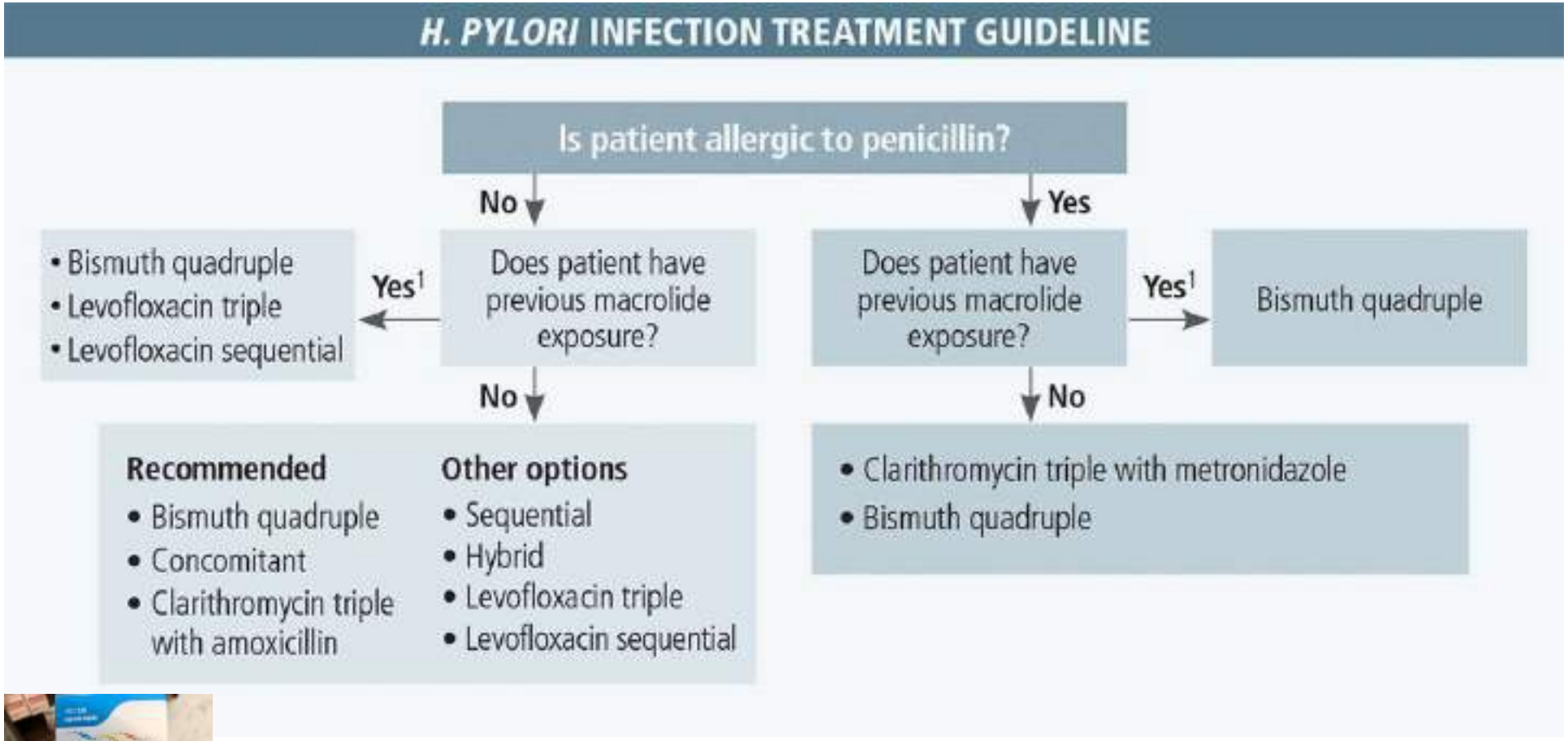
# PUD-Related Complications

## Stenosis and obstruction

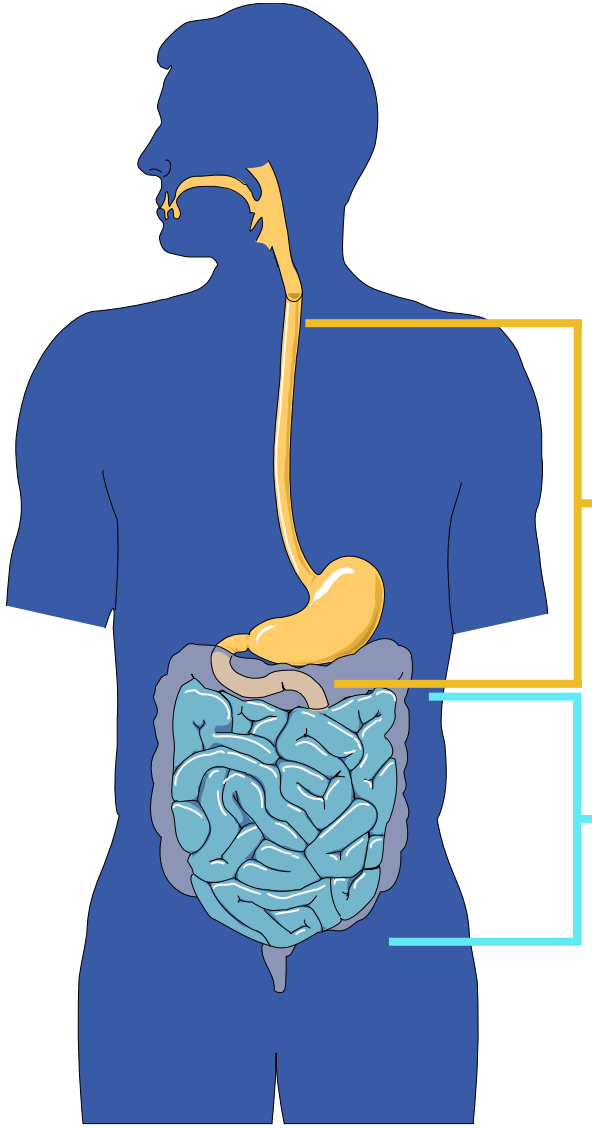
- Gastric outlet obstruction is the least common ulcer-related complication, occurring in 1% of patients. A patient may have relative obstruction secondary to ulcer-related inflammation and edema in the peripyloric region. This process often resolves with ulcer healing. A fixed, mechanical obstruction secondary to scar formation in the peripyloric areas is also possible.
- The latter requires endoscopic (balloon dilation) or surgical intervention. Signs and symptoms relative to mechanical obstruction may develop insidiously. New onset of early satiety, nausea, vomiting, increase of postprandial abdominal pain, and weight loss should make gastric outlet obstruction a possible diagnosis.

| Definizione Trattamento | Composizione | Durata |
|---|---|---|
| **Triplice Terapia Standard** | • Inibitore di Pompa Protonica<br>• Claritromicina 500 mg / bid<br>• Amoxicillina 1 g / bid * | 10-14 giorni |
| **Triplice Terapia Modificata** | • Inibitore di Pompa Protonica<br>• Levofloxacina 250 o 500 / bid<br>• Amoxicillina 1 g / bid * | 10 giorni |
| **Terapia Sequenziale** | • Inibitore di Pompa Protonica<br>• Amoxicillina 1 g / bid | 5-7 giorni |
| | poi<br>• Inibitore di Pompa Protonica<br>• Metronidazolo 500 mg / bid<br>• Claritromicina 500 mg / bid † | 5-7 giorni |
| **Terapia Concomitante** | • Inibitore di Pompa Protonica<br>• Amoxicillina 1 g / bid<br>•Metronidazolo 250 mg / qid<br>•Claritromicina 500 mg / bid † | 7-10 giorni |
| **Quadruplice Terapia con Bismuto** | • Inibitore di Pompa Protonica<br>• Metronidazolo 250 mg / qid<br>• Tetraciclina 250 mg / qid ‡<br>• Bismuto subcitrato 120 mg / qid | 10 giorni |
| **Terapia Ibrida** | • Inibitore di Pompa Protonica<br>• Amoxicillina 1 g / bid | 7 giorni |
| | poi<br>• Inibitore di Pompa Protonica<br>• Amoxicillina 1 g / bid<br>•Metronidazolo 250 mg / qid<br>•Claritromicina 500 mg / bid | 7 giorni |

# H. Pylori treatment




# NSAIDs related GI  side effects

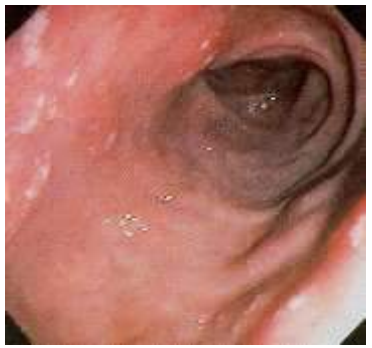


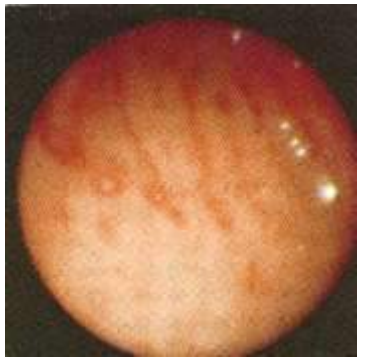
Upper GI symptoms

Intestinal symptoms

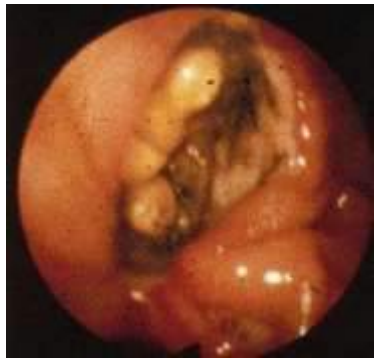
# Gastrointestinal Lesions induced by NSAIDs

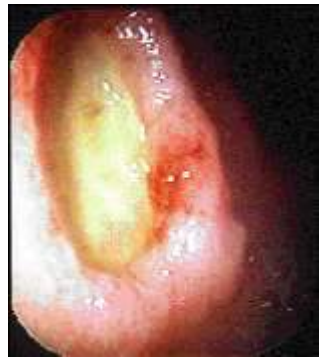
1. Acute Mucosal Lesions:
   - •Petequia
   - •Erosions
   - •Acute Ulcers



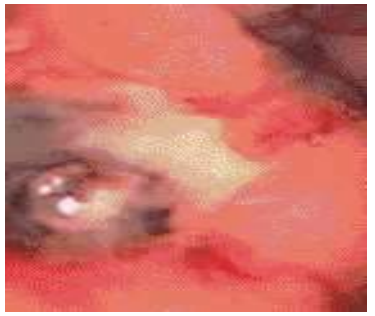


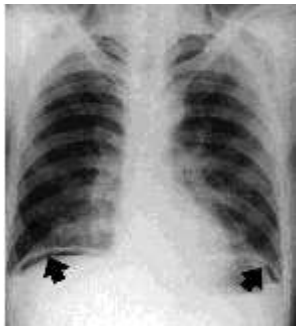
2. Chronic/Deep GD Ulcers





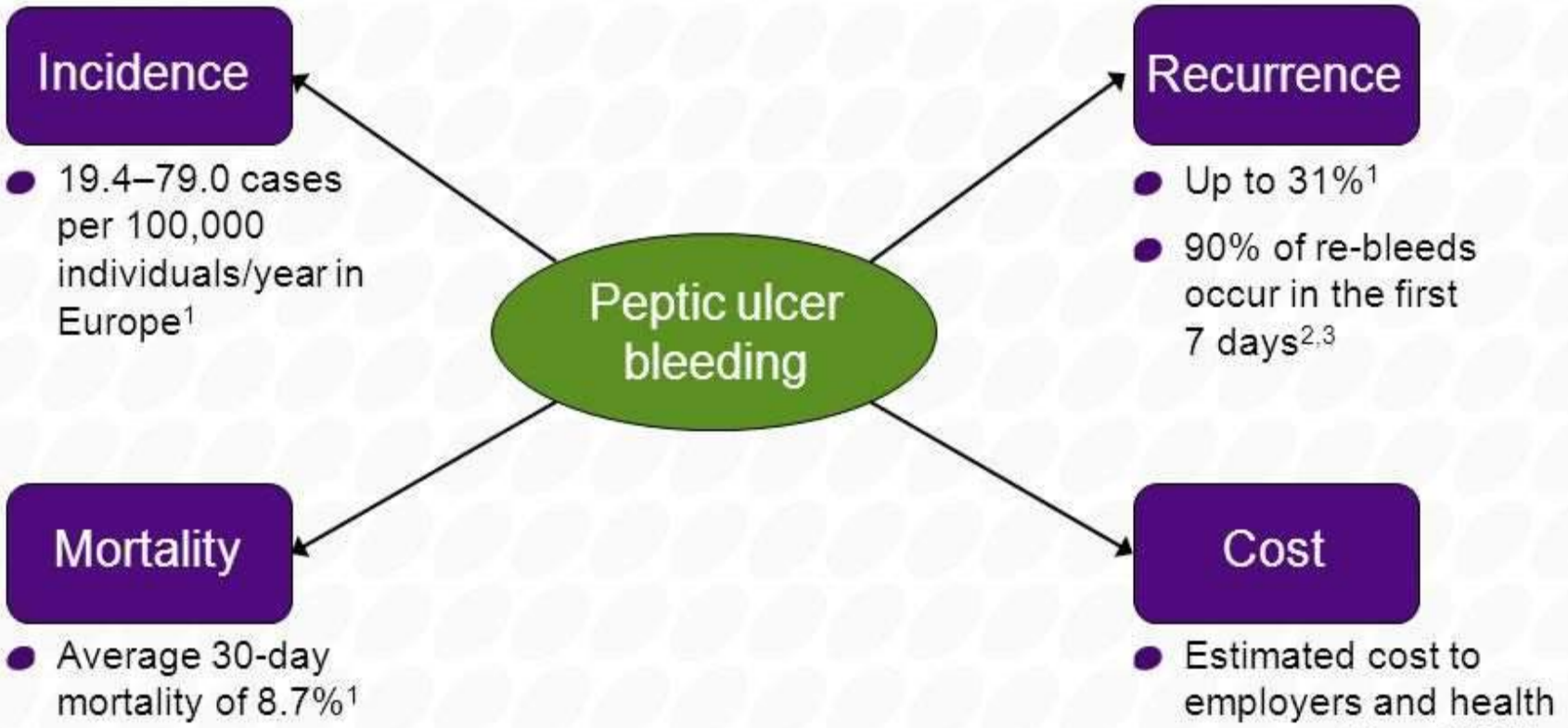
3. Complications:
   - • Perforations (rare)
   - •obstructions (rare)
   - •bleeding [“PUB”]





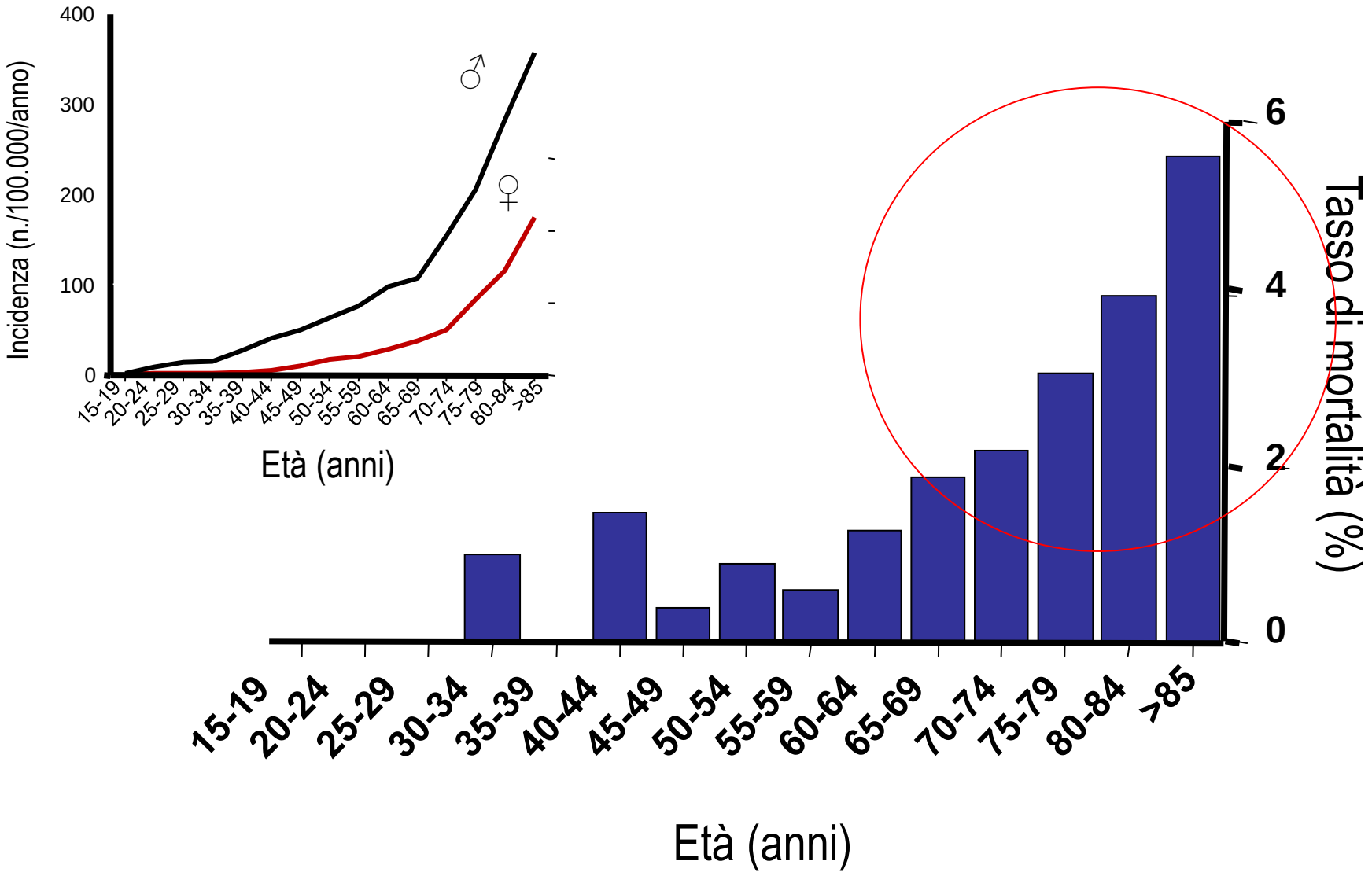
*Fiorucci S. Dig & Liv Dis 2003*

# Peptic ulcer bleeding is a substantial health issue




[1]Lau JY, et al. Gastroenterology 2008;134(4 Suppl 1):A32; [2]Bini EJ & Cohen J. Gastrointest Endosc 2003;58:707–1; [3]Chiu PW, et al. Gut 2003;52:1403–7; [4]Sonnenberg A & Everhart JE. Am J Gastroenterol 1997;92:614–20

# Italia:Tasso di mortalità per età



# Gastrointestinal bleeding: risk factors

1. Age >65 year
2. History of  peptic ulcer or GI bleeding
3. High doses  of  NSAID
4. Multiple NSAIDs (or ASA + NSAID)
5. Concomitant use of corticosteroids
6.  Concomitant  use of anti-coagulants
7. H. pylori infection

# Aspirin: benefits and harms

**Aspirin is an anti-thrombotic, analgesic, antipyretic and anti-inflammatory drug**

**The use of aspirin is associated with a 2-4 fold increase in the risk of GI bleeding**

**Aspirin (low doses)**

**is the major cause of GI bleeding**

*The US Preventive Services Task Force Meta-analysis *Ann Internal Med 2002*; 136:157

# Risk factors: the NSAID structure

| Drug | R.R. (I.C. 95%) |
|---|---|
| Ibuprofen | 2.0 |
| ASA < 325* | 1.8 (1.2-2.3) |
| Diclofenac | 2.8 (1.4-2.3) |
| Sulindac | 3.1 (1.6-2.7) |
| Naproxen | 3.2 (1.7-2.9) |
| Indomethacin | 3.4 (1.9-3.1) |
| Piroxicam | 4.8 (2.7-5.2) |
| Ketoprofen | 5.2 (2.7-6.4) |

**COX-2 vs COX-1**

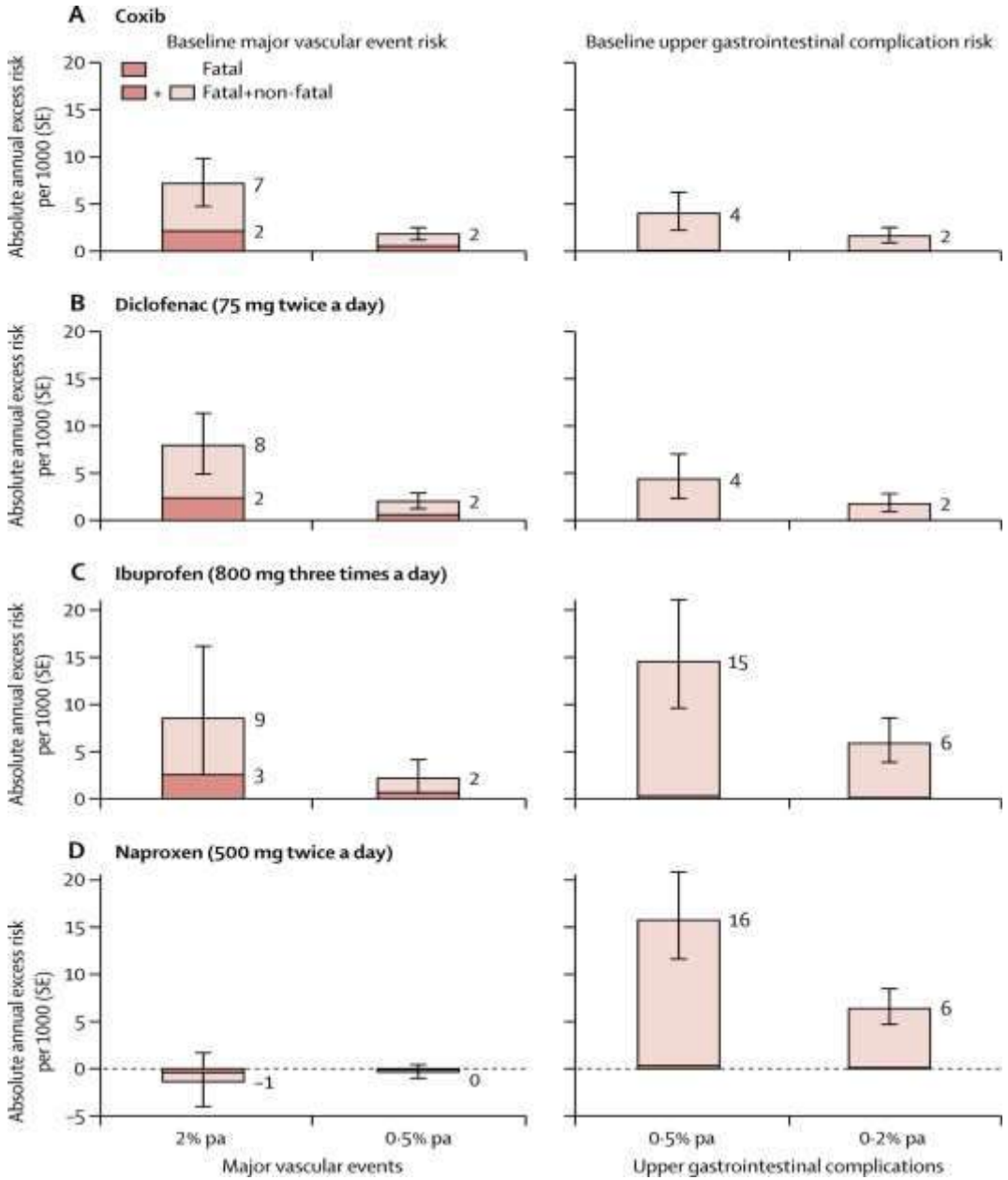
*The US Preventive Services Task Force Meta-analysis *Ann Internal Med 2002*; 136:157

“COXIBS are safer then conventional NSAIDs for the GI tract but their use increases the risk of thrombotic events”

*FitzGerald G. Coxibs and cardiovascular disease. New Engl J Med, 2004; 351:1709-1711*

# Therapy of NSAID-Related Gastric or Duodenal Injury

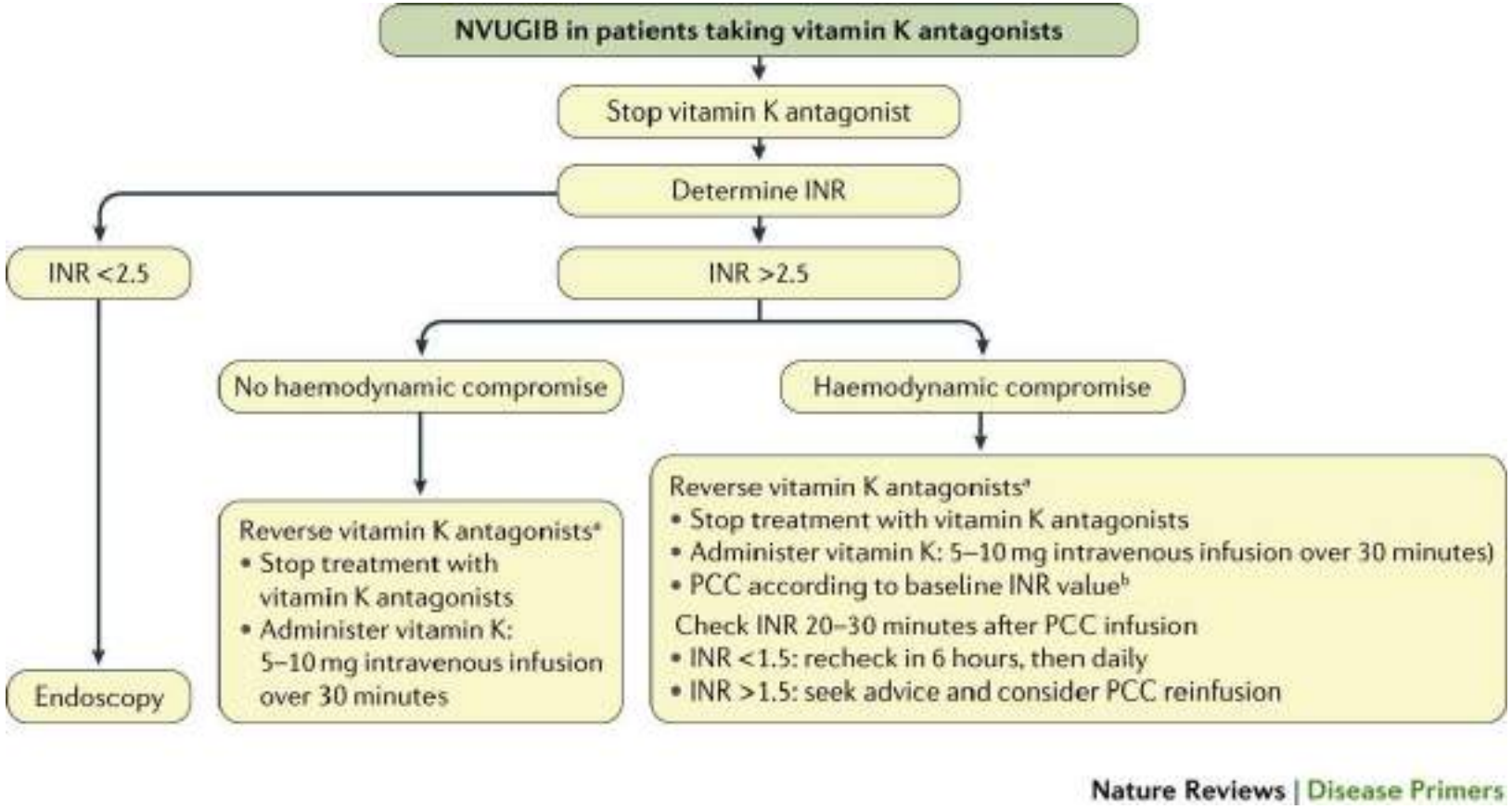
- Medical intervention for NSAID-related mucosal injury includes treatment of an active ulcer and primary prevention of future injury.
- **Ideally, the injurious agent should be stopped as the first step in the therapy of an active NSAID-induced ulcer. If that is possible, then treatment with one of the acid inhibitory agents ($H_2$ blockers, PPIs) is indicated.**
- Cessation of NSAIDs is not always possible because of the patient's severe underlying disease.
- Only PPIs can heal GUs or DUs, independent of whether NSAIDs are discontinued.




*The Lancet* 2013 382769-779DOI: (10.1016/S0140-6736(13)60900-9)

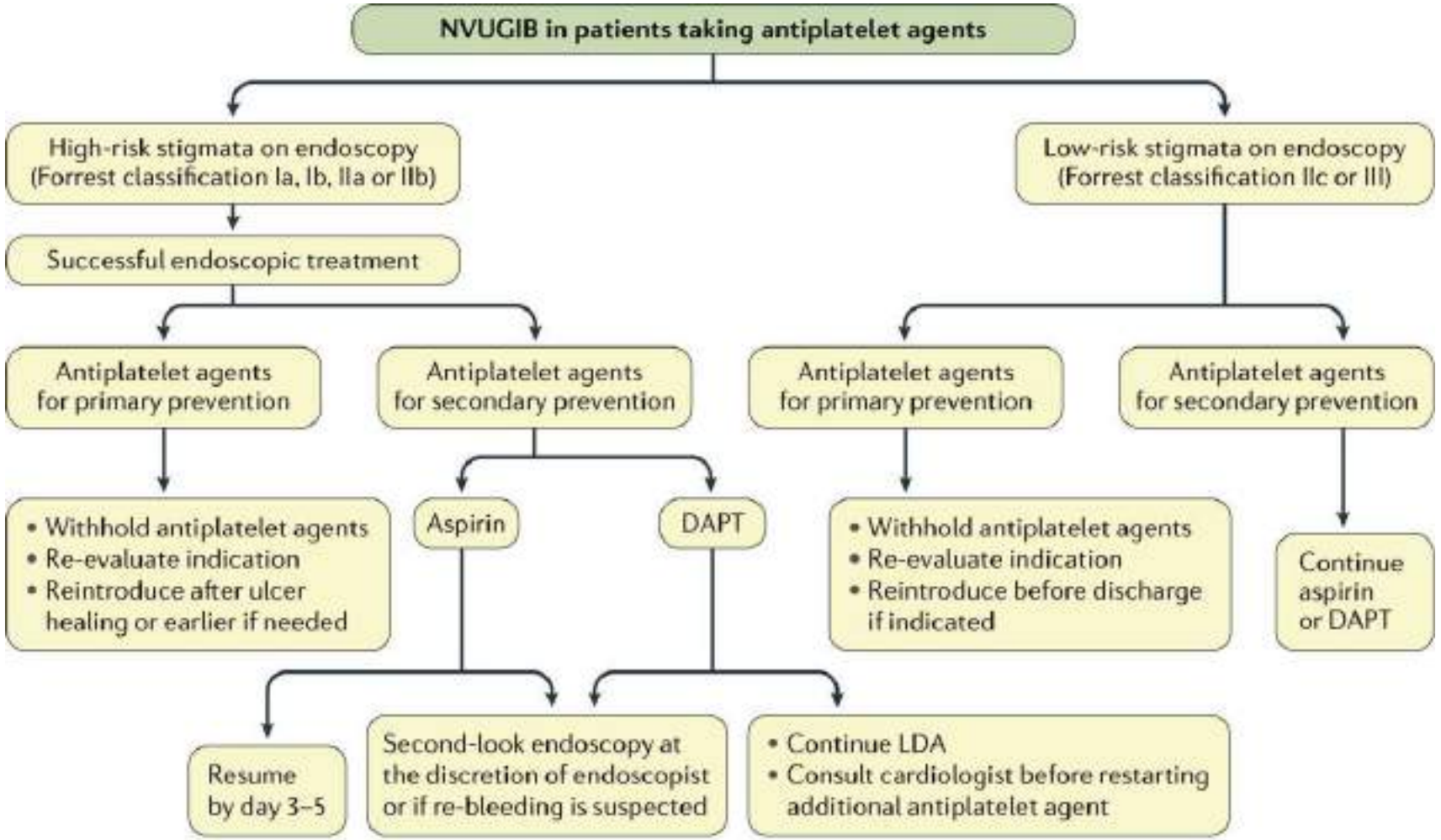
| | No/Low NSAID GI Risk | NSAID GI Risk |
|---|---|---|
| No CV risk (no aspirin) | Traditional NSAID | Coxib or<br>Traditional NSAID + PPI<br>Consider non-NSAID therapy |
| CV risk (consider aspirin) | Traditional NSAID + PPI if GI risk warrants gastroprotection | A gastroprotective agent must be added if a traditional NSAID is prescribed |
| | Consider non-NSAID therapy | Consider non-NSAID therapy |

# Management of Upper GI bleeding in those using vitamin K antagonists

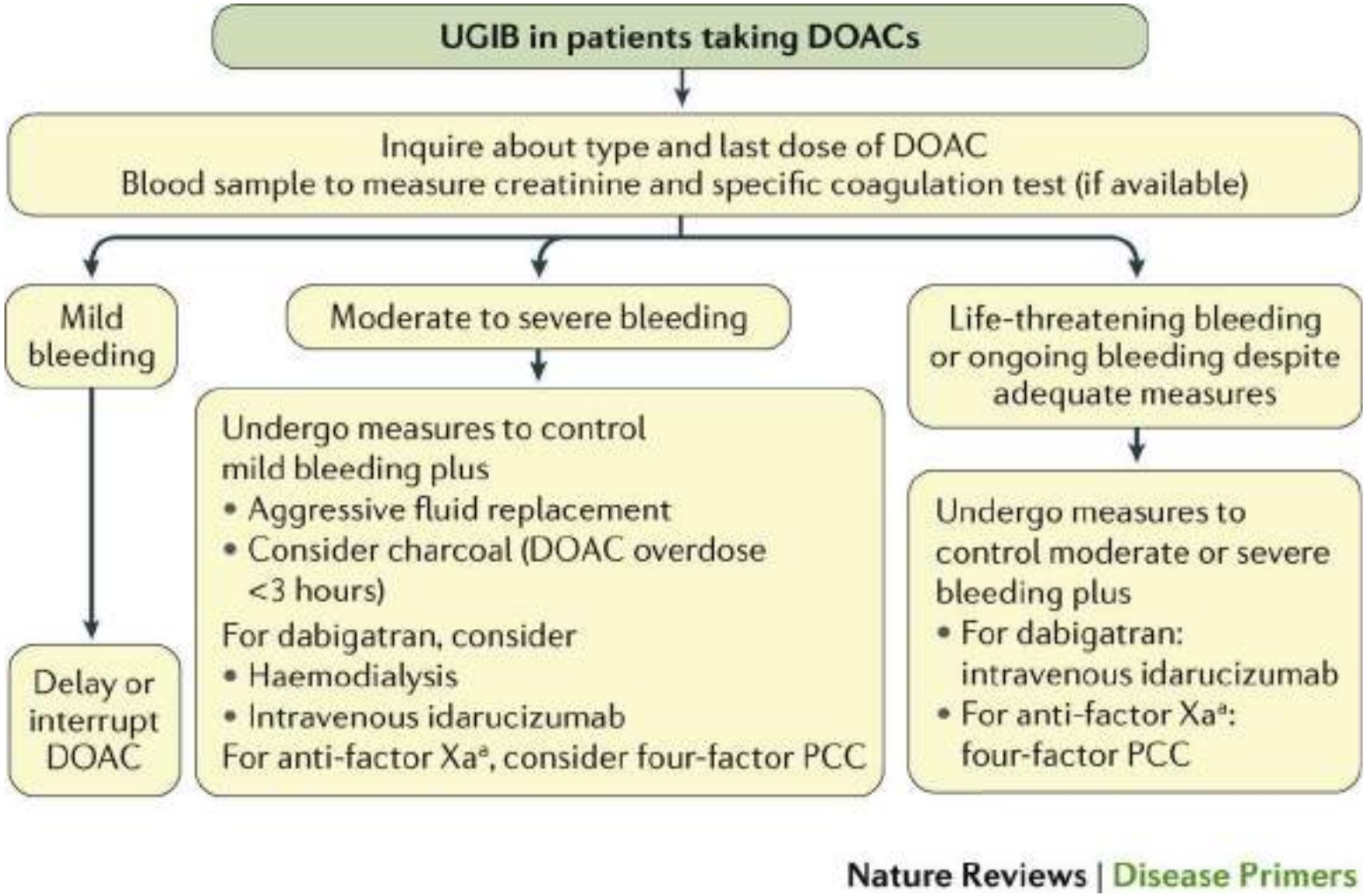



Lanas, A. et al. (2018) Non-variceal upper gastrointestinal bleeding
*Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2018.20

# Management of upper GI bleeding in those using antiplatelet agents



# Management of upper GI bleeding in those on DOACs



# PUBs that fail to heal under appropriate therapy

The majority (>99%) of GUs and DUs heal with the conventional therapy outlined above.

Once poor compliance and persistent *H. pylori* infection have been excluded, NSAID use, either inadvertent or surreptitious, must be excluded. In addition, cigarette smoking must be eliminated. For a GU, malignancy must be meticulously excluded.

Next, consideration should be given to a gastric acid hypersecretory state such as ZES.

More than **90% of refractory ulcers (either DUs or GUs) heal after 8 weeks of treatment with higher doses of PPI (omeprazole, 40 mg/d; lansoprazole 30–60** mg/d).

Surgical intervention may be a consideration at this point.

# PU Surgical therapy

The development of pharmacologic and endoscopic approaches for the treatment of peptic disease and its complications has led to a substantial decrease in the number of operations needed for this disorder.

**Surgical intervention in PUD is almost exclusively reserved to the treatment of an ulcer-related complication.**

**Gastrointestinal bleeding and perforation, and gastric outlet obstruction are the three complications that may require surgical intervention.**

# Surgical therapy

## Indication for surgical therapy

### 1. Upper GI bleeding

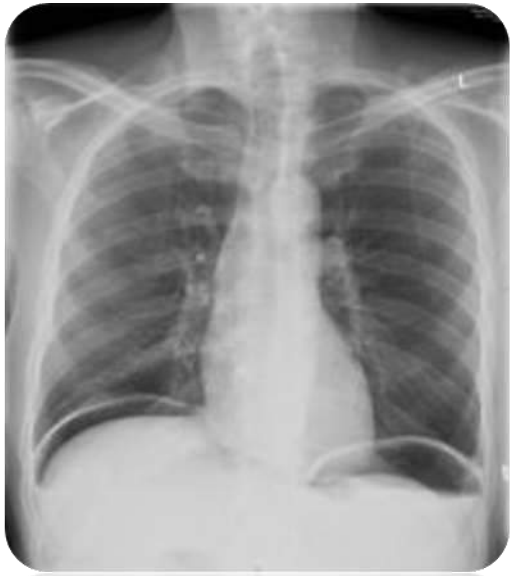
**Hemorrhage is the most common ulcer-related complication, occurring in ~15–25% of patients.** Bleeding may occur in any age group but is most often seen in older patients (sixth decade or beyond). Parenterally and orally administered PPIs also decrease ulcer rebleeding in patients who have undergone endoscopic therapy. The majority of patients stop bleeding spontaneously, but endoscopic therapy is necessary in some. Patients unresponsive or refractory to endoscopic intervention will require surgery **(~5% of transfusion-requiring patients**).

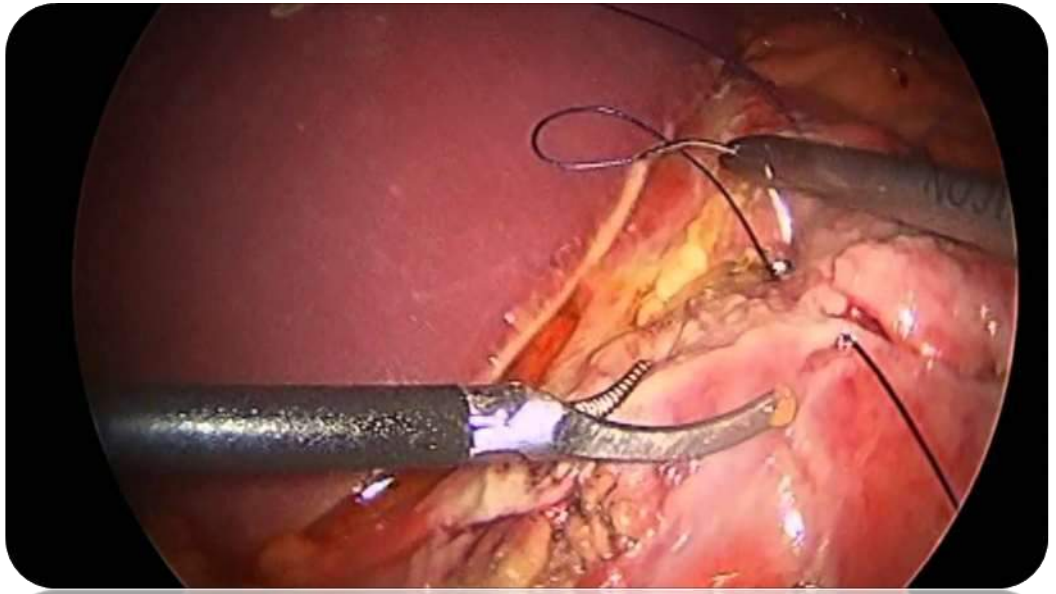
# Surgical therapy

## 2. PU perforation

**Free peritoneal perforation** occurs in ~2–3% of DU patients. As in the case of bleeding, up to 10% of these patients will not have antecedent ulcer symptoms. Concomitant bleeding may occur in up to 10% of patients with perforation, with mortality being increased substantially.

Peptic ulcer **can also penetrate** into adjacent organs, especially with a posterior DU, which can penetrate into the pancreas, colon, liver, or biliary tree





# Surgical therapy

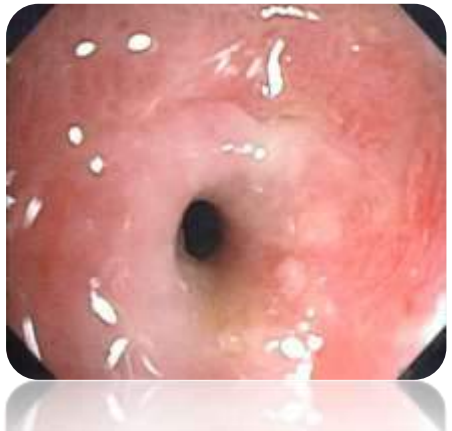
### 3. Ostruction

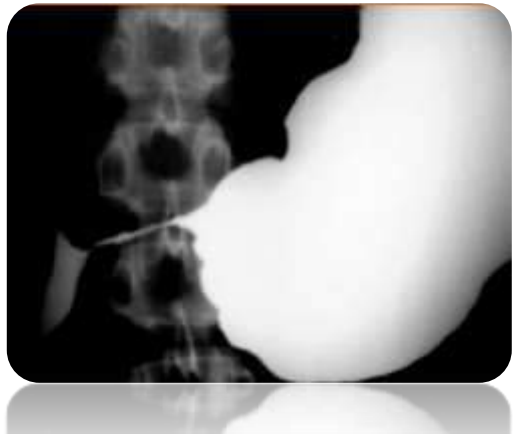
**Pyloric channel ulcers or DUs can lead to gastric outlet obstruction in ~2–3% of patients.**

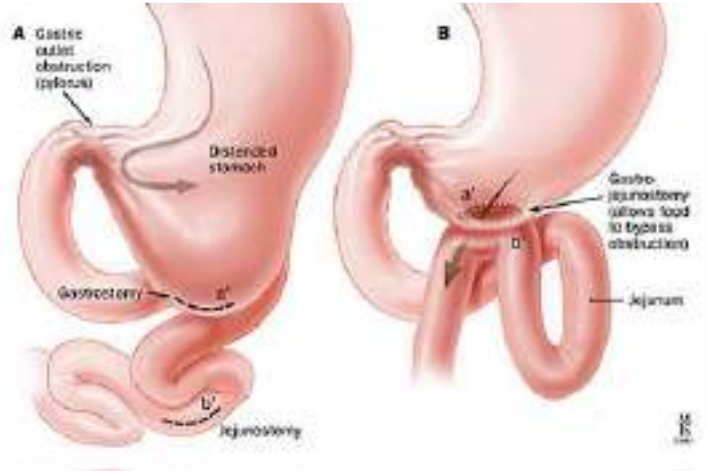
This can result from chronic scarring or from impaired motility due to inflammation and/or edema with pylorospasm. Patients may present with early satiety, nausea, vomiting of undigested food, and weight loss.

Conservative management with nasogastric suction, intravenous hydration/nutrition, and antisecretory agents is indicated for 7–10 days with the hope that a functional obstruction will reverse.

If a mechanical obstruction persists, endoscopic intervention with balloon dilation may be effective. Surgery should be considered if all else fails.





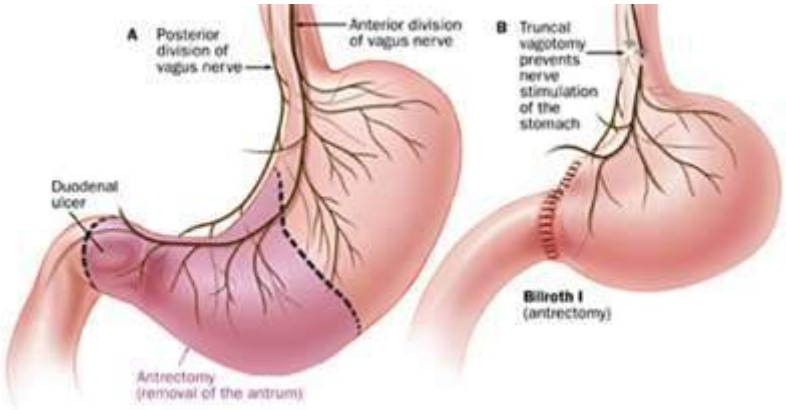


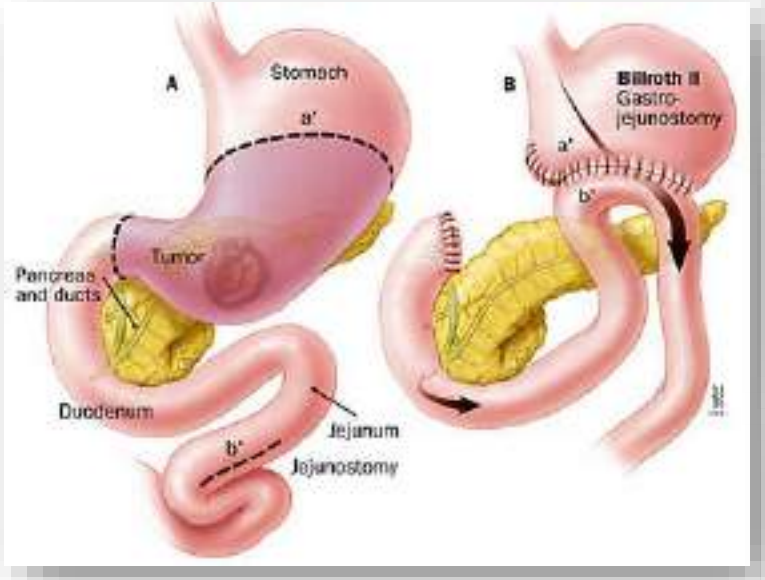
# Surgical therapy

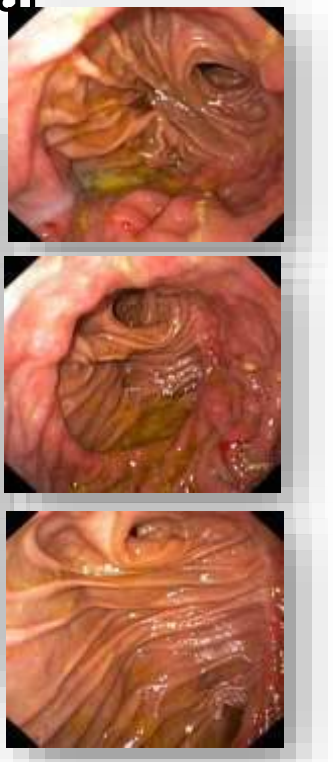
**Antrectomy** is aimed at eliminating an additional stimulant of gastric acid secretion, gastrin. Two principal types of reanastomoses are used after antrectomy:

**gastroduodenostomy (Billroth I) or gastrojejunostomy (Billroth II)**

Although Billroth I is often preferred over II, severe duodenal inflammation or scarring may preclude its performance.

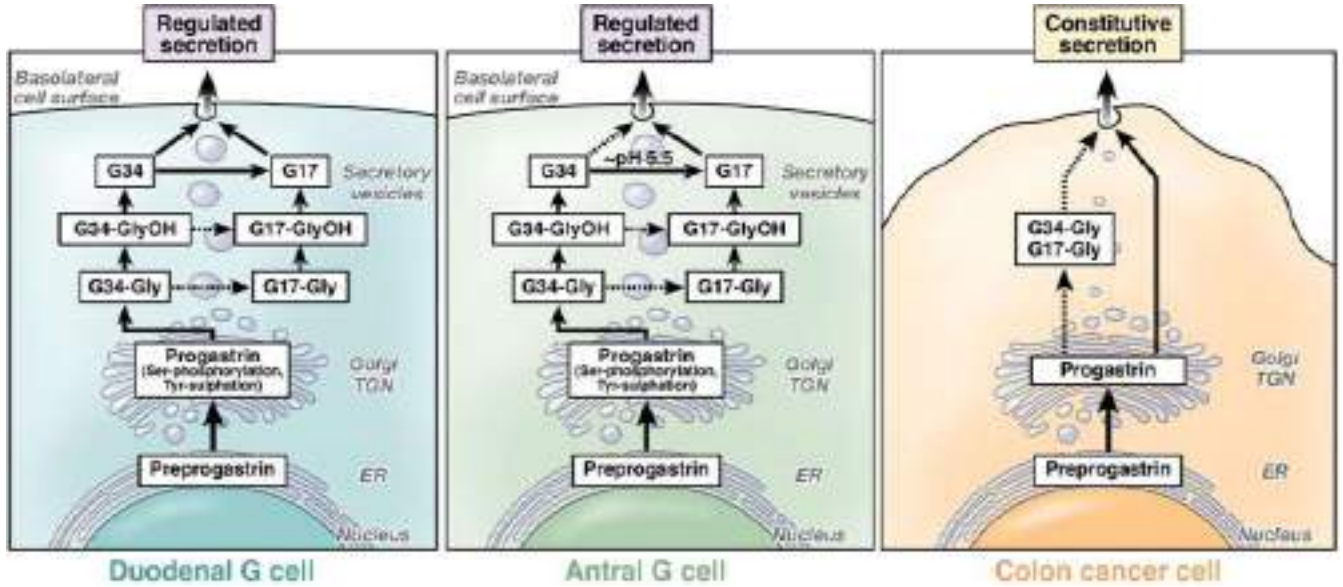


# Zollinger–Ellison Syndrome

**Severe peptic ulcer diathesis secondary to gastric acid hypersecretion due to unregulated gastrin release from a G cell endocrine tumor (gastrinoma).**



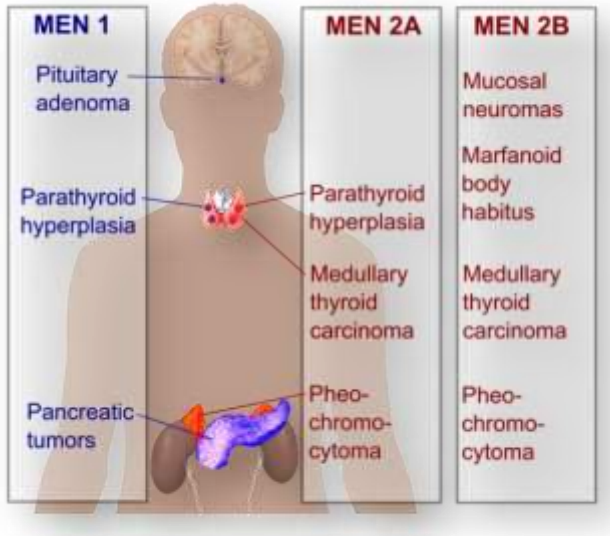
# Zollinger–Ellison Syndrome

## Epidemiology

- The incidence of ZES **varies from 0.1 to 1% of individuals presenting with PUD**. Males are more commonly affected than females, and the majority of patients are diagnosed between ages 30 and 50.
- Although 75% to 80% of **gastrinomas are sporadic,** 20% to 25% are diagnosed in the setting of **multiple endocrine neoplasia type 1 (MEN1).**

# Zollinger–Ellison Syndrome and MEN I

- Gastrinomas can develop in the presence of **MEN I syndrome** ( in ~25% of patients).
- This autosomal dominant disorder involves primarily three organ sites: **the parathyroid glands (80–90%), pancreas (**40–80%), and **pituitary gland** (30–60%).
- The genetic defect in MEN I is in the long arm of chromosome 11 (11q11-q13).
- In view of the stimulatory effect of calcium on gastric secretion, the hyperparathyroidism and hypercalcemia seen in MEN I patients may have a direct effect on ulcer disease.
- Resolution of hypercalcemia by parathyroidectomy reduces gastrin and gastric acid output in gastrinoma patients. An additional distinguishing feature in ZES patients with MEN I is the higher incidence of gastric carcinoid tumor .



# Zollinger–Ellison Syndrome

**Gastric acid hypersecretion is responsible for the signs and symptoms observed in patients with ZES.**

**Peptic ulcer is the most common clinical manifestation, occurring in >90% of gastrinoma patients**.

Initial presentation and ulcer location (duodenal bulb) may be indistinguishable from common PUD. Clinical situations that should create suspicion of gastrinoma are ulcers in unusual locations **(second part of the duodenum and beyond**), ulcers refractory to standard medical therapy, ulcer recurrence after acid-reducing surgery, ulcers presenting with frank complications (bleeding, obstruction, and perforation), or **ulcers in the absence of *H. pylori* or NSAID ingestion**.

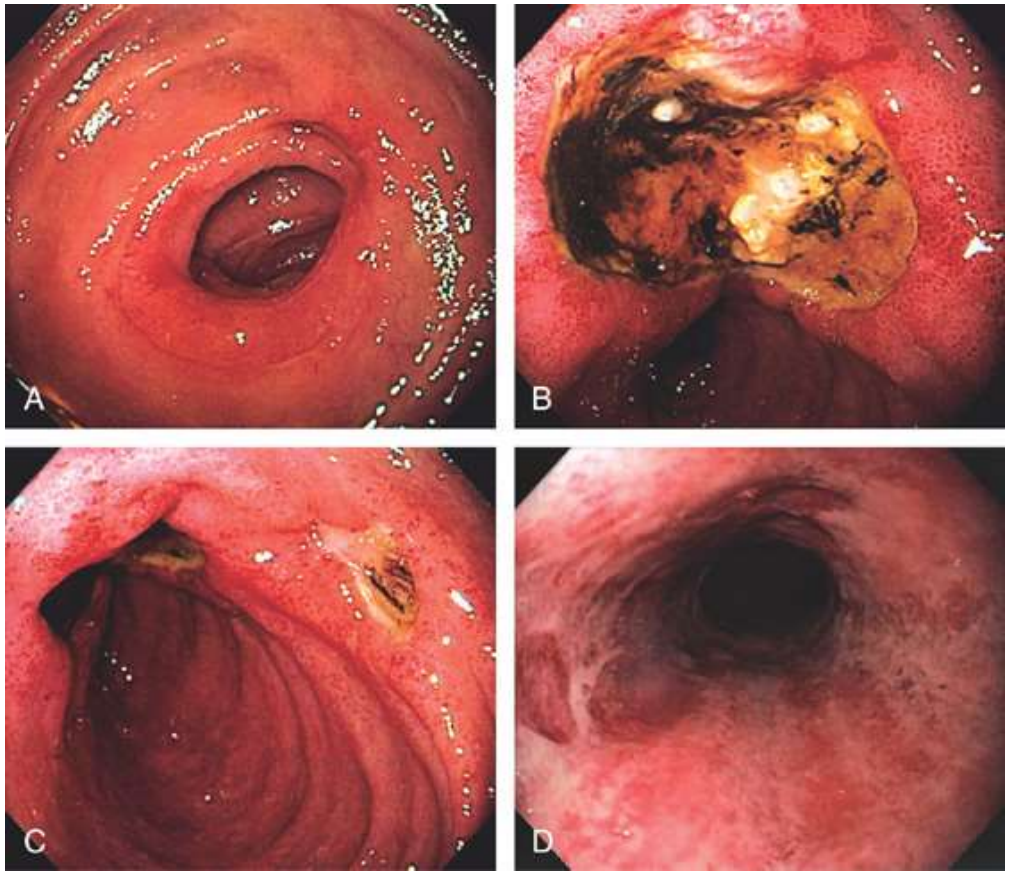
# Zollinger–Ellison Syndrome

**Diarrhea, occurs in up to 50% of patients.** Although diarrhea often occurs concomitantly with acid peptic disease, it may also occur independent of an ulcer.

Etiology of the diarrhea is multifactorial, resulting from marked volume overload to the small bowel, pancreatic enzyme inactivation by acid, and damage of the intestinal epithelial surface by acid.

The epithelial damage can lead to a mild degree of maldigestion and malabsorption of nutrients.

# Zollinger–Ellison Syndrome endoscopy findings



# Zollinger–Ellison Syndrome diagnosis

- The first step in the evaluation of a patient suspected of having ZES is to obtain a fasting gastrin level.
- **Fasting gastrin levels are usually <150 pg/mL.**
- Virtually **all gastrinoma patients will have a gastrin level >150–200 pg/mL.** Measurement of fasting gastrin should be repeated to confirm the clinical suspicion.

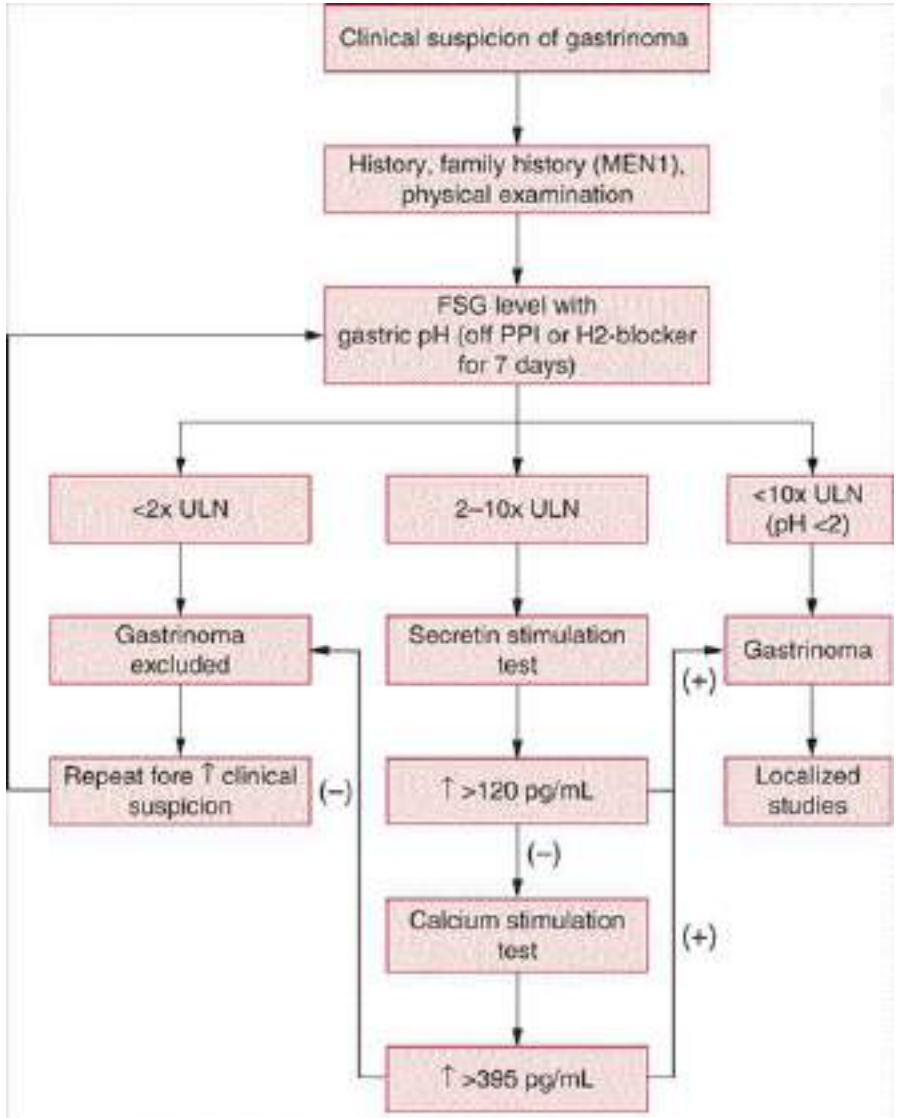
# Hypergastrinemia

| |
|---|
| Hypochlorhydria or achlorhydria with or without pernicious anemia |
| Retained gastric antrum |
| G-cell hyperplasia |
| Renal insufficiency |
| Massive small bowel resection |
| Gastric outlet obstruction |
| Other conditions (rheumatoid arthritis, vitiligo, diabetes, pheochromocytoma) |

# Zollinger–Ellison Syndrome

## Diagnosis

- **The next step in establishing a biochemical diagnosis of gastrinoma is to assess acid secretion.**
- If the technology for measuring gastric acid secretion is not available, a basal gastric pH 3 virtually excludes a gastrinoma.



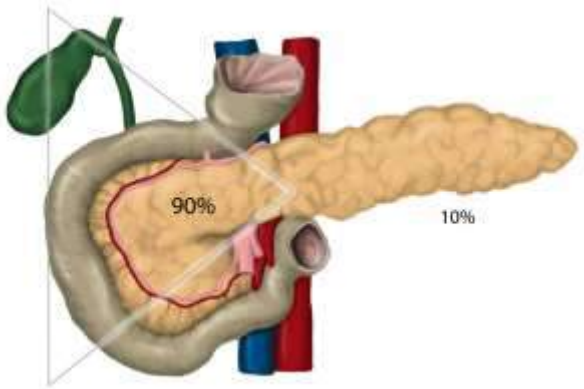
# Zollinger–Ellison Syndrome

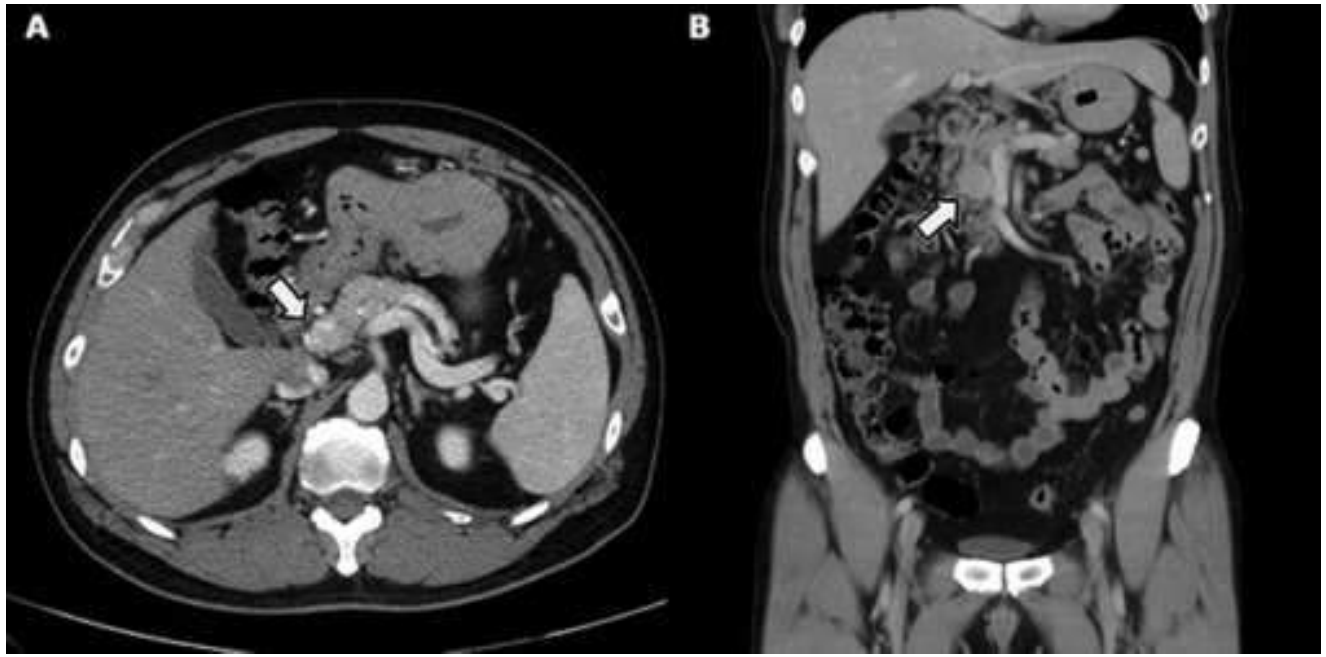
**Tumor Distribution**

Over 80% of these tumors are found within the hypothetical

**Gastrinoma triangle**

(**confluence of the cystic and common bile ducts superiorly, junction of thee second and third portions of the duodenum inferiorly, and junction of the neck and body of the pancreas medially).**



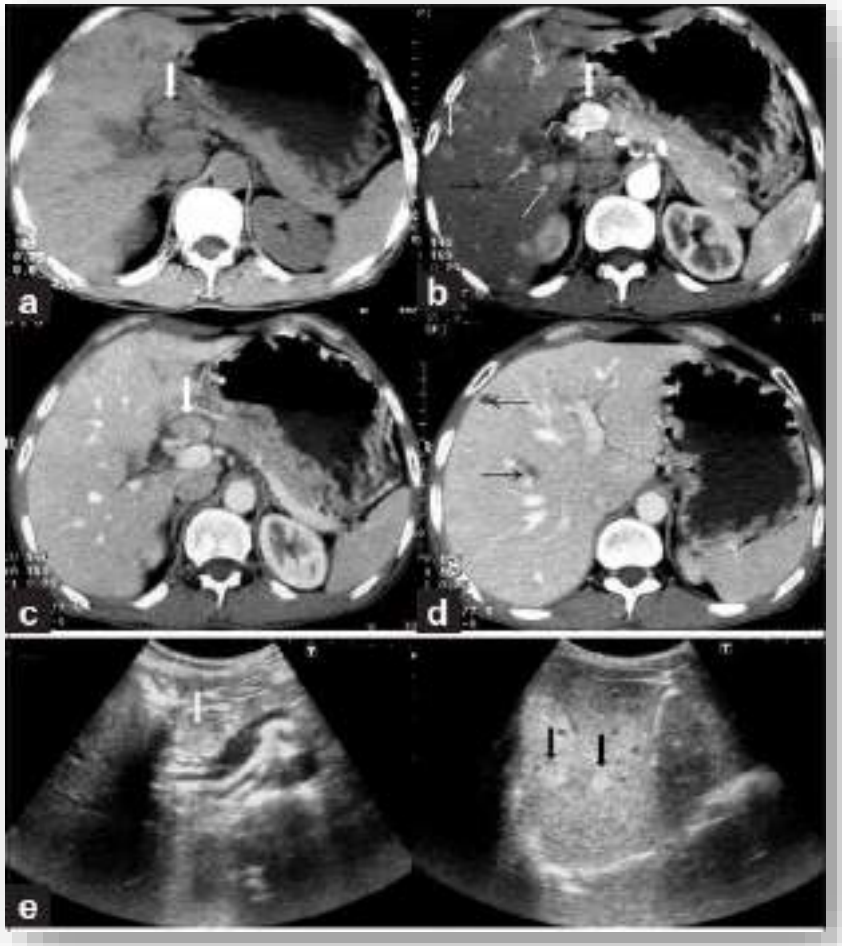



# Zollinger–Ellison Syndrome

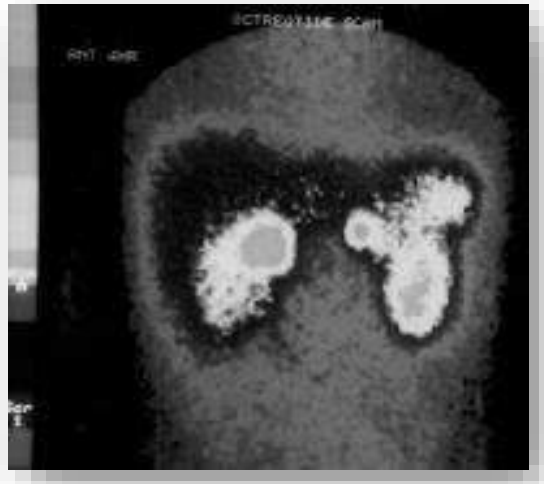
**Tumor Distribution**

- **Duodenal tumors** constitute the most common nonpancreatic lesion; between 50% and 75% of gastrinomas are found here. Less-common extrapancreatic sites include stomach, bones, ovaries, heart, liver, and lymph nodes.
- **More than 60% of tumors are considered malignant,** with up to 30–50% of patients having multiple lesions or metastatic disease at presentation.
- Histologically, gastrin-producing cells appear well-differentiated, expressing markers typically found in endocrine neoplasms (chromogranin, neuron-specific enolase).

# Zollinger–Ellison Syndrome




## SZE octreoscan



# Zollinger–Ellison Syndrome

## Tumor Localization

Multiple imaging studies need to be utilized in an effort to enhance tumor localization

| | Sensitivity, % | |
|---|---|---|
| **Study** | **Primary Gastrinoma** | **Metastatic Gastrinoma** |
| Ultrasound | 21–28 | 14 |
| CT scan | 55–70 | >85 |
| Selective angiography | 35–68 | 33–86 |
| Portal venous sampling | 70–90 | N/A |
| SASI | 55–78 | 41 |
| MRI | 55–70 | >85 |
| OctreoScan | 67–86 | 80–100 |
| EUS | 80–100 | N/A |

***Abbreviations:*** CT, computed tomography; EUS, endoscopic ultrasonography; MRI, magnetic resonance imaging; N/A, not applicable; OctreoScan, imaging with $^{111}$In-pentreotide; SASI, selective arterial secretin injection.

# Zollinger–Ellison Syndrome

- Treatment of functional endocrine tumors is directed at ameliorating the signs and symptoms related to hormone overproduction, curative resection of the neoplasm, and attempts to control tumor growth in metastatic disease.
- **PPIs** are the treatment of choice and have decreased the need for total gastrectomy. Initial PPI doses tend to be higher than those used for treatment of GERD or PUD. The initial dose of omeprazole or lansoprazole should be in the range of 60 mg in divided doses in a 24-h period..
- The ultimate goal of surgery would be to provide a definitive cure

# Zollinger–Ellison Syndrome

- **Chemotherapy** (streptozotocin, 5-fluorouracil, and doxorubicin), IFN-, and hepatic artery embolization lead to significant toxicity without a substantial improvement in overall survival. $^{111}$In-pentetreotide has been used in the therapy of metastatic neuroendocrine tumors; further studies are needed. Several novel therapies are being explored, including radiofrequency or cryoablation of liver lesions and use of agents that block the vascular **endothelial growth receptor pathway (bevacizumab, sunitinib).**
- **Surgical approaches including debulking surgery and liver transplantation for hepatic metastasis have also produced limited benefit. Therefore, early recognition and surgery are the only chances for curing this disease.**
- **The overall 5- and 10-year survival rates for gastrinoma patients are 62–75% and 47–53%, respectively.**
- **Individuals with the entire tumor resected or those with a negative laparotomy have 5- and 10-year survival rates >90%.** Patients with incompletely resected tumors have 5- and 10-year survival of 43% and 25%, respectively.

# Gastritis

**The term *gastritis* should be reserved for histologically documented inflammation of the gastric mucosa.**

- Gastritis is not the mucosal erythema seen during endoscopy and is not interchangeable with "dyspepsia."
- The etiologic factors leading to gastritis are broad and heterogeneous.
- Gastritis has been classified based on time course (**acute vs. chronic**).

# Gastritis: etiology

**Acute gastritis**

A. **Acute *H. pylori* infection**

B. Other acute infectious gastritides

1. Bacterial (other than *H. pylori*)

2. Viral,  Parasitic and  Fungal

C. **NSAIDs**

**D. Alcohol**

**II. Chronic atrophic gastritis**

**A. Type A: Autoimmune, body- predominant**

**B. Type B: *H. pylori*–related, antral-predominant**

**C. Indeterminant**

III. Uncommon forms of gastritis

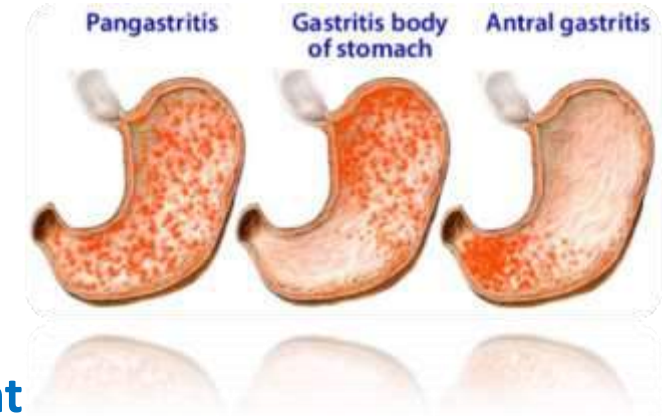
A. Lymphocytic

B. B. Eosinophilic

C. C. Crohn's disease

D. D. Sarcoidosis

E. E. Isolated granulomatous gastritis

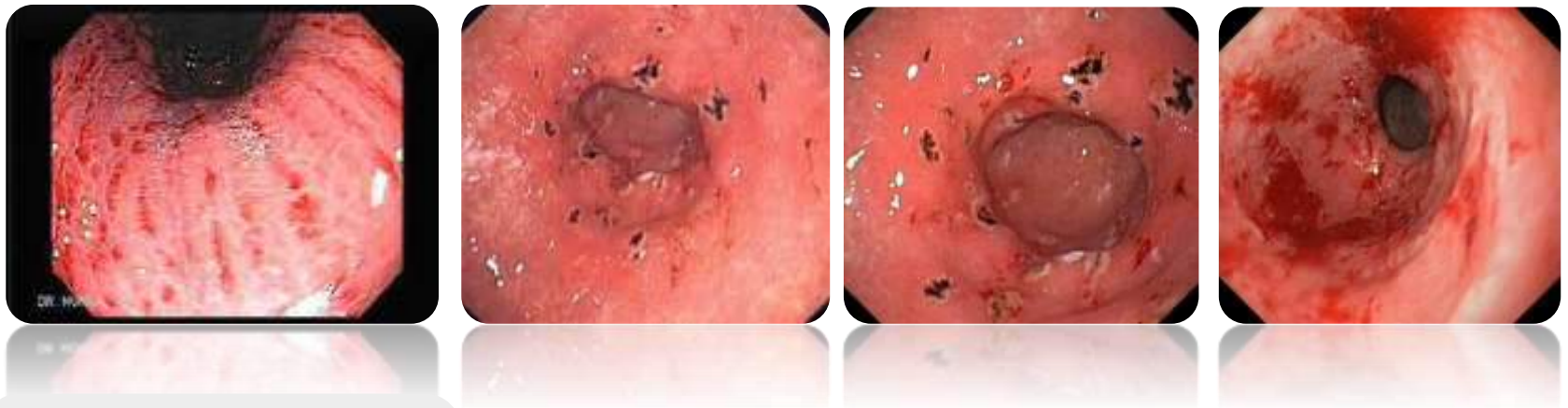


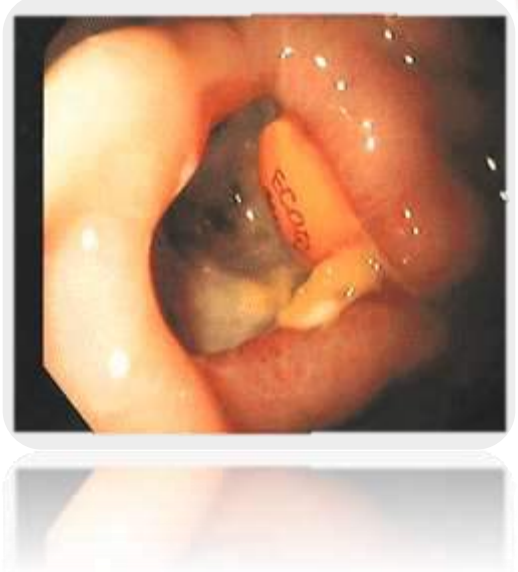
# Acute gastritis

**The most common causes of acute gastritis is the H.Pylori infection**

Acute infection with *H. pylori* induces gastritis. However, *H. pylori* acute gastritis has not been extensively studied. It is reported as presenting with sudden onset of epigastric pain, nausea, and vomiting, and limited mucosal histologic studies demonstrate a marked infiltrate of neutrophils with edema and hyperemia. If not treated, this picture will evolve into one of chronic gastritis.

# Acute gastritis endoscopy





**Therapy**

Antisecretory drugs IV infusion

Endoscopic therapy (argon plasma, etc)

Surgery

# Crhonic gastritis

Chronic gastritis is identified histologically by an inflammatory cell infiltrate consisting primarily of **lymphocytes and plasma cells,** with very scant neutrophil involvement.

Distribution of the inflammation may be patchy, initially **involving superficial and glandular portions of the gastric mucosa**.

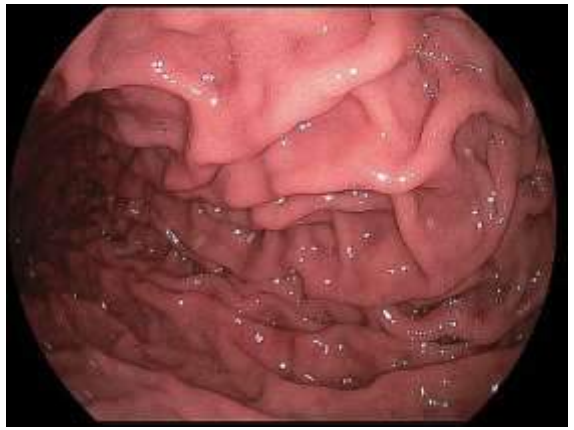
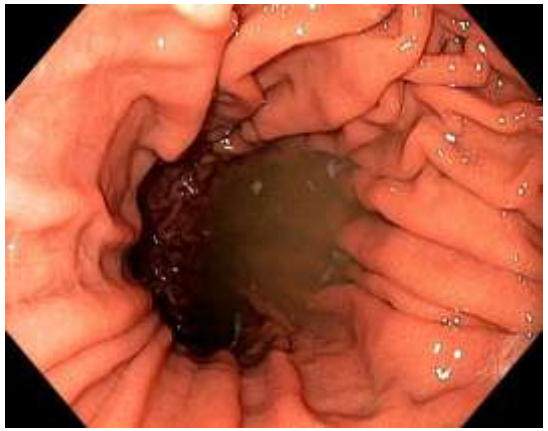
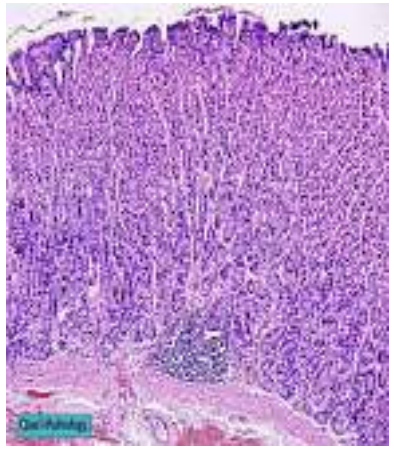
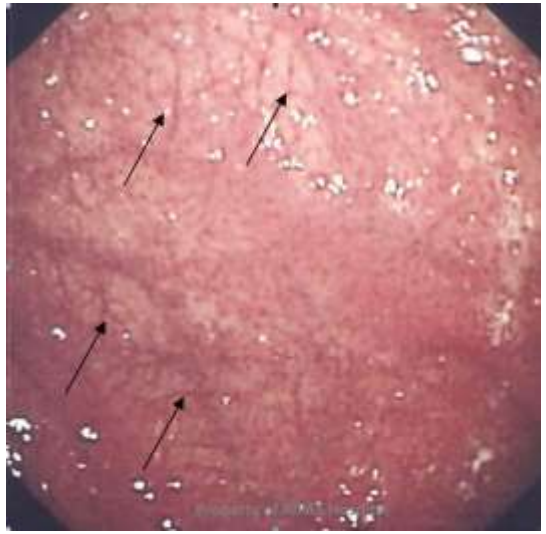
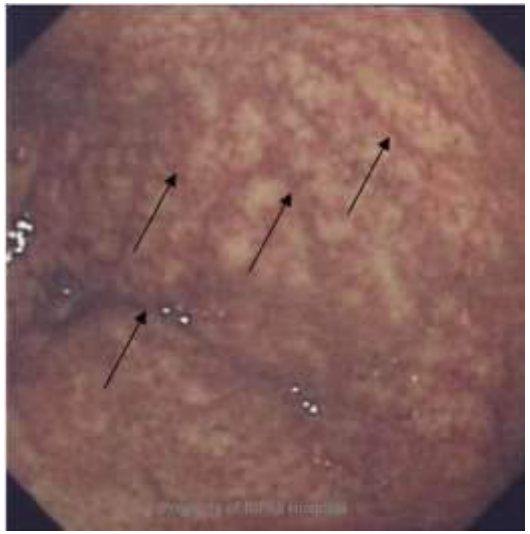
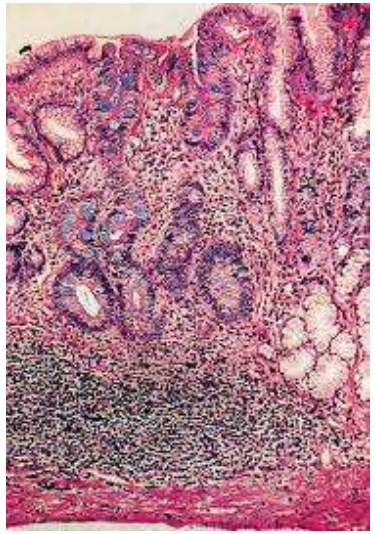
This picture may progress to more severe glandular destruction, with atrophy and metaplasia.

Chronic gastritis has been classified according to histologic characteristics. These include superficial atrophic changes and gastric atrophy.

# Crhonic gastritis

- The early phase of chronic gastritis is ***superficial gastritis***. The inflammatory changes are limited to the lamina propria of the surface mucosa, with edema and cellular infiltrates separating intact gastric glands. Additional findings may include decreased mucus in the mucous cells and decreased mitotic figures in the glandular cells. The next stage is ***atrophic gastritis***.
- The **inflammatory infiltrate extends** deeper into the mucosa, with progressive distortion and destruction of the glands. The final stage of chronic gastritis is ***gastric atrophy***. Glandular structures are lost, and there is a paucity of inflammatory infiltrates.
- Endoscopically, the mucosa may be substantially thin, permitting clear visualization of the underlying blood vessels.

# Chronic gastritis endoscopy

# Type A chronic  gastritis

- The less common of the two forms involves primarily the **fundus and body**, with antral sparing. Traditionally, this form of gastritis has been associated with pernicious anemia  in the presence of circulating antibodies against parietal cells and IF; thus, it is also called ***autoimmune gastritis***.

- **Antibodies to parietal cells** have been detected in >90% of patients with pernicious anemia and in up to 50% of patients with type A gastritis.
- The parietal cell antibody is directed against $H^+$,$K^+$-ATPase. T cells are also implicated in the injury pattern of this form of gastritis.

# Type A chronic gastritis

- Parietal cell antibodies and atrophic gastritis are observed in family members of patients with pernicious anemia.
- These antibodies are observed in up to 20% of individuals over age 60 and in ~20% of patients with **vitiligo and Addison's disease**.
- About half of patients with pernicious anemia have antibodies to thyroid antigens, and about 30% of patients with thyroid disease have circulating antiparietal cell antibodies.
- Anti-IF antibodies are more specific than parietal cell antibodies for type A gastritis, being present in ~40% of patients with pernicious anemia. Another parameter consistent with this form of gastritis being autoimmune in origin is the higher incidence of specific familial histocompatibility haplotypes such as HLA-B8 and -DR3.

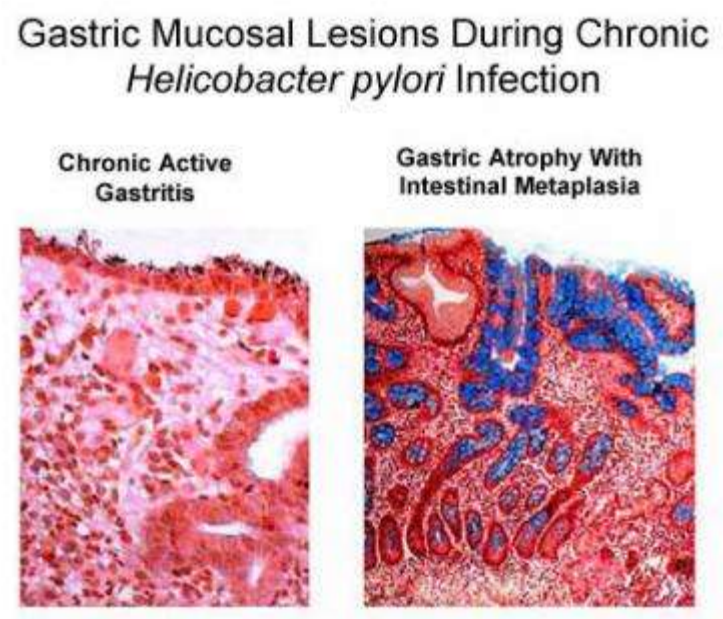
# Type  B gastritis

- **Type B, or antral-predominant, gastritis is the more common form of chronic gastritis. *H. pylori* infection is the cause of this entity. Although described as "antral-predominant,"** this is likely a misnomer in view of studies documenting the progression of the inflammatory process toward the body and fundus of infected individuals.
- The conversion to a pan-gastritis is time-dependent–estimated to require 15–20 years.

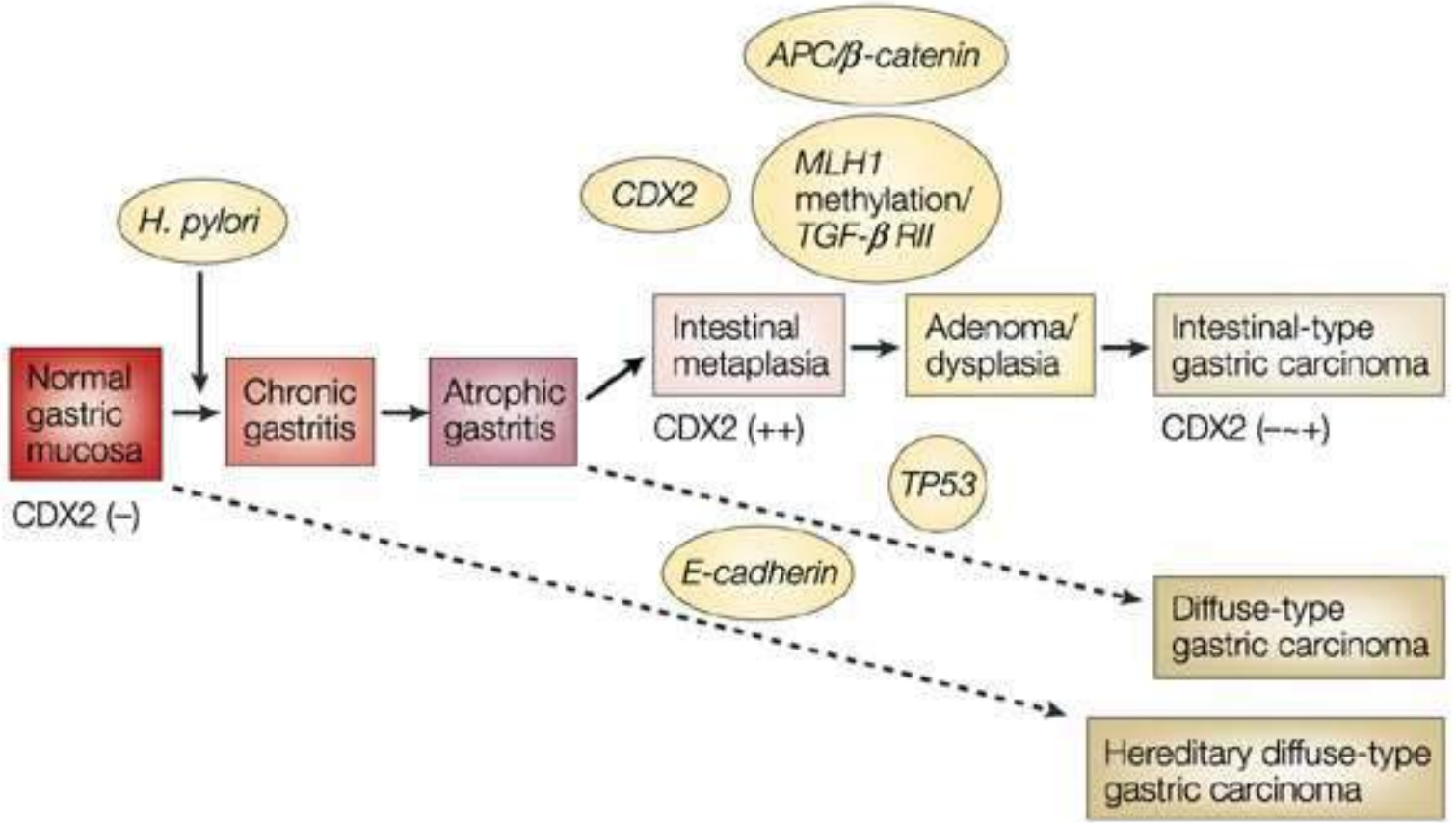
- This form of gastritis increases with age, **being present in up to 100% of persons over age 70.**

# Type B gastritis

- **Histology improves after *H. pylori* eradication**. The number of *H. pylori* organisms decreases dramatically with progression to gastric atrophy, and the degree of inflammation correlates with the level of these organisms.
- Early on, with antral-predominant findings, the quantity of *H. pylori* is highest and a dense chronic inflammatory infiltrate of the lamina propria is noted, accompanied by epithelial cell infiltration with polymorphonuclear leukocytes.



**Progression to intestinal-type gastric cancer.** ***H. pylori*** infection leads to superficial gastritis over a period of weeks. The presence of proinflammatory host polymorphisms and the *H. pylori cag* pathogenicity island increase the risk of developing gastric atrophy, intestinal metaplasia, and gastric adenocarcinoma. Epigenetic inactivation of *E-cadherin* via promoter hypermethylation may also contribute to intestinal-type gastric cancer.



# Chronic gastritis: dysplasia

**TABLE 54-3** Padova International Classification System for Gastric Dysplasia

| Category | Definition | Histologic Description |
|---|---|---|
| I | 1.0 Normal<br>1.1 Reactive foveolar hyperplasia<br><br>1.2 Intestinal metaplasia | 1.0. Normal gastric architecture with absent or minimal inflammatory infiltrates<br>1.1. The general architecture is well preserved, with evidence of hyperproliferative epithelium, enlarged nuclei, and mitotic figures<br>1.2. *Type I.* Closely resembles the morphology of the small intestine, with absorptive enterocytes, well-defined brush borders, and well-formed goblet cells<br>*Type II.* Incomplete metaplasia with irregular mucous vacuoles, absence of brush borders, and difficult-to-identify absorptive enterocytes; cells secrete mainly sialomucins<br>*Type III.* Same as type II, except cells secrete mainly sulfomucins |
| II | Indefinite for dysplasia | Unable to discern whether cells are neoplastic or non-neoplastic; usually found in the setting of inadequate biopsy specimens and presence of architectural distortion and nuclear atypia |
| III | Noninvasive neoplasia | Phenotypically neoplastic epithelium that is confined to glandular structures inside the basement membrane; includes adenomas<br>Should be divided into "low-grade" and "high-grade" |
| IV | Suspicious for invasive cancer | Presence of neoplastic epithelium where invasion cannot be clearly identified |
| V | Invasive cancer | Invasive carcinoma |

*Adapted from Rugge M, Correa P, Dixon M, et al. Gastric dysplasia: The Padova International Classification. Am J Surg Pathol 2000; 24:167-76.*

# Chronic gastritis: treatment

Treatment in chronic gastritis is aimed at the sequelae and not the underlying inflammation. Patients with pernicious anemia will require parenteral vitamin $B_{12}$ supplementation on a long-term basis. **Eradication of *H. pylori* is recommended**

# Gastric cancer

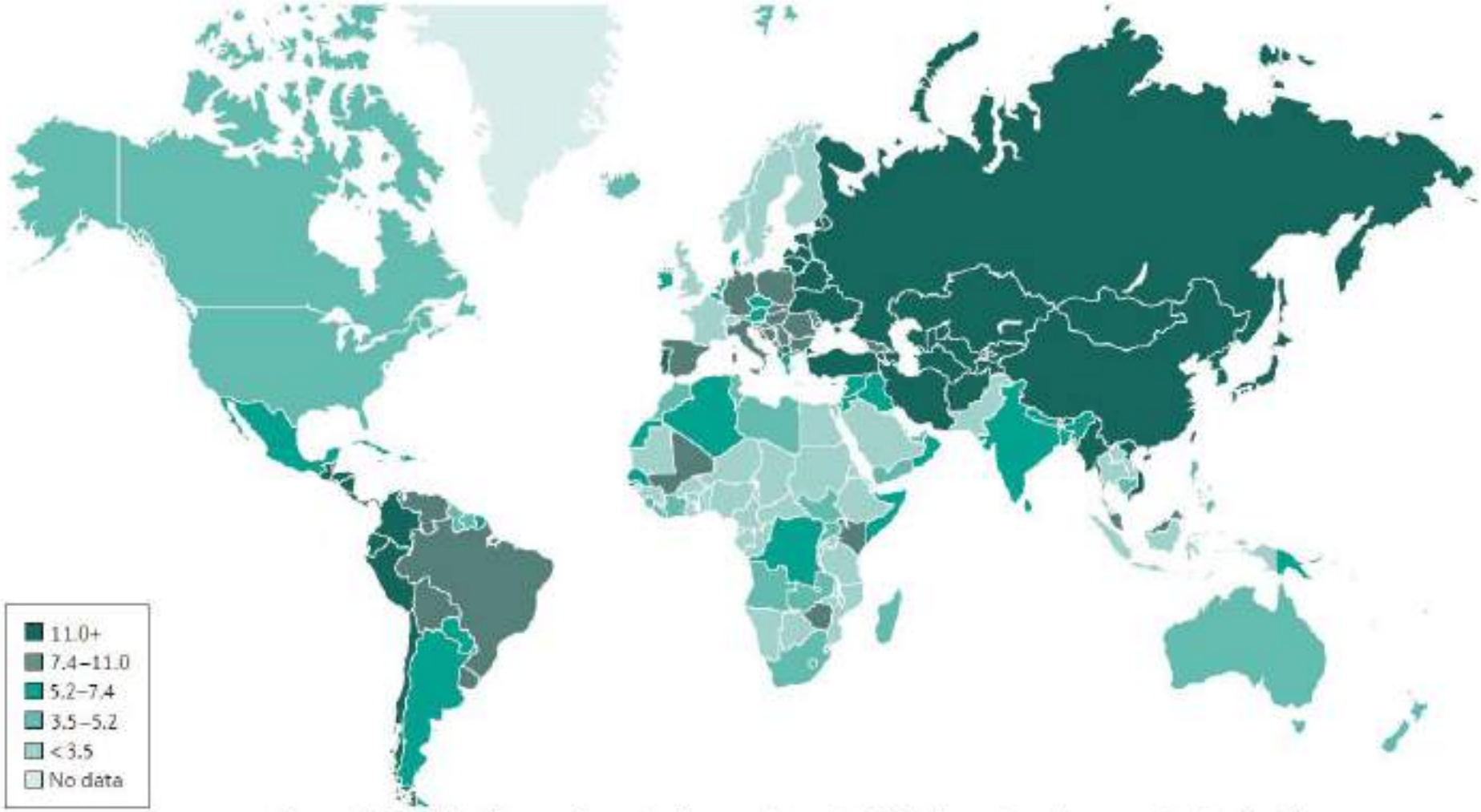



Figure 1 | **Global incidence of gastric adenocarcinoma in 2012.** The estimated age-standardized incidence (per 100,000 population) of gastric adenocarcinoma (GAC; the main type of stomach cancer) is shown for men and women combined. Endemic areas with high rates of GAC include the countries of Eastern Europe, many South

# Gastric cancer

## Pathology

85% of stomach cancers are adenocarcinomas (GAC)

- Familial genetic cancer (3-5%)
- Mesenchymal tumors (GIST)

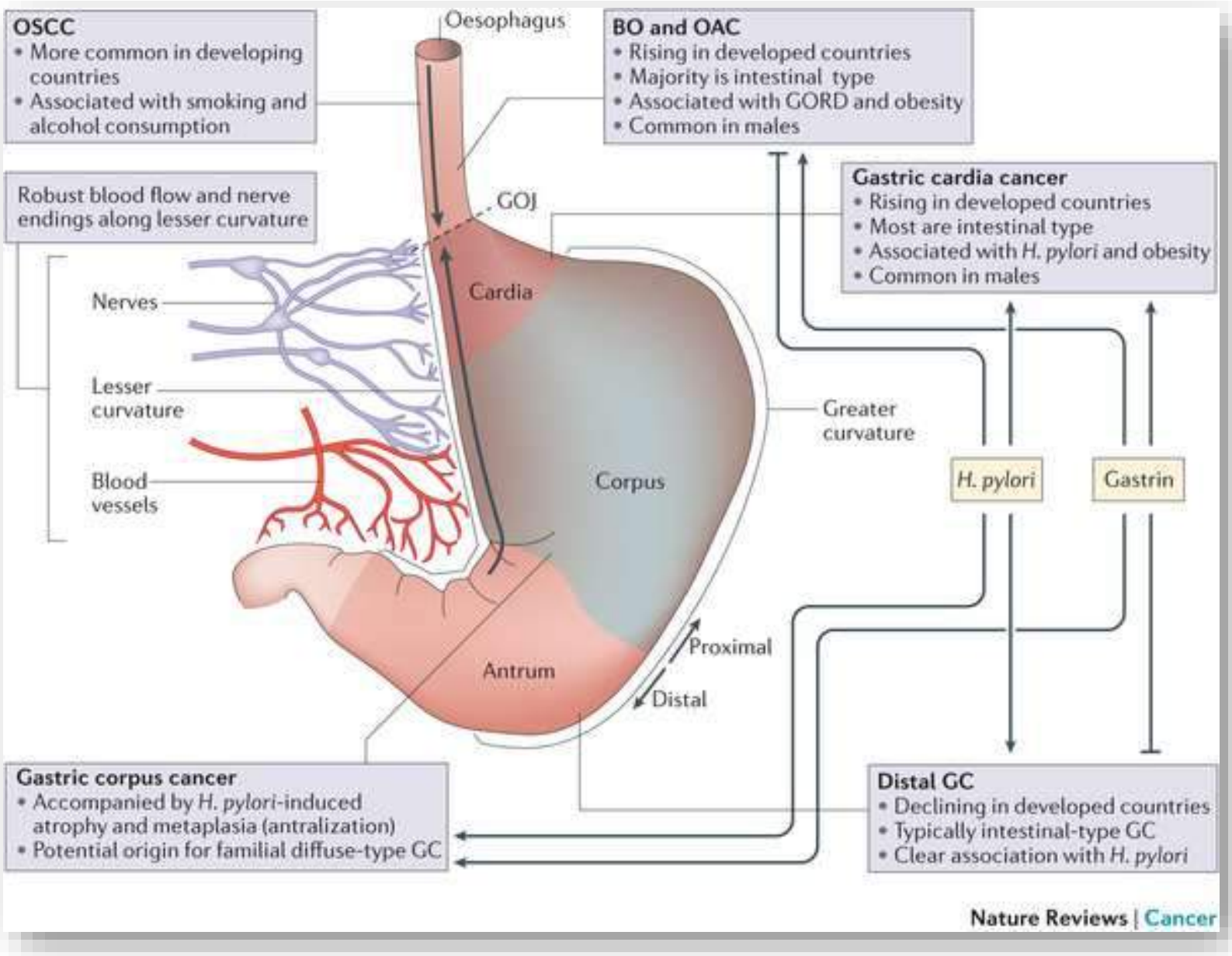
-Lymphoproliferative disorders

-Neuroendocrine tumors

# Gastric adenocarcinoma

- The  incidence and mortality rates for gastric cancer have decreased markedly during the past 75 years. The mortality rate from gastric cancer in the United States has dropped in men from 28 to 5.8 per 100,000 persons, while in women the rate has decreased from 27 to 2.8 per 100,000.
- Nonetheless, 21,260 new cases of stomach cancer were diagnosed in the  Europe with a mortality rate of  11,210  in 2007. **Gastric cancer incidence has decreased worldwide but remains high in Japan, China, Chile, and Ireland.**
- The risk of gastric cancer is greater among lower socioeconomic classes.
- Migrants from high- to low-incidence nations maintain their susceptibility to gastric cancer, while the risk for their offspring approximates that of the new homeland.
- These findings suggest that an environmental exposure, probably beginning early in life, is related to the development of gastric cancer, with dietary carcinogens considered the most likely factor(s).

# Gastric and esophageal cancers

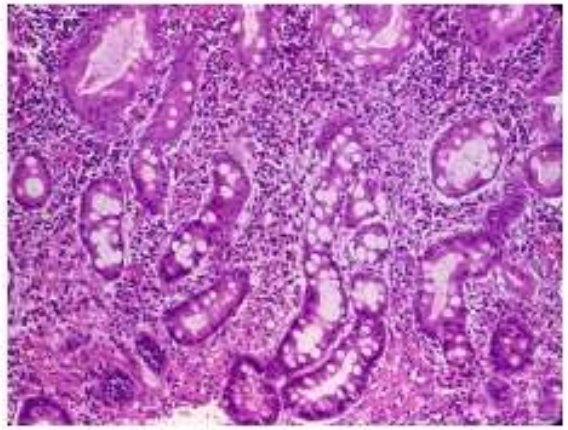


# Gastric adenocarcinoma

**Pathology.**

Gastric adenocarcinomas may be subdivided into two categories: a ***diffuse type***, 50%of cases, in which cell cohesion is absent, so that individual cells infiltrate and thicken the stomach wall without forming a discrete mass; and an ***intestinal type***, 34%, characterized by cohesive neoplastic cells that form glandlike tubular structures.

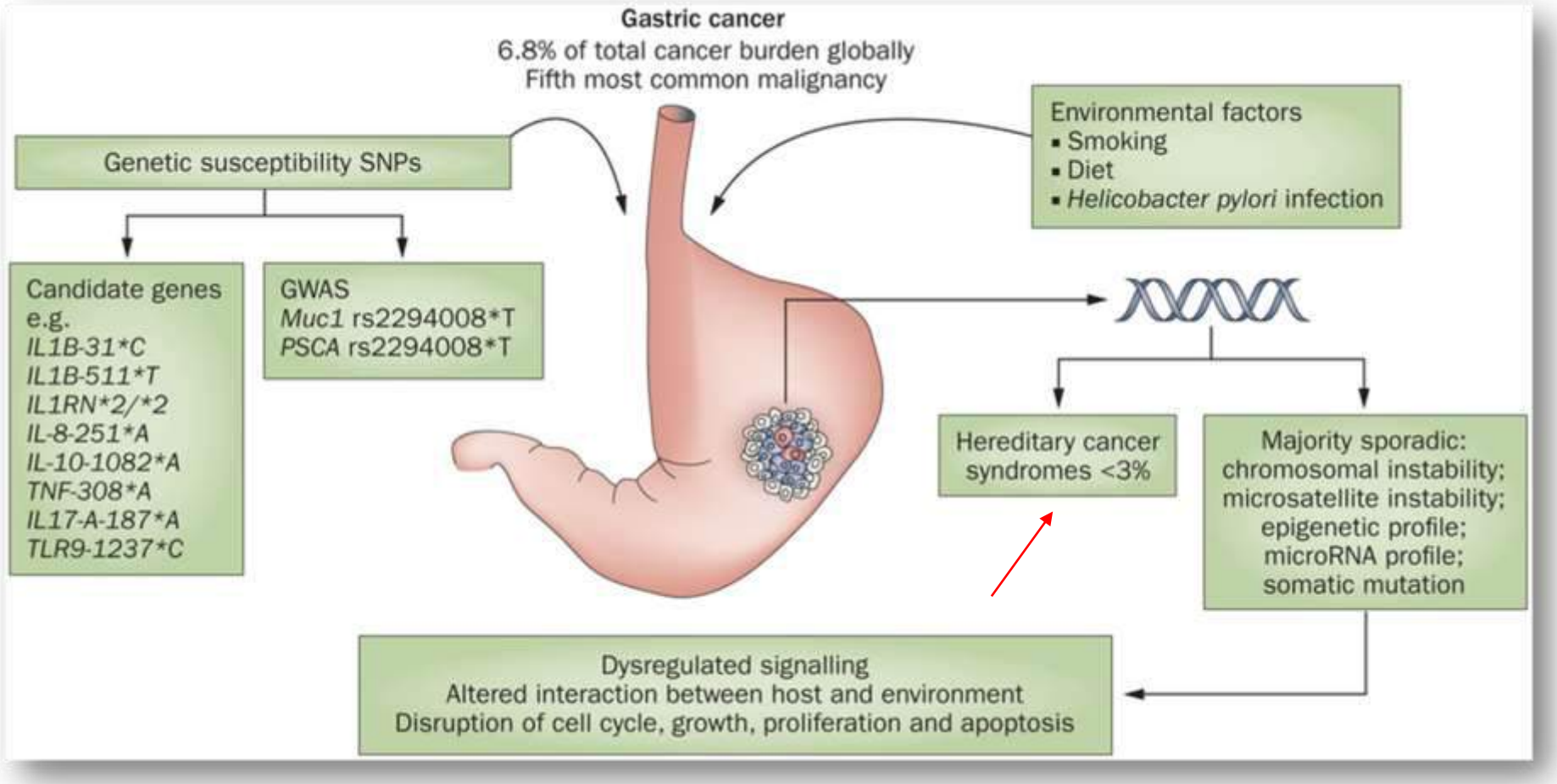
***Unclassified,15%***



# Gastric adenocarcinoma

- The intestinal type (H. pylori +) associates with chronic atrofic gastritis, intestinal metaplasia and dysplasia, less aggressive
- The diffuse type of gastric adenocarcinoma occurs in younger patients

# Gastric cancer: genetic




AJ Bass *et al. Nature* **000**, 1-8 (2014) doi:10.1038/nature13480

# Gastric cancer: genetic

Most gastric cancers are sporadic, but 5% to 10% of cases have a family history of gastric cancer.

**Hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and familial intestinal gastric cancer (FIGC) are three major syndromes accounting up to 3% to 5% of hereditary familial gastric cancer. Other hereditary cancer syndromes are:**

- Hereditary non-polyposis colon cancer (HNPCC 13% lifetime risk, predominantly intestinal type)
- Familial adenomatous syndrome (FAP, 10% risk)
- Peutz Jeghers syndrome (PJS, 29% risk)
- Juvenile polyposis syndrome (JPS, 21%)
- Li-Fraumeni syndrome
- Hereditary breast and ovarian cancer syndrome
- Phosphatase and tensin homolog (PTEN) or hamartoma tumor (Cowden's) syndrome.

# Gastric cancer: genetic

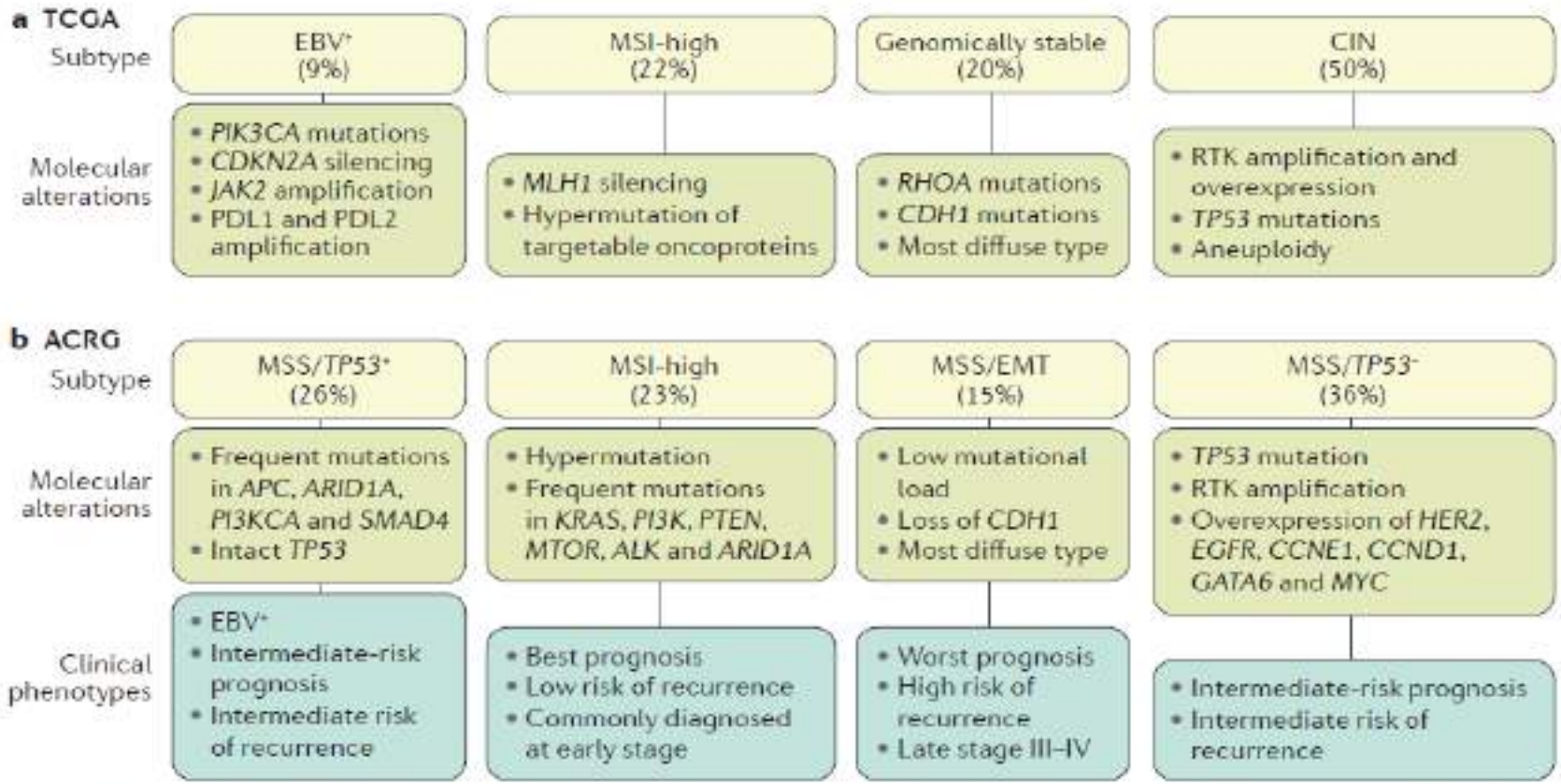



Figure 4 | **Molecular classification of gastric adenocarcinoma. a** | The Cancer Genome Atlas (TCGA) Research Network analysis identified four molecular subtypes of gastric adenocarcinoma (GAC) — Epstein–Barr virus-positive (EBV+) tumours; microsatellite instability (MSI)-high tumours; genomically stable tumours; and tumours with chromosomal instability (CIN) — based on 295 primary GACs analysed using six platforms: copy number variations, whole-exome sequencing, DNA methylation, RNA sequencing, microRNA sequencing and reverse-phase protein array. Each subtype has its unique molecular alterations as indicated. **b** | The Asian Cancer Research Group (ACRG) identified four subtypes of GAC based on gene expression in 300 primary GACs from a single institution: tumours that are microsatellite stable and have intact *TP53* (MSS/*TP53*+); MSI-high; microsatellite stable and expressing epithelial–mesenchymal transition signatures (MSS/EMT) and microsatellite stable and have *TP53* mutations (MSS/*TP53*−). The ACRG subtyping also provided useful clinical information as indicated. These two classifications have some similarity and may guide novel target therapies to improve unsatisfactory outcomes, although neither have been validated as clinically relevant tools as yet.

# Gastric cancer: genetic

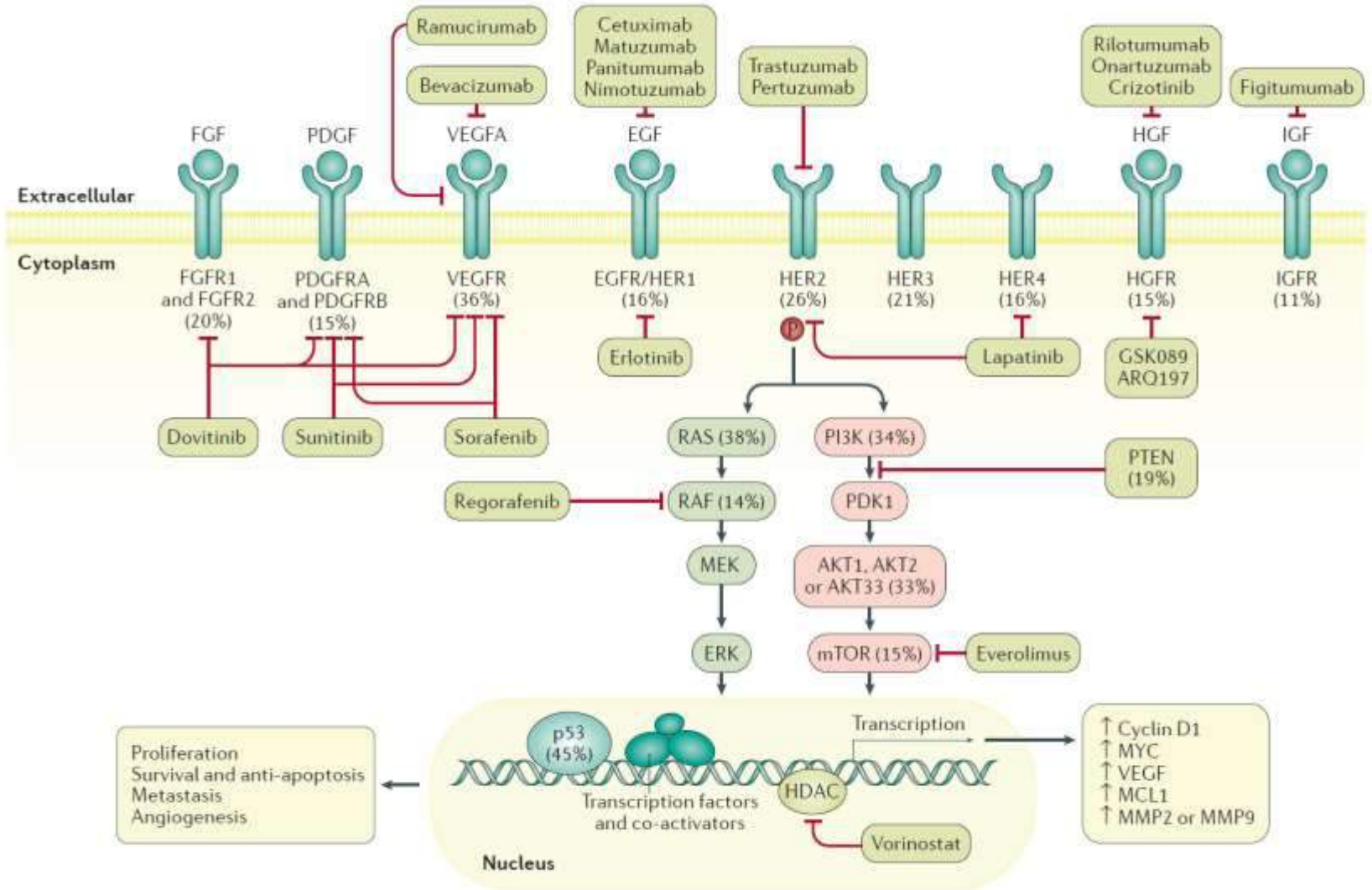



Figure 5 | **Molecular alterations in receptor tyrosine kinases and *TP53* and potential target therapy in gastric**

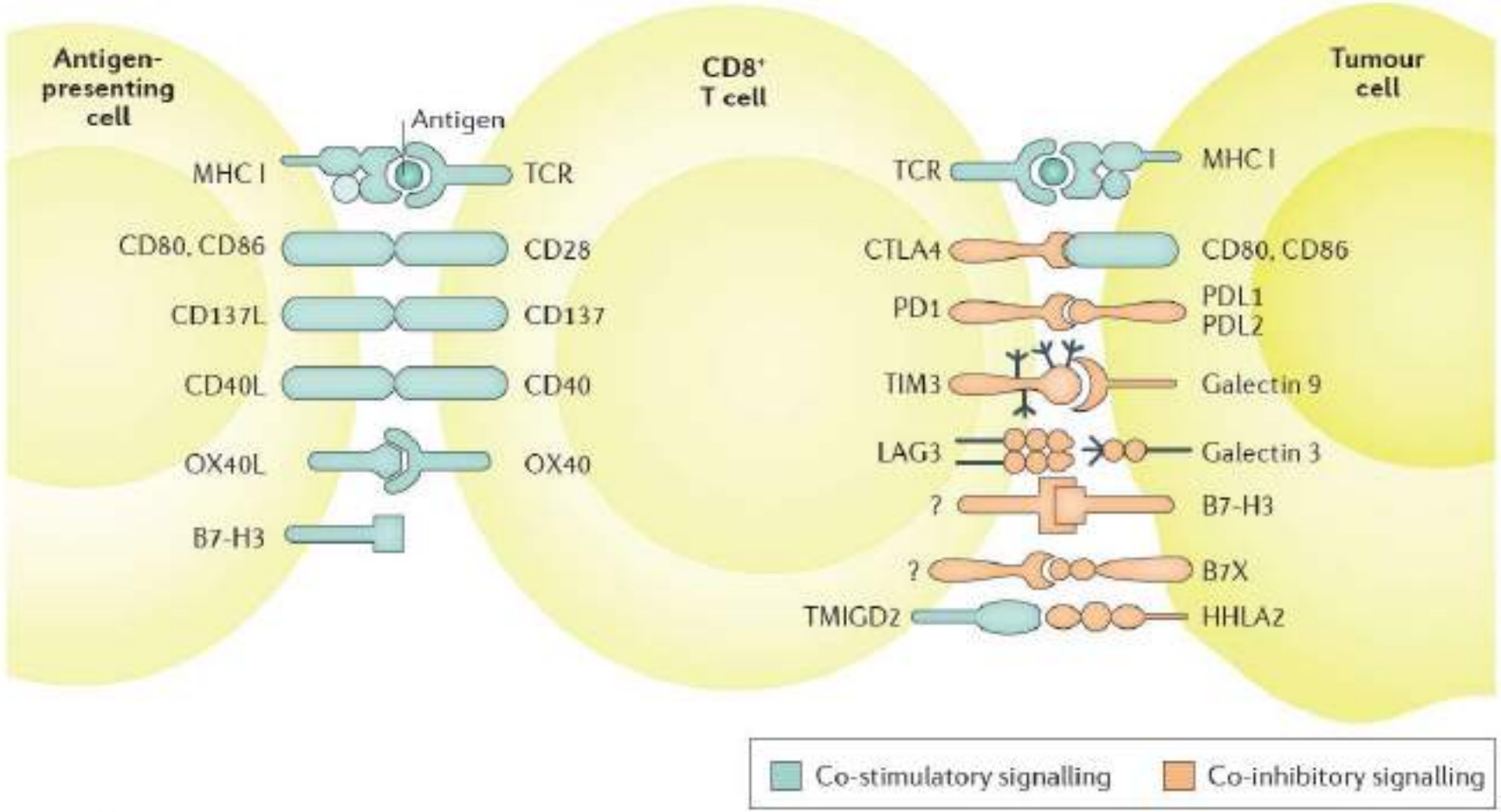



Figure 7 | **Adaptive T cell response controlled by co-stimulatory and co-inhibitory signalling in the tumour microenvironment.** T cell-mediated adaptive tumour immune responses are controlled by co-stimulatory and co-inhibitory signalling. For example, enhanced expression of inhibitory checkpoint proteins (including programmed cell death 1 ligand 1 (PDL1), PDL2, programmed cell death 1 (PD1) and cytotoxic T lymphocyte protein 4 (CTLA4)) by tumour cells is a common feature in gastric adenocarcinoma, protecting the cancer from T cell destruction. Immune checkpoint therapy targets

# Gastric adenocarcinoma: risck factors

**BOX 54-1 Risk Factors for Gastric Adenocarcinoma**

**Definite**
Hp infection
Chronic atrophic gastritis
Intestinal metaplasia
Dysplasia*
Adenomatous gastric polyps*
Cigarette smoking
History of gastric surgery (esp. Billroth II)*
Genetic factors:
- Family history of gastric cancer (first-degree relative)*
- Familial adenomatous polyposis (with fundic gland polyps)*
- Hereditary nonpolyposis colorectal cancer*
- Peutz-Jeghers syndrome*
- Juvenile polyposis*

**Probable**
High salt intake
Obesity (adenocarcinoma of the cardia only)
Snuff tobacco use
History of gastric ulcer
Pernicious anemia*
Regular aspirin or other NSAID use (protective)

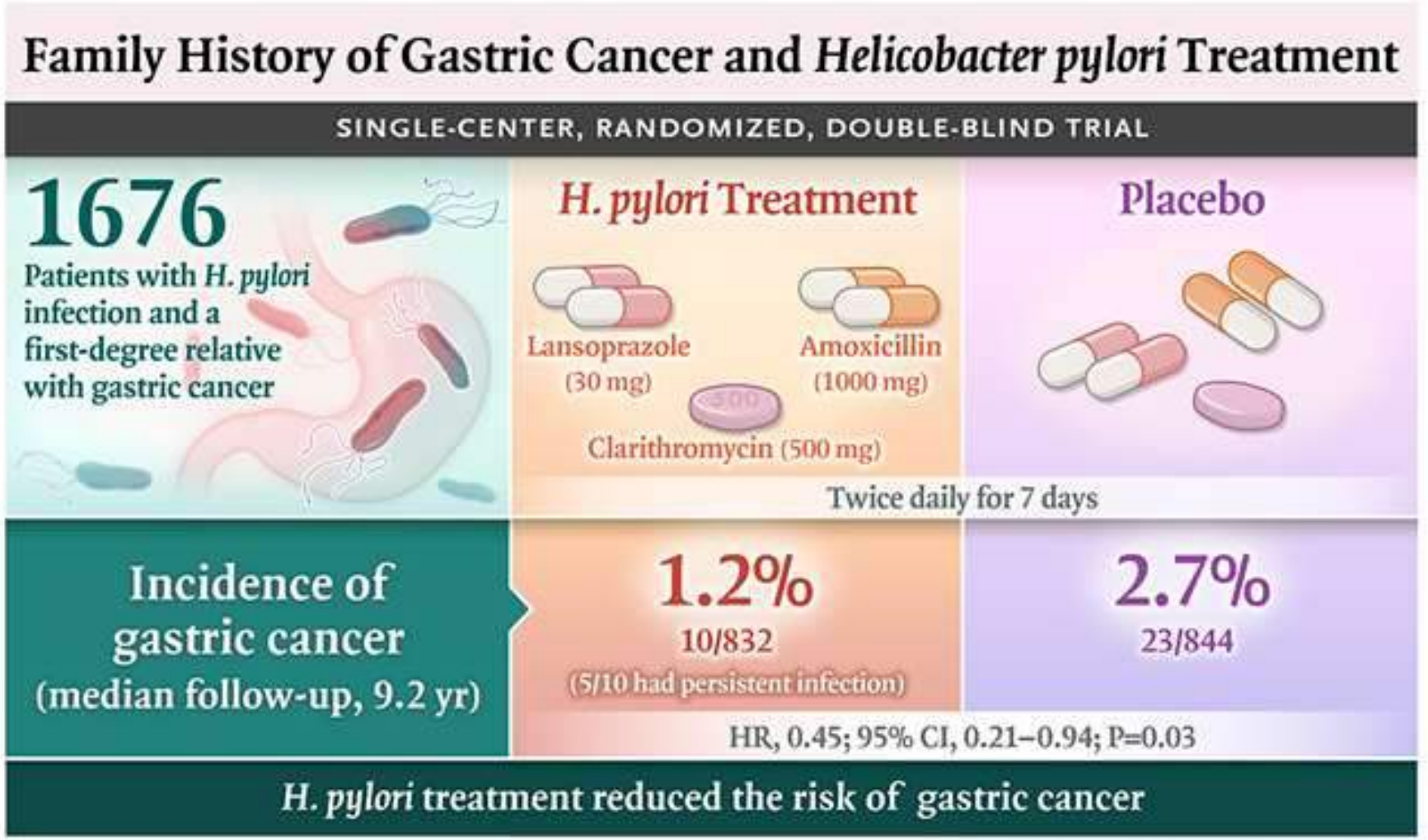
**Possible**
Statin use (protective)
Heavy alcohol use
Low socioeconomic status
Ménétrier's disease
High intake of fresh fruits and vegetables (protective)
High ascorbate intake (protective)

**Questionable**
Hyperplastic and fundic gland polyps
Diet high in nitrates
High green tea consumption (protective)

*Surveillance for cancer is recommended in patients with this risk factor.

# Gastric adenocarcinoma and H. pylori

The NEW ENGLAND JOURNAL of MEDICINE




I.J. Choi et al. 10.1056/NEJMoa1909666

# Gastric adenocarcinoma

## Clinical Features

- **Gastric cancers, when superficial and surgically curable, usually produce no symptoms.**
- As the tumor becomes more extensive, patients may complain of an insidious **upper abdominal discomfort varying in intensity from a vague**, postprandial fullness to a severe, **steady pain**.
- **Anorexia**, often with slight nausea, is very common but is not the usual presenting complaint.
- **Weight loss** may eventually be observed, and nausea and vomiting are particularly prominent with tumors of the pylorus;
- **Dysphagia** and early satiety may be the major symptoms caused by diffuse lesions originating in the cardia.

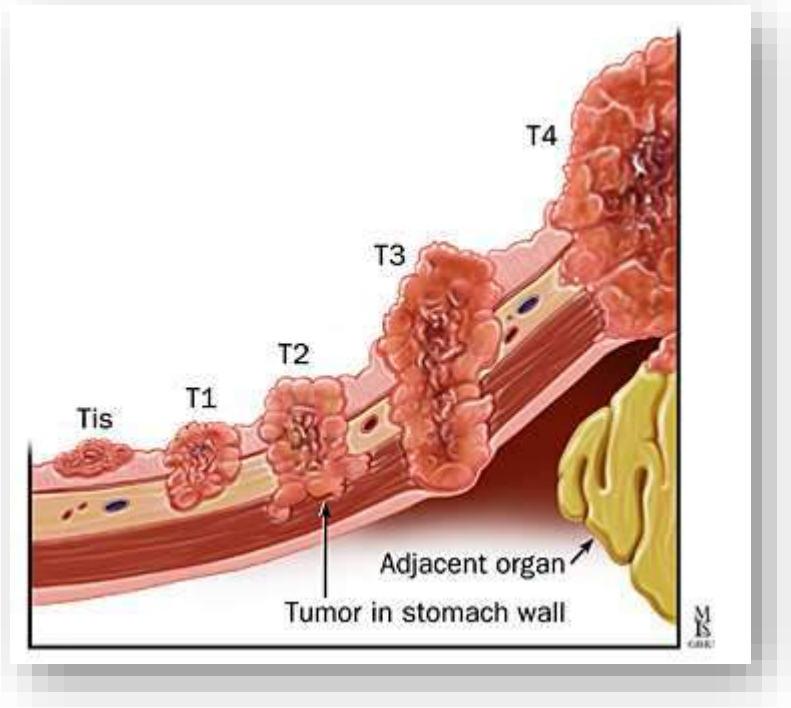
# Gastric adenocarcinoma

## Clinical Features

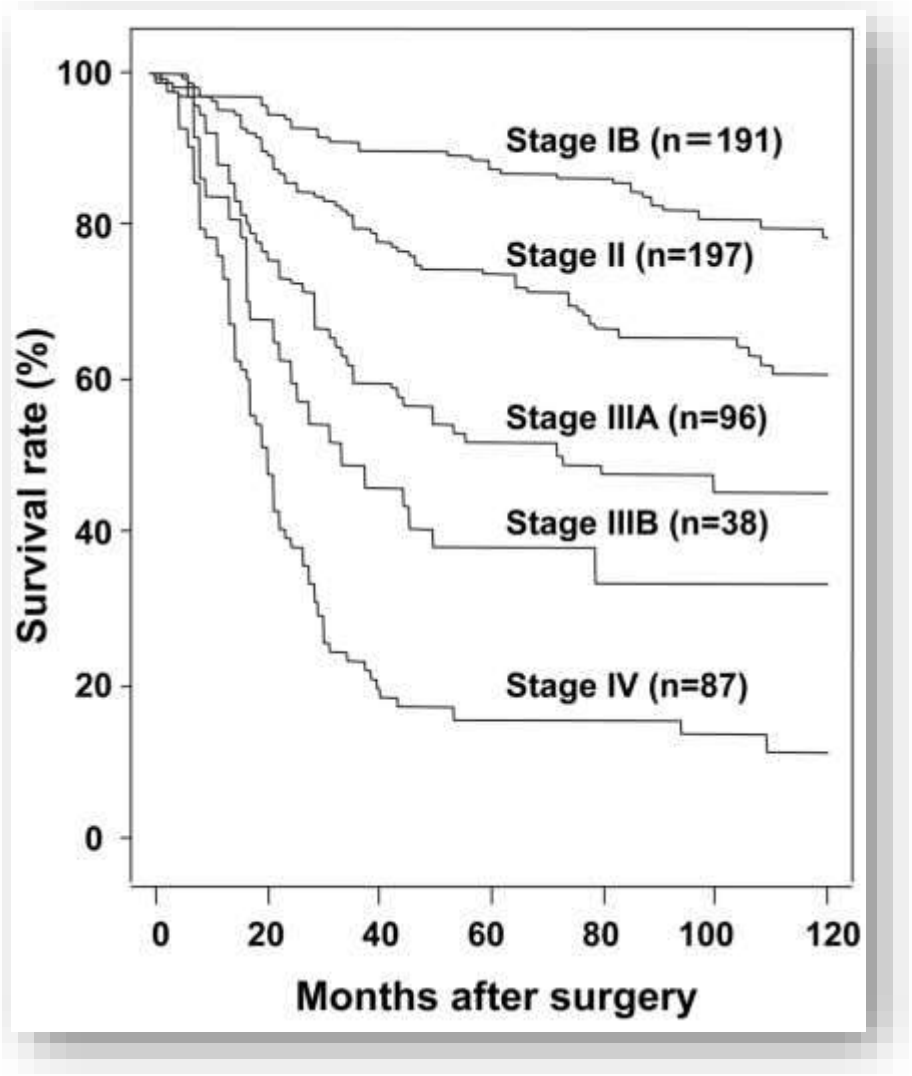
- **Weight loss** may eventually be observed, and nausea and vomiting are particularly prominent with tumors of the pylorus;
- **Dysphagia** and early satiety may be the major symptoms caused by diffuse lesions originating in the cardia.
- There are no early physical signs. A **palpable abdominal mass** indicates long-standing growth and predicts regional extension.
- The presence of **iron-deficiency anemia** in men and of occult blood in the stool in both sexes mandates a search for an occult gastrointestinal tract lesion.

# Gastric cancer staging

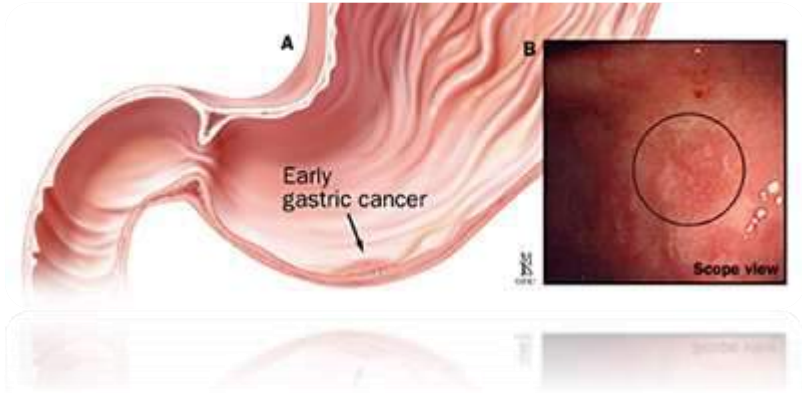
| Stage | Description |
|---|---|
| **T Stage** | |
| Tis | Carcinoma in situ; intraepithelial tumor without invasion of the lamina propria |
| T1 | Tumor invades lamina propria, muscularis mucosa, or submucosa. |
| T1a | Tumor invades lamina propria or muscularis mucosa. |
| T1b | Tumor invades submucosa. |
| T2 | Tumor invades the muscularis propria. |
| T3 | Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures. |
| T4 | Tumor invades serosa (visceral peritoneum) or adjacent structures. |
| T4a | Tumor invades serosa (visceral peritoneum). |
| T4b | Tumor invades adjacent structures.* |
| **N Stage** | |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in 1 to 6 regional nodes |
| N2 | Metastasis in 7 to 15 regional nodes |
| N3 | Metastasis in more than 15 regional nodes |
| **M Stage** | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

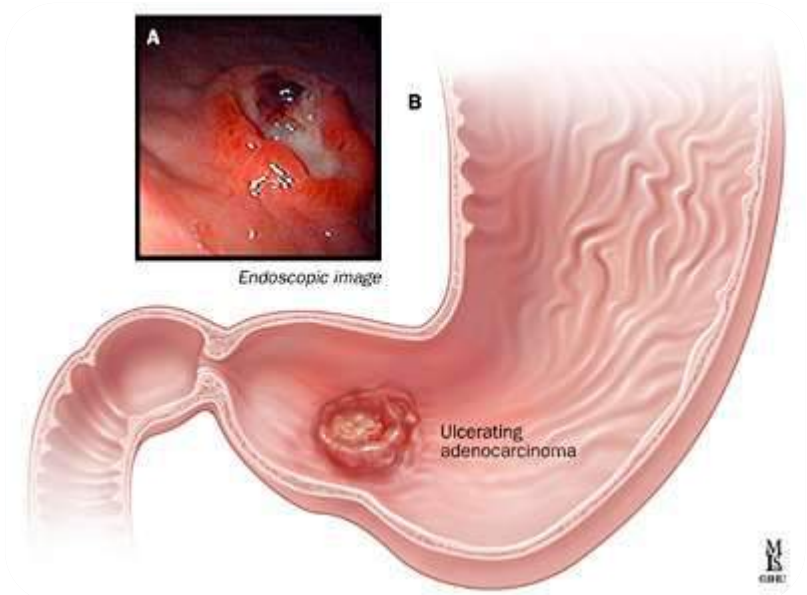


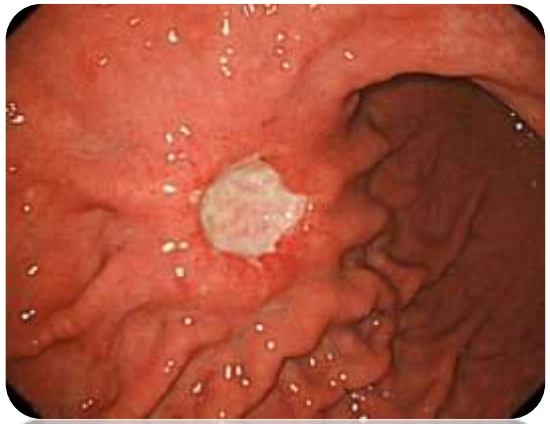
# Gastric cancer: outcome

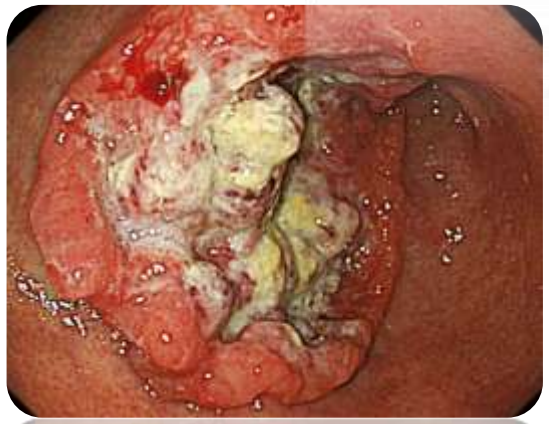


# Gastric cancer endoscopy

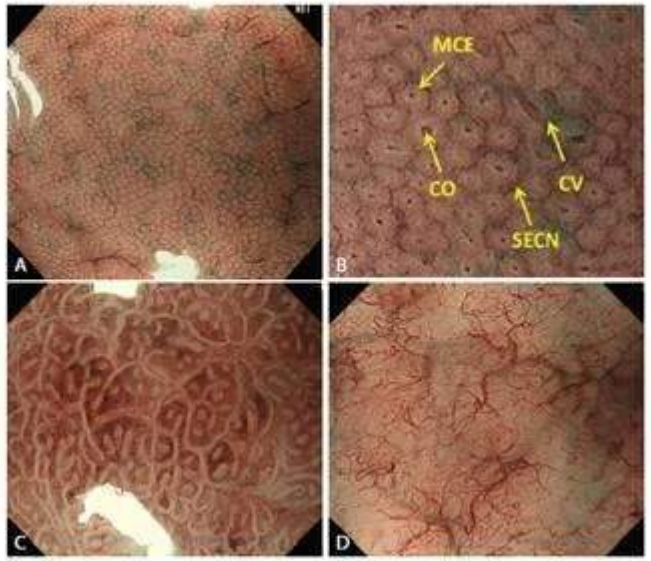


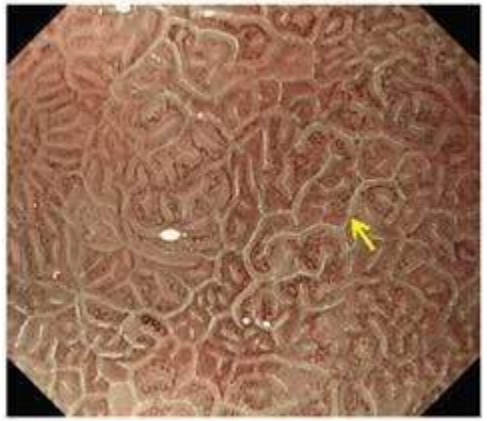



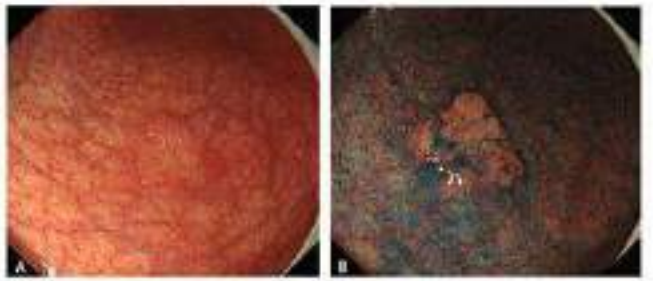





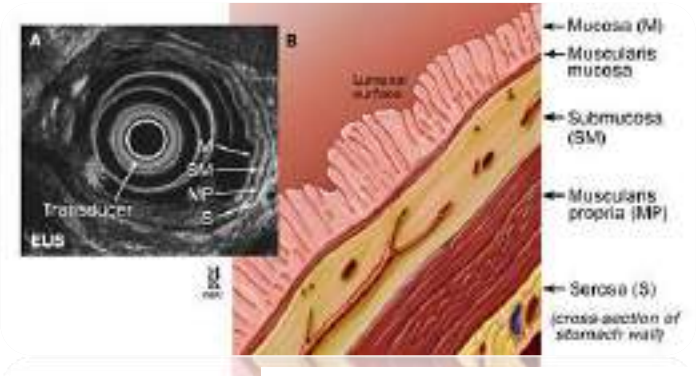
# Gastric cancer endoscopic magnification and chromoendoscopy





# Gastric acancer:  ecoendoscopy



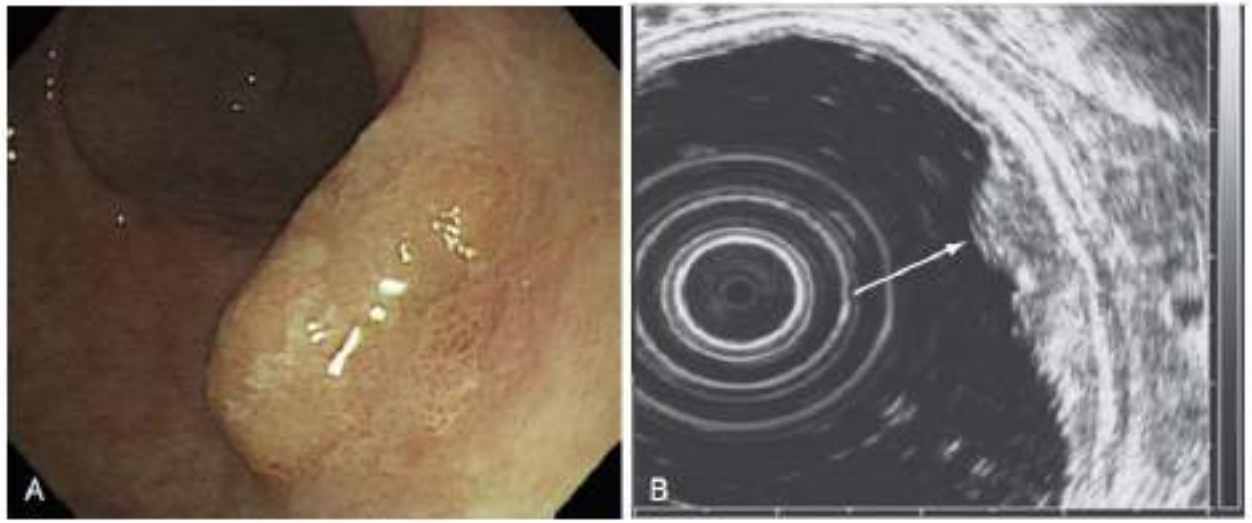



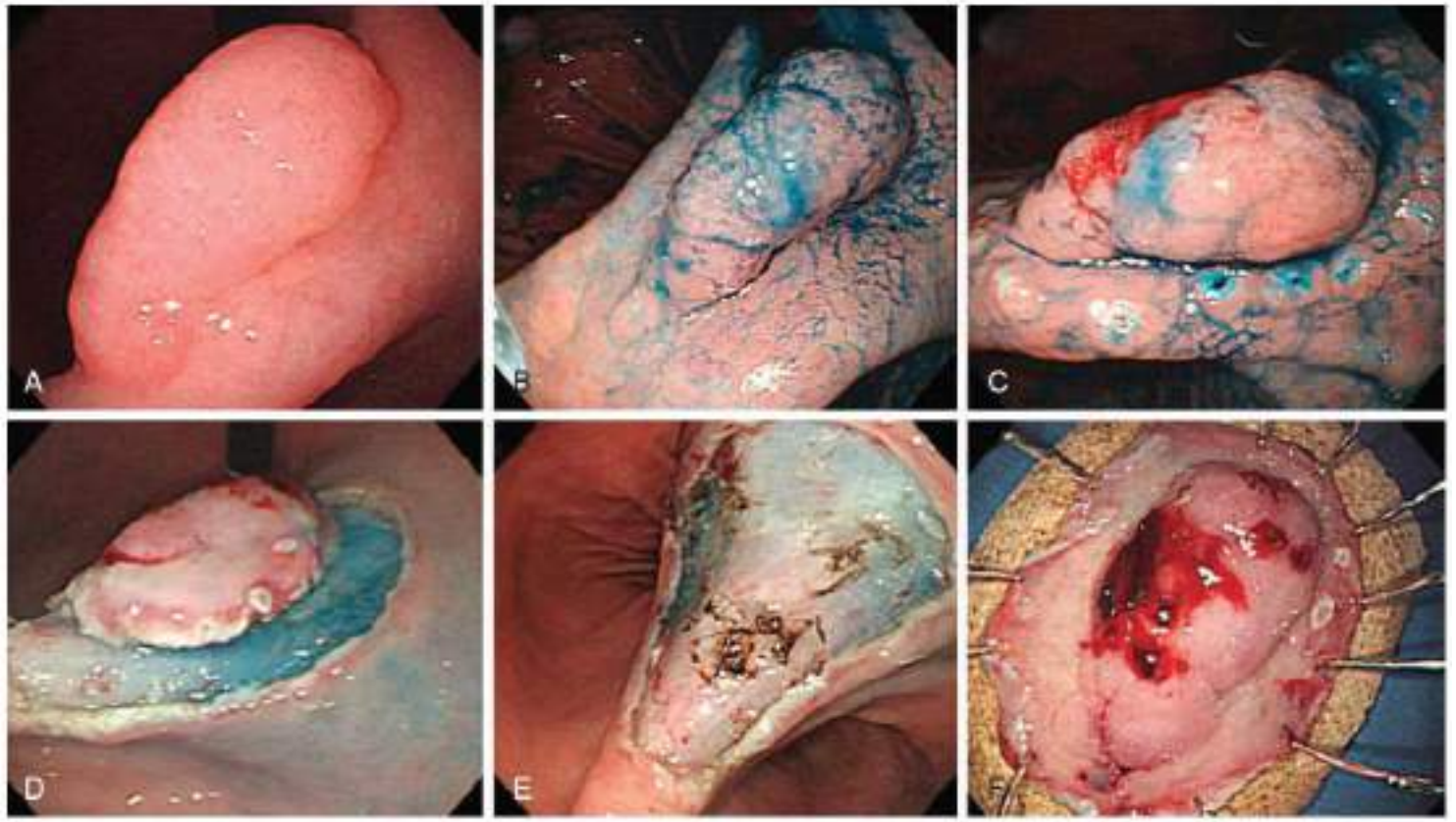

FIGURE 54-8. Gastric cancer staging. *A*, Endoscopic image of an early gastric cancer showing a 25-mm protruding mass located on the posterior wall of the antrum. *B*, EUS image of the lesion, showing the hypoechoic mucosal mass *(arrow)* with an intact submucosal layer. *(From Kim JH, Song KS, Youn YH, et al. Clinicopathologic factors influence accurate endosonographic assessment for early gastric cancer. Gastrointest Endosc 2007; 66:901-8.)*

# Gastric cancer endoscopic resection

Endoscopic resection either by endoscopic mucosal resection or endoscopic submucosal resection is offered to select patients **with early gastric cancer with negative lymph nodes who meet selection criteria at centers of expertise**.

Standard selection criteria have a high- probability of en bloc resection, intestinal type adenocarcinoma confined to the mucosa/submucosal, and absent venous or lymphatic invasion and tumors with diameters less than 20 mm without ulceration or 10 mm nonpolypoid flat or depressed lesions. Expanded criteria are under active investigation.
**Ten percent of mucosal and 20% of submucosal lesions will have lymph node metastasis and should be investigated carefully.**

# Gastric cancer: endoscopic mucosal resection



# Gastric cancer endoscopic resection

**If prior criteria are not met, or an incomplete resection is performed, patients are referred for gastrectomy with regional lymph node resection.**

Successful endoscopic resection may offer a 5-year overall survival of 84% to 96% depending on the depth of the tumor compared to gastrectomy survival rates up to 98%, but no randomized trials have compared both.

Synchronous or metachronous gastric cancers can be found within 5 years in up to 9.2% of patients. *H. pylori* have been associated with metachronous gastric lesions and eradication is recommended.

# Gastric cancer surgery

Patients with localized, resectable gastric cancer have the best chance of long-term survival with surgery alone.

**The main goal of surgery is complete resection with adequate margins (more than 4 cm), and only 50% of patients will obtain R0.**

**Unresectability criteria are an invasion of major vasculature structure (aorta, hepatic artery, celiac axis or proximal splenic artery), bulky adenopathy outside the surgical field and the presence of linitis plastica; although, the latter is debatable.**

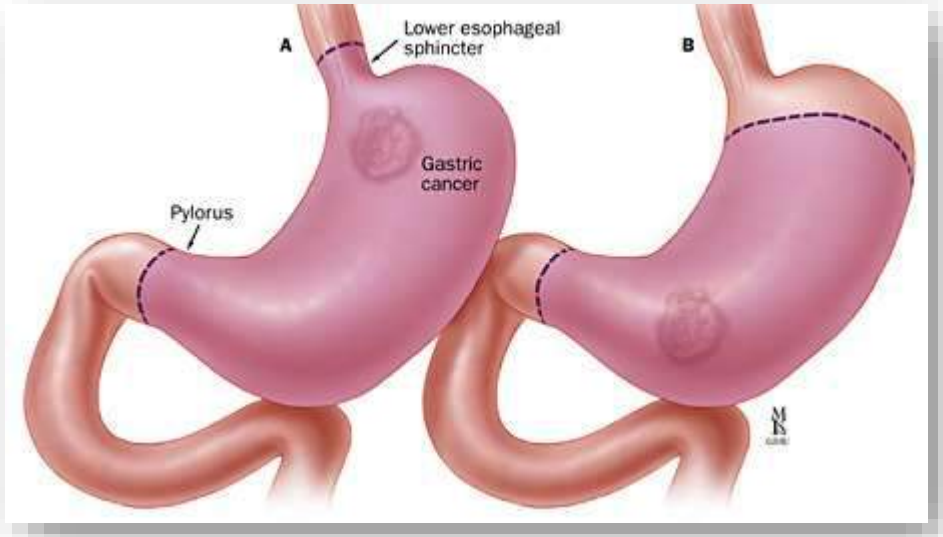
# Gastric cancer surgery

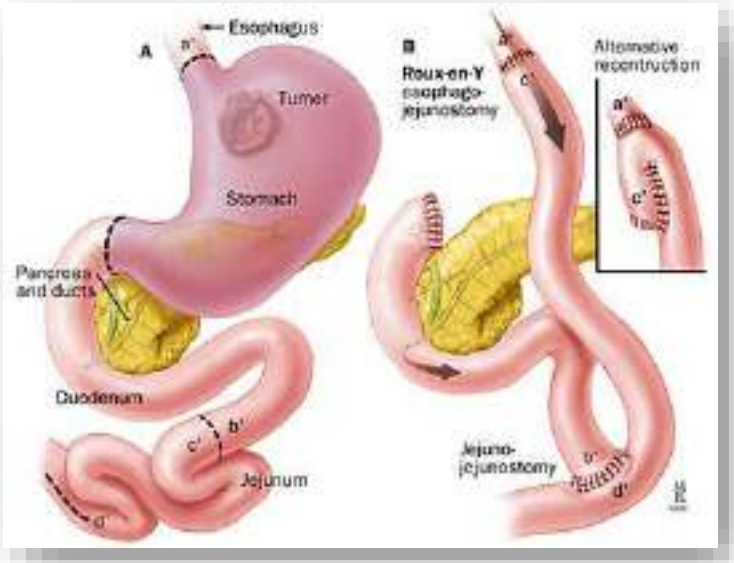
Most surgeons prefer total gastrectomy, but technique depends on location with proximal lesions requiring total resection and some distal lesions partial resection.
Large mid-gastric lesions or diffuse disease should be offered total gastrectomy.

Routine or prophylactic splenectomy should be avoided.

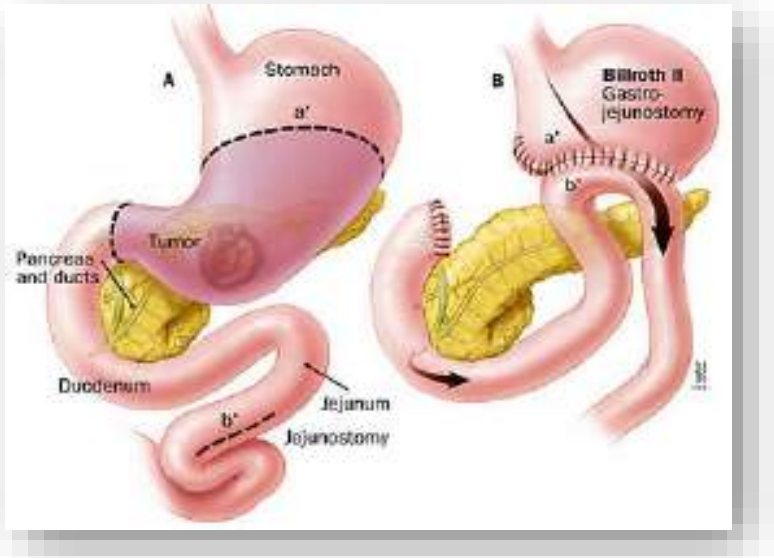
Standard surgical techniques  includes D2 resection (meticulous resection of all regional lymph nodes) which differs from the conservative type of lymphadenectomy  which carries a less operative morbidity and mortality (standard D1 resection, removal of only perigastric lymph nodes).

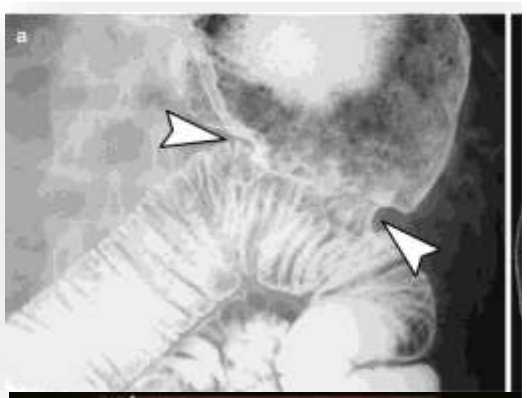
# Gastric cancer surgery
# total gastrectomy

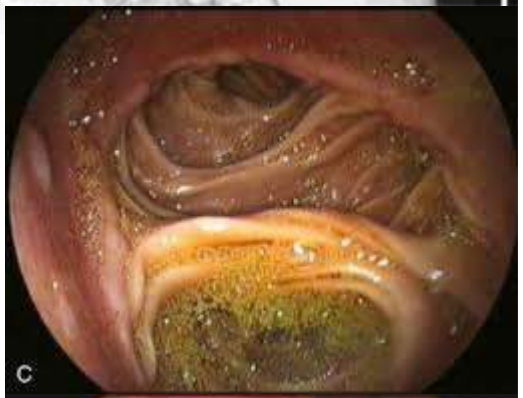


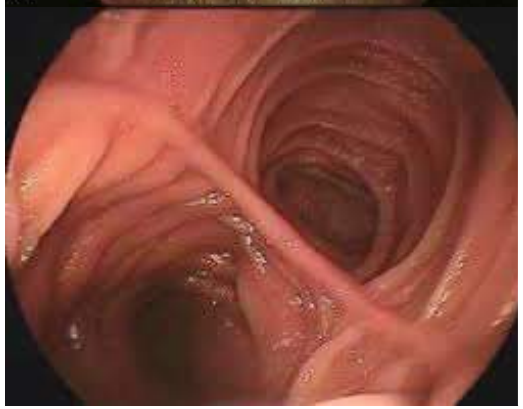



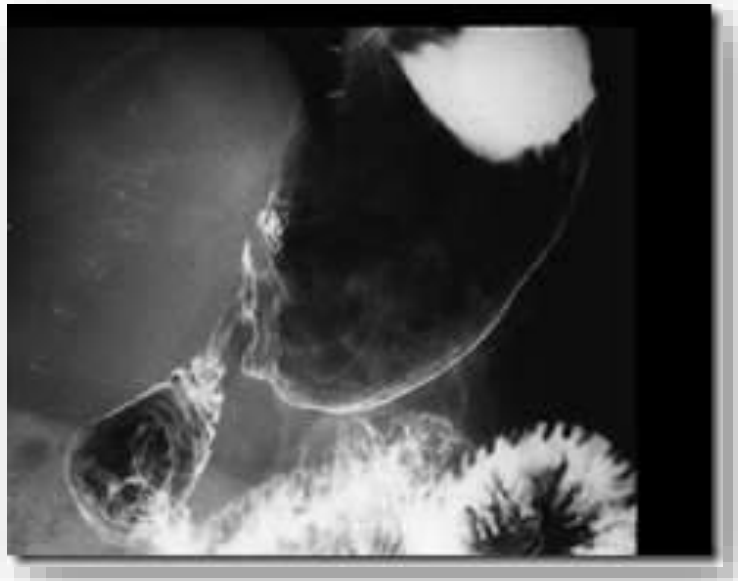
# Gastric cancer surgery: BI and BII





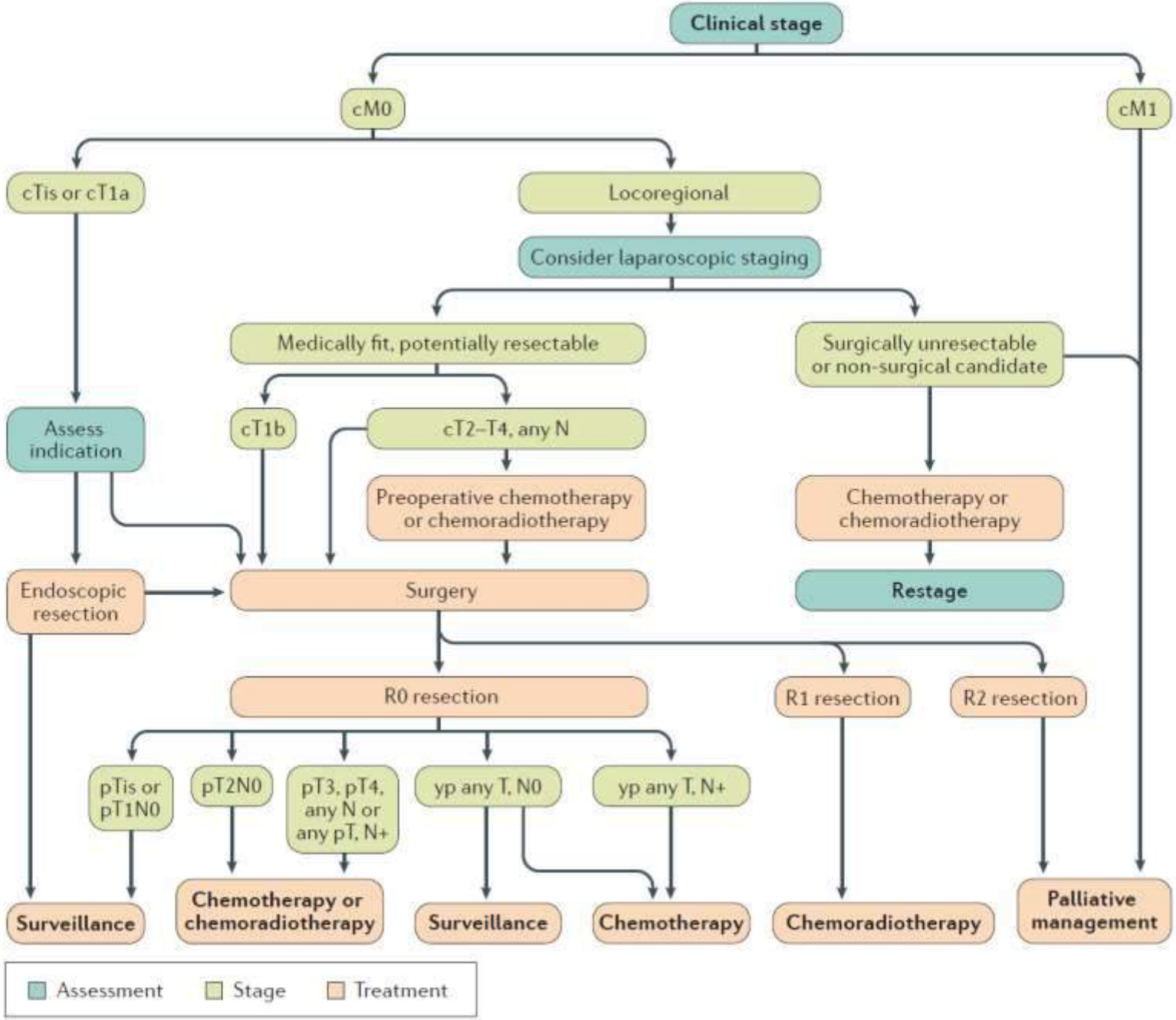



Figure 9 | **A representative treatment algorithm for gastric adenocarcinoma.** The schematic shown here is derived

# Gastric adenocarcinoma Chemotherapy

ADENOCARCINOMA of the stomach is relatively sensitive to chemotherapy

- Fluorouracil (5-FU) is the most commonly used drug in the treatment of gastric cancer with a response rate around 21%.
- In an attempt to improve this rate, drug combinations have been tried; the most common is 5-FU, doxorubicin, and mitomycin C (FAM) with a response rate of 33% and an acceptable degree of toxicity .

# Gastric adenocarcinoma
# Chemotherapy

## Neoadjuvant and Adjuvant Therapy for Locally Advanced Resectable Disease

Surgical resection alone is potentially curative but only in early gastric cancer stages as seen in long-term survival rates on reported 5-year overall survival.
It significantly declines from 75% for stage I to 35% for stage II and 25% or less for stage III, pushing research efforts to improve results using neoadjuvant (preoperative) or adjuvant (postoperative) therapies.

Neoadjuvant chemotherapy has been shown to downstage primary tumors and regional lymph nodes to attempt higher long-term curative resections.
**Neoadjuvant therapy should be offered to patients at high risk of developing distant metastases (bulky T3/T4, perigastric nodes, linitis plastica, or positive peritoneal cytology) sparing unnecessary surgery in case an emerging metastasis appears**

# Gastric adenocarcinoma Chemotherapy

Antibodies targeting the EGFR, a member of the *HER* family of receptor tyrosine kinases, such as cetuximab (EXPAND trial) and panitumumab (REAL-3 trial), have also been added to a chemotherap backbone (CX and EOC, respectively) in gastroesophageal adenocarcinoma with worse toxicit profile and a detrimental effect on overall survival. The consistently negative data from two large phase III trials confirmed that cetuximab and panitumumab cannot be recommended in the first-line therapy advanced gastroesophageal adenocarcinoma.

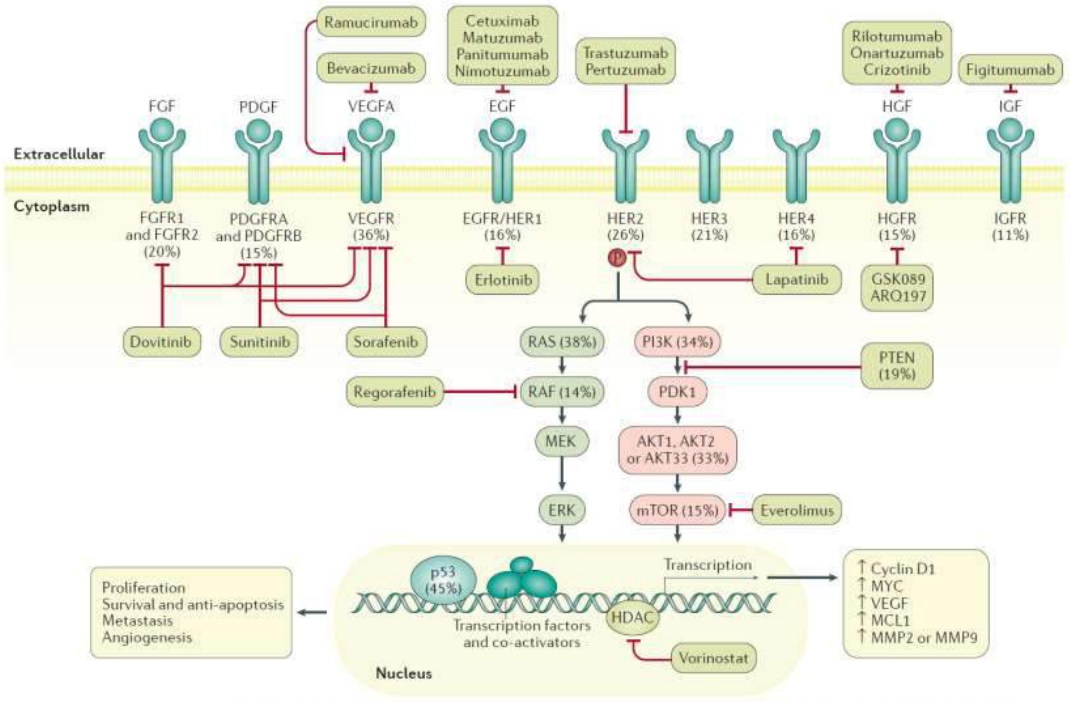



Figure 5 | **Molecular alterations in receptor tyrosine kinases and *TP53* and potential target therapy in gastric**

# Gastric adenocarcinoma
# Immune checkpoint inhibitor

Table 2 - Overview of immune checkpoint inhibitor trials in gastric cancer.

| Study | Number of Patients | Treatment | Setting | Response Rate (Complete Response Rate) - % | Disease Control Rate - % | Progression-free Survival - Months | Overall Survival - Months | Treatment-related Grade 3-4 Toxicity - % |
|---|---|---|---|---|---|---|---|---|
| Ralph C, et al. (26) | 18 | Tremelimumab 15 mg/kg every 3 months | Metastatic Second-line | 5.6 (0) | 22.2 | 2.8 | 4.8 | - |
| Bang Y-J, et al. (27) | 114 | Ipilimumab 10 mg/kg every 3 weeks for 4 doses, then every 12 weeks | Maintenance after first line | 1.8 (0) | 33.4 | 2.7 | 12.7 | 22.8 |
| | | Placebo | | 7.0 (0) | 47.4 | 4.9 | 12.1 | 8.9 |
| KEYNOTE-012 (17) | 39 | Pembrolizumab 10 mg/kg every 2 weeks | Metastatic Previously treated (85%) | 22.0 (0) | 36.1 | 1.9 | 11.4 | 13 |
| KEYNOTE-059 (18) Cohort 1 | 259 | Pembrolizumab 200 mg every 3 weeks | Metastatic 2+ lines of treatment | 12 (3) | 27 | 2.0 | 5.5 | 18 |
| KEYNOTE-059 (18) Cohort 2 | 25 | Pembrolizumab (200 mg every 3 weeks) + CDDP + fluoropyrimidine | Metastatic Treatment-naive | 60 (4) | 80 | 6.6 | 13.8 | 16 |
| KEYNOTE-059 (18) Cohort 3 | 31 | Pembrolizumab 200 mg every 3 weeks | Metastatic Treatment-naive | 26 (7) | 36 | 3.3 | 20.7 | 23 |
| Segal NH, et al. (38) | 28 | Durvalumab 10 mg/kg every 2 weeks | Previously treated | 7.0 (-) | 25.0 | - | - | - |
| JAVELIN (23) | 62 | Avelumab 10 mg/kg every 2 weeks | Metastatic Second-line | 9.7 (0) | 29 | 1.5 | - | 9.9 |
| JAVELIN (23) | 89 | Avelumab 10 mg/kg every 2 weeks | Metastatic Maintenance | 8.9 (2.2) | 57.3 | 3.0 | - | 9.9 |
| CheckMate-032 (20) Group 1 | 59 | Nivolumab 3 mg/kg every 2 weeks | Metastatic Previously treated (100%) | 12 (2) | 32 | 1.4 | 6.2 | 17 |
| CheckMate-032 (20) Group 2 | 49 | Nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks | Metastatic Previously treated (98%) | 22 (2) | 41 | 1.4 | 6.9 | 47 |
| CheckMate-032 (20) Group 3 | 52 | Nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks | Metastatic Previously treated (100%) | 8 (0) | 37 | 1.6 | 4.8 | 27 |
| ATTRACTION-2 (21) | 493 | Nivolumab 3 mg/kg every 2 weeks | Metastatic 2+ lines of treatment | 11 (0) | 40.3 | 1.6 | 5.2 | 10 |
| ATTRACTION-2 (21) | 493 | Placebo | | 0 (0) | 25.0 | 1.4 | 4.1 | 4 |
| KEYNOTE-061 (25) | 592 | Pembrolizumab 200 mg every 3 weeks | | 16 (4)[§] | - | 1.5 | 9.1 | 14 |
| | | Paditaxel (weekly) | | 14 (3) | - | 4.1 | 8.3 | 35 |
| JAVELIN 300 (24) | 371 | Avelumab 10 mg/kg every 2 weeks | Metastatic | 2.2 (0.5) | 22.2 | 1.4 | 4.6 | 9.2 |
| | | Chemoterapy[#] | Third-line (86%) | 4.3 (0.5) | 44.1 | 2.7 | 5.0 | 31.6 |

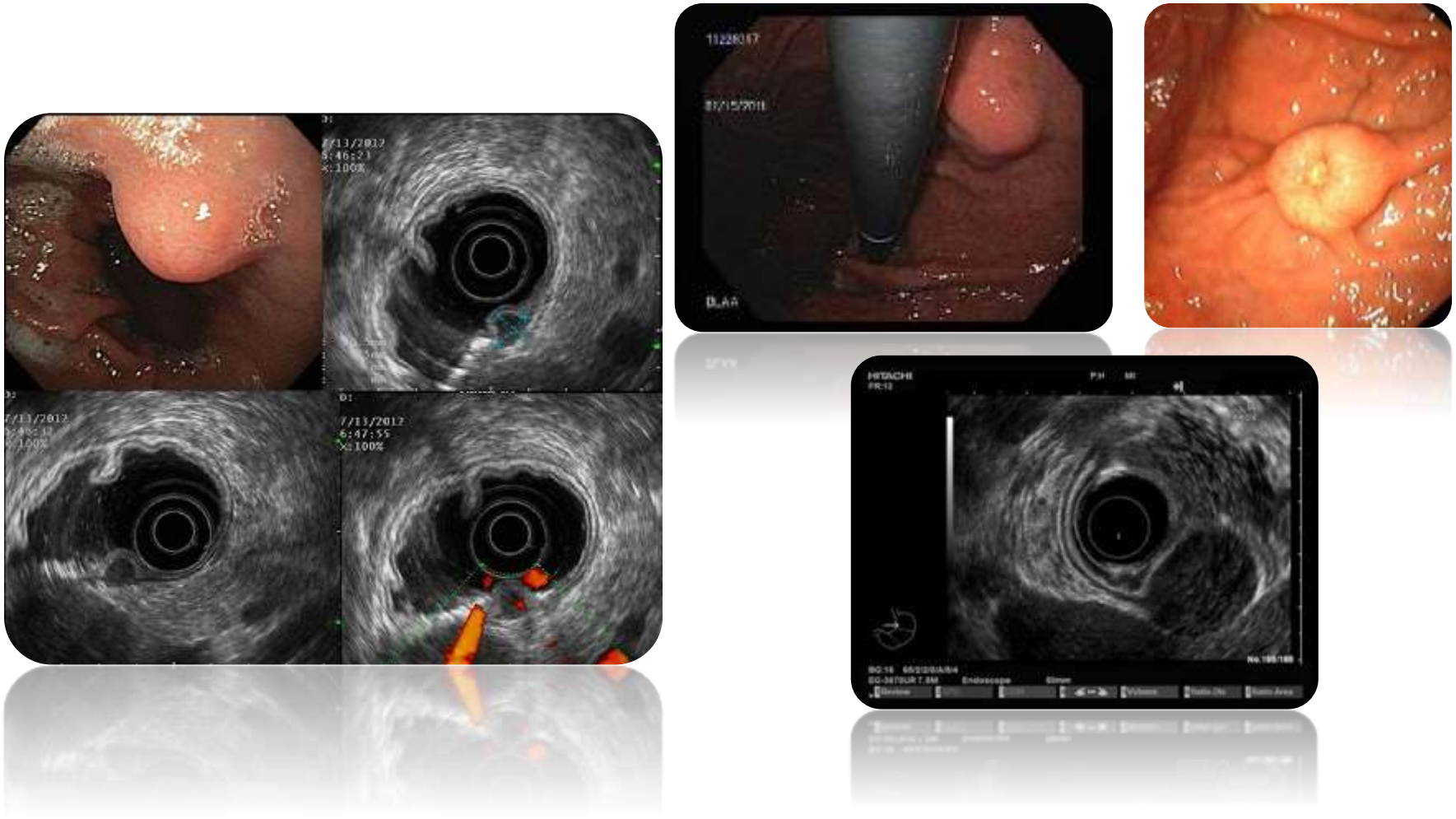
[#] Physicians' choice of chemotherapy (either paclitaxel or irinotecan).
[§] Combined positive score (CPS) ≥ 1%

# GIST

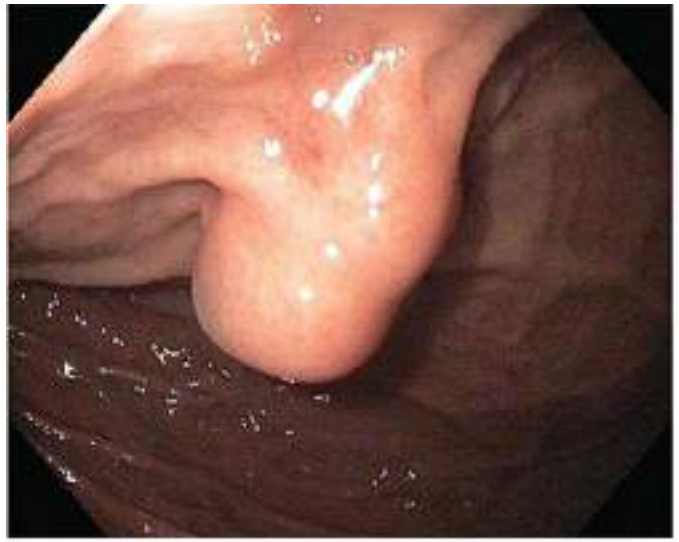
## Gastrointestinal stromal tumors (GISTs)

- GISTs make up 1–3% of gastric neoplasms.
- They most frequently involve the anterior and posterior walls of the gastric fundus and often ulcerate and bleed. Even those lesions that appear benign on histologic examination may behave in a malignant fashion.
- These tumors rarely invade adjacent viscera and characteristically do not metastasize to lymph nodes, but they may spread to the liver and lungs.
- The treatment of choice is surgical resection. Combination chemotherapy should be reserved for patients with metastatic disease. All such tumors should be analyzed for a mutation in the **c-*kit* receptor**. GISTs are unresponsive to conventional chemotherapy; ~50% of patients experience objective response and prolonged survival when treated with **imatinib mesylate (Gleevec)** (400–800 mg PO daily), a selective inhibitor of the c-*kit* tyrosine kinase.
- Many patients with GIST whose tumors have become refractory to imatinib subsequently benefit from sunitinib (Sutent), another inhibitor of the c-*kit* tyrosine kinase.

# GIST ecoendoscopy



# GIST endoscopic removal



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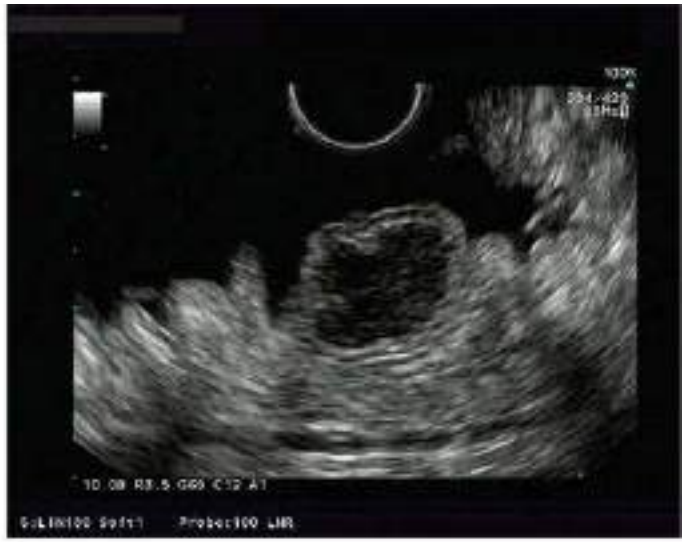

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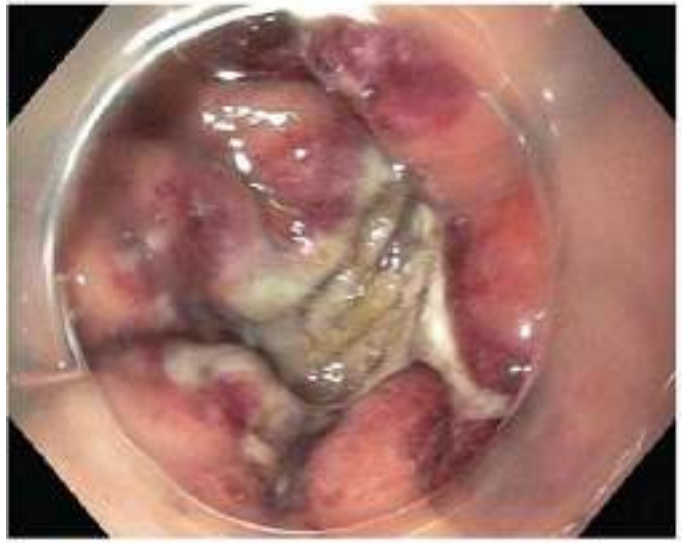

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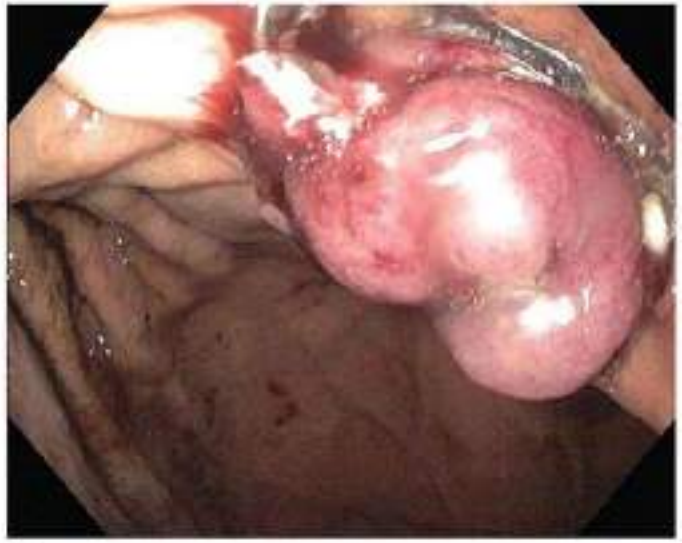
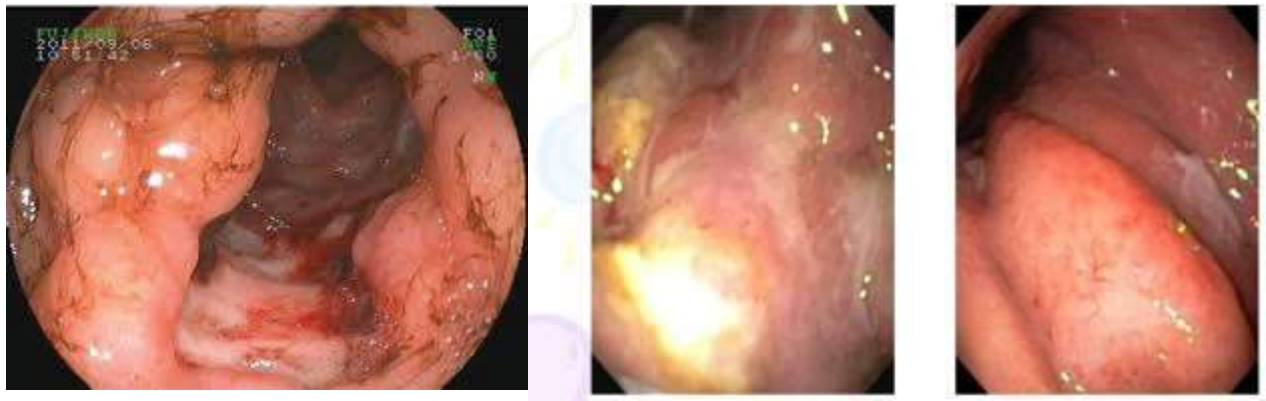


D

# Gastric lymphoma

Primary Gastric Lymphoma

- Primary lymphoma of the stomach is relatively uncommon, accounting **for ~2% of all lymphomas**. The stomach is, however, the most frequent extranodal site for lymphoma, and gastric lymphoma has increased in frequency during the past 30 years The diagnosis of lymphoma of the stomach may usually requires a biopsy at gastroscopy or laparotomy.
- The macroscopic pathology of gastric lymphoma may also mimic adenocarcinoma, consisting of either a bulky ulcerated lesion localized in the corpus or antrum or a diffuse process spreading throughout the entire gastric submucosa and even extending into the duodenum. Microscopically, the vast majority of gastric lymphoid tumors **are non-Hodgkin's lymphomas of B cell origin; Hodgkin's disease involving the stomach is extremely uncommon.** Histologically, these tumors may range from well-differentiated, superficial processes [mucosa-associated lymphoid tissue (MALT)] to high-grade, large-cell lymphomas. Like gastric adenocarcinoma, infection with *H. pylori* increases the risk for gastric lymphoma in general and MALT lymphomas in particular. Gastric lymphomas spread initially to regional lymph nodes and may then disseminate. Gastric lymphomas are staged like other lymphomas.



# Gastric lymphoma

Primary Gastric Lymphoma

## Treatment

- **Antibiotic treatment to eradicate *H. pylori* infection has led to regression of about 75% of gastric MALT lymphomas and should be considered before surgery, radiation therapy, or chemotherapy are undertaken in patients having such tumors**
- The need for a major surgical procedure **has been questioned, particularly in patients with preoperative radiographic evidence of nodal involvement**, for whom chemotherapy [CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)] plus rituximab is effective therapy. A role for radiation therapy is not defined because most recurrences develop at distant sites.