Diseases of the stomach and duodenum

Peptic ulcer and H. pylori infection
Parts of the Stomach

Regions of the stomach:
- cardiac
- pyloric
- body
- antrum
- duodenum
- pyloric sphincter
- esophagus
- circular muscle layer
- longitudinal muscle layer
- gastric pits
- gastric glands
- blood vessels
- oblique muscle layer
- circular muscle layer
- longitudinal muscle layer
- connective tissue layer

(b) Gastric gland

- Lamina propria
- Mucous cells
- Neck
- Parietal cells
- Smooth muscle cell
- G cell
- Chief 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:
   
   Pepsinogen (42 kDa) $\xrightarrow{\text{HCl (pH < 3)}}$ Pepsin (35 kDa)

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: receptors
Gastric parietal cell undergoing transformation after secretagogue-mediated stimulation. cAMP, cyclic adenosine monophosphate. (Adapted from SJ Hersey, G Sachs: Physiol Rev 75:155, 1995.)
Parietal cells and acid secretion: pharmacology
Gastric mucosal barrier
Role of prostaglandins
Platelet aggregation
Nociception
Immediate phase PGs

COX-1

PHOSPHOLIPASES

Homeostasis
Inflammation
GI integrity
Immunosuppression
Immune cell development
Allergic responses
Male fertility

PPARs

COX-2

Kidney development
Tumorigenesis
Female Fertility

Fever
Angiogenesis
Delayed phase PGs
Bone resorption
ARACHIDONIC ACID

COX-1

TxA₂
Platelets

PGI₂
Kidney

PGE₂
Stomach

COX-2

PGE₂
CNS

PGE₂
Endothelium

PGI₂
Macrophages

Sinovial cells

Chondrocytes
The mechanism of actions of aspirin and NSAIDs depend on the inhibition of cyclo-oxygenase activities.
Effects of NSAIDs on Thromboxane and Prostacyclin

Platelet

COX-1

Nonselective NSAIDs/ASA

COX-2 Inhibitor

Thromboxane (TxA₂)

Promotes Platelet Aggregation

Hemostasis

Thrombosis

Endothelial Cell

COX-1

COX-2

Prostacyclin (PGI₂)

Inhibits Platelet Aggregation

Gastric emptying
Diagnostic procedure for gastric disorders

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

PUD 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.
Duodenal ulcers

DUs are estimated to occur in 6–15% of the Western population.
The incidence of DUs declined steadily from 1960 to 1980 and has remained stable since then.
The death rates, need for surgery, and physician visits have decreased by >50% over the past 30 years.
The reason for the reduction in the frequency of 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

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 ulcers

Pathology - Duodenal Ulcers

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

Pathology- Gastric Ulcers

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,
Peptic ulcers

Pathophysiology-Duodenal ulcer

*H. pylori* and NSAID-induced injury account for the majority of DUs.

Many acid secretory abnormalities have been described in DU patients. Of these, average basal and nocturnal gastric acid secretion appears to be increased in DU patients as compared to controls; however, the level of overlap between DU patients and control subjects is substantial.

The reason for this altered secretory process is unclear, but *H. pylori* infection may contribute.
Peptic ulcers

Pathophysiology- Gastric Ulcers

As in DUs, the majority of GUs can be attributed to either *H. pylori* or NSAID-induced mucosal damage. GUs that occur in the prepyloric area or those in the body associated with a DU or a duodenal scar are similar in pathogenesis to DUs. Gastric acid output (basal and stimulated) tends to be normal or decreased in GU patients. When GUs develop in the presence of minimal acid levels, impairment of mucosal defense factors may be present.
H. pylori

- *H. pylori* is a gram-negative bacillus that has naturally colonized humans for at least tens of thousands of years. It is noninvasive and lives in gastric mucus, with a small proportion of the bacteria adherent to the mucosa.
- Its spiral shape and flagella render *H. pylori* motile in the mucus environment. This organism has several acid-resistance mechanisms, most notably a highly expressed urease that catalyzes urea hydrolysis to produce buffering ammonia. *H. pylori* is microaerophilic (requiring low levels of oxygen), is slow-growing, and requires complex growth media in vitro.
- It was discovered in 1992 by Warren and Marshall that earned the Nobel prize in 2005.
- Publication of complete genomic sequences of *H. pylori* took place in 1997.

The Nobel Prize in Physiology or Medicine 2005
Barry J. Marshall, J. Robin Warren
H. pylori- The bacterium

H. pylori 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 strategically designed to live within the aggressive environment of the stomach. 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-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.
- 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.
- Spontaneous acquisition or loss of *H. pylori* in adulthood is uncommon.
- The very low incidence among children in developed countries at present is probably due, at least in part, to improved living standards and increased use of antibiotics.
- Humans are the only important reservoir of *H. pylori*.
- Children may acquire the organism from their parents (more often from the mother) or from other children. Whether transmission usually takes place by the fecal-oral or the oral-oral route is unknown.
H. pylori- The bacterium

- 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).*

- 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 cytokine production.
**Gastric infection H.pylori factors**

- **Bacterial factors:** *H. pylori* is able to facilitate gastric residence, induce mucosal injury, and avoid host defense. Different strains of *H. pylori* produce different virulence factors.

The inflammatory response to *H. pylori* includes recruitment of neutrophils, lymphocytes (T and B), macrophages, and plasma cells.

Elevated concentrations of multiple cytokines are found in the gastric epithelium of *H. pylori*–infected individuals, including interleukin (IL) 1β, IL-2, IL-6, IL-8, tumor necrosis factor (TNF) and interferon (IFN-).

Additional mechanisms by which *H. pylori* may cause epithelial cell injury include (1) activated neutrophil-mediated production of reactive oxygen or nitrogen species and enhanced epithelial cell turnover and (2) apoptosis related to interaction with T cells (T helper 1, or T_{H}1, cells) and IFN-.
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.
Schematic of the relationships between colonization with *Helicobacter pylori* and diseases of the upper gastrointestinal tract among persons in developed countries. Essentially all persons colonized with *H. pylori* develop a host response, which is generally termed chronic gastritis. The nature of the interaction of the host with the particular bacterial population determines the clinical outcome. *H. pylori* colonization increases the lifetime risk of peptic ulcer disease, noncardia gastric cancer, and B cell non-Hodgkin's gastric lymphoma [odds ratios (ORs) for all, >3]. In contrast, a growing body of evidence indicates that *H. pylori* colonization (especially with cagA+ strains) protects against adenocarcinoma of the esophagus (and the sometimes related gastric cardia) and premalignant lesions such as Barrett's esophagus (OR, <1). While the incidences of peptic ulcer disease (cases not due to nonsteroidal anti-inflammatory drugs) and noncardia gastric cancer are declining in developed countries, the incidence of adenocarcinoma of the esophagus is rapidly increasing. [Adapted from Blaser MJ: Hypothesis: The changing relationships of Helicobacter pylori and humans: Implications for health and disease. J Infect Dis 179:1523, 1999, with permission.]
H. Pylory and DU

How gastric colonization 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.
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- Diagnosis

Tests for H. pylori can be divided into two groups: invasive tests, which require upper gastrointestinal endoscopy and are based on the analysis of gastric biopsy specimens, and noninvasive tests

- If endoscopy is performed, the most convenient biopsy-based test is the biopsy urease test, in which one large or two small antral biopsy specimens are placed into a gel containing urea and an indicator. The presence of H. pylori urease elicits a color change, which often occurs within minutes but can require up to 24 h.

- Histologic examination of biopsy specimens for H. pylori is also accurate, provided that a special stain (e.g., a modified Giemsa or silver stain) permitting optimal visualization of the organism is used. If biopsy specimens are obtained from both antrum and corpus, histologic study yields additional information, including the degree and pattern of inflammation, atrophy, metaplasia, and dysplasia.

- Microbiologic culture is most specific but may be insensitive because of difficulty with H. pylori isolation. Once the organism is cultured, its identity as H. pylori can be confirmed by its typical appearance on Gram's stain and its positive reactions in oxidase, catalase, and urease tests. Moreover, the organism's susceptibility to antibiotics can be determined; this information can be clinically useful in difficult cases.
H. pylori- Diagnosis (2)

- **Noninvasive H. pylori testing is the norm if gastric cancer does not need to be excluded by endoscopy.**

- The most consistently accurate test is the **urea breath test**. In this simple test, the patient drinks a labeled urea solution and then blows into a tube. The urea is labeled with either the nonradioactive isotope $^{13}$C or a minute dose of the radioactive isotope $^{14}$C. If *H. pylori* urease is present, the urea is hydrolyzed and labeled carbon dioxide is detected in breath samples.

- **The stool antigen** test, another simple assay, is more convenient and potentially less expensive than the urea breath test but has been slightly less accurate in some comparative studies.

- **SeroLogic assays** measuring specific IgG levels in serum by enzyme-linked immunosorbent assay or immunoblot.

- **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.
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
Epidemiology of NSAIDs induced GI bleeding

Studio caso-controllo Spagna-Italia su EDS
Tasso di mortalità per età

Incidenza (n./100.000/anno)

0 100 200 300 400

Tasso di mortalità (%)

0 2 4 6

Età (anni)
Gastrointestinal bleeding: risk factors

1. Age >65 year
2. History of peptic ulcer or GI bleeding
3. High doses of a NSAID
4. The use of two NSAIDs (or ASA + NSAID)
5. The use of corticosteroids
6. The 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
Aspirin: benefits and harms

Large multicenter trials have demonstrated that also low doses of aspirin (75-100 mg/d) increase the incidence of gastrointestinal bleeding (2-4/1000 in middle aged persons and 4-12/1000 in older persons).

The US Preventive Services Task Force Meta-analysis  
*Ann Internal Med 2002; 136:157*
Pathogenesis of NSAIDs/ASA induced gastric injury

Gastrointestinal side effects are related to the mechanism of action of NSAIDs /ASA (i.e. COX inhibition)
Effects of NSAIDs on Thromboxane and Prostacyclin

Platelet

Thromboxane (TxA₂)
- Promotes Platelet Aggregation
- Hemostasis
- Thrombosis

Endothelial Cell

Prostacyclin (PGI₂)
- Inhibits Platelet Aggregation

COX-1
Nonselective NSAIDs/ASA
COX-2 Inhibitor
COX-2

COX-2 selectivity of NSAIDs

Percent inhibition of COX-1 when COX-2 is inhibited by 80%

Warner T. et al., PNAS 1999
# Risk factors: the NSAID structure

<table>
<thead>
<tr>
<th>Drug</th>
<th>R.R. (I.C. 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>2.0</td>
</tr>
<tr>
<td>ASA &lt; 325*</td>
<td>1.8 (1.2-2.3)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>2.8 (1.4-2.3)</td>
</tr>
<tr>
<td>Sulindac</td>
<td>3.1 (1.6-2.7)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>3.2 (1.7-2.9)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>3.4 (1.9-3.1)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>4.8 (2.7-5.2)</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>5.2 (2.7-6.4)</td>
</tr>
</tbody>
</table>

Cumulative incidence of PUB

Sicurezza gastro-intestinale dei Coxibs

<table>
<thead>
<tr>
<th>Studio</th>
<th>95% CI</th>
<th>Weight</th>
<th>RR (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bombardier et al</td>
<td>54.4%</td>
<td>0.46 (0.34-0.63).</td>
<td></td>
</tr>
<tr>
<td>Goldestein et al.</td>
<td>13.8%</td>
<td>0.39 (0.21-0.72)</td>
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</tr>
<tr>
<td>Langman et al.</td>
<td>17.1%</td>
<td>0.73 (0.46-1.17)</td>
<td></td>
</tr>
<tr>
<td>Silverstein et al.</td>
<td>14.6%</td>
<td>0.48 (0.27-0.87)</td>
<td></td>
</tr>
<tr>
<td>Total (CI 95%)</td>
<td>100.0%</td>
<td>0.50 (0.40-0.63)</td>
<td></td>
</tr>
</tbody>
</table>

0.1 0.2 1 5 10

Favorevole al trattamento  Favorevole al controllo

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

Investigator-Reported Thrombotic Cardiovascular Events in the VIGOR Study Compared with Phase IIb/III OA Study

CARDIOVASCULAR SAFETY PROFILE OF ROFECOXIB: A META-ANALYSIS:
A. Reicin, E. Barr, D. Shapiro - EULAR ORAL PRESENTATION, SAT. JUNE 16: 12:00 - 13:00
Causes of Non-Hp and Non-NSAID Ulcer Disease

**Infection**
- Cytomegalovirus
- Herpes simplex virus
- *Helicobacter heilmannii*

**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.
- 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. Tarry stools or coffee-ground emesis indicate bleeding.
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 tender, boardlike abdomen 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.

• In addition to permitting direct visualization of the mucosa, endoscopy facilitates photographic documentation of a mucosal defect and tissue biopsy to rule out malignancy (GU) or *H. pylori*. Endoscopic examination is particularly helpful in identifying lesions too small to detect by radiographic examination, for evaluation of atypical radiographic abnormalities, or to determine if an ulcer is a source of blood loss.
Upper GI endoscopy
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 has been reported to occur in up to 30% of the U.S. population. 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.
Duodenal bleeding - video
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.
Gastric Outlet 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.
Before the discovery of *H. pylori*, the therapy of PUD was centered on the old dictum by Schwartz of "no acid, no ulcer." Although acid secretion is still important in the pathogenesis of PUD, eradication of *H. pylori* and therapy/prevention of NSAID-induced disease is the mainstay of treatment.
## PUD Therapy

<table>
<thead>
<tr>
<th>Drug Type/Mechanism</th>
<th>Examples</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acid-suppressing drugs</strong></td>
<td></td>
<td></td>
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<tr>
<td>Antacids</td>
<td>Mylanta, Maalox, Tums, Gaviscon</td>
<td>100–140 meq/L 1 and 3 h after meals and hs</td>
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<tr>
<td><strong>H₂ receptor antagonists</strong></td>
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<tr>
<td></td>
<td>Cimetidine</td>
<td>400 mg bid</td>
</tr>
<tr>
<td></td>
<td>Ranitidine</td>
<td>300 mg hs</td>
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<tr>
<td></td>
<td>Famotidine</td>
<td>40 mg hs</td>
</tr>
<tr>
<td></td>
<td>Nizatidine</td>
<td>300 mg hs</td>
</tr>
<tr>
<td><strong>Proton pump inhibitors</strong></td>
<td>Omeprazole</td>
<td>20 mg/d</td>
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<tr>
<td></td>
<td>Lansoprazole</td>
<td>30 mg/d</td>
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<td></td>
<td>Rabeprazole</td>
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<td>Pantoprazole</td>
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<td></td>
<td>Esomeprazole</td>
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<td><strong>Mucosal protective agents</strong></td>
<td>Sucralfate</td>
<td>1 g qid</td>
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<tr>
<td></td>
<td>Misoprostol</td>
<td>200 g qid</td>
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<td></td>
<td>Bismuth subsalicylate (BSS)</td>
<td>See anti-<em>H. pylori</em> regimens (Table 287-4)</td>
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## H. Pylori treatment

<table>
<thead>
<tr>
<th>Regimen, Duration</th>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Drug 3</th>
<th>Drug 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Line Treatment</strong></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| Regimen 1: OCA  
(10 days)<sup>a</sup> | Omeprazole<sup>b</sup> 
(20 mg bid) | Clarithromycin 
(500 mg bid) | Amoxicillin 
(1 g bid) | — |
| Regimen 2: OCM  
(7–14 days) | Omeprazole<sup>b</sup> 
(20 mg bid) | Clarithromycin 
(500 mg bid) | Metronidazole 
(500 mg bid) | — |
| **Second-Line Treatment<sup>c</sup>** | | | | |
| Regimen 3: OBTM  
(14 days)<sup>d</sup> | Omeprazole<sup>b</sup> 
(20 mg bid) | Bismuth subsalicylate 
(2 tabs qid) | Tetracycline HCl 
(500 mg qid) | Metronidazole 
(500 mg tid) |
H. Pylori eradication - sequential

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pantoprazole (40 mg twice daily) + amoxicillin (1 g twice daily)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pantoprazole (40 mg twice daily) + clarithromycin (500 mg twice daily) + tinidazole (500 mg twice daily)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 (H₂ 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.
Management of patients taking NSAIDs

1. Age >65 year
2. History of peptic ulcer or GI bleeding
3. High doses of a NSAID
4. The use of two NSAIDs
5. The use of corticosteroids
6. The use of anti-coagulants
7. H. pylori infection

* Consider CV safety of coxibs
<table>
<thead>
<tr>
<th>No/Low NSAID GI Risk</th>
<th>NSAID GI Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CV risk (no aspirin)</td>
<td>Traditional NSAID</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>CV risk (consider aspirin)</td>
<td>Traditional NSAID + PPI if GI risk warrants gastroprotection</td>
</tr>
<tr>
<td></td>
<td>Consider non-NSAID therapy</td>
</tr>
</tbody>
</table>
PUBs that fail to heal under appropriate therapy

The majority (>90%) 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 or the idiopathic form, which can be excluded with gastric acid analysis.

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). This higher dose is also effective in maintaining remission. 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.
1. 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.
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.
Afferent Loop Syndromes

- Two types of afferent loop syndrome can occur in patients who have undergone partial gastric resection with Billroth II anastomosis.
- The more common of the two is bacterial overgrowth in the afferent limb secondary to stasis. Patients may experience postprandial abdominal pain, bloating, and diarrhea with concomitant malabsorption of fats and vitamin B$_{12}$.
- Cases refractory to antibiotics may require surgical revision of the loop. The less-common afferent loop syndrome can present with severe abdominal pain and bloating that occur 20–60 min after meals. Pain is often followed by nausea and vomiting of bile-containing material. The pain and bloating may improve after emesis. The cause of this clinical picture is theorized to be incomplete drainage of bile and pancreatic secretions from an afferent loop that is partially obstructed. Cases refractory to dietary measures may need surgical revision.
Surgery related complication

- Dumping syndrome consists of a series of vasomotor and gastrointestinal signs and symptoms and occurs in patients who have undergone vagotomy and drainage (especially Billroth procedures).

- Two phases of dumping, early and late, can occur.

- Early dumping takes place 15–30 min after meals and consists of crampy abdominal discomfort, nausea, diarrhea, belching, tachycardia, palpitations, light-headedness, and, rarely, syncope. These signs and symptoms arise from the rapid emptying of hyperosmolar gastric contents into the small intestine, resulting in a fluid shift into the gut lumen with plasma volume contraction and acute intestinal distention. Release of vasoactive gastrointestinal hormones (vasoactive intestinal polypeptide, neurotensin, motilin) is also theorized to play a role in early dumping.

- The late phase of dumping typically occurs 90 min to 3 h after meals. Vasomotor symptoms (light-headedness, palpitations, tachycardia, and syncope) predominate during this phase. This component of dumping is thought to be secondary to hypoglycemia from excessive insulin release.

- Dumping syndrome is most noticeable after meals rich in simple carbohydrates (especially sucrose) and high osmolarity. Ingestion of large amounts of fluids may also contribute. Up to 50% of postvagotomy and drainage patients will experience dumping syndrome to some degree. Signs and symptoms often improve with time, but a severe protracted picture can occur in up to 1% of patients.
Maldigestion and Malabsorption

- Weight loss can be observed in up to 60% of patients after partial gastric resection. A significant component of this weight reduction is due to decreased oral intake. However, mild steatorrhea can also develop. Reasons for maldigestion/malabsorption include decreased gastric acid production, rapid gastric emptying, decreased food dispersion in the stomach, reduced luminal bile concentration, reduced pancreatic secretory response to feeding, and rapid intestinal transit.
Surgery related complication

Gastric Adenocarcinoma

- The incidence of adenocarcinoma in the gastric stump is increased 15 years after resection. Some have reported a four- to fivefold increase in gastric cancer 20–25 years after resection. The pathogenesis is unclear but may involve alkaline reflux, bacterial proliferation, or hypochlorhydria. The role of endoscopic screening is not clear, and most guidelines do not support its use.
Zollinger–Ellison Syndrome

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

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.
- Gastrinomas are classified into sporadic tumors (more common) and those associated with multiple endocrine neoplasia (MEN) type I (see below).

Pathophysiology

- Hypergastrinemia originating from an autonomous neoplasm is the driving force responsible for the clinical manifestations in ZES. Gastrin stimulates acid secretion through gastrin receptors on parietal cells and by inducing histamine release from ECL cells. Gastrin also has a trophic action on gastric epithelial cells. Long-standing hypergastrinemia leads to markedly increased gastric acid secretion through both parietal cell stimulation and increased parietal cell mass. The increased gastric acid output leads to peptic ulcer diathesis, erosive esophagitis, and diarrhea.
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 the second and third portions of the duodenum inferiorly, and junction of the neck and body of the pancreas medially).

- **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

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.

**Diarrhea**, the next most common clinical manifestation, is found 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.
SZE endoscopy findings
• Gastrinomas can develop in the presence of MEN I syndrome (~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.
SZE diagnosis

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.
**Table 8** Differential diagnosis of hypergastrinemia (7)

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypochlorhydria or achlorhydria with or without pernicious anemia</td>
</tr>
<tr>
<td>Retained gastric antrum</td>
</tr>
<tr>
<td>G-cell hyperplasia</td>
</tr>
<tr>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Massive small bowel resection</td>
</tr>
<tr>
<td>Gastric outlet obstruction</td>
</tr>
<tr>
<td>Other conditions (rheumatoid arthritis, vitiligo, diabetes, pheochromocytoma)</td>
</tr>
</tbody>
</table>
Diagnosis

• The next step in establishing a biochemical diagnosis of gastrinoma is to **assess acid secretion**.

• Nothing further needs to be done if decreased acid output is observed. In contrast, normal or elevated gastric acid output suggests a need for additional tests. Up to 12% of patients with common PUD may have comparable levels of acid secretion.

• If the technology for measuring gastric acid secretion is not available, a basal gastric pH 3 virtually excludes a gastrinoma.
Tumor Localization

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensitivity, %</th>
<th>Primary Gastrinoma</th>
<th>Metastatic Gastrinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>21–28</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>CT scan</td>
<td>35–59</td>
<td>35–72</td>
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<tr>
<td>Selective angiography</td>
<td>35–68</td>
<td>33–86</td>
<td></td>
</tr>
<tr>
<td>Portal venous sampling</td>
<td>70–90</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>SASI</td>
<td>55–78</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>30–60</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Octreoscan</td>
<td>67–86</td>
<td>80–100</td>
<td></td>
</tr>
<tr>
<td>EUS</td>
<td>80–100</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
SZE octreoscan
• **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. Dosing can be adjusted to achieve a BAO <10 meq/h (at the drug trough) in surgery-naive patients and to <5 meq/h in individuals who have previously undergone an acid-reducing operation. Although the somatostatin analogue has inhibitory effects on gastrin release from receptor-bearing tumors and inhibits gastric acid secretion to some extent, PPIs have the advantage of reducing parietal cell activity to a greater degree. Despite this, octreotide may be considered as adjunctive therapy to the PPI in patients with tumors that express somatostatin receptors and have peptic symptoms that are difficult to control with high-dose PPI.

• The ultimate goal of surgery would be to provide a definitive cure
Therapy of metastatic endocrine tumors in general remains suboptimal; gastrinomas are no exception. Medical approaches including 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. 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 are infectious.
- 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.
- The highly acidic gastric environment may be one reason why infectious processes of the stomach are rare. Bacterial infection of the stomach or phlegmonous gastritis is a rare, potentially life-threatening disorder characterized by marked and diffuse acute inflammatory infiltrates of the entire gastric wall, at times accompanied by necrosis. Elderly individuals, alcoholics, and AIDS patients may be affected.
- Other types of infectious gastritis may occur in immunocompromised individuals such as AIDS patients. Examples include herpetic (herpes simplex) or CMV gastritis. The histologic finding of intranuclear inclusions would be observed in the latter.
Acute gastritis endoscopy

Therapy
Antisecretory drugs IV infusion
Endoscopic therapy
Surgery
Chronic 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.
Chronic 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 A chronic gastritis

- The parietal cell–containing gastric gland is preferentially targeted in this form of gastritis, and achlorhydria results.
- Parietal cells are the source of IF, lack of which will lead to vitamin B$_{12}$ deficiency and its sequelae (megaloblastic anemia, neurologic dysfunction).
- Gastric acid plays an important role in feedback inhibition of gastrin release from G cells. Achlorhydria, coupled with relative sparing of the antral mucosa (site of G cells), leads to hypergastrinemia.
### 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.
- **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: treatment

Treatment in chronic gastritis is aimed at the sequelae and not the underlying inflammation. Patients with pernicious anemia will require parenteral vitamin B\textsubscript{12} supplementation on a long-term basis. **Eradication of *H. pylori* is recommended**
H. Pylori eradication prevents gastric cancer

![Graph showing the relationship between H. Pylori eradication and gastric cancer risk](chart.png)
Gastric cancer

Estimated incidence from gastric cancer in men, 2012
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 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 cancer

Pathology

- **About 85% of stomach cancers are adenocarcinomas**, with 15% due to lymphomas and gastrointestinal stromal tumors (GIST) and leiomyosarcomas.

- Gastric adenocarcinomas may be subdivided into two categories: a **diffuse type**, 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**, characterized by cohesive neoplastic cells that form glandlike tubular structures.
Gastric adenocarcinoma

Etiology

- The long-term ingestion of high concentrations of nitrates in dried, smoked, and salted foods appears to be associated with a higher risk. The nitrates are thought to be converted to carcinogenic nitrites by bacteria. Such bacteria may be introduced exogenously through the ingestion of partially decayed foods, which are consumed in abundance worldwide by the lower socioeconomic classes.

- Bacteria such as *Helicobacter pylori* may also contribute to this effect by causing chronic gastritis, loss of gastric acidity, and bacterial growth in the stomach.

- The effect of *H. pylori* eradication on the subsequent risk for gastric cancer in high-incidence areas is under investigation.

- Serial endoscopic examinations of the stomach in patients with atrophic gastritis have documented replacement of the usual gastric mucosa by intestinal-type cells. This process of intestinal metaplasia may lead to cellular atypia and eventual neoplasia.

- *H. pylori* has not been associated with the diffuse, more proximal form of gastric carcinoma.
Molecular subtypes of gastric cancer.
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. 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. A careful assessment is of particular importance in patients with atrophic gastritis or pernicious anemia.

• Unusual clinical features associated with gastric adenocarcinomas include migratory thrombophlebitis, microangiopathic hemolytic anemia, and acanthosis nigricans.
# Gastric cancer staging

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

*Adjacent organ
Tumor in stomach wall

Tis T1 T2 T3 T4
Gastric cancer: outcome

![Survival rate graph showing different stages and their survival rates. Stage IB has the highest survival rate, followed by Stage II, Stage IIIA, Stage IIIB, and Stage IV.](image-url)
Gastric cancer: outcome
Gastric adenocarcinoma: ecoendoscopy
Endoscopy GI cancer: endoscopic magnification and chromoendoscopy

Figure 5 Endoscopic findings of superficial elevated (0 IIa) type early gastric cancer in the gastric antrum. Histological type differentiated (intestinal) type. (A) Conventional white light imaging shows a slightly elevated lesion. The light reflection suggests something different in surface morphology. (B) Indigo carmine chromoendoscopy demonstrates a well-demarcated superficial elevated lesion with an irregular surface pattern.
Endoscopic treatment
mucosal resection (endoscopy)
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.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Chemotherapy regimen</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinto et al. 2007</td>
<td>38</td>
<td>Cetuximab + FOLFIRI</td>
<td>44</td>
<td>8</td>
<td>16</td>
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<tr>
<td>Woell et al. 2008</td>
<td>51</td>
<td>Cetuximab + oxaliplatin/irinotecan</td>
<td>63</td>
<td>6.2</td>
<td>9.5</td>
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<tr>
<td>Pinto et al. 2009</td>
<td>48</td>
<td>Cetuximab + cisplatin/docetaxel</td>
<td>41.2</td>
<td>5</td>
<td>9</td>
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<tr>
<td>Han et al. 2009</td>
<td>40</td>
<td>Cetuximab + mFOLFOX6</td>
<td>50</td>
<td>5.5</td>
<td>9.9</td>
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<tr>
<td>Kanzler et al. 2009</td>
<td>49</td>
<td>Cetuximab + FUFIRI</td>
<td>42</td>
<td>8.5</td>
<td>16.6</td>
</tr>
<tr>
<td>Yeh et al. 2009</td>
<td>35</td>
<td>Cetuximab + 5FU/LV/cisplatin</td>
<td>69</td>
<td>11</td>
<td>14.5</td>
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<tr>
<td>Zhang et al. 2009</td>
<td>49</td>
<td>Cetuximab + cisplatin/capecitabine</td>
<td>48</td>
<td>5.2</td>
<td>NS</td>
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<tr>
<td>Lordick et al. 2010</td>
<td>52</td>
<td>Cetuximab + FUFOX</td>
<td>65</td>
<td>7.6</td>
<td>9.5</td>
</tr>
<tr>
<td>Enzinger et al. 2010</td>
<td>245</td>
<td>Cetuximab + ECF/IC/FOLFOX</td>
<td>58/38/51</td>
<td>5.6/5/5.7</td>
<td>10.0/8.6/10.0</td>
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<tr>
<td>Moehler et al. 2011</td>
<td>49</td>
<td>Cetuximab + FOLFIRI</td>
<td>46</td>
<td>9</td>
<td>16.5</td>
</tr>
<tr>
<td>Kim et al. 2011</td>
<td>44</td>
<td>Cetuximab + XELOX</td>
<td>52.3</td>
<td>6.5</td>
<td>9.8</td>
</tr>
</tbody>
</table>
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 \textit{c-kit} receptor. GISTs are unresponsive to conventional chemotherapy; ~50% of patients experience objective response and prolonged survival when treated with \textit{imatinib mesylate (Gleevec)} (400–800 mg PO daily), a selective inhibitor of the \textit{c-kit} tyrosine kinase.
- Many patients with GIST whose tumors have become refractory to imatinib subsequently benefit from sunitinib (Sutent), another inhibitor of the \textit{c-kit} tyrosine kinase.
GIST ecoendoscopy
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 require 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.

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.
Gastric cancer surgery
Endoscopic palliation

A. Gastric outlet obstruction (stenosis of pylorus)
   Gastric cancer

B. Stent
   Patent pylorus restored with an expandable metal stent

Duodenum
Distended stomach
<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity/Specificity, %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive (Endoscopy/Biopsy Required)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid urease</td>
<td>80–95/95–100</td>
<td>Simple; false negative with recent use of PPIs, antibiotics, or bismuth compounds</td>
</tr>
<tr>
<td>Histology</td>
<td>80–90/&gt;95</td>
<td>Requires pathology processing and staining; provides histologic information</td>
</tr>
<tr>
<td>Culture</td>
<td>–/–</td>
<td>Time-consuming, expensive, dependent on experience; allows determination of antibiotic susceptibility</td>
</tr>
<tr>
<td><strong>Noninvasive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology</td>
<td>&gt;80/&gt;90</td>
<td>Inexpensive, convenient; not useful for early follow-up</td>
</tr>
<tr>
<td>Urea breath test</td>
<td>&gt;90/&gt;90</td>
<td>Simple, rapid; useful for early follow-up; false negative with recent therapy (see rapid urease test); exposure to low-dose radiation with 14-C test</td>
</tr>
<tr>
<td>Stool antigen</td>
<td>&gt;90/&gt;90</td>
<td>Inexpensive, convenient; not established for eradication but promising</td>
</tr>
</tbody>
</table>

*Note: PPI, proton pump inhibitor.*
Diagnosis

• Barium studies of the proximal gastrointestinal tract are still commonly used as a first test for documenting an ulcer. The sensitivity of older single-contrast barium meals for detecting a DU is as high as 80%, with a double-contrast study providing detection rates as high as 90%. Sensitivity for detection is decreased in small ulcers (<0.5 cm), presence of previous scarring, or in postoperative patients.

• A GU may represent benign or malignant disease. Typically, a benign GU also appears as a discrete crater with radiating mucosal folds originating from the ulcer margin. Ulcers >3 cm in size or those associated with a mass are more often malignant. Unfortunately, up to 8% of GUs that appear to be benign by radiographic appearance are malignant by endoscopy or surgery. Radiographic studies that show a GU must be followed by endoscopy and biopsy.
Indication for *H. pylori* treatment (e.g., peptic ulcer disease or new-onset dyspepsia)

- **Test for *H. pylori***
  - **Positive**
    - **First-line treatment** (Table 144-2)
  - **Negative**
    - *H. pylori* not the cause

Wait at least 1 month after treatment finishes (no antibiotics, bismuth compounds, or proton pump inhibitors in the meantime)

- **Second-line treatment** (Table 144-2)
  - **Positive**
  - **Negative**
    - **Urea breath test***
      - **Positive after second-line treatment**
        - Third-line treatment; endoscopy with *H. pylori* culture and sensitivity testing; treat according to known antibiotic sensitivities
      - **Negative after third-line treatment**
        - Refer to specialist
          - **Consider whether treatment is still indicated**

Any remaining symptoms are not due to *H. pylori*
Gastric cancer staging

- **Primary tumor (T):**
  Tis = carcinoma in situ: intraepithelial tumor without invasion of lamina propria
  T1 = tumor invades lamina propria or submucosa
  T2 = tumor invades muscularis propria or subserosa
  T3* = tumor penetrates serosa (visceral peritoneum) without invasion of adjacent structures
  T4**,*** = tumor invades adjacent structures

- A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments or into the greater or lesser omentum without perforation of the visceral peritoneum.
  **Structures adjacent to the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.***
  ***Intramural extension to the duodenum or esophagus is classified by the depth of greatest invasion in any of these sites, including the stomach.***

- **Regional lymph nodes (N):**
  Include the perigastric nodes along the lesser and greater curvatures, and the nodes along the left gastric, common hepatic, splenic, and celiac arteries.
  N0 = no regional lymph node metastasis
  N1 = metastasis to 1–6 regional lymph nodes
  N2 = metastasis in 7–15 regional lymph nodes
  N3 = metastasis in more than 15 regional lymph nodes

- **Distant metastasis (M):**
  M0 = no distant metastasis
  M1 = distant metastasis
Surgical therapy

- The procedure that provides the lowest rates of ulcer recurrence (1%) but has the highest complication rate is vagotomy (truncal or selective) in combination with antrectomy.
Surgery related complication

- Dietary modification is the cornerstone of therapy for patients with dumping syndrome. Small, multiple (six) meals devoid of simple carbohydrates coupled with elimination of liquids during meals is important.
- Antidiarrheals and anticholinergic agents are complementary to diet. Guar and pectin, which increase the viscosity of intraluminal contents, may be beneficial in more symptomatic individuals.
- Acarbose, an α-glucosidase inhibitor that delays digestion of ingested carbohydrates, has also been shown to be beneficial in the treatment of the late phases of dumping.
- The somatostatin analogue octreotide has been successful in diet-refractory cases. This drug is administered subcutaneously (50 g tid), titrated according to clinical response. A long-acting depot formulation of octreotide can be administered once every 28 days and provides symptom relief comparable to the short-acting agent. In addition, patient weight gain and quality of life appear to be superior with the long-acting form.
Type B Chronic gastritis

- Seropositivity for *H. pylori* is associated with a three- to sixfold increased risk of gastric cancer. This risk may be as high as ninefold after adjusting for the inaccuracy of serologic testing in the elderly.
- The mechanism by which *H. pylori* infection leads to cancer is unknown, but it appears to be related to the chronic inflammation induced by the organism. Eradication of *H. pylori* as a general preventative measure for gastric cancer is being evaluated but is not yet recommended.
- Infection with *H. pylori* is also associated with development of a low-grade B cell lymphoma, gastric MALT lymphoma.