

Peptic Ulcer Disease

Pathogenesis · Morphology · Clinical consequences

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Learning objectives

- Explain why host defenses fail in chronic peptic ulceration
- Trace the effects of H. Pylori, NSAIDs, and impaired perfusion
- Recognize typical gross and microscopic ulcer morphology
- Relate morphology to hemorrhage, perforation, and obstruction

Clinical and morphologic integration

Peptic ulcer disease: A defined lesion

- Chronic ulceration predominantly affects the stomach or proximal duodenum.
- An ulcer is a tissue defect associated with sustained acid-peptic injury.
- H. Pylori infection, NSAIDs, and smoking dominate the etiologic context.
- The usual setting is pre-existing chronic gastritis.

Chronic ulcer ≠ any superficial erosion

Two principal sites, one shared mechanism

Proximal duodenum

Duodenal disease usually involves the first few centimeters beyond the pylorus.

Distal stomach

Gastric disease commonly involves the lesser curvature at the body–antrum junction.

Location reflects acid load and mucosal vulnerability

Regional physiology explains ulcer geography

Antrum → gastrin

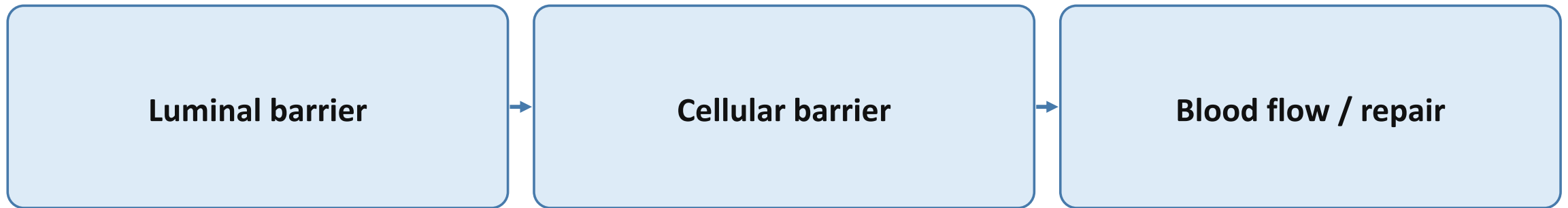
Antral G cells stimulate gastrin release and downstream acid secretion.

Body/fundus → acid

Body and fundus parietal cells secrete gastric acid.

Gastric defense is an integrated system

- Healthy epithelium resists exposure to acid and peptic enzymes.
- Mucus, bicarbonate, epithelial integrity, prostaglandins, and blood flow act together.



Loss of several protective functions amplifies injury

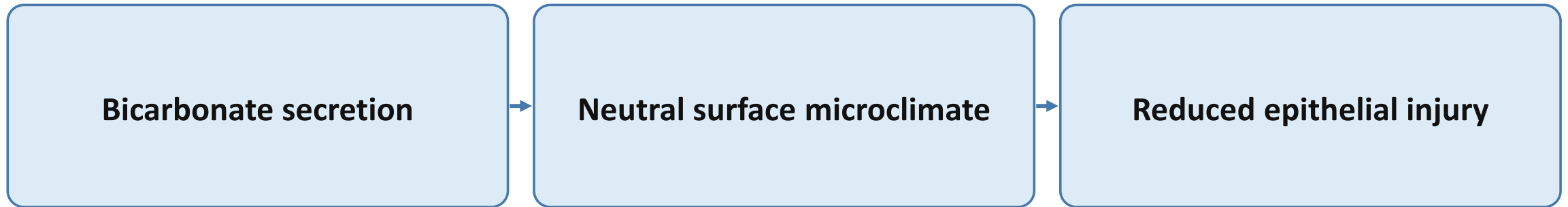
Mucus creates a protected surface microenvironment

- Foveolar secretions generate a mucus–phospholipid coating.
- The mucus layer limits direct luminal contact with epithelial cells.
- Within the unstirred fluid layer, bicarbonate maintains near-neutral surface pH.

The surface pH is not the same as luminal pH

Bicarbonate prevents acid damage at the epithelium

- Surface cells secrete bicarbonate into the overlying mucus.
- Local neutralization reduces acid exposure adjacent to cell membranes.

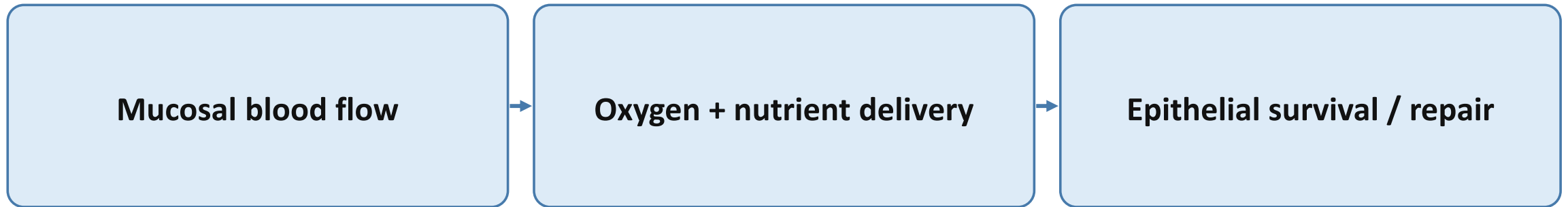


Epithelial integrity limits back-diffusion

- An intact epithelial barrier restricts movement of luminal acid and enzymes.
- Compromised barrier permits damaging material to reach the lamina propria.
- Foveolar cells renew rapidly, supporting surface restitution.

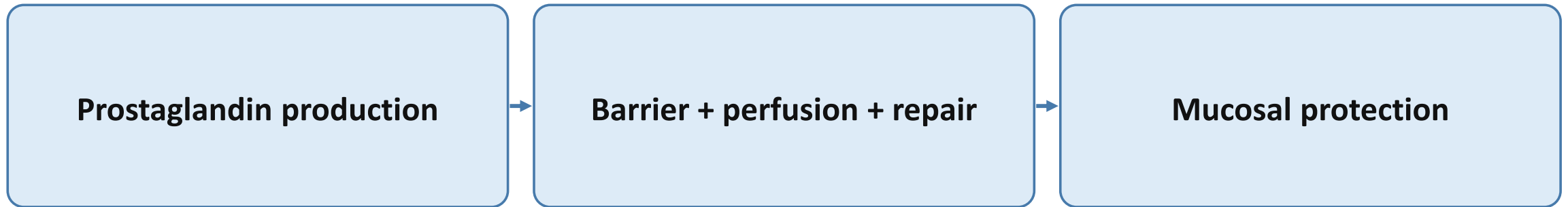
Perfusion sustains repair and acid clearance

- The mucosal vasculature supplies oxygen and nutrients.
- It also removes acid that penetrates the epithelial barrier.
- Ischemia creates vulnerability even without an increase in acid output.



Prostaglandins coordinate multiple defenses

- PGE₂ and PGI₂ promote mucus, bicarbonate, and phospholipid secretion.
- They support mucosal blood flow and epithelial restitution.
- They also restrain acid secretion.



Ulceration is a failure of balance

- Damaging forces: Gastric acid and peptic enzymes.
- Protection: Mucus, bicarbonate, intact epithelium, blood flow, repair.
- Ulcers form when chronic injury overwhelms these defenses.

DAMAGING FORCES
acid · pepsin

DEFENSIVE FORCES
barrier · blood flow · repair

ULCER if injury exceeds protection

Acid is necessary context; Impaired defense is equally important

Chronic gastritis provides the tissue background

- PUD generally evolves in chronically inflamed gastroduodenal mucosa.
- Not every patient with gastritis develops a peptic ulcer.

Chronic gastritis



Altered acid / defense balance



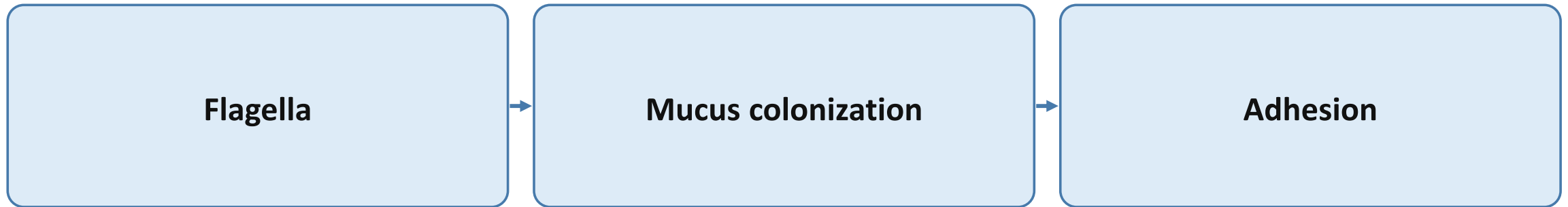
Chronic ulcer

Three dominant etiologic pathways

H. Pylori	Antral inflammation, increased acid and lower duodenal bicarbonate
NSAIDs	COX inhibition and loss of protective prostaglandins
Smoking	Reduced blood flow, oxygenation, and healing

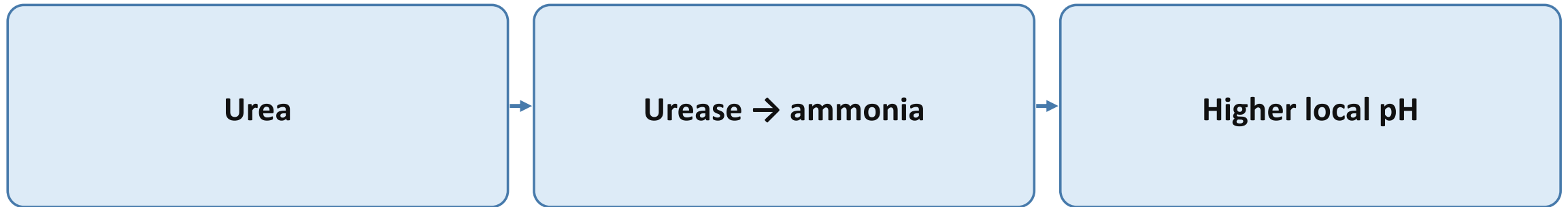
H. Pylori is adapted to the mucus niche

- The organism resides in surface mucus close to foveolar cells.
- Flagella permit movement within mucus and away from acidic niches.
- Adhesins mediate attachment to epithelial surfaces.



Urease supports bacterial persistence

- H. Pylori urease converts endogenous urea to ammonia.
- Ammonia buffers acidity near the organism.
- Persistence supports long-term gastritis and its complications.

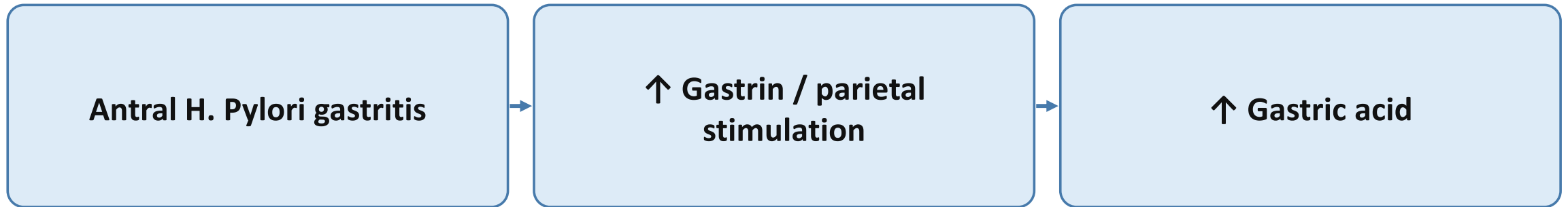


Bacterial products modify the inflammatory response

- CagA and VacA are among studied H. Pylori virulence factors.
- CagA can alter epithelial signaling and structural organization.
- Pathogenic outcome reflects bacterial traits interacting with host factors.
- Direct causality for specific clinical outcomes remains difficult to prove.

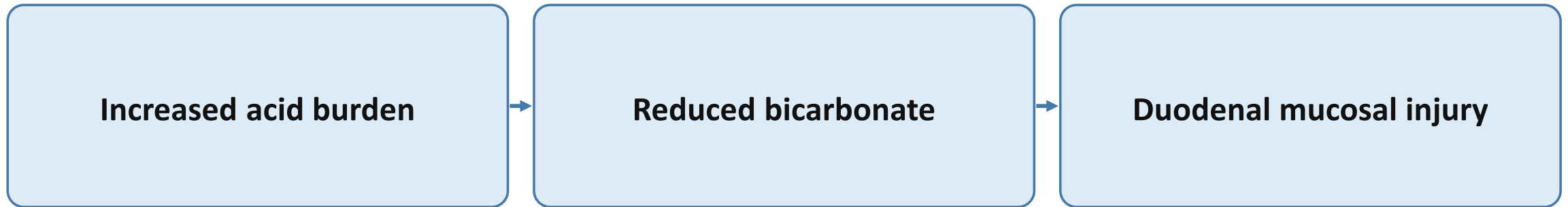
Antral-predominant gastritis alters gastrin physiology

- Antral inflammation enhances gastrin production.
- Parietal-cell expansion in the gastric body increases acid output.
- This secretory phenotype increases peptic-ulcer susceptibility.



Duodenal bicarbonate is also reduced

- The common H. Pylori-associated PUD phenotype includes reduced duodenal bicarbonate secretion.
- Increased acid delivery and weaker neutralization act in the same direction.



Acid hypersecretion favors duodenal ulceration

Antral phenotype

Antral-predominant H. Pylori gastritis commonly retains or increases acid secretion.

Duodenal ulcer risk

The proximal duodenum is vulnerable to excessive acid-peptic load.

Atrophic gastritis shifts the acid phenotype

Acid-preserved gastritis

Loss of parietal cells in body/fundus
lowers acid secretion.

Atrophic, hypoacid gastritis

Gastric mucosal atrophy is associated
with lower antral/duodenal ulcer risk.

One infection can lead to divergent outcomes

- Antral-predominant disease may be associated with increased acid output and ulceration.
- Extensive atrophy may instead lower acid production and associate with intestinal metaplasia.

Antral inflammation → ulcer

Body/fundus atrophy → metaplasia

Schematic branches / outcomes

Pattern of gastritis matters more than infection status alone

Why does only a subset develop ulcers?

- H. Pylori infection is common, but clinical PUD is not inevitable.
- Host inflammatory and defense responses vary.
- Bacterial pathogenicity also varies among isolates.
- The precise transition from gastritis to PUD is incompletely understood.

NSAIDs reduce the prostaglandin defense network

- COX inhibition reduces synthesis of PGE₂ and PGI₂.
- Mucus, bicarbonate, perfusion, and repair are compromised.
- Acid-mediated injury becomes more likely at the same luminal acid exposure.



COX-1 predominates, but COX-2 also contributes

COX-1 contribution

Nonselective NSAIDs generally have substantial gastrointestinal toxicity.

COX-2 contribution

Selective COX-2 inhibition does not eliminate mucosal injury risk.

Several drug exposures amplify ulcer risk

NSAIDs	Directly impair protective prostaglandin synthesis
Corticosteroids + NSAIDs	Potentiation listed Table 17.3
Low-dose aspirin + H. Pylori	Increased gastric injury with concurrent infection

H. Pylori and aspirin are clinically synergistic

- The combination increases gastric injury risk beyond either isolated exposure.
- Medication history and infection status both matter.

H. Pylori gastritis



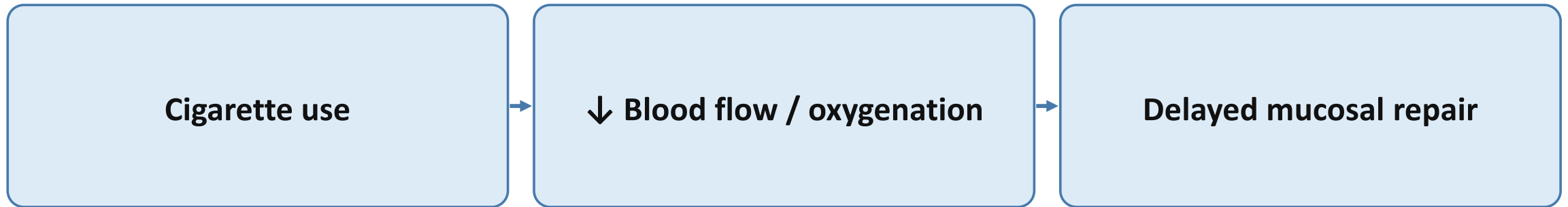
Aspirin exposure



Amplified gastric injury

Smoking impairs tissue-level resilience

- Smoking is an established clinical association with PUD.
- Reduced mucosal perfusion and oxygenation impair the capacity to heal.
- Synergy with H. Pylori for gastric ulcers.



Perfusion-limiting exposures increase vulnerability

Cardiovascular disease	Reduced oxygenation / mucosal blood flow (proposed mechanism)
Cocaine use	Vasoconstrictive reduction in mucosal blood flow
Chronic obstructive pulmonary disease	Listed associated risk condition

Hypersecretory states broaden ulcer distribution

- Zollinger–Ellison syndrome causes excessive gastric acid production.
- Ulcers can involve the stomach, duodenum, or jejunum.
- Atypical distribution warrants attention to hypersecretory causes.

Endocrine hypersecretion



Excess acid



Distal / multiple-site injury

Ectopic gastric mucosa can injure adjacent bowel

Duodenal gastric heterotopia	Local acid secretion and peptic injury
Meckel diverticulum	Ileal ulceration near ectopic gastric mucosa
Esophageal inlet patch	Local acid-peptic injury

Less common etiologic associations

Alcoholic cirrhosis	Primarily duodenal PUD association
Psychological stress	May increase gastric acid secretion
Endocrine-cell hyperplasia	Parietal-cell growth / increased acid output
CMV or HSV	Uncommon infection-related ulcer disease

Risk-factor assessment should be causal

More injurious exposure

High acid burden: Gastrin stimulation, Zollinger–Ellison syndrome, ectopic acid secretion.

Less effective protection

Weak mucosal defense: NSAIDs, smoking, compromised perfusion, chronic inflammation.

Changing epidemiology reflects changing exposures

Falling H. Pylori prevalence

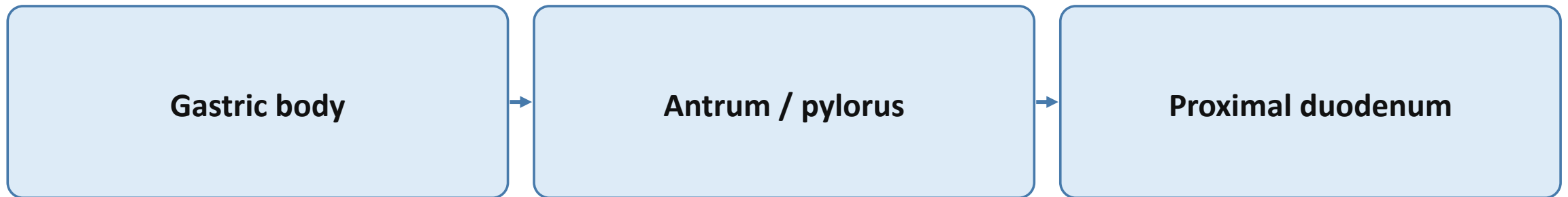
H. Pylori-related disease has declined as infection prevalence decreases.

Increasing NSAID exposure in older age

Older adults have increasing NSAID-associated ulcer disease account.

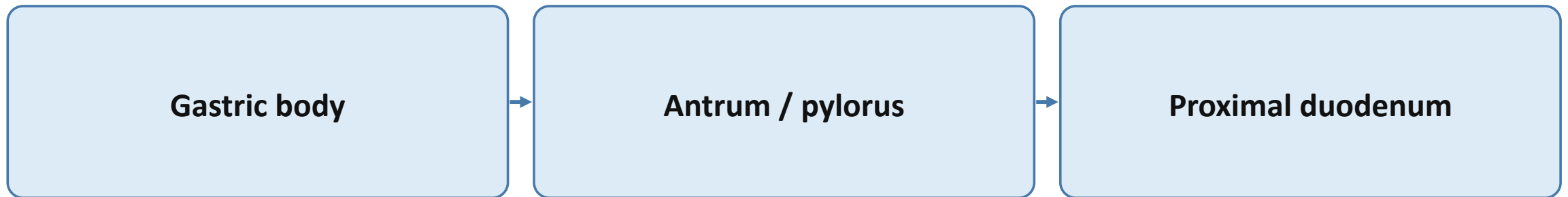
Proximal duodenum is the dominant site

- Typical chronic duodenal peptic ulcers lie only a short distance beyond the pyloric valve.
- The location is consistent with excessive gastric acid delivery.



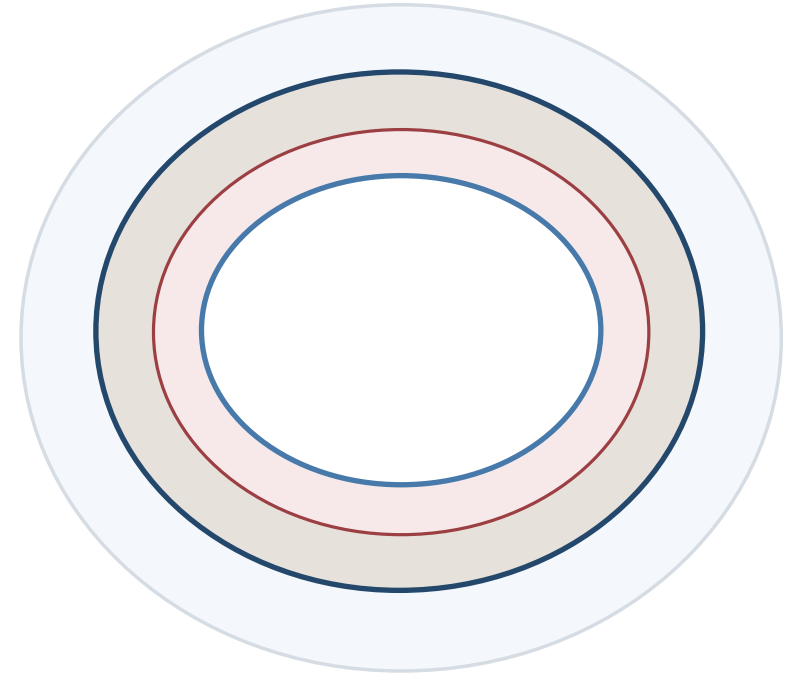
Gastric ulcers favor the lesser curvature

- Most common location: Lesser curvature near the body–antrum interface.
- The distribution differs from the proximal duodenal predilection.



Gross ulcer shape is diagnostically informative

- Chronic peptic ulcers are round or oval.
- The defect is sharply punched out and well demarcated.
- The floor is often smooth and clean.



Schematic en-face ulcer crater

The typical ulcer margin is not heaped up

Peptic configuration

Peptic ulcer: Margin usually flush with surrounding mucosa; May overhang.

Concerning neoplastic configuration

Neoplastic ulcer: Heaped-up, irregular margins raise concern for carcinoma.

Margin appearance helps—not proves—etiology

- A clean punched-out crater suggests a benign peptic pattern.
- Heaped-up margins are more characteristic of cancer.
- Morphology is not a substitute for appropriate lesion evaluation.
- Ulcer appearance alone cannot categorically exclude malignancy.

Why is the ulcer base often clean?

- Acid and peptic enzymes digest surface exudate.
- As debris is removed, the base appears smooth and relatively clean.
- Active inflammation and granulation tissue persist beneath the surface.

Peptic digestion of exudate



Clean-appearing crater



Underlying tissue injury

Chronic peptic ulcers have layered histology

- Superficial fibrinoid or necroinflammatory material.
- Predominantly neutrophilic active inflammation.
- Granulation tissue with immature vessels.
- Deep collagenous scar and remodeled vessels.

Surface exudate

Neutrophils

Granulation tissue

Fibrosis

Schematic cross-sectional strata, not a tissue image

Surface exudate records active tissue injury

- A thin fibrinoid layer may cover an active ulcer.
- Fibrinoid debris reflects injury at the exposed ulcer surface.
- This zone should be distinguished from the deeper healing response.

Neutrophils indicate ongoing active inflammation

- Neutrophils predominate in the active superficial inflammatory zone.
- The infiltrate occurs above deeper chronic repair tissue.
- Active injury and repair can coexist in one chronic lesion.

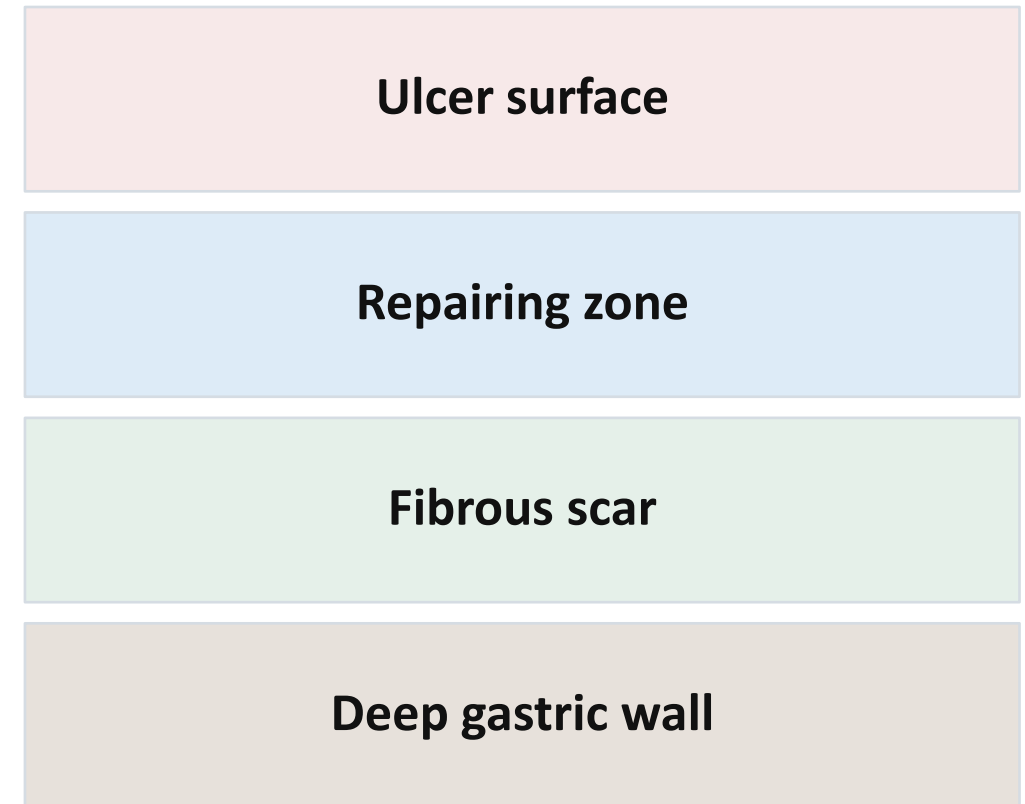
Granulation tissue provides the reparative bed

- New vessels emerge within an inflammatory stromal matrix.
- Neutrophils and mononuclear leukocytes can be present.
- Granulation tissue sits beneath the active surface zone.



Chronic ulcers create a collagenous scar

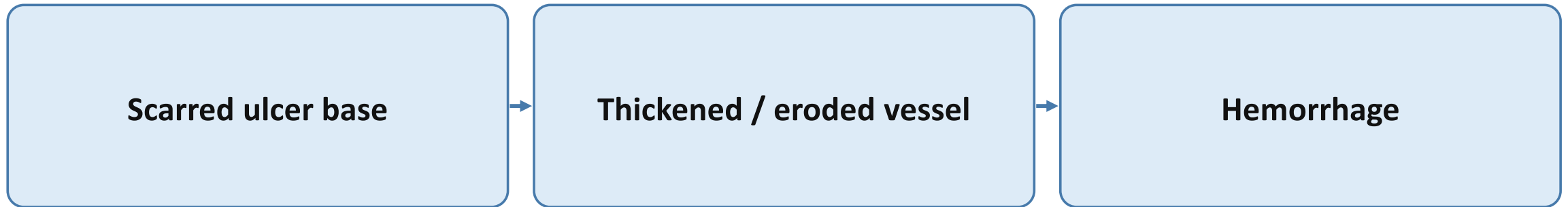
- A deeper collagenous layer lies beneath granulation tissue.
- The fibrotic reaction can involve the full thickness of the wall.
- Scar contraction distorts local wall architecture.



Schematic cross-sectional strata, not a tissue image

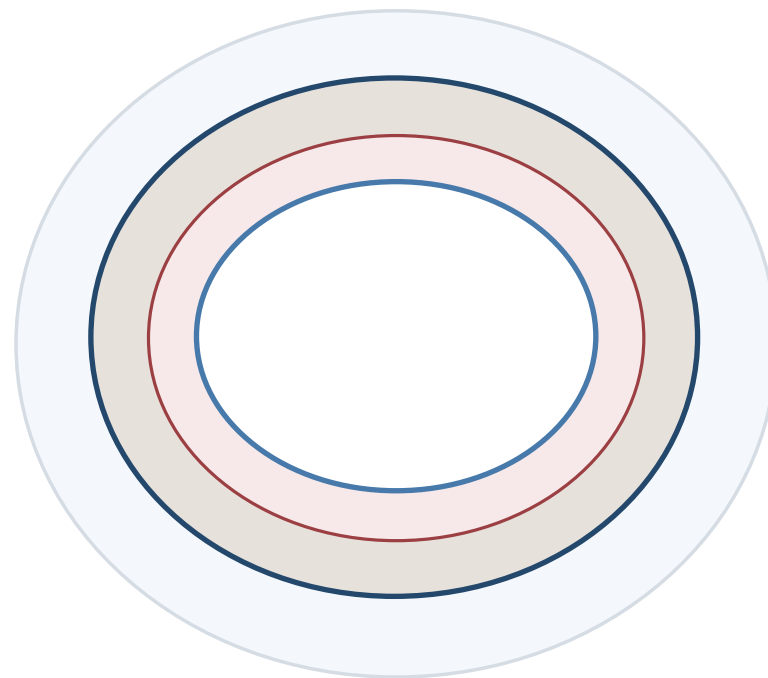
Remodeled vessels explain severe hemorrhage

- Larger vessels within the ulcer scar often have thickened walls.
- Some are thrombosed, while erosion of others can cause life-threatening bleeding.



Radiating mucosal folds reflect contraction

- Deep fibrosis pulls adjacent mucosa toward the crater.
- Mucosal folds may radiate outward from the ulcer.
- The fold pattern is a morphologic consequence of chronic scarring.



Schematic en-face ulcer crater

Duodenal foveolar metaplasia may be protective

- Gastric-type mucin cells can appear in chronically damaged duodenal mucosa.
- Gastric-type epithelium tolerates acid better than native intestinal epithelium.
- This as a possible protective response.

Chronic acid exposure



Gastric-type metaplasia



Improved acid tolerance?

Most peptic ulcers occur singly

>80%

Solitary ulcer

- More than 80% of patients have a solitary peptic ulcer.
- Multiplicity is possible and may alter etiologic reasoning.

An erosion is not equivalent to chronic PUD

Superficial erosion

Erosion: Superficial mucosal tissue loss, often accompanying acute injury.

Chronic deep ulcer

Chronic ulcer: A deeper defect with granulation and fibrous scarring.

Deep injury creates bleeding and perforation risk

- Expansion into scarred vessels produces clinically important hemorrhage.
- Full-thickness tissue destruction can breach the wall and cause perforation.

Vessel involvement → bleeding

Transmural loss → perforation

Schematic branches / outcomes

Bleeding is the most frequent major complication

15–20%

Bleeding

- Bleeding develops in 15%–20% of affected patients Table 17.4.
- It may be the initial presentation and may be life threatening.

Gastrointestinal blood loss has two clinical faces

Visible hemorrhage

Overt hemorrhage: A presentation requiring urgent clinical recognition.

Iron deficiency anemia

Chronic or occult blood loss: Can manifest as iron deficiency anemia.

Why does a benign ulcer sometimes bleed massively?

- A chronic crater reaches and injures larger arteries or veins.
- The altered vessel lies within inflamed fibrotic tissue.
- Loss of vessel integrity allows major luminal hemorrhage.

Deep ulceration



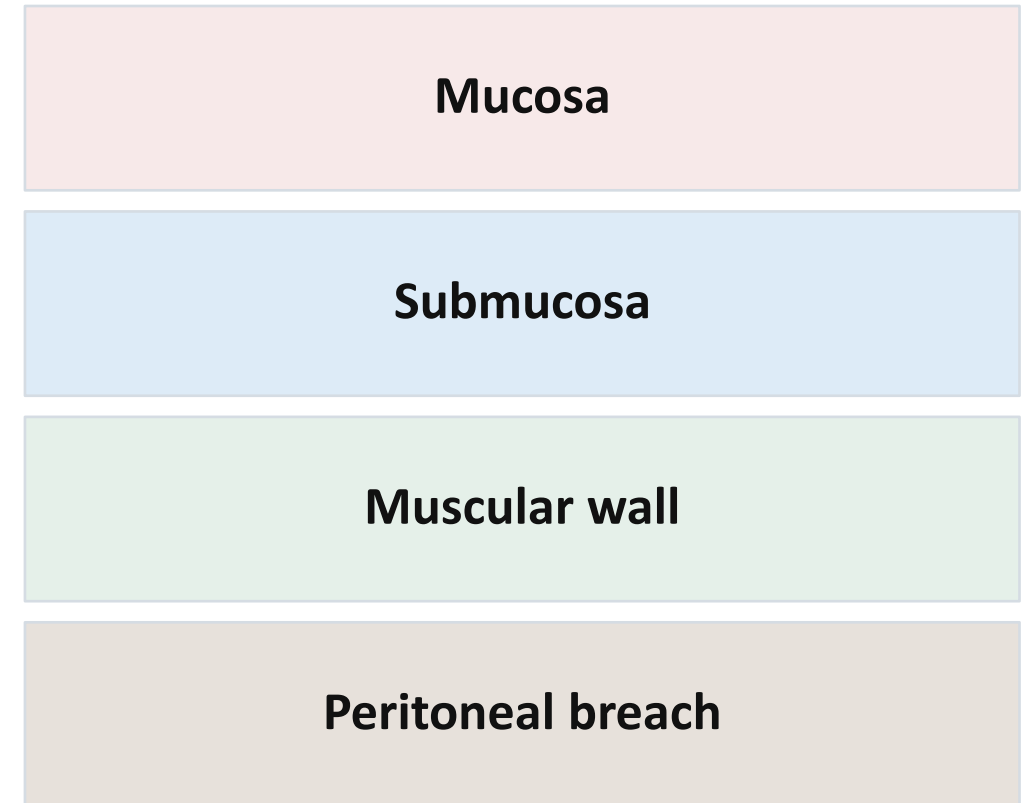
Vessel-wall injury



Acute hemorrhage

Perforation crosses the entire wall

- Deep ulceration may extend through all wall layers.
- Peritoneal contamination produces a surgical emergency.
- The lesion is no longer confined to the mucosa and submucosa.



Schematic cross-sectional strata, not a tissue image

Free subdiaphragmatic air is an imaging clue

- Perforation can release luminal gas into the peritoneal cavity.
- Upright abdominal radiography may reveal air beneath the diaphragm.
- This is an interpretive sign of possible hollow-viscus perforation.

Wall perforation



Free intraperitoneal gas



Subdiaphragmatic air

Penetrating ulcers may cause referred pain

Localized epigastric pain

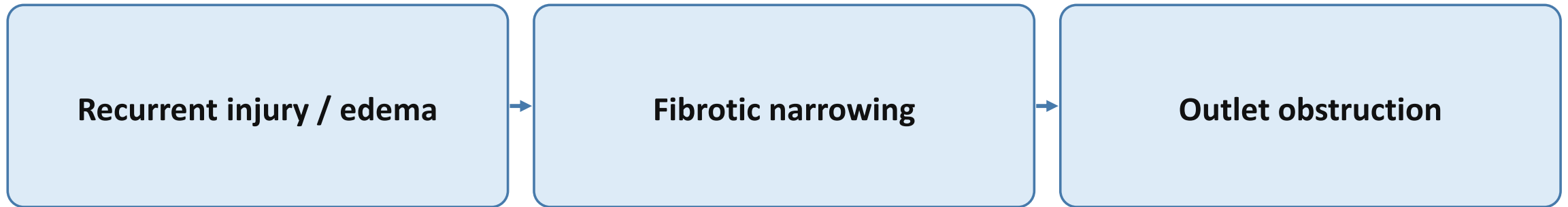
Usual pain: Epigastric burning or aching.

Pain outside epigastrium

Penetrating ulcer pain may be perceived in the back, left upper quadrant, or chest.

Scar and edema can obstruct gastric emptying

- Chronic ulcer healing produces edema and fibrotic contraction.
- Narrowing is most associated with pyloric-channel ulcers.
- Duodenal ulceration can also produce obstruction.



Obstruction has a characteristic symptom pattern

- Crampy, incapacitating abdominal pain may develop.
- Vomiting can be substantial with severe narrowing.
- Total obstruction with intractable vomiting is uncommon.

Major PUD complications in one view

Bleeding	15%–20%; Most frequent; May be first presentation
Perforation	Up to 5%; Serious acute complication
Obstruction	About 2%; Usually chronic edema or scar

Ulcer-related mortality is complication-weighted

Bleeding ~25% of ulcer deaths

Bleeding accounts for about 25% of ulcer-related deaths Table 17.4.

Perforation ~ $\frac{2}{3}$ of ulcer deaths

Perforation accounts for about two-thirds of ulcer-related deaths in that table.

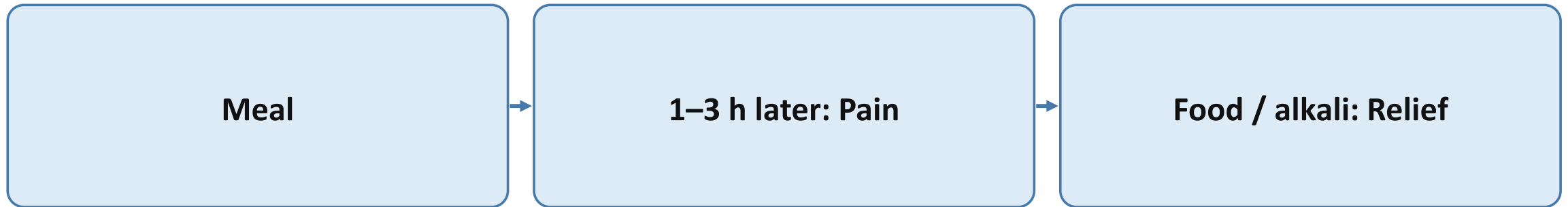
These are shares of ulcer-related deaths—not patient mortality rates

Typical ulcer pain is epigastric and burning

- The classic symptom is burning or aching in the epigastrium.
- Pain may fluctuate over the day and recur.
- Clinical assessment must also consider hemorrhage or perforation.

Meal-related timing is a useful historical clue

- Pain commonly appearing 1–3 hours after meals.
- Pain may improve after food or alkali.
- This is a typical pattern, not a diagnostic requirement.



Nocturnal pain occurs pattern

- Symptoms can worsen at night.
- Frequent pain around 11 p.m.–2 a.m.
- Clinical presentations are not uniform and timing does not localize every ulcer.

Not all patients present with pain

Dyspeptic symptoms

Some patients report nausea, vomiting, bloating, or belching.

Complication-driven presentation

Others first present with anemia, hemorrhage, or perforation.

Weight loss requires interpretation in context

- Significant weight loss is included among reported PUD manifestations.
- Symptoms alone are insufficient to assign a benign cause.
- An atypical ulcer configuration warrants evaluation for an alternative diagnosis.

H. Pylori is detectable on gastric biopsy

- Organisms generally reside in surface mucus over foveolar epithelium.
- Routine H&E may show organisms; Special stains or IHC improve recognition.
- Antral mucosa is commonly colonized, but distribution can be patchy.

Noninvasive tests assess H. Pylori infection

Urea breath test	Detects the consequence of bacterial urease activity
Fecal bacterial detection	Noninvasive organism-based testing
Serologic antibodies	Evidence of anti-H. Pylori immune response

Biopsy-based H. Pylori tests complement histology

Histologic detection	Demonstrates organisms and mucosal inflammation
Rapid urease test	Detects bacterial enzyme activity
Culture or PCR	Can identify organism or bacterial DNA

Treatment targets infection and luminal acid

- H. Pylori eradication addresses a major cause of persistent gastritis.
- Proton pump inhibitors suppress gastric acid production.
- Combining etiologic treatment with acid suppression supports healing.

Eradicate H. Pylori



Suppress acid with PPI



Allow ulcer healing

Withdrawal of injurious drugs matters

- Remove or reassess NSAID exposure where clinically feasible.
- Even selective COX-2 inhibitors can impair mucosal protection.
- Persistent exposure can hinder healing despite acid suppression.

Eradication reduces the recurrence burden

<20%

Recurrence following clearance

- Recurrence below 20% after successful H. Pylori clearance.
- The figure concerns recurrence following successful eradication—not untreated natural history.

Chronic PUD differs from stress-related injury

Chronic peptic ulcer

Chronic PUD is linked to sustained gastritis, acid imbalance, granulation, and scarring.

Stress-related mucosal injury

Acute stress-related ulcers often arise with physiologic stress and ischemia and lack the mature chronic scar pattern.

Case: Recurrent epigastric pain with antral gastritis

HYPOTHETICAL TEACHING VIGNETTE

- Hypothetical: A patient has epigastric pain and chronic antral H. Pylori gastritis.
- Which physiologic sequence best explains an associated proximal duodenal ulcer?
- Identify the changed acid and bicarbonate pathways.

Mechanisms to consider

Antral inflammation

Acid secretion

Duodenal mucosal protection

Case interpretation: Secretory and defense imbalance

- Antral inflammation promotes gastrin and parietal-cell stimulation.
- Gastric acid delivery increases while duodenal bicarbonate defense falls.
- The proximal duodenum becomes vulnerable to chronic peptic injury.

↑ Gastrin / acid



↓ Duodenal bicarbonate



Proximal duodenal ulcer

Case: Older adult using NSAIDs with bleeding

HYPOTHETICAL TEACHING VIGNETTE

- Hypothetical: An older adult taking NSAIDs develops melena and iron deficiency anemia.
- What protective system has been compromised?
- What ulcer-base structure explains possible massive hemorrhage?

Mechanisms to consider

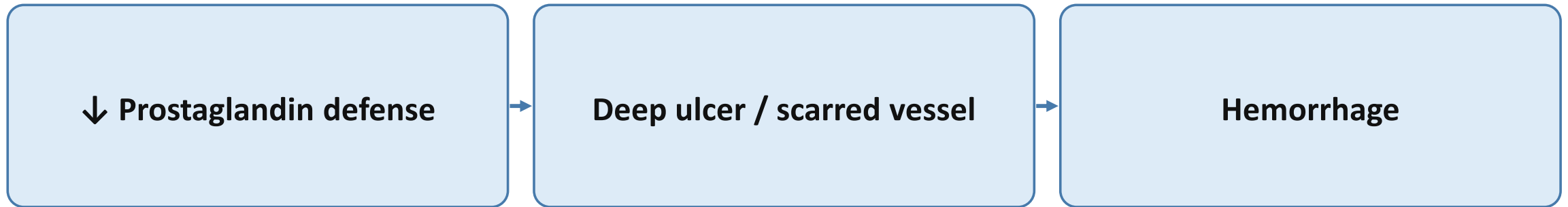
NSAID exposure

Chronic crater

Vessel injury

Case interpretation: Drug effect meets ulcer anatomy

- COX inhibition reduces protective prostaglandins.
- Ulceration may extend to thickened vessels within fibrous scar.
- Vessel injury can produce life-threatening hemorrhage.



Pathology differential: Peptic versus malignant crater

Typical margin	PUD: Level / possible overhang; Cancer: Often heaped up
Floor	PUD: May be smooth and clean after peptic digestion
Stromal response	Chronic PUD: Granulation and deep fibrous scar
Interpretation	Gross appearance supports but never proves benignity

Integrated model of chronic peptic injury

- Infection or hyperacidity can increase luminal injury.
- NSAIDs, smoking, and ischemia can reduce defensive capacity.
- Persistent injury causes a crater with acute inflammation, granulation, and scarring.

Increased acid-peptic load

Reduced mucosal defenses

**Chronic ulcer →
complications**

Schematic branches / outcomes

Five diagnostic anchors

- Predilection: Proximal duodenum or gastric lesser curvature
- Shape: Solitary, sharply punched-out round/oval crater
- Histology: Superficial active injury over granulation and scar
- Complications: Bleeding, perforation, obstruction
- Etiology: H. Pylori, NSAIDs, cigarette use

References and image provenance

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Ch.17, pp.696–702.
- Primary PUD text: pp.701–702; complication frequencies from Table 17.4, p.702.
- Robbins Figs. 17.13–17.14: mucosal protection and H. pylori gastritis pathogenesis.
- Robbins Fig. 17.17: chronic peptic ulcer morphology; Tables 17.3–17.4: risk factors and complications.