Peptic Ulcer Disease:
Diagnosis & What's New in Management

| 2024–2025 Updates

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Based on 2024 ACG Guidelines & Latest Evidence

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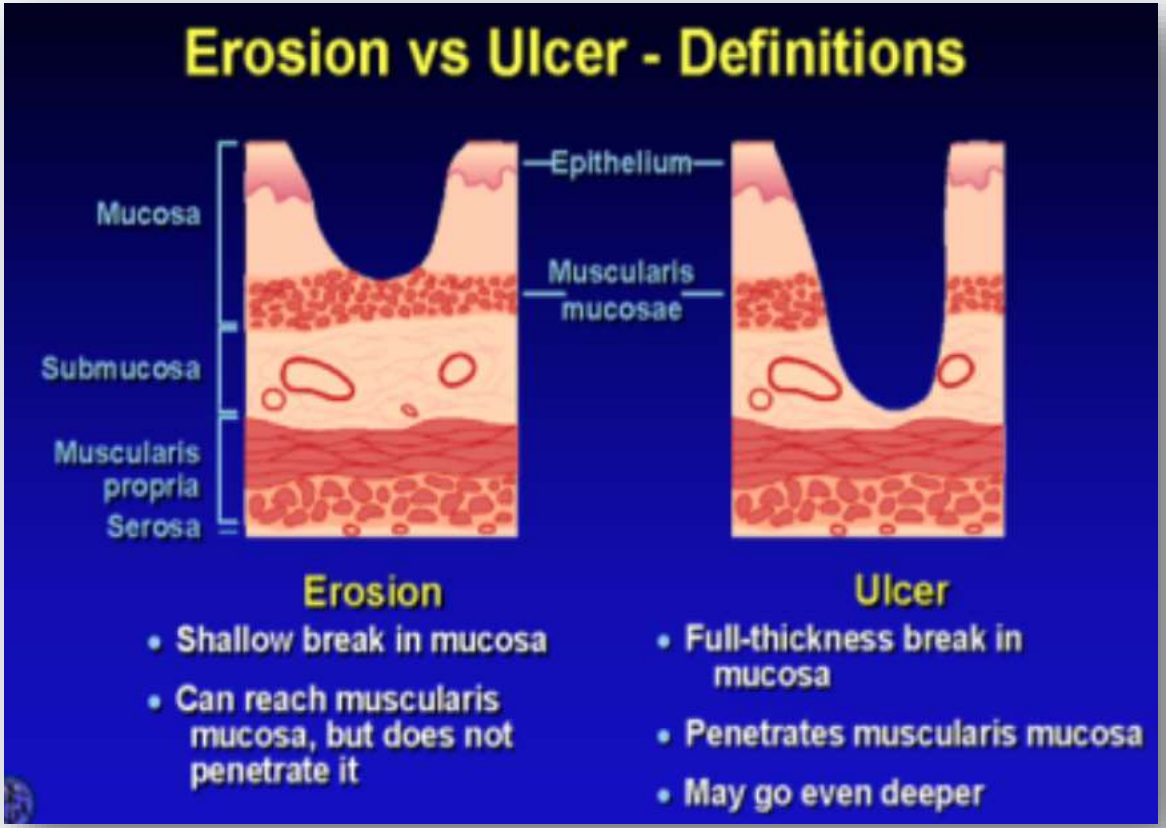
Learning Objectives

- Define peptic ulcer disease (PUD) and recall its epidemiology
- Identify the major etiologies: H. pylori, NSAIDs, and idiopathic ulcers
- Describe the clinical presentation and appropriate diagnostic workup
- Apply current first-line and salvage treatment strategies per 2024 ACG guidelines
- Recognize the role of vonoprazan (PCAB) and novel therapies
- Manage NSAID-induced ulcers and complications (bleeding, perforation)
- Counsel patients on prevention and follow-up strategies

Epidemiology & Pathophysiology

Ulcer vs Erosion



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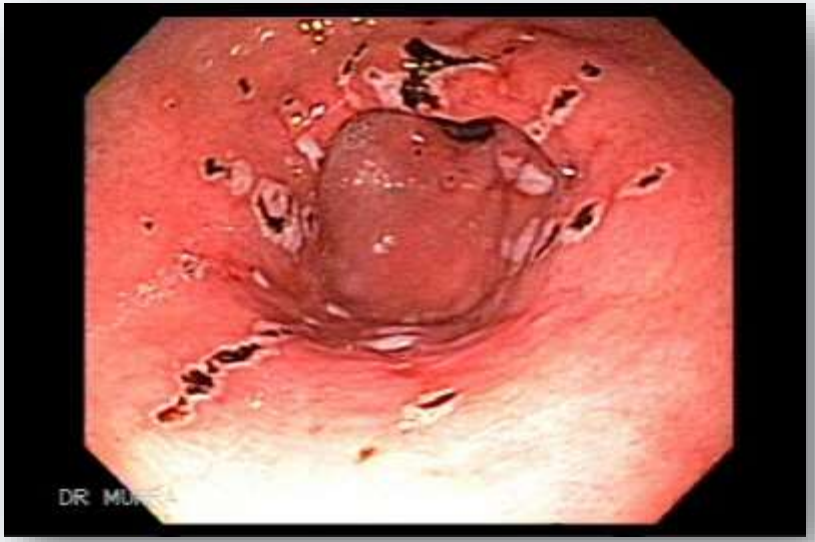
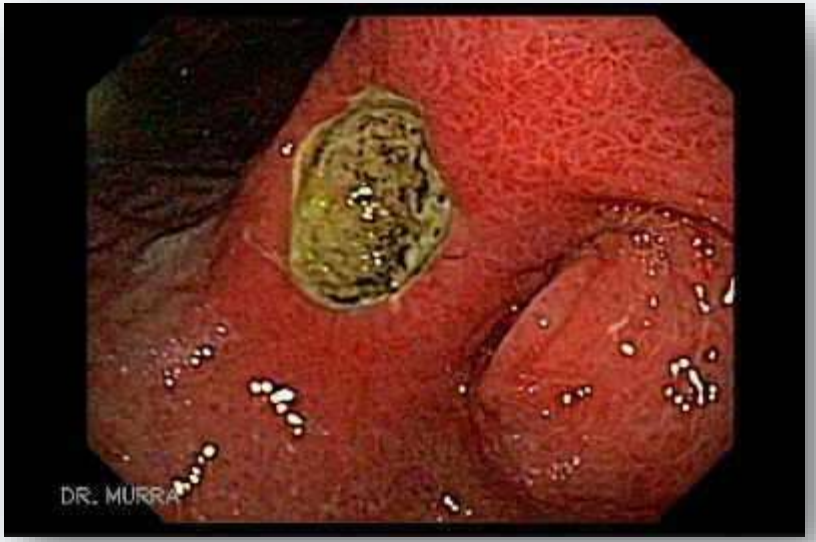




Epidemiology of Peptic Ulcer Disease

~500K
New cases/year (USA)

4M
Annual ulcer recurrences (USA)

~10%
Lifetime prevalence in adults

> 90 %
local Studies in AUH

- **Duodenal ulcers (DU):** most common; >95% in bulb/pyloric channel; peak age 30–55 years
- **Gastric ulcers (GU):** antrum (60%) & lesser curvature (25%); peak age 55–70 years
- DU incidence declining due to H. pylori eradication; GU incidence unchanged (NSAID/aspirin-driven)
- H. pylori classified as Group 1 carcinogen by WHO — linked to gastric adenocarcinoma and MALT lymphoma
- Higher H. pylori prevalence in non-White populations, crowded/poor sanitary conditions, immigrants from endemic regions

Pathophysiology

Mucosal Injury (Aggressive Factors)

- HCl acid & pepsin overproduction / hypersecretion
- H. pylori virulence factors: CagA, VacA toxins → mucosal damage
- NSAIDs: systemic COX-1 inhibition → decreased prostaglandins → impaired mucosal protection
- Bile reflux, ischemia

Mucosal Defense (Protective Factors)

- Mucus-bicarbonate barrier lining epithelium
- Phospholipid layer & surface hydrophobicity
- Rapid epithelial restitution & renewal
- Prostaglandin E2 and I2 (stimulate mucus & bicarbonate)
- Adequate mucosal blood flow & microcirculation

Etiologies

Key Etiologies

- **H. pylori infection:** ~70–80% of DU; ~50–60% of GU — colonises gastric epithelium causing chronic inflammation
- **NSAIDs & low-dose aspirin:** systemic + topical COX-1 inhibition; gastric ulcers 4× more common than duodenal in NSAID users
- **Idiopathic ulcers** (<5–10%): Zollinger-Ellison syndrome (gastrinoma), systemic mastocytosis, stress ulcers, CMV, Crohn's disease

Medications that increase the risk of ulceration

- **Oral anticoagulants** (eg, warfarin, direct oral anticoagulants [DOACs])
- **Antiplatelet agents** beyond aspirin (eg, clopidogrel)
- **SSRIs** which may impair platelet aggregation
- **Corticosteroids**, which primarily increase risk when used concurrently with NSAIDs
- **Bisphosphonates** and certain chemotherapy

Lifestyle and environmental factors

- **Smoking**: causal link between smoking initiation and the development of both gastric and duodenal ulcers.
- **Alcohol, Caffeine, Spicy/citrus Foods, and stress** do **NOT** cause PUD but may aggravate symptoms and impair healing
- **High BMI:** has been causally associated with an increased risk of PUD
- **Salt:** enhance H. pylori colonization.
- **Defensive factors**: High-Fiber Diets, Vitamin A & C, Probiotics

Clinical Presentation & Diagnosis

Clinical Presentation

Symptoms

- Epigastric burning or gnawing pain (cardinal symptom)
- Duodenal ulcer: pain relieved by food or antacids; nocturnal awakening
- Gastric ulcer: pain may worsen with eating
- Nausea, bloating, early satiety, anorexia
- Up to 70% may be asymptomatic (especially elderly on NSAIDs)

Alarm Features (Red Flags) — Urgent Endoscopy

- Unintentional weight loss
- Progressive dysphagia / odynophagia
- GI bleeding: hematemesis, melena, or hematochezia
- Persistent vomiting (suggests outlet obstruction)
- Iron-deficiency anaemia on labs
- New-onset symptoms in patient aged >60 years

Duodenal vs. Gastric Ulcer

- DU: age 30–55, more common in men, H. pylori dominant etiology
- GU: age 55–70, NSAID use prevalent; malignancy must be excluded
- **ALL gastric ulcers must be biopsied to exclude malignancy**
- Repeat endoscopy in 8–12 weeks to confirm GU healing

Complications

- **GI Bleeding** (most common): hematemesis, melena, hematochezia
- **Perforation**: acute abdomen, peritonitis, free air under diaphragm
- **Penetration**: into adjacent organs (pancreas most common)
- **Gastric Outlet Obstruction**: chronic scarring; vomiting

Diagnostic Approach

Upper GI Endoscopy (Gold Standard)

- Visualise ulcer: location, size, depth, base & edge characteristics
- Biopsy ALL gastric ulcers to exclude malignancy
- Rapid urease test (CLO test) for H. pylori on antral biopsy
- Urgent endoscopy within 24h for acute upper GI bleeding
- Forrest classification guides management of bleeding ulcers

Non-Invasive H. pylori Testing

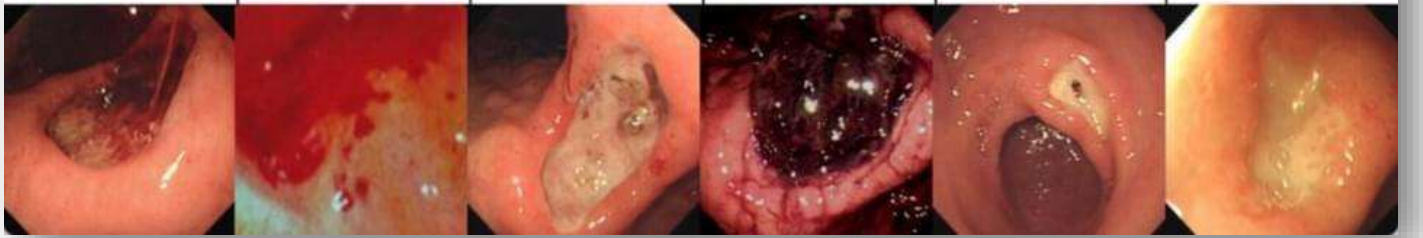
- **13C-Urea Breath Test (UBT)** — preferred; high sensitivity & specificity
- **Stool Antigen Test** — accurate, inexpensive, good for follow-up
- **IgG Serology** — **NOT** recommended post-treatment (remains positive after eradication)
- Stop PPIs ≥2 weeks and antibiotics ≥4 weeks before testing to avoid false negatives
- **Test of cure:** UBT or stool antigen ≥4 weeks post-treatment (mandatory per 2024 ACG)

Forrest Classification of Bleeding Ulcers

- Ia: Spurting haemorrhage (active) / Ib: Oozing → High risk; urgent endoscopic therapy
- IIa: Non-bleeding visible vessel (NBVV) → High re-bleed risk (~50%); endoscopic therapy recommended
- IIb: Adherent clot → Intermediate risk; consider removal + therapy; IIc: Flat spot → Low risk (<10%)
- III: Clean ulcer base → Very low re-bleed risk (<5%); medical management; early discharge safe

Forrest Classification		
Stage	**Characteristics**	**Re-bleeding**
Ia	Spurting Bleed	60 - 100 %
Ib	Oozing Bleed	50%
IIa	Non-Bleeding Visible Vessel	40 - 50 %
IIb	Adherent Clot	20 - 30 %
IIc	Flat Spot in ulcer crater	7 - 10 %
III	Clean Base Ulcer	3 -5 %

Ia	Ib	IIa	IIb	IIc	III
Spurting bleed	Oozing bleed	Non-bleeding visible vessel	Adherent clot	Flat spot in ulcer crater	Clean base ulcer



Management — 2024 ACG Guidelines & Updates

H. pylori Eradication: 2024 ACG Guidelines

KEY UPDATE 2024: Clarithromycin-based triple therapy REMOVED as first-line. Antibiotic resistance to clarithromycin, levofloxacin & metronidazole now exceeds 30%.

First-Line Regimen	Drugs & Doses	Duration	Notes
Optimized Bismuth Quadruple (BQT) - PREFERRED	PPI + Bismuth + Tetracycline + Metronidazole	14 days	Preferred 1st-line; effective across resistance patterns
Vonoprazan Dual Therapy	Vonoprazan 20mg BD + Amoxicillin 1g TDS	14 days	FDA-approved 2022; new PCAB class (Voquezna Dual Pak)
Vonoprazan Triple Therapy	Vonoprazan + Amoxicillin + Clarithromycin	14 days	Only if susceptibility confirmed OR no prior macrolide
Rifabutin Triple (Talicia®)	PPI + Amoxicillin + Rifabutin 50mg TDS	14 days	For penicillin allergy or prior BQT failure

Test of cure is MANDATORY for ALL patients: UBT or stool antigen ≥4 weeks after completing therapy (NOT serology)

Vonoprazan (P-CAB): A New Era in Acid Suppression

Mechanism of Action

- Potassium-Competitive Acid Blocker (P-CAB / PCAB)
- Reversibly blocks H+/K+-ATPase by competing with K+ ions
- Does NOT require acid activation (unlike PPIs) — active immediately
- More stable in acidic environments → stronger & sustained acid suppression
- Works regardless of meal timing or CYP2C19 genotype

Clinical Superiority vs. PPIs

- Eradication: 84.7% (triple) & 78.5% (dual) vs. 78.8% with lansoprazole triple
- Superior in clarithromycin-resistant H. pylori strains
- First new acid-suppressant class FDA-approved in USA in >30 years
- FDA-approved May 2022 as Voquezna® (Phathom Pharmaceuticals)
- No nocturnal acid breakthrough unlike PPIs

Advantages over PPIs

- Faster onset: effective within 1–2 hours of first dose
- No CYP2C19 polymorphism dependency (predictable effect)
- No requirement for enteric coating or timing with meals
- Consistent, reliable intragastric pH >4 maintenance

Limitations & Adverse Effects

- Limited long-term comparative safety data versus PPIs
- Higher cost; limited availability outside US and Japan
- Common side effects: diarrhea, dysgeusia, candidiasis, headache
- Potential drug interactions (under ongoing investigation)

Salvage Therapy: When First-Line Fails

Treatment failure = positive test of cure post-treatment. NEVER retreat with the same regimen. Use susceptibility testing to guide choice.

2nd Line: No Prior BQT

- Optimized BQT for 14 days (if not used as first-line)
- Antibiotic susceptibility testing preferred before choosing regimen
- Levofloxacin-based therapy: ONLY if susceptibility confirmed (resistance >37%)
- Avoid clarithromycin unless susceptibility confirmed

2nd Line: After Failed BQT

- Rifabutin triple therapy (Talicia®) — 14 days
- PPI or Vonoprazan + Amoxicillin + Rifabutin 50mg TDS
- Active against many multidrug-resistant H. pylori strains
- Susceptibility testing strongly encouraged before prescribing

NEW 2024 ACG: Antibiotic Susceptibility Testing (AST)

- 2024 ACG: First time AST formally incorporated into the treatment algorithm — recommended when first-line therapy fails
- Methods: culture-based (endoscopic biopsy) or molecular PCR from stool/biopsy (detects resistance mutations)
- Resistance rates: clarithromycin 22–31%, levofloxacin 37%, metronidazole >50% — AST guides appropriate regimen selection
- Novel agent: Rifasutenizol (TNP-2198) entering Phase 3 trials — dual mechanism; active against multidrug-resistant strains

NSAID-Induced Ulcers: Risk Stratification & Prevention

HIGH RISK	MODERATE RISK	LOW RISK
• Prior GI bleeding or ulcer • On anticoagulants • Multiple (≥3) risk factors • High-dose NSAIDs	• Age ≥65 years • 1–2 risk factors • Concurrent corticosteroids • Concurrent SSRIs	• Age <65 years • No other risk factors • Low-dose NSAID use • No H. pylori infection
AVOID NSAIDs if possible; use alternative analgesia + daily PPI	**Use COX-2 inhibitor alone OR traditional NSAID + PPI**	**No gastroprotection generally required**

- **NSAIDs** increase upper GI bleeding risk **~4-fold**; gastric ulcers 4× more common than DU in NSAID users
- **Low-dose aspirin** 75 mg/day: **2.3× bleeding risk** — prescribe PPI for all CV patients needing chronic aspirin
- **H. pylori + NSAID** use is synergistic — test and eradicate H. pylori in ALL patients before starting chronic NSAIDs
- **COX-2 inhibitors** (celecoxib): reduced GI risk but increased cardiovascular risk — individualize treatment choice

Management of Bleeding Peptic Ulcer

1. Initial Resuscitation

- 2 large-bore IV cannulae; crossmatch blood
- IV fluid resuscitation; transfuse if Hb <7 g/dL
- IV PPI: 80 mg bolus then 8 mg/hr infusion
- Risk stratify: Glasgow-Blatchford Score
- GBS ≤1: consider outpatient management
- IV erythromycin 250 mg 30 min pre-scope (enhances gastric emptying)
- NPO; monitor vitals & urine output closely

2. Endoscopic Therapy

- Urgent endoscopy within 24h for acute UGIB
- Within 12h if massive/ongoing haemorrhage
- Forrest Ia/Ib/IIa: Dual endoscopic therapy (injection + thermal/mechanical)
- Hemostatic clips, multipolar electrocoagulation, heater probe
- Over-the-scope clips (OTSC/Ovesco) for deep/fibrotic ulcers
- TC-325 hemostatic powder as bridge/rescue therapy
- No second-look endoscopy routinely recommended

3. Rescue & Prevention

- Re-bleeding: repeat endoscopic therapy
- Persistent bleeding → interventional radiology (embolisation)
- Surgery: rare in modern era (<5% of cases)
- Continue high-dose IV PPI 72h post-hemostasis
- Resume aspirin early (1–3 days) if CV indication
- Test & eradicate H. pylori after bleeding episode
- Idiopathic ulcers: long-term daily PPI recommended

EUS-guided angiotherapy & thermal ablation are emerging options for refractory non-variceal UGIB


Hemospray

Modality	Clinical Role & Target Lesion	Mechanism of Action	Key Advantages	Key Limitations	Key Performance Notes
Combination Therapy (Epinephrine Injection + Thermal or Mechanical)	First-line for actively bleeding ulcers **(FIa, FIb)** and non-bleeding visible vessels **(FIIa)**	Epinephrine injection creates tamponade and vasoconstriction, which then allows for a clearer field to apply definitive therapy (thermal coagulation or clip).	Significantly more effective than epinephrine injection alone. Supported by high-quality evidence	Requires multiple devices and technical proficiency.	The ESGE strongly recommends this combination approach for active bleeding
Through-the-Scope (TTS) Clips	First-line mechanical option or part of combination therapy for **FIIa** lesions. Also effective for bleeding vessels.	Direct mechanical compression of the bleeding vessel.	Well-studied, multiple sizes, and ease of access	Risk of slippage or incomplete closure on large, fibrotic ulcers. Can be challenging to deploy in difficult positions like the duodenal sweep	
Thermal Therapy (Heater Probe, Bipolar/Multipolar Coagulation)	First-line thermal option or part of combination therapy for active bleeding (FIa, FIb) and FIIa	Uses heat to cause edema, coagulation of tissue proteins, and vessel sealing.	Well-studied, ease of access, compatible with injection therapy	Risk of perforation and delayed bleeding, especially with indiscriminate use	
Over-the-Scope Clips (OTSC)	Preferred treatment for **recurrent** bleeding after initial hemostasis Increasingly used for large, fibrotic ulcers.	Deploys a larger, stronger clip cap-mounted on the endoscope tip, capable of grasping more tissue.	Grasps a large area, durable, and associated with a lower risk of rebleeding compared to standard modalities	Requires removing the endoscope to mount the device, which can be challenging in patients with ongoing bleeding. Difficult to position on some lesions	ESGE suggests considering OTSC for persistent refractory bleeding and recommends its use for recurrent hemorrhage
Hemostatic Sprays/Powders (e.g., TC-325)	A "**bridge**" therapy for persistent bleeding refractory to standard modalities. Useful for **large, oozing surfaces** where targeting a single point is difficult	A mineral powder that is sprayed onto the bleeding site, forming a mechanical barrier and concentrating clotting factors.	Easy and rapid application over a large area without precise targeting	Risk of **rebleeding** after 24-72 hours, device malfunction (catheter clogging), and it can cause biliary obstruction if used near the ampulla	The recommendation is weak due to low-quality evidence, but it is a useful rescue tool

What's New in 2024–2025?

Innovations & Emerging Therapies

Rifasutenizol (TNP-2198) — Phase 3

- Novel antibiotic entering Phase 3 evaluation (2024–2025)
- Dual mechanism: nitroimidazole + benzimidazole moieties
- Active against multidrug-resistant H. pylori strains
- Promising results in clarithromycin & metronidazole-resistant cases

Probiotics as Adjunctive Therapy

- Lactobacillus & Bifidobacterium strains as adjuncts to eradication
- Reduce antibiotic-associated GI side effects by 30–50%
- May modestly improve eradication rates (meta-analysis data)
- 2024: Not yet in ACG guidelines; widely used as adjunct in Asia

H. pylori Vaccine Research

- Phase 2/3 trials underway globally. Oral & parenteral candidates targeting BabA, OipA, CagA antigens — potential future prevention strategy

Innovations & Emerging Therapies

Molecular Susceptibility Testing

- PCR-based stool or biopsy tests for resistance mutations
- Detects clarithromycin, levofloxacin, tetracycline resistance genes
- 2024 ACG: First formal recommendation for AST in algorithm
- Enables precision-guided, targeted H. pylori therapy

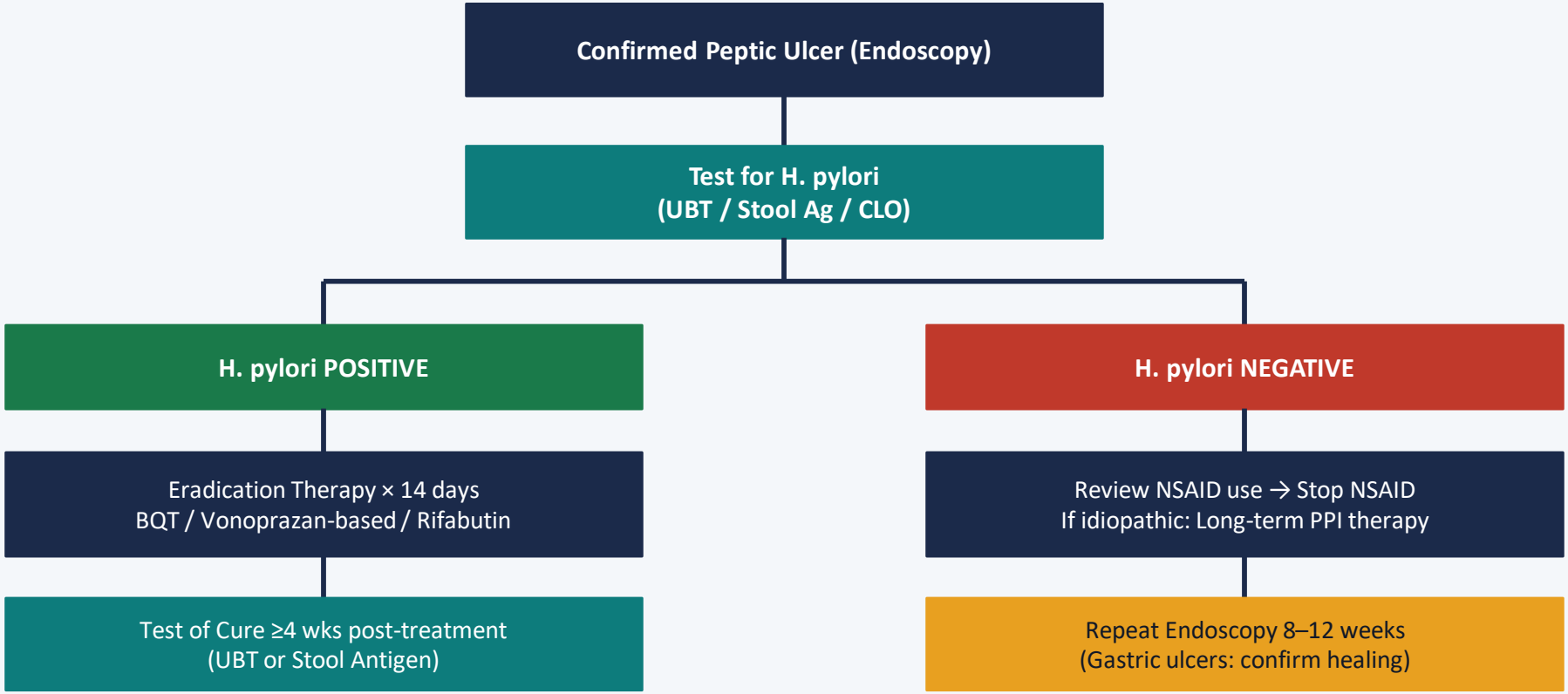
Advanced Endoscopic Hemostasis

- TC-325 (Hemospray®): hemostatic nanopowder for bridge therapy
- Over-the-scope clips (OTSC): superior closure of large/fibrotic ulcers
- EUS-guided angiotherapy: emerging for refractory bleeding
- Second-look endoscopy: no longer routinely recommended

H. pylori Vaccine Research

- Phase 2/3 trials underway globally. Oral & parenteral candidates targeting BabA, OipA, CagA antigens — potential future prevention strategy

Management Algorithm Summary



Follow-Up & Patient Counselling

Follow-Up Protocol

- All patients: Test of cure ≥4 weeks post-eradication (UBT or stool antigen)
- Gastric ulcers: repeat endoscopy at 8–12 weeks to confirm complete healing
- Non-healing or persistent GU: re-biopsy to exclude malignancy
- Continue PPI during eradication course and 4–8 weeks after completion
- Annual review if on long-term PPI, NSAIDs, or aspirin

Patient Education

- Complete the full antibiotic course — do not stop early even if feeling better
- Avoid NSAIDs and aspirin unless medically essential
- If NSAIDs essential: always take with food and PPI co-prescription
- Smoking cessation: nicotine impairs mucosal blood flow and healing
- Limit alcohol intake: exacerbates mucosal injury and delays healing
- Return urgently if: melena, haematemesis, severe abdominal pain

Follow-Up & Patient Counselling

Special Populations

- Elderly: higher bleeding risk; PPI prophylaxis with NSAIDs/aspirin
- Pregnancy: avoid bismuth & tetracycline; use amoxicillin-based regimens
- Liver disease: adjust antibiotic doses; avoid metronidazole overdose
- Renal impairment: bismuth caution; dose-adjust antibiotics accordingly

Prevention Summary

- Screen and eradicate H. pylori in all confirmed PUD patients
- Use lowest effective NSAID dose; prefer COX-2 inhibitor if available
- Co-prescribe PPI with NSAIDs in moderate-to-high risk patients
- Test and treat H. pylori before starting chronic NSAID therapy
- Early eradication of H. pylori may reduce long-term gastric cancer risk

Key Takeaways

01 H. pylori & NSAIDs cause >90% of peptic ulcers — always test for both in every patient diagnosed with PUD

02 2024 ACG: Clarithromycin-based triple therapy is REMOVED from first-line — BQT or vonoprazan-based regimens preferred

03 Vonoprazan (P-CAB): FDA-approved 2022 — superior acid suppression vs. PPIs; higher eradication rates vs. PPI-based regimens

04 Antibiotic susceptibility testing NOW recommended when first-line fails — resistance >30% for clarithromycin & levofloxacin

05 Test of cure is MANDATORY for ALL patients — UBT or stool antigen ≥4 weeks post-treatment (NOT serology)

06 All gastric ulcers need biopsy at endoscopy + repeat scope at 8–12 weeks to confirm healing and exclude malignancy

07 Emerging: Rifasutenizol (Phase 3), molecular AST, TC-325 hemostatic powder, and H. pylori vaccine trials underway

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