

Refractory Ulcers

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Disclosures

Consultant

- Phathom Pharmaceuticals

Peptic Ulcer Disease

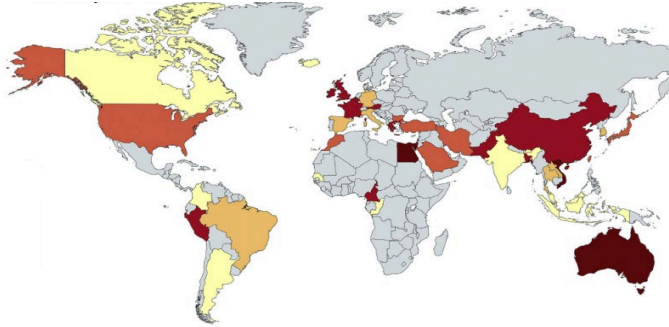
- PUD incidence: 1/100 to 1/800
 - *Helicobacter pylori* infection, NSAID use, smoking
- **Refractory** PUD: endoscopically proven ulcer > 5 mm diameter that does not heal after 8-12 weeks of PPI treatment
 - 5-10% GU and DU are refractory to 12 weeks of PPI therapy
- **Recurrent** PUD: endoscopically proven PUD > 5 mm in diameter that recurs after healing
 - 5-30% within the first year based on whether *Helicobacter pylori* has been successfully eradicated

Refractory PUD Risk Factors

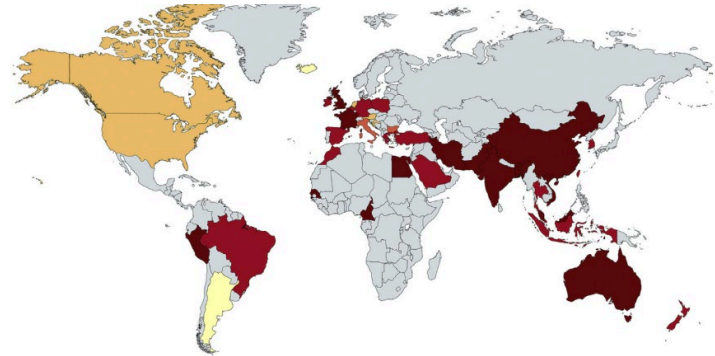
- Significant overlap in the risk factors for refractory and recurrent peptic ulceration
 - Persistent *Helicobacter pylori* infection
 - Use of culprit medications/exposures
 - Impaired healing
 - Comorbid diseases

High Rates of Global *H pylori* Antibiotic Resistance

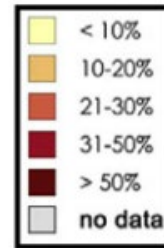
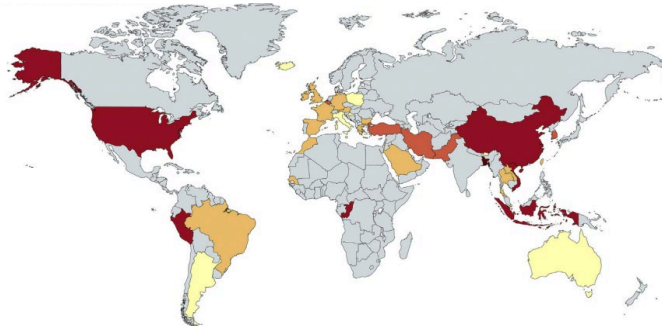
Clarithromycin resistance: 22% (95% CI: 7%, 37%)



Metronidazole resistance: 20% (95% CI: 13%, 27%)



Levofloxacin resistance 37% (95% CI: 23%, 39%)



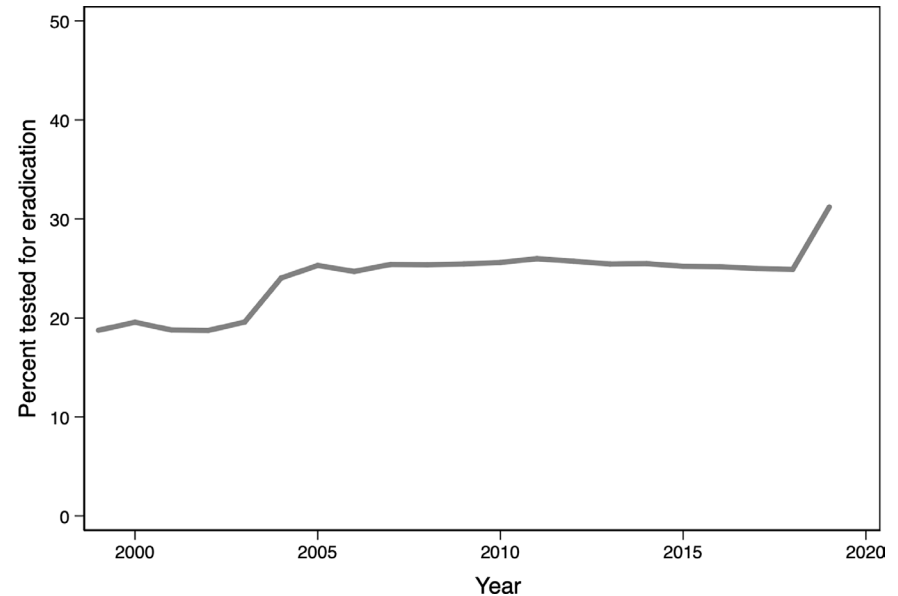
- VERY limited US data (< 1000 *H pylori* isolates across 3 studies)
- More recent data, even higher rates

Savoldi A et al. *Gastroenterology*. 2018;155:1372-1382.

H pylori: Post-Eradication Therapy Management

- ALL patients should have non-serological *H pylori* testing -- urea breath, fecal Ag, or RUT/CLO -- to confirm eradication (repeat biopsies acceptable depending on clinical scenario)^[1]
 - At least 4 weeks following therapy to avoid false positives due to *H pylori* shedding^[2]
 - Off PPI or bismuth therapy for at least 2 weeks to avoid false negative^[2]
- Historically low rates of eradication confirmation

Frequency of confirmation testing: Nationwide US Veterans Cohort^[1]



Culprit Medications/Exposures

- Continued use of NSAIDs/ASA
- Other medications: glucocorticoids, cytotoxic agents, bisphosphonates, olmesartan
- Substance use: cocaine, tobacco exposure

Impaired Healing

- Ulcer characteristics: intense inflammatory response, dense scarring, low mucosal blood flow impairing angiogenesis and tissue repair
 - Ulcer size: GU heal at approximately 3 mm/week
 - Large ulcers may be associated with fibrosis, take longer to heal
- Comorbid illness: uremia, respiratory failure, organ transplantation, cirrhosis, critical illness
- Smoking: suppresses mucosal cell proliferation and induces apoptosis

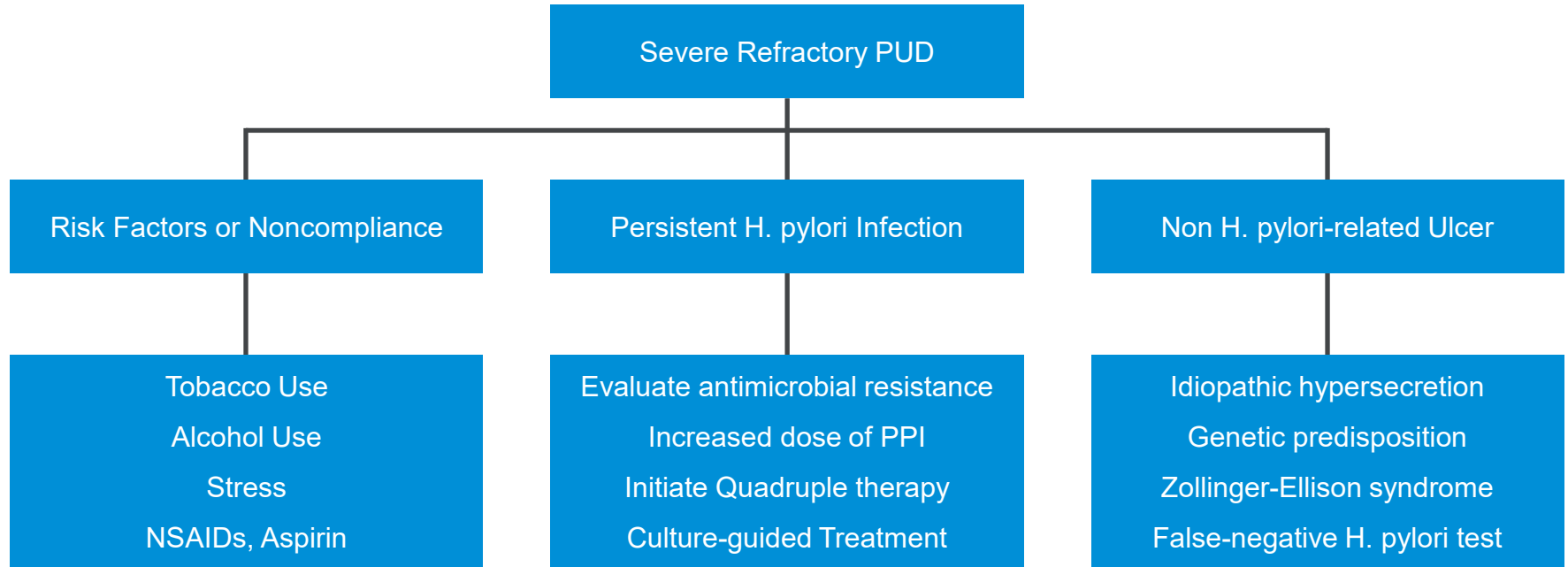
Ineffective Acid Suppression

- Adherence to Therapy
 - Non-adherence to antisecretory therapy
 - Tolerance to H2RAs
 - Rapid p450 mediated metabolism of PPI
- Acid hypersecretion
 - ZE syndrome (gastrinoma): fasting serum gastrin 150-1000 pg/ml off anti-secretory medications; confirm with provocation testing
 - Hyperparathyroidism
- Idiopathic gastric acid hypersecretion: postprandial hypersecretion of acid and hypergastrinemia with accelerated gastric emptying

Rare Causes of Refractory PUD

Crohn's	Sarcoidosis	Lymphoma
Eosinophilic gastritis/enteritis	Tuberculosis	Syphilis
CMV	IgG4 Sclerosing disease	Mesenteric ischemia

Differential of Refractory PUD



Diagnosis of Refractory PUD

- Should be suspected in patients with endoscopically proven PUD with persistent or recurrent dyspepsia
- Diagnosed via EGD for evaluation of symptoms or surveillance to document healing after initial therapy of GU
 - Symptoms: persistent or recurrent bleeding or luminal complications (perforation, stricture, obstruction)
- Associated symptoms or findings suggestive of acid hypersecretion: diarrhea, weight loss, esophagitis, thickened gastric folds

Repeat Endoscopy After PUD Diagnosis

- GU: Recommended at 8-12 weeks
 - Can help determine underlying etiology
 - Biopsies should be performed to exclude malignancy and other causes of ulceration; four quadrant biopsies
 - If suspicious for malignancy (e.g., nodularity at the edges of the ulcer or infiltration of the surrounding tissue creating a raised appearance), use jumbo forceps with more extensive sampling along the edges
 - Biopsy the gastric antrum and body for *Helicobacter pylori*
- Not recommended for DU

Management of Refractory or Recurrent PUD

- Re-evaluate risk factors
 - Compliance with antisecretory therapy
 - Continued NSAID use
 - Use of medications/substances associated with PUD or that may impact healing
 - Risk factors associated with poor ulcer healing
- If still unsure: obtain fasting serum gastrin and serum calcium levels

Management of Complications

- Hemorrhagic complications: endoscopic therapy, surgery, and transcatheter embolization
- Luminal complications: endoscopic dilation for stricture and surgery for perforation and obstruction

Management of Refractory or Recurrent PUD

- Eradicate *H. pylori*
 - Use molecular testing for antibiotic sensitivity
 - Avoid clarithromycin-based therapy
 - Use quadruple therapy or rifampin-based therapy
 - Confirm eradication (off PPI x 2 weeks)
- Avoid culprit medications/substances
 - Drug testing

Antisecretory Therapy

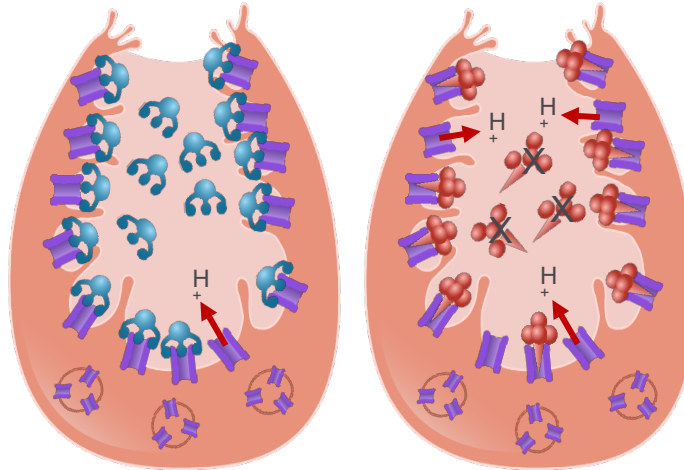
- BID PPI is usually effective for healing PUD refractory to once daily standard dose PPI
 - 40 mg dose of omeprazole produced better healing than continued standard H2RA (96% versus 57%)
 - >90% of refractory ulcers heal with an additional 8 weeks of PPI
 - Repeat EGD at 12 weeks
- Long-term acid inhibition should be offered once the ulcer has healed in at-risk patients (not required for *H pylori* associated ulcers after eradication)
- PCABs appear to be equally effective as PPI (may be able to use once daily)

Mechanisms of Action: P-CAB vs PPI

P-CAB^[1,2]

- Bind to active and inactive proton pumps
- Long plasma $T_{1/2}$
- Stable in acid
- Primarily metabolized via *CYP3A4/5*

Gastric parietal cell



PPI^[1,2]

- Bind to active proton pumps
- Short plasma $T_{1/2}$
- Unstable in acid
- Primarily metabolized via *CYP2C19*



Proton pump



P-CAB



PPI



Tubulovesicle

Surgical Management

- Reserved for PUD that fails to heal after twice-daily PPI for 24 weeks
 - Other correctable factors have been addressed
- Includes truncal vagotomy and drainage procedure (pyloroplasty or gastrojejunostomy), selective vagotomy and drainage, highly selective vagotomy, or partial gastrectomy
- No contemporary comparative studies of medical vs surgical therapy

Summary and Recommendations

- Refractory PUD: Non-healing after 12 weeks of treatment with PPI
- Biopsies of the ulcer and *H pylori* should be performed
 - Molecular testing for *H. pylori*
- Consider alternative etiologies
- BID PPI for additional 8-12 weeks
- Consider surgery if non-healing persists > 24 weeks