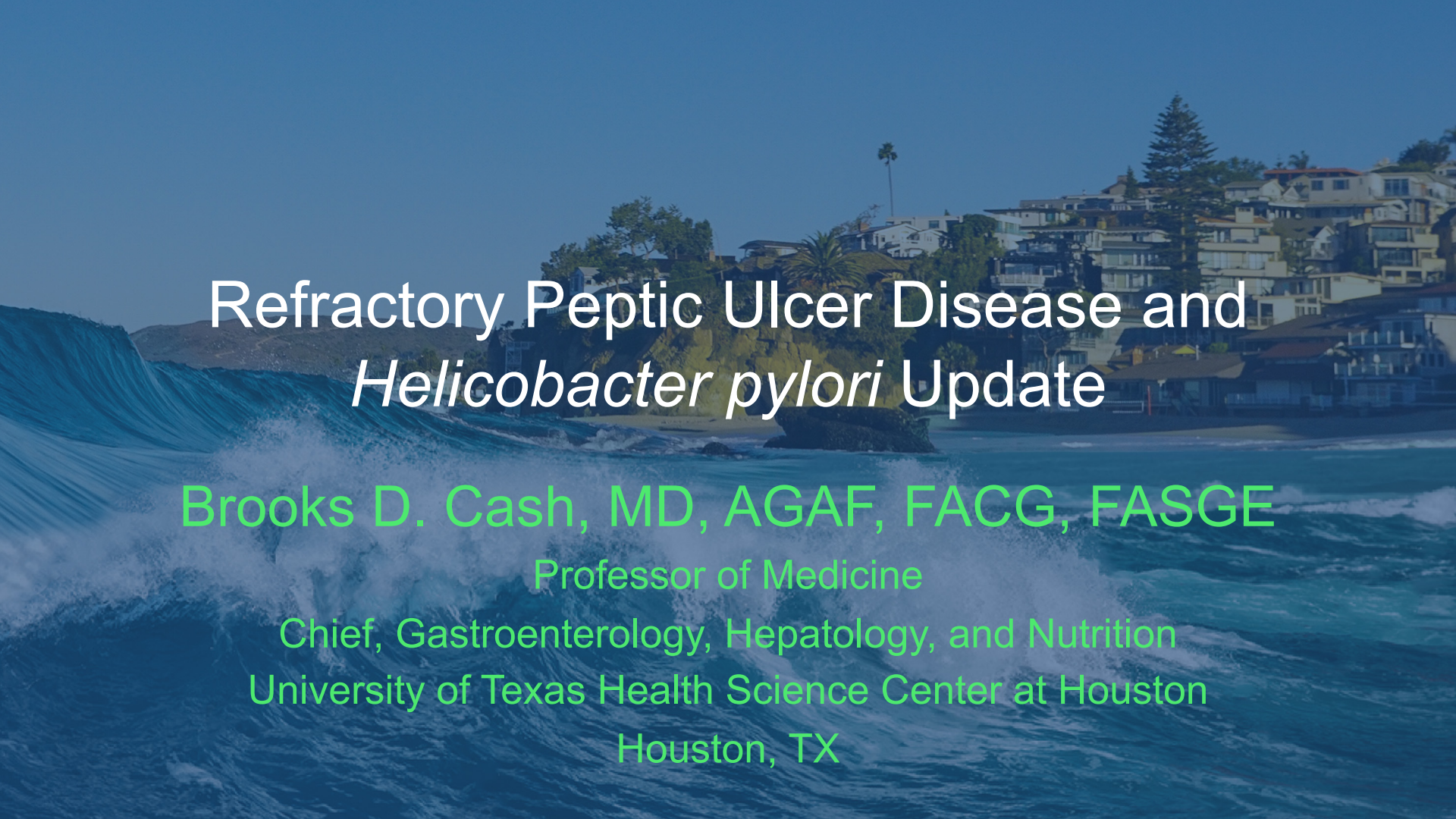

2023 SCSG
GI SYMPOSIUM



Refractory Peptic Ulcer Disease and *Helicobacter pylori* Update

Brooks D. Cash, MD, AGAF, FACG, FASGE

Professor of Medicine

Chief, Gastroenterology, Hepatology, and Nutrition

University of Texas Health Science Center at Houston

Houston, TX

Disclosures

- Brooks D. Cash, MD has served as a consultant and speaker for Phathom Pharmaceuticals

Peptic Ulcer Disease

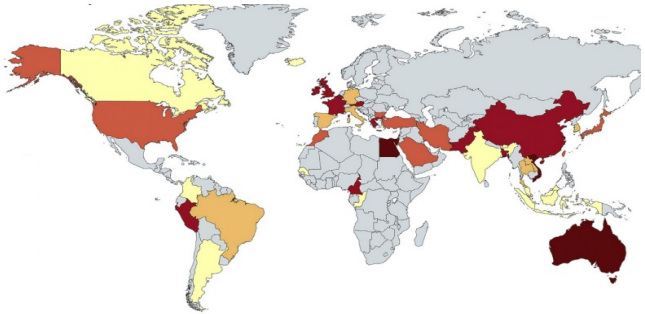
- PUD incidence: 1/100 to 1/800
  - *Helicobacter pylori* infection, NSAID use, smoking
- **Refractory** PUD: endoscopically proven ulcer > 5 mm diameter that does not heal after 8–12 weeks of PPI treatment
  - 5–10% GU and DU can be considered “refractory”
- **Recurrent** PUD: endoscopically proven PUD > 5 mm in diameter that recurs after healing
  - 5–30% within the first year

Refractory PUD Risk Factors

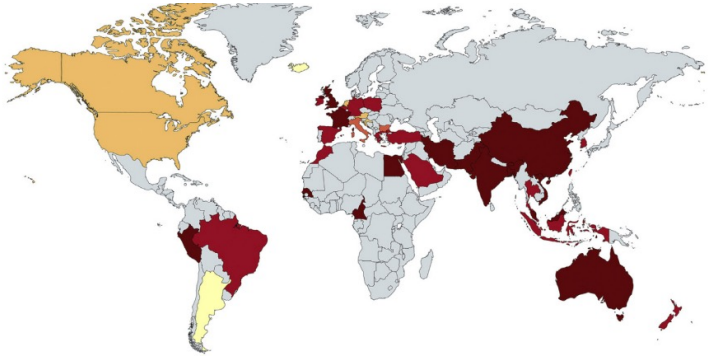
- Significant overlap in the risk factors for refractory and recurrent peptic ulceration
  - Persistent *Helicobacter pylori* infection
  - Use of culprit medications/exposures
  - Impaired healing
  - Comorbid diseases

High Rates of Global *H pylori* Antibiotic Resistance

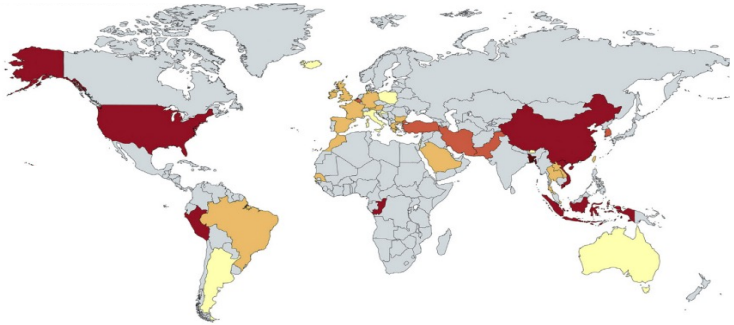
Clarithromycin resistance: 22% (95% CI: 7%, 37%)

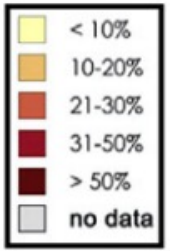


Metronidazole resistance: 20% (95% CI: 13%, 27%)



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





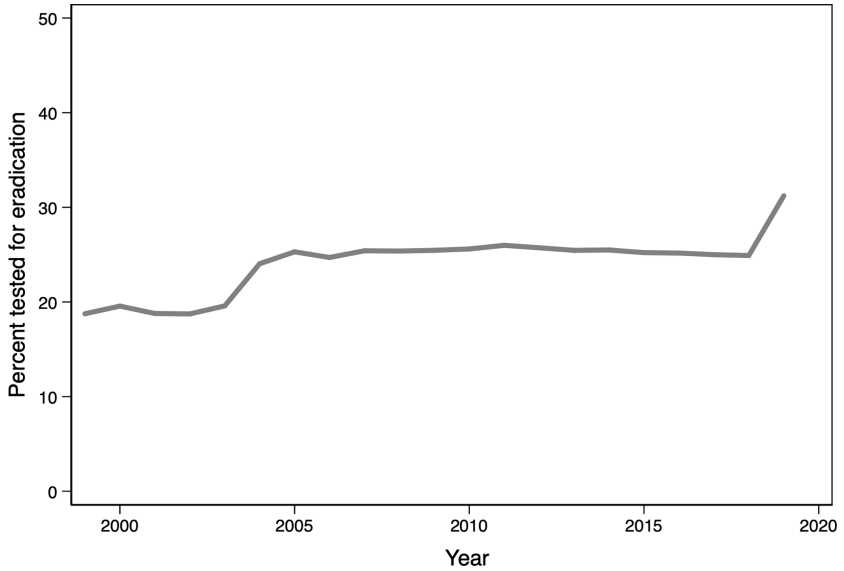
- VERY limited US data (< 1000 *H pylori* isolates across 3 studies)
- More recent data, even higher rates

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]



1. Kumar S et al. 2021;19:305-313.e1; 2. Shah SC et al. DDW 2022.

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

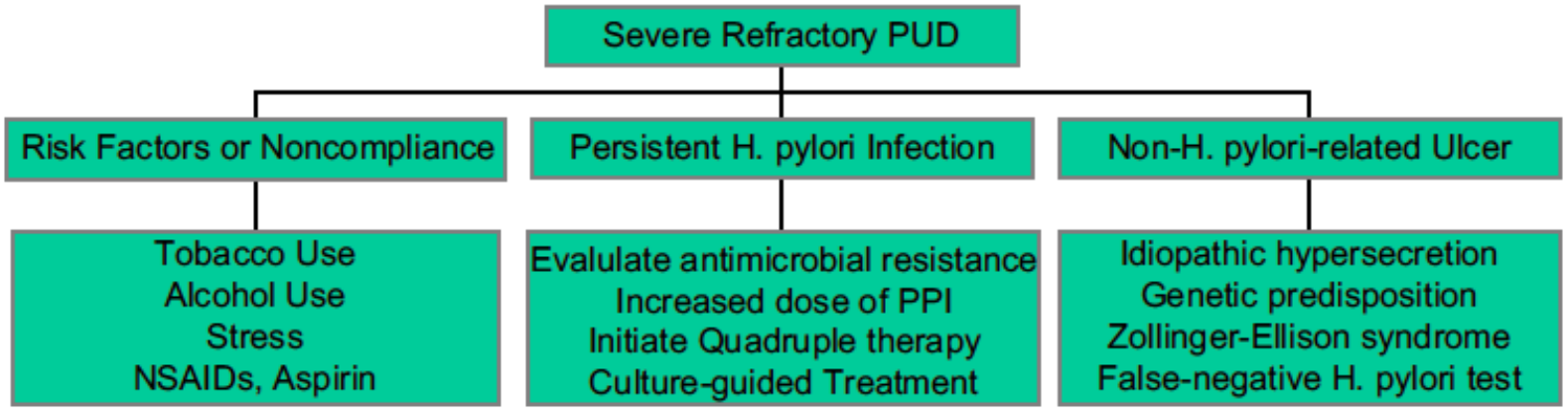
Ineffective Acid Suppression

- 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

- Diagnosed via EGD for evaluation of symptoms or surveillance to document healing after initial therapy of GU
- Suspect in patients with persistent or recurrent dyspepsia, 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; take 10–12 samples
  - 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 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 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 PUD 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)

Factors Impacting Efficacy of *H pylori* Therapy

Susceptible bacteria treated with

Optimized doses & dosing intervals[a]

Longer duration 14d > 10d > 7d[a,b]

Optimized gastric pH[a,b]

High patient adherence[a]

a. Shiotani A et al. *Therap Adv Gastroenterol*. 2021;14:17562848211064080; b. Shah SC et al. *Gastroenterology*. 2021;161:1443-1459.

Core Principles for Selecting *H pylori* Eradication Treatment Regimen

Review patient's prior antibiotic exposure[a,b]

US survey[c]

< 40% of providers

Ideally, susceptibility testing to guide treatment selection[b]

- Using only optimized therapies to reliably achieve > 90%, preferable > 95% cure rates in adherent patients[b]

Avoid macrolide and fluoroquinolone-based regimens if ANY prior exposure (high likelihood of *H pylori* resistant strains)[d,a]

Most frequent primary therapy used to treat *H pylori* infection, 2014 (United States)[c]

Therapy	Duration	%
Standard triple therapy*	14 d	53
Standard triple therapy*	10 d	27
Quadruple therapy#	14 d	9
Sequential therapy$	10 d	3
Standard triple therapy*	7 d	3

Ensure appropriate gastric acid suppression that is sustained[b]

Ensure appropriate dosing of antibiotics (may need to consider BMI)[b]

*PPI, clarithromycin, and amoxicillin (or metronidazole); #PPI, bismuth, metronidazole, and tetracycline (or doxycycline if tetracycline is not available); $PPI and amoxicillin for 5 days (d) followed by PPI, clarithromycin, and tinidazole (or imidazole or metronidazole) for 5 days.

1. Liou JM et al. *Gastroenterology*. 2018;155:1109-1119; 2. Shah SC et al. *Gastroenterology*. 2021;160:1831-1841; 3. Murakami TT et al. *Prev Med*. 2017;100:216-222; 4. Ong S et al. *Helicobacter*. 2019;24e12654.

Antimicrobial Susceptibility Testing for *H Pylori* Is Now Available: When, How, Why

Traditional Approach

Tests

- Stool Antigen
- Urea Breath Test
- Endoscopy with RUT or histopathology

Outcome

- **Empiric Therapy:** low eradication rates +/- opposes antimicrobial stewardship

Antimicrobial Susceptibility Testing

When Ideally for **initial** diagnosis or after **failed** treatment

How 1) **PCR** or **NGS** of stool; 2) **PCR** or **NGS** of gastric biopsy; 3) **culture** from gastric biopsy

Why Use results to **guide** appropriate antibiotic **selection**

Where Available at multiple labs across the US

NGS, next-generation sequencing; PCR, polymerase chain reaction.

Graham DY, Moss SF. *Am J Gastroenterol*. 2022;117:524-528.

Susceptibility Testing Options

Culture[a]

- Clarithromycin
- Levofloxacin
- Metronidazole
- Amoxicillin
- Tetracycline
- Rifabutin or rifampin?*

Molecular[a,b]

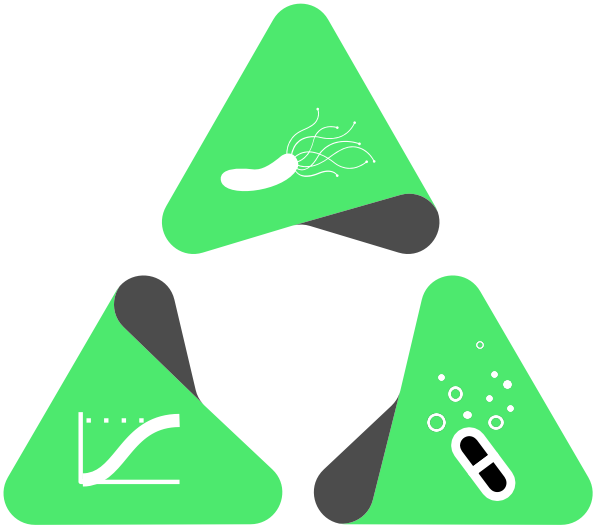
- Clarithromycin (also PCR)
- Levofloxacin
- Metronidazole
- Amoxicillin
- Tetracycline
- Rifabutin

*Rifampin results are not equivalent to rifabutin[a]
Do not order and if provided ask for a refund (expert opinion)

1. Graham DY et al. *Am J Gastroenterol*. 2022;117:524-528; 2. Dore MP et al. *Aliment Pharmacol Ther*. 2022;55:S14-S21.

Acid Suppression Is a Key Factor in *H. pylori* Eradication Therapy

H. pylori replication[1-4]



Growth-dependent antibiotics[1,2,4]

Antibiotic stability in acid[1,5]

H. pylori = *Helicobacter pylori*.

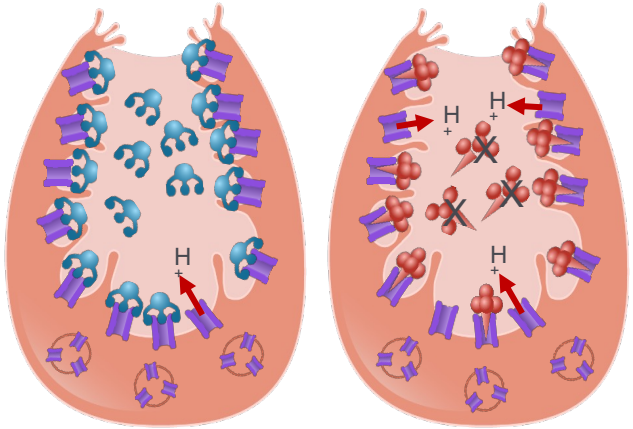
1. Scott DR et al. *F1000Res*. 2016;5:F1000 Faculty Rev-1747; 2. Scott D. *Gut*. 1998;43(suppl 1):S56–S60; 3. Ierardi E et al. *Antibiotics (Basel)*. 2020;9:293; 4. Shah SC et al. *Gastroenterology*. 2021. doi:10.1053/j.gastro.2020.11.059; 5. Erah PO et al. *J Antimicrob Chemother*. 1997;39:5–12.

Acid Suppression: P-CABs 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

1. Oshima T et al. *J Neurogastroenterol Motil*. 2018;24:334-344; 2. Miftahussurur M et al. *Pharmaceuticals*. 2020;13:276.

Relative Potency of PPIs and P-CABs

- PPIs differ with respect to level of acid suppression and subsequent *H pylori* eradication rates[a,b]
- Esomeprazole and rabeprazole are less susceptible to *CYP2C19* polymorphisms, so more reliably effective across *CYP2C19* genotypes[a,b]
- Higher dosing, greater frequency, and the use of a more potent PPI are associated with higher eradication rates[a,b]

Meta-analysis[b]

Drug	OME Dose Equivalent	
Pantoprazole 20 mg	4.5 mg	1st Gen
Lansoprazole 15 mg	13.5 mg	Lower potency
Omeprazole 20 mg	20 mg	
Esomeprazole 20 mg	32 mg	2nd Gen
Rabeprazole 20 mg	36 mg	Higher potency
Vonoprazan 10 mg	60 mg	

OME, omeprazole.

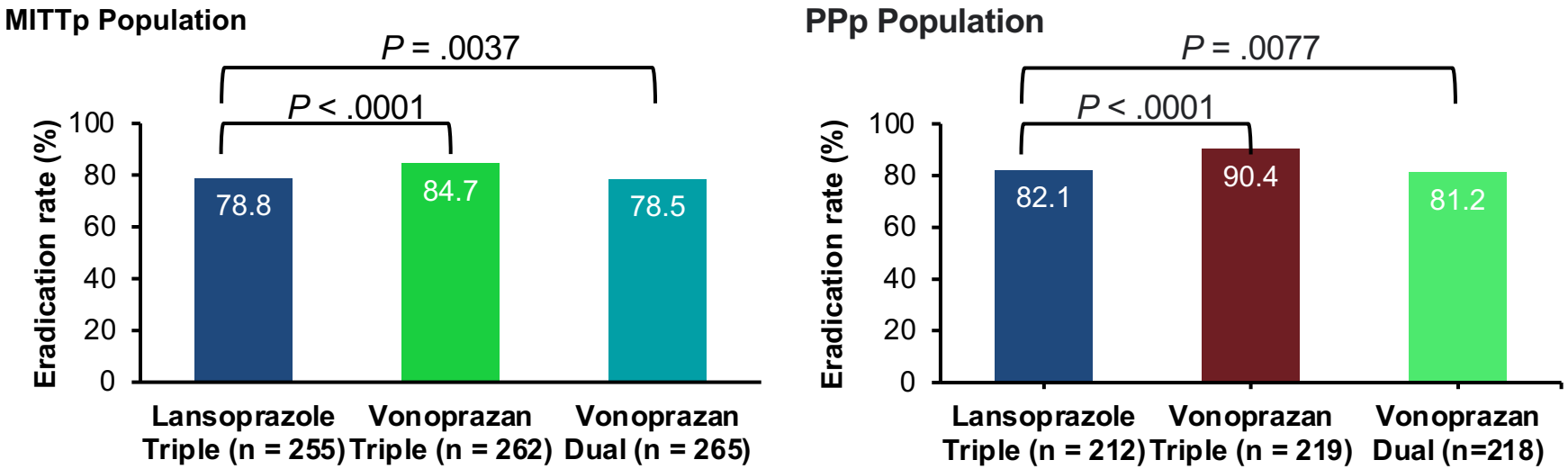
a. Graham DY et al. *Clin Gastroenterol Hepatol*. 2018;16:800; b. Ierardi E et al. *World J Gastroenterol*. 2019;25:5097-5104.

pHalcon-HP Phase 3 Study

Efficacy

- Both vonoprazan-based triple and dual therapy regimens were non-inferior to lansoprazole triple therapy in patients with *H pylori* strains not resistant to clarithromycin/amoxicillin

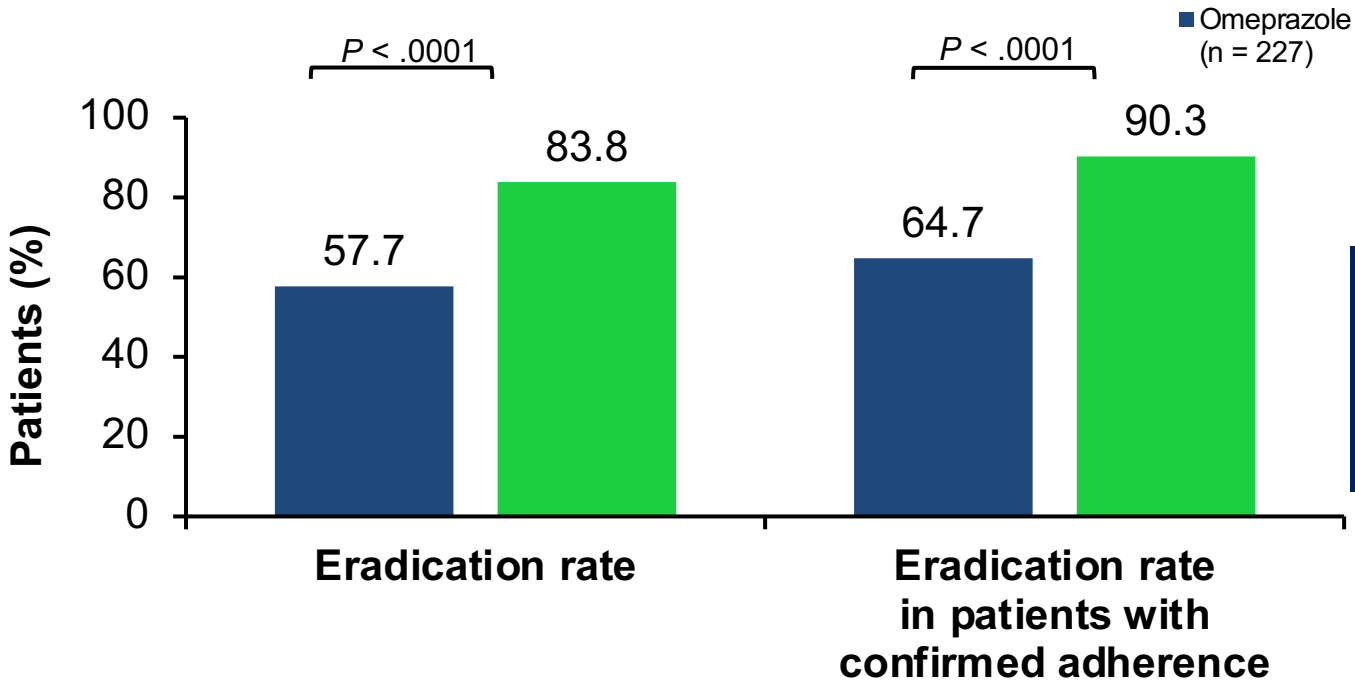
Primary Endpoint (Non-Inferiority)



MITTp, modified intention-to-treat primary; PPp, per-protocol primary.

Chey WD et al. *Am J Gastroenterol*. 2021;116:S634.

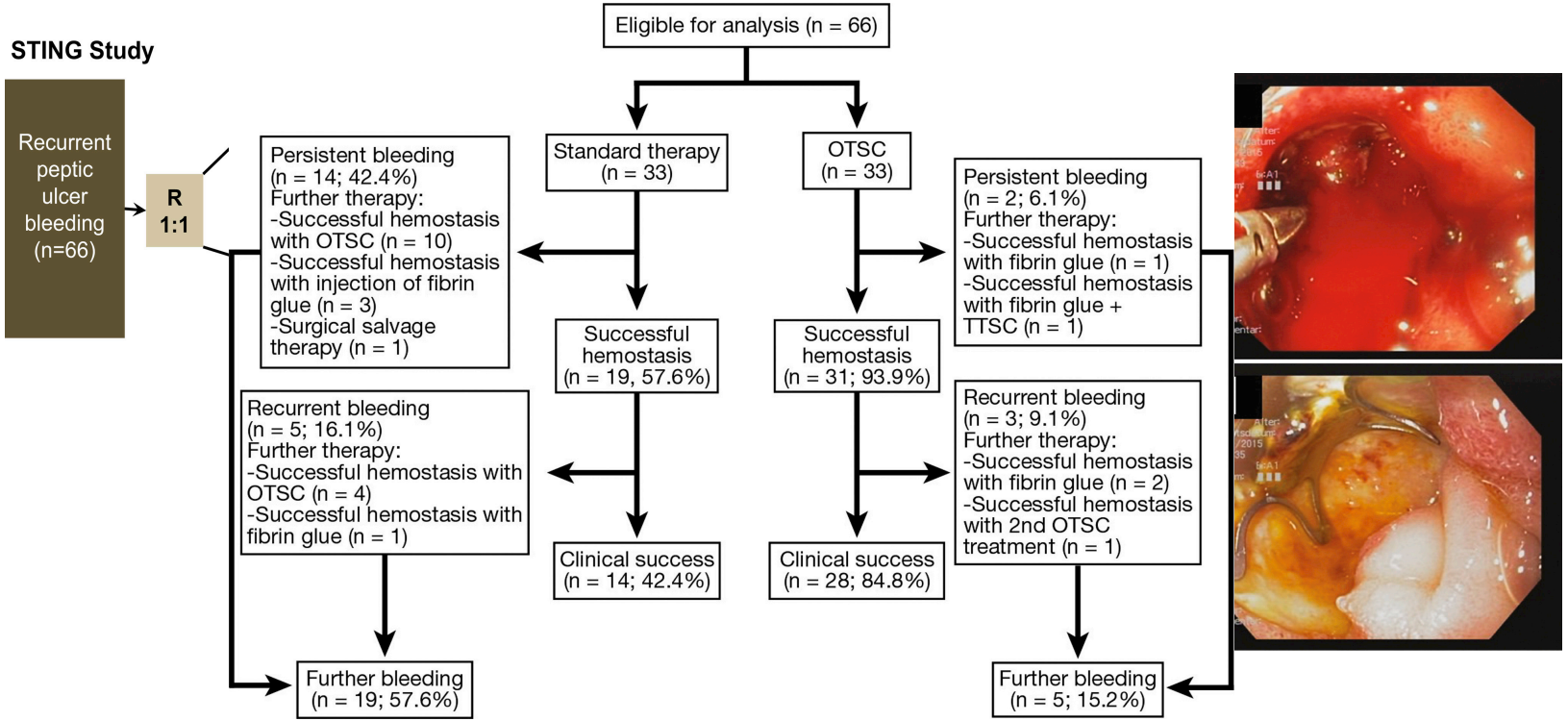
Rifabutin-Based Triple Regimen for *H Pylori* Infection



Total daily doses in RHB-105 are:
- Omeprazole 120 mg
- Amoxicillin 3000 mg
- Rifabutin 150 mg

Graham DY et al. *Ann Intern Med*. 2020;172:795-802.

Alternative Hemostatic Approaches for Recurrent Bleeding: STING Study



Schmidt A et al. *Gastroenterology.* 2018; 155:674-86.

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

Gurusamy KS, Pallari E. *Cochrane Database of Systematic Reviews*. 2016, Issue 3. Art. No.: CD011523.

Summary and Recommendations

- Refractory PUD: Non-healing after 12 weeks of PPI
- Biopsies of the ulcer/antrum/body and if *H pylori* + molecular testing if available
  - Do not use triple therapy
  - Become familiar with emerging alternative therapies
    - P-CAB based
    - Rifabutin based
  - Verify eradication
- Consider alternative endoscopic approaches, etiologies
- BID PPI for additional 8–12 weeks; role of P-CABs unproven
- Consider surgery if non-healing persists > 24 weeks