Helicobacter: Cases and update

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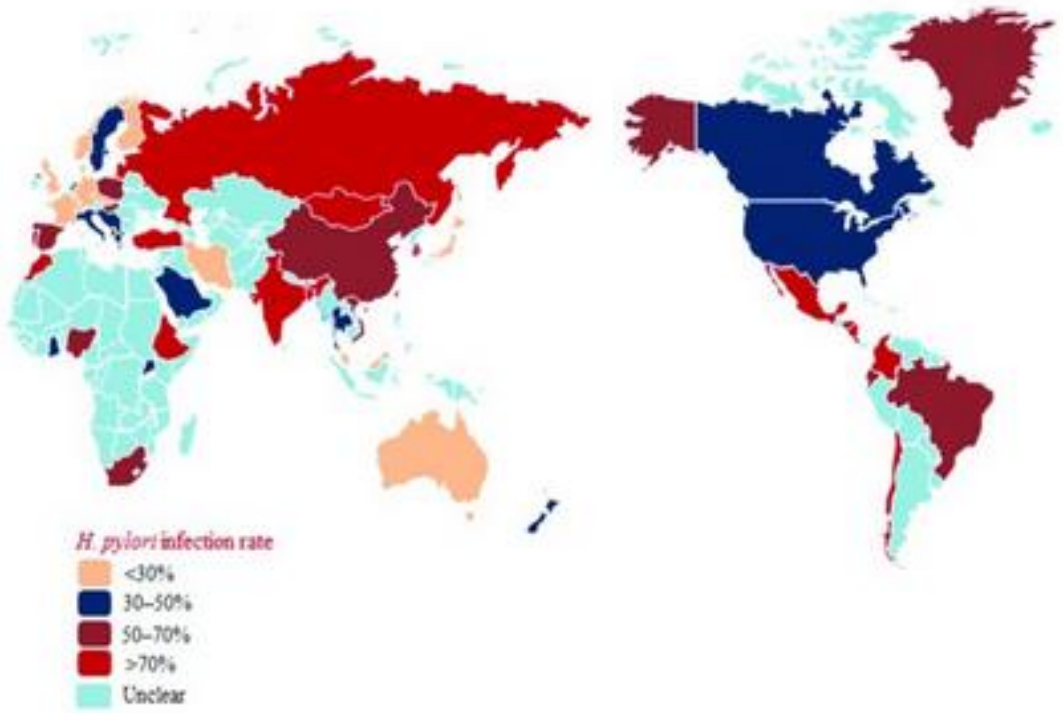
NZ point prevalence study at CMDHB (2012)

- European 7.7%
- Maori 34.8%
- Pacific people 31.3%
- Asians 23.8%

Hsiang et al. NZMJ 2013.

H. Pylori Infection Rates
Global Prevalence

- Prevalence higher in developing countries[a]
- Prevalence in US varies with socioeconomic status, age, geographic location, and race/ethnicity[b]



a. Hu Y, et al. Front Cell Infect Microbiol. 2017;7:168; b. Saleem N, et al. Curr Treat Options Gastroenterol. 2020:1-12.

Consequences of H Pylori infection

- Dyspepsia/non specific GI symptoms
- Gastric and duodenal ulcers
- Gastric cancer
- Gastric mucosa-associated lymphoid tissue (MALT) lymphoma

Indications for H Pylori testing

- Uninvestigated dyspepsia
- Functional dyspepsia
- Aspirin or NSAIDs
- Family history of gastric cancer
- Unexplained iron deficiency

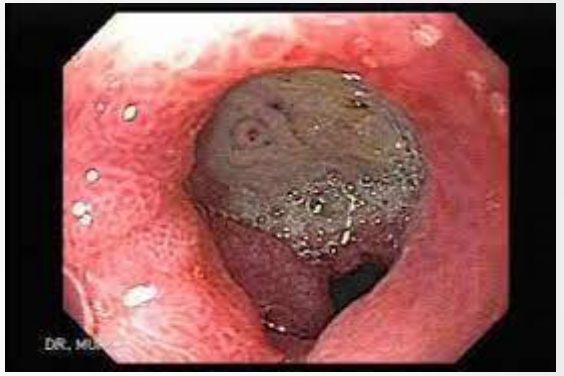
Case 1 Mr DM

- 45 year old Caucasian man
- 2 month history of epigastric pain
- No dysphagia but few episodes of vomiting the past week
- Denies NSAIDs or bleeding
- Using OTC Mylanta with variable benefit
- Non smoker
- Father died of stomach cancer

Question

- What would you do next?
- A) Check H Pylori serology
- B) Begin empiric omeprazole 20mg daily
- C) Refer for a gastroscopy
- D) Order a HP stool antigen test

Case 1 progress



- HP stool antigen positive
- Blood tests otherwise all normal
- Gastroscopy showed H pylori related duodenal ulcer

- What treatment regimen would you start?

Antibiotic resistance in NZ (2012)

- Metronidazole resistance 49.3%
- Clarithromycin resistance 16.4%
- Moxifloxacin resistance 9.5%
- Tetracycline resistance 0%

- Compared to 1999, metronidazole resistance increased significantly from 32.7% to 49.3%
- Clarithromycin resistance increased from 7% to 16.4%
- OAC triple therapy eradication rate = 85.7% in groups where clarithromycin resistance <15% vs 64.9% if clarithromycin resistance >15%

H. Pylori Antimicrobial Resistance Most Recent US Data

	Years of study	CLA	MET	AMOX	TET	LEVO	RIF
Houston VA[1]	2009-2013	16	20	0	1	31	N/A
Alaska[2]	2000-2016	30	43	2	< 1	14	N/A
US RCT[3]	2017-2018	17	44	6	3	58	0
Rhode Island[4]	2018-2019	30	33	1	< 1	30	< 1
US RCT[5]	2019-2021	22	65	2	N/A	N/A	N/A

N/A/, not applicable; TET, tetracycline; RIF, rifampicin; VA, Veterans Affairs.

1. Shiota S, et al. Clin Gastroenterol Hepatol. 2015;13:1616-1624; 2. Mosites E, et al. J Glob Antimicrob Resist. 2018;15:148-153; 3. Hulten KG, et al. Gastroenterology. 2021;161:342-344.e1; 4. Argueta EA, et al. Gastroenterology. 2021;160:2181-2183.e1; 5. Mégraud et al, Am J Gastroenterol 2021; 116: in press

First-Line Treatment Recommendations
What Do the Guidelines Say?

Treatment Regimen	Toronto Consensus Report, 2016	Maastricht V/Florence Consensus Report, 2016	ACG Guidelines 2017
Bismuth quadruple therapy	**Recommended**	**Recommended** (only choice if high CLR and MTZ resistance)	**Recommended**
Concomitant therapy	**Recommended**	**Recommended if regional CLR resistance is high, or if bismuth unavailable**	**Recommended**
PPI-based CLR triple therapy	**Recommended only if CLR resistance < 15%, or proven eradication success > 85%**	**Recommended if regional CLR resistance is low**	**Recommended if regional CLR resistance < 15% and no prior macrolide exposure**

Levofloxacin-based regimens and sequential and hybrid therapies are also available but not recommended nor widely used.

Table adapted from Fallone CA, et al. Gastroenterology 2019;157:44-53.

Do you ask patients about their previous antibiotic exposure prior to prescribing HP Rx?

- Considerations prior to prescribing:
- 1) Ask patients about prior antibiotic exposure (US national survey <40% providers ask)
- 2) Avoid macrolide and quinolone based regimens if ANY prior exposure, given high likelihood of harboring H pylori resistant strains
- 3) Duration ideally 14 days
- 4) Patient education re importance of completing full course of treatment
- 5) Anticipatory guidance re side effects eg GI upset

Case 1

- Given triple therapy with OAC
- Symptoms improved for 2-3 weeks then recurred.

- What would you do now?
- A) Give him quadruple therapy
- B) repeat HP stool antigen test
- C) Increase omeprazole to higher dose, no further testing required
- D) stop omeprazole now, repeat HP stool antigen next week
- E) Repeat gastroscopy

Case 2 Mr WL

- 60 year old Chinese man
- Intermittent epigastric discomfort especially when hungry
- Previous multiple gastroscopies 2011, 2017 and 2020 in China
- All showed HP related gastritis and intestinal metaplasia
- Has had 2 previous courses of quadruple therapy
- First course = amoxicillin, clarithromycin, bismuth, PPI
- 2nd course = levofloxacin, ornidazole, bismuth, PPI

Question

- What would you do now?
- A) retreat with quadruple therapy but with tetracycline
- B) Advise no further treatment as he has minimal symptoms
- C) Gastroscopy for culture and sensitivities

Case 2 progress- Culture results

- Sensitive to amoxicillin, tetracycline
- Resistant to clarithromycin, metronidazole, moxifloxacin

Question

- What do you do now?
- A) Quadruple therapy with bismuth, tetracycline, amoxicillin + PPI
- B) Use something else other than bismuth as bismuth has been used twice before eg rifabutin
- C) Call for help (!)

Case 2 (cont'd)

- Advised to use quadruple therapy with bismuth, amoxicillin 1g tds (higher dose), tetracycline + PPI
- Backup treatment = rifabutin, amoxicillin + PPI

- Repeat HP stool antigen 8 weeks later → negative
- Patient should have ongoing gastroscopy surveillance for intestinal metaplasia

Case 3- Ms SW

- 39 year old Chinese woman
- Heartburn, burping, occasional regurgitation of food
- Has had 2 previous courses of triple therapy (OMC) June 2020 + March 2021 without success
- History of amoxicillin allergy in childhood → rash

- Gastroscopy showed mild gastritis.
- Culture showed sensitivity to amoxicillin + tetracycline, resistant to clarithromycin + metronidazole

What do you do now?

- A) Penicillin “allergy” in childhood is unlikely to be a true allergy, prescribe quadruple therapy with bismuth, amoxicillin, tetracycline + PPI
- B) Give up- we have no other options that don’t include amoxicillin
- C) Refer immunology to test for penicillin allergy

Letter from immunology, ADHB

- "It is statistically extremely unlikely that she is truly allergic to penicillin given the above history. She is suitable for a single dose penicillin challenge with one dose of co-amoxiclav."
- Patient should be observed 1 hour then discharged
- Antihistamines prescribed for late urticarial reaction

Take home points from this case

- Amoxicillin is now mainstay for refractory HP infection due to low rates of resistance
- Penicillin "allergy" is reported in >10% of patients
- Only <1% of the population have a true penicillin allergy
- Immunology clinic referral useful in cases like these when there is not much other option

How often do you confirm eradication success after treatment?

- A) Never
- B) Only if patients are high risk for complications of H pylori (eg family history of gastric cancer, established intestinal metaplasia or remain symptomatic)
- C) Always, irrespective of additional risk factors or persistent symptoms

Timing of repeat testing

- To avoid false positive due to H pylori shedding: conduct at least 4 weeks following therapy
- To avoid false negative: Conduct when off PPI therapy for at least 1-2 weeks

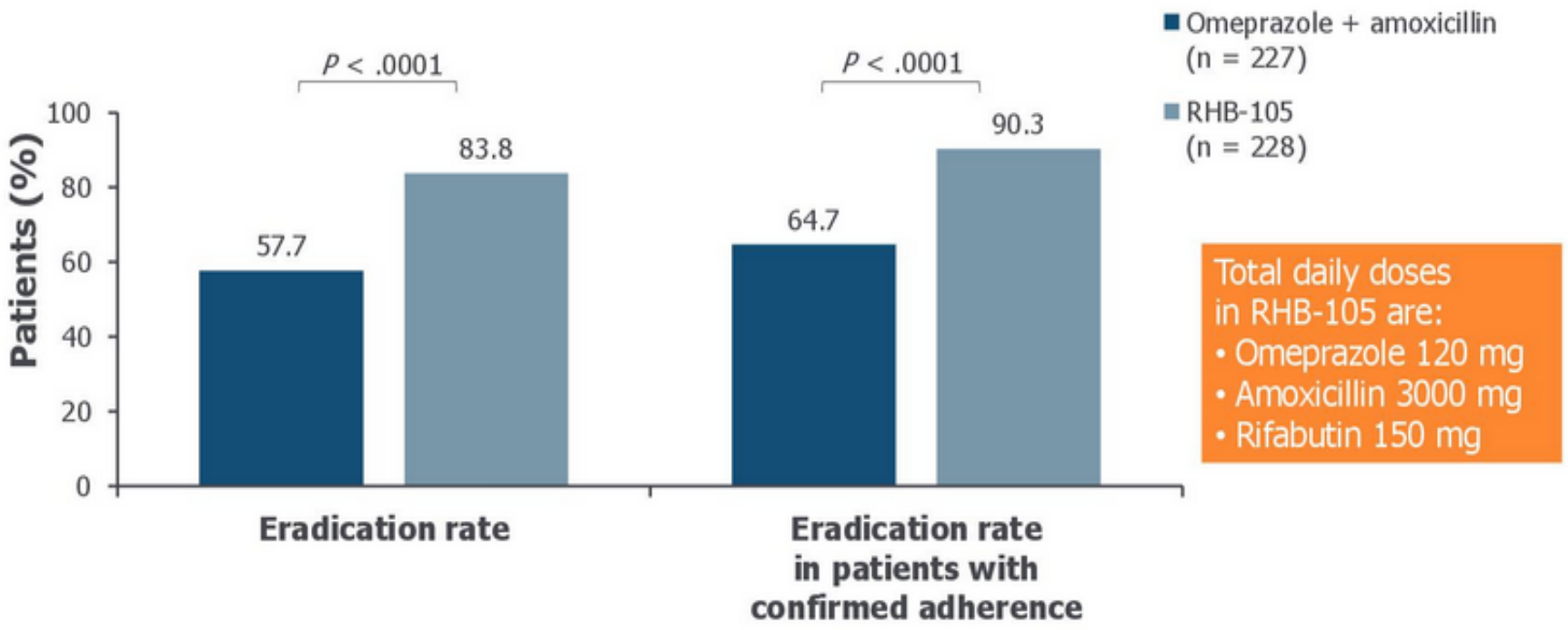
Should we test family members of patients for H pylori?

- Yes, especially if there is family history of gastric cancer as don't want patient to be reinfected
- Yes in certain ethnic groups where prevalence is high
- No testing in children if asymptomatic

What's new in HP therapies?

- FDA approval of triple combination of omeprazole- rifabutin- amoxicillin in 2019 for "treatment of H Pylori infection in adults".
- Development of regimens based on potassium-competitive acid blocker
- P-CAB provides superior control of intragastric pH compared with PPIs, allowing for enhanced antimicrobial efficacy and stability
- Phase 3 RCT in US and Europe comparing 2 vonoprazan-based regimens with a PPI-based regimen

Rifabutin-Based Triple Regimen (RHB-105) for *H. Pylori* Infection



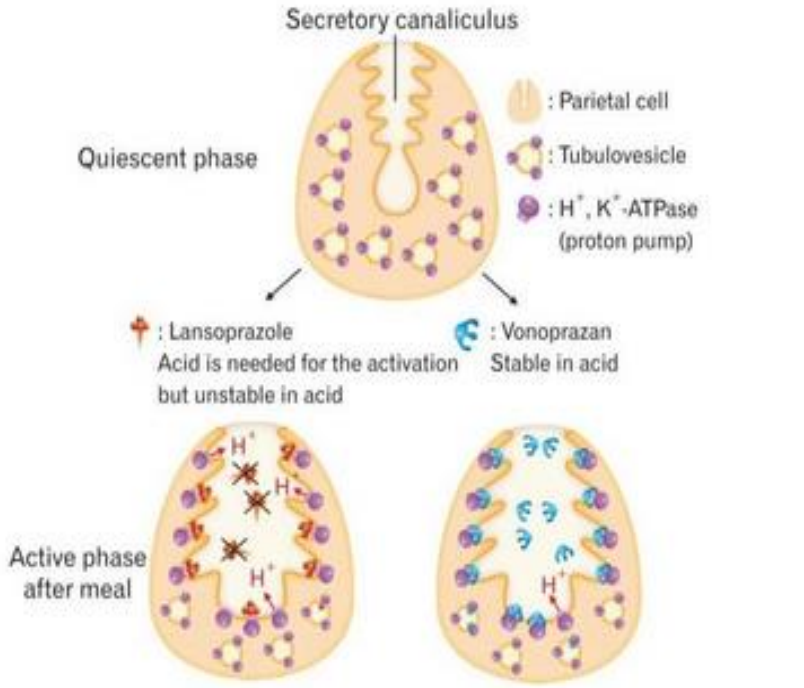
Total daily doses in RHB-105 are:
- Omeprazole 120 mg
- Amoxicillin 3000 mg
- Rifabutin 150 mg

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

P-CABs Mechanism of Action

P-CABs

- Rapidly and reversibly inhibit the proton pump preventing acid production
- Able to elevate gastric pH to a higher level than PPIs
- Have dose-dependent effects on acid production
- Exert full effect from the first dose



Vonoprazan stably accumulates in the acidic secretory canaliculus and noncovalently binds to proton pump with a very slow dissociation rate and can inhibit newly exposed proton pump for a long time.

Oshima T, et al. J Neurogastroenterol Motil. 2018;24:334-344; Scarpignato C, et al. Aliment Pharmacol Ther. 2015;42:1027-1029.

Potassium-competitive acid blockers

- Licensed in some Asian and South American countries
- Faster onset of action and more profound control of acid secretion than PPIs
- Examples = revaprazan, vonoprazan, tegoprazan and fexuprazan

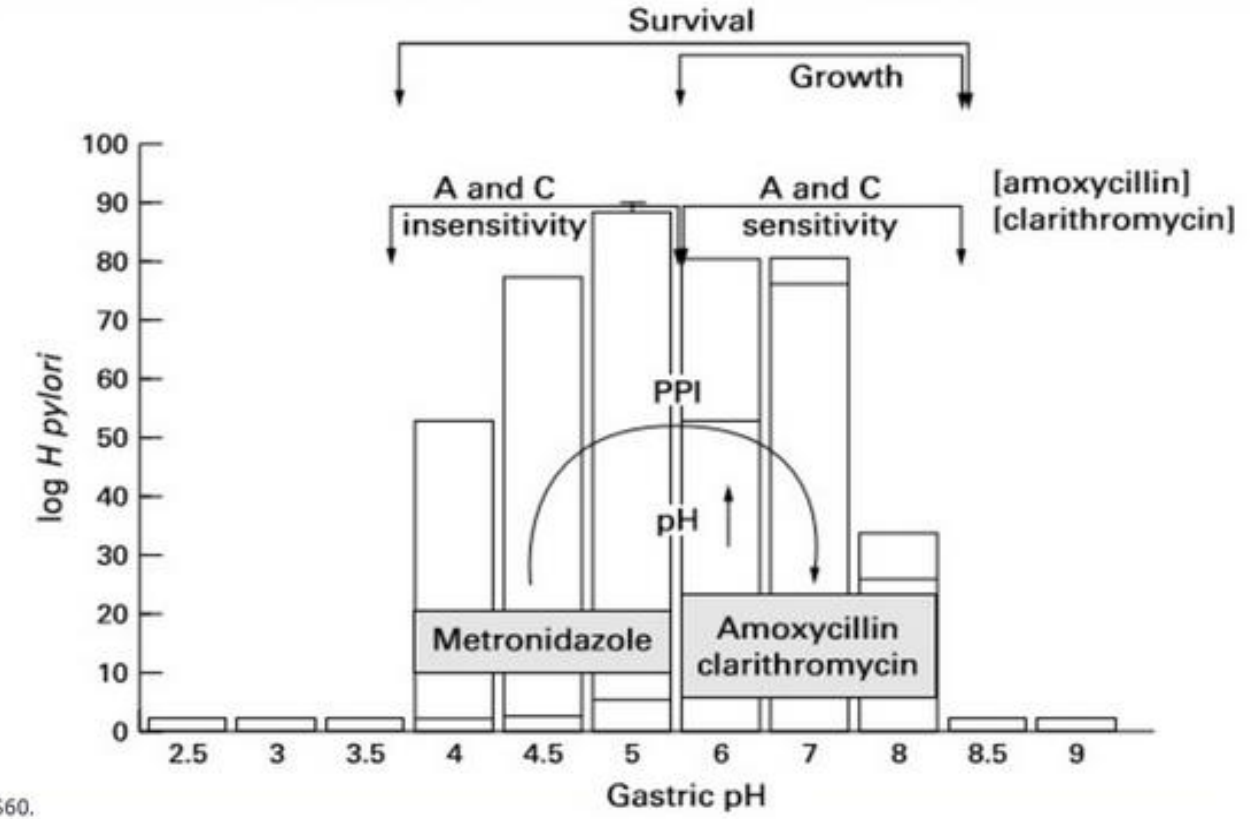
Degree of Control of Intragastric Acidity With Vonoprazan 20 mg Daily

	pH Holding Time[a] (% of 24-Hour Recording Period)	
	pH > 4	pH > 5
Day 1	62.7	49.2
Day 4	82.9	75.3
Day 7	85.2	78.6

- By comparison, esomeprazole 40 mg daily for 5 days: pH > 4 for 70%[b]

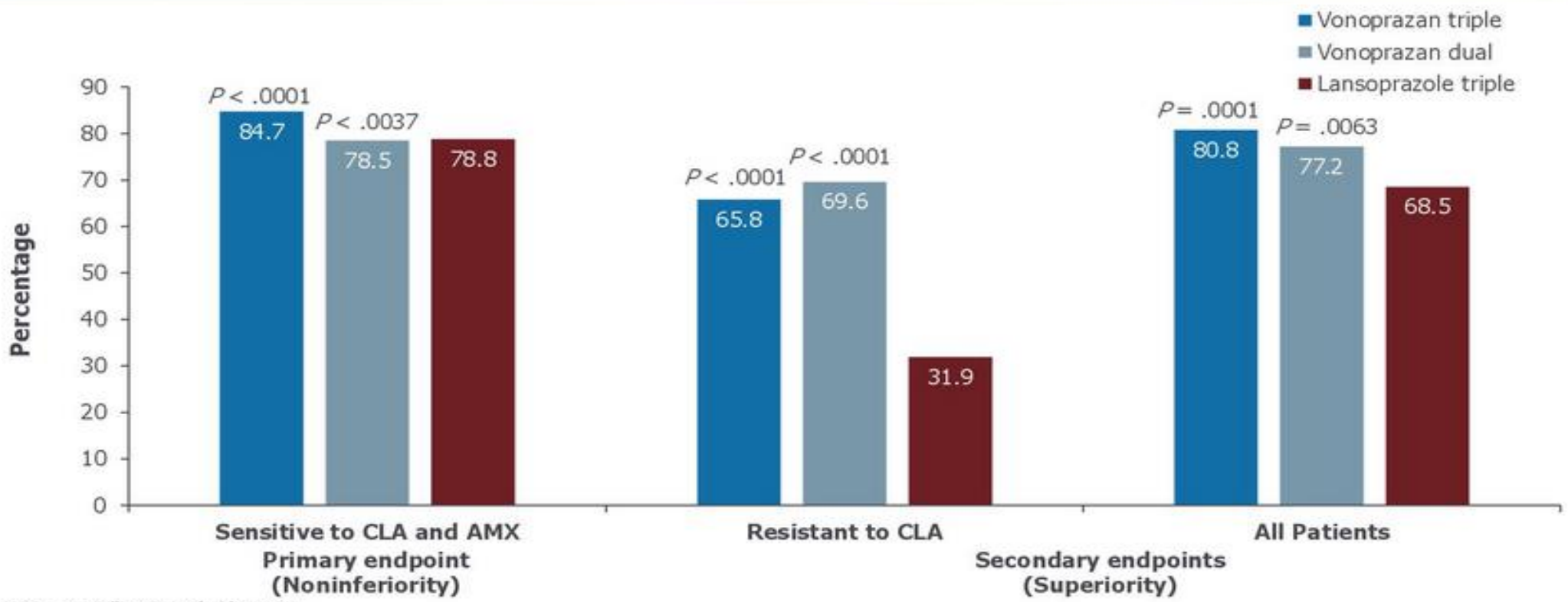
a. Jenkins H, et al. Aliment Pharmacol Ther. 2015;41:636-648; b. Esomeprazole magnesium [PI] 2010.

Life and Death of *H. Pylori*
Why Elevating pH Helps in Eradication



Scott D, et al. Gut. 1998;43:S56-S60.

HP-301: Efficacy
Comparison of Vonoprazan-Based and Lansoprazole-Based Regimens



AMX, amoxicillin; CLA, clarithromycin.

Chey W, et al. Am J Gastroenterol. In press.

HP-301: Safety
Comparison of Vonoprazan-Based and Lansoprazole-Based Regimens

	Vonoprazan Triple	Vonoprazan Dual	Lansoprazole Triple
All TEAEs	34.1%	29.9%	34.5%
Diarrhea	4.0%	5.2%	9.6%
Nausea	1.7%	1.7%	2.6%
Taste disturbance	4.3%	0.6%	6.1%
Headache	2.6%	1.4%	1.4%
Serious TEAEs	1.7%	1.4%	0.9%

TEAE, treatment-emergent adverse event.

Chey W, et al. Am J Gastroenterol. In press.

Current Status of P-CABs

Agent	Status
Vonoprazan	2 new drug applications submitted to FDA in Sept. 2021 Approved in Japan for EE, GERD, GU, DU and *H. pylori* infection Also approved in Philippines, Singapore, Thailand, Argentina, Peru, South Korea, Taiwan, Malaysia, Ecuador, China, Indonesia, Brazil, and Mexico
Revaprazan	Approved in South Korea and India for "gastritis," GU, DU
Tegoprazan	Investigation new drug application approved by US FDA in June 2020 for GERD Approved in South Korea for EE, NERD, GU, and *H. pylori* infection
Fexuprazan	Phase 3 trial in South Korea for EE Additional clinical trials are ongoing

DU, duodenal ulcer; EE, erosive esophagitis; GERD, gastroesophageal reflux disease; GU, gastric ulcer; NERD, nonerosive reflux disease.

Abdel-Aziz Y, et al. Aliment Pharm Therap. 2021;53:794-809.

Summary

- H pylori infection is common
- HP stool antigen test and not Helicobacter serology
- Amoxicillin is now mainstay of HP treatment due to low rates of resistance
- Consider referral to immunology if dubious history of penicillin allergy in the context of resistant HP infection
- Test of cure important >4 weeks after treatment
- New treatments available eg rifabutin, pCABs with much improved HP eradication rates