

Management of *Helicobacter pylori*



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Disclosures: William D. Chey, MD

- **Board Member/Advisory Panel**
 - American College of Gastroenterology, GI Health Foundation, International Foundation of GI Disorders, Rome Foundation
- **Consultant**
 - Abbvie, Ardelyx, Atmo, Biomerica, Gemelli, Ironwood, Nestle, QOL Medical, Redhill, Salix/Valeant, Takeda, Vibrant
- **Research Support**
 - NIH, FDA, Commonwealth Diagnostics, Salix
- **Stock Options**
 - Coprata, Dieta, Kiwi Bioscience, Isothrive, Modify Health
- **Other**
 - Patents: My Nutrition Health, Digital Manometry, Rectal Expulsion Device

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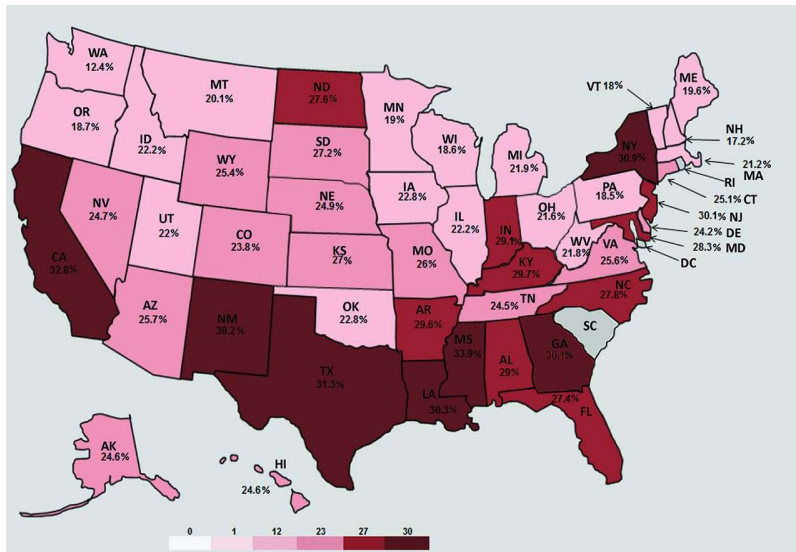
Management of *Helicobacter pylori*

- Epidemiology
- Indications for testing and treating
- Diagnosis
- First line treatment
- Post-treatment testing
- Salvage treatment
- Antibiotic sensitivity testing

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H. pylori: Regional US Prevalence

Race/Ethnicity	Prevalence
United States	35%
Caucasian	26%
African American	54%
Hispanic	60%
Alaska Native/ Native American	75%
Elderly >60 years	50%
Asian*	70%

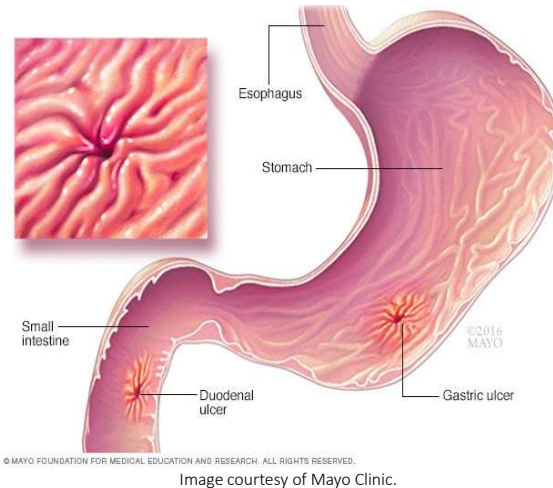


*NYC-based Asian population (Perez-Perez, Guillermo Ignacio, et al. *Journal of Urban Health* 2005;82(3):510-516).
 Everhart JE, et al. *Journal of Infectious Disease*. 2000;181(4):1359-1363.
 Hooi JKY et al. *Gastroenterology*, 2017;53:420-429;
 Kamboj AK, et al. In *Mayo Clinic Proceedings*, 2017;92(4):599-604.
 Jalaly JB, et al. *The Journal of Applied Laboratory Medicine*, 2018;2(6), 904-913.

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H. pylori Clinical Consequences

- **Complications of untreated or undertreated *H. pylori*:**
 - Chronic Gastritis
 - Atrophy
 - Intestinal Metaplasia
 - Gastric and duodenal ulcers
 - Gastric cancer
 - Gastric mucosa-associated lymphoid tissue lymphoma



• Saleem N, et al. *Curr Treat Options Gastroenterol.* 2020;1-12.

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Other Indications for *H. pylori* Testing & Treating

- **Uninvestigated dyspepsia**
- **Functional dyspepsia**
- **Aspirin or NSAIDs**
- **Unexplained iron deficiency**
- **Idiopathic thrombocytopenic purpura**
- ***Hp* is now considered an infectious disease and treatment is recommended whenever it is identified**

Chey et al. Am J Gastroenterol 2017;112:212

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Diagnostic Tests

Nonendoscopic

- Antibody detection
- Urea breath test
- Fecal antigen test

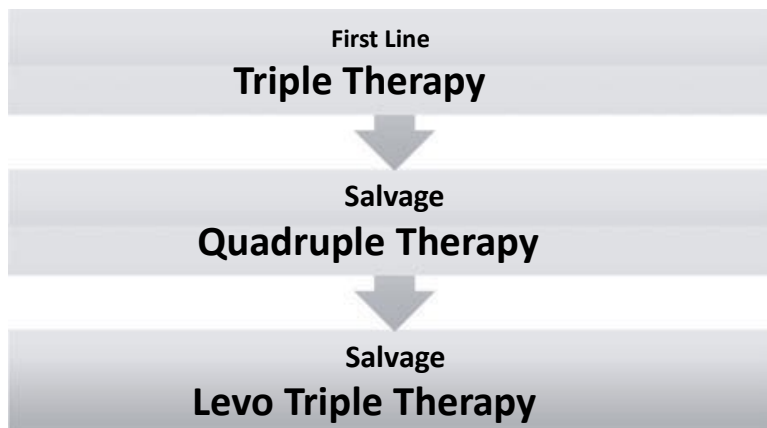
Endoscopic

- Rapid urease test
- Histology
- Culture/Molecular

Withhold PPI for 7-14 days before testing
Withhold bismuth and antibiotics 2-4 weeks before testing

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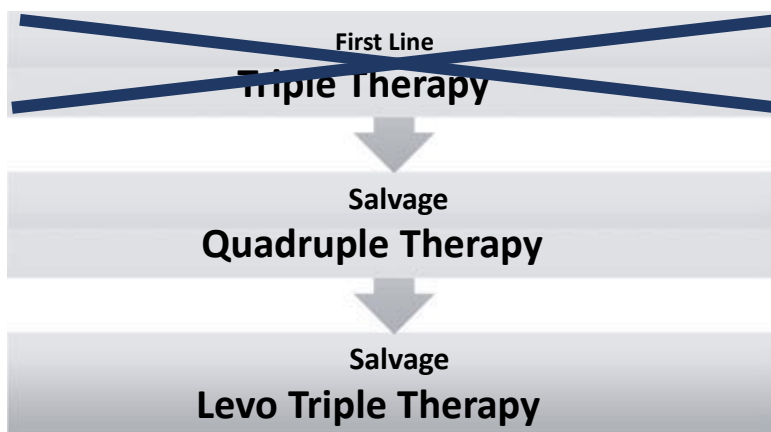
Current US Treatment Paradigm for *H. pylori*



Vakil & Vaira, J Clin Gastroenterol 2013;47:383-388

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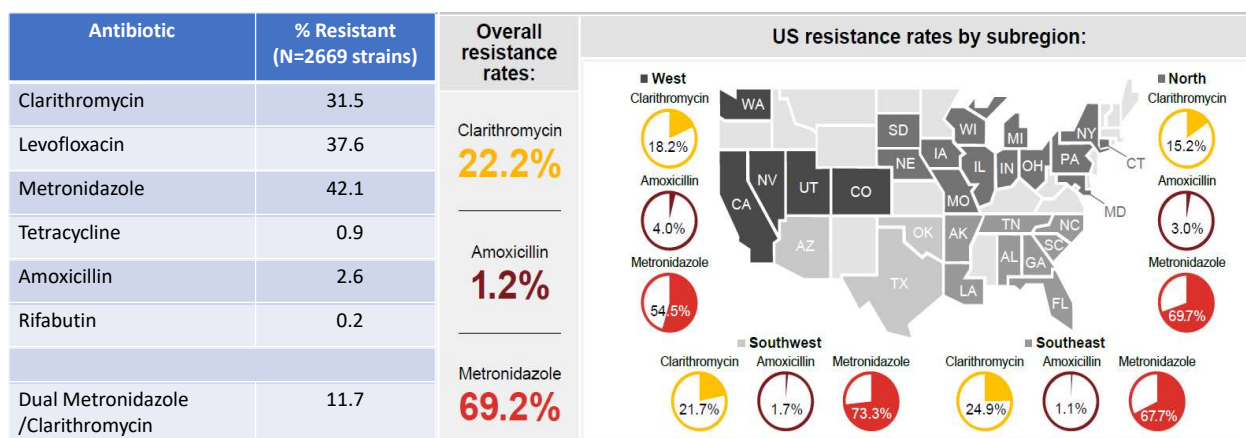
Current US Treatment Paradigm for *H. pylori*



Vakil & Vaira, *J Clin Gastroenterol* 2013;47:383–388

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H. pylori Antibiotic Resistance Rates in the US



Antibiotic susceptibility testing performed on 2669 strains from the US between 2011-2021
Ho J et al, *Am J Gastroenterol* 2022;117:1221

381 patients with *H. pylori* from the US underwent antibiotic sensitivity testing between 12/2019-1/2021

Megraud et al. *Am J Gastroenterol* 2023;118:269–275

Chey et al. *AJG* 2024

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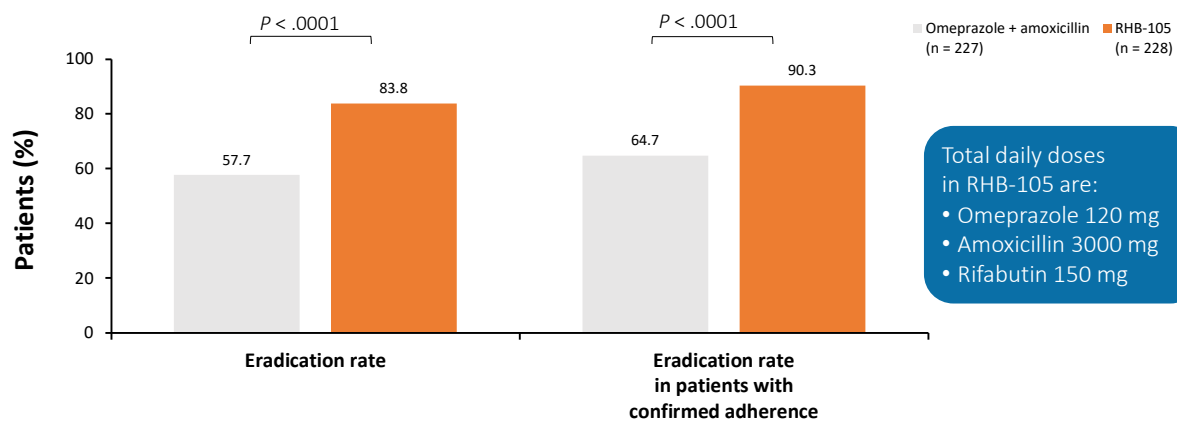
New developments since the 2017 ACG Guideline?

- FDA approval in 2019 of combination capsules containing omeprazole-rifabutin-amoxicillin
 - Indication: "treatment of *H. pylori* infection in adults"
- Development & validation of potassium-competitive acid blocker (PCAB) based regimens
 - PCABs provide superior intragastric pH control compared to PPIs -- enhancing antimicrobial efficacy and stability
 - Phase 3 RCT in US and Europe comparing 2 vonoprazan-based regimens with a PPI-based regimen^[a]

• a. ClinicalTrials.gov. NCT04167670.

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Rifabutin-Based Triple Regimen (RHB-105) For *H. pylori* Infection

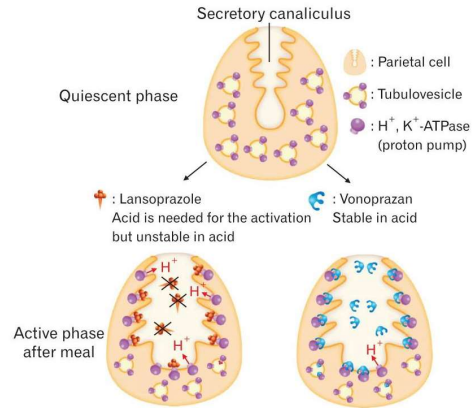


Graham DY, et al. *Ann Intern Med.* 2020;172:795-802

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Potassium Competitive Acid Blockers

- AKA: P-CABs
- Licensed in parts of Asia and South America
- Examples: revaprazan, vonoprazan, tegoprazan, and fexoprazan
- Rapidly & reversibly inhibit the proton pump
- Greater gastric acid suppression than PPIs
- Full effect after the first dose

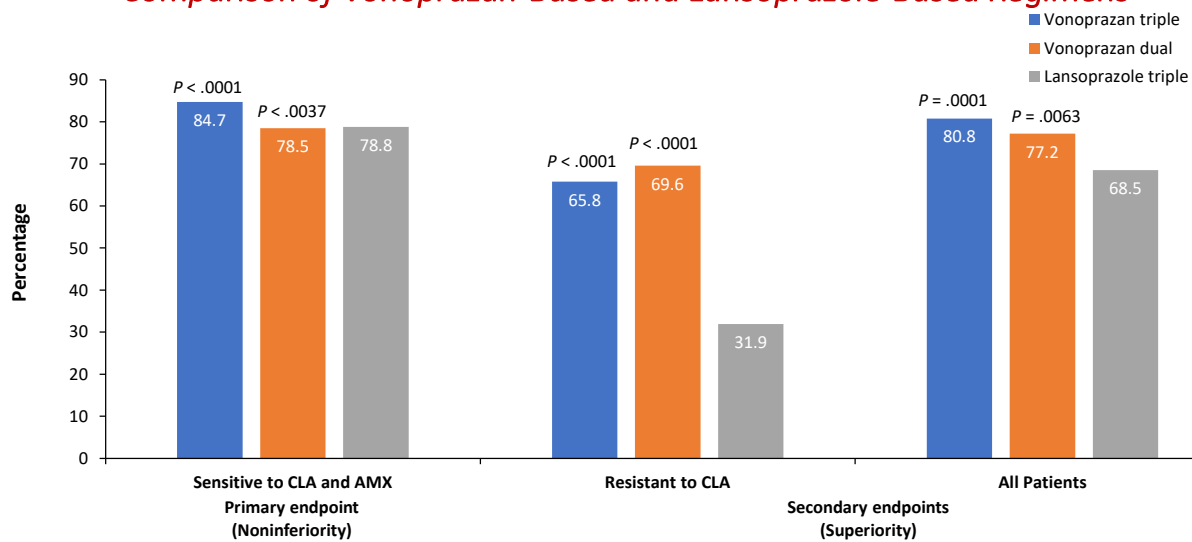


Vonoprazan stably accumulates in the acidic secretory canaliculus and noncovalently binds to proton pump with a very slow dissociation rate and can inhibit newly exposed proton pump for a long time.

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

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US & Europe RCT: Comparison of Vonoprazan-Based and Lansoprazole-Based Regimens

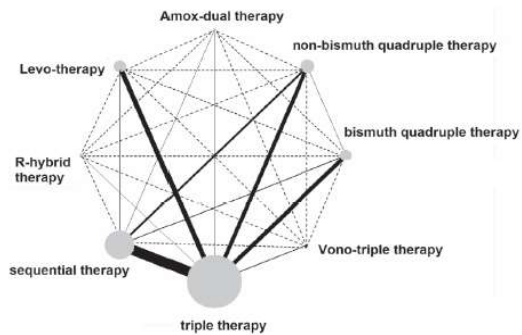


• AMX, amoxicillin; CLA, clarithromycin.
Chey W, et al. Gastroenterol. 2022;163:608-19.

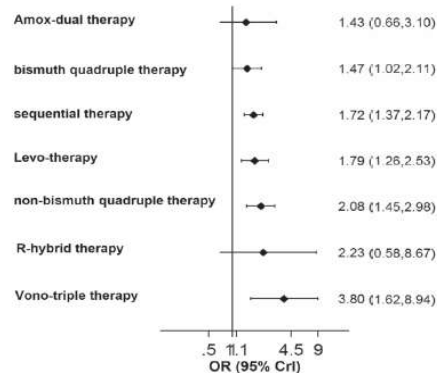
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Treatment of *H. pylori*: Network Meta-Analysis

Network map of all 28 *H. pylori* first line treatment regimen comparisons (12 direct, 16 indirect).



Forest plot of *H. pylori* first line treatment regimens compared directly with triple therapy.



Take Home Point: Vonoprazan triple therapy was the most effective and PPI triple therapy was the least effective

Rokkas et al *Gastroenterol* 2021;161:495-507

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H. pylori Treatment Considerations Prior to Prescribing Therapy

- Review patients' past antibiotic use history
 - National survey: < 40% of providers ask
- Avoid macrolide and fluoroquinolone-based regimens if **ANY** prior exposure, given higher likelihood of *H. pylori* resistance
- Treat for 14 days and emphasize importance of adherence

Sugano K, et al. *Gut*. 2015;64:1353-1367; Shah SC, et al. *Gastroenterology*. 2021;160:1831-1841; Ong S, et al. *Helicobacter*. 2019;24:e12654; Liou JM, et al. *Gastroenterology*. 2018;155:1109-1119; Murakami TT, et al. *Prev Med*. 2017;100:216-222.

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Regimens for Treatment Naïve Patients

Regimen	Drugs (doses)	Dosing frequency	FDA approval	Recommendation
Bismuth quadruple	PPI (standard dose) ¹	b.i.d.	No ²	STRONG (moderate quality of evidence)
	Bismuth subcitrate (120 - 300 mg) or subsalicylate (300 mg) ³	q.i.d.		
	Tetracycline (500 mg) ⁴	q.i.d.		
	Metronidazole (500 mg)	t.i.d. or q.i.d.		
Rifabutin triple 5	Omeprazole (10 mg) ¹	4 capsules t.i.d.	Yes	CONDITIONAL (low quality of evidence)
	Amoxicillin (250 mg)			
	Rifabutin (12.5 mg)			
PCAB dual 6	Vonoprazan (20 mg)	b.i.d.	Yes	CONDITIONAL (moderate quality of evidence)
	Amoxicillin (1000 mg)	t.i.d.		
PCAB triple 7	Vonoprazan (20 mg)	b.i.d.	Yes	CONDITIONAL (moderate quality of evidence)
	Clarithromycin (500 mg)			
	Amoxicillin (1000 mg)			

Chey et al. AJG 2024

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1st Line Regimens for Treatment Naïve Patients with *H. pylori* infection Without Antibiotic Susceptibility Testing

No Penicillin Allergy

- Optimized BQT
- Rifabutin Triple
 - PCAB Dual
- PCAB-Clarithromycin Triple*

Penicillin Allergy**

- Optimized BQT

* Avoid in those with previous macrolide exposure

** May require formal allergy testing

BQT=bismuth quadruple therapy, PCAB=potassium competitive acid blocker

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Post-Therapy *H. pylori* Testing

- *Whenever H. pylori infection is identified and treated, testing to prove eradication should be performed using a urea breath test, fecal antigen test or biopsy-based testing at least 4 weeks after the completion of antibiotic therapy and after PPI therapy has been withheld for 1-2 weeks*
- There may be infrequent situations which make eradication testing impractical or unnecessary

Chey et al. Am J Gastroenterol. 2017;112:212

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Post-Therapy *H. pylori* Testing

- **Urea breath test**
 - Perform >4 wks after completion of therapy
 - May be accurate when done 2 weeks after therapy
- **Fecal antigen test**
 - Perform >4 wks after completion of therapy
 - Monoclonal test preferred
- **Biopsy-based testing**
 - histology ± RUT
 - requires multiple biopsies

Chey et al. Am J Gastroenterol. 2017;112:212

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Salvage Therapy for *H. pylori*

- Do not use the same antibiotics
- Stress the importance of compliance and review possible side effects
- Treat for 14 days
- Consider culture and sensitivity testing before using regimens containing a macrolide or quinolone
 - NGS can be done on fixed tissue or stool
- Role of pharmacogenetic testing?

Chey, et al. Am J Gastroenterol 2017;112:212
Song M, Ang TL. World J Gastroenterol 2014;20(6): 1517

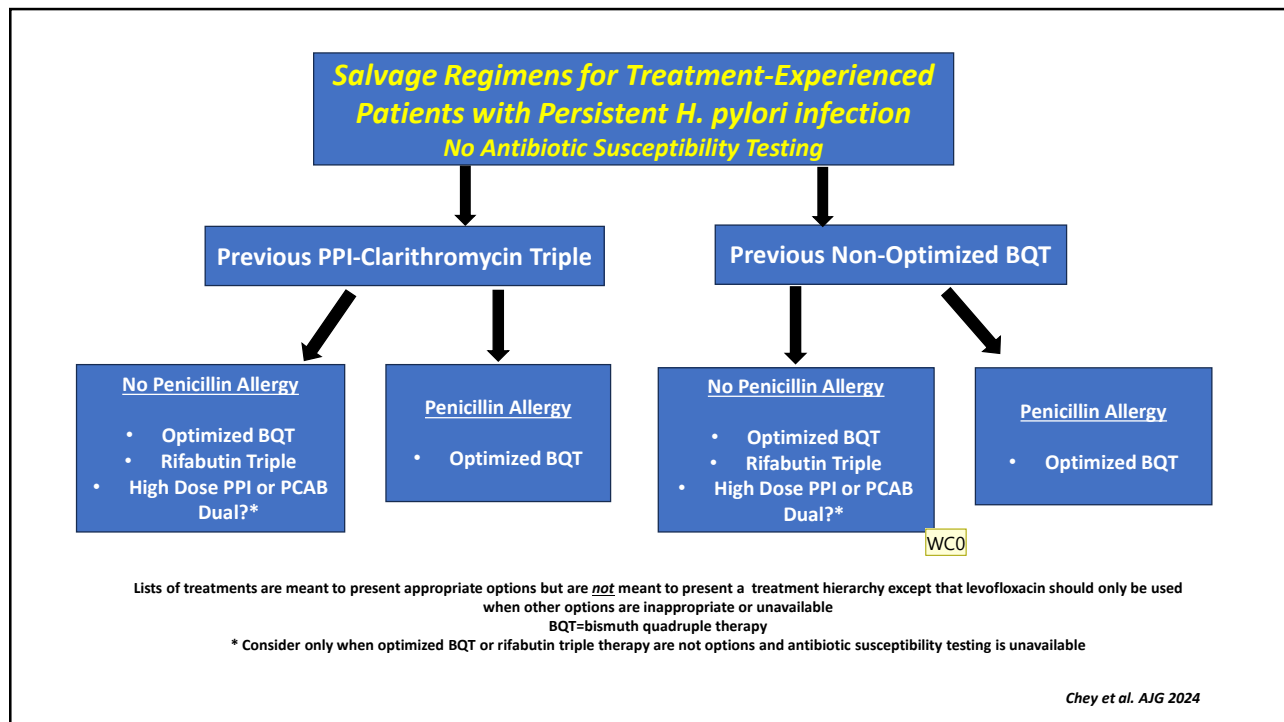
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Regimens for Patients with Persistent Infection

Regimen	Drugs (doses)	Dosing frequency	AST required?	Recommendation*
Optimized bismuth quadruple ¹	PPI (standard dose) ²	b.i.d.	No	CONDITIONAL (very low quality of evidence)
	Bismuth subcitrate (120 - 300 mg) or subsalicylate (300 mg)	q.i.d.		
	Tetracycline (500 mg)	q.i.d.		
	Metronidazole (500 mg)	t.i.d. or q.i.d.		
Rifabutin triple	PPI (standard to double dose) ²	b.i.d.	No	CONDITIONAL (low quality of evidence)
	Amoxicillin (1000 mg)	b.i.d. or t.i.d.		
	Rifabutin (50 – 300 mg) ³	q.d., b.i.d., or (Talicia™ which contains 50 mg t.i.d.) ³		
Levofloxacin triple ⁴	PPI (standard dose) ²	b.i.d.	Yes	CONDITIONAL (low quality of evidence)
	Levofloxacin (500 mg) ⁴	q.d.		
	Amoxicillin (1000 mg) or Metronidazole ⁵ (500mg)	b.i.d.		
P-CAB triple ⁶	Vonoprazan (20 mg)	b.i.d.	Yes	No recommendation (evidence gap)
	Clarithromycin (500 mg)			
	Amoxicillin (1000 mg)			
High dose dual therapy ⁷	Vonoprazan (20 mg) ⁸ or PPI (double dose)	b.i.d. or t.i.d.	No	No recommendation (evidence gap)
	Amoxicillin (1000 mg)	t.i.d.		

Chey et al. AJG 2024

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Antibiotic Sensitivity Testing

- Traditional Culture & Sensitivity
 - Cumbersome
 - Technically challenging
 - Expensive
 - Not widely available
- Molecular Testing
 - fresh, frozen, paraffin embedded gastric bxs
 - PCR, fluorescently-labeled nucleic acid hybridization
 - Identify mutations associated with resistance to specific antibiotics
 - More scalable & less costly than culture & sensitivity

Chey et al. Am J Gastroenterol 2017;112:212
Nishizawa et al. Front Mol Biosci 2014;1:19

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Slide 23

WCO See comment on slide 4 about HDDT.

Chey, William, 2024-01-22T23:18:33.722

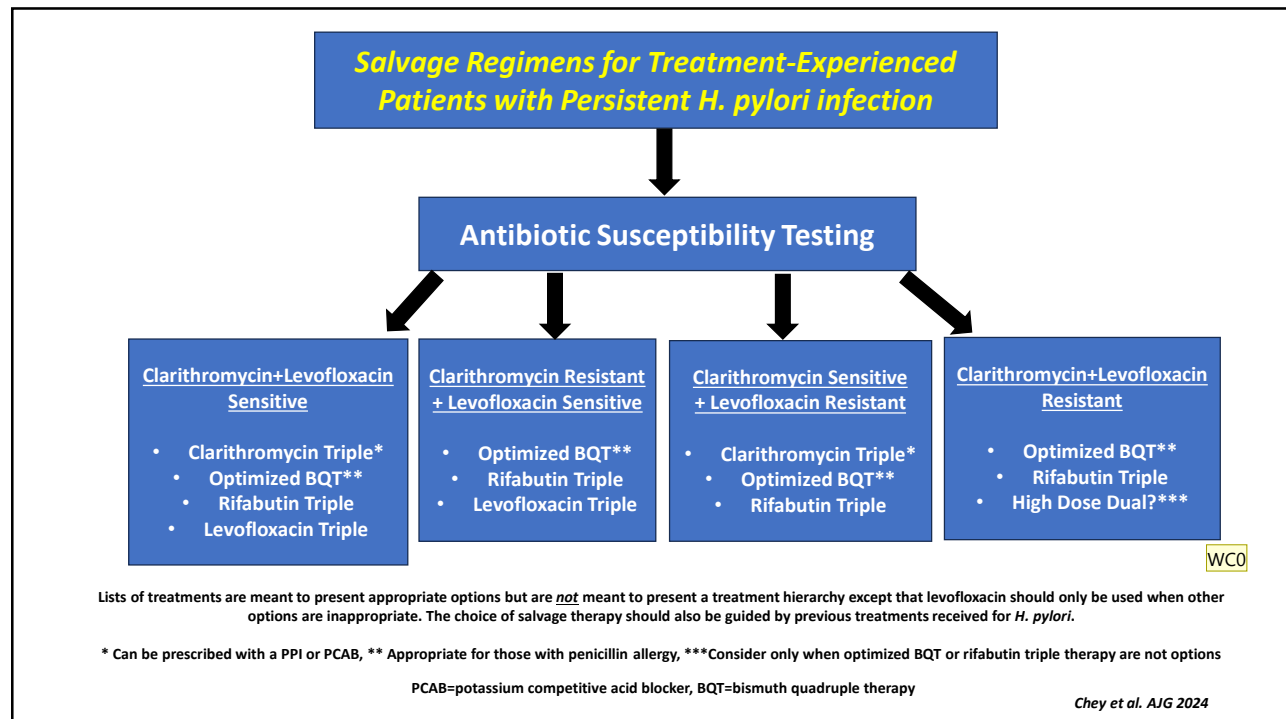
Next Gen Sequencing vs. Agar Dilution to Determine Antibiotic Sensitivity of *H. pylori*

Antibiotics	PyloriAR NGS culture isolate	Culture (MIC)		Sensitivity, %	Specificity, %	Predictive value, %		Accuracy, %	Agreement, κ coefficient
		(+)	(-)			PPV	NPV		
Clarithromycin n = 170 95% CI	(+)	28	3	93.3 77.9–99.2	97.9 93.9–99.6	90.3 75.2–96.6	98.6 94.7–99.6	97.1 93.3–99	0.90012 ($P < .0001$) 0.8671–0.9253
	(-)	2	137						
	—	—	—						
Metronidazole n = 170 95% CI	(+)	68	9	70.1 50–79	87.7 77.9–94.2	88.3 80.2–93.4	68.8 61.7–75.2	77.6% 70.63–83.7	0.5588 ($P < .0001$) 0.4458–0.6543
	(-)	29	64						
	—	—	—						
Levofloxacin n = 57 95% CI	(+)	31	4	93.9 79.8–99.3	83.3 62.6–95.3	88.6 75.9–95	90.9 72.1–97.5	89.5 78.5–96	0.78161 ($P < 0.0001$) 0.61689–0.94633
	(-)	2	20						
	—	—	—						

- 170 *Hp* isolates paired culture & sensitivity vs. Next Gen sequencing of fixed, paraffin-embedded gastric biopsies
 - Very few isolates were resistant to amoxicillin, rifabutin or tetracycline
 - Most reliable results with NGS were for clarithromycin and levofloxacin

Hulten et al. Gastroenterology 2021;161:1433

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WCO As in the guideline we do not recommend HDDT as salvage therapy, I think we should keep the question mark to make clear this is not evidence based and to reflect what we recommended in the guideline. I also think it should only be listed in the one box - otherwise, why didn't we recommend or suggest it in the guideline?

Chey, William, 2024-01-22T23:17:36.737



References

- Everhart, J. E., et al. (2000). Everhart JE, et al. *Journal of Infectious Disease*, 181(4), 1359-1363.
- Hooi, J. K. Y., et al. (2017). Hooi JKY et al. *Gastroenterology*, 53, 420-429.
- Kamboj, A. K., et al. (2017). Kamboj AK, et al. In *Mayo Clinic Proceedings*, 92(4), 599-604.
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