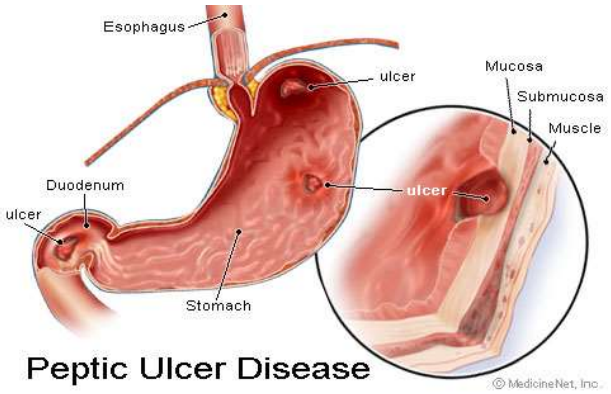
Treatment Resistant H Pylori



23 May 2023

H. pylori resistance to antibiotics is a major clinical challenge, and it is only increasing!

FAST 15

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Special interest in GI & gut microbiome

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- Past President
- Wound Care Instructor
- BOD

No disclosures
No commercial associations

AASPA American Association of Surgical Physician Assistants

Stony Brook School of Health Professions

QUESTION

What percent of H Pylori patients do you find to be resistant to your initial antimicrobial therapy?

- A. <10%
- B. About 25%
- C. About 50%
- D. >75%

H Pylori: Need to know

Unlike other bacteria, parasites, and viruses, H. Pylori has learned to survive the harsh acidic environment of the stomach.

After colonization, the *H.pylori* infection persists for years, decades, or even a lifetime.

H pylori is present on the gastric mucosa of 40–60% of people >60 y/o, including persons who are asymptomatic. In developing countries, the prevalence of infection may be >80% in adults.

Person-to-person transmission of *H.pylori* is likely because intrafamilial clustering of infection occurs.

Acute epidemics of gastritis suggest a common source for *H pylori*.

Key point- check family members!

H Pylori: Need to know

The leading cause for the development of chronic active gastritis and PUD.

NSAID exposure with chronic H pylori infection account for 90% of PUD!

"Approximately 40 percent of all gastric cancers in both resource-abundant and resource-limited countries are solely attributable to *H. pylori.*"

Studies have demonstrated an association between *H. pylori* infection and mucosa-associated lymphoid tissue lymphoma (MALToma)."

If an ulcer does not heal after H Pylori therapy –consider malignancy!

Helicobacter pylori CagA gene sequences

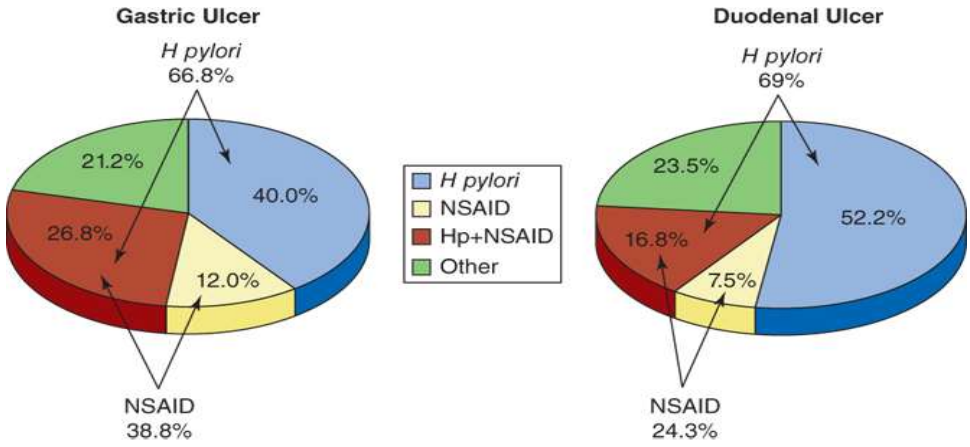
The first-identified bacterial protein involved in human cancer

Found via biopsy

Antibodies to CagA protein are detectable in gastric tissue and serum and permit the identification of infection with presumably more virulent organisms

The *cagA* gene-encoded CagA protein is delivered into gastric epithelial cells via bacterial cell secretion.

Hatakeyama M. Structure and function of Helicobacter pylori CagA, the first-identified bacterial protein involved in human cancer. Proc Jpn Acad Ser B Phys Biol Sci. 2017;93(4):196-219. doi: 10.2183/pjab.93.013



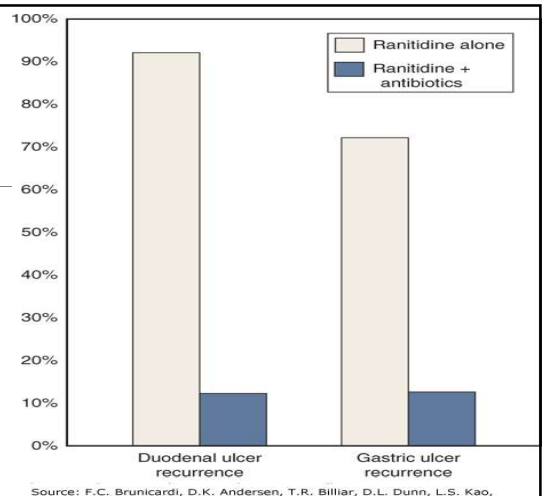
Source: J.B. Halter, J.G. Ouslander, S. Studenski, K.P. High, S. Asthana, M.A. Supiano, C. S. Ritchie, K. Schmader, W.R. Hazzard, N.F. Woolard: Hazzard's Geriatric Medicine and Gerontology, 8e: Copyright © McGraw Hill. All rights reserved.

Prevalence of gastric and duodenal ulcer in older patients divided according to the presence of H pylori infection and/or NSAID use.

Citation: Chapter 85 Upper Gastrointestinal Disorders, Halter JB, Ouslander JG, Studenski S, High KP, Asthana S, Supiano MA, Ritchie CS, Schmader K. *Hazzard's Geriatric Medicine and Gerontology, 8e;* 2022.

Without complete *H pylori* eradication…85% of patients with an ulcer will have a recurrence within a year!

Helicobacter treatment dramatically decreases the recurrence rate of duodenal and gastric ulcers

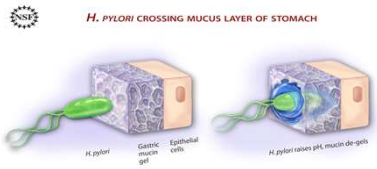


Source: F.C. Brunicardi, D.K. Andersen, T.R. Billiar, D.L. Dunn, L.S. Kao, J.G. Hunter, J.B. Matthews, R.E. Pollock: Schwartz's Principles of Surgery, 11e Copyright © McGraw-Hill Education. All rights reserved.

(Reproduced with permission from Peek RM, Blaser MJL: Pathophysiology of Helicobacter pylori-induced gastritis and peptic ulcer disease, Am J Med. 1997 Feb;102(2):200-207.)

Chapter 26 Stomach, Brunicardi F, etal
Schwartz's Principles of Surgery, 11e; 2019.

H Pylori & pH



-Grows optimally at a pH of 6.0–7.0 and would be killed or not grow at the pH in the gastric lumen.

-Gastric mucus is impermeable to acid and has a strong buffering capacity.

-On the lumen side of the mucus, the pH is low (1.0–2.0); on the epithelial side, the pH is about 7.4. H pylori burrows deep in the mucous layer near the epithelial surface!

-*H pylori* produces a protease that modifies the gastric mucus and reduces the ability of acid to diffuse through the mucus.

-*H pylori* produces potent urease activity, which produces ammonia= more buffering of acid.

-Destruction of the epithelium is common, with glandular atrophy.

Diagnosis

Most infected individuals systemically produce specific antibodies to a variety of *H. pylori* antigens.

Ideally off PPI for 7-14 days and antibiotics for 4 weeks

Urea breath test (^{13}C labeled urea → exhaled labeled CO_2)] preferred if not having endoscopy

Stool fecal antigen

Biopsy (endoscopic sampling @ two sites for rapid urease and histology)

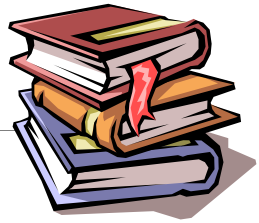
Blood work: second line: Antibodies to *H. pylori* can be detected by serum ELISA test.

These serum antibodies persist even if the *H pylori* infection is eradicated, and the role of antibody tests in diagnosing active infection or after therapy is limited.

Immunoglobulins: IgM, IgA, IgG

Personal note:
Symptomatic patient after therapy, I have found negative stool and a positive Serum IgA!

H Pylori Danger signs Endoscopy for:



- N & V
- Weight Loss (5% TBW)
- Anemia
- Blood in the stool
- Dysphagia +/- odynophagia
- Early Satiety
- Odynophagia/Dysphagia
- Evidence of *Complications*
- Especially NEW ONSET in >50 y/o age group (esp. Caucasian)

Before treating…. Ask "the question"

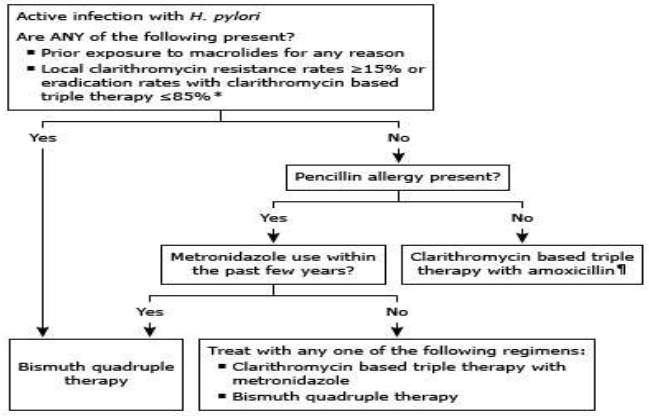
"Any recent antibiotic use?"

"Any antibiotic therapy ever?"

"If there is a history of *any* treatment with macrolides or fluoroquinolones, then clarithromycin- or levofloxacin-based regimens, respectively, should be avoided given the high likelihood of resistance. Resistance to amoxicillin, tetracycline, and rifabutin is rare, and these can be considered for subsequent therapies in refractory *H pylori* infection."

- AGA Clinical practice guidelines 2021

Initial approach to antibiotic treatment for *Helicobacter pylori* infection



- Bismuth quadruple therapy consists of bismuth, metronidazole, tetracycline, and a PPI.
- Clarithromycin based triple therapy with amoxicillin consists of clarithromycin, amoxicillin, and a PPI.
- Clarithromycin based triple therapy with metronidazole consists of clarithromycin, metronidazole, and a PPI.

UpToDate®

Over the years, these regimens have been repeatedly modified to overcome the evolving resistance of H. pylori strains to antibiotics

Bismuth Quadruple therapy 14 days

High dose PPI twice a day
- Defined as DOUBLE the standard dose

BISMUTH SUBSALICYLATE 300-524 mg four times a day

Tetracycline 500mg four times a day

Metronidazole 500mg three to four times a day

My favorite first line!

First line therapy

<u>Clarithromycin Triple:</u>
Omeprazole 40mg Q12h + Clarithromycin 500mg Q12h + Metronidazole 500 q12h or Amoxicillin 2000mg for 14 days

Consider + rifaximin

Consider Nitazoxanide

or
<u>Clarithromycin Concomitant</u>
Omeprazole 40mg Q12h + Clarithromycin 500mg Q12h + Metronidazole 500 **AND** Amoxicillin 1000mg for 14 days

Urea breath test is done if the 1st line regimen fails

Battling resistance

"The usual cause of refractory *Helicobacter pylori* infection (persistent infection after attempting eradication therapy) is antibiotic resistance."

Identify other contributing etiologies, including inadequate adherence to therapy and insufficient gastric acid suppression."

- AGA Clinical practice guidelines 2021

Mechanisms of resistance: the Germ

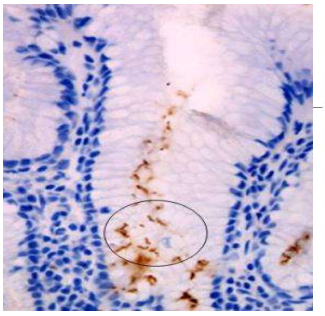
1. Outer membrane proteins: Adhesion to host cell
2. The outer lipopolysaccharide: adhere to host cells
3. The exotoxins: The vacuolating toxin injuries gastric mucosa
4. The secretory enzymes:
   - The urease : Neutralize gastric acid
   - The mucinase, lipase and protease (mucosal injury)

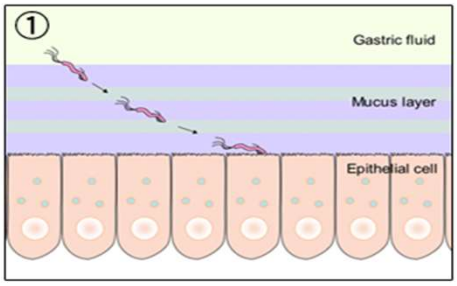
Podophyllotoxin may inhibit*

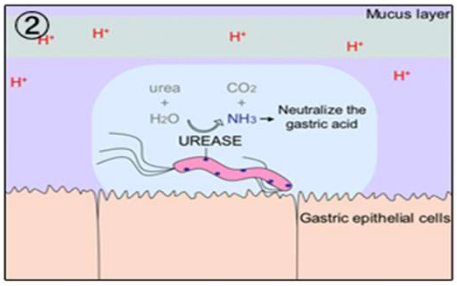
5. Flagella With flagella & a spiral shape, the bacterium drills into the mucus layer of the stomach, and can either be found suspended in or under the gastric mucosa or attached to epithelial cells.
6. Effector cytotoxin: The cytotoxin associated gene A
7. Actively mobile!

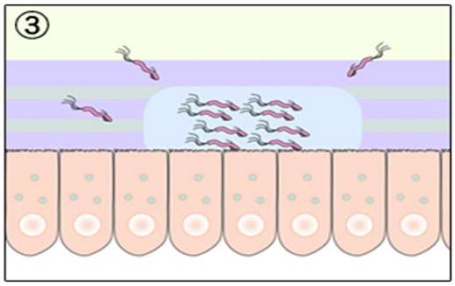
* International Journal of Molecular and Clinical Microbiology 12(1) (2022) 1632-1642

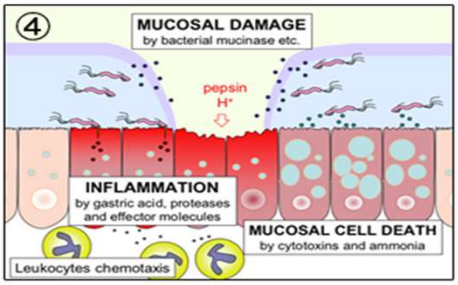
HELICOBACTER PYLORI









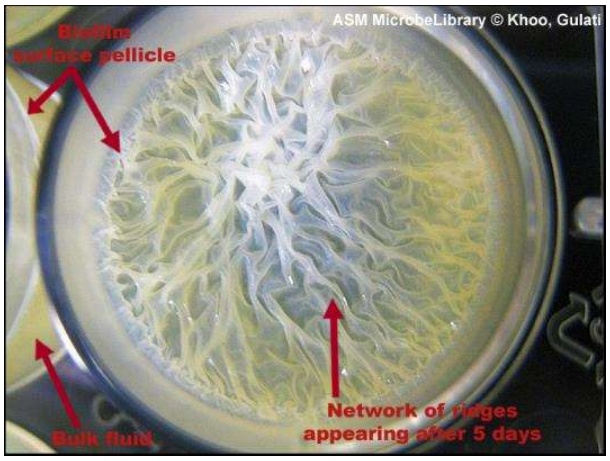


Vinay Kumar MBBS, MD, FRCPath, Abul K. Abbas MBBS
Robbins Basic Pathology

Mechanisms of resistance

8. BIOFILMS

"Biofilms are a SUPER BIG DEAL in H Pylori!"
-Simons



American Society For Microbiology ©

H Pylori biofilm

Microorganisms adhere to a surface & create a sugary slime layer around it which protects the bacteria from external threats.

Bacteria with biofilm structures can be up to 1000x more resistant to antibiotics.

H Pylori survive the gastric acid, invade the gastric epithelium, and are encapsulated into a self-produced matrix to form biofilms.

"Targeting biofilms might be an effective strategy to alleviate *H. pylori* drug resistance. Anti-biofilm agents have been investigated as alternative or complementary therapies to antibiotics to reduce the rate of drug resistance."

Chong Hou, Fangxu Yin, Song Wang, Ailing Zhao, Yingzi Li & Yipin Liu (2022) Helicobacter pylori Biofilm-Related Drug Resistance and New Developments in Its Anti-Biofilm Agents, Infection and Drug Resistance

Example: Nitazoxanide

Mechanisms of resistance

BACTERIAL FACTORS

PATIENT FACTORS

- Health Literacy: complex treatment to remember
- Smoker
- Presence of ulcers
- Genetics

INADEQUATE ANTIBIOTIC DOSING FOR BACTERIAL LOAD

INADEQUATE REPORTING and resistance testing

Battling resistance

1. Antibiotic resistance!
2. Lifestyle management!
3. Confirm compliance/Health literacy

   Inadequate acid suppression is a common cause!
4. Consider reinfection
5. Consider biofilm
6. Minimize/stop NSAIDS/ASA
7. Genetics: CYP2C19 genotyping
8. Inadequate length (14 days is ideal)
9. Stop smoking– it's an independent risk factor of eradication failure

SUZUKI, T., etal (2007). Influence of smoking and CYP2C19 genotypes on H. pylori eradication success. *Epidemiology & Infection, 135*(1), 171-176

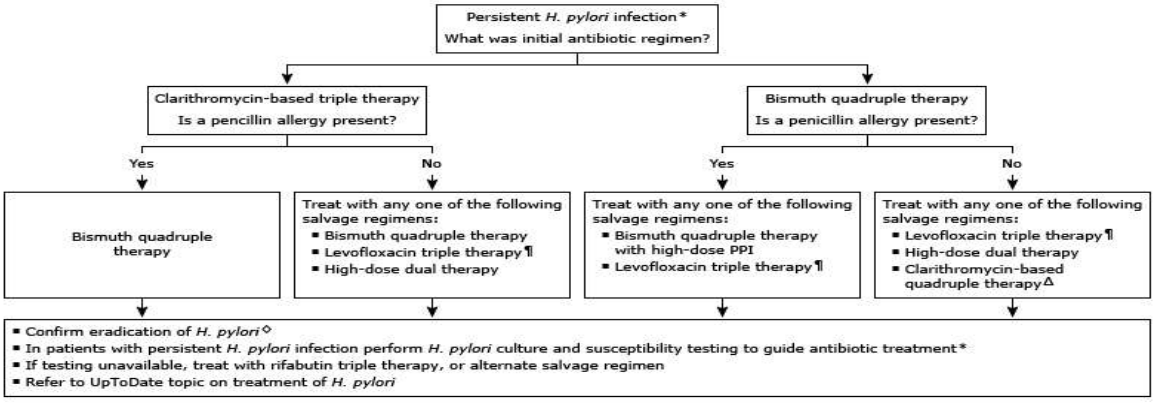
Lifestyle

1.Stop smoking

2. GERD Lifestyle changes if needed

3. DIET -AVOID
   - Liver, oysters,
   - Salted, pickled, vinegar, fermented & smoked foods
   - Food that trigger heartburn/GERD in the patient

4. DIET- INCLUDE
   - Bitter vegetables
   - Pre-biotic foods (fiber, garlic, onions, apples, oats)



- Clarithromycin-based triple therapy consists of clarithromycin, amoxicillin/metronidazole, and a PPI.
- Bismuth quadruple therapy consists of bismuth subsalicylate or bismuth subcitrate, metronidazole, tetracycline, and a PPI.
- Levofloxacin triple therapy consists of levofloxacin, amoxicillin/metronidazole, and a PPI.
- High-dose dual therapy consists of amoxicillin and a PPI.
- Rifabutin triple therapy consists of rifabutin, amoxicillin, and a PPI.
- Clarithromycin-based concomitant therapy consists of clarithromycin, amoxicillin, nitroimidazole (eg, metronidazole), and a PPI.

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Second line therapy

1. Quadruple regimen of PPI, tetracycline, metronidazole, and bismuth is the most commonly used second line therapy

   Hojo M, et al. Pooled analysis on the efficacy of the second-line treatment regimens for *Helicobacter pylori* infection. *Scand J Gastroenterol*;36:690–700

2. Rifabutin 300 mg/day, PPI, amoxicillin
3. Efficacy of levofloxacin-based second-line therapy is decreasing due to an increasing levofloxacin resistance. (*Mégraud et al 2013*) BUT…Levofloxacin works better with nitazoxanide

Nitazoxanide

Nitazoxanide is a first-line choice for the treatment of illness from *Cryptosporidium parvum* or *Giardia lamblia.*

Nitazoxanide is an antibiotic with microbiological characteristics similar to those of metronidazole, of comparable cost, and no discernible resistance.

Nitazoxanide 500 mg bid, levofloxacin 500 mg once daily, omeprazole 40 mg bid and doxycycline 100 mg twice daily were prescribed for 14 days with 88% eradication

- Abd-Elsalam et.al, A 2-week Nitazoxanide-based quadruple treatment as a rescue therapy for Helicobacter pylori eradication: A single center experience. Medicine (Baltimore). 2016

KEY POINT: Consider Nitazoxanide

4. Rifaximin Second line

14 day PPI, Amoxil 500 Q12h, Levofloxacin 250 BID, Rifaximin 400 Q8h

- Chung, Woo Chul. "Efficacy of Rifaximin Add-On Levofloxacin Regimen as Third-Line Rescue Therapy of Helicobacter Pylori Eradication." *J Gstro Hepato* 8: 1-4.

Not first line

The less-frequent applications of rifaximin may reduce the resistance rate to *H. pylori*.

As a non-absorption agent, rifaximin has little interaction with other drugs and with tiny impact on normal flora outside the gastrointestinal tract

- Wang Y, Effectiveness and Safety of Rifaximin-Containing Regimens for Helicobacter pylori Eradication: Systematic Review – Are They Potential Eradication Regimens?. *Infect Drug Resist*. 2022;15:3733-3749 https://doi.org/10.2147/IDR.S371131

Overall, adding probiotics increase tolerance and eradication

Lactobacillus Acidophilus, Lactiplantibacillus plantarum, Bifidobacterium lactis, and Saccharomyces boulardii

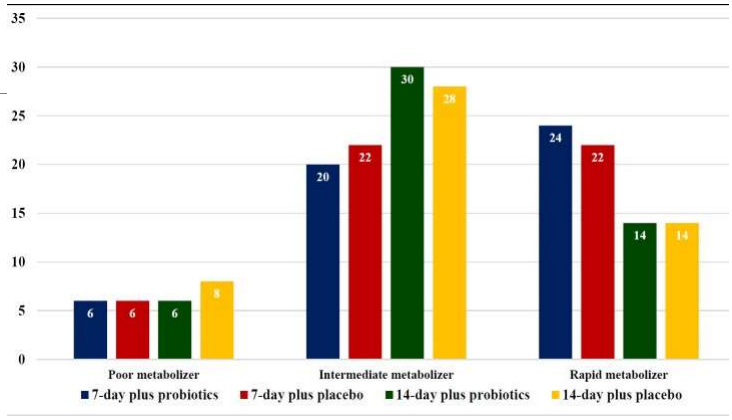
- Need doses in the billions to be effective
- Not yet in AGA guidelines

Poonyam P, et.al . High Effective of 14-Day High-Dose PPI- Bismuth-Containing Quadruple Therapy with Probiotics Supplement for Helicobacter Pylori Eradication: A Double Blinded-Randomized Placebo-Controlled Study. Asian Pac J Cancer Prev. 2019 Sep 1;20(9):2859-2864

Viazis N, et.al. A Four-Probiotics Regimen Combined with A Standard Helicobacter pylori-Eradication Treatment Reduces Side Effects and Increases Eradication Rates. Nutrients. 2022; 14(3):632. https://doi.org/10.3390/nu14030632

Rates of resistance

Add Probiotics and check CYP2C19 gene!



Poonyam P, Chotivitayatarakorn P, Vilaichone RK. High Effective of 14-Day High-Dose PPI- Bismuth-Containing Quadruple Therapy with Probiotics Supplement for Helicobacter Pylori Eradication: A Double Blinded-Randomized Placebo-Controlled Study. Asian Pac J Cancer Prev. 2019 Sep 1;20(9):2859-2864

Third line….

If 2nd line quadruple drug therapy fails then:

<u>Culture of endoscopic guided biopsy is done and treatment is given based on antimicrobial susceptibility</u>

OPTIONS:

- PPI, amoxicillin, rifabutin
- Nitazoxanide combination
- Rifaximin combination

Confirm eradication

Eradication of *H. pylori* infection can be confirmed with:

- Urea breath test **BEST**
- Stool antigen testing
- Upper endoscopy-based testing—if ulcer follow-up is needed

H. pylori serology should not be used to confirm eradication of *H. pylori*.

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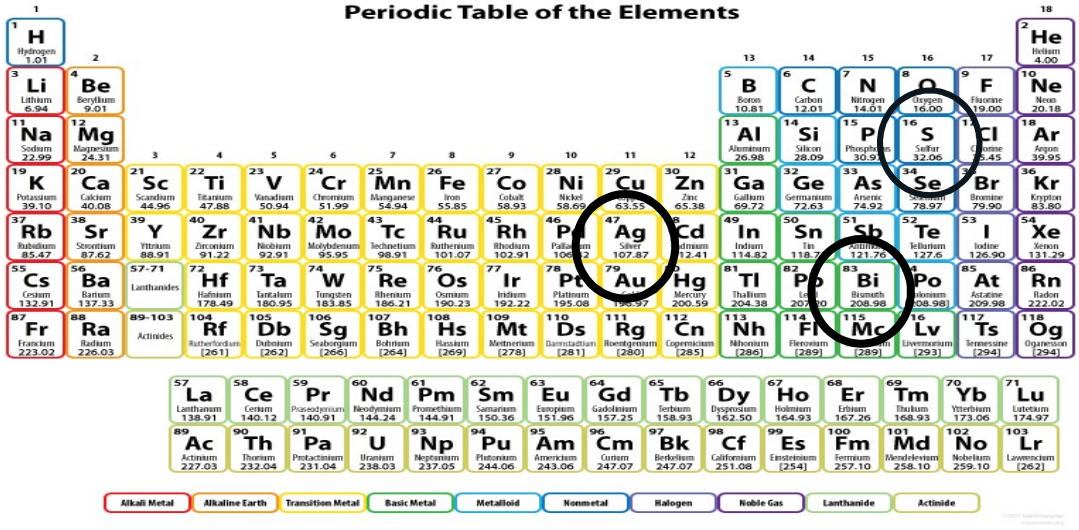
The future …



The future targets biofilms & more

Silver nanoparticles

- Pop R, Tăbăran A-F, Ungur AP, Negoescu A, Cătoi C. Helicobacter Pylori-Induced Gastric Infections: From Pathogenesis to Novel Therapeutic Approaches Using Silver Nanoparticles. *Pharmaceutics*. 2022; 14(7):1463

Peptide therapy: BPC-157

- Sikiric, Predrag; et.al Current Pharmaceutical Design, Volume 17, Number 16, 2011, pp. 1612-1632(21) Bentham Science Publishers
- Xue XC, et.al. Protective effects of pentadecapeptide BPC 157 on gastric ulcer in rats. World J Gastroenterol. 2004 Apr 1;10(7)

Delafloxacin (Baxdila)

Rifaximin – great promise for the future

Fecal Transplant (Oral)

- Zhi-Ning Ye, Harry Hua-Xiang Xia, Ran Zhang, Lan Li, Li-Hao Wu, Xu-Juan Liu, Wen-Rui Xie, Xing-Xiang He, "The Efficacy of Washed Microbiota Transplantation on *Helicobacter pylori* Eradication: A Pilot Study", *GI Research and Practice*, vol. 2020,

In summary: You can beat H Pylori

Acid suppression is vital

Ask about previous antibiotic therapy –germ resistance is a major cause

Consider testing family members

Bismuth quadruple therapy is a great start

Encourage patient compliance and lifestyle modification

Consider Nitazoxanide therapy

Consider Rifaximin

Use DB-RCT to select probiotics to support

Additional References

Xiao-Qin Wang, Hong Yan, Paul D. Terry, Jian-Sheng Wang, Li Cheng, Wen-An Wu & Sen-Ke Hu (2012) Interaction between Dietary Factors and *Helicobacter Pylori* Infection in Noncardia Gastric Cancer: A Population-Based Case-Control Study in China, Journal of the American College of Nutrition, 31:5, 375-384

StemmermannGN, Fenoglio-PreiserC: Gastric carcinoma distal to the cardia: a review of the epidemiological pathology of the precusors to a preventable cancer. Pathology 34: 494– 503, 2002.

Hussein NR: *Helicobacter pylori* and gastric cancer in the Middle East World J Gastroenterol 16: 3226– 3234, 2010.

Hooi JKY, Lai WY, Ng WK, et al. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. Gastroenterology 2017;153:420–429.

Plummer M, Franceschi S, Vignat J, et al. Global burden of gastric cancer attributable to Helicobacter pylori. Int J Cancer 2015;136:487–490.

Linz B, Balloux F, Moodley Y, et al. An African origin for the intimate association between humans and Helicobacter pylori. Nature 2007;445:915–918.