1. **What are the new recommendations?**
   Per the 2024 ACG guidelines, bismuth quadruple therapy (BQT) remains first line in addition to two additional regimens: rifabutin triple therapy (RTT), and potassium-competitive acid blocker (PCAB) dual therapy.[1]
   a. BQT consists of proton pump inhibitor (PPI), bismuth salt, tetracycline, and metronidazole. A single-center retrospective analysis evaluated eradication rates of BQT compared to clarithromycin triple therapy and observed higher eradication rates in the 14-day BQT than clarithromycin therapy (87% vs 70%, P = 0.0052). These results support keeping BQT as first line therapy, especially with rising H. pylori resistance rates to clarithromycin.[2]
   b. RTT includes rifabutin, PPI and amoxicillin. In a Phase 3, double-blind trial, RTT was found to have higher H. pylori eradication rates than those on amoxicillin with omeprazole (83.8% vs 57.7%, P < 0.001). This supports the novelty of rifabutin in H. pylori infection treatment with little to no resistance reported.[3]
   c. PCAB dual therapy (vonoprazan (PCAB) and amoxicillin) was considered noninferior to the lansoprazole-clarithromycin triple regimen with both having 79% eradication rates.[1] PCABs offer a more potent mechanism to facilitate faster and more prolonged acid suppression compared to PPIs and offers a lower pill burden alternative.
   d. Dosage considerations (cost): **14 day therapies are recommended over 10 days.**

BQT[a] ($)	PPI: standard dose BID Bismuth subsalicylate: 262mg QID Tetracycline[a] 500mg QID Metronidazole 500mg TID
RTT[b] ($$$) (Talicia per capsule/per day) Note: Talicia contains a rifabutin strength lower than what is commercially available (Rifabutin tablet size: 150mg per tab)	Omeprazole 10mg/120mg Amoxicillin 250mg/3000mg Rifabutin[a] 12.5mg/150mg Dosing: 4 capsules TID
PCAB dual therapy[a] ($$$) (Voquezna DualPak)	Vonoprazan[a] 20mg BID Amoxicillin 1000mg TID

[a] Pylera is a combination tablet with bismuth subsalicylate, tetracycline, and metronidazole. Now available as generic. Consider checking www.costplusdrugs.com if cost prohibitive.
[b] Combo therapy and rifabutin alone not routinely covered by insurance. Savings card available for commercially insured patients.

2. **How does BQT therapy work against H. pylori?**
   a. **Since susceptibilities are not routinely performed, multiple antibiotics are given that have assumed activity against H pylori to increase likelihood of active therapy. Non-antimicrobials have some activity against H pylori and improve efficacy of antibiotics.** Developing resistance to a non-antimicrobial is thought to be uncommon.
   b. PPI or PCABs play a significant role at increasing cure rates when used with antibiotics. In addition to PPIs having mild bacteriostatic effects, PPIs and PCABs are also thought to increase gastric pH promoting H. pylori replication while creating a more stable environment for acid-labile antibiotics leading to improved eradication.[1]
   c. Bismuth salts prevent H. pylori from adhering to the GI mucosal wall and have bactericidal effects on H. pylori's cell wall.[1]

3. **Can we substitute other agents in BQT?**
    a. **<u>Doxycycline is an option but not recommended by AJG due to decreased efficacy. Use only if alternative first line therapies cannot be initiated in a timely manner or are cost prohibitive. Limited supply of tetracycline will be available inpatient. Outpatient coverage should be confirmed as additional authorization is often required.</u>**
    b. Mixed literature exists regarding the use of tetracycline vs. doxycycline in the setting of BQT. Per the AJG guidelines, tetracycline is preferred over doxycycline due to better H. pylori eradication rates. Doxycycline is not recommended despite acknowledging issues with availability and cost making it challenging to implement in clinical practice.[1]
    c. In a multicenter retrospective review of approximately 1000 patients who completed treatment for H. pylori and tested for cure, eradication rates of doxycycline (70%) were lower than tetracycline (87%) and clarithromycin triple therapy (79%). Notably, only 5% of patients were on the doxycycline quadruple therapy.[2] Additional studies querying prescription data has found similar findings of slightly lower efficacy with doxycycline-based BQT compared to tetracycline.[5] Poor adherence contributing to lower efficacy should also be considered as this is a common issue with most H. pylori regimens.

4. **Why are clarithromycin-related regimens no longer recommended?**
    a. **<u>Due to increased resistance and higher risk for treatment failure, clarithromycin-based therapies are not recommended as first line therapy unless susceptibilities are confirmed.</u>**[1] Obtaining susceptibilities is uncommon due to accessibility of testing.
    b. In a review of H. pylori resistance data across the United States (Washington, California, Texas, Minnesota, New York, Rhode Island, and Alaska) between 2011 and 2021, clarithromycin, metronidazole, and levofloxacin resistance rates exceeded 30% while amoxicillin, rifabutin, and tetracycline resistance remained low.[6]
    c. Fred Hutchinson Cancer Research Center has also published some more recent local data from 110 patients suggesting >20% clarithromycin resistance. Resistance was noted to be higher among Asians compared to non-Asians.[7]

5. **Would intravenous antibiotics be effective against H. pylori?**
    a. **<u>There is limited data recommending a standard IV regimen. Holding H. pylori treatment would be preferred since patients are often on empiric broad spectrum antibiotics due to a secondary intraabdominal infection. Based on resistance data available, the following Quad-parenteral alternative to guideline therapy could be considered when necessary: PPI, ampicillin, doxycycline or levofloxacin, and metronidazole at standard dosing.</u>** Despite metronidazole resistance increasing, increased dosing of 1.5 g per day may be utilized to increase eradication rates.[1] When patients can tolerate PO, switching to BQT should be considered to complete a total duration of 14 days.
    b. The ACG guidelines do not mention alternative IV treatment. Amoxicillin has been observed to obtain high concentrations in gastric mucosa. As a result, oral therapy is thought to be preferred for the treatment of H. pylori.[8]
    c. In a systematic review of a limited pool of data evaluating the efficacy and safety of IV antibiotics, suggested regimens included a PPI, clarithromycin, ampicillin, and metronidazole or a PPI, levofloxacin, and metronidazole.[9] Neither of these regimens are similar to first line therapies and increasing resistance may compromise efficacy.

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