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Addressing the global challenge of *Helicobacter pylori*-induced dyspepsia and peptic ulcer disease: socioeconomic, clinicopathologic, and clinico-pharmacological implications of the new treatment guidelines

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ABSTRACT

Helicobacter pylori-related dyspepsia and peptic ulcers persist as major health challenges in low- and middle-income countries (LMICs) like India, Nigeria and by extension other Subsaharan nations, where high infection rates, antibiotic resistance, and inequities converge. The 2024 American College of Gastroenterology guidelines endorse Bismuth Quadruple Therapy (BQT) – a 14-day regimen combining a proton-pump inhibitor, bismuth, tetracycline, and metronidazole – and vonoprazan, a potassium-competitive acid blocker, both showing high efficacy. However, real-world adoption is hindered by prohibitive costs (especially in regions reliant on out-of-pocket spending), fragmented diagnostics, cultural distrust of biomedicine, and unregulated antibiotic use. Genetic factors, such as polymorphisms in Asian populations reducing proton-pump inhibitor effectiveness, further impede treatment. Bridging this gap demands strategies: WHO-coordinated antibiotic resistance surveillance, tiered drug pricing for LMICs, regionally tailored protocols integrating genetic testing, and community health worker-led education to address cultural barriers. Parallel policies, like community-based insurance, could enhance access to novel therapies while curbing antibiotic misuse. Without these reforms, advancements like BQT and vonoprazan risk excluding vulnerable populations. Aligning biomedical innovation with equity necessitates shifting from universal guidelines to adaptive frameworks that address genetic, socioeconomic, and cultural determinants of *H. pylori* outcomes globally.

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Helicobacter pylori; peptic ulcer disease; antibiotic resistance; dyspepsia; quadruple therapy; health equity

Introduction

Helicobacter pylori (*H. pylori*) is a spiral-shaped, gram-negative bacterium that infects the stomach's epithelial lining, often evading the host's immune system for decades due to its adaptable mechanisms.[12] Identifying *H. pylori,* as seen in Figure 1, as a cause of peptic ulcer disease marked a significant shift, turning a debilitating illness into one effectively treated with antibiotics. Nevertheless, the rise of antibiotic resistance continues to pose frustrating challenges.[1,7,30] Over half the global population is affected by *H. pylori* infection, with rates up to 70.1% in Africa and Nigeria reporting 87.7%, the highest globally.[15] Most *H. pylori* infections are asymptomatic, but some experience a spectrum of outcomes ranging from benign conditions, such as dyspepsia, gastritis and peptic ulcers, to malignant ones like gastric cancer and Mucosa-associated lymphoid tissue (MALT) lymphoma.[4] Symptoms include abdominal pain, dyspepsia, nausea, and gastrointestinal bleeding.[4,15]

The American College of Gastroenterology has issued a new guideline focusing on evidence-based treatment protocols for managing *H. pylori* infection in North America. It employs the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to evaluate treatment recommendations, assessing their strength based on available evidence.[4] The purpose of this commentary is to critically analyze the socioeconomic, clinicopathologic, and clinico-pharmacological implications of this new guideline especially in low-resourced nations and proffer recommendations.

Overview of the conventional treatment approach to peptic ulcer disease[PUD (triple therapy)]

The classical triple therapy consisting proton pump inhibitor (PPI), clarithromycin and amoxicillin or metronidazole (for Penicillin allergic individuals) given for 7 to 14

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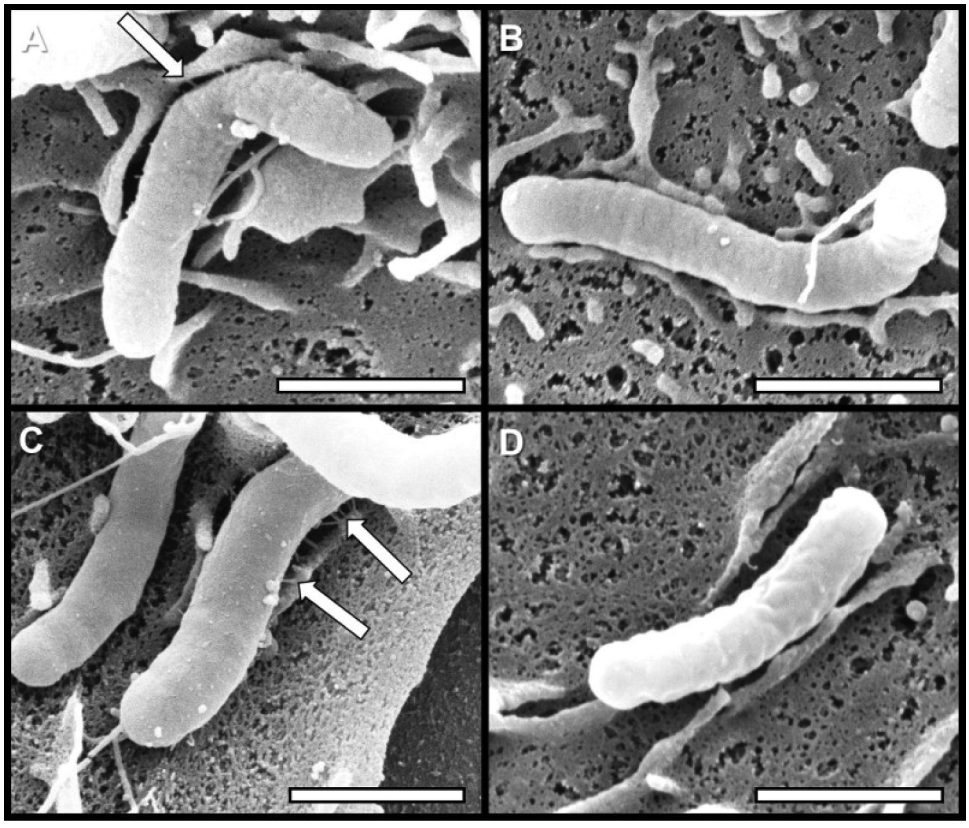

Figure 1. High resolution electron microscopy imagery of H.pylori[12] - Haley KP, Blanz EJ, Gaddy JA. High resolution electron microscopy of the *Helicobacter pylori* Cag type IV secretion system pili produced in varying conditions of iron availability. J Vis Exp. 2014;(93):e52122. Published 2014 Nov 21. doi:10.3791/52122. Arrows indicate pili formed at the host–pathogen interface and bars indicate micrometer measurements of media[a- medium alone, B -medium supplemented with 100 µm iron chloride, C - medium supplemented with 200 µm dipyridyl, and D - medium supplemented with 200 µm dipyridyl plus 250 µm iron chloride prior to co-culture with human gastric cells].

days has been the most widely used regimen, recommended by globally convened consensus meetings like the Maastricht international consensus and the Brazilian consensus.[4,5,21] The wide acceptance of this regimen was based on its relative simplicity, optimal safety profile, affordability and high efficacy- as studies earlier conducted consistently showed good results of over 90% eradication rates.[6,20] However, more recent publications have suggested that this level has dropped significantly to around 70% in many areas and even as low as 60% in some regions unfortunately.[17,27]

According to the Maastricht IV/Florence consensus report, there are several explanations for the decrease in efficacy of the standard triple therapy: compliance, high gastric acidity, high bacterial load, type of strains. However, the most important is the increase in *H. pylori* resistance to clarithromycin.[5] In order to address this, a study was conducted and it was recommended that the treatment regimen should be selected according to areas of low and high clarithromycin resistance.The prevalence is said to be low if <20% & high if >20%.[5] This alongside other implicating factors such as noncompliance and polypharmacy, further led to the development of new regulations.[5,6]

The ACG guideline recommendation

The ACG initiated the development of this clinical practice guideline to provide evidence-based guidance for the management of patients with *Helicobacter pylori* infection in North America. This guideline employed the Grading of Recommendations, Assessment, Development, and Evaluation methodology to systematically evaluate 11 questions concerning population, intervention, comparison, and outcome, leading to the formulation of recommendations. In areas where the evidence was lacking or where the subject did not fit the GRADE framework, a consensus among experts was reached to establish six essential concepts for treatment-naive and treatment-experienced patients. Below is Table 1, highlighting these concepts.

Table 1. The new ACG Guidelines.[4]

	For Treatment- Naïve Patients	For Treatment- Experienced Patients
1	Optimized Bismuth Quadruple Therapy (BQT) is strongly recommended as a first line option.	Optimized Bismuth Quadruple Therapy is suggested for patients who have not previously reserved BQT.
2	Rifabutin triple therapy is suggested as a first line treatment option.	Optimized BQT or Rifabutin triple therapy are suggested for previously treated patients with PPI- Clarithromycin triple therapy
3	Dual therapy with potassium competitive acid blocker (PCAB) and amoxicillin are suggested as first line treatment options.	In those previously treated with BQT, BQT is still suggested over Quinolone-based therapy.
4	If clarithromycin susceptibility is unknown, PCAB-Clarithromycin triple therapy is suggested over PPI-Clarithromycin triple therapy.	Levofloxacin triple therapy is suggested in levofloxacin sensitive *H. pylori* strains when optimized BQT or Rifabutin triple therapy has previously been used or unavailable.
5	Concomitant therapy is not suggested over bismuth quadruple therapy.	There is insufficient evidence in North America to recommend high dose Proton Pump Inhibitor or Potassium competitive acid blocker dual therapy
6	Penicillin allergy – employ the use of optimized Bismuth Quadruple therapy	There is insufficient evidence to suggest that probiotic therapy improves the efficacy or tolerability of *H. pylori* eradication therapy

A tabulation of the newly released ACG guidelines.

Socioeconomic implications

Asides the challenges that come with implementing this new treatment guidelines i.e local drug regulatory hurdles and the need for healthcare personnel training to adopt newer therapies in low- and middle-income countries (LMICs),[24] for physicians in resource-constrained health systems, the problem of availability and financial burden plays a significant role in prescribed choice regimens,[14,31] but newer options have also been recently published to indirectly cause treatment failure due to patients not being able to afford the complete course of treatment.[23]

Moreover, since most new medicines and vaccines are typically tested in high-income countries, the introduction of new guidelines may be met with skepticism in LMICs. This skepticism arises from ethical dilemmas and the mistrust among local populations due to the historical lack of drug trials in their regions.[24] Consequently, this situation affects their perceptions of the trustworthiness of medications, despite the potential benefits these guidelines could bring.

Despite their noted increased efficacy in some climes, the availability of new recommendations like BQT, rifabutin, and vonoprazan is also a concern in its adoption into patient care in low-income countries.[8,23] Unlike the traditionally recognized triple therapy, it has been observed that newer drug choices like Vonoprazan are not yet available in some markets which could be attributed to cost minimization during healthcare and the need for cost-effectiveness[13,23]

Due to the finances involved, insufficient advanced molecular tests focused on the sensitivity and susceptibility of different medications to *H. pylori* in different demographics are being conducted in resource-limited areas like the Sub-saharan.[8,31] This allows for the possibility of inadvertent inequalities in the quality of treatment offered as the outcomes are evaluated using a different subject group and show a need for more research to be done on this.[8,9,23] In health settings like Japan where a unified national health insurance system bears the cost of bulk procurement of recommended medications, a transition to newer guidelines is considered to be more swiftly tolerated as the challenges involving cost and drug availability are bypassed from the patients' perspective and shouldered by the responsible bodies.[13,14] In the absence of a unified health system, patients enrolled in personal health insurance schemes could benefit from new therapeutic recommendations when capitation for the treatment of *H. pylori* is increased as in health reforms implemented recently in Nigeria.[2]

Clinicopathological and clinico-pharmacological implications

The treatment approach for *H. pylori* infection has significantly evolved in recent years due to increasing antibiotic drug resistance and varying successful eradication rates. Historically, triple therapy, which included proton pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole, was the standard first-line treatment. However, global rise in clarithromycin and metronidazole resistance has led to declining success rates, prompting a shift toward different and more effective regimens.[29] Bismuth quadruple therapy (BQT), which includes bismuth alongside a PPI and antibiotics, has emerged as an option, especially in regions where resistance to clarithromycin is prevalent.[22] Additionally, newer agents such as vonoprazan have been integrated into therapeutic regimens, further enhancing treatment outcomes.[26]

The classic quadruple therapy, involving omeprazole, bismuth subcitrate, metronidazole, and tetracycline, consistently achieves higher eradication rates compared with standard triple therapy. A multicenter, randomized, active-controlled trial that assessed the efficacy of bismuth-based quadruple therapy with omeprazole,

bismuth biskalcitrate, metronidazole, and tetracycline using a single-triple capsule of bismuth, metronidazole, tetracycline compared with triple therapy with omeprazole, amoxicillin, and clarithromycin in treatment of patients with *H.pylori* infection and duodenal ulcers, demonstrated that a quadruple regimen involving bismuth citrate potassium, metronidazole, and tetracycline, when administered with omeprazole, was significantly more effective than clarithromycin-based triple therapy in previously untreated patients.[10,19]

The success of these drugs lies in the mechanism by which they exert their action on *H. pylori*. PPIs play a critical role in this treatment by reducing gastric acid secretion, through the inhibition of the H+/K+ ATPase enzyme in gastric parietal cells. This increases the stomach's pH, creating a more favorable environment for antibiotics and improving their stability.[28] Bismuth exerts bactericidal activity against *H. pylori*, protecting the gastric mucosa, disrupting the bacterial cell wall, inhibiting bacterial enzymes, and preventing bacterial adhesion to the gastric epithelium.[3] Vonoprazan, a novel potassium-competitive acid blocker, acts as an alternative to proton pump inhibitors (PPIs) by targeting and inhibiting the K+/H+ ATPase pump, effectively reducing gastric acid secretion. Unlike traditional PPIs, it demonstrates a faster onset of action and provides longer-lasting acid suppression, enhancing therapeutic efficacy in acid-related disorders.[11] These mechanisms, combined with the standard antibiotics targeting bacterial protein synthesis and DNA, provide a synergistic effect, leading to the effective eradication of *H. pylori* and quicker mucosal healing[3,11]

A meta-analysis done by Alessia Savoldi et al., (2018), which included studies from 65 countries, highlighted the alarming rates of antibiotic resistance in various regions. Clarithromycin resistance was observed in ≥ 15% of cases in 11 out of 15 countries studied. Metronidazole resistance reached ≥ 15% in 12 of these 15 countries, with the highest recorded in Israel.[29] According to these research findings, BQT has been recommended as the first-line treatment in areas with high clarithromycin resistance. BQT efficacy was demonstrated by a study performed by Kim et al. (2019), where a 88.2% *H. pylori* eradication rate was achieved following 2 weeks of BQT.[18]

The introduction of vonoprazan-based therapies has further advanced treatment outcomes. Studies have shown that vonoprazan combined with amoxicillin achieved a 93.4% eradication rate after a 10-day continuous therapy.[25] This enhanced eradication rate reflects vonoprazan's effective acid suppression, which optimizes the efficacy of antibiotics, particularly in cases where PPIs may be less effective.

While these newer treatments are highly effective, they are not free of side effects. Common adverse effects including bitter taste, nausea, diarrhea, and vomiting, can negatively impact patient compliance and ultimately, the success rates of eradication.[32] Even vonoprazan, despite its efficacy, shares a similar side effect profile, including nausea, abdominal distension, diarrhea, and constipation.[16] These side effects highlight the need for tailored patient treatment plans to ensure adherence to therapy, which is crucial for successful eradication and the prevention of disease relapse.

Recommendations

(1) Increased accessibility of newer treatment regimens: Health authorities and pharmaceutical companies should prioritize making newer and more effective therapies, such as Bismuth Quadruple Therapy (BQT) and vonoprazan-based regimens, available in low- and middle-income countries (LMICs). This would address the gap in treatment efficacy caused by the unavailability of these drugs, especially in regions where clarithromycin resistance is high.
(2) Subsidization and health insurance integration: National health insurance schemes should consider including these newer treatment options in their coverage, with emphasis on bulk procurement to lower costs for both the health system and patients. In countries without universal health coverage, increasing the capitation for *H. pylori* treatment in private insurance schemes could improve access to advanced therapies for patients.
(3) Focus on Local Antibiotic Resistance Surveillance: Governments and healthcare organizations should invest in local molecular diagnostic capabilities to accurately identify *H. pylori* antibiotic resistance patterns. This would allow for personalized treatment regimens based on regional resistance profiles, increasing the likelihood of successful eradication.
(4) Public health campaigns: Awareness programs should be designed to educate populations about *H. pylori* infection risks, the importance of completing prescribed treatments, and the dangers of antibiotic resistance. Early detection and proper adherence to prescribed regimens can significantly reduce the disease burden and prevent more severe complications such as gastric cancer.
(5) Research: There is a need for more clinical research in LMICs to assess the efficacy of newly recommended regimens like vonoprazan-based therapies in various populations. Additionally,

further studies should be conducted on the cost-effectiveness and long-term outcomes of newer regimens in diverse socioeconomic settings.

(6) Adverse effect mitigation: To ensure patient adherence, healthcare providers should emphasize tailored treatment plans that address potential side effects of the recommended therapies. Adjunctive therapies, patient education on managing side effects, and regular follow-ups should be prioritized to optimize treatment compliance and outcomes.

(7) Optimizing existing treatments: for regions where newer therapies are inaccessible. This includes using available antibiotics more effectively, or investigating cost-effective herbal or traditional alternatives to manage *H. pylori* infections, although this area is gray and obscure.

(8) Policy formulation: for LMICs so as to strictly regulate the ease of access to over-the-counter antibiotics by enforcing that only doctor-approved prescriptions should be given attention and courtesy.

(9) Ethical considerations in drug trials for LMIC populations: center around equitable participation and post-trial access, informed consent, and benefit sharing. Researchers have a moral obligation to include these communities in studies relevant to their health issues, as seen with *H. pylori* trials where local representation is crucial. Informed consent processes must be culturally sensitive where community engagement can improve understanding. Trials should also ensure tangible benefits for local populations, such as continued access to effective treatments, illustrated by initiatives that invest profits into local healthcare. Transparency in reporting all trial outcomes is vital for maintaining scientific integrity.

Conclusion

The new guidelines from the American College of Gastroenterology represent a pivotal advancement in combating antibiotic resistance for *H. pylori*-induced peptic ulcer disease. While not without controversy – and likely to face skepticism from dissenting factions – these protocols are a critical leap forward in an era of escalating antimicrobial futility. However, socioeconomic inequities and clinicopathological complexities (as illustrated above in Figure 2), particularly in low- and middle-income countries, threaten to render these innovations inaccessible to those who need them most. Bold action is non-negotiable: global health equity

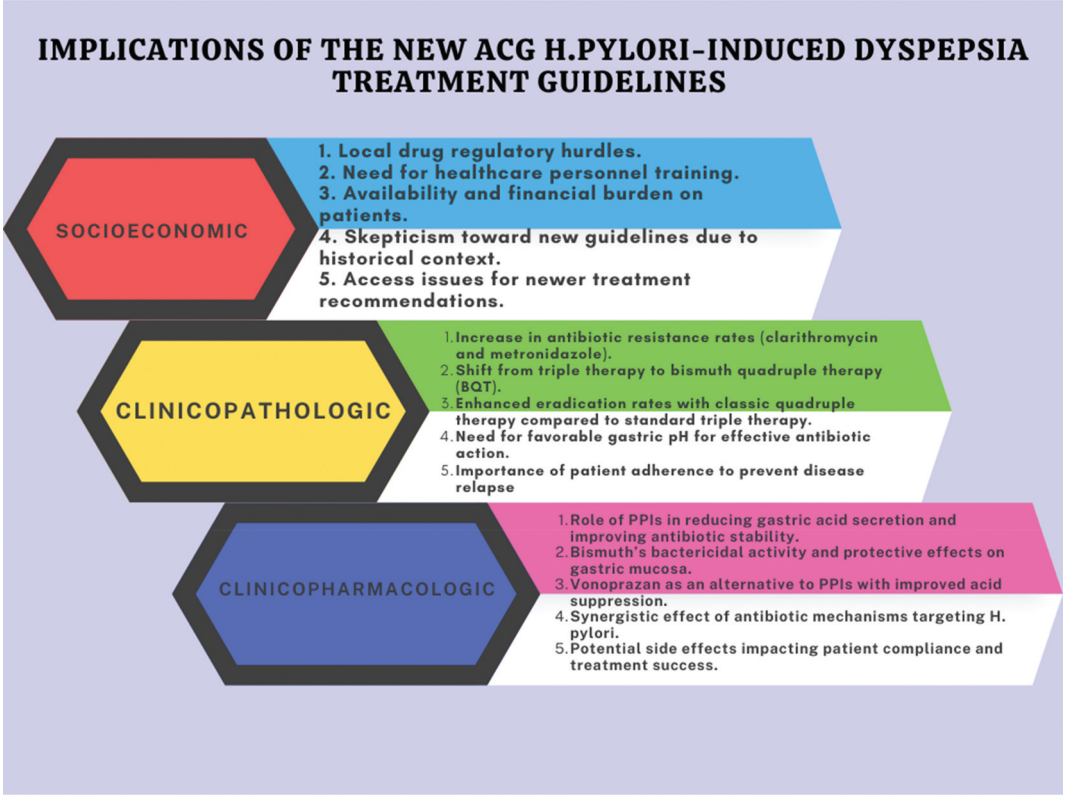

Figure 2. A summarized content illustration of the implications discussed earlier and associated with the new ACG guidelines.[2,3,8–11,13,14,16,18,19,22–26,28,29,31,32]

demands urgent prioritization of drug affordability, localized resistance monitoring, and culturally adaptive care models. Only through a unified strategy – spanning healthcare systems, policymakers, and research – can we transform these guidelines from aspirational frameworks into lifelines for vulnerable populations. The fight against *H. pylori* is not just clinical – it is a moral imperative to bridge the chasm between scientific progress and human suffering.

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Writing, Editing, Data Curation: All authors
Final review, Validation and Supervision: P.A, A.M.A

Data availability statement

The data supporting the features of this study are available within the article and were used under due and free permission and ethical scholastic guidelines.

Abbreviations

H. pylori	*Helicobacter pylori*
PUD	Peptic Ulcer Disease
ACG	American College of Gastroenterology
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
PPI	Proton Pump Inhibitor
BQT	Bismuth Quadruple Therapy
PCAB	Potassium Competitive Acid Blocker
MALT	Mucosa-Associated Lymphoid Tissue
LMICs	Low- and Middle-Income Countries

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