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Impact of Antibiotic Shortage on *H. Pylori* Treatment: A Step-Wise Approach for Pharmacist Management

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Abstract

The current drug shortage crisis involving multiple oral antibiotics has significantly impacted preferred therapeutic options for treatment of H.pylori infection. Pharmacists may help alleviate the impact of this shortage through a proposed step-wise approach which includes proper inventory management, verification of indication, evaluation of regimen, therapeutic monitoring, and communication with patients and providers regarding alternative therapy or symptomatic relief.

Introduction

Helicobacter pylori (*H. pylori*) is a highly motile, curved, Gram-negative rod found in the human stomach that is associated with numerous gastrointestinal health conditions including peptic ulcer disease (PUD), chronic gastritis, and gastric cancer.[1, 2] This pathogen, the only known bacterium to colonize the acidic human stomach, survives the harsh environment by producing urease. Production of this enzyme catalyzes the hydrolysis of urea to ammonia, thus elevating the pH of the stomach to neutral as needed for survival. In addition, *H. pylori* achieves further protection from the stomach environment by swimming to penetrate the mucus layer, attaching to epithelial cells, and ultimately causing inflammation.[3] This successful human pathogen is estimated to infect 50% of the global population.[4] The signs and symptoms associated with PUD are gnawing pain, burning discomfort, and tenderness in the epigastric area. *H. pylori* infection usually is transmitted via the gastro-oral or fecal-oral route. Many patients become colonized during early childhood and remain asymptomatic throughout their lives. Infection with *H. Pylori* has been associated with low socioeconomic status, increased age, crowding, and poor sanitation.[5] Increased levels of education may be a protective factor.[6]

Treatment Options for *H. Pylori*

A compilation of regimens published in February of 2012 combined evidence from multiple sources including the American College of Gastroenterology (ACG) Guideline (2007), the Canadian Helicobacter Study Group Consensus (2004), and the Dyspepsia Working Group (2005) and found a total of 30 known *H. Pylori* treatment regimens for adults.[7]

The percentage of regimens in this compilation that contain one or more currently shorted drugs is high. Seven of these 30 treatment regimens contain tetracycline (23%), two regimens utilize doxycycline, and 15 regimens contain clarithromycin (50%), despite recent data indicating clarithromycin resistance rates as high as 30%-40%. Three regimens include levofloxacin as the primary antibiotic, and one regimen contains rifabutin. Most of these regimens are combinations of a proton pump inhibitor (PPI) and 2 or 3 antibiotics to overcome antibiotic resistance. There are also two treatment regimens containing only one antibiotic (amoxicillin) but the efficacy of these combinations is low (70-77%) or unknown.[7] Figure 1 illustrates the primary antimicrobial component of each of these 30 anti-*H.pylori* regimens.

General therapy in the United States includes a PPI, clarithromycin, and amoxicillin or metronidazole (i.e. clarithromycin-based “triple therapy”) or a PPI or histamine type-2 receptor antagonist (H₂RA), bismuth, metronidazole, and tetracycline (bismuth “quadruple therapy”).[1] Due to increasing resistance rates to clarithromycin, use of triple therapy regimens as first-line therapy is discouraged unless the regimen has been proven to be highly effective locally.[8, 9]

Patients who undergo subsequent (salvage) treatment after demonstrating drug resistance to the initial prescribed *H.pylori* eradication regimen are less likely to achieve a successful outcome if they have been previously exposed to antibiotics in a treatment regimen, thus the greatest potential for eradicating *H. pylori* is through appropriate medication selection when choosing the first course of therapy.[1] Thus, the national drug shortage problem is further complicated by

drug resistance and underscores the importance of pharmacist involvement in antibiotic selection.

Antibiotic Shortage: Implications for Patient Care

The supply of tetracycline capsules has been affected by a drug shortage since July 2011. Both Teva Pharmaceuticals and Watson Pharmaceuticals have stated that all tetracycline capsules are temporarily unavailable due to shortage of the active ingredient and neither company can state a release date.[10, 11] Clarithromycin immediate-release tablets are in short supply due to either “an import ban on their products” (Ranbaxy Pharmaceuticals) or manufacturers (Abbot, Mylan, and Sandoz) stating they “could not provide a reason for the shortage”.[10] In addition, doxycycline hyclate capsules and tablets are backordered due to shortage of raw material (Mutual Pharmaceuticals), supply and demand (Watson and Heritage), or reason not provided (Lannett, Mylan, Par, VersaPharm, and West-Ward.)[12] These three shorted antibiotics are included in 25 of 30 (83%) of the 30 regimens described in Figure 1.

Ramifications of untreated infections include persistence or exacerbation of the disease and the possibility of transmission to uninfected individuals. In cases of drug shortage or financial difficulty it is recommended to hold the antibiotic until the appropriate drugs become available, although a PPI can be administered for symptomatic treatment of ulcers.[13]

Pharmacist Role: A Step-wise Approach

We propose the following step-wise approach to management of antibiotic shortage in the treatment of *H.pylori* infection.

1. Shortage validation and proper inventory management

Pharmacists are often the first to recognize a looming drug shortage when unable to order an adequate supply, and are thus in the ideal position to implement a shortage management plan. The American Society of Health-System Pharmacists (ASHP) has published guidelines for managing drug shortages in hospitals and health systems recommending pharmacists take the lead in determining strategies and processes for dealing with the shortages.[14] Community-based pharmacists can use the information contained in these guidelines to customize strategies for the outpatient setting as well.

The first step in our approach is to confirm the cause and estimated duration of the drug shortage through contact with manufacturers or distributors. Information regarding manufacturing shortages is also available online through the Food and Drug Administration, Centers for Disease Control and Prevention, and the ASHP Drug Shortages page (www.ashp.org/shortages). After verifying the shortage, the pharmacist should next quantify all available inventory.

Pharmacists in chain environments may borrow this strategy from their health system colleagues and conduct a chain-wide inventory to determine supply across the entire system. In addition, independently owned pharmacies may opt to use their networks to complete the inventory process potentially enabling pharmacists to provide patients with more options to fill needed prescriptions.

Once the supply has been quantified and located, it is critical to determine the anticipated duration of the shortage using the same sources previously described. Using historical dispensing records and purchase history, pharmacists may predict the magnitude of the impact the shortage might have on the patient population served at the pharmacy. Once this information is known, pharmacists can begin developing strategies for managing the shortage for the expected duration. Options for pharmacists in health-system settings includes centralization of drugs in short supply within the pharmacy, sharing of repackaged sterile injectables for use within the same health-system, and educating prescribers on alternative agents for use.[15] Similarly, community pharmacists may consider restricting loaning or selling the product to other pharmacies, ordering through alternate distributors, stocking a variety of dosage forms or strengths, considering therapeutically equivalent products, and communicating information about the shortage to prescribers and patients.

2. Verification of indication

All pharmacists have the opportunity to verify the indication for any order or prescription for a medication in short supply in order to preserve the medication for those patients in greatest need. While this can be done more easily in the acute care setting through restrictions enforced by the medical staff of the hospital, the authors propose a similar method in the community setting where the pharmacist would take the lead in educating prescribers and patients about drug shortages and the importance of reserving inventory for those with compelling indications for use. Pharmacists who work in managed care organizations should facilitate alternative recommendations during times of prolonged drug shortage so as to minimize clinical and financial impact on patients.

Pharmacists practicing in the community setting may be presented with a prescription regimen that does not have an indication but includes one of the shorted antibiotics. Shorted antibiotics, such as clarithromycin, may be dispensed in combination with other antibiotics as part of an *H.pylori* eradication regimen but may also be found in combination regimens for other indications (i.e. mycobacterial infection).[16] In this scenario, it is the opinion of the authors that community pharmacists may help address the antibiotic shortage by calling prescribers to confirm indication and

suggest an alternative regimen that does not include a shorted antibiotic, even in cases where the aforementioned antibiotic may be temporarily in stock. Pharmacists may not find physicians to be cooperative, however, as evidenced by an anticipated committee resolution to be introduced at the American Medical Association (AMA) 2013 meeting stating routine pharmacist inquiries “for verification of the rationale behind prescriptions, including diagnosis, treatment plan, ICD-9 codes and/or previous medications/therapies that were tried/failed, and for routine pharmacist calls for such verification of this rationale, to be an inappropriate interference with the practice of medicine and unwarranted.”[17] In-house pharmacies, such as those found in community health centers, may have access to patient medical records and thus have the ability to confirm indication without a time-consuming, uncompensated call to the prescriber.

3. Evaluate appropriateness of regimen

Clinical, hospital, and community pharmacists have a shared responsibility to review *H. Pylori* orders for appropriateness of therapy. Pharmacists may improve the odds of treatment success by verifying that the prescribed treatment choice works locally (i.e. ≥ 90 or 95% success rate). It is possible that pharmacist recommendations for appropriate treatment may be in conflict with consensus statements when study results are not consistent with local treatment results, and pharmacists may find themselves recommending higher than usual doses of drugs (i.e. 500 mg of clarithromycin, metronidazole, and tetracycline) or longer durations (14 day) unless shorter durations have been shown locally to be equally effective. In addition, pharmacists should perform medication history reviews to confirm the patient has not recently taken the antibiotic included in the anti-*H. pylori* regimen in the past, and in the case of treatment failure, confirm drugs for which resistance is likely to have developed are not reused.[9]

4. Patient and Provider Communication

Pharmacists may employ a variety of methods to communicate with other health-care providers and patients regarding updates on the antibiotic shortage such as newsletters, fax announcements, and telephone calls. Research by Issets et al found that pharmacist collaboration with physicians can reduce drug cost and prevent errors.[18] Community pharmacists may also help reduce patient frustration with drug shortages by informing customers of drug shortages at the time of prescription drop-off and providing counseling on options for symptomatic relief of *H.pylori*-associated symptoms.

Prescribers may call upon the pharmacist to suggest regimens that do not contain the shorted antibiotics, or may simply drop the shorted antibiotic from their prescribed regimen (i.e. changing quadruple therapy to triple therapy without evidence

of efficacy). Only five of the 30 regimens compiled by the Pharmacist’s Letter utilize antibiotics other than the currently shorted tetracycline, clarithromycin, and doxycycline. These alternative regimens vary and may include amoxicillin alone or in combination with rifabutin or levofloxacin. However, these regimens should be considered potentially inadequate due to lack of efficacy data or data showing efficacy below the $>80\%$ (intention to treat) or $>90\%$ (per protocol) threshold.[7]

5. Monitoring Therapy

Last, pharmacists play an important role in monitoring treatment safety and efficacy. Pharmacists should counsel patients regarding adverse effects of antimicrobials associated with anti-*H. Pylori* regimens including carcinogenicity (metronidazole), disulfiram-like reactions (metronidazole), increased risk of tendinitis and tendon rupture (fluoroquinolones), and drug-drug interactions such as CYP3A induction (rifabutin).[9] Patient counseling regarding potential adverse effects of anti-*H. pylori* regimens is critical since poor adherence is an important predictor of treatment failure.[1] Ideally, all patients treated for *H.pylori* infection should receive testing to confirm eradication of infection, particularly those with *H.pylori*-associated ulcer or lymphoma, persistent dyspeptic symptoms, or who have undergone resection of early gastric cancer. Testing should be performed no sooner than 4 weeks after completion of treatment, and options may include endoscopy, fecal antigen test (FAT), or urea breath test (UBT).[1] Pharmacists may also be called upon to counsel patients on point-of-care-testing (POCT) kits that detect IgG antibodies to *H.pylori* in whole blood. These kits are designed for professional in vitro diagnostic use only, but are available without a prescription over the internet.[19]

Conclusion

The step-wise approach outlined by the authors is one method to manage drug shortages to minimize the impact on patient care and models some successful strategies that have been used by health-system pharmacists for many years. In addition to the steps listed above, pharmacists may become advocates for drug shortages by sharing their frustrations and outlining opportunities for improvement with local, regional, and national legislators. For example, pharmacists may opt to obtain access to key politicians in their geographic area, pursue writing campaigns, or invite the politicians to their practice setting to observe how pharmacies operate during drug shortages.[20] The drug shortage crisis has resulted in a lack of first-line treatment regimens for *H. pylori* infection, and pharmacists in all practice settings are uniquely positioned to take a lead in managing the antibiotic shortage.

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Fig. 1 - Distribution of the use of different antibiotic in *H. Pylori* treatment regimens