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Assessment and analysis of H.pylori infection treatment strategies of St. Vincent Hospital's family and internal medicine clinics

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Assessment and analysis of *H. pylori* infection treatment strategies of St. Vincent Hospital's family and internal medicine clinics

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Background

Helicobacter pylori Infections

H. pylori is a gram-negative, spiral-shaped bacteria[1]. This bacteria has different adaptations that allow it to remain in the gastrointestinal tract, such as flagella to assist with resisting contractions produced by the small intestine[1]. *H. pylori* also produces an enzyme called urease, which alkalinizes the harsh, acidic environment in the stomach, making it a more habitable place to live[1,2]. *H. pylori* infections can cause serious problems for patients, starting with chronic gastritis or ulcers in the stomach, small intestine, or esophagus[1-6]. A seemingly benign infection can eventually progress to gastric lymphoma or cancer, and *H. pylori* is technically considered a carcinogen[1-4,6-8]. Infection is correlated with low socioeconomic status[2-4,6,9], low education level[3,9], and African American race[3,4]. *H. pylori* infection has a genetic component[4] and is transmitted amongst families living in the same household[1,9]. Therefore, someone whose parent or sibling has had a gastric ulcer or stomach cancer caused by *H. pylori* is more likely to have *H. pylori* colonization[1].

Diagnostic Testing for *H. pylori*

There are three main objective methods used to diagnose a patient with an *H. pylori* infection. The first method, a urease breath test, is by far the most convenient method. This test measures urease activity produced by the bacteria. While noninvasive, inexpensive and convenient, follow-up results after treatment may have the potential to be falsely negative. If a patient has taken antibiotics and a proton-pump inhibitor <4 weeks before administration of the test, it may not be able to detect the small amount of resistant bacteria still present in the stomach[1].

Biopsy-based testing is usually done in the hospital setting. Biopsies involve an endoscopy procedure that obtains a sample from the stomach. This type of testing is considered the “gold standard” of diagnostic *H. pylori* testing[1]. Obtaining a sample of actual bacteria also allows the ability to

determine sensitivities to antibiotics. While biopsy-based testing is very specific, it only evaluates a small portion of the stomach and may not be completely sensitive to *H. pylori* presence. It is also invasive and expensive[1].

The other method of testing mentioned in the ACG guidelines is fecal antigen testing. Fecal antigen testing involves looking for the presence of antigens to *H. pylori* in the stool. This option is cost-effective for many patients but is not used as widely as the urea breath test. Fecal antigen testing results can also be affected by antibiotic and proton-pump inhibitor (PPI) use so waiting at least four weeks after discontinuing antibiotics is crucial for an accurate result[10].

Treatment Options

There are multiple treatment options for treating *H. pylori* infections, and most treatment options include two or more antibiotic classes in conjunction with a PPI[2,4-5,8]. The main workhorses of treating an *H. pylori* infection are the macrolide and fluoroquinolone (FQ) classes of antibiotics. Macrolides include erythromycin, clarithromycin, and azithromycin. Commonly used fluoroquinolones include levofloxacin and ciprofloxacin. The most recent American College of Gastroenterology (ACG) *H. pylori* treatment guidelines provide specific recommendations for using these antibiotics based on kidney function, previous antibiotic exposure, and whether or not the infection is a reoccurrence[4]. The most common regimens seen at St. Vincent's primary care centers mimic the ACG guidelines and include the bismuth quadruple (bismuth subsalicylate, a PPI, tetracycline, and metronidazole) and clarithromycin triple (PPI, clarithromycin, and amoxicillin OR metronidazole) regimens. The ACG's recommended first-line treatment for an initial *H. pylori* infection is specified in Table 1.

Table 1. Guideline-directed initial *H. pylori* treatment therapy[4]			
Presence of true penicillin allergy	**Previous macrolide exposure**		
		Yes	No
	Yes	**Bismuth quadruple** **Levofloxacin triple** **Levofloxacin sequential**	**Bismuth quadruple** **Clarithromycin triple*** **Concomitant**
	No	**Bismuth quadruple**	**Clarithromycin triple**[†] **Bismuth quadruple**

Bismuth quadruple: PPI + Bismuth subcitrate/subsalicylate + Tetracycline + Metronidazole x 10-14 days

Clarithromycin triple: PPI + Clarithromycin + Amoxicillin OR Metronidazole x 14 days

*with Amoxicillin

†with Metronidazole

Levofloxacin triple: PPI + Levofloxacin + Amoxicillin x 10-14 days

Levofloxacin sequential: PPI + Amoxicillin x 5-7 days, then add Levofloxacin + Nitroimidazole x an add'l 5-7 days

Concomitant: PPI + Clarithromycin + Amoxicillin + Nitroimidazole x 3-10 days[4]

Need for Study

Antibiotic Resistance Overview

Unfortunately, macrolides and fluoroquinolones are among the worst culprits for inducing antibiotic resistance, which has impacted the ability to successfully treat *H. pylori*. In fact, in 2017 the World Health Organization (WHO) named *H. pylori* a high priority bacterium for antibiotic research and development due to high rates of resistance[2,11-12]. Antibiotic resistance can arise when mutations occur in the genetic material of bacteria that change the way the bacteria respond to the antibiotic. In macrolides' case, a mutation occurs at the ribosome (site that the drugs bind to) and decreases the macrolides' affinity for the ribosome[2,4-5,11,13-14]. For fluoroquinolones, the bacteria develop DNA changes

in the enzyme that these drugs bind to (DNA gyrase) and limits binding ability of fluoroquinolones[2,4,11,14]. Eventually *H. pylori*'s ability to synthesize and replicate its DNA are diminished[14]. This can lead to infections that aren't cured by first-choice regimens and the need to use less optimal, more expensive antibiotics with undesirable side effects arises. It has been shown that susceptibility of the bacteria to the antibiotic regimen is the greatest determinant of treatment success[4-6,8]. Metronidazole is also a medication commonly used for *H. pylori* that has significant worldwide resistance, but this project will not focus on these rates as this resistance can often be overcome by increasing the treatment dose or duration[4,8,14]. Amoxicillin and tetracycline (TCN) are also used commonly in *H. pylori* treatment regimens, but their resistance rates are consistently very low worldwide[2,4,6,8,11,14] and will not be focused on in this project.

***Helicobacter pylori* Resistance**

Resistance can occur by many mechanisms, such as the overuse and overprescribing of antibiotics. In general, it has been proven that countries who have high resistance rates have higher prescription antibiotic consumption[8,14]. When looking at the *H. pylori* organism specifically, it has previously been proven that *H. pylori* eradication rates are higher in patients who have previously received a macrolide[5]. As shown in Table 1, the most recent ACG guidelines recommend that if a patient has been exposed to a medication in the macrolide class of antibiotics that they should avoid using another macrolide, since there is a high probability that the H. pylori in their stomach will have developed resistance to it during the previous exposure[4-6,11]. There have been multiple studies that explore *H. pylori*'s increasing resistance rates around the world. The commonly accepted resistance rate threshold for a medication that indicates the highly resistant medication class should be avoided and another agent should be chosen is >15%[4,6,8]. Past this threshold, *H. pylori* treatment success rates significantly decline.

Worldwide resistance rates sorted by region were collected in a 2018 meta-analysis and can be found in Table 2[6]. As shown in Table 2, many parts of the world have resistance rates greater than the accepted threshold for treating with clarithromycin or levofloxacin[6]. *H. pylori* contracted in a different part of the world may be more resistant to initial antibiotic treatment strategies used in the United States. Thus, it may be beneficial to take recent travel and home country into account when selecting an initial *H. pylori* treatment regimen. One region that was recognized for significant levels of *H. pylori* resistance is Latin America. While one meta-analysis shows the American region to have a resistance rate at or below the 15% threshold[6] and another shows overall resistance rate in Latin America to be only 12%[8], there is variety between actual countries. In 2007, the countries with the highest consumption of macrolides per capita were Venezuela, Argentina, and Chile[8]. The same three countries saw a significant increase in fluoroquinolone use over a ten-year period[8]. Peru had the highest prevalence of *H. pylori* resistance at 50%[8]. In contrast, Mexico, Uruguay, and Colombia saw decreases in their macrolide use[8] and the lowest clarithromycin resistance rate was well below the threshold at 2% in Paraguay[8]. Given this wide variety of resistance rates among Latin America, each country's resistance rates should be taken into consideration to determine whether clarithromycin or levofloxacin is appropriate for initial treatment. Along with differing resistance rates, there is a large part of the population that has increased activity of the enzyme that metabolizes the PPI component of treatment, CYP2C19[8]. This may decrease the effectiveness of the PPI, as it is being cleared too fast to have a therapeutic effect.

Table 2. Primary Resistance Rates of Clarithromycin and Levofloxacin by World Region[6]		
Region	**Clarithromycin Resistance Rate**	**Levofloxacin Resistance Rate**
Africa Region Cameroon, Congo, Senegal	15%	14%
Americas Region Argentina, Brazil, Canada, Colombia, Peru, USA	10%	15%
Eastern Mediterranean Region Egypt, Iran, Morocco, Pakistan, Saudi Arabia	33%	19%
European Region Austria, Belgium, Bulgaria, Croatia, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Poland, Spain, Netherlands, Turkey, UK, Multicentric/International	18%	11%
Southeast Asia Region Bangladesh, Bhutan, India, Indonesia, Thailand	10%	30%
Western Pacific Region Australia, China, Japan, South Korea, Laos, Malaysia, New Zealand, Singapore, Taiwan, Vietanam	34%	19%

While there is a good idea of resistance rates of other countries, there is not a good estimate of the resistance rates specific to the United States, let alone the Indianapolis patient population. The most recent study done by the Houston VA Medical Center reported resistance rates for clarithromycin to be 16% and levofloxacin to be 31%[16].

Objectives

Since resistance to H. pylori is such a significant problem worldwide and resistance rates are not well published in America, more definitive data is needed to determine whether St. Vincent's prescribed regimens are truly resulting in successful eradication of *H. pylori* infections, and whether protocol to incorporate the risk of resistance as a treatment regimen determinant need to be formulated. The main objective of this project is to identify what percentage of *H. pylori* infections diagnosed at St. Vincent's Family Medicine and Internal Medicine clinics are being successfully treated with current, guideline-directed therapy. The secondary objective of this project is to obtain a general understanding of *H. pylori* resistance rates to clarithromycin and levofloxacin in the Indianapolis area based on treatment failure rates. Any conclusions able to be drawn about local resistance and how Indianapolis compares to the rest of the world may help guide future treatment decisions among prescribers.

Methods

This project was a retrospective chart review that looks at past patient data from St. Vincent's Internal Medicine and Family Medicine clinics. St. Vincent's electronic medical record, Athena, was used for chart review. St. Vincent's pharmacy services database, Enterprise, was used to obtain prescription filling information. All data was extracted to and managed using the Ascension installation of REDCap (Research Electronic Data Capture). REDCap provides a secure way to track data while ensuring proper

handling of personal identifying information (PHI)[17,19]. This project did not require an Institutional Review Board approval; instead, the project was approved by St. Vincent's Quality Improvement Committee.

Inclusion Criteria

Patients in the review were $\geq$ 18 years old at the time of diagnosis, patients at either St. Vincent's Internal Medicine or Family Medicine clinics and were diagnosed with *H. pylori* in between the date range of February 1st, 2017 to August 31st, 2018. The beginning of this date range falls approximately one month after the most recent ACG guidelines were published. A patient list was generated using a query from Athena using the ICD codes B96.81 (*H. pylori* as the cause of diseases classified elsewhere), K29.70 (gastritis, unspecified, without bleeding) or A04.8 (bacterial infections intestinal).

Data Collection

Each patient's labs, clinical documents, medications, fill history and relevant outside records were reviewed and pertinent patient information was documented in REDCap. This information was used to fill in a pre-written questionnaire; items on the questionnaire can be found in Table 3. These questions were written in yes-no format whenever possible; other choices were multiple choice and written response. For multiple choice answers, an "Other" category was given for treatment decisions that did not match pre-populated answers.

Table 3. Relevant Patient Data Components
H. pylori diagnosis (Y/N)
Presence of allergy to any component of the treatment regimen
Prescription for a macrolide or a fluoroquinolone in the last year
Presence of drug interactions with patient's existing medication list at start of regimen
Type of *H. pylori* treatment regimen (clarithromycin triple, bismuth quadruple, etc.)
Zip code patient lives in Indianapolis or within 25 miles of Indianapolis
Recent travel outside the United States within 1 year and country of destination
Diagnostic test used to diagnose *H. pylori* infection (Urea breath test, fecal antigen test, or biopsy-based test)
Diagnosis date of *H. pylori*
Methods of follow-up and timing in relation to completion of treatment regimen
Presence of clinic visits starting 4 weeks after treatment completion with *H. pylori* symptoms or another positive diagnosis of *H. pylori*
Whether or not the prescriptions were filled
Whether or not the prescriptions were picked up by the patient
Patient picked up medications prescribed for *H. pylori* (all, some, or none)
What type of second line treatment regimen was prescribed, if applicable, and whether or not it was appropriate.

Whether or not the patient was diagnosed with *H. pylori* and diagnosis date of *H. pylori* were collected to exclude those who did not fit the criteria of the project. Presence of allergies to any component of the treatment regimen were collected to identify improper treatment initiation. It was also used to identify potential reasoning for failed treatment, since an allergic reaction could have potentially resulted in stopping the treatment regimen prematurely and/or result in a delay of infection resolution. Prior fluoroquinolone use is not mentioned in the ACG guidelines but was collected regardless to explore the possibility that prior use may impact successful therapy, since fluoroquinolones are another class of antibiotics that are notorious for high resistance rates. Zip code was collected to ensure the patient lives in Indianapolis or within a 25-mile radius. This ensures that the data collected will accurately reflect the typical Indianapolis patient population. Recent travel outside the United States within 1 year and to where was collected to determine whether the patient may be harboring *H. pylori* from other countries where resistance rates to clarithromycin or levofloxacin may be higher or lower than the appropriate threshold of $\geq$15%. Fill rates were determined by using Enterprise for patients who filled at St. Vincent's Pharmacy and by looking at insurance claims for patients filling at an outside pharmacy. This was collected to assess whether the patient was truly taking the regimen that was prescribed. Choice of treatment regimen, prior macrolide use within one year, diagnostic testing methods, methods and timing of follow-up, and second-line treatment for failed treatment were collected to ensure recommendations made by the ACG guidelines were followed appropriately. Each patient's home medication regimen charted on that day and the *H. pylori* treatment regimen prescribed was assessed using Lexicomp's drug interaction report to assess any potential that therapy could be rendered less effective.

Each individual patient was assessed by the researcher using the objective data above and the ACG guidelines as guidance and was sorted into "Failed," "Successful," or "Unknown Outcome" groups. Each patient was also determined to have received "Appropriate" or "Inappropriate" therapy. The

"Inappropriate" group was further explored to try and determine potential protocol changes that may assist healthcare team members in improving *H. pylori* treatment. The "Failed" treatment group was assessed in tandem with their appropriateness of therapy to try and determine whether causes of failure stemmed from potential resistance to treatment or inappropriate therapy.

Results

Patient Characteristics

There were 105 patient records that were populated through the EMR inquiry. Forty-one patients either received tests for *H. pylori* that resulted in a negative result or were diagnosed with a different gastric condition, such as gastritis. These patients were excluded from analysis. The remaining sixty-four patient records were analyzed.

The mean age of the total population was 44.31 years old, with a standard deviation of 14.75 years. The youngest patient in the group was 18.99 years and the oldest patient was 81.27 years. All patients initially identified through Athena lived in an address with a zip code that was within a 25-mile radius of Indianapolis (105 out of 105).

Out of the 64 patients that were diagnosed with *H. pylori*, the urea breath test (UBT) was the most commonly used diagnostic test with 42 patients. There were 4 patients that were diagnosed using fecal antigen testing and 15 patients that were diagnosed using a biopsy-based test. Two patients were not tested and 1 patient's record did not specify what test was given.

There were 6 patients that had allergies to one or more medications in the treatment regimens. Five out of six patients had penicillin allergies documented; none received amoxicillin-containing regimens. One patient had a documented allergy to omeprazole; the first-line regimen contained pantoprazole instead and no adverse effects from the pantoprazole were documented.

An overwhelming 46 out of 64 patients required translator services, with the majority (32 out of 46) speaking Spanish. There were a total of 10 different languages spoken amongst those needing translators. A complete breakdown of native languages can be found, along with additional analysis of patient population parameters, in Figure 1.

Figure 1.

Patient age

Total Count (N)	Missing	Unique	Min	Max	Mean	StDev	Sum	Percentile						
								0.05	0.10	0.25	0.50 Median	0.75	0.90	0.95
105	0 (0.0%)	105	18.99	81.27	44.31	14.75	4,653.07	22.44	25.73	33.65	43.41	54.14	65.59	71.40

Lowest values: 18.990123000472288, 19.414612666014133, 19.885532671216154, 21.829332566719373, 22.094909546397258

Highest values: 72.64214870941909, 74.97484547937329, 75.00507653590878, 76.32737154082561,

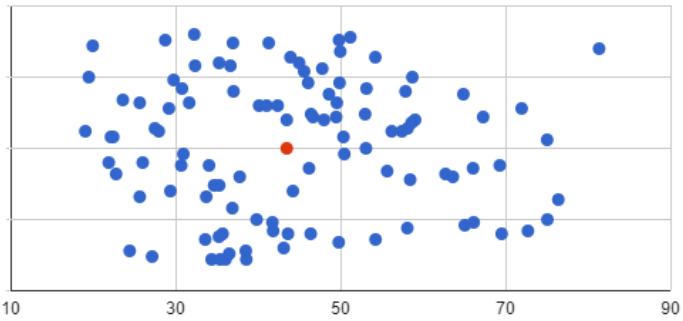

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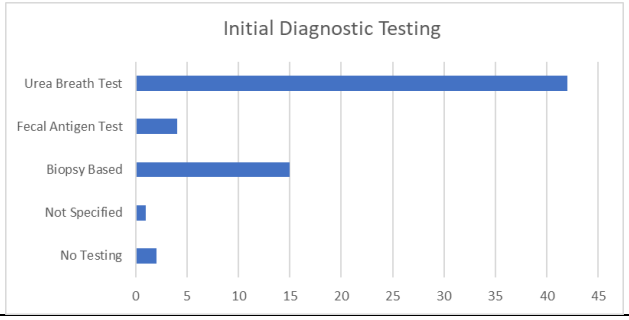
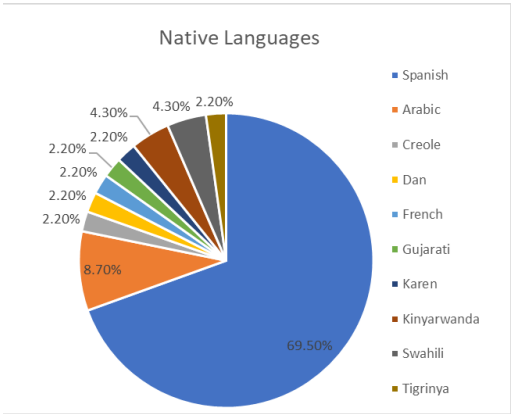
Figure 1., continued.

Initial Diagnostic Testing



Native Languages



Treatment

For brevity, regimens will be abbreviated; please see Table 5 for an abbreviation guide. Of the first-line treatments prescribed for the 64 patients diagnosed with *H. pylori*, the CTA regimen was the highest prescribed regimen with 27 patients. This regimen is made up of clarithromycin 500 mg, amoxicillin 1 gram, and a PPI of normal or double strength dosage[4]. All medications are taken twice daily for 14 days.

The second highest treatment for initial therapy was the "Other" category consisting of 19 patients. This category was made up of all regimens that did not follow the recommendations made in the guidelines. The most common regimen in the "Other" category was an MBQ regimen, with 11 patients. The standard BQ regimen is normally made up of a PPI taken twice a day plus bismuth subcitrate or subsalicylate, metronidazole 250-500 mg, and tetracycline 500 mg taken four times a day for 10-14 days. In the MBQ regimen the tetracycline is replaced by doxycycline, a derivative of tetracycline that has a similar mechanism of action. There were two patients that received PPIs alone; the reason documented in the chart for both patients was pregnancy. A complete breakdown of initial treatment options can be found in Figure 2.

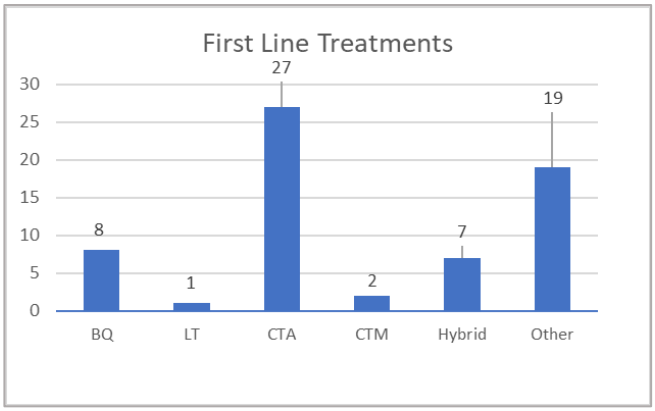
Three patients had received a macrolide within 1 year of *H. pylori* treatment initiation. One patient was still prescribed the CTA regimen, one patient received the BQ regimen (non-macrolide containing), and one patient received hybrid therapy with clindamycin replacing the clarithromycin component. Three patients had received a fluoroquinolone prescription within 1 year of *H. pylori* treatment initiation, and all three were appropriately treated with non-fluoroquinolone containing regimens.

There were 44 identified drug interactions; some patients had one interaction and a select few had two interactions. There were 2 interactions where no action was needed (category B), 8 interactions

where increased monitoring was necessary (category C), and 22 interactions where modification should have been considered (category D). The most frequent category D interaction was an interaction between the tetracycline/doxycycline and bismuth subsalicylate of the BQ and MBQ regimens. Nineteen patients received the BQ or MBQ regimens; the interaction populated for each of these patients. There were only two interactions in which there was a chance of decreased concentration of an antibiotic. Clarithromycin-diazepam was one of these interactions; in this case the patient was only taking as needed for seizures. The other interaction was doxycycline and sucralfate, which could have been clinically significant. The rest of the interactions were related to increased toxicity of home medications.

Figure 2.

First Line Treatments



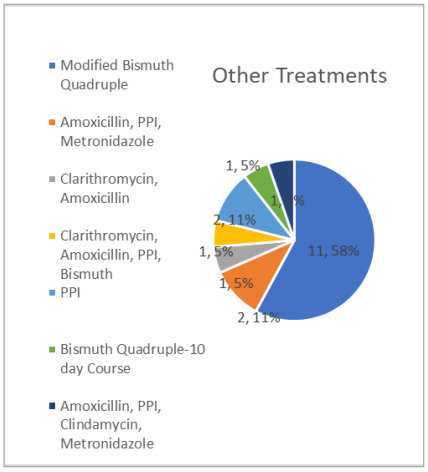


Table 5.

Abbreviation Guide

BQ	Bismuth quadruple
MBQ	Modified Bismuth quadruple
CTA	Clarithromycin triple w/amoxicillin
CTM	Clarithromycin triple w/metronidazole
LS	Levofloxacin sequential
LT	Levofloxacin triple

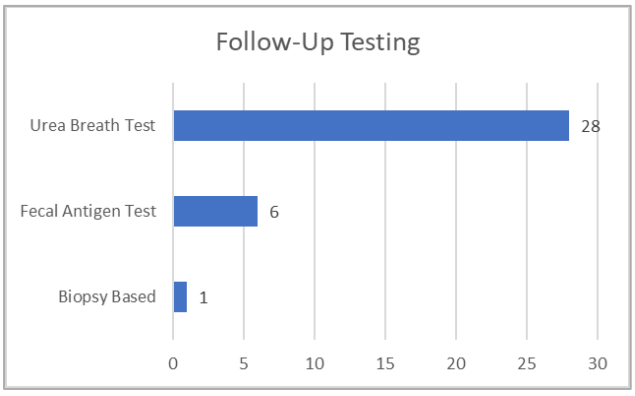
Follow-Up and Second-Line Therapy

Thirty-five patients out of 64 received follow-up testing after completion of therapy. The urea breath test remained the most popular testing method in follow-up therapy with 28 patients, followed by 6 patients with fecal antigen testing and 1 patient with a biopsy-based test.

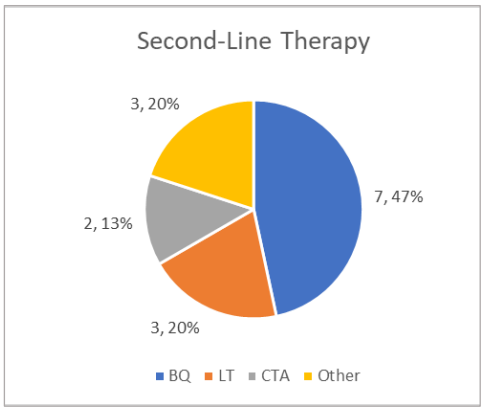
Out of the 35 patients who were retested, 11 patients had positive *H. pylori* test results. Curiously, 15 patients were given second-line treatment, which indicates four patients were given second-line therapy without being re-tested. Bismuth quadruple was the most common choice for second-line therapy with 7 patients. Of the 15 patients prescribed second-line therapy, 11 patients' regimens were deemed appropriate. Complete analysis of second-line therapy can be found in Figure 3.

Figure 3.

Follow-Up Testing



Second-Line Therapies



Appropriateness and Success of Therapy

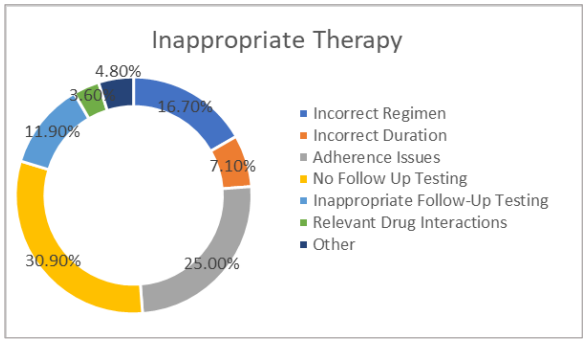
Overall treatment regimen, treatment duration, follow-up testing procedures, and relevant drug interactions were observed on Athena to determine the appropriateness of therapy. Patients who filled at St. Vincent's pharmacy were determined adherent or nonadherent by looking at fill history through Enterprise. For patients who filled at an outside pharmacy, presence of insurance claims were relied on to determine adherence to the regimen. Absence of an insurance claim from an outside pharmacy was deemed not picked up and was considered inappropriate therapy. Any progress notes by providers were

also read to look for notes about adherence. Only 15 patients received appropriate therapy out of the 64 patients who received *H. pylori* treatment. The biggest determinant of inappropriate therapy for the remaining patients was the absence of follow-up testing (30.9% of errors), followed up by adherence issues (25% of errors) and an incorrect regimen being prescribed (16.7% of errors). A complete analysis can be found in Figure 4.

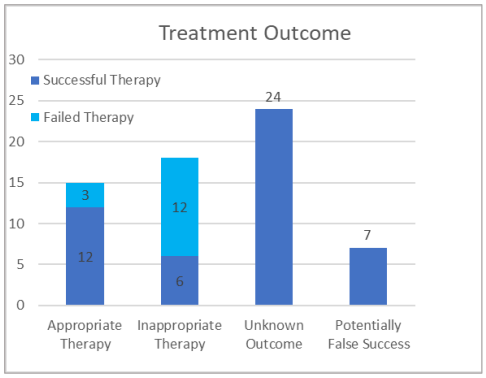
Without taking appropriateness of therapy into account, there were 18 successful treatments defined by an appropriate negative follow-up *H. pylori* test and 15 failed treatments defined by a positive follow-up *H. pylori* test. There were 24 patients whose outcomes could not be determined due to lack of follow-up, and there were 7 patients who had negative *H. pylori* tests taken <4 weeks of antibiotic therapy, leaving the possibility of a falsely negative test. This information can also be found in Figure 4.

Figure 4

Inappropriate Therapy



Overall Treatment Outcomes



Discussion

H. pylori infection continues to be a significant issue among patients in the United States. It can be a difficult infection to treat, as it has been shown that different countries have varying levels of resistance[6,8,15]. A meta-analysis that looked at treatment eradication rates of the bismuth quadruple and clarithromycin triple therapy and found that while the overall eradication rates were 77.6% and 68.9% respectively, a high heterogeneity between the trials was found[20]. In this project, the overall *H. pylori* eradication rate of patients with a known outcome was slightly lower at 54.5%. Of the 8 patients who received the BM regimen first-line, 4 had negative *H. pylori* tests, making the eradication rate lower at around 50%. The CTA regimen had an even lower eradication rate of around 37%. When adjusted to only include patients with known outcomes, the eradication rates become 80% and 55.6%, respectively. While our data was limited by sample size and the amount of patients lost to follow-up and with unknown outcomes, this project still provides comparable eradication rates to current data.

The variety of different treatment options can make it challenging for providers to choose an appropriate regimen. The ACG guidelines have a total of eight first-line regimens to choose from, with additional regimens developed for salvage therapy. In this project, it was discovered that an incorrect regimen was the third highest reason for inappropriate treatment. Some of the incorrect regimens contained pieces of the therapy recommended by the ACG but were missing key components. One of the biggest misunderstood regimens in this project was the bismuth quadruple regimen, as many prescribers substituted doxycycline in place of tetracycline.

While replacing tetracycline with doxycycline may seem reasonable given their identical mechanisms of action and similarities in structure[21,22], there are some significant differences in doxycycline that may lower effectiveness of the regimen. Tetracycline and doxycycline have differences in protein binding; tetracycline has protein binding of about 55%-65%[21] while doxycycline is highly protein bound at >90%[22]. This may result in lower concentrations of the drug being systemically

absorbed because it is binding to protein in the plasma at a higher degree. Protein-bound drug does not have systemic action since it remains in the plasma. While not extensively demonstrated in this project, highly protein bound drugs can interact with other highly protein bound drugs and increase the risk of toxicity. The bioavailability of doxycycline also becomes reduced at higher stomach pH[22]. Tetracycline does not have this reported effect[21]. This may be important because these patients will be taking concomitant PPIs, which reduce acid production in the stomach and therefore make the stomach environment more alkalotic. Concomitant use of these two medications together may result in less doxycycline being absorbed and available for treatment of the infection.

The data on substituting doxycycline for tetracycline is conflicting; a 1992 study found that only 65% of patients taking a modified bismuth triple therapy (regimen did not include the PPI component) achieved eradication of *H. pylori* compared to 92% of patients taking a traditional regimen containing tetracycline ($p = 0.004$)[23,24]. There are more recent studies that replace the metronidazole component with amoxicillin in addition to replacing tetracycline with doxycycline taken twice a day that have had some successful results[24-26]. However, there is no way to extrapolate this data to use doxycycline with a traditional bismuth quadruple regimen containing metronidazole. No head-to-head studies comparing bismuth quadruple therapy to a modified bismuth quadruple therapy with doxycycline exist at this time. Given the lack of data and the discouraging results using doxycycline with metronidazole in a bismuth triple regimen, it may be best practice to avoid replacing tetracycline with doxycycline until additional data is published.

The heterogeneity of eradication rates[20] and the variety in resistance rates around the world[6,8] make it difficult to choose an appropriate regimen. Finding recent places of travel in Athena proved to be a challenge and place of origin is not consistently documented in Athena, so this project's representation of possible *H. pylori* infections from other countries is limited and wholly unreliable.

However, while countries of origin and travel were difficult to find, need for a translator was found to be consistently documented among all patients. As shown in Figure 1., this project's small patient population was extremely diverse, encompassing ten different languages from all over the world. At St. Vincent, in-house translators are available for Spanish-speaking patients but for other languages, a telephone or video interpreter is used. Historically, patients who receive interpreter services in a practice setting overall receive significantly more recommended preventative services, made more office visits, and had more prescriptions written and filled[27]. However, while telephone translation is more cost-effective and convenient, problems such as inadequate clarity of sound, inability of the interpreter to respond to visual cues from the provider and patient, and cultural barriers in which some patients are uncomfortable speaking with an unknown voice[28] can impact the effectiveness of using the service.

Language is not the only difference among patients from other countries. There are many different cultural factors that may hinder a patient's adherence. Among minority populations, an inherent distrust of the health system may exist due to perceived inequal treatment of minority populations[29].

Low socioeconomic class is also another barrier to adherence. Many of the patients in our project were self-pay and did not have insurance coverage. Pricing of individual medications can vary significantly based on pharmacy, but for someone without insurance tetracycline itself is over $300 for a 14-day supply[30], and a full bismuth quadruple regimen may cost even more. Other patients were Medicaid or Medicare patients, which may result in forcing treatment options that are covered instead of the ones truly indicated on an individual patient basis.

Patient understanding is key in multi-drug regimens such as those used in *H. pylori* treatment, and the language barrier and culture can make this treatment even more difficult. In Arab patients, there is a belief that obtaining healthcare is important, but ultimately true recovery comes from God[31].

They may not view the *H. pylori* regimen as important for eradication as providers or those of other cultures, so it is important to respectfully acknowledge this belief and stress the importance of taking the complete regimen. In addition, some cultures, particularly Hispanic patients, may view illness as evil done by another person or outside source[29]. This may limit the perceived importance of preventative medicine such as follow-up treatment and annual exams. Certain cultures may rely on other herbal or alternative medicine therapies[29,31], which may interact with components of the antibiotic regimen. For instance, both garlic and honey can be used for symptoms of gastritis, but both can interact with Cytochrome P 450 (CYP) 3A4 enzyme substrates[32,33], such as clarithromycin. This can increase risk of toxicity or lower effectiveness if taken together.

Of all identified adherence issues, 80% occurred with patients who needed a translator. Of patients who needed a translator, 76.1% had inappropriate therapy of some kind. Of patients lost to follow-up, a vast majority (~88%) required a translator. Translation services are a great start in trying to expand healthcare services to non-English speaking patients, but our project showed that it isn't doing quite enough. Options to increase cultural awareness may include involving social work professionals, respectfully inquiring the patient about their individual beliefs about health care and treatment, and avoiding stereotypes based on age or race[29]. Staff education about various cultures and their beliefs would also be beneficial in better understanding patients' views of the healthcare system. Overall, a more inclusive approach to other cultures healthcare preferences would benefit both the provider and the patient.

Weaknesses

This project was a retrospective chart review of a small sample size, so it is limited in its capacity to expand to other institutions. Because *H. pylori* has such diverse infection and resistance rates around the world, however, it is difficult to establish consistency among multiple locations. The time frame

started only one month after the ACG guidelines were released, so there is the possibility that old guidance was still being used for treatment decisions.

A significant weakness during this study was looking only at whether patients had visited a different country within one year of diagnosis. *H. pylori* can often be asymptomatic for years before causing issues for patients[4], and a one-year time frame may have been inappropriate in determining where their *H. pylori* infections originated. As mentioned previously, Athena did not have consistent reporting of travel habits and patients were not often questioned about them during these visits. In addition, there were situations in which a patient may not have been traveling but had family members who had multiple risk factors for *H. pylori* infection. According to the ACG guidelines, if one family member has *H. pylori,* other family members are at higher risk for contracting *H. pylori* as well[1,3-4,9]. Looking at birth country, race, and socioeconomic status may have been more insightful to determine possible contraction location and to explore additional risk factors.

Conclusion

While this project was not truly able to assess whether ACG-guideline directed therapy is resulting in successful eradication to a large degree, it was able to identify inconsistencies between St. Vincent's treatment habits and the ACG guidelines. Poor follow-up testing is a significant barrier to completely eradicating *H. pylori* and preventing the long-term risks that come with infection.

This project was also able to identify that an underserved population makes up the majority of *H. pylori* infection cases. These patients are already at risk of successful treatment and *H. pylori* regimens of multiple drugs several times a day may compound that risk. This project was able to break down the main reasons that patients are treated inappropriately and identify potential areas of protocol change that can help increase patient's chances of completely eradicating *H. pylori* infections.

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