Navigating Gastrointestinal Challenges: Insight Into GERD and H. Pylori Management

Editor's Note: The is a transcript of a presentation on May 14, 2025. It has been edited and condensed for clarity. To obtain credit for participation **CLICK HERE.**

Module 1: Overview of GERD and *H. pylori* infections

Philip O. Katz, MD: This slide illustrates the burden of GERD. It's highly prevalent, approximately 2.5% to 30% of the world's population might have GERD. The range of disease goes from a nonerosive, that is an endoscopy that has got normal mucosa, to advanced stages of erosive esophagitis. GERD has significant associations with morbidity and has a clear reduction in health-related quality of life. The disease can be chronic. In fact, it most often is, and, in certain conditions, it might be progressive if left untreated.

GERD has varied presentations as illustrated here, both pictorially and in words. There is a categorical disease hypothesis on the left of the picture and a continuous spectrum of disease hypothesis on the right. And then the words speak to varied symptom presentations, classic symptoms being heartburn and regurgitation. Nonerosive reflux disease or NERD, and erosive reflux disease, with a worldwide prevalence favoring the nonerosive type. And then there are patients who develop complications in lower frequency, but nevertheless quite serious, and that is Barrett's esophagus and esophageal adenocarcinoma.

If we shift to the picture, the categorical disease hypothesis is that the patient presents as a nonerosive reflux disease patient and essentially stays there. Or presents as an erosive esophagitis patient and stays there, with the possibility of developing complications, such as peptic strictures or esophageal ulcers. And then, frankly, about 10% develop Barrett's esophagus and they will be at risk for esophageal adenocarcinoma. The continuous spectrum hypothesis implies that one starts as a nonerosive reflux disease patient who moves to an erosive reflux disease patient and progresses to Barrett's esophagus. Unfortunately, none of the hypotheses have been proven to be absolute, so one has to think potentially in terms of both.

Now, the pathophysiology of GERD is balanced between protective factors and those that create injury. Whenever there is a reflux episode, acid or gastric contents hit the esophageal mucosa and there is an esophageal acid clearance mechanism that is reflexive. When this is intact, the reflux episode is cleared better. Over time, that can deteriorate and enhance injury. Mucosa has a series of protective mechanisms which, over time, with continuous reflux, might be in some respect eroded, such that the refluxate can reach nerve endings and cause symptoms. Patients have variable esophageal sensitivity. In fact, women tend to have different sensitivity than men. The volume or frequency of gastric acid and reflux numbers all potentially can relate to injury.

Now, *H. pylori* is also a worldwide disease, perhaps more common than GERD, a difficult comparison, quite frankly. And it's affected by many factors, predominantly geography and socioeconomic, today. It tends to be acquired in childhood, but presents at different ages. They usually persist, unless diagnosed and treated, and not always are symptomatic. The disease is believed to be transmitted fecal-orally or oral-to-oral, such that in areas of crowding, big families, and in low socioeconomic areas, the disease spread seems to be greater. It is definitely associated with peptic ulcer disease and is clearly a risk for gastric cancer, demonstrated by the World Health Organization distinguishing that. Treatment may be hampered by rising rates of antibiotic resistance and requires personalized care, in many cases, in order to eradicate the infection.

The organism colonizes the gastric mucosa, and probably more patients are colonized than ever are symptomatic. And, in fact, many people will have the disease for life and will never know it. The predominant site of infection is in the antrum or the lower stomach, but may spread to the body and change the outcome of the disease. Antral predominant infection usually can lead to a gastric or duodenal ulcer and when the disease spreads and there is atrophy, acid secretion is affected and perhaps the risk for cancer increases.

Module 2: Diagnosis of nonerosive GERD, erosive GERD, and *H. pylori* infections

Philip O. Katz, MD: One of the ways to think about GERD is using a guideline-directed definition and evaluation. In this case, a condition in which the reflux of gastric contents into the esophagus results in symptoms and/or complications which is objectively defined by the presence of mucosal injury seen on endoscopy or the presence of abnormal esophageal acid exposure seen on reflux monitoring, either wireless or catheter based.

Now, this diagnostic algorithm is one way to work through the options for diagnosis and it speaks to the typical symptoms, in this case meaning heartburn and/or regurgitation, without alarm symptoms. So, no dysphagia, no bleeding, nothing suggestive of a complication. And the symptoms are sufficient in frequency and intensity to impair quality of life. That is, bringing the patient to a provider of care. In this situation, an uncomplicated presentation, today's guidelines recommend a once-daily proton pump inhibitor trial for approximately 8 weeks. The 8-week time span relates to both the time that symptoms maximally improve and perhaps to achieve healing without ever knowing that the patient has erosive disease. If the relief of symptoms is complete, then the patient likely has GERD. Now, this does not account for overlap, but the complete relief portion of this is important because the goal, in most cases, is to use the lowest dose possible to manage symptoms. The first step is recommended to discontinue the proton pump inhibitor. Whether acutely or with a taper does not typically matter at this stage of the diagnostic algorithm. If symptoms recur, it therefore means that an indefinite or a long-term need for medication exists and it is suggested that a diagnosis be made at that time. This differs from previous algorithms that suggested that one would double the dose of a proton pump inhibitor, change the dose of a proton pump inhibitor or add a second drug empirically. Similarly, if the trial does not result in complete relief, that is an indication for a diagnostic intervention. It's recommended this be done with an endoscopy, looking specifically for mucosal abnormalities and other parts of the GERD process, like hiatal hernias and strictures. And this be done off of a proton pump inhibitor

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for 2 to 4 weeks because there's evidence that erosive esophagitis might recur that quickly and should a reflux monitoring study be done, it would be very clear that the PPI was no longer affecting gastric output. If you demonstrate erosive esophagitis as indicated by the Los Angeles Grading System or clear evidence of Barrett's esophagus which is placed at 3 cm, then the diagnosis is confirmed. If, on the other hand, you can't substantiate that, it is recommended that a reflux monitoring study be done while off therapy. If you have access to a wireless capsule, it can be placed at the time of endoscopy, eliminating the need for further travel for the patient and a 96-hour or shorter monitoring study can be done. Alternatively, there are other ways to do reflux monitoring which we can discuss as we move. If that is normal, then one has to consider other causes for symptoms.

At this point, we are going to move for a case discussion which will be done by my colleague.

Jonathon Firnhaber, MD: Well, thank you, Dr. Katz. With that algorithm in mind, let's move forward and discuss a case of GERD. So, we have a 62-year-old male who is being seen by his primary care clinician, that's us, following an emergency department visit last week for severe epigastric and chest pain and vomiting. ECG then was normal at the emergency department and there was no evidence of cardiac ischemic, presumably we had cardiac enzymes and he had a full evaluation. So, at his follow-up visit today, key findings on history and physical examination include chronic cough, hoarseness, and bloating. He describes persistent regurgitation and heartburn.

So, let me bring Dr. Heidelbaugh and Dr. Katz into the conversation as well. The questions that we really need to consider with this patient, and with that diagnostic algorithm in mind, is for whom should we consider diagnostic endoscopy vs either stool or breath testing, in essence testing for *H. pylori* vs looking for more severe disease. How should we prioritize those and really what's the role of empiric treatment vs diagnostic treatment? And my thoughts on this, I'll look forward to Dr. Heidelbaugh and Dr. Katz's comments here, I think we need a little more history, right? The question to me is chronicity and is this something that is a brand-new, acute problem that just brought this person to the ED. If that's the case, maybe a different set of pathophysiologic changes than if this is more exacerbation of something that's been chronic.

So, what do my colleagues have to say?

Joel Heidelbaugh, MD: Sure, so this is certainly very, very common. I think every day in the United States, a patient of this age and/or gender, or otherwise, is certainly coming into the ER for evaluation of what they may be concerned about relative to a heart attack. And, in this case, it's certainly reassuring that there's no evidence of cardiac ischemic. But nonetheless, as you know, many of these patients who present are going to have GERD or it's going to be called GERD and it may be nonerosive disease, it may be erosive disease. So, relative to the chronicity, I certainly agree. I think we've got to know how long the patient's had these symptoms. I think we've got to know the severity of the symptoms and I also think we've got to know if the patient has tried any over-the-counter therapy first or if they've been evaluated for this. So, on first flush, going back to the algorithm, I think empiric PPI treatment is certainly reasonable, but if a patient has tried a PPI and has done that for several months or certainly longer than 8 weeks, they're describing key extraesophageal manifestations of GERD here and I think referral for upper endoscopy is certainly warranted.

Philip O. Katz, MD: This is somewhat of a complex patient who presents to the emergency room with symptoms that are most certainly consistent with GERD, but nevertheless are not considered typical. Epigastric and chest pain do occur in the absence of heartburn, and vomiting can often be confused with regurgitation, but those occur in the setting of gastroparesis. Cough, hoarseness and bloating are all symptoms that can be associated with gastroesophageal reflux disease, but in general require a precise diagnosis prior to investing in long-term treatment. Empiric trials are common here, despite the guidelines suggesting that perhaps that's not ideal, so clinicians need to be careful if they choose not to move right to objective testing.

So, if I did not have clear evidence of improvement of the symptoms that brought this patient to the emergency room, which does occur spontaneously in viral illnesses and other acute syndromes, then I would consider doing an endoscopy in this patient. On top of that, there are background symptoms that are not new and how that relates to the ER presentation is a little bit tricky. As a gastroenterologist, if this patient were sent to me, and sometimes that does happen in a direct fashion, then I would do an endoscopy with a plan to do appropriate biopsies and reflux monitoring if I didn't get a clear diagnosis.

In general, I don't consider *H. pylori* infection as something that presents with acute symptoms. So, where screening or testing for *H. pylori* in this patient based on the reason that they went to the ER is something that is worth a discussion and consideration by the primary care clinician.

Jonathon Firnhaber, MD: Completely agree and I think the difficult part about this case is, 1, age and 62 is not terribly old, but adds the potential for extra elements of pathophysiology. Number 2, there are some at least vague red flag symptoms there with the vomiting and the chronic cough and hoarseness to say maybe this isn't simple GERD after all. Maybe there's an element of erosive disease and really the question is, is this someone who moves on to upper endoscopy, even in the midst of a PPI trial or the very start of a PPI trial for further diagnostic evaluation.

Joel Heidelbaugh, MD: I totally agree and I would also want to know about tobacco use and history, alcohol use and history, family history of GI malignancy, weight loss, unexplained anemia, all the red flag symptoms that certainly that you alluded to are going to prompt a little bit more urgent or emergent and certainly a deep dive into work-up.

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Jonathon Firnhaber, MD: And one of the things a primary care physician should be best at is getting more history, so I think that's one of the key things that we need here is a bit more data.

Module 3: Treatment of nonerosive and erosive GERD

Philip O. Katz, MD: Let's talk about the treatment of both nonerosive and erosive GERD. Once again, we can use the guideline-directed treatment process, understanding that this always can be modified based on the clinical situation, the provider's direction and how the patient reacts to the recommendations.

Now, we recommend lifestyle modifications for all of our patients, where possible. These so-called lifestyle modifications are based in data as well as common sense. There's a clear relationship between weight gain and the development of GERD symptoms. That has been shown in multiple studies and it is very clear, clinically, that the obese patient is more likely to have reflux. And there are some studies demonstrating that weight loss actually does improve symptoms, and for obvious health reasons, it would be ideal to lose weight. So, from a GERD standpoint, we recommend weight loss.

The supine position, particularly when one is asleep, increases the risk for reflux, delays esophageal clearance and therefore offers the opportunity for greater injury. While we're asleep, we don't swallow, so our reflexes are inhibited, so we recommend avoiding food before going to bed. The normal stomach empties close to completely in 4 hours. It does so over time, varied by patient. So, to make things relatively simple, we offer that the patient should try to avoid meals within 2 to 3 hours of going to bed.

Smoking is not good for anything, quite frankly, although some people do seem to believe that it helps them in some way. Smoking does actually affect acid secretion and sometimes can inhibit the effect of H2 blockers and can affect the lower esophageal sphincter such that it might increase GERD. Trigger foods are trickier because there's not a lot of direct evidence that trigger foods increase GERD, but they do clearly increase symptoms. So, avoidance of citrus products, coffee, alcohol and other things are not absolutely necessary, but, in simple terms, if they cause symptoms, we recommend that the patients reduce them or avoid them.

Now, elevating the head of the bed 6" is associated with increased esophageal acid clearance during the sleeping hours, probably based on gravity. It's very hard to prove that there is improvement in overall symptoms or injury with this, so, in general, we make this an optional intervention. I note here very clearly to the patients that sleeping on pillows is not the way to do this, frankly, because of sliding in the bed and changing posture such that the increased intraabdominal pressure might actually increase reflux. So, if you can't elevate on a wedge or elevate your bed on blocks, it is best to sleep in a traditional manner.

Now, medications are the mainstay of treatment of reflux disease, as they are many diseases, and, as we've evolved, it is very clear that proton pump inhibitors are substantially better than histamine receptor antagonists, so much so that the H2 blockers are rarely written in a prescription form except as adjunct drugs. So, PPIs are the drug of choice, in general given once a day. There are potassium competitive acid blockers in development and one that's approved, but in general, early treatment is with PPIs. When a patient responds, we try to discontinue or reach the lowest effective dose and, in the patients with nonerosive reflux disease in which progression of injury is rare, if there is an opportunity for on-demand or intermittent treatment even though that treatment is not specifically FDA-approved, we do our best to reach the lowest effective dose. There are safety concerns with long-term PPI use, many of which are difficult to prove, but nevertheless have to be taken into consideration as one considers long-term therapy.

The most common adverse events related to proton pump inhibitors are abdominal pain, diarrhea and headaches. In the acute studies, those are no different than placebo, but nevertheless they do occur in the concert of being used and the diarrhea sometimes needs to be differentiated from a simple drug side effect or perhaps a *clostridium difficile*-associated diarrhea or some other enteric infection. That usually can be ascertained by stopping the drug, but is beyond the scope of a major discussion now. Pneumonia has been raised as a potential adverse event, it's very hard to prove. Similarly, long-bone fractures have been part of a warning by the FDA and concern for chronic kidney disease, although the FDA has not placed that kind of warning on the drug.

I'm pleased to turn the discussion over to my colleague, Dr. Heidelbaugh, to continue with the program.

Joel Heidelbaugh, MD: So, centering back on guidelines and guideline-directed therapy for the treatment of GERD, there's a new drug called vonoprazan and it is a potassium-competitive acid blocker or PCAB that leads to the inhibition of the proton potassium ATPase-mediated secretion of gastric acid in the stomach. The proton potassium - ATPase is an enzyme in the parietal cells of the stomach and the way vonoprazan works is that it reversibly binds to the pump and inhibits production of gastric acid. So, this mechanism of acid suppression is actually quite different from the mechanism of action of the proton pump inhibitors.

When we think of efficacy and safety of vonoprazan in treatment of erosive esophagitis, one randomized, active comparator trial of adults with erosive esophagitis looked at healing specifically and found that vonoprazan 20 mg compared to lansoprazole 30 mg daily for a period of up to 8 weeks shows superiority in healing in the vonoprazan group. For maintenance, they re-randomized for those with erosive esophagitis healing to vonoprazan 10 mg daily, 20 mg daily, or lansoprazole 30 mg daily for 24 weeks.

And the endpoints, as seen on endoscopy, showed that at 8 weeks, approximately 93% of patients taking vonoprazan vs approximately 85% of patients taking lansoprazole showed healing of the erosive esophagitis and this is in a noninferiority trial. Healing rates for Los Angeles Grade C and D erosive esophagitis were 92% and 72%, respectively. After 24 weeks, nearly 81% of patients receiving

vonoprazan 21 mg compared to nearly 79% of those receiving vonoprazan 10 mg were compared to lansoprazole at about 72%, again in a noninferiority trial. So again, showing superiority for both doses of vonoprazan compared to lansoprazole. And for maintenance, Los Angeles Grade C and D came in at about 75% to 77% for vonoprazan compared to about 61.5% for lansoprazole. Again, a statistically significant difference.

Looking at adverse events, 30% to 56% of patients treated with vonoprazan for healing and maintenance phases really had impressive statistics, but minimal severe or serious adverse outcomes, ranging from .5% to about 5.5% for severe and about .5% to 4.5% serious. In 29% to 50% of patients treated with lansoprazole for healing and maintenance phases, about .8% to 2.7% had severe adverse events compared to about .5% to 2.5% serious. So, about the same in terms of adverse event risk for both vonoprazan and lansoprazole in this trial. The most common adverse event reported was non-bloody diarrhea during the healing phase.

Dr. Firnhaber, I'm going to pass it to you to talk a bit more about efficacy and safety of vonoprazan for nonerosive disease.

Jonathon Firnhaber, MD: Thank you and let me bring up a trial that was released back in 2024 that really gives us some good information on how we see the safety and efficacy of vonoprazan in nonerosive disease. It's a relatively small trial but still has some important information. Let me walk you through that. So, this was a randomized, placebo-controlled trial of adults with at least 4 days per week of heartburn, but they were all endoscoped and found to not have erosive disease. So, in this trial, basically compared placebo, there was roughly 250 patients, for the first 4 weeks, then a group was randomized to vonoprazan 10 mg, a group to vonoprazan 20 mg, each one had about 250 patients. At the end of 4 weeks, the placebo arm was then split apart to move over to vonoprazan 10 or 20 mg, so really paralleled the other vonoprazan arm that was already in place. So, the primary endpoint here was percentage of days without daytime or nighttime heartburn which really can interpret as complete symptom relief.

So, let's look at the actual trial data. There are 2 graphs here, the first one at the top basically shows placebo vs vonoprazan, 10 mg vs 20 mg. A couple of important things to see here. Number 1, you notice that the placebo actually saw some improvement. These patients weren't actually placebo-treated. They didn't have an acid-reducing medication, but they were allowed antacid. So, that helps to see some actual benefit in the placebo arm. Number 2 takeaway is if you look at the 10 and 20 mg vonoprazan curves, one, they're not all that different, meaning that dose-wise, it didn't make a whole lot of difference which dose the patients received, but, 2, notice how quickly compared to placebo those curves separated from baseline. Even within day 1 to 2, a substantial number of patients saw very quick improvement in symptoms, even to the point that they had heartburn-free days, 24 hours with no symptoms.

Once the trial got out to about the seventh day, you'll notice the curves essentially flattened, meaning maximum efficacy was seen by the week mark and then continued on to the 28-day point. So, drop down next to the curve below, the graph below, that shows what placebo did when they switched the placebo arm over to an active treatment arm. A few important points. One is that we very quickly saw that same improvement in symptoms and, number 2, I think it's really critical to see that the placebo arm and the converted over to vonoprazan and the vonoprazan arm that had been on the study drug all along, paralleled each other. Why I think that's important is because we didn't really see in this trial that there was a drawback to 30 days of symptom, 30 days of no treatment basically. So, what that tells us is most of our patients don't necessarily come into see us on day 1 of their symptoms. A lot of times, they've waited for a while and they've got ongoing symptoms. The question is always have we seen some adverse effects or some complications in that time that they may have waited to come in to see us. Data here says, nope, even if they were 30 days out, we didn't lose anything in the non-treatment arm. The patients who switched over, the placebo arm, is essentially what our patients do is they had nothing and then we start a medication and we see that they very quickly approximate the curve that they would've seen if they had been on the medication for longer. So, no delay, the delay in treatment doesn't really cause a change in the efficacy of the medication.

In terms of adverse events, a few more adverse events in the vonoprazan-treated patients. You'll notice though that placebo still had 16% adverse events. Most of those were nausea, very few serious events in either arm. Once that extended to the 20-week trial data, about a third of vonoprazan-treated patients had adverse events. Again, mostly nausea, very few of those were considered serious adverse events. And everything that was listed as a serious adverse event was considered unrelated to study treatment by the site investigators. So, very unlikely that this was truly due to medication; more that it was other factors. Treatment discontinuation rates were low, up to 2.5% and as low as 0.8%, depending on the arm.

So, that then leads us to dosing. So, for erosive esophagitis, 20 mg daily, the higher dose, for the first 8 weeks, basically the healing phase, and that follow up with 10 mg daily for up to 6 months, which is the maintenance phase. Dose is a bit lower for heartburn only and that's the 10 mg dose for up to 4 weeks. It is important to know that dose reduction is needed in patients with a GFR less than 30. In that case, the 20 mg dose is not used and you drop down to 10 mg, and also for more significant hepatic impairment for healing of erosive esophagitis, that is also the 10 mg dose. Drug interactions are few. Some antiretroviral medications will interact with vonoprazan. Keep in mind that it's a weak inhibitor of both 2C19 and 3A4, so clopidogrel, in particular, if you remember that is a pro-drug, clopidogrel needs 2C19 pathway to convert to an active form, vonoprazan may decrease the conversion of clopidogrel to its active form, decrease its efficacy.

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Same thing, even though vonoprazan is a weak 3A4 inhibitor, it is also metabolized by 3A4. So, drugs that are strong 3A4 inducers may increase the clearance and the conversion of vonoprazan to its inactive form.

So, with that, let me hand back to Dr. Heidelbaugh for another case to review.

Joel Heidelbaugh, MD: Thank you very much. Alright, so another case. This is a 47-year-old female who presents to her primary care clinician for follow-up after an 8-week course of PPI treatment. Initially, she presented with symptoms of heartburn and regurgitation and she was given a PPI without any diagnostic testing.

I'll highlight this simply because these medications are available over the counter and most of the patients we see are probably going to start self-directed therapy and that's probably reasonable initially. I always remind people at this stage, and I have to remind myself too, but I think it's always important that we know what medications patients are taking, even if they're not prescription medications and they're over-the-counter medications because they may not fully disclose that. So, I don't want a patient to minimize that they have heartburn to some degree and regurgitation and they're taking an over-the-counter medication and having us not know because, as Dr. Firnhaber mentioned, most patients aren't going to come to us on day 1. It's hard to know when day 1 is, but we want to keep track of that as best as we can.

So, we optimize the PPI therapy and if a patient gets good symptom relief, then we can continue GERD treatment and we can discuss long-term GERD management options relative to whether or not a patient has alarm signs or symptoms, relative to whether or not they have a family history of upper GI malignancy or whether or not they have identifiable extraesophageal manifestations of GERD. Like in the previous case we discussed, the patient had hoarseness and chronic cough.

So, ultimately, let's take our case here, and this patient has unsatisfactory symptom relief. The recommendation at that point, especially if they've tried a PPI for 8 weeks, is to perform diagnostic EGD or upper endoscopy, ideally with the patient off the PPI for 2 to 4 weeks. We recognize this may be a challenge. Some patients we see have symptoms so severe that it's not sustainable or not tenable for them to go off the medication because of significant symptom burden. But, if possible, you can have them stop the PPI before the diagnostic EGD. So, if the EGD is normal, then you might want to consider reflux monitoring because I think, at that point, we've got to take a look and say do we really have the right diagnosis, okay? Keep in mind, an EGD is not going to show reflux. We're looking for complications of erosive esophagitis and other reflux disease. So, you could consider reflux monitoring and, at that point, it will be imperative to have the patient off a proton pump inhibitor. If there's no evidence of GERD on reflux monitoring and no evidence of complications on the upper endoscopy, then you can probably safely rule out GERD and think for other causes, whether or not this is a functional dyspepsia issue or a host of other causes, probably outside of the scope of what we're talking about today, but it's important to think about other causes.

If the EGD is abnormal, then the abnormality will get graded into a schematic of erosive esophagitis based upon degree of erosions, based upon circumferential diameter and whether or not there is presence of Barrett's esophagus, specifically long-segment greater than 3 cm. And the endoscopist very well may obtain biopsies here as well. At that point, if there is evidence of erosive esophagitis and Barrett's, then we've confirmed the diagnosis of GERD. And, if the abnormal EGD is pointing in this direction, we also want to think about other causes for symptoms that may be identified and certainly this is where we get into our discussion about treating mucosal disease and treating the abnormality.

So, with respect to this case and this algorithm, I'll invite Dr. Firnhaber and Dr. Katz to weigh in as well.

Philip O. Katz, MD: This case is the classic, typical presentation. GERD can present at any age, so being 47 is perfectly fine. Symptoms are equally common in men and women, so the sex or gender is not particularly relevant. These are typical symptoms without warning signs. An appropriate optimized PPI trial was given, the patient's not well and now presents for further evaluation. Now, one could argue at this point that you would want to empirically double the dose or optimize. There will be talk about switching to a PCAB as a therapeutic trial. However, the care provider seeks to do that, once again one is looking for complete symptom relief. Now, arguably, I don't treat anyone long-term without an intervention. So, I, in terms of discussing long-term options, would always talk about an endoscopy. But in theory, if the patient had continued symptom relief once PPIs had been optimized, one can discuss long-term treatment options. The easy side is if optimizing PPIs does not work, does not provide satisfactory symptom relief for the patient, in which case the algorithm that we previously discussed is the one that one should entertain. An endoscopy, followed by reflux monitoring, off proton pump inhibitor, off PCAB, off any medication if it is available and feasible.

Jonathon Firnhaber, MD: This is one that really seems to me like what we see almost every day in clinic. There aren't any red flags, and the treatment approach was really quite reasonable, empiric PPI. The optimized part, though, I think is an important one, and we sometimes lose sight of the fact that patients don't take medications perfectly, so the optimize may be a dose adjustment, but we also need to be cognizant of whether or not the patient is taking the medication correctly in the first place. So, asking are they taking this intermittently, are they taking this first thing in the morning with breakfast? Ideally, a PPI should be taken first thing in the morning on an empty stomach. We may not have remembered to give all those instructions when the drug was initially started or perhaps the patient had been self-treating already and just not doing a very good job of it. So, one of the key things as we're thinking of this is trying to be sure that the optimized PPI part is really, truly optimized.

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Module 4: Treatment of *H. pylori* infections

Jonathon Firnhaber, MD: Let's move on to discuss treatment of *H. pylori* infection. Before we discuss treatment per se and any of the specifics, we need to be certain that we've got some information about diagnosis. Unfortunately, this does involve statistics, but when I think about the 3 options that we have at our disposal as primary care physicians, urea breath test, stool antigen assay, and I'm going to put way down on the list, serum antibody testing, because it's not nearly as helpful.

When we think about the sensitivity of a urea breath test vs stool antigen assay, they're very similar. So, neither of these is considered a screening test. For a screening test, we'd like to have super-high sensitivity and we're willing to tolerate lower specificity, but this is a diagnostic test. Nonetheless, stool antigen assay with a sensitivity of 94% is pretty impressive, meaning that the risk of false negatives is relatively low. Specificity, on the other hand, very high for both and slightly higher for the stool antigen assay, but if we're comparing the 2, stool antigen assay is going to get us a little bit more accurate data. Urea breath test is still a very reasonable option.

Antibody testing has complications. Specificity is a bit lower. Antibodies don't stay around in the serum for a super-long time, so we may not necessarily see positive antibodies. We can't count on that test being nearly as accurate, but the 2, urea breath test and stool antigen assay, are both very reasonable for diagnostic.

The landscape of *H. pylori*, not surprisingly, is changing and, with 1, a long-time recognition of *H. pylori* is the pathogen that it is and, 2, with longer-term use of antibiotics, not surprisingly antibiotic resistance has changed over time. The chart here shows us the resistance to different agents that are used to treat *H. pylori* based on region and what I'll point out is that it doesn't really matter. Depending on where you are, clarithromycin still has around 15-ish percent resistance, amoxicillin relatively low, 1% to 4% depending on the region of the US, metronidazole resistance, on the other hand, is fairly high, upwards of 50%, and even in the southwest, nearly 75% of *H. pylori* are metronidazole resistant. That influences us, importantly, because we don't always have that data in front of us. We're oftentimes treating empirically. We need to be aware of, in general, where the antibiotic resistance patterns are so that we're not necessarily relying on a drug that is becoming increasingly ineffective against *H. pylori*.

So, there are new antibiotics, rifabutin in particular, that have been studied as additional agents that we can use in our treatment of *H. pylori*. And finally, PCABs have been introduced into the treatment algorithm as well and I'll show you where that is here next.

So, the charts here are from the American College of Gastroenterology guidelines for the treatment of *H. pylori*. On the far left, treatment of infection in North America, importantly we need to start with treatment-naive individuals. This is most of who we see and the optimized bismuth quadruple approach is considered the gold standard. It's 3 check boxes and they're all green. Let me touch on the optimized part because it's really a critical piece. It's not just some bismuth and some tetracycline and maybe doxycycline. The optimized part is really specific. Number 1, bismuth is dosed at 300 mg 4 times daily. Whether it's the subcitrate or subsalicylate, not that relevant. Importantly, the tetracycline can't be substituted. The efficacy of doxycycline, even though we would think that they should be fairly similar in terms of outcomes, tetracycline is more effective than doxycycline. So, the optimized part emphasizes that we use tetracycline and not other tetracycline agent. Metronidazole, again, dosed 1.5 to 2 grams daily, so it's 500 mg either 3 or 4 times per day. And then PPI is added in.

So, that is the ideal. We do recognize that not every patient either can take . . . perhaps they've got a penicillin allergy, perhaps they've got another reason why one of those agents is not going to be a possibility. We have options with rifabutin triple therapy and also vonoprazan dual therapy as back-up choices for empiric treatment. And again, for patients who are treatment-naive.

Things get a little bit messier when we talk about treatment-experienced and salvage sounds like a little bit of a Hail Mary pass which is not really the case, but nonetheless, if someone has been treated for *H. pylori*, they have follow-up testing at at least 4 weeks and we recognize that they haven't cleared the infection, now we have to drop back to an approach for treatment-experienced individuals. So, you see nothing gets the full green light. Everything is in the suggested category, meaning we don't have great data to say here is what is optimal, but we have some decent options.

So again, optimized bismuth quadruple therapy in those who we're treating both empirically, or if we have antibiotic sensitivity data, we can use that. A reasonable choice also, just like with treatment-naive individuals, is rifabutin triple approach. The vonoprazan dual approach, there's not enough data to be able to say one way or the other, but vonoprazan triple and levofloxacin triple approach are other additional options in those that have antibiotic sensitivity data. Penicillin allergy, again, we can go back to the optimized bismuth quadruple approach and should be fine there. So, the question is whether someone can take amoxicillin or not. But when you get down to the very bottom of the treatment-experienced individuals, again things become a little bit more difficult. We simply have to incorporate more data into our decision. And, on the right are the components of each of those therapies.

Let me hand it back to Dr. Heidelbaugh to now talk about what is new on the block, as I alluded to.

Joel Heidelbaugh, MD: Thank you, Dr. Firnhaber. So, yes, definitely new to the block, not only new guidelines that were published at the end of 2024, but again vonoprazan, with an indication for treatment for *H. pylori*, and this is a game changer. So, you will hear of dual pac and triple pac, dual pac being vonoprazan and amoxicillin, and triple pack being vonoprazan, amoxicillin and clarithromycin. And these were FDA-approved several years ago. One study was a randomized, active comparator trial looking at efficacy rates of treatment of vonoprazan and amoxicillin vs vonoprazan, amoxicillin and clarithromycin vs lansoprazole, amoxicillin and clarithromycin. And

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ultimately what they found was vonoprazan regimens were not inferior to lansoprazole, but superior in the resistant strains compared to the clarithromycin- and amoxicillin-resistant strains. The information that Dr. Firnhaber gave, I think, is really important and so one of the things you'll notice right now is the main recommended therapy is quadruple therapy which contains metronidazole. But data also shows that an almost 70% resistance rate, so a lot of this is going to have different geographical variants.

A lot of this is going depend on availability. A lot of this is going to depend on patient preference. But I think the guidelines that Dr. Firnhaber outlined will help guide us in clinical practice. And, back to this randomized, active comparator trial, the adverse events were slightly, were essentially similar across all of the treatment groups. It can be challenging for any patient to take any of these regimens for several weeks.

So, let's jump to another case. This is a 46-year-old male who presents for evaluation after failure to respond to a PPI-clarithromycin triple therapy course. Let's assume he took the whole course. And urea breath test has confirmed that *H. pylori* infection persists.

So, as Dr. Firnhaber alluded to, there will be a segment of patients who have received treatment and now go into what's called salvage therapy. So, this algorithm highlights salvage regimens for treatment-experienced patients with persistent *H. pylori* infection. It is going to be very difficult to do antibiotic susceptibility testing. It's just not widely available and we typically won't be able to do this before choosing a regimen and we typically won't be able to do this after choosing a regimen if the patient has a treatment failure. So, if you look at a couple of options, if you look at previous PPI and clarithromycin triple therapy, it's important to highlight whether or not a patient has the penicillin allergy component. If they do, then optimizing the bismuth quadruple therapy is certainly reasonable and, again, according to current guidelines, that's going to be the most recommended therapy. If there's no penicillin allergy, again optimizing bismuth quadruple therapy's going to be important, but you can also consider rifabutin triple therapy. There are some areas where rifabutin is not readily available, but you can also consider high-dose PPI or PCAB for dual therapy.

If you're in a situation with previous nonoptimized bismuth quadruple therapy and the patient has a penicillin allergy, then you want to optimize that therapy. Again, it can be challenging to take that many pills every day, especially 4 bismuth pills every day for 2 weeks. Sometimes patients don't tolerate that well. If the patient doesn't have a penicillin allergy, then again optimizing bismuth quadruple therapy is important, but also considering the other options again. So, rifabutin triple therapy or high-dose PPI or PCAB dual therapy.

Dr. Firnhaber, thoughts on this?

Jonathon Firnhaber, MD: This is difficult because there, as much as we would like to have a really clear step-by-step algorithm, it simply doesn't exist, the data simply isn't out there. And I think the important part to consider is what a patient is both able to afford and also what they're willing to take. As you pointed out, 4-time-a-day anything is very difficult to take, especially if you're extending that out for 2 weeks. I think there's a whole lot of discussion with the patient, trying to figure out what their ability to take medications—afford medications is—and also some clarification of the importance of eradication of *H. pylori*. I think the difficult part for a lot of people is recognizing a bacteria that you can't see, can't necessarily feel, but nonetheless keeps showing up on a lab test is really worthy of treatment. It sometimes is difficult to convince individuals that this is truly worthy of their time and effort and of taking something 4 times a day and then for them to come back to say, gosh, this treatment didn't work the first time around and now we're going to try something that may be even more complicated, more expensive, more challenging to take. It really does take a lot of coaching. I think we can come up with the algorithm just fine, but trying to have patients dial into that and actually be accepting of that approach is a whole different story.

Joel Heidelbaugh, MD: I agree, and I'll also add to that risk. So, right now, while a patient may not necessarily feel substantial effects of *H. pylori* infection, as we know it does carry significant risk of ulcer disease or GI malignancy.

Module 5: Multidisciplinary Care

Jonathon Firnhaber, MD: I think we'd be remiss to not include a more broad subset of healthcare professionals when we're addressing GERD and *H. pylori* infection. We, a lot of times, will put that mantle on our own shoulders as primary care physicians and say we can do it all, in many cases with the help of our GI colleagues, but we can expand that even more. Most of the patients that we see with GERD and *H. pylori* are certainly managed by us. We see them as a primary care physician or provider and manage most of those cases. A really important time though is for us to not just have in our own minds when we dial in and incorporate the care from one of our gastroenterology colleagues, but we need to communicate that to our patients as well so they've got a good idea of not just the plan today, but the plan for what if this doesn't work in 2 weeks, 4 weeks, 6 weeks. How do we approach this from here so that we're all on the same page?

One important part that unfortunately not everyone has access to, but how fortunate you are if you do, is bringing in a dietician. In our clinical setting, we're fortunate to have 2 dietitians who actually are really helpful when we've got patients with difficult-to-control acid reflux symptoms, namely because there are so many dietary components and dietary triggers for reflux that hearing it from me as a physician vs hearing it from a dietician can also bring in, here's some not only changes to your diet, limiting alcohol, decreasing smoking, etc, but some simple dietary management options that can help improve symptoms. Hearing that as a really a more team-based approach, I think is a very important message for our patients to hear.

Finally, when we do refer to our gastroenterology colleagues, they've completed their evaluation, they send the patient back to us with data, here's what the plan is, obviously primary care physicians and providers are really important in that element to be able to, again, communicate that back to the patient, translate those GI

recommendations into plain English and translate them into a plan that we can all not just agree upon, but all follow. So, a lot of considerations when we're thinking do we want to take this on ourselves or is this a medical condition where we can spread the wealth just a bit, not only incorporate our specialist colleagues but others as well.

Philip O. Katz, MD: For consistency, it would be ideal if the primary care clinician would be directly involved and, in most cases, be the primary manager of the clinical situation. Except in places of major complication, this should be done relatively easily.

Key Concepts

Joel Heidelbaugh, MD: I think the main key concepts are that PPIs are the mainstay of treatment for GERD, both nonerosive and erosive versions of GERD. They've been around for decades. They've got a lot of great data and they have a lot of proven efficacy relative to treatment and maintenance of disease and symptoms. We know upper endoscopy has a very key role in the diagnosis of GERD and erosive esophagitis as well as other complications. I think a very key point is that if a patient has not improved substantially on a PPI for 8 weeks, don't hesitate to think about reaching out to your colleagues who perform endoscopy as at least getting a baseline is certainly going to be necessary. Now, if it's negative or unremarkable, then you can go back to the drawing board, consider reflux testing, impedance testing and whether or not GERD is the actual diagnosis. But, if there are abnormalities, it's important to highlight that because the patient may follow up relative to surveillance based on the findings.

Vonoprazan is an example of a new class of medications called PCABs, or potassium competitive acid blockers. They can be considered for the treatment of severe erosive esophagitis. And you're going to hear about vonoprazan and you're going to hear about the PCABS again as we go forward.

It's important to optimize bismuth quadruple therapy because that's the preferred regimen for treatment-naive patients with *H. pylori*.

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