[MUSIC PLAYING]

KENNETH FASANELLA: As you can see, a topic that 10 or 15 years ago when I started talking about it was able to be done in one talk, and now it's becoming more and more challenging, to the point where I don't think I can do it anymore, especially with H. pylori, as all of the literature coming out-- the guidelines that were just published in January of this year alone were 28 pages long. And that's just for treatment.

But I hope to get through today, allowing us to get a little bit better functional understanding of both the anatomy of the stomach, as it pertains to acid secretion, as well as the physiology of gastric acid secretion and the physiology of GERD and how the breakdown and the defense mechanisms can lead to that disease state and go through some of the diagnostic and treatment algorithms that I use and that you'll be responsible for when it comes to boards type questions.

I'm also going to review acid-related pathophysiologic states within the stomach. Why do we care? Because it's extremely expensive part of our overall medical expenditure-- about $25 billion back in 2012 and about 39% for prescribed medications of that expenditure. So unfortunately, now you can see I have a very horrible picture that I had to make myself, because I had to remove all copyrighted pictures that I had in my talk. So I spent a lot of time coming up with PowerPoint art.

Anyway, what this represents is that we have really two functional areas in the stomach, consisting of fundus corpus and antrum and G-cell. This is where you're going to find your oxyntic gland area, which is composed of parietal cells. It's approximately 80% of the gastric surface area. And it's located in this portion of the stomach.

So that's going to be your acid-producing portion of the stomach, whereas the antrum is going to be predominantly G-cells, or about 20% of the surface area. And that is going to be more of the physiology of acid secretion control.

As far as the different types of acid production that we have, there's two basic states. And one is the fasting and basal output that's going to be there when it's not postprandial. And this is lowest in the early morning and highest in the afternoon to evening.

And during that period of time, if you have thought, sight, smell, taste of food-- that's going to

stimulate acephalic phase-- vagally-stimulated, producing approximately 50% of your acid secretion through vagal-induced acetylcholine release. This is how our parietal cells work, essentially, through functional input of various hormones, as well as mediators consisting of gastrine, which is going to have both direct effects on expression of the potassium proton ATPase or potassium proton pump, and through simulated release of the interchromatin-like cells, which secrete histamine.

This is going to be more of a neurologic input. And this is going to be more through other mechanisms. Now what is our defense against this?

Well, as you can see, the stomach, both the milieu and the stomach layer itself, has a pH gradient. Now this highest pH-- I should say highest amount of acid, or lowest pH, is going to be in the stomach lumen. And as you progress towards the actual endothelium and underlying layers, it's going to be progressively more neutral.

This gradient is maintained through a mucous layer and bicarbonate secretion within it. And bottom line is, prostaglandins are very much responsible for maintaining this gradient and the protection of our gastric mucosa.

And these are released by capillary endothelial cells and macrophages in the lamina propria. Responsible enzymes are COX-1 and 2 for generating prostaglandins. And obviously, and you all know, through the fact that COX-antagonists were generated, that COX-1 is responsible for a lot of gastric mucosal production. And that's why COX-2 selective antagonists were invented-- to try to protect the stomach.

Now this is performed through both the stimulation of mucus and bicarbonate, but also phospholipid production and nitric oxide-fueled stimulation of epithelial blood flow. Now let's talk a little bit about GERD. It's very common in the United States.

As you can see, 5% to 10% of Americans have heartburn at least daily and even more on a monthly basis. And the estimated lifetime prevalence is somewhere between a quarter and a third of Americans.

What are the typical symptoms that we less often see in a GI clinic? Well, you need to know that obviously heartburn regurgitation and water brash or hypersalivation are the typical symptoms that you're going to see in reflux. And those are the ones that are often going to be treated by primary care physicians and, in this day and age, self-directed treatment with all the

OTC medications that are available.

But the atypical symptoms that we're going to get from the pulmonary clinic or the E and T clinics sending patients to us are going to be the ones like hoarseness, globus sensation, chronic cough, throat clearing, asthma, and other bronchiolitis type lung situations that are thought to maybe be at least partially responsible.

Now what is the pathophysiology? What has to break down in the normal physiologic state in order to have GERD? Well, normally you have three basic defense mechanisms against acid reflux. And the first-line is a barrier.

So you have to have a well-opposed diaphragmatic hiatus with your lower esophageal sphincter. Any breakdown in that or hypotension in the LES can result in loss of barrier function. Secondly, you need to have good clearance mechanisms-- so salivation and peristalsis.

If either of those break down, then you have poor clearance mechanisms. And lastly, epithelial resistance, such as your intercellular tight junctions, mucus production-- those are obviously necessary to help prevent tissue breakdown.

Now certainly, as you can see here, I also added the delayed gastric emptying. Now that's not one of the primary mechanisms that we try to keep maintained. But if there is a breakdown in gastric emptying, then obviously you have prolonged period of time that these contents can be maintained in the stomach for them to reflux up. And that can certainly be a cause of people who have refractory GERD.

Now you need to think about the medications that your patients are on when they present with these problems. And this is especially a problem in the people with overlying or overlapping pulmonary disorders. So in the population that I see, a lot of these patients are on xanthines. But also keep in mind, the reason why it's often recommended to minimize caffeine and nicotine intake is its effect on transient lower esophageal sphincter relaxations, increasing their frequency.

Now a lot of these medications and the additional beta agonists, anticholinergics, benzodiazepines, and sildenafil, amongst the other acetylcholinesterase inhibitors, are going to decrease your LES tone. And also, some of them will have an effect on peristalsis. The calcium channel blockers, in addition, will have a negative effect on peristalsis.

So testing strategies for GERD are going to include empiric therapy. This is probably the most often used and is a fairly cost effective initial strategy-- roughly 80% sensitivity and about 60% specificity for a two-month trial on BID PPI for diagnosing GERD based on response. Barium swallow is often something that I find helpful and is the correct boards answer for a lot of these patients that are presenting, especially if dysphagia is part of their symptom presentation.

Endoscopy in certain select cases, pH testing with a sensitivity and specificity around 90%, and with symptom association being very important-- manometry and impedance monitoring-- we'll talk about some of those different tests separately. So barium swallow can be helpful, again, because it helps you assess anatomical evaluation and breakdown in barrier functions. But it also gives you some information about motility disturbances.

And some people who have refractory GERD will have stasis esophagitis, secondary to something like achalasia. And you'll see a barium swallow that looks more like this. So every now and then, you'll pick these up, utilizing a cheap, easy, effective test with just about zero risk.

So it's about 33% sensitive for pH document in GERD and about 25% for esophagitis, looking at the mucosal changes. But bottom line is, I find it helpful more for motility and anatomy.

What are the indications for endoscopy? Well, anybody who presents with alarm signs or symptoms-- so if they're having weight loss or dysphagia, that is an indication. Certainly, odynophagia should be a fairly rapid indication for an endoscopy without a lot of wait time.

And the people who are at risk for Barrett's esophagus-- the ones that you should try to select as needles from the haystack of all the people with GERD, in order to try to not bankrupt our country, would be especially Caucasian males over 50 years who have five to 10 years of GERD symptoms, whether or not they've been controlled with acid suppression. People with first degree relatives of Barrett's-- this was data out of Mayo by Yvonne Romero, showed odds ratio about 1.6 with first degree relatives.

Now what are you looking for? You're essentially wanting to screen for Barrett's. And you're also wanting to assess for mucosal damage. So here you see a patient that has reflux esophagitis. Here you see a little bit of an annular stricture.

And this may be a Barrett's tongue-- hard to know until they've healed up. But bottom line, these are the kind of changes that we're looking for. And if we see these, then we know the

patient has GERD.

Other things that you might see that are of note-- you see a esophagus that looks like this, then you clearly have a motility abnormality. They shouldn't be retaining their own saliva. If you see something that looks like this with a lot of coating of saliva and what looks like an atypical pattern of esophagitis, you may be looking at stasis esophagitis or a clearance problem.

If you see something like this with pulsion diverticula or epiphrenic diverticula-- if you see something that looks like this, which is what's described as the esophageal rosette sign, you're thinking, this may be a patient with a hypertensive LES or achalasia.

And if you see a dilated bag of an esophagus, then you know what you're going to find on the barium swallow. You also should be looking to make sure that they don't have GE junction cancer.

Now how do we classify esophagitis? This is the most widely referenced classification system, but it's not used much anymore. And I'll go over why.

So you'll see this a lot in old literature. Nowadays, you're going to see the newer LA classification. The reason for this is really under grade 4.

It's no longer really thought that you should grade esophagitis based on whether or not somebody has Barrett's or a stricture, because they can have perfectly healed esophagitis and still have Barrett's or a stricture. So that's why the LA classification was developed.

And you'll see us referencing this. And it's always good to have a reminder. What are we looking for?

Well, grade A should be one or more mucosal breaks less than five millimeters meters in length. Grade B, they can be much longer than five millimeters in length. But if they're not bridging, then they're grade B.

If they're bridging from one fold to the next, then they're grade C. And grade D involves 3/4 of the circumference.

So the majority of patients won't have endoscopy findings like this. And those are the ones that we're left wondering, well, what do you have? Do you really have acid reflux or not?

And this brings up the entity known as Non-Erosive Reflux Disease, or NERD. And this is

where ambulatory pH testing can come into play. Obviously, if you have people on endoscopy who have the previously pictured findings, you don't need to do ambulatory pH testing in that cohort of patients. The diagnosis is already made, whereas in these NERD patients, this helps to confirm GERD in patients who have persistent symptoms despite maybe a trial of acid suppression therapy.

What questions does it answer? Well, it answers, whether or not you have NERD, especially the symptom correlation with acid reflux episodes. And it requires you to be tested off meds.

So this is something to keep in mind. If you're ever referring or personally performing these tests, you need to take your patients off PPI for a week-- for at least a week-- and at least three days or 60 hours off H2 receptor antagonists, in order to get the hypergastronemia state back towards normal. It also helps explain whether or not they have atypical symptom correlation with acid reflux episodes.

So what are the different mechanisms by which we can do these types of tests? Ambulatory pH monitoring with the traditional trans-nasal catheter is a 24-hour test. Then there's the Bravo test system that most of you who have been doing this for at least a year or two have seen, which is wireless in 48 hours. It's the more common modality used these days, simply because of patient preference and the duration of testing.

The box used to look like this. They've changed it in the last couple of years. But the capsule that is implanted on the esophagus six centimeters above the top of the gastric folds looks like this after it's implanted.

A newer kid on the block is impedance, typically combined with pH testing. And this is based on electrical conductance. And this has the ability-- or the advantage of this is the ability to assess for non-acid reflux. Basically, it works based on electrical inductance of electrolyte-containing fluid, as opposed to a baseline lack of electrolyte-containing fluid.

So if you have a baseline electrical conductance, air is going to increase your impedance. Electrolyte-containing solutions are going to decrease your impedance, or improve inductance. And then as the bolus passes, you're going to go back towards baseline.

And if you have these electrodes at multiple different levels above your LES-- and using that, you can see either traversing from the top of the esophagus down towards the bottom. Or if it's going in the opposite direction, you can see a reflux episode. This is often combined with

pH to tell whether or not whatever you're seeing, going up or down, is acidic or not. And so you'll see a graph that looks more like this with a pH probe, showing you whether or not this bolus that's going up or down is acidic.

Manometry is helpful if you have a suspicion of a hypertensive LES, if you have a suspicion of poor peristalsis or any other significant motility disorder, such as scleroderma, and for a pre-surgical evaluation of anti-reflux surgery. Traditional manometry would have looked like this. You're not going to see that in this institution anymore.

As of about two years ago, we switched over to high res manometry. And we were fairly late in the game for that. But bottom line, this was a very useful test, especially if it was done in expert hands that were used to looking at people's esophagus in this manner, which is what we had when Dr. [INAUDIBLE] was reading these.

And essentially, what you're seeing is esophageal peristalsis and LES relaxations. So you should see it like this. You should see peristalsis and LES relaxation corresponding nicely like that.

And if you see something like this, where you have decreased peristalsis and residual pressure at the LES, that's consistent with achalasia. If you see something like this, where you just see pretty much flatline everywhere and no pressure at the LES, that's more consistent with scleroderma.

And then if you get a high res manometry, which is what we have now, the correlate would be something like this, where you see a nice wave of pressure traveling with time, as well as LES relaxation right below that bolus wave, versus something like this, where you're having pan-pressurization of the esophagus and no relaxation of the LES. which you're going to see in achalasia.

So I know Dr. Leventhal is going to go over that kind of physiology testing with you more, if he hasn't already. I can't remember when his [INAUDIBLE] lecture is. But that's something that's going to be reviewed in his talk. So we're trying not to overlap too much on that.

What are the goals of GERD therapy? Well, first, obviously you want to control symptoms so that your patients will be less concerned about their symptoms and have a better quality of life and seek less health care treatment. And you want to promote healing, prevent recurrence, and prevent the complications, such as stricture bleeding and Barrett's esophagus and, by

way of preventing Barrett's, hopefully preventing esophageal adenocarcinoma.

The two components of initial therapy would be lifestyle modifications and pharmacotherapy. We're going to go over lifestyle modifications very briefly. These are the things that you'll see touted in a lot of literature, especially trying to minimize the use of medications. But a lot of it, interestingly, has absolutely no evidence at all.

So it's interesting that that's the case. But really, the only two things on this list that have any evidence are weight loss and having a three-hour break after your last evening meal before you go to sleep. This decreases nocturnal reflux about sevenfold. And this certainly has a significant effect as well. All of the rest of the things are basically theoretical, based on nicotine and caffeine, increasing transient LES relaxations and carbonated beverages, increasing pressure, and so forth.

So patient-directed therapy would now include PPIs and H2 receptor antagonists, as well as the older medications that were really just antacids, such as calcium carbonate or alginic acid. And when symptoms persist despite therapy, or alarm symptoms or signs develop, then the patient should have medical evaluation and treatment.

Of note, you'll see a lot of your patients coming in and saying that they stopped their PPI after two weeks, because that's what it said on the medication insert. That is the recommended period of time that the OTC medication is approved for. So it's going to say that on the over-the-counter medications. Obviously, it doesn't say that on a 30-day prescription.

Acid suppression-- a couple of take-home points on H2 antagonists versus PPIs I want you to know-- so H2 receptor antagonists provide symptom relief in about 30% to 80%. Healing rates of erosive esophagitis are lower, certainly, than PPIs. And they're useful to treat non-erosive GERD or mild esophagitis.

It may require drug holidays to maintain effectiveness because of tachyphylaxis being a significant issue with this class of medications. So after about four weeks, people tend to find that daily administration leads to loss of effect. Rebound hypersecretion lasts for about three days after withdrawal, as opposed to PPIs where it lasts longer.

The proton pump inhibitors provide the most complete and sustained acid suppression with healing rates greater than 80%. And as a group, they're roughly equivalent. Despite all the marketing that you've seen, they're roughly equivalent.

Now is there statistical difference in the duration with which you'll have a pH greater than five in the stomach after taking Nexium compared to taking AcipHex or omeprazol? Yes, there is a statistically significant difference. But there's not a clinically significant difference between having your pH greater than five for 14 hours instead of 12.

So that's the bottom line. And healing rates of esophagitis are not significantly different. What are the healing rates of esophagitis? Between these different groups, you're going to find roughly twice the rapidity of healing with PPIs, compared to H2 receptor antagonists. And you're going to reach somewhere around 85%, versus somewhere around 48% healing rates for esophagitis.

Escalation of pharmacotherapy-- when you're doing that with PPIs, it's important to remember that graph that we showed a few slides ago. We're doubling the dose, which is effectively what you're doing with Nexium. It doesn't double the duration of treatment.

So increasing the frequency to BID makes a lot more sense than dose escalation does, as your initial escalation of pharmacotherapy. And subsequently, once you've done that, you can potentially add a bedtime H2 receptor antagonist for nocturnal breakthrough symptoms, where you can see studies with pH monitoring have shown significant reduction of nocturnal acid breakthrough on that regimen.

This is where pH and impedance monitoring can be helpful while done on medication, as opposed to Bravo testing, which is not very helpful when done on medication. pH and impedance can tell you how much of your reflux episodes are acidic and might actually be responsive to acid suppression therapy.

This is an old slide from the late '90s when they were still looking at maintenance of healing with PPIs. And I just want to illustrate that once you've established that the patient has healed, what is the rough maintenance of healing rate with PPIs? It's about 90% long-term. This is at one year.

So long-term use has been deemed safe, despite a lot of more recent observational literature coming out suggesting to the contrary. Initial fears for carcinoid tumors have not played out. Atrophic gastritis, acceleration of development of atrophic gastritis in the setting of H. pylori infection was an initial fear that hasn't been deemed to be too clinically significant.

People can have B12 deficiency in setting of long-term PPIs, as well as iron deficiency. It's

something to keep in mind to potentially test for in your patients on high-dose therapy. Subsequent safety issues that do have some data to support their concern-- odds ratios are not huge. But C. difficile is significant. Hip fracture risk, and especially in high-dose acid suppression long-term, is significant.

Community-acquired pneumonia-- probably not as clinically significant. And hypomagnesemia hasn't been found to be very common. Subsequent safety concerns over the incidence of chronic kidney disease with acute interstitial nephritis and dementia have been controversial.

Recently, there was a contradictory finding with another observational trial in dementia. So who knows? The jury is out at this point in time.

But right now, a consensus statement was recently put out last year by our societies that for most patients with an indication, benefits outweigh the risks. So we're at least protected by societal guidelines.

Let's move on to peptic ulcer disease. This is something that you're going to see a lot of during your GI fellowship, because it's fairly common. Prevalence lifetime in men-- 11 to 20%. In women, 8 to 11% with half a million new cases annually. Old data, but still probably holds up, especially with NSAID use not going down.

Pathogenesis is mainly in the breakdown of the mechanisms that protect the mucosa from the high concentrations of acid and pepsin. And those things that can break down those mechanisms include H. pylori and NSAIDs. So we're going to talk a little bit about pathogenesis of H. pylori. We'll talk about treatment later.

Obviously, the infection is fairly prevalent. And when it happens, it causes mucosal inflammation. And these bacteria produce urea so that they can survive in the acidic environment, because the breakdown of urea produces sodium bicarbonate and ammonia. Not sodium-- bicarbonate and ammonia.

Now bacteria will thrive in this hostile environment. Because of this, they live in the mucus bi-layer where they can essentially be in that less acidic surface of the mucosa. And they cause gastric and duodenal ulcers by different mechanisms, which is one of the things I want you to know as a take-home point from this lecture. If you don't already know this, it's an important thing to take home.

NSAIDs cause this effect by inhibition of protective prostaglandins, as I alluded to at the beginning of the talk when I was talking about mucosal physiology that provides our defense mechanisms. That's going to cause reduction in mucosal blood flow, a decreased mucin, decreased bicarbonate secretion, microvascular injury through inhibition of nitric oxide, and subsequent ischemia and free radical formation. Regular use increases GI bleeding risk five to sixfold.

And serious complications occur in a small but significant percentage of regular users. So that's one thing to note. But what's also important to note is that if you have H. pylori and you take NSAIDs, there is a synergistic effect. It increases your risk about tenfold. And not all NSAIDs are created equal.

So in a 2013 meta analysis of quite a few people in 750 trials, they looked at different NSAIDs and their predisposition to causing ulcer formation and found that diclofenac was lower than the ones that you typically use over-the-counter. And another meta analysis kind of ranked them in the following order of increasing risk. So it found that ibuprofen was relatively low risk, diclofenac was higher risk, naprosyn was higher, indomethacin, ketoprofen were the highest.

Now how do people typically present? Well, with dyspepsia, it's probably most common in the outpatient world. But in the inpatient world, GI bleeding and perforation, which actually occurs in a pretty significant percentage of patients.

Up to 10% of patients with GI bleeding do not have any prior pain, especially in elderly-- so something to keep in mind. 7% of ulcers perforate. And GI hemorrhage happens in approximately 15% of stomach ulcers and can result in up to a 10% mortality rate. This has probably dropped in more recent years, but still fairly significant.

And if you have chronic ulceration, you can also end up with a gastric outlet obstruction, if it's affecting the pylorus. So all of these are complications you can see. When we find it, we need to find the cause and discontinue it.

Obviously if it's NSAIDs, discontinue them. We need to eradicate H. pylori. But we also need to provide the patient with anti-secretory therapy and PPI BID if endoscopic haemostasis is necessary, based on a *JAMA* article of 2014. Bottom line is, we're still seeing a lot of people using PPI drips. But they do not have established efficacy superior to BID IV.

This is randomized trial data. So keep that in mind. A lot of your attendings that you're

rounding with-- educate them. Give them the paper. Maybe we'll help reduce hospitalization costs a little bit.

And then follow-up BGD for gastric ulcer-- this is not always necessary. If you have a bunch of typical ulcers that are superficial in the antrum, you don't need to be bringing these people back. But if you have an ulcer that's complicated or greater than one and 1/2 centimeters, you need to bring them back to establish that it's healing.

There is some data that suggests if you biopsy the mess out of it the first time, you don't need to do that-- that you can reach pretty good sensitivity for cancer if you get seven biopsies of the ulcer with regular forceps or four biopsies with jumbo forceps. But you're not going to find many of the people who are scoping with you willing to do that in somebody who's coming in with an acute hospitalization for a GI bleed.

As far as peptic ulcer disease prevention for NSAID users, you want to avoid anti-coagulants or corticosteroids. Use the lowest effective dose. Consider COX-2 antagonists.

Now as you all know from having done internal medicine, COX-2 antagonists are mostly associated with increased risk of cardiovascular complications. So that's a contraindication to their use. And secondly, if somebody has to be on a baby aspirin, it completely negates the gastroprotective effects of COX-2 antagonists. So it's not worthwhile to have that increased expenditure, compared to regular NSAIDs.

You want to consider whether prophylactic therapy with a PPI or misoprostol is appropriate, because they significantly reduce the relative risk of ulcer development while on NSAIDs. So how do you make such a risk assessment? Well, this was published back in 2009 with some guidelines in the prevention of gastric ulcers from our society's *American Journal-- Red Journal.*

And you can certainly look it up with this reference from 2009. But the bottom line is, they came up with a risk assessment where if you had certain risk factors, which, moving onto the next slide, low risk was no risk factors and young age. Moderate risk-- one to two risk factors. High risk was greater than two risk factors.

Going back, what are the risk factors? History of complicated ulcer, uncomplicated ulcer disease, age greater than 65, high dose NSAIDs, incompetent use of anti-coagulants or SSRI use. And if you have no risk factors, NSAIDs alone at the lowest effective dose, shortest

course possible is reasonable without any gastric protection. If you have moderate risk consisting of one to two risk factors, you should have anti-ulcer co-therapy.

Consider COX-2 alone as an alternative if no cardiovascular risk factors. And if you have high risk, in general, you should avoid NSAIDs, including COX-2's. And if medication is necessary, you should definitely administer PPI co-therapy.

So moving on to H. pylori-- how are we doing on time? Actually, pretty well. So this is a spiral-shaped microaerophilic gram-negative bacteria, has full [INAUDIBLE] to enhance its mobility through viscous solutions. And it has urease composing 5% of its organism weight to help it survive in that environment.

This bug has been with us at least for multiple millennia. And its prevalence is greater than 80% in developing countries, by age 50 in developed countries. Probably 50% over age 60-- but this is really more of a cohort issue. It seems that if you go back to people that were born in the '20s, it had a much higher cohort than people born in the '60s, for example.

And that may have been due to surviving the depression, less of a developed country atmosphere at the time that those people were being raised. And transmission is fecal or oral. It seems to be higher in people whose mothers are infected than in their fathers.

But there is familial clustering. And in endemic areas, even the municipal water supplies have been found to be positive for it-- so again, getting at the mechanisms of peptic ulcer disease and the setting of H. pylori infection.

Duodenal ulcer is going to be developing at a different time in someone's life cycle or course of infection than a gastric ulcer for the following reasons. So in the initial period of time when people are infected, they're going to get an antral-predominant gastritis, which is going to cause a hypergastrinemic and hypersecretory state. And that's when they're going to be at most risk for duodenal ulcer formation.

Basically, these people have been found to have gastric output three times normal and duodenal ulcer patients up to six times normal. And that favors H. pylori colonization within the duodenal bulb because of gastric metaplasia that forms there. And also going to precipitate bile salts in the duodenum, which are normally inhibitory to H. pylori and decrease duodenal bicarbonate secretion.

So all of these things can lead to duodenal ulcer. Gastric ulcer, on the other hand, is going to

be more typically late in the time frame of infection when people no longer have a hypersecretory state, but rather have pangastritis. So you'll see, especially if you have somebody with atrophic gastritis who you're doing an endoscopy on and you're trying to rule out H. pylori in the setting of a gastric ulcer and you're only taking biopsies just above the pylorus, you're probably going to miss it.

Your sensitivity of biopsies is going to be very low, because these patients-- H. pylori tends to migrate up into the body and fundus region, even. And so bottom line is, you may not find it to be antral-predominant infection any longer.

But anyway, in these pangastritis patients, they have actually decreased acid secretion. And the primary mechanism is impairment of mucosal defenses in this population.

What is the pathogenesis? Couple of terms that are important-- vacuolating toxin A, or VacA, which is an exotoxin which causes gastric tissue damage via passive [INAUDIBLE] transport. It is expressed via the cytotoxin-associated gene A, or CagA. So you'll see CagA a lot in H. pylori literature, because that is the gene that is required for, essentially, pathogenic strains of H. pylori.

If they don't express CagA, much more infections don't result in any ulcer, whereas 85% to 100% of patients with duodenal ulcers have CagA-positive strains. So something to keep in mind for boards type questions.

As far as indications for testing-- so I'm just going to refer you. This is a really nice article that was put out in the *Red Journal* in January of this year. These are the new treatment guidelines by Che et al. And they were very interesting.

It's a long paper, as you can see-- 212 to 238. It's a 26 or 27-page document, lots of references. But it's a lot of updates since the previous guidelines from 2007. And I know that during the period of time that I've been practicing, which is 2007 to 2017, a lot of our treatment algorithms are kind of being thrown out the window at this point in time, as far as their effectiveness.

And secondly-- this is an important point-- testing for H. pylori infection is indicated in the following patients. These didn't use to be in the guidelines. So these are new updates. ITP has even been found to be associated with maybe some relationship to H. pylori infection.

And there have been multiple trials showing response of ITP to successful eradication. But the old tried and true-- obviously, people with active peptic ulcers, history of documented peptic ulcer, gastric MALT lymphoma, or after resection of early gastric cancer-- you want to test them and treat them.

People who are on chronic aspirin use or are getting ready to start aspirin use or new NSAID use definitely should be tested and treated, if positive. It's controversial whether or not people who have established NSAID use already should be tested and treated. Maybe that will be in the next guidelines.

And they added these two-- uninvestigated dyspepsia and functional dyspepsia should be tested and treated based on about 10% of people with functional dyspepsia getting better if you test and treat positive. And document successful eradication. They're really harping on documentation of successful eradication in these days because of the escalation and macrolide or clarithromycin resistance.

So it should be performed if the clinician plans to offer treatment for positive results. Never test-- if you ever see a boards question that talks about testing and not treating, that would be definitely the one to pick as wrong. [LAUGHING] And deciding which test use in which situation obviously relies on whether or not an endoscopy is indicated. If one is indicated, you should definitely biopsy. And they advocate in the guidelines to biopsy patients with dyspepsia who have normal-looking stomachs.

What are the different options for testing out there? Obviously histology, which is unfortunately expensive, but has excellent sensitivity and specificity if you get enough biopsies. If you do one, not so great. You have to get multiple biopsies.

Rapid urease testing is inexpensive. This is what you'll see referred to as the CLO test, which we used to do in the lab. But Kevin essentially took it out of the lab, even before I was established as an attending, because people would leave it sitting in the room where they tested it and not check it and not follow up on it. So he considered it a medical legal issue that he removed from the lab.

So bottom line is, it's a good test. It's just not used, unfortunately, in this environment. But the other thing to keep in mind is, it's not a good test while on PPI.

Culture is becoming more prevalently available. It wasn't all that available several years ago.

But this can be a very useful thing to help us determine antibiotic susceptibilities. PCR, I don't believe is available in our institution.

As far as non-endoscopic testing, these are the ones that you're mostly going to be using-- an antibody testing has really fallen out of favor, mainly, I think, because of confusion and how it should be used. It can document people having been previously exposed who are not actively infected. So it's not very reliable to represent active infection and is of no use to document people who are post-treatment and whether or not they've responded and eradicated. And for that reason, I don't think it's even available in this hospital anymore.

Now the two that you're going to most often use these days for documentation of eradication and sometimes for just testing nowadays-- the fecal antigen testing and urea breath testing. This one is dependent on urease being active. So it's not going to work in an acid-suppressed environment.

So if you're going to do urea breath test, the patient needs to be off PPI for several weeks beforehand. Fecal antigen testing does not have that issue. So in that case, you could even do it in the midst of treatment.

Some people have advocated for after week one of treatment, doing fecal antigen testing to predict response. That's not in the guidelines yet. But it is something that you can check immediately after they've gone through their antibiotics course.

Testing to prove eradication should definitely be done in anybody with a previous ulcer, persistent dyspepsia, people with a history of MALT lymphoma, and people who've undergone resection of early gastric cancer. That's something that's important. That's from the previous guidelines. And they're persistent in these guidelines.

Antibiotic resistance patterns-- no talk on H. pylori would be complete without talking about antibiotic resistance. So this is something that's become a big issue and was reflected in the most recent guidelines. Clarithromycin resistance and metronidazole resistance are fairly prominent, as you can see. But this one doesn't seem to be as significant when it comes to responses to regimens, whereas this one does.

Triple therapy with amoxicillin, clarithromycin, and PPI for less than 14 days is completely out. So that's still considered a first-line treatment in North America, but only at 14 days. So anybody treating H. pylori for less than 14 days with triple therapy, it's out. Keep that in mind.

Take that home.

The other first-line therapies-- there's lots of them now. There's a lot more than there used to be. It used to be triple therapy or quadruple therapy. You're done. Easy to remember.

Not anymore. Now there's about six different first-line regimens that can be considered, based on your penicillin-- lack or presence of penicillin allergy and lack or presence of previous macrolide exposure and local rates of clarithromycin resistance. [PHONE TONES] Excuse me.

In North America, clarithromycin resistance has been found, at least as of this article, to be about 12.9%. But it's much higher than that in a lot of areas around the country. And this is an article over 2004.

So over the last several years, Che, out of Michigan, published a population cohort in their local area in five-year intervals and found that it was roughly susceptible to clarithromycin at around 80% in every five-year interval up to 2015. So that means that they have resistance of greater than 15% in Michigan, which probably means we're similar around here, though we don't have any published data for Western Pennsylvania. And it's now recommended that any area with an established resistance pattern greater than 15% shouldn't be using triple therapy as first-line for treatment.

This is a busy slide because it's in the guidelines now. But just to shrink it down and kind of go through it-- take-home points-- I've kind of alluded to this. Is there a penicillin allergy, and is there previous macrolide exposure for any reason? That means including a Z-Pak.

So that's probably responsible for a lot of the development of clarithromycin resistance in this country. Z-Paks have been handed out like candy. But--

AUDIENCE: Did they put a time frame on that exposure? Like, if you had a Z-Pak five years ago-- yeah.

KENNETH FASANELLA: OK. So that's one of the important questions you need to ask your patient. Have you ever had a Z-Pak? OK, you're not getting triple therapy. And it breaks it down whether or not you have penicillin allergy and previous macrolide exposure. So no, no; no, yes; yes, yes-- and these are your different options.

So bismuth quadruple, concomitant, clarithromycin triple therapy with amoxicillin-- so what is concomitant? That's basically triple therapy plus Flagyl. Sequential therapy, which is going to be a PPI and amoxicillin, followed by a PPI, amoxicillin, [INAUDIBLE]-- there's all kinds of

regimens now.

Levofloxacin triple therapy and levofloxacin sequential are now first-line therapies. So I suggest you guys go out and kind of peruse the guidelines next time you have a patient that needs to be treated, because they're easily Google-able. And they're available as a PDF, even on your iPhone if you're outside of the network.

And also, the up-to-date chapter reflects all that as well. So it's a really nicely done chapter that is, in fact, up to date. So go ahead and use that. But it does reflect the newest data that has been put out in our guidelines, as of January.

And salvage treatment is also reviewed there. So you can kind of go down these algorithms based on whether or not your patient has a quinolone allergy or not and whether or not they have a penicillin allergy, and follow it through to whether or not it's recommended to just put them on bismuth quadruple. That's going to be based on whether or not they previously got bismuth quadrupole.

You're going to see rifabutin triple therapy now as one of the salvage therapies, which is not something that we had even heard of in our clinical practice before the last few years. So keep in mind.

And so I'll ask a couple of questions that I think I used to like to put throughout the talk. But since this is being recorded, I saved them for the end. So all of the following are associated with duodenal ulcers except? Exactly.

Which of the following has not been associated with chronic proton pump inhibition? Good. And a little case vignette-- 61-year-old man with a history of CAD with a remote, non-drug-eluting stent, in the history of RA has a bleeding gastric ulcer while on ibuprofen. Sounds pretty real world.

After he undergoes endoscopic haemostasis, all of the following are correct, except? This is not such an easy one, so we'll kind of go through this. This is appropriate-- one or the other. Notice I put "or."

Check fecal antigen. That's a good thing to do. Maintain in observation for 72 hours-- yes.

AUDIENCE: [INAUDIBLE]

KENNETH FASANELLA: Not necessarily, no. And this is the thing that I want to try to trip you up with. Patient should not be sent home on low-dose ibuprofen. If you go through the algorithm where we talked about risk factors, he has greater than two risk factors for developing an ulcer. And he's currently admitted with one of them. So ultimately, these patients should not be on NSAIDs at all.

And with that, I'll conclude my talk. If you have any questions, I'll be happy to try to answer them.

AUDIENCE: It sounds like we're going to be testing everybody for H. pylori-- anybody who's on aspirin, anybody who's [INAUDIBLE].

KENNETH FASANELLA: It's controversial. There's a few things they left out, like, for example, they said, we're not ready at this point to recommend treatment for people, for example, that have inflammatory polyps in their stomach. There's just a lack of data for a few indications that may evolve into the next set of guidelines.

But yeah, for the most part, anybody coming in with dyspepsia symptoms, they're recommending. They're not recommending it for GERD. So that's another subset of patients they're not recommending H. pylori, because it's controversial.

There's a fair number of people who may be in the hypersecretory state of antral-predominant gastritis that would respond to H. pylori treatment in the setting of GERD. There's also a fair number of people that may have redeveloped their ability to produce more acid if they're in more late life stage of GERD.

And it's been found that, interestingly, prevalence of H. pylori or presence of H. pylori gastritis actually has reduced Barrett's esophagus, at least in association studies-- cross-sectional analysis. And again, that's probably because a lot of the people that were tested were older and had no longer antral-predominant gastritis, but rather the somewhat protective state of lower acid secretion in gastritis.

So the jury's out a little bit. But definitely a lot more people are getting tested. Iron deficiency anemia is now one of the indications. Yeah. Interestingly, in people who haven't been found to have any other source of iron deficiency anemia, including younger people, H. pylori has been found to reduce your iron absorption. And people have responded to eradication.

So again, it's a heterogeneous disease, as we discussed. It's going to be somewhat difficult to predict how people are going to respond. And that may be based on whether or not they have

early infection versus late infection.

But now it's in the guidelines. Iron deficiency anemia-- test for H. pylori.

AUDIENCE: It's almost like you need an endoscopy. There's probably a reason [INAUDIBLE] without a biopsy for H. pylori.

KENNETH FASANELLA: Well, if you're doing an endoscopy to investigate GERD and you don't see any gastritis, that's not an indication to test. But if you're doing an endoscopy for dyspepsia, you should be doing biopsies for H. pylori, based on 2017 guidelines. So something to keep in mind.

AUDIENCE: Or even iron deficiency anemia now, we should be grabbing gastric biopsies [INAUDIBLE].

KENNETH FASANELLA: Apparently so.

[INTERPOSING VOICES]

If they already have an indication for endoscopy, yes. If they don't, then there's a lot of patients that we probably should be testing and treating without necessarily having to refer for endoscopy. And that's something to keep in mind for your clinics. Any other questions?

AUDIENCE: [INAUDIBLE]

KENNETH FASANELLA: Histology is one of the methods by which we diagnose it on the inpatient setting, yes. Are they doing stool fecal antigens inpatient?

AUDIENCE: Yes.

AUDIENCE: Yeah, they took serologies out.

KENNETH FASANELLA: I know they took the serologies out. I've noticed that in the last couple times I've done inpatient service. OK. All right. Thank you, guys.