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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Decreased Antibiotic Resistance & Overcoming the Risk of Helicobacter Pylori

Dr. Buch:
Decreased resistance to antibiotics has adversely affected our ability to eradicate Helicobacter pylori. So how can we overcome this growing threat to our patients? This is *GI Insights* on ReachMD, and I'm your host, Dr. Peter Buch. Here to guide us through this topic is Dr. Cynthia Sears, who is a professor of medicine at the Johns Hopkins University School of Medicine, and a professor of microbiology and immunology at the Bloomberg School of Public Health. Welcome to the program, Dr. Sears.

Dr. Sears:
Thank you Dr. Buch. It's really a pleasure to be here. Thank you for inviting me.

Dr. Buch:
It's a pleasure to have you. Let's dive right in. What are the pros and the cons for each test of Helicobacter?

Dr. Sears:
Well, typically, there are three possibilities. One is the urea breath test. The second is the stool antigen test, and the third, of course, is a stomach biopsy. Each are pretty good, but they do have pros and cons. So the urea breath test is certainly not available in all hospitals. It requires specialized equipment, and it requires a radioactive carbon on the on the urea in order to do the breath test. So, a little bit cumbersome but probably considered the gold standard for the field. The stool antigen test, far and away, is the easiest test that just detects an antigen of the H. pylori in the stool, so that it detects both live and dead organisms as a possibility, but most of the time when people have active symptoms, we assume it's detecting live bacteria. And like any lab test, it's very sensitive, but it's not perfect. And then biopsy, of course, requires a procedure. So that is most cumbersome, most expensive. But if you do have to have an endoscopy and a biopsy is done, the tests that are done on the biopsy, either histology typically, or a rapid urease test are effective in making the diagnosis. So, bottom line, they're all good ways to diagnose H. pylori. The simplest and most available is the stool antigen test.

Dr. Buch:
Dr. Sears, some of our audience members might be wondering about the serum test. Could you address that for them, please?

Dr. Sears:
So, serology is not a way to make the diagnosis of active Helicobacter pylori. It's a great epidemiological tool. It's used in mass treatment campaigns in Asia as a way of identifying those who are exposed, and then treating them. But it does not tell you that there's active infection, so we strongly discourage using that as a diagnostic method.

Dr. Buch:
The treatment of Helicobacter is empiric, so how do we maximize this treatment?

Dr. Sears:
Yes, you know, a Helicobacter pylori, despite the fact it infects over half the individuals on the globe, is a difficult bacterium. It's one for which we tend not to have regional or even local antibiotic resistance patterns. So you're absolutely right, we're typically guessing a little bit, or using averages based on what we know. So I always say there's rules of the road. The very first thing the clinician needs to do is to assess the patient's antibiotic exposure history, particularly to the drugs levofloxacin, metronidazole, and clarithromycin. In the United States, we pretty much assume that clarithromycin resistance is too high, because of how much we've used that drug in this country, that triple therapy based on clarithromycin is likely not to be effective, and right behind that is levofloxacin. And the issue with both of those drugs is a single base mutation is sufficient to make an organism resistant to those drugs. So prior exposure, even if it's decades earlier, has been shown to correlate with current antibiotic resistance. So first thing, figure out what the patient's been exposed to. The

second thing is to talk to the patient about adherence. These are not easy regimens to take in general, so discussing with the patient in detail the regimen, what's required, how much communication there should be is really an important feature. Adherence here is every bit as important as, say, in HIV therapy. You know, where it's each pill every day. So you really want to nurse people through the entire regimen so they take all the drugs. The other point I always think about is the dose of the antisecretory agent, so the PPI that will be used. We're tilting towards increased doses of these, particularly in a place like the United States, where many of us may be rapid metabolizers of this class of drugs, and so for the antibiotics to work in the stomach, you've got to get that pH up in the stomach, and that's dependent on the PPI delivery to the stomach and its duration of action. And those, I think, are key points. The last thing is you really have to get the patient set up to accept that they're going to take the drugs for a full two weeks.

Dr. Buch:
Can you just discuss a little bit about the potential for metronidazole resistance in the country?

Dr. Sears:
Yeah, metronidazole resistance is creeping up though a difference between clarithromycin, levofloxacin versus metronidazole is that in the case of metronidazole, it appears that if we use higher doses of the drug, that we can overcome that resistance, at least in some patients. Now, metronidazole is not the easiest antibiotic to take. It's probably most people know, there's an Antabuse or disulfiram reaction, so you can't drink any alcohol while you're taking metronidazole. And it can leave a metallic taste in your mouth and will make some people nauseous. So higher doses is definitely harder to take, but they do appear to overcome that resistance in many patients.

Dr. Buch:
For those of you just joining us, this is *GI Insights* on ReachMD. I'm Dr. Peter Buch, and joining me is Dr. Cynthia Sears, who is discussing Helicobacter pylori. So, when we're talking about Helicobacter pylori and this is something you alluded to previously, how do we overcome pill burden with your patients?

Dr. Sears:
Well, that's a tough one. The only simple way perhaps we have is to use some of the combination pills that are available. Now, even in that situation you're usually talking about taking three to four capsules, three to four times a day, so it's not exactly a low pill burden. The combination pills tend to be more expensive so cost can be decreased by simply prescribing the individual medications.

Dr. Buch:
And also the way that it's dispensed. Is it not dispensed for ten days of use rather than fourteen?

Dr. Sears:
Yeah, that's a good point. We really are tilt you know, a lot of the recommendations still say ten to fourteen days, but I think in general, the field is tilting towards fourteen to just try to get those cures.

Dr. Buch:
Thank you. So let's move on to this one. It's the new kid on the block. Can you discuss when to use a new medication that includes rifabutin, omeprazole and amoxicillin?

Dr. Sears:
Yeah, so you're absolutely right, new kid on the block. I don't know that I know the answer to your question. I think the field has not settled out on this. Certainly the data that was published in the annals about a year ago now is very encouraging. And it was done at multiple sites, I think 55 sites across the United States. Again, so a broad distribution, that's encouraging. And the outcomes were strong, and it was overall about, in excess of 80% responded to, the rifabutin, omeprazole, amoxicillin PPI combination versus a lower percent. It was compared to just amoxicillin and omeprazole, so the high-dose dual type of therapy which had a lower response rate, around 60%. If it was if you looked at those who were adherent it did push it up towards 90%, and that's typically where we're aiming. We'd love to see at least 90% of patients respond to the therapy.

Despite all those positives, I think you still have to say it was only a couple hundred patients. It was just over 200 in each arm of the study, and I think we're still early in the evolution of this drug. It was encouraging that they did not see or detect any rifabutin resistance during, either at the time, I guess it was mostly at the time the patients entered, they had an endoscopy and biopsy, and cultures. However, there is concern about the evolution of rifabutin resistance, if this is used extensively. And that has importance, because this particular drug is important in the treatment of Mycobacterial infections including tuberculosis. In addition, there is this rare complication affecting the spinal cord that has been reported. It did not occur in the doses that are included in these capsules are considered relatively low.

So, you know, encouraging study. May be helpful. I think we haven't seen it compared in our population's data, quadruple therapy in particular, which is probably more time-honored tested in the United States, but not an easy regimen to take either. So, I've heard some

comments from physicians that they're not seeing the types of responses that they hoped for, so I think the clinicians just need to be alert. I'm not discouraging use, I just think we have to have our eyes wide open and see where the data takes us over time. I'll just add one more thing, the guidelines for H. pylori therapy, the most recent ones really date to about 2017. Two at least are recommending using this as a salvage therapy after there've been other previous courses. Of course, that recommendation antedates the annals paper that was published. The American College of Gastroenterology is more open to the use of this particular combination.

Dr. Buch:
That brings a phrase to mind from one of my mentors from many years ago. Never, when it comes to a new medication, never be the first, and never be the last to use a new medication, and I've always adhered to that philosophy.

Dr. Sears:
I just add that in the world of infectious disease and antimicrobial resistance, we don't have a drug that resistance has not emerged to over time, you know. So we've been learning this very hard lesson about being careful with important medications in the therapy of patients.

Dr. Buch:
Thank you. And finally, why aren't we doing better with retesting after H. pylori treatment?

Dr. Sears:
Yes, so I would emphasize to everyone that this is standard of care. So if you treat someone for H. pylori infection, you want to test whether or not a cure has occurred. And one of the obstacles for physicians is that that testing should occur at least four weeks, and more ideally later, around eight weeks, perhaps, so to ascertain whether or not you have succeeded. And so why do you have to delay? Well, these drugs, and particularly these combinations knock the bug way back, but in order to detect it by our tests, we have to let the organism grow back. And so, if you have failed, you need to give it enough time that the organism can multiply up enough that our diagnostic test has sufficient sensitivity to detect it. So why are we failing? Well, it's probably two-pronged. Lack of education perhaps. A lack of helping people understand how important this is to do, so you understand whether or not you succeeded in treating that patient. And then the second is just operational, I think. You know, all of us forget things that we have to do if we have to wait a couple months. So I think we need to improve, you know, our management in the sense of chart reminders, or something to help us all remember that we need to circle back and get that test.

Dr. Buch:
This has been a incredibly useful conversation on the growing threat to our GI patients of Helicobacter. I want to thank Dr. Cynthia Sears for sharing her insights. Dr. Sears, it was great speaking with you today.

Dr. Sears:
Thank you so much and I wish everyone well.

Dr. Buch:
For ReachMD, this is Dr. Peter Buch. To access this episode as well as others from the series, visit ReachMD.com/GIInsights, where you can Be Part of the Knowledge. Thanks for listening, and see you next time.