Speaker 1:

Hey there. Welcome back to another episode of ENT in a nutshell. Today, I'm joined by Dr. Garret Choby and we will be discussing AERD. Dr. Choby, thanks so much for being here.

Dr. Garret Choby:

Thanks for having me. It's great to be here.

Speaker 1:

And to start, I just want to say chronic rhinosinusitis is a big topic and we'll be focusing mainly on AERD, which you'll be explaining in more detail later. But, other episodes will include other iterations of how we address chronic rhinosinusitis. But to get started, why don't you tell us a little bit about how patients with AERD present to clinic?

Dr. Garret Choby:

Yeah. Patients with AERD are certainly an interesting patient cohort. They're classically thought of as some of the most difficult to treat patients with chronic rhinosinusitis. One of the interesting aspects about them is that they classically present later in life than the average chronic sinusitis patient. Most commonly, they don't present until the third or fourth decade of life. And there's a fairly typical pattern which they present. So most patients first develop some sort of nasal symptoms, whether that's congestion, rhinorrhea, or otherwise, a few years later on average they'll develop asthma, and then lastly, many times several years later is their first reaction to an aspirin or NSAID product. So it's a fairly interesting, typical pattern of the way they present.

Speaker 1:

Yeah. And there's a diagnostic criteria or maybe a triad that's described. What is that?

Dr. Garret Choby:

So classically, this disease was referred to as Samter's triad, but of course, more recently, as some of those nomenclature has gone away, it's now referred to as AERD or aspirin exacerbated respiratory disease. And it's this classic triad of symptoms. So the first one is nasal polyposis, the second is asthma, and the third one is a reactivity to aspirin or NSAID products. And it should be known this is not an allergy, even though it's commonly referred to as an allergy to aspirin, but it's simply a reaction to those products.

Speaker 1:

And what's typically the overlap between CRS and asthma and AERD? What is... What's the difference and how are they related?

Dr. Garret Choby:

So if you look closely, you end up seeing this aspirin sensitivity probably more often than you think. There's been a number of numbers quoted out there, but in folks who have both nasal polyps and asthma, approximately 40% of them will also have a sensitivity to aspirin. There's been a number of quotes and numbers quoted about the general chronic rhinosinusitis population, but in general, somewhere about five to 10% of those probably have some form of AERD amongst general CRS patients.

Speaker 1:

So when you see a patient in clinic, we kind of discussed the symptoms that you'll see and now I want to dive into pathophysiology. This is complex and not entirely understood, but what do we know about AERD and what causes it?

Dr. Garret Choby:

It's a really disease. The short answer is we, we don't know exactly what causes it. There's a couple of interesting factors that are more common in AERD patients. First of all, females are twice as likely as males, maybe there would be some sort of a gender component to it, if you will. There's also a small association with both obesity and smoking. So maybe those things are playing a role. The current thought is that it may be an epigenetic phenomenon. So not something you're born with, but something that has altered or methylated your genetics over time and things have changed. The bottom line is, it's really an acquired metabolic condition, and it has to do with the arachidonic acid pathway.

Speaker 1:

Uh-uh (negative).

Dr. Garret Choby:

Bringing back bad memories.

Speaker 1:

You mentioned the arachidonic acid pathway for our listeners. Can you try to paint a picture in our heads? What the arachidonic acid pathway is and how it pertains to AERD and what... The basics of what we should know?

Dr. Garret Choby:

Yeah, I'll do my best to paint a bit of a word picture here to give the listeners an idea. So arachidonic acid is something that produced in our cells and it either goes one of two ways. The first branch point is towards the prostaglandin pathway and that is usually enacted by cyclooxygenase that's COX-1 or COX-2. The second way is towards the leukotriene pathway and the enzyme there is 5-lipoxygenase and those enzymes will come into a role later. Prostaglandin in some ways, especially prostaglandin E2 is an anti-inflammatory prostaglandin that diminishes inflammation. Whereas the majority of leukotrienes are pro-inflammatory and cause increased inflammation, which of course contributes to this disease process.

Speaker 1:

And it sounds like the leukotrienes are going to be more active in this process compared to the other side of the pathway.

Dr. Garret Choby:

That's right. So there's a number of leukotrienes out there and they are processed. The ones we really care about are things called cysteinyl leukotrienes and a bit later on the talk today, when we talk about some of the markers of the disease, we'll discuss that as far as biomarkers go.

Speaker 1:

And one of the things I like to talk about with pathophysiology is, what happens if a patient shows up with AERD and they don't want to be treated or we don't treat it? What are the complications involved?

Dr. Garret Choby:

So for the most part, these patients have very debilitating symptoms and that's in regards to both the nasal polyposis, as well as the asthma. So largely it's a quality of life issue. However, if these patients are completely untreated, they will likely end up in the emergency room multiple times for asthma exacerbations.

Speaker 1:

And when you consider these patients, what else is on the differential diagnosis?

Dr. Garret Choby:

So a lot of things can be. Classically, these patients may be treated as routine nasal polyp patients for many years. Certainly other things like allergic fungal sinusitis can be a differential diagnosis, especially for those folks who are in the South or Southwest, and Churg-Strauss disease or EGPA is also something that can be considered on the differential for these patients.

Speaker 1:

So someone comes to your clinic, they have this triad of asthma, nasal polyposis, and maybe they can recognize an aspirin sensitivity. What's your workup for these folks?

Dr. Garret Choby:

So classically, the workup consists of a number of things as they're coming to a rhinologist or ENT office. The vast majority will get, or have come with a sinus CT scan. These scans are usually quite dramatic and show complete pansinusitis and polyposis throughout. We also do usually get some blood work. We've typically focused on a CBC with differential, mostly looking for the eosinophil level as most of these patients do have eosinophilia. We often also get an IgE level as well. And then lastly, if this is a strong disease in the differential diagnosis at our institution and many others, we will also get a marker called a urine leukotriene E4 level, and this can be a specific marker of this disease process. It can be really helpful when identifying aspirin tolerant patients from our AERD patients.

Speaker 1:

So when you work these folks up, sometimes we talk about an official diagnosis. Is there one that applies here that you can do a test or find out exactly that they have AERD?

Dr. Garret Choby:

As opposed to many things like rheumatologic diseases, where you need things like, three major factors and two minor factors. It's not quite so specific with this disease process. Now, you really need to have all three of those things if at all possible. So the nasal polyposis, the asthma, then some sort of history of reaction to the aspirin products. However, if folks don't have a true history of that reaction or perhaps are avoiding aspirin, because they've been told that in the past, an elevated urine leukotriene E4 level is also a pretty sensitive marker for that. If they have both polyposis and asthma. Now, as opposed to classic CRS diagnosis with things like 12 weeks of symptoms and objective findings, it's a little more specific than that. The gold standard has classically been an aspirin challenge where either a lysine nasal

spray or aspirin to be given to the patient, and they've been checked for reaction. We do that less frequently now, unless they're going to undergo a postoperative aspirin desensitization.

Speaker 1:

So, once you've made this official diagnosis... There are lots of different types of treatments that we'll discuss, but why don't you start with the medical management for these patients?

Dr. Garret Choby:

So the first step in medical management is avoidance of aspirin or NSAID products. Again specifically, this is the Cox-1 inhibitors because when these patients take these medications, all of that arachidonic acid pathway subsequently gets shunted towards the leukotrienes, which is the pro-inflammatory thing. So the first step in medical management is avoidance of aspirin and NASID products. The second one is topical steroids. A number of options are out there. Simple steroid sprays are probably not the most effective thing for this population like fluticasone. We like things like budesonide or mometasone added to saline rinses, oral steroids also play a significant role here and are considered a part of appropriate medical management, and then of course managing their asthma with things like inhaled corticosteroids are also important for general medical management of the disease.

Speaker 1:

And when you talk about oral steroids, is that ongoing or do you do burst and tapers every now and then?

Dr. Garret Choby:

Many of these patients have been on a number of courses of oral steroids before they come to see you because this is a very refractory disease. We typically will use oral or systemic steroids for short term symptom control. So a number of verses are out there. We typically do a burst and taper with about 40mg of prednisone over 12 days. But the benefit of this is probably about eight to 10 weeks in total. So it is, it is a short-term benefit.

Speaker 1:

Sure. So when we look at options for more long-term benefit, we... I imagine start talking about surgery. How do you decide when to operate? And what's your approach to operative considerations for these patients?

Dr. Garret Choby:

So the vast majority of patients will end up undergoing endoscopic sinus surgery. And many of them have already undergone many previous surgeries. At least in one study that has been shown that AERD patients on average undergo 10 times more surgery than a non-AERD patient. So it is significant. The goal of surgery in these cases is complete removal of all polyps and complete opening of all sinuses. This is what would be classically big hole surgery. So large antrostomies, complete ethmoidectomies skeletonizing everything, sphenoidotomies taken up to the skull base and then large frontal sinus openings. We do have a low threshold in this population to do advanced frontal sinus procedures like Draf IIb or Draf III procedures. I personally don't do those very often as a primary surgical option, but as the majority of patients are getting a revision surgery, we will jump to that pretty quickly in many cases. Mostly to allow for more effective delivery of topical therapy.

Speaker 1:

And does surgery do the trick in patients? Is it the final stop for them?

Dr. Garret Choby:

In most cases, it's not. As with most CRS patients, surgery is not a cure for them. And that is certainly true with AERD patients and most patients will also need long-term ongoing medical therapy, including topical steroids, as well as some more advanced therapies in many cases.

Speaker 1:

So after you operate on these patients, open up all the sinuses widely, what is the next step for these patients to try to control this disease?

Dr. Garret Choby:

So for many of these patients, especially those who have undergone multiple previous surgeries and have been shown to have refractory disease, we'll consider one of two options for long-term medical management. The first is aspirin desensitization, and the second one is a bit newer and that's biologic therapy.

Speaker 1:

And aspirin desensitization, from my understanding, is usually performed by an allergist, who you work with. What does aspirin desensitization look like? It sounds kind of crazy to give aspirin to a patient who has a sensitivity to aspirin.

Dr. Garret Choby:

Yeah, it's a great question. Again, it's not an allergy, so it's not the same as giving immunotherapy or allergy shots, but in practicality we thought about along lines as well. It's classically done an ICU setting because you worry about setting these patients into a very bad asthma attack, but in our institution in many others as well, it's now done as a two-day long process in the office. We'll typically do this about two to three weeks following their surgery, and they will get initial [inaudible 00:12:12] in the office. Usually with a lysine nasal spray followed by progressive, plus we higher doses of ingested steroids over the two day period until they get to about 650mg b.i.d. as their initial desensitization dose.

Speaker 1:

Do they continue that dose long-term?

Dr. Garret Choby:

In general, that's continued for a long-term therapy, lifelong or something along those lines. However, there are some challenges with long-term aspirin therapy, including some side effects that can occur.

Speaker 1:

Tell me more.

Dr. Garret Choby:

Most commonly if there's an issue it's either due to gastritis. So reflux or gastritis symptoms from high dose aspirin or in some cases because they need another surgery or something along those lines, they may have to stop their aspirin therapy. In my patients, if they've been desensitized, I'm willing to operate on a baby aspirin of 81mg, and it can quickly be brought back up to speed. But for other surgeries like cranial surgery or orthopedic surgery it may need to be stopped completely. In which case you need a full desensitization later on, which can be a challenge for them.

Speaker 1:

We talked about aspirin desensitization, but it sounded like you were also going to mention another type of medical therapy following surgery. What else is coming down the pipe?

Dr. Garret Choby:

So the new kids on the block, if you will, are biologic therapy. And these are really targeted therapies that are evolving our treatment of both polyposis patients, as well as AERD patients. The first one's been out there for a while, and that is zileuton in that is a 5-lipooxygenase inhibitor. So directly works in that leukotriene pathway to inhibit its production along the way. The ones that are newer and have been used more and more recently are dupilumab, which is an IL-4 inhibitor, as well as things like mepolizumab, which is an anti-IL-5 inhibitor. And these are really targeting mostly the eosinophil pathways in order to minimize their production and their ability to produce inflammation this state.

Speaker 1:

And what are some of the challenges that come with these new biologic therapies?

Dr. Garret Choby:

There are a number of challenges, especially for things like mepolizumab or benralizumab. They're classically indicated mostly for refractory asthma and there's a lot of hoops to jump through from an insurance standpoint and getting them covered and it can be quite challenging. Dupilumab is the first one that was approved specifically for nasal polyposis and in general, is much easier to get covered. The main challenge is the expense of these drugs. On average, their cost per year is 35 to 40,000. And from all the preliminary data, once the medication has stopped, all symptoms returned. So as far as we're aware, this would need to be a lifelong medical therapy at very high medical expense.

Speaker 1:

So if these patients receive the treatment that is recommended, how do they do from a long-term outcome standpoint?

Dr. Garret Choby:

So we found that our patient population, as well as many other centers with good, quote-unquote, "big hole" surgery followed by good topical medical therapy like budesonide or mometazone, paired with an aspirin desensitization or a biologic therapy. Many of these patients have very good long-term outcomes, and that's been shown in multiple studies. Don't get me wrong, it's still a difficult refractory disease to treat, but outcome seem to be much better with this current regimen than previously published studies.

Speaker 1:

And to be clear, this is a chronic disease, and sometimes that has to be really communicated to patients.

Dr. Garret Choby:

Correct. I think many patients, when they think about surgical therapy especially, think that it's like a knee joint surgery. Take out the old joint, put in the new joint, dust off your hands and see again in 20 years. It's important to communicate well with patients that this is a surgery, for instance, is a treatment tool in an ongoing paradigm of treatment for their chronic long-term, longstanding disease process.

Speaker 1:

Sure. I'll do a summary here in a sec, but is there anything else that you think is worth adding or anything we didn't talk about?

Dr. Garret Choby:

I think one of the things I'll just highlight again, is that many patients who come to see you with polyposis and asthma may not have yet had their first aspirin reactivity yet. So even if you ask them that question, they may say, I haven't taken aspirin in a while, or I haven't had a reaction to it. It does not necessarily rule out this disease process. I think it's important to consider that you may benefit from getting a urine leukotriene level in these patients. And that can be really helpful and counseling them as well, that they may get a reaction later on as their disease develops is also important.

Speaker 1:

And one thing that we didn't talk about is, is there a specific level of urine leukotriene at which you become more concerned that they do have AERD?

Dr. Garret Choby:

So in general, at our institution and many others, there's a specific assay that we use. And in that assay levels of less than 104 are considered normal, above 104 considered elevated, but in our institution we've done... We've published some data showing that a cutoff level of 166 is really the definitive cutoff point for AERD patients. It should be noted that if someone is on zileuton therapy, it will be artificially lowered. So to keep that in mind, as well as some of these patients are already on that, but in general terms a level of 166 is considered a relatively pathognomonic for AERD.

Speaker 1:

And now that you've mentioned ongoing therapy for my understanding, if someone's on steroid therapy, that can also throw off eosinophilia when you do blood work.

Dr. Garret Choby:

Great point. It can definitely lower the eosinophil level. We don't quite know for sure the effects on the urine leukotriene E4 level. Some preliminary data shows it's probably not as altered as the eosinophil level, but that remains a point of probably debate.

Speaker 1:

Thanks so much for being here. Just quickly to summarize, AERD is a constellation of symptoms that includes aspirin sensitivity, nasal polyposis, and asthma. These patients present with these symptoms often the third to fourth decade of life, which can be odd for them cause they all of a sudden have

asthma and they hadn't previously. And sometimes they'll present with a history of sinus surgery that hasn't been entirely successful. The cause of this disease is related to a dysregulation of the arachidonic acid metabolism pathway that pushes things more towards the leukotriene side. Workup includes a CT scan of the sinuses, which will likely show pansinusitis and aspirin challenge. And urine leukotrienes can also be helpful in diagnosis. Treatment is multifaceted and includes comprehensive sinus surgery, oral leukotriene antagonists, and 5-lipoxygenase inhibitors can be used. And the new kids on the block, as you said, are biologic therapy, including mepolizumab, dupixent and others, but these are expensive and aren't always able to be used. Aspirin desensitization is also a treatment that can be very successful, but of course is not covered by everyone. Dr. Choby, anything else to add?

Dr. Garret Choby:

The last thing I'll mention is that treating this disease is best done by a multi especially team. Allergists are great partners in treating this disease and help a ton with medical therapy and workup. And then of course our skills are necessary for the sinus surgery as well as ongoing therapy for these patients.

Speaker 1:

Awesome. Thank you so much.

Dr. Garret Choby:

Thank you.

Speaker 1:

As we bring this episode to a close, I will finish with a few questions. I'll ask a question, wait, five or so seconds for you to think or press pause and then give the answer. So the first question is what are the symptoms of AERD more historically known as Samter's triad? These three symptoms that we see in patients with AERD are asthma, nasal polyposis and aspirin sensitivity.

Next question. What is typically used as an elevated urine leukotriene level for patients with AERD? Currently we use a urine leukotriene level of about 166ng/ ml at which levels higher than this or more suggestive of AERD.

And finally, what are the medical treatments for AERD and how do they work? We're looking for five of them. There are several medical therapies for AERD there's montelukast, which is a leukotriene antagonist. There's a zileuton, which is a 5-lipoxygenase inhibitor, there's aspirin in the form of aspirin desensitization, mepolizumab, which is an anti-IL-5, and dupixent, which is an anti-IL-4. Thanks so much for listening and we'll see you next time.