

Dr. Mariam Hanna:

Hello, I'm Dr. Mariam Hanna, and this is *The Allergist*, a show that separates myth from medicine, deciphering allergies and understanding the immune system.

I sat for dinner with a room full of gastroenterologists and allergists, and had the most intriguing conversation about the reluctance for long-term management for patients with EoE, when there's seemingly, amongst gastroenterologists, no reluctance to treat their IBD patients long-term.

So here I was, scratching my head. One causes strictures and bad things like fistulas and cancer, and the other one—well, what about remodeling, everyone? Do we know if everyone is impacted with remodeling? Can you predict to what degree, or do we still not know enough? Will we miss an opportunity for our pediatric patients specifically, 10 to 20 years from now? Are we going to regret this moment?

Then the appetizers came around, and the conversation in the room flipped to elimination diets. How strictly do you eliminate? "I'm just putting them on their way to an anaphylactic food allergy," was my argument. And what about drugs that we have available?

Why are we in 2026 using diets and acting like the Stone Age, dealing with these patients like the patients who come in and tell me about their atopic dermatitis getting better with their elimination diet, when we know better, or when we can address remodeling better?

So I laughed at this dinner. I really enjoyed my meal and the conversation, but honestly, I had more to unpack. I had this desire for this conversation, which is why I am especially excited to have today's guest with us.

Dr. Seema Aceves is Professor of Pediatrics and Medicine at the University of California, San Diego, and Rady Children's Hospital. She directs the Eosinophilic Gastrointestinal Disorders Clinic and leads an NIH and CURED-funded research program focused on the mechanisms and clinical impact of tissue remodeling in eosinophilic esophagitis. She has authored more than 150 publications on EoE and eosinophilic gastrointestinal diseases, including consensus and severity guidelines.

She is also the co-inventor of budesonide oral suspension, which is FDA-approved for the treatment of EoE, a member of the American Society for Clinical Investigation, and holds the UCSD Pediatrics MRD Endowed Chair.

With that, Dr. Aceves, welcome to the podcast!

Dr. Seema Aceves:

Thank you, Mariam. It's a pleasure to be here. Thanks for having me. I'm looking forward to the conversation.

Dr. Mariam Hanna:

I'm looking forward to it as well. It's like part two of my dinner is about to ensue.

On the remodeling side specifically—because this, I think, is what lights my fire as to why aren't we intervening on a lot more of these kids—what's actually happening in the esophagus when EoE persists over time?

Dr. Seema Aceves:

I think this is incredibly clear, especially in adults, because if you don't treat—there were studies as far back as 2013 from Alex Straumann's group showing that if you don't treat, the natural history is to stricture.

It's like airways remodeling. If you don't treat it, it's going to keep wounding and trying to heal, rewounding and trying to heal, and then it's going to form fibrosis, angiogenesis, muscle hyperplasia, and all the things we think about with the airways, except this time it's happening in the esophagus.

The pathogenesis is probably fairly similar. This is an injury to the epithelium, which cries out with things like TSLP and IL-33, bringing in innate and adaptive immune cells, along with eosinophils and mast cells. That sets up this cascade that's really driven through antigen-specific T cells—there's a paucity of data, but that's probably what's happening. These pathogenic effector T cells come in and start up this injury process.

Then it basically becomes a feed-forward loop. The fibrosis gets going, changing the physical property that the structural cell lives on. That changes the fibroblasts, including the regenerative fibroblasts that lay down tissue. It now becomes more predisposed to laying down rigid extracellular matrix—things like aggrecan and osteocalcin, things made by bone and cartilage rather than adipocytes and soft cells. This keeps rolling around and around until you do something to stop that process.

Dr. Mariam Hanna:

Here's the argument: if you're going to make this analogy between preschool asthma and EoE, some preschool asthma remits in early childhood and adolescence. Are we all going to have persistence, or is there a proportion that's going to remit and I could just watch and wait?

Dr. Seema Aceves:

The studies right now show that once you have EoE, even when you're young, it seems not to go away permanently.

It may have a waxing and waning course that we miss because we treat everyone like they've got persistent disease. The problem is there's no surrogate marker, no PFT, and you can't look at the skin like atopic dermatitis. You have to get an endoscopy with a biopsy over and over again, which is really hard financially and psychologically on families and kids. So we treat everyone like they're persistent.

The follow-up studies we have to date do not show that this goes away in most people. 95 to 99% of patients seem to have chronic disease that does not go away. They may have episodes where it's gone for a while, but if you lose them to follow-up, adolescence will come back sometimes with a stricture in place—they've been gone for two years, and now they're having food impactions.

Dr. Mariam Hanna:

Fair enough. Are eosinophil counts a good judge of how things are going?

Dr. Seema Aceves:

That's becoming more and more controversial. The anti-IL-5 studies, including benralizumab, got rid of eosinophils, but didn't get rid of the rest of the disease pathology. It didn't get rid of symptoms, architectural features, or change the transcriptomic profile.

Eosinophils seem to be a good biomarker, but whether they are that disease modifier you're looking for—meaning just because you get rid of eosinophils, you've gotten rid of remodeling—that is far from clear. We are understanding more and more that the eosinophil is only a biomarker and probably not the best endpoint, but the one we have and have fought for to follow, and it's easy to see on histology. It will stick around for a long time.

The more information you can get, the better. If your pathologist will tell you about basal zone hyperplasia or subepithelial fibrosis, every piece of information is really helpful—except for symptoms. Symptoms can be all over the place, and you can't use them as a surrogate marker.

Dr. Mariam Hanna:

That was my next question! If we didn't scope them, could we just follow their symptoms?

Dr. Seema Aceves:

You cannot. There is a huge disconnect, whether you're a child or an adult, between symptoms, inflammation, and the remodeling process.

By the time food impactions start happening and people realize they have dysphagia, you're way behind the 8-ball because there's already stricture in place. Adult data shows that what gastroenterologists call fibrostenotic disease is recalcitrant to most therapies. There's a little bit of data that biologics—in this case, dupilumab is approved for EoE in the US—are showing help with strictured patients. But you can't use symptoms instead.

The good news is that there is something called the Esophageal String Test, available at least in the US. You can probably get it—it's the old Giardia string test. You swallow it and tape it—it's called a string, but it really is like a thread, incredibly thin. I explain this to kids when they say, "I can't swallow a string and leave it there for an hour!" But it's the size of a thread. You tape it to the cheek. It has a little BB in it that weights the dissolvable capsule, which is made of gelatin. You swallow that, the gelatin capsule melts, and the string stays in for an hour. You pull it out and send it off to the company, and they'll give you a yes/no answer with a cutoff for eosinophil markers.

In terms of remodeling, Amanda Muir at CHOP has shown that she can find periostin on this string. So there may be ways to try and gauge remodeling using less invasive things. You really have to find the right GI partner to work with.

Then you've brought me to my favorite soapbox: this is an allergic disease, and allergists need to help take care of this person. We're not going to scope, but there will be string tests or sponges—there will always be something coming down the pipeline that can help us.

We had very preliminary data from skin tape stripping showing that ceramides and sphingolipids are not the same as healthy in kids who have EoE but absolutely no history of eczema. So there may be markers in places we haven't looked at. I have this hypothesis that there's a unified epidermal barrier or something that looks like skin, even though the esophagus embryologically comes from the trachea and lungs. It's a mixed organ, with stratified squamous epithelium like the skin.

My point is that there will be surrogate markers coming down the pipeline that we haven't thought about yet. But this is an allergic disease. We know how to take care of T2 inflammation, we know the consequences of it, we know when to add a biologic (at least in the context of asthma), and we know how IgE-mediated food allergy interacts with EoE. We know that there's a risk with OIT and things like that. So I think this is very much an allergist's disease.

The other thing is someone has to explain this to your patient, right? Someone's got to explain the concept of epithelial barrier dysfunction, which is truly not a concept that is familiar to GI folks—even in the IBD world, they don't think of it as a barrier disease, they think of it as an immune disease. So I think there's a lot of educating.

Dr. Mariam Hanna:

Absolutely. Absolutely. And as an allergist, my interest in EoE started because of immunotherapy, because of exposure therapies that we've started to do, even sublingual immunotherapy to aeroallergens, right? And you're discussing this suddenly. Not all my oral immunotherapy patients undergo a scope. Am I missing some that have no symptoms, because some of EoE has no symptoms? Am I triggering some of that? And then the ones that do have classic symptoms, I have sent for scopes, and I've been scared of what the pathology results look like in those patients, because it's clear disease in those people. Can you comment on that?

Dr. Seema Aceves:

From what we understand today—which is really the tip of the iceberg in terms of the interaction between OIT, especially for foods, and EoE—a recent meta-analysis showed that OIT causes EoE in a small percentage of patients that we're aware of, like in that 4 to 5% range.

A lot of folks, like you know, will stop their OIT because they feel lousy and they don't want to push through it. So they may have stopped because they have EoE, and now we've missed it. Just follow their symptoms and see if the dysphagia or whatever they had is persistent, because for some people it seems like you either unmask the disease or unmask the symptoms enough that the person will complain about the disease.

OIT to foods can definitely trigger EoE. SLIT, I think we don't know nearly as much about. Certainly SLIT to aeroallergens can cause EoE, but I wouldn't say it's common—it's nowhere in the 4 to 5% range. And we don't know if SLIT to foods causes EoE. It really doesn't seem to do that from the literature that I've seen and the talks I've heard about it.

So maybe that is the way to go. If you have someone with IgE-mediated food allergies—that's one risk factor for EoE right there, which you can't get around if you're thinking about OIT or SLIT—if it's a male, if there's any family history of dysphagia, strictures, or dilations, things that make you think, "I wonder if this is the person who might develop EoE," maybe you're going to choose to do a lower dose OIT or just straight SLIT in the hope that you don't invoke these pathogenic effector T cells to the food to which you're trying to desensitize them. Because I suspect that is exactly what happens, right?

You're trying to get rid of IgE-mediated allergy, you want these tolerogenic T cells, but in some people you're probably invoking a pathogenic T cell against that same food, and now it goes to the esophagus and sets up this whole barrier problem.

But I don't think everyone needs a scope. The string is not approved for diagnostics, it's only approved for use in people who you know have EoE and to follow them. But something like an Esophageal String Test is the perfect application. You can get someone to swallow a string for an hour and say, "Yeah, it looks like stone-cold negative, let's just keep going and work our way through it. Let's give you some famotidine, let me try a PPI," which I wouldn't do in an OIT

person that you're going to get a scope for, because you might actually treat it, right? They may be PPI-responsive. So does that answer your question?

Dr. Mariam Hanna:

It does. I mean, the tricky part is that these patients often have to wait to get a scope. Access to endoscopy in pediatrics is actually quite the nightmare, and the wait times are much longer than they are in the adult population. And these patients are often on long-term therapy where we then see them less and less frequently as they get more and more into maintenance.

So I'm often left struggling with these patients that have been started on immunotherapy, have GI symptoms: are we going to discontinue altogether, are we going to do a brief trial of PPI, are we going to reduce their dose and cross our fingers and our toes and hope for something to resolve and then move forward again? What do you do with them?

Dr. Seema Aceves:

So I usually see them when somebody's worried about the question that you're asking, so I kind of come at it at a very different point in their course. But the conversation is going to be shared decision-making, like you do with everything else for your patient, right?

My way of treating these patients is just to treat through their potentially OIT-induced EoE. I'll just give them a topical steroid and I'll say, "If your goal is to get rid of, or at least desensitize to, your IgE-mediated food allergy that is driving anxiety, you're carrying Epi, and your child is becoming more and more afraid to eat, let's just treat your EoE. And let's let you get through your protocol, and then let's call it a day. Once you're on maintenance, let's try and stop your drugs, and then let's take a look and see if it's still there or not."

And so that is what I do when patients really want to get through their OIT. I think it's really important to try and get rid of that IgE-mediated food allergy if that's the family's goal, which it usually is.

Dr. Mariam Hanna:

Okay, but then flip on me to the other side of the conversation about preventing structural disease and strictures and fibrosis. How do you tackle that, or how do you approach the patient that needs that to be thought of as well, both short- and long-term?

Dr. Seema Aceves:

Remember that your stricture risk doubles for every decade of life that goes by. So this is, although it starts early in life, it also is a slow brew. You're probably not going to do anything terrible to sort of the average person in a three- to six-month period of time.

That is one of the problems with EoE: we don't have risk stratification methods, right? We don't know who's going to be at risk for a stricture or the rate at which they're going to get there. And some kids will always have some inflammation left behind, and they will never have a stricture. They'll not even necessarily have a rigid esophagus if you're lucky enough to get an EndoFLIP on them.

So the struggle is real in terms of what you're saying, right? And I think though it is really a conversation with your family: "If this does not go away, I'm willing to try a two-month trial of PPI because I know it's going to take you six months to get to GI. Let's try and treat through this, but then we're going to stop the PPI, and we're going to see if you still have symptoms. And if you do, I'm really going to recommend that you go and have an endoscopy done so that we don't leave this sitting for years and years thinking that we're fine."

At the end of the day, right, you're a consultant in someone else's life, and they'll do what they want. But providing that information is really critical. And again, I think that's why allergists need to be involved in this disease.

We know that even though there's no marker in the blood for T2 inflammation, we know this is a chronic low-grade inflammation of some sort, right? If you have asthma, you have eczema, and you have EoE, you have more than enough surfaces involved that you probably have sort of a systemic T2 type of inflammation going on, whether or not you have an elevated CRP or other markers of systemic inflammation. Your system is revved up to drive T2 inflammation, and so these diseases are going to play off of each other. That's kind of my point: as the allergist, make sure that all the diseases are controlled so you don't necessarily give them that opportunity to play off of one another.

Dr. Mariam Hanna:

Absolutely. I love that "we are consultants on people's lives." That's like me telling people to get rid of cats. Yeah, no, it's the same effect, they'll just get rid of me!

One of the things that we discussed at this dinner is dietary therapy. And I get the consequences of dietary therapy in adults are also very different from pediatrics. So, approaches to dietary therapy, or is this still the Stone Ages that we can't crack out of, like treating their eczema by milk elimination and gluten elimination?

Dr. Seema Aceves:

Right, so I mean, the data shows that milk elimination or 4-food elimination in kids or adults has a 30 to 40% overall response rate, right? So what I tell people is this is not going to work for everybody.

The way I will approach it: say somebody comes to you and they have just rampant EoE, and the family really wants to do an elimination diet. What I do is try and strike a deal, and what I say

is, "Listen, I want to get rid of this disease so we're at ground zero. I also want to do what you want to do for your child—I want to help you get there. I can't promise we're going to get there, but I do want to help you try as best as you can. But please let me get rid of this first, and we'll ask the question backwards. Let me put your child on a topical steroid, get rid of that—because that, especially in little kids, is 70 to 80% effective. It's very unlikely that it's not going to work. So let's do that for three months, make sure it's gone, make sure your child is healthy, eating, feeling good. And then if you really want to do an elimination diet, let's take milk away, stop your drug, and see if it holds the inflammation at bay. And if it does, you can just continue doing that. And if it doesn't—because this disease does come back—if it doesn't, and you want to do a 4-food elimination, we'll do that. And if that still doesn't work, then you have really done your very best, and I don't have a test to tell you what the food is."

So I'm not going to do a bunch of IgE testing. And I do test for milk, wheat, egg, and soy, and I tell the family, "I'm using this information backwards. If you go on a diet and you've got a big positive test, I'm going to bring you here to do an oral food challenge in case you lose your tolerance."

I think again, there's so much education that goes with this disease. My GI doc is in a room, in and out. I'm in there for like an hour! And it just takes a lot of time to explain this to people and to get them to sort of wrap their minds around food allergy, two different ways of mediating it, one playing off of the other, what's the cross-talk, what are the risks and benefits.

So I think Stone Ages, I wouldn't say we're quite that bad. David Hill at CHOP has shown that there are milk-specific T cells, they respond to milk in culture, and they have a certain TCR and a different profile than the other pathogenic effector T cells. So if that type of test actually is commercialized and validated, and then the trial is done that, yes, you have these T cells and I take milk out of your diet and you get better, that's huge! Then you can have a really good conversation with your parents, your families, your patient, and say, "You look like this might actually work for you, let's try it."

Dr. Mariam Hanna:

All right, then I'll stop my Stone Age analogy then, I understand!

You may have answered this earlier in our conversation, but are there any other kind of things coming down the pipeline that is going to help us at better predicting who's that child that's going to go very hard into remodeling and fibrosis and strictures and get more that stenotic type disease versus the one with like low-grade inflammation and will probably squeak by with just a bit of heartburn or something?

Dr. Seema Aceves:

Yeah, the short answer is we don't, but I think we're going to get something, hopefully.

Our lab has been working on different stains, and it does seem like there may be some markers that are different, like at the very outset, like at diagnosis, that at least in children seem to align with the trajectory and sort of multiple features of the trajectory in a moderate way—so that one stain is sort of able to reflect Eos and basal zone hyperplasia and fibrosis and IC scores right from the get-go.

If that is really, really true—our cohort is not big enough to say that it is really, really true, and the paper's not in yet—but I'm hoping, because I'm sure we're not the only people looking at things like this, right? That one day we'll be able to stain a biopsy at diagnosis and go, "You look like the person that I'm going to try five different things before I get to something that works. So maybe I just start you on higher doses of medicines, more medicines, biologic, whatever happens to be available at that time when we're really confident of this."

Or, "You don't have a lot of this marker. You definitely have active EoE, but I think you're going to be easy to treat. Let me give you an elimination diet, or a whiff of a PPI, or a low-dose topical steroid. And then when you're better, the way I think you're going to be, I don't need to scope you again for another couple of years, because I'm really comfortable that you're going to be fine."

And then the opposite—so that buys less scopes for the person who's getting better. The hope would be that it buys less scopes also for the person that's going to be hard to treat, right? Because then you're going to hit hard at the beginning and get it under control, and then say, "All right, it didn't take me six endoscopies to get you to a therapy that actually works for you."

But it's taken time to get there because the disease is new, you need a scope, you need people who want to stain biopsies and look at them over and over again, right? And then on top of it, yeah, it hasn't been around that long. So it just takes time to figure these things out.

But I am hopeful that there will be markers that will help us. I really like EndoFLIP. It's just that you can't do it in everybody, right? But it tells you the rigidity of the esophagus. If you've got a three-year-old with a rigid esophagus, I would recommend being way more aggressive with that three-year-old than the three-year-old who's fine. But again, if you can't get a scope, you may never be able to get a FLIP.

Dr. Mariam Hanna:

Fair enough. Cautious optimism for the future is what I'm calling that!

All right, time to wrap up and ask today's allergist, Dr. Seema Aceves, for her top three key messages to impart to patients and physicians on today's topic, esophageal remodeling. Dr. Aceves, over to you.

Dr. Seema Aceves:

Okay. Well, number one: EoE is a Type 2 inflammatory disease, and as the allergist, please get involved and help take care of these folks. They really do need us, and somebody who understands the consequences of long-term, chronic T2 inflammation under or not under control.

Number two: remember that this is a clinicopathologic diagnosis. The onus is on the clinician to make the diagnosis and treat EoE, and to treat it chronically—don't lose your person to follow-up. So that's the other important point: remember that not all Eos in the esophagus equate to EoE.

And then number three: I think early interventions can be disease-modifying. This disease, like asthma, starts early. And when I say early intervention, it can still be an adult that's only seeming to have had disease for a couple of years, as opposed to coming in with a stricture having had disease for a long time. So early intervention, I think, probably makes a difference in the natural history of this disease. So please, ask the question, and then do something about it, and then follow up on the answer.

Dr. Mariam Hanna:

Perfect. Thank you, Dr. Aceves, for joining us on today's episode of *The Allergist*.

Dr. Seema Aceves:

My pleasure. Thank you.

Dr. Mariam Hanna:

This podcast is brought to you by the Canadian Society of Allergy and Clinical Immunology and produced in collaboration with Podcraft Productions. The opinions shared by our guests are their own and do not necessarily reflect the views of the CSACI. Please remember that this podcast is for informational purposes only and does not provide any individualized medical advice.

For show notes and relevant links from today's discussion, visit csaci.ca. While you're there, check out the "Find an Allergist" tool to connect with a specialist near you. If you enjoyed this episode, we'd love your support: subscribe wherever you get your podcasts, leave a review, and a five-star rating—it helps others find the show.

And remember: epithelial barrier dysfunction is on many different levels, and FLIPs would be wonderful to have! Thanks for listening. Sincerely, *The Allergist*.