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 didn't exactly graduate last year, and yet in such a short span, our recommendations in management in some allergic diseases, here we go again, where I trained and gave the correct responses on my role at college exams, have changed. I'm crushed. It makes me feel really old, just like my white hairs these days. Case in point, an eight-year-old boy came in, recurrent throat symptoms, abdominal pain and avoiding milk because as he repeatedly had told his mother, it did not sit well in his stomach. No other features of concern, no hives, no angioedema, no respiratory symptoms. And for me, it said "Rule out milk allergy." Skin test was negative. But the weird thing about this kid was he also had this weird behavior around food in general. This kid liked sauces. He intensely loved ketchup. He needed a dip for everything. Water or a drink was always at the table and a ridiculously slow chewer. So a young keen allergist.
Long story short, I thought of eosinophilic esophagitis, sent off a referral to my neighborhood gastroenterologist, told them, "Skin test doesn't help guide management. Let's try a trial off your one trigger food," that being milk. Fast-forward to today, so he definitely has EoE, as really that good from the history. Thankfully, has pathologically had remission and now not on any medications. Strictly avoids dairy in all forms. Positive skin testing to milk these days, serum-specific IgE to milk that will raise your eyebrows. The unintended consequences of avoidance, again, glaringly apparent. When we see each other, we don't say it. And the family's happy. His eating behaviors are all reversed and he feels great. But for me, I feel like I'm playing allergic disease whack-a-mole in my specialty.
Today, we're going to review eosinophilic esophagitis, a young disease with many things for us to learn with our esteemed colleague, Dr. Edmond Chan. Dr. Edmond Chan is a pediatric allergist at BC Children's Hospital. He's a clinical professor and clinical investigator at the University of British Columbia and serves on Food Allergy Canada's advisory board, as well as co-leads the EoE program right inside BC Children's Hospital. His primary interest is food allergy, but if you really talk to him, his secondary interest is eosinophilic esophagitis. Dr. Chan, thank you so much for taking the time out of your busy schedule to join us and welcome to the podcast.

Dr. Edmond Chan:
Thank you for inviting me, Dr. Hannah. Pleasure.

Dr. Mariam Hanna:
Okay, so I have to provide context, first of all, to today's discussion. Our speaker with an incredibly busy schedule agreed to our conversation within under 24 hours. And may I add, he's on holiday. But this is how passionate he truly is about eosinophilic esophagitis. So let's get going. What is the currently accepted definition for eosinophilic esophagitis?

Dr. Edmond Chan:
So eosinophilic esophagitis, or abbreviated EoE, is a chronic allergic inflammatory disorder that if left untreated, has the risk of evolving into stricture. And the inflammation involves many cells beyond eosinophils. So there's other variables like barrier defects, other inflammatory cells and

mediators such as T-cells. And so that's the sort of pathophysiology behind it. But the definition also includes what patients experience. So the typical symptoms of difficulty swallowing or food getting stuck or food impaction plus mandatory is esophageal biopsy. So endoscopy and biopsy with the biopsy showing 15 or more eosinophils per high-powered field. I might add that included with this definition as an allergist, I typically describe how EoE patients often have a background of allergic conditions, to the extent where now the literature describes EoE as one of the steps of the quote, unquote "allergic march". So that's where children go through atopic dermatitis, food allergy, asthma, allergic rhinitis, and you may as well add EoE to that list nowadays.

Dr. Mariam Hanna:
I completely agree with you. This landscape's changed a lot in this past decade. For you, as someone with a keen interest in EoE, what are the big changes that have happened in this disease landscape, let's say over this past decade? What really sticks out for you?

Dr. Edmond Chan:
Yeah, that's a good timeframe to think about because we created our EoE clinic here at BC Children's Hospital in around 2011. So it's been just over a decade. And even in that sort of relatively short period of time, there's been quite big changes. So the thing as an allergist that has impacted my practice the most is this evolving consensus in literature that allergy testing is not accurate for uncovering food triggers of EoE, which has led to an emphasis on other ways that allergists can contribute to EoE management, which to this day, remains a multidisciplinary approach.
The other change, the second change that's been quite big is that proton pump inhibitors, PPIs, are no longer a mandatory diagnostic criterion for EoE. So it used to be, in the old days, we had to have a patient go on a trial of PPI and only if they failed that trial did they have EoE. These days, it's a therapeutic option only, not mandatory. Another big change is increasing acceptance of allowing patients to start or continue oral or sublingual food immunotherapy or oral allergen sublingual immunotherapy despite having EoE, and this is quite often center specific, but in general, there's emerging acceptance of that. And the other big change is Health Canada-approved medications. So for the longest time, there were no licensed medications for this disease, but now we have, for example, a Health Canada-approved oral dispersible budesonide tablet, and a biologic called dupilumab.

Dr. Mariam Hanna:
You have given me so much fuel for the next 20 minutes, so be careful what you've just provided me with here. So let's first do the medical management side. So you talked about oral dispersible tablets for budesonide. You talked about proton pump inhibitors that have changed and we're going to touch on biologics, but let's leave that one off for a second. So is PPI responsive reflux EoE or is it reflux, or what has changed with proton pump inhibitors in the medical management in making this diagnosis? We don't have to trial them. What has changed here?

Dr. Edmond Chan:

Yeah, so the main change to keep it like a simple train of thought is that there used to be a condition in between gastroesophageal reflux and EoE, and the literature called that PPI responsive esophageal eosinophilia, like what you were describing. And it became quite cumbersome. The patients would have to go two separate endoscopy procedures, and then what used to happen is you would do the first one and then prove there's eosinophils in the esophagus, in the biopsy, and then say to the patient, "You have to do this PPI medication for about two months and then come back and repeat the whole day all over again with the general aesthetic and the endoscopy and the biopsy. And then if you did not respond to that PPI, then you would have EoE."
So with that being so cumbersome, the newer literature has completely removed that. And so you just get your first endoscopy proving you have eosinophils in the esophagus, and that's enough together with the symptoms to diagnose EoE. So it's just really made it much more straightforward. If you hadn't heard of that PPI-REE condition, then that's great, and then if you used to be confused by the condition, now you can just completely forget about it.

Dr. Mariam Hanna:
Push it aside. I love it.

Dr. Edmond Chan:
Yeah.

Dr. Mariam Hanna:
So the role of oral steroids or inhaled swallowed steroids in EoE, when is it used? How long is it used for? Why is it used?

Dr. Edmond Chan:
Yeah, so I'd like to start by distinguishing between classic oral corticosteroids like prednisone for example, and what we're talking about with EoE, which is a topical swallowed corticosteroid to coat the esophagus. And so the classic prednisone oral steroids, we don't want patients on that because of their propensity to cause nasty side effects. And when you stop them, then the condition just really rebounds, much like with other allergic conditions. So with these oral topical swallowed steroids, what's happening is you're swallowing a much smaller dose of the corticosteroid, and traditionally, it was an asthma medication, so either an asthma puffer or the viscous solution that would go into a nebulizer. That was used off-label and swallowed and with, for example, the viscous budesonide off-label use, it would be compounded with an agent to make it more viscous such as a Splenda or something like that.
Now the latest advance is that Health Canada has approved this oral dispersible tablet, which contains budesonide that I mentioned before. And so the patient just puts the tablet in the mouth and pushes it against the roof of the mouth and then swallows it and it has this new technology which also helps to coat the esophagus. So yeah, that's what we're referring to when we're talking about oral topical swallowed corticosteroid. It's something at a lower dose which coats the esophagus.

Dr. Mariam Hanna:

And you don't have to think that it was that many years ago where we were getting the ampules of fluticasone and mixing it with Splenda and teaching patients how to do it. It really does feel like we were MacGyver at some point to try to get the right dose of steroid into their esophagus, wouldn't you say?

Dr. Edmond Chan:
Definitely. And the fascinating thing is the Splenda, to use it for compounding, that was one approach, but then over the years, other compounding vehicles worked just as well. So things like honey or just something that's a bit viscous or thick, it just did the trick really, and some parents even mixed it on their own at home, applesauce.

Dr. Mariam Hanna:
So now fast-forward to ultra deluxe biologics and eosinophilic esophagitis. Can you walk us through a little bit of that?

Dr. Edmond Chan:
Yeah, so biologics, there's an increasing number of them to treat allergic conditions. And the one that has been approved for EoE so far, it's been approved now down to 12 years of age. And it really is something that is attractive because dupilumab treats a variety of allergic conditions. So it has an indication, a longstanding one for severe atopic dermatitis. It has one for asthma, it has one also for nasal polyps. But in the case of EoE, it has a more recent indication. And the exciting thing is that it not only reduces the eosinophils on biopsy, but it also helps to treat symptoms.
And it's so far unique in that fashion and there's clinical trials underway for other biologics to see if they can also emulate the success in clinical trials of dupilumab where it's helped with both the symptoms as well as the biopsy counts. But while it's exciting, we also now are at this juncture where we're trying to figure out which patients with EoE to prescribe it for, because the biologic medications tend to be very expensive. And so the next sort of really important thing to figure out is whether we can have some type of severity scales, for example, to say what type of severity would be best for treating EoE?

Dr. Mariam Hanna:
And how do you make that decision right now in the clinic for patients or with patients?

Dr. Edmond Chan:
Yeah, so there's actually no official guidelines right now for what type of severity to offer it when it comes to EoE, this dupilumab biologic medication. There is a proposed severity index, abbreviated I-SEE, which stands for Index of Severity for EoE. It's been recently published and includes scores for symptoms, complications, inflammatory features on histology, for stricture development. And above a certain score, you are either severe or you can even be of moderate severity. And so we need more research into scales like that to see if they can be validated and we can apply them to the clinical situation.
Very interesting additional score that probably should be added is some type of score for degree of allergy. So does the EoE patient also have, for example, severe asthma, severe allergic

rhinitis, severe atopic dermatitis? And that could elevate the score. Before we have that type of formal score, there are quote, unquote "expert recommendations". There's a yardstick which really revolves around that concept that in the setting of limited healthcare resources, which is germane for pretty much every single healthcare system, how can we best decide which subset of EoE patients to prescribe the biologic for? And so roughly speaking, it's that EoE patient who's severe EoE, but also additionally, ideally has manifestations of asthma, allergic rhinitis, atopic dermatitis, all those type two conditions.

Dr. Mariam Hanna:
Okay. So your first passion is food allergy, and I've held it off until this long. So we got to talk about elimination of foods as an approach to the management of EoE. You want to give us a quick overview of where we are today with dietary elimination?

Dr. Edmond Chan:
Yeah, sure. So medical management, we already talked about. The second management arm is with food elimination. And then a third, which we won't really dwell on very much because I'm not a gastroenterologist, is dilation for strictures, which should only be done by experienced endoscopists. Now, when it comes to food elimination, there's been three main arms to that. The first is the elemental diet. These are amino acid type of formulas. The second is food allergy testing to uncover triggers of EoE. And the third is what we call empiric elimination. So just really stopping certain foods to see if it'll help EoE.
With the first one, the elemental diet, over the years, it has become not a very practical option for a variety of reasons. So in young children, for example, they don't get the chance to develop oral motor skills in eating solids, and that can really create longstanding food aversion type problems. There's poor taste, there's high cost. And when you're avoiding essentially all foods, including allergenic foods, there's increased risk of future anaphylactic food allergy, kind of like your eight-year-old patient, Dr. Hanna, who started out having cow's milk trigger the EoE and then ended up with potentially anaphylactic milk allergy. So that risk is to a greater effect when you're on an elemental diet.
Now for food testing, that's gone through a very confusing decade where just over a decade ago, there was literature suggesting that the combination of skin prick and patch testing could reliably and accurately elicit food triggers of EoE. The problem was that it was center-specific, so it was done mainly at one center in the US and then when other centers around the world tried to replicate that, they couldn't. And in the follow-up studies from other centers, the accuracy of skin prick specific IgE testing, patch testing was no better than really flipping a coin. And so now all of the guidelines actually strongly discourage skin prick or blood testing or patch testing to look for food triggers of EoE. And therefore, if I've just described that the elemental diet is not practical and that skin prick specific IgE blood testing and patch testing is not accurate, then we're left with for food elimination, those who want that, the empiric elimination route. Now, that route is also a little bit confusing because there's different options for how many foods to avoid. There's one option which is starting out with just a single food to eliminate, like your patient, the dairy elimination. And then there's another option which eliminates six foods. And those six food categories include: milk, wheat, egg, soy, nuts and seafood. Now as you can

probably gather, eliminating one of those foods is easier for the patient in terms of daily life than eliminating six and such a large number of allergenic foods.
And so there isn't great consensus in the literature, but probably evolving consensus that we should do what you did with your patient, start with the easier approach. And interestingly, in our EoE clinic, we've always done it that way. Seeing children especially, it's not easy to deliver a message as a physician that you need to avoid so many allergenic foods. And it's always been in the back of my mind since day one. If I'm telling a young child to avoid peanut and tree nuts and fish, I'm very worried that they will convert, which is going to be a recurring theme that I'm going to harp on, to potentially anaphylactic food allergy when they're doing this avoidance. And over the years now, we have had primary prevention guidelines for infants, which say that the best way to increase risk of food allergies is not to introduce it early. So effectively, if we're telling atopic children and patients not to eat these allergenic foods, we're doing what these prevention guidelines don't want us to. So this is really a topic that's very near and dear to my heart, as you can tell.

Dr. Mariam Hanna:
Okay. I'm going to directly quote out of your last article that you shared with me: "The relationship between eosinophilic esophagitis and oral immunotherapy remains complex. And the question of whether this represents causation, unmasking or coincidence remains unanswered." I loved this and tweeted this and gave you full credit. I actually loved this like many months ago. However, in a patient with EoE, if it's in remission, can we consider tackling their food allergies with oral immunotherapy? Do you think that's on the slate or too risky?

Dr. Edmond Chan:
So the answer to that really depends on who you ask. It's still what I would categorize as a controversial topic. I certainly am of the mindset that it needs to be an option for patients with anaphylactic food allergy. And just in the same way that you started our conversation with a story, I'm going to tell you a story as well, Dr. Hanna. So this is one particularly memorable story that I feel only an allergist taking care of EoE can address. And so I have a patient with multiple food allergy and EoE who at the age of 10 years, went to a resort and ordered a simple lemonade and then had a severe grade four anaphylactic reaction, which meant decreased level of consciousness, presumably low blood pressure, plus eventually when he ended up in emergency, had O2 sats in the 80s, which is low. And so after the reaction was thankfully managed and the patient survived, the family subsequently learned that the restaurant had added raw egg to that lemonade drink without their knowledge of all things.
And so despite many in the specialty making blanket statements about SLIT or OIT to treat food allergy making EoE worse, and therefore it has to be some type of absolute contraindication. I started him, this patient, on food immunotherapy almost two years ago because to him and his family, the food allergy had a much bigger impact on his quality of life than the EoE. And they actually had a lot of difficulty finding an allergist who was willing to embark on this journey with them. And so to this day, he's doing really, really well. We're able to control his EoE with medical management, and really, it's a win. And so I'm not of the mindset that this should be for everyone with the combo of food allergy and EoE, but for those who feel that the benefits outweigh the risks, I do feel that in the era of shared decision-making, it needs to be presented

as an option. And if it isn't, it's unfair to the patient and will result in them, for example, flying to the United States.

Dr. Mariam Hanna:
Well said. Shared decision-making for another role to play in the allergies discussion. I feel like we are experts at shared decision-making in our specialty. I have one last question for you, and you alluded to it. We are not surgeons, we are not gastroenterologists, we do not scope the patients. So what is our role as allergists if some of these criteria require histology or remission on scope or biopsy results in managing eosinophilic esophagitis?

Dr. Edmond Chan:
Yeah, so I really strongly feel that the allergist has many important roles in the management of EoE patients in the multidisciplinary team. And this is despite the literature now stating that skin testing, specific IgE blood testing, is not accurate for eliciting food triggers of EoE. Despite that, I feel we have so many other things to offer EoE patients. So first of all, coming back to this food allergy testing, it's simply explaining the role of it, what we've done during this interview, talking about how it's not accurate for eliciting food triggers, but it does have a role in the workup for anaphylactic food allergy. So just really educating families about that. Then counseling about the risks of prolonged avoidance of allergenic foods, similar to your patient who went on that dairy elimination.
So I feel that we should, at the outset of offering these food elimination therapies, simply state that there's a risk. It could be small, we just don't know what the magnitude of that risk is, but there's a risk because these are atopic individuals of conversion to anaphylactic responses after avoidance. And I don't feel that very many other specialists are able to describe that risk to families. The other thing is offering oral food challenge procedures for patients who've avoided certain foods for a long time. And so if a patient's been on food elimination and has been very adherent to it and hasn't had an accidental exposure, and somehow a test is done suggesting that they're sensitized, then what if they want to go back to eating that? How are we going to safely reintroduce it?
So that's where the allergist needs their complete skill sets to offer the family. Of course, there's other associated allergic conditions such as asthma, allergic rhinitis, atopic dermatitis that needs to be managed optimally. There's so many patients where it's associated, but it's not being managed properly. There's helping families and patients decide what severity warrants biologics, which we previously talked about. And then last but not least, deciding when to start or continue immunotherapy, for example, food immunotherapy or aeroallergens sublingual immunotherapy despite the presence of EoE.

Dr. Mariam Hanna:
I have to share with you my new spiel about when I tell patients to avoid a food for EoE, you will laugh at this, but we talk about the risk of converting. And then I say, "Like any good diet, an occasional cheat day may be protective and prevent you from developing bad outcomes. And in this kind of diet, we recommend an occasional cheat day. So we don't talk about an anaphylactic food allergy to this common food trigger you've just avoided."

Dr. Edmond Chan:
That's wonderful.

Dr. Mariam Hanna:
That's my pearl, is the cheat day.

Dr. Edmond Chan:
That's wonderful. We do that in our program too. We actually coined this phrase for our patients, quote, unquote "liberalized avoidance", which includes that cheat day. So let's say once a week, they have a bit of pizza or something, and then strict elimination is where it's a hundred percent avoided, and that's where you could have a higher risk of this conversion.

Dr. Mariam Hanna:
Exactly. Exactly. All right, time to wrap up and ask today's allergist, Dr. Edmond Chan, for his top three key messages to impart to patients and/or physicians on today's topic, eosinophilic esophagitis. Dr. Chan, I hand over the mic one more time to you.

Dr. Edmond Chan:
Okay, Dr. Hanna. Well first of all, I've thoroughly enjoyed our discussion. This is such a rapidly evolving field and topic of EoE, and it's really very exciting to be able to share all this information. So my first takeaway is that endoscopy and biopsy is still mandatory for diagnosis, but PPI is no longer a diagnostic criterion and it's a therapeutic option. So that's number one. My second takeaway is that skin or blood testing for allergic food triggers of EoE is not accurate as we discussed, and therefore, empiric elimination to as few foods as possible to minimize risk of conversion to anaphylactic responses is a better approach. And then the last one is that the allergist has many important roles in management of EoE patients in the multidisciplinary EoE team, as we discussed.

Dr. Mariam Hanna:
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