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. For years, we've been generating more and more data in food allergy—risk factors, diagnostic tools, prevention strategies—but translating that evidence into day-to-day practice and clinical decisions hasn't been that straightforward.

Take an example: you're seeing a four-month-old infant, moderate eczema, the parents are anxious, they've read about early peanut introduction, they're worried about reactions, and they're asking if testing should come first. So what do you do? Do you risk stratify based on eczema severity? Do you just order testing? Go straight to introduction, or maybe refer them for a food challenge whenever that'll happen?

These are the exact decisions where evidence should guide us, but the reality is the data across risk factors, diagnosis, and prevention hasn't always been easy to translate. In today's episode, we're going to unpack a series of major systematic reviews that tackle these questions head-on, from early life risk prediction to peanut allergy diagnosis and the role of atopic dermatitis.

I'm joined today by the person that you think of first when you think of systematic reviews in allergy and immunology these days. He's going to walk us through what this actually tells us and how it could change what we do in clinic starting tomorrow. Allow me to introduce: Dr. Derek Chu is a clinician-scientist and assistant professor at McMaster University in allergy and clinical immunology.

He directs the Allergy Challenge Clinic at McMaster University Medical Centre, focusing on diagnosis, research, and treatment. His work centres on preventing and managing food allergy and anaphylaxis, alongside advancing evidence synthesis and guideline development. Systematic review genius. Dr. Chu leads and collaborates on major clinical trials and international initiatives and plays a key role in developing global allergy guidelines.

His research has been widely published and has helped shape evidence-based allergy care and therapeutic approaches globally at this point. Dr. Chu, thank you so much for taking the time to join us and welcome to the podcast.

Dr. Derek Chu

Thanks so much, Mariam. Really looking forward to it.

Dr. Mariam Hanna

So, Derek, when we connected, I actually asked you to pick your faves in terms of systematic reviews and you went across some food allergy and atopic dermatitis ones as we're going to dive into. But before we go and unpack these systematic reviews, what distinguishes a question

that's actually, like, worth getting into versus just a lot of hype on social media and will just generate more noise and not be useful?

Dr. Derek Chu

Well, at the end of the day, what we're looking for is clinically actionable information that will directly inform a recommendation to do or not to do a certain course of action or an alternative course of action. So that's typically why we link all our work to a guideline effort because then we will do the review and then the guideline will help contextualize that, put that in context of other decision factors and then also how can clinicians use it day-to-day.

Dr. Mariam Hanna

Amazing. So from getting inspired by your patients to finding things that are priorities in the community to making them actionable and then we get the guidelines. So, again, we're going to go through three of these guidelines. So we're going to go through the *JAMA Pediatrics* review first, if that's okay with you. And in this one, we're going to talk about early life risk factors from this systematic review. And we're not going to make you regurgitate the whole thing, obviously. But what did you learn? What was the most reproducible or clinically meaningful predictors of food allergy? What every family wants to know these days.

Dr. Derek Chu

Yeah. So this, just to your point, what you're touching upon... so this review in part came out of the JTF work, the Joint Task Force work.

The bottom line is that there are a number of major and minor risk factors. We looked at over 2.8 million participants in over 190 studies that have evaluated over 340 different risk factors that people have been considering. And this is too much for any one of us to think about in clinical practice. And it's a lot of, as you were saying, noise.

So the ones that really distilled out actually were two main classes. There are major risk factors and then minor risk factors. The major risk factors are things like eczema, family history, the severity of the eczema as it increases. But there were other important ones that came out, such as recent migration to a new country, as well as early life antibiotics. These are things that people did not really have on the radar.

But then there are other ones that are more minor, such as male sex, caesarean delivery, having a filaggrin sequence variation—or previously we would have called this mutation—and then being first-born. So these are all things that previously some people had put some weight on, had not put some weight on. And what we did through that review was be able to synthesize and clarify actually where the evidence actually falls.

And importantly, this shows overall that food allergy you can get to from more than one path. So we have the parent, we have in clinic parents that have come in and said, "What's wrong? Why is my kid allergic to milk or egg or food, or sorry, or peanut? I did everything right." "I tried to

introduce, I thought I did everything." And they feel such a great degree of shame or of guilt, right?

And I think it's in part misplaced. They tried their best. There are other factors that we need to get at. And this is what I hope to help illuminate in terms of: number one, how can we better improve what we know now, but also what can we do for the future to improve primary prevention?

So if you look in that study, Figure 3 is your go-to. You can totally use as a shared decision-making tool; you can use that at bedside if you want, it's a piece or part of a handout. And that essentially lists every single one of the most important risk factors, the point estimate, the confidence intervals, and how much it influences potential risk.

Dr. Mariam Hanna

Okay, so Figure 3 was exactly what I was going to ask you about: how you translate that. But essentially, this is a tool that can be taken straight to the bedside, as you said, in talking about the number of risk factors the child has, and how much that increases that particular child's risk.

Dr. Derek Chu

Yeah, exactly.

Dr. Mariam Hanna

Okay, so what's still missing in this? Is there still stuff to dig in this mechanistically, or any other predictive models—like how many high points they have, or major or minor criteria?

Dr. Derek Chu

That's great. So that you're touching on one point. So we do have a follow-up studies that are going to look more at some of the factors that were uncertain, as well as dig deeper into some of the factors that were certain, but they need more granularity. Now, there are some caveats to any one prediction model to have it done in the right way properly, is going to take some work.

And the other big thing is that we would ideally have other investigators share their data to make sure that we can externally validate it. But the last thing is implementation—what can we do data with these factors. So now the clinicians can use a quasi-risk calculator knowing what's major, what's minor, what to put their attention on. And it can be one major factor, but can also be the constellation of minor that will increase someone's risk.

Dr. Mariam Hanna

Absolutely, because I think as we have increased awareness and knowledge of risk, there's been overstressing certain risk factors versus others and not contextualizing it appropriately.

Take peanut as an example, which is the other practice parameter and GRADE review that you have pointed us to. So we're going to go into that.

Our advancements in reducing and getting rid of peanut allergy. What did this data look like as you were going through this practice parameter?

Dr. Derek Chu

The peanut allergy practice parameter really brings up a few key points, which is: you do a test if it's going to change practice. Okay, so that brings us back to whenever you see the patient, they will come to you with maybe a suspicion for food allergy that can be on a spectrum. Maybe they have no history whatsoever and a relative has it—like a distant relative—and they're worried about introducing.

So they suspect they themselves have food allergy and are coming to you as a new referral for testing. Well, yes, maybe what is articulated verbally is, "I want to test," but what actually they want is clarity. "Am I allergic or not allergic?" That's the outcome that they're looking for. So in routine clinical practice, we might be focused on, "Do I do this skin prick test or not?" That's not actually what the patient's saying.

So reading between the lines is so crucial and looking at their baseline risk. So this patient is extremely low risk. You may have another patient, however, that's going to be: two days ago I had peanut and I had full-blown anaphylaxis. I was in the ER. There was a rapid onset of progression of symptoms. Very clearly could be the case. But at the same time for both these scenarios, a skin prick test might not change anything.

One person, very high certainty that they're going to be allergic. And as we've shown in the practice parameter, if you do the corresponding pre-test probability to post-test probability, a negative skin test—even from the person with anaphylaxis yesterday with rapid onset symptoms—it's not going to change you from 99% certainty to 0% certainty. It's going to get you from like 99% to maybe 90, which is not going to change anything if it was negative.

And likewise, that person with absolutely no history whatsoever and just a distant relative, you're probably going to say your epidemiologic chance, which we showed in the JAMA risk factors paper, is in the range of 5 to 7%. If that's the case and I do a skin prick test on you, even if the skin prick test is large, like 10 millimetres, that's going to get me from like 5% chance that you're allergic to maybe 20 at best—20, 30% chance that you're going to be allergic.

So at the end of the day, I've done a test. I've put the patient through harm. They've been uncomfortable. They're itchy. And for our young ones, they may be crying and so on. And for what? We have not necessarily rendered a definitive diagnosis for them. And that has massive implications socially on quality of life, what their day-to-day practice will be, what is involved in schools, school forms, epinephrine usage, all this kind of stuff.

So getting a diagnosis right—and a major theme that Practice Parameter was about—be sensible and **judicious** with your testing and exactly will your test deliver the outcome that you and more importantly the patient and family are really looking for.

Dr. Mariam Hanna

I love it: being sensible, reading between the lines. So how did this GRADE approach change prior guidance, though?

Dr. Derek Chu

Right. So no one had, previous to this, people had done food allergy in general. There was not, I think, a previous—particularly in the Joint Task Force—a GRADE specific guideline. And what brings up very importantly is that right now a lot of us learn the cutoffs.

The classic... a Royal College exam cutoff. What's the cutoff for peanut? What's the cutoff for specific IgE for peanut? What's the cutoff for skin prick test peanut? What's it for milk, for egg, blah, blah, blah? As it turns out, if you look carefully at all the diagnostic data, they're not set up right. And that those studies are not... they're done and they, at the time, may have been appropriate and have done massive amounts for getting us to where we are now.

But now we have the luxury of looking back 20/20 and seeing: well actually, we only recruited people on the extremes. Those that we were certain that were allergic, those we were not on the extreme that we're certain were not allergic. But what we actually need to know, if we want a clear cutoff, is we need to recruit everybody.

We need to create the full spectrum of pre-test probability or uncertainty, or in other words, our suspicion for this patient actually being allergic. So this is precisely what inspired CIHR and others, the Ministry of Health, to fund a national initiative that we're running called TITAN, to improve the quality of diagnosis, to improve the delivery of high-quality food challenges, and to improve how we actually address diagnosis and therefore management.

So if anyone's out there is interested in joining TITAN, it is a national and growing, actually international, initiative collecting diagnostic data.

Dr. Mariam Hanna

Improving the future through TITAN, and I love the name. Tell me about overtesting and misusing of diagnostics a little bit. We're still doing it. Like, it actually doesn't matter. Like, it's continuing to happen. Where is it happening? Or at what level is it happening?

Dr. Derek Chu

I think the classic story that we hear is a patient has gone to ER or has gone to ER and then seen their primary care clinician and the corresponding clinicians appropriately, in the desire to

make the patient as safe as possible—because maybe they ate something that weren't certain what they reacted to—tell them, "Okay, avoid all nuts."

And then you're like, "Okay, well, when you hear the story, you might actually hear, actually, they were eating all the nuts before, no problem." Except maybe they had something new. Maybe they had Brazil nut for the first time, or maybe they had... they never were eating peanut, they were always eating tree nuts for the entire time. But then now this was their first exposure to peanut, and then they had a reaction.

Well, they didn't need to avoid those other tree nuts, number one. So, or they may see someone and then an allergist, for instance, and that momentum in the diagnosis that's coming from before, implicit in the recommendations from the primary care physician or the emergency physician is a diagnosis till they see an allergist.

And then when they see the allergist, that there's the potential for diagnostic momentum to continue and feed into it by overtesting with a panel. And panel testing—part of what we showed in the peanut allergy diagnostic parameter and others—is that panel testing is going to be contributing to many, many false positives, will not necessarily inform whether or not your patient should introduce the food.

And importantly, if the patient's eating it, don't skin test them to it. That's such a common issue, because there are so many patients that we've seen come through, they're eating the food, they're told to avoid all foods only on the basis of the skin test, even though they were eating it before.

And so we do need to de-implement some of that diagnostic momentum. And then as we've all learned in medicine, you know, be skeptical of any previous diagnosis coming in, and try to address any diagnostic momentum to confirm, and then get at what we were saying before about rendering the appropriate diagnosis.

Dr. Mariam Hanna

I love this. I'm actually, like, memorizing a lot of words here. We're going to de-escalate this diagnostic momentum. I love it. Okay, we're going to move on to the next article that you pointed us to. And this one is a topic near and dear to many allergists: atopic dermatitis. We've even touched on it as one of the major risk factors earlier on in this discussion.

The AD guidelines are really built on multiple linked systematic reviews. This one looks different and the figure looks different. What makes this guideline methodologically different from prior iterations other than the picture looks different?

Dr. Derek Chu

So the eczema guidelines are really a major advancement in evidence-based dermatology, evidence-based eczema care. Number one, we systematically synthesize all the available

evidence. Number two, we involve patients and caregivers as partners throughout the entire guideline development process.

We had a multidisciplinary panel—everyone from dermatologists to allergists to primary care to paediatricians, family medicine. We had nurses on board as well, as well as our patient partners and methodologists as well. And the concept was to systematically address every single question beyond just having some narrative synthesis.

So we would go out and have very specific prioritized interventions to look at—comparators, outcomes—that all were prioritized by all our stakeholders involved, and then deliver the best available evidence, critically appraised, to make decisions on.

So we would weigh everything from where the benefits of each one intervention compared to alternatives, what are the harms, what are the practical issues that you need to consider, what are the decisional factors that... like cost, equity, access, feasibility—that all have to go in with each one of the interventions.

And so we address everything from topical treatments. It was the only topical treatments comparative systematic review that was done in a large network analysis involving all topical prescription therapies, all systemic therapies—including light therapy. It also involved dietary management—some of which we've already touched upon in the past in terms of dietary elimination—as well as bleach baths and allergen immunotherapy.

Dr. Mariam Hanna

Perfect. And where did you find that the evidence spoke strongly and then other areas were kind of a little bit more **grey** and lower certainties in that area?

Dr. Derek Chu

Yeah. So there's great evidence for many of the topical treatments and there's... and same thing, systemic treatments, especially those that are the new systemic agents. The conventional ones we have a lot more challenges with.

And really, we do need good evidence about properly caring for those patients that cannot access the current available advanced systemic agents like Dupi, Lebri, Nemo, as well as Tralo—as well as the corresponding JAK inhibitors. But those ones would be like cyclosporine, methotrexate. Like really, who in these do we need to use these on?

Or, for instance, on all our local applications, we have to go through EAP, but they always ask the patient to have beyond say, you know, mycophenolate. That's one trial. And the rest is observational data. Where is this coming from? Is that as the demand compared to multiple RCTs that have addressed dupilumab and lebrikizumab and tralokinumab and the JAK inhibitors that have, like, very clear upsides and downsides?

So those are some parts. Bleach bath is a very important adjunct—low certainty evidence, but it could work. And so we recommended in those that are mild to... don't, maybe don't have them on the top of your list. If they're moderate to severe and still persistent, you may want to consider as an as an add-on.

And then similar for allergen immunotherapy—except depending a little bit more on: number one, the certainty being actually higher than bleach baths—is actually pretty decent RCTs. I think almost 2,000 patients in a **JACI: In Practice** review that we published. And number two, that it would... it would definitely make sense in the multimorbid patient.

So those that have concomitant allergic rhinitis, asthma—these are very clearly the case. And I think this work, as well as eczema guidelines and other work that's going on, is really pushing this idea of allergists considering the whole patient. What is, again, coming back to: what is the patient's overall objective and where are they at right now? And is it just one disease or is actually multiple things I need to think about?

Dr. Mariam Hanna

All right. And does this move us closer to prevention? Can I prevent atopic dermatitis? I know we didn't touch on this with this systematic review, but can we prevent it?

Dr. Derek Chu

Okay, okay, well, great, great question. So we actually do have a prevention systematic review, but we did not send it to you. It is in *JACI: In Practice.* It's called, I think, *Theory and Evidence* or *Theory and Principles of How to Prevent Atopic Eczema*.

Dr. Mariam Hanna

Do you oversleep, Derek? Okay, yes. Keep going. Keep going.

Dr. Derek Chu

So that's there in *JACI: In Practice*. It was great work with our colleagues in Australia. And I get very little sleep, but there's a lot to do. Allergy doesn't sleep.

Dr. Mariam Hanna

It does not sleep. And itch is very disruptive to sleep. What can you tell us just in a nutshell, if you don't mind? Now I'm curious about prevention of atopic dermatitis.

Dr. Derek Chu

So the bottom line is there's conflicting evidence for routine intense moisturization. Great work done by our European colleagues, although there's been some conflicting work from our Irish colleagues, as well as a recent trial done in the States called CASCADE that have all suggested

that maybe actually routine intense moisturization early on in life might actually be effective in decreasing the incidence of atopic dermatitis.

And then I think the second component that is merging this with the food allergy piece is, as always, we tell our patients: moisturize frequently, but also with clean hands.

Dr. Mariam Hanna

Clean hands, yes.

Dr. Derek Chu

You're not using soiled hands, especially with food, to moisturize your baby. So this may often mean you moisturize them... when we hear about moisturizing from parents, we often hear maybe once or twice a day, that kind of thing. But some things that we can do to prompt them are, say, maybe moisturize with every diaper change, with every feed, et cetera, et cetera, et cetera.

So they're really getting used to it as part of their routine. But similar to the food allergy piece, a lot more for prevention of low certainty evidence. So now what's important is we can identify some risk factors for food allergy. We know some risk factors for eczema, but the preventative evidence for eczema, beyond moisturization, there's not a lot there.

You will see shortly our prevention systematic review for food allergy randomized trials that will be coming out in the near future that addresses this whole package. And therefore, we need more than just random care. We need randomized care. So we need new big randomized trials that will transform this landscape.

This is, again, why CIHR and others, including CSACI, have graciously funded us to develop the first Canadian research capacity to address new RCTs, prevention of eczema, and prevention of food allergy. So we have the SHAPE randomized trial that is just rolling out, and we're going to address some of these issues.

Dr. Mariam Hanna

I love it. It's not random. It has to be randomized. I love this. Okay, pick for me three changes allergists should implement immediately based off of this work that you've done so far. I mean, we've talked a lot more than three publications, but that's okay. What would be kind of the three big changes that you want allergists to go back to their clinics next week and implement?

Dr. Derek Chu

I think the first is addressing... I think, going to what we were saying, the merge of these concepts, addressing the whole patient and really getting at, like we were saying before, reading between the lines and what is the outcome that you're trying to deliver to the patient? Because again, as the fiduciary, we're trying to translate to them how to navigate the space.

We've got ChatGPT nowadays. We've got all sorts of AI chatbots. We've got people's figures of notions. We've got social media. But at the end of the day, the patient may come in and have something that they articulate, but that is not necessarily what is going to be their ability to synthesize all the available information, their past experience into a specific outcome.

And that's where we as physicians need to understand the evidence, understand the patient experience, and synthesize those together to be their fiduciary, to be their guide in the journey as to: where can I get you the best health outcomes possible that can address anything from testing, that can address anything from dietary management of eczema, that can address multi-morbidity.

Number two is about what we're addressing here is that we need high-quality definitive diagnoses, especially in the food allergy space. And this is a huge health equity piece, a systems piece about developing allergy care pathways and developing that capacity for food challenge. If you're interested in joining forces with TITAN and others, very happy to get hooked up. You can email me. By all means, we'll get you sorted.

And then the third bit is about encouraging the culture of randomized care. So we do really need to encourage this culture of incorporating the advancement of the science of allergy into routine clinical practice, into our culture. So if that means referring to a randomized trial, that's one bit.

Number two, maybe joining up with a major academic centre so that we can actually push things forward. It doesn't necessarily mean a major commitment and business to the routine clinical practice of medicine. It might mean that you just allow access to the EMR, we get the ethics approvals, and then therefore the research team at the academic centre helps you out.

That's exactly the model that we're trying to do and help out. And therefore, if we can help you and your patients with randomized care so that we can actually improve the future, then I think that's going to be a massive improvement to, to the evidence-based allergy medicine that we all aspire to.

Dr. Mariam Hanna

I love it. That's sensational. Alright, perfect. That's a wrap. Thank you, Dr. Chu, for joining us on today's episode of the Allergist.

Dr. Derek Chu

Thanks, Mariam. It's been a pleasure.

Dr. Mariam Hanna

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