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.
Ladders, ladders everywhere, they've started a global sensation. It's not like the Taylor Swift global sensation, but we've definitely started to stir things up with these ladders. Should we incorporate them, get them started from the time of referral? And if it's really all just so easy, why have we not eradicated all milk and egg allergy by now? Here to answer these fascinating questions and more is a dear colleague and friend of mine, Dr. Douglas Mack. Dr. Douglas Mack is a pediatric allergy, asthma, and immunology specialist and an assistant clinical professor in the Department of Pediatrics at McMaster. He's the treasurer of the CSACI and co-author of Guidelines on the Prevention of Allergy, Epinephrine Use, Anaphylaxis, Oral Immunotherapy, and speaks internationally about the treatment of food allergy and, you guessed it, food ladders. Dr. Mack, thank you so much for joining us on today's episode. And welcome to the podcast.

Dr. Douglas Mack:
Yeah, thank you so much for having me. I'm looking forward to talking about this subject.

Dr. Mariam Hanna:
Okay, so, big topic. Let's start with the overarching question. Are there different phenotypes to our milk and egg allergic children?

Dr. Douglas Mack:
I think, to be honest with you, this is probably the most fundamental question that we can ask. And I think the vast majority of my patients who have milk or egg allergy are going to outgrow this. And I think of these as a naturally, spontaneously resolving phenotype that for the most part, no matter what I do as an allergist or the parents or whatever, these kids are going to outgrow this. And I think this is somewhat predetermined. I think this is something that we look, even from a genetic perspective, many of these kids who have a very specific type of mutation. There was an article published in the Journal of Allergy and Clinical Immunology, and they found that if patients had a significant mutation in a gene called filaggrin, that they were more likely to have persisting milk or egg allergy. And I think this is what we see. Even some of the very early studies that was just published at around a year of age.

These patients in Ireland who used a ladder, the ones that were harder to really get through or couldn't progress through even at a year of age, tended to have a higher IgE level than those more likely to be successful on these ladders. So, yes, I think there are phenotypes. The phenotype I'm most concerned about is the phenotype that is unlikely to outgrow this. And I this is where we need to be sensitive, as this is where we can run into trouble with treatments.

Dr. Mariam Hanna:
Can we predict the sensitive ones? Are we at a point where we can say flagrant mutations, so maybe our bad atopic dermatitis patients, or higher than X IgE level, maybe those are the kids

that are going to get into trouble with this ladder. Are we at a point where you can confidently say, we can pick out these kids early?

Dr. Douglas Mack:
It's a great question. We could have a gestalt about this. You and I, have been in practice long enough, can predict some of this, but many times we're completely surprised. We see children who shouldn't be able to tolerate a product, but they do, or those who we think will sail through it but can't. Yes, we can look at these factors and try to predict, using skin testing, blood work, degree of eczema, age, and other allergies. We can make generalizations as to where these kids are going to go, but we're not always right, are we? And, I think this is one of the challenges that we face. So I think we do our best, but it's very difficult for us to look forward five or 10 years, and say, what's going to be happening with this kid?

I'm not even convinced that, components have been terribly helpful in this regard.
And there was a recent study that looked at the entry food challenges for patients that were going into a Phase Two study for a baked milk OIT. And, there was absolutely no way to predict whether skin prick testing, serum IgE level, component levels. None of these were predictive of whether or not these patients were going to outgrow it. I mean, there may have been trends, and I think you and I can estimate that, but there's no great way of predicting this, unfortunately.

Dr. Mariam Hanna:
I've been in the office with you long enough to know it's no better than the flip of a coin sometimes. Let's just predict it when we walk in the door. It's either going to go well or not well that day.

Dr. Douglas Mack:
That's right.

Dr. Mariam Hanna:
So Dr. Mack, at some point in our practice and careers, we've seen this shift from the word 'ladders' being used for non-IgE mediated food allergy to today when we refer to ladders for IgE mediated food allergy. Can you walk me through when this shift happened?

Dr. Douglas Mack:
Yeah, families have been using ladders for decades. What we've done is put a framework to what we've witnessed happening. Back in 2008, Sinai in New York published articles looking at how many patients with milk or egg allergy were tolerant of baked forms. This was based on the observation that families were making that their kid could eat muffins and cake, it’s not that this was discovered by Sinai. The parents already knew this. And I think ladders have been similarly used by parents, and you've seen this in your practice as well, that without even they come back to us like, well, he's already eating pancakes, or he's had some cheese and he's been fine. And this is something our parents are doing without us even doing it. What a ladder does is put some structure to that. And these were my colleague Karina Venture and others. She's really been behind a lot of this, and I think published this in 2013 for non-IgE mediated food allergy.

But not long after that, in 2014 and 2015, a number of studies, or at least guidelines and parameters, suggested that these could be used in patients who have IgE mediated food allergy, but primarily for those that were relatively lower risk. So, this has really moved its way along to the point where now a number of different countries have these. There's been a number of studies as to how we can use these in different populations. But this has really been a progressive comfort level with this. And I think this is something that, once again, we've been seeing really become structured over the past ten years or so.

Dr. Mariam Hanna:
So structured, and it's a ladder. Is this a form of OIT? Because that's ultimately the question: are you doing like oral immunotherapy light with these guys that are going to resolve, or are you pushing the stubborn ones over the line into reaction? How would you classify these ladders then?

Dr. Douglas Mack:
Right, I think it really depends on how you define OIT. And so we published an article where we called these approaches Dietary Advancement therapies and that we tried to separate it, and there was overlap. Myself and Katherine Ignostu and Matt Greenhot, we looked at the groups that were lower risk and they were able to tolerate baked products, they were able to tolerate ladders. But if you were of a particular phenotype where you were higher risk, are you doing OIT? And the way I define OIT is, it's a therapy that is used primarily in patients that are unlikely to outgrow the food allergy that they have. And that doesn't mean that we don't treat patients who are going to outgrow them. But I think, strictly speaking, OIT is when a patient is very unlikely to outgrow them. And I think this is where the challenge arises. Am I doing OIT? Am I not? It depends. And I think if we are looking at a patient who strictly is unlikely to outgrow, for example, their milk allergies, there's been a number of studies looking at this, Israeli studies that have looked at this, where they showed an extraordinarily high rate of epinephrine use in reactions using baked products as a form of strict OIT in the patients that are unlikely to outgrow it. A recent phase two study, once again out of New York, showed very similar rates of reactions to standard OIT. In fact, the epinephrine use was about 20% in these patients, with very similar cofactors. I mean, this is very similar to our kind of higher risk OITs. Exercise, menstruation, illness were the most common cofactors. And what was interesting about strict OIT in these patients with strict baked milk OIT, that 50% of these epinephrine treated reactions were two to three hours after the dose. And I think this is, I think, one of the challenges that we face: that yes, I am probably doing some kind of OIT, especially in my patients who are higher risk and unlikely to outgrow it, but what am I doing in those patients that are not? And I think it's tempting to think of this as a way of hastening this along, but I often wonder if we're patting ourselves on the back for providing structure to a naturally occurring process. And I think this is something that I wrestle with on a regular basis. And there may be, there's a tipping point where I can redirect these kids at a very early age. And some of that data coming out of Ireland is suggestive to some degree of that. But I don't think we know the answer. So, that's how I'm going to answer this. I think realistically, it is clearly in some patients a form of OIT. But I think in my high-risk patients, it is actually quite a high-risk form of OIT.

Dr. Mariam Hanna:
So, if we're not very good at predicting, should we be running all these guys as baked oral challenges in the office, or can we start them at home?

Dr. Douglas Mack:
Yeah, it's a great question, and I've done this like four times today. And I really think it just depends on the patient. When I look at a patient to try to figure out if they are going to be amenable to a ladder or baked egg ingestion or baked milk ingestion? Some would say just do it right off the bat at six months of age, seven months of age. And yes, there is data to support doing that at a very young age, that these kids may do actually really very well. And I think that it is relatively safe for those patients. But let's just say let's forget about those kids that are under a year for a second because the majority of our kids that we're seeing are older than that, and families may not be comfortable, and we're working through other issues. When I look at a kid, I look at what are my favorable characteristics, and I typically will say my favorable characteristics are a younger age, obviously non-IgE mediated allergy. If they've had prior mild or non-anaphylactic reactions, that's a great kid. Non-asthmatic or mild, controlled or treated asthma, like regularly treated asthma, is something we need to think about. Small or declining skin prick testing or blood work. I'd like to see that; if that's the case, I feel more comfortable with those kids' high previously reaction threshold. If they can drink a half a cup of milk and they're fine, chances are they're going to be fine with most of my baked products. But I think the kids that I get worried about, those younger kids, those other kids, I may recommend that they may try to progress at home. And I think that maybe they'll do the first challenge in my office, possibly. But those kids, I may say you can start to gently move your kid along through that. And there are caveats to that. But the kids that are unfavorable and the kids that I'm always going to be doing most of my introduction of baked food in the office are going to be my older kids. Right. I think these are the kids that scare me the most. My older kids. And I don't have a defined cut off, I'm going to be honest with you. Four to five, I get a little bit skittish around four to five, suggesting that they do this at home. Eight or nine, once again, I get much more concerned, and I think if they have persisting allergy, they've had prior severe or anaphylactic reactions, they're asthmatic, which a lot of these older kids are, larger escalating skin testing. These are the kids that I get much more concerned about. And certainly, if they can't tolerate baked products in my office or can tolerate only a small amount of it, I'm going to be extremely cautious about recommending that these guys move forward. I think this is where we run into trouble. I'm going to be honest with you. I think for years, we thought that these were very safe because guess what? We were doing them. And for the vast majority of these kids, they were safe because most of these kids outgrow it. Once again, I'm not worried about those low-risk kids. I'm the most worried about those kids that when we do this, they're high risk and they have some instability, whether it's uncontrolled asthma, whether it's intercurrent illness or whatever. And unfortunately, these are the kids that we've had some bad outcomes with. And I think these are the kids that I think is a bit of a wake-up call for us, that yes, these are reasonable, but we have to stop thinking of this as one procedure across the entire population. We have to think of this as separate procedures, depending on the population and the phenotype that we're treating. And I think that, to me, is how I look at every single kid when I'm in my office. And there are the

clearly cut ones on either side. It's the kids in the middle that I think are a bit more challenging, aren't they?

Dr. Mariam Hanna:
Yeah, they are. Listen, I think you've mentioned skin testing, blood work, genetics, past history, cofactors of asthma. What you haven't said to me yet is, what is the utility of fresh food skin testing? Now, we grew up in a region where fresh food skin testing, i.e., a slurry of the baked product, would be used as a skin prick test on the day of challenge. Is there any utility to that? What is the predictive value of that?

Dr. Douglas Mack:
Right, here's the thing I'm going to say to you. If walking into my office, a patient has a 75% to 80% probability of being able to tolerate baked products, my test, to be valuable, has to be better than that, right? And I think that this is what's important. And I think what we've not demonstrated is that any of these approaches are really any better at predicting this. In fact, some of them are much worse. Our fresh food skin testing, and I'm going to just put this out there for when it comes to just about any food. And so, you know, we don't do any fresh food skin testing at all for peanuts or whatever because they have not been validated. And we put food on the skin, we may well get a positive skin test, but we have no idea how to interpret that. And I think that's really important. And I think the same thing applies for the baked slurries. Now, the one thing I will say in their defense is, if it's negative, we feel relatively confident that these kids are going to pass, but if it's positive, it's anyone's guess as to whether or not these are useful. I don't do them. I think that in the end, they talk us out of food challenges or progressions more than encourage us to consider this. And a patient coming into my office already has a high probability of passing this. So I'll tell you right off the bat, and this isn't just for baked. I think we really have to be very critical of the fact that we have not validated fresh food skin testing. And I think, unfortunately, this is something that is still happening. And we gave this up, about a decade ago.

Dr. Mariam Hanna:
Loud and proud! We gave up fresh food skin testing. There's no validation to that.

Dr. Douglas Mack:
No validation.

Dr. Mariam Hanna:
So now a harder question. Counseling. What is the degree of counseling that these patients require for a baked milk or egg challenge or for introduction?

Dr. Douglas Mack:
It's a great question, and I think it does depend on the patient that I'm working with, to be 100% honest with you. I think, look, if I'm thinking of this as a formal form of OIT in a patient who is probably not going to outgrow this, quite honestly, I'm not going to do baked milk or egg OIT in a patient that I'm thinking about outgrowing. But if people are doing this, they really need to treat

this like OIT and provide that degree of counseling. The shared decision-making behind this, I think, is critical. I think there was a nice article that came out, and I did like it. It came out about a year ago. And what it did is it gave warning signs, and it gave a little bit of a guide as to when people should be concerned. It was a Canadian article that looked at this, and I think what they did is they just said, parents, here are your things to watch out for: things like asthma, things like infection, things like recurrent mild reactions, a severe reaction, especially those that are having epinephrine. And I did this because what it did was provide a bit more structure to just, 'hey, off you go.' And I think that was an important part of counseling. Now, whether or not we provide a written handout of exactly how these patients should progress, I generally will, either type that out, or I may use a pre-made type of a ladder, depending on the patient, depending on the parents. But I generally will provide some degree of guidance as to what foods to try next, or what foods that I might want them to try in the next four to six months or a year. I may not tell them, 'go walk your way all the way through it,' but I will walk them through how to do that. And once again, it does depend on the patient and the age that drinks. But I think discussing that, making sure they tell us if their child has been given asthma medications, puffers, if they're having asthma symptoms. Once again, if we look at all of the dietary advancement therapies for milk and egg, and we published this last year, if we look at all of them that are near fatal or fatal reactions, every single one of those patients was asthmatic. Every single one. And the majority of them were not controlled, partially controlled, untreated, or in the midst of an exacerbation. And that's where we end up with these tragic results. And every single one of them has been asthmatic. So, to me, and we can talk about how quickly to escalate these kids, but if there's one modifiable factor that we know about, it's ensuring that these patients have perfectly controlled asthma. And if they develop asthma while they're on that one year of coming in to see us, or six months before they come in to see us, if they develop asthma or asthma symptoms, we have to have a hard look at their control before we recommend that they progress on this ladder.

Dr. Mariam Hanna:
I'm going to flip the page on you for a second, and we're going to go to our potentially lower-risk kids, infants. So think six months, four to six months when they're first getting query diagnosed and sent to you from primary care. You've mentioned it already across the pond, there's this kind of notion of should we just be introducing baked milk, baked egg, getting them started on the ladder with just suspected allergy while awaiting to be seen by an allergist? A lot of us have waitlists that are many months in duration, and perhaps that delay puts them in that higher-risk category that we are mentioning. If this is any form of immunotherapy, if this is better off being started younger, should we be implementing that in Canada? Are we at a time point where we can do this broadly?

Dr. Douglas Mack:
Here's what I would say to you on that. I don't think we have the data. I think that what the Irish groups have said, and I really do like what they're doing. They're really pushing it. But I don't think we know yet what the outcomes for these patients are. And if we are actually changing the face of these kids' allergy, we might be. I think it is distinctly possible, once again, but we don't have high quality, and we're doing a review, a systematic review of this in meta-analysis

currently. And what is striking to me is that most of the data that is being published even today is observational. It's observational, it's experiential, it's what have you done, what worked? And these are critical articles, these are critical studies. But what we really need, and this was a systematic review in 2017 said the same thing, we need good randomized control data. We've done lots of things in the field of allergy that have, with the absolute best intentions, for example, delaying introduction of food, by the way, with the best intention. And what we realized is that it was actually harmful. And I'm not saying this is harmful, but I think before we can draw firm conclusions, we need to have good quality data, and we need to have randomized control trials that suggest this. So I have a hard time suggesting that primary care can do this. I think they probably can in our very low-risk population. Regardless, my parents are doing this already, right? So you know that many of our patients, their families are already doing this without even knowing. They may even be halfway down that ladder before they even come to see me. That happens all the time. They come in, well, I'm already eating baked goods. Like, great, don't stop it, okay? Do not stop that. Keep it going. But I just don't know that we know really what we're going to be doing with these kids and what is the safest way of managing them. So that's how I'm going to answer that. I think it does depend on the training, it does depend on the region, and it does depend on the age of the population. I don't have a problem with it. They certainly suggested that it is reasonably safe, but I think we have to have caveats, and they have to know when to stop pushing if these kids are having issues. Because once again, some of that data that was just published, it worked in 87% of the kids. Those other out of Ireland, that 10%, ven at a year of age, they were already different. And I think that's one of our challenges. They were already distinctly different at that age. And I think that's something that's sobering, from my perspective. When that division occurs, I don't know. I don't think anyone does.

Dr. Mariam Hanna:
Excellent final comments about sobering times that we're in and changing times that we're in and likely to change over the next decade as well. All right, time to wrap up and ask today's allergist Dr. Douglas Mack for his top three key messages to impart to patients and physicians on today's topic food ladders. Dr. Douglas Mack. Over to you.

Dr. Douglas Mack:
Listen, I think there are three main things. The first is that these are not for every patient. And I think that's one, this is not for every patient. Number two, I think it's not without risk, and I think that patients have to be responsive and report their reactions to physicians, but we need to understand who is lower and who is higher risk. And I think we have to, in our minds, start to separate those because I believe these are separate procedures depending on the risk group that we're looking at. The final thing is, it is unclear whether it changes the course of this disease. It is, and I think that a lot of us with the best intentions are hopeful that this will help these kids to outgrow this faster and maybe it doesn't. But for us to be clear on this, we need higher quality data and I think this is what our field is lacking.

We need to understand what is the mechanism, how this works, and whether or not in good controlled data, whether or not this changes the course for all of these phenotypes, not just the kids that are already halfway outgrown it.

Dr. Mariam Hanna:
That's perfect. Thank you, Dr. Douglas Mack, for joining us on today's episode of the Allergist.

Dr. Douglas Mack:
Thanks for having me, it was a lot of fun.

Dr. Mariam Hanna:
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