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. You have two patients. One family wants maximum protection and is willing to push through every single side effect, and the other just wants to reduce anxiety around accidental exposures and avoid reactions as much as possible. Same diagnosis, but should they get the same OIT protocol? And for years, we've been asking, "Does OIT work?" But that's no longer the right question. The real question now is: what dose are we aiming for and why? Because high-dose and low-dose OIT don't just differ in numbers; they perhaps reflect fundamentally different treatment philosophies. And whose choice is that, anyways?

To help us break this down, what actually matters in practice, and how to choose the right approach for the right patient, I'm joined today by a special guest who brings deep expertise in oral immunotherapy and a practical lens to this evolving space. Dr. David Fleischer trained at the University of Pennsylvania, Emory University School of Medicine, and Johns Hopkins University School of Medicine, where he completed his pediatric residency and allergy and immunology fellowship. He's currently section head of allergy and immunology and director of the Allergy and Immunology Center at the Children's Hospital Colorado and professor of pediatrics at the University of Colorado School of Medicine. Sound like a mouthful? That's not it. A globally recognized expert in food allergy, his work focuses on the natural history, prevention, and treatment of food allergy, including oral and sublingual immunotherapy, and—what we'll touch on as well—epicutaneous immunotherapy. He serves as global PI for multiple phase 3 peanut epicutaneous immunotherapy trials, and he's authored and spoken extensively in this field. Dr. Fleischer, thank you so much for taking time out of your busy schedule to speak with us, and welcome to the podcast.

Dr. David Fleischer Thank you so much, and thanks for that kind introduction. They're longer than they should be, but I appreciate it, so thank you. It's great to be here.

Dr. Mariam Hanna I love it. You've been busy in this space. Thank you for making this work. I'll get you to dive right in. When we say low-dose versus high-dose OIT, are we actually defining very different protocols and different practices?

Dr. David Fleischer Yeah, I think the problem is there are so many different protocols that are out there. So, it's: what do you use? And we certainly use a different protocol. We go up to 1,000 milligrams for our maintenance dose, so we go high-dose. But the LOMO study that came out—that you're probably mentioning that we're going to talk about—really showed that 30 milligrams can do just as well as 300 milligrams. And we know from the DEVIL study from Brian Vickery years ago that 300 milligrams does just as well as 3,000. So, low and slow may be the way to go here in some patients, for sure. So, I think there's different options for different patients, and it all depends on really what the goals are, like you said, for the patients. Where do they want to get to, and how quickly do they want to get there?

Dr. Mariam Hanna And are these doses fundamentally solving different problems, like protection versus possible remission and reintroduction into their diets?

Dr. David Fleischer That's ultimately the holy grail: getting to the point whether it's remission, whether you call it a clinical remission, or a cure, or long-lasting tolerance. I think the first and foremost priority for these therapies, and really what the first goal should be, is protection. So, by being on something—on whatever therapy you choose—you'll either have less severe reactions or, hopefully, no reaction at all. That's really the primary; so, that's what we call desensitization, right? But ultimately, when you talk to these families, they want to get rid of these allergies, too. They want to get to the point where they can just eat it freely. They don't want to be doing these therapies forever. They want their child to get rid of it. So, that's where you get into the remission, sustained responsiveness versus a clinical remission is what we're trying to call it, where they can eat it freely in their diet and their tests are going negative, things like that. So, that's really, I think, the ultimate goal for parents, for sure. But getting there, and how you get there, and how long it takes to get there, and whether that will be long-lasting as well, is a big question to have.

Dr. Mariam Hanna Yeah, and that's part of kind of the new set of questions that we have all about immunotherapy. So, let me start with this. Do the different high-dose versus low-dose immunotherapy protocols then result in different immunologic responses, like at the immune level?

Dr. David Fleischer I don't think they do. I mean, I think, you know, you're going to get a lowering of the IgE levels. You're going to get a rise in the IgG4 levels. You're going to get a rise in the threshold that you can tolerate. So, I think ultimately, how you get to the point you want to get to really depends on, again, really a decision-making process with the family, as you first mentioned with those patients. What do you want to do? How quickly do you want to get there? And what's the safest and easiest way to get there? By going low and slow, you don't have to do as many up-doses. You don't have to come in as often. There are probably less GI side effects as you get into lower doses versus higher doses, like with oral immunotherapy. But again, I always tell parents that this immunotherapy is a marathon, not a sprint. All immunotherapies are three to five years. When you look at allergy shots, right—you know, you don't get better completely in one year. You've got to look at this as the long-term picture as kind of a three to five-year process. So yes, you can get to a higher level quicker if you want to go to higher doses, but not everybody wants to come in and do all those doses and risk those reactions as you get higher GI side effects or possible EoE-like symptoms as you get into bigger doses. So again, I think it's really clarifying exactly what the goals are of the patients and how quickly they want to get there. But as you mentioned, there are other therapies that can get you there, too, that work on even lower doses of therapy, right?

Dr. Mariam Hanna Right. And so, this is where we're looking at the SLIT and EPIT or epicutaneous immunotherapy data. Do those lower antigen doses then result in a lower ceiling effect, or are we going to get there?

Dr. David Fleischer Let's look at the data from Edwin Kim, who's done most of the research with peanut sublingual immunotherapy besides the study that I did in adolescents and adults, which is a whole different world when you start talking about adolescents, adults, and trying to do immunotherapy for foods, because compliance is just a big issue with anything daily. But

when you look at his one to four-year-old data—and I would argue that's four milligrams that you're using at that point—a lot of those kids are probably swallowing the sublingual immunotherapy. So, I consider it almost "baby oral immunotherapy" at four milligrams in those little ones, right? But it worked quite well. I mean, the desensitization is somewhere in the 60 to 80 percent range, depending on protocol or intention-to-treat. When you look at remission rates, that drops a little bit—but it drops with most studies—but it was about 50 to 60 percent maybe had some remission. And it really pointed to also there, when you broke it down by age stratification: as you looked at the one to two-year-olds, your remission rates were higher than your three to four-year-olds, right? So, the younger you are, the better the therapies tend to work, because you're just catching these patients when maybe their immune system is less mature, their Ig levels aren't as high, so you're not fighting off these high levels. But sublingual immunotherapy at four milligrams—or "baby OIT" if you want to call it—even lower than that 30 milligrams, still works quite well to get patients to multiple levels of peanut protection. And the nice thing about sublingual immunotherapy is, at least with studies we've seen, maybe the exercise rule isn't as important to have to manage; and avoiding exercise the hour before and two hours after illness is probably not as big a thing. You probably don't want to dose when you have a really big febrile illness or don't feel well, like the flu, but your average cold you probably could dose through with sublingual immunotherapy. It's much more forgiving, I think, at lower doses, is what I'm saying, too; and I think that's what you're seeing with the 30 milligram versus 300 or 1,000 with oral. So, I do think sublingual immunotherapy is an option, and you guys in Canada have been doing very good studies in Canada with those and actually making real-world products, not just using extracts and things like that, so you've proven that this is a safe and effective treatment. And the FDA, at least in the U.S., is looking at tablets, but there are companies now that make sublingual products that we will actually start using in our practice, hopefully in the next few months, because we want to have sublingual as an option because there's less up-doses. Again, the exercise rules and illness don't have effects, and again, low and slow is not a bad way to go, I think.

Dr. Mariam Hanna I want to get at this sustained unresponsiveness and remission, because, one, the definitions are a little bit elusive depending on the trial that you look at, and, two, is there meaningful data to say one way causes this to happen more than the other, or one phenotype is more likely to get there more than the other? So, can we unpack that a little bit, if you don't mind?

Dr. David Fleischer I wish we could unpack it completely. We don't have the precision medicine; that is the problem, right? I mean, we still don't know why some patients get food allergy in the first place. We certainly don't know why some outgrow it and others don't, or some outgrow it sooner than others. Why did only 20% outgrow peanut versus 80-90% milk and egg by five years of age, right? And which ones do that? And we don't have the targeted precision medicine to say: "You're best for this therapy, and this is going to be best what works for you." It really comes down to what are the—I look at, when I look at any of these immunotherapies, I look at three things: the efficacy, how well it works, right? And then that's the goal of the parents and how quickly they want to get there, the safety of it, and then the practicality of it—how easy is it to use, and is it going to fit into the daily activities that you have to do? I know we didn't talk about the epicutaneous immunotherapy, and I'll just mention that briefly now, just because I

think that's a good option as well. That's even lower dose immunotherapy at 250 micrograms, so you're talking a thousandth of a peanut. But the test study that just came out when we presented the results at the AAAAI meeting in February showed that in four to seven-year-olds, about 50% of those patients were responders by definition. And again, there were additional patients that still responded to the drug, but didn't meet an endpoint. Same thing with Outmatch, where you can argue 70% may have hit a targeted endpoint, but still there are probably 20% that are still responding to the drug. So, epicutaneous immunotherapy is another option that's low and slow, and you don't have to worry about illness, exercise at all, or NSAID use. I mean, it's a very practical kind of product to use, and we're probably about a year away from that being FDA-approved, which is going to be good. So, to have three different options, it just depends. You have to be a little more patient with the epicutaneous immunotherapy because you're using such a low dose. But back to your question about clinical remission or sustained responsiveness, it's a term that's gone over changed. It used to be sustained responsiveness, and now the newer term is remission. And I'll argue a clinical cure or a clinical remission is a term that we're trying to use publishing our data with our OIT program. But basically, what you do is you're stopping the therapy for anywhere from one to up to six months—like in the IMPACT trial was six months long, and you lost a lot of those patients after six months. But in clinical studies, you're looking for a sustained effect. I think in a clinical program, I don't do that. I don't stop the therapy because why am I going to risk losing up to 60% to 70% patients to desensitization loss over that time period when, if they're eating it in their diet, again, their tests are going lower or their tests are becoming negative, what do you call that? I call that a clinical remission at that point, in my opinion, because again, if you're eating it regularly in your diet and you're not having side effects from it and you're getting to normal doses of things, we've got to call a spade a spade at some point and say: "This is a clinical remission." And then the decision is, what do you do with EpiPens and things like that, or epinephrine and things like that over time, right? So you have to determine that with a decision-making process. Can you get rid of the EpiPens at some point? I mean, the hard part with peanut and the tree nuts and the seeds, as you know, is you have to actively seek those in your diet to keep them in the diet, right? Versus if it was milk or egg or wheat, you're going to find those things in your diet all the time. So you don't have to worry about peanut allergy coming back, because we know there is recurrent peanut allergy in a small study that I did 20-something years ago, where 8% can come back. So we're trying to prevent that from coming back. So we tell patients: "If you're eating peanut once a week, several times a month, in some significant amount, and your tests are negative, I'm going to call that a clinical remission." And we've gotten to that point with these little ones that we start—when we start them in infancy and toddlerhood, right when they fail early introduction—by four or five years of age, they're just eating peanut and they know nothing different.

Dr. Mariam Hanna What about reaction rates between the different doses of OIT? So we've talked about like 30, 300, 1,000. We said historically 3,000. We won't touch on that one as much. But reaction rates across the different forms of OIT. Let's leave EPIT and SLIT away or "baby OIT" away from this for now.

Dr. David Fleischer Yeah, I mean, the biggest thing that's been shown is with any of these therapies, honestly, is you're more likely to have a reaction on therapy than if you just avoided

the food. So that's the biggest trade-off that families have to decide: if the benefit of being on the therapy and increasing your threshold outweighs those side effects and the risks of being on that therapy. And for most patients, they really feel that's worth the risk. And I look at it as a calculated risk—at least with oral immunotherapy, you know, you're giving your child the dose, you're mentally and physically prepared to treat a reaction versus if you had one, just so you come home or you're coming from school or you're at a restaurant or friend's house and you eat something, you don't know what's in it and suddenly have a reaction, you're not ready to maybe treat, you don't know what to do exactly. But here, you know, you're giving your child the dose and you're watching them carefully. I mean, the risk of a reaction, if you look in some of the big studies that got a product approved for peanut immunotherapy that is now no longer—not going to be used anymore, unfortunately—the reaction, systemic reaction rate was almost 15%, right? So it can be as high as 15%, but I think it's not that high depending on how you look at number of reactions per doses and things like that versus percentage of reactions within patients. So when you look at a per-dose reaction rate, it's quite low. So I tell parents, yes, you're going to have an increased risk of a reaction, but it's still quite low. In our patient population, since our median age in the OIT group is around two and a half years, our reaction/anaphylaxis rate is about 1 to 2%, to be honest. So it is quite low, but it is higher than if you just avoided the food. And it's not just allergic reactions. You can have an allergic reaction in the esophagus that can happen in 5 to 10% of patients, they say. Although we don't really know the exact number because most patients don't get endoscopies done to prove that you've got the eosinophilic esophagitis-like disease. But GI side effects, when you look across studies, about 10%, 12% drop out because of GI side effects. So those are the two big things: allergic reactions and then GI/gastrointestinal side effects from the therapy from OIT that you really have to worry about. But you do have to worry about the cofactors increasing or decreasing those risks by exercise, illness, and things like that. So from a practicality standpoint, it does have some issues where other therapy is a little more practical to use, like EPIT and SLIT.

Dr. Mariam Hanna And are those reaction rates or side effects higher between 300 and 1,000, for example?

Dr. David Fleischer From what I've seen, yeah, there are more reactions and more time to get there, relatively speaking. When you're up-dosing more, you're just more likely to have more reactions, right? But you get a higher level of protection. You may get to a clinical remission, I believe, possibly quicker; but there's been no head-to-head study of really looking how patients get to that sustainable responsiveness or remission rates with the different doses.

Dr. Mariam Hanna Fair. And what patients or allergens are better suited for like low versus high-dose OIT? We talked about like goals and preferences, but is there a particular patient phenotype or an allergen that's better suited for either approach?

Dr. David Fleischer No, I don't think so. I mean, if you've got someone that's had a really bad anaphylactic reaction, you may want to consider just going really low at first with those patients just to give them the confidence that they're not going to necessarily have an anaphylactic reaction to the therapy just because they've had a severe reaction before. And when you look at these clinical trials, there are patients that are excluded primarily for the reasons of the

double-blind challenges that have to be done and the risk of doing challenges. So they exclude patients with severe asthma or certain levels of inhaled steroids or exacerbations and things, or they've had severe anaphylaxis and been intubated—which is rare, but being in the ICU is still another risk factor. So they just exclude those patients. But those are the ones that probably need it the most. And maybe those are the ones you want to go really low and slow with, because the patients may be very anxious as well to do the therapy. And then if you can get them to that 30 milligram and not have to up-dose them a lot, and then do a challenge later—and like they did in the LOMO study and show that they can get to a thousand milligrams still by going low—that may be enough for them. Some patients want to get to 300 milligrams, which is about a peanut, which is—in studies, mathematical modeling studies—when you get to that 300 milligram level, you reduce your risk of cross-contaminated product reactions by 99%, essentially. So again, it really depends on what your goal is. If your goal is just to get to that level, then maybe you go low. If your goal is to get to free eating, then maybe you really need to get to higher doses. But longer therapy, I worry about kids just being in compliance as kids get older doing these therapies because as you get—especially with OIT—why it's so much easier to do in one to three-year-olds or one to four-year-olds is because they're just not in after-school sports. They're not going to be missing school to up-dose and things like that at important ages. So I do think it's good to have options that really show that low-dose works really well and you don't have to push these patients to higher levels where you may get more reactions or more GI side effects.

Dr. Mariam Hanna And before we get too far away from it: you said in maintenance in patients that have clinical remission that maybe we're dosing them once a week or reducing the frequency of dosing, with one of the big barriers being exercise precautions in the more active children. Do those exercise precautions change in maintenance? Is the age-old question I keep getting asked.

Dr. David Fleischer Yeah, I know. I keep getting that too. I mean, at some point, you've just got to let them exercise and eat like they normally do. But I think the nice thing about getting the dose down to once a week is kids aren't in sports seven days a week. So they're usually three to four days a week. So it just makes it much easier. So I think you just have to be practical with these therapies. You've got to adapt. I mean, as a food allergist, you know, you have to be adaptive. Things you think are going to be the same in one patient are completely different. The numbers, the reactions you have... So, food allergy is just—it's fun, but it's confusing, and I often feel that there's just—there's more of an art to the science to it sometimes.

Dr. Mariam Hanna So it keeps you humble every day. I agree.

Dr. David Fleischer No, we had a bad reaction the other day that I would never have expected, but it just—it happens. But I think the big thing is that parents really just don't want to do nothing at this stage in their lives with their kids. They really don't want to sit around and wait for reactions to happen. So many more patients, as I'm sure you've seen, come in very proactive and say, "Look, I don't want to... I want to do something." Even if my child may outgrow it, if they can outgrow it sooner and have a better quality of life during those four to six years when they may outgrow it, then why not do a therapy if it's safe and effective and practical to do, right? And

if we've got three or four choices or five or six choices, and we've got Xolair too as an option—but that's not a great option for every patient because it's a shot and nobody likes shots. So, but if I've got five or six things in my toolbox to use, that's pretty cool. And then parents can choose along with providers when we do those consults for food immunotherapy: "What's the best therapy that fits you at this time?" And if it doesn't fit and it changes, you change to something else.

Dr. Mariam Hanna Perfect. You touched on Xolair. Let's talk about that and other biologics as well coming into this landscape. How's that going to change our dosing conversation? It sounds like we're going to add an extra option and a longer consult, but what else?

Dr. David Fleischer Yeah, no, Xolair, I think, is a good drug for the right patient, too. I think if you've got multiple food allergies, you're highly atopic, got some asthma, allergic rhinitis—it can help with other atopic things, but it's really meant as just the protection. It's not disease-modifying. So, that's the problem. You stop the drug and your protection goes away. So you're not inducing anything permanent. So, I think there's several subsets of patients where we look at Xolair. I've got young patients that have never been able to do anything with milk, egg, or wheat. They want to use that as a bridge to oral immunotherapy. Now that's an off-label use of Xolair because it's supposed to be strict avoidance. But I think if I use that to get them on the food and get them off Xolair in a few years, that's judicial use of that drug, obviously, I think, in that way. Then there are older patients that also have maybe milk or egg or wheat, but have also peanut and tree nut and seafood. They don't care about the nuts and the seafood, but they sure as heck want to eat milk and egg and wheat, right? So they want to do some OIT. And then there are the true patients that the indication is truly for, where you just don't do any OIT while you're on Xolair. They just want protection and they're willing to do it. But it's got its downsides. It's one to three shots and it's every two to four weeks, and those shot numbers can change and the frequency can change as you get bigger. And there are better biologics coming for anti-IgEs with another molecule from a company that's looking at maybe injections every two to three months. So if you can get a quarterly injection, or there's blocking antibody from another company that may be an injection every six months. So if you can get down to quarterly or biannually injections, that's pretty good. So I think it's an option for patients, but it's not for everyone. And I think other biologics that are coming—they looked at dupilumab, and dupilumab did not work for food allergy. They did two studies, one with OIT and one with peanut-allergic patients. And the company's not going for the indication for food allergy. It does lower your Ig levels and skin tests. So it's deceptive in that way, but it doesn't seem to desensitize. And then there are biologics like BTK inhibitors. Remember, Bruton's data were presented at the AAAAI as well. Acalabrutinib data from a previous adult study showed that within two days of using that drug, you can get to four grams of protein, which is crazy. With just two days, four doses, right? So I think, again, we worry about what some of these other drugs are used for. And if you eliminate BTK—the Bruton's tyrosine kinase—completely, you have an immune deficiency. So we worry long-term about some of these things. But Xolair's got 20 years of safety data. Epicutaneous immunotherapy has actually 20 years of safety data from the first phase. So you've got some good safety data with some of these things. So I just—you have to worry about some of the—there's some oncological drugs that are being considered, like a multiple myeloma drug in conjunction with dupilumab to knock out B-cells and knock out IgE production. I just

worry about some of those bigger-gun ones, because you have to explain those drugs where they're used already. And you say, "Well, this drug is used in cancer," and I can use an anti-IgE that just blocks IgE. Which drug are you going to choose? Probably the one that's been around for 20 years and just blocks IgE, right? So we have to be cognizant of what these drugs are used for and how easily it's going to be to explain them and the safety of them. And then you need long-term data on these things, because short-term, yeah, I could use the BTK—the Bruton's tyrosine kinase inhibitors—maybe for two weeks before a trip to Europe or something for someone that wants protection and use it. Or you could use it as a bridge to get them desensitized, to get them on OIT at higher doses. So I think there's different ways to be creative with these things. But I always tell families: "It's a good time to have food allergy." I don't want you to have food allergy, but it's not a bad time to have it because there's a ton of research going on with different things that are coming. So there's a lot more stuff coming. And again, the more choices we have for patients and families, that's really what I want. And then the families can really choose what's best. And then we need to get to the point where we get to precision medicine with food allergy. I just don't know when we're going to get there. It's probably not going to be in my lifetime, but we'll get there at some point.

Dr. Mariam Hanna AI's on it. I don't know.

Dr. David Fleischer I know, I know.

Dr. Mariam Hanna Now there's exponential learning we can all have now.

Dr. David Fleischer Maybe it will. I hopefully have another 20 years of my career, so maybe it will come in 20 years, but we'll see.

Dr. Mariam Hanna All right, coming soon and/or in 20 years. All right, time to wrap up and ask today's allergist, Dr. David Fleischer, for his top three key messages to impart to patients and physicians on today's topic: high-dose versus low-dose versus baby-dose versus EPIT versus SLIT versus the options are expanding with biologics. Dr. Fleischer, over to you.

Dr. David Fleischer I think the first thing is that parents want to do something. So, do therapies. Don't be afraid of these things. I mean, this is going to be the mainstay of treatment. I mean, the years of when I first started was avoidance, and that's it. I think families, as I mentioned, want to do something. So I think allergists need to be prepared for that conversation, that they need to get on board with these therapies, that there are safe options. The second one is that there are options and there are more options coming. And it really comes down to establishing the goals of what these therapies are for the patients and making sure you can fit those goals. And the third is: be flexible, too, is that you can switch between things. If one thing doesn't work, don't get discouraged. There's more coming. And it's a fun time to be a food allergist, because I can do something now, right? Before, I was just holding—sitting on my hands, too, like parents—and saying, "I'll see you back in a year or two." So it's a really fun time to do these things now. So I think the variety of options just give us a lot of things to be hopeful for. And the more research like you're doing in Canada and around the world is really going to get food allergy, hopefully, to that precision point, like you said, in the next 10, 20 years. So the future really is targeting the

right therapy for the right patient. We'll get there. I just hope it's quicker than what I'm saying. But they always talk about what's the surrogate for the food challenge, and I don't know if there's ever going to be a surrogate for that. But it's a conversation that we're having, which is much different than we would have had 20 years ago, right?

Dr. Mariam Hanna Absolutely. Absolutely. It's a fun time to be a food allergist. I love it. Thank you, Dr. Fleischer, for joining me

Dr. David Fleischer. It's a fun time to be an allergist in general. You're very welcome.

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