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 hate vomit. There, I said it. It turns my stomach even thinking about it. Profuse, protracted vomiting, turning ashen gray in color, maybe pallor with or without lethargy, and perhaps some diarrhea. But that's not really what you would write home about, given the torrential vomiting. Dry heaving back to vomiting. That's really the highlight of this condition. Lots and lots of vomiting. We're humbled when we witness the profoundness of this condition in person. We each likely have a terrible FPIES story or have heard of one. One done in the hospital—we had one recently—went down fast, hypotension, went to the ICU; another child vomiting in clinic. That one we actually had no previous suspected condition of FPIES. We didn't think it was going to be FPIES. And there you go. Vomiting. Today's guest is going to set us straight on this unique condition in the world of food allergy. It's my distinct pleasure to introduce to you Dr. Nowak-Wegrzyn. She is a professor of pediatrics at NYU Grossman School of Medicine and director of pediatrics, allergy, and immunology division at Hassenfeld Children's Hospital. Her research focuses on egg and milk allergies, food-induced anaphylaxis, novel approaches to food allergies, including FPIES. She serves on the AAAAI board of directors and is an associate editor for the Annals of Allergy, Asthma, and Immunology, the Journal of the American College. Dr. Nowak-Wegrzyn is known for her work in leading the creation of the first consensus guidelines, aka the Bible of FPIES, for the diagnosis and management of Food protein-induced enterocolitis syndrome . Dr. Nowak-Wegrzyn, welcome to the podcast.

Dr. Nowak-Wegrzyn: Thank you, Mariam, and thank you for having me.

Dr. Mariam Hanna: Let's start first with the basics for everybody to get on the same page. How do we define FPIES?

Dr. Nowak-Wegrzyn: FPIES is a form of food allergy, and it is a non-IgE mediated food allergy. So it means that we typically have negative skin tests, blood tests, so classic allergic antibody does not play a role, and it has a distinct phenotype. In an acute form, it presents as projectile, profuse vomiting that can be 5, 10, 20 episodes, and it starts within two to four hours after eating the food. So this is much more delayed than classic food allergy and is frequently accompanied by those very upsetting symptoms of pallor, lethargy, floppiness, low muscle tone, and some patients may become hypotensive.

Dr. Mariam Hanna Is there a difference in the age of presentation that you see with FPIES patients?

Dr. Nowak-Wegrzyn: Well, we know that most of the time it starts in infancy, so shortly after the food is introduced. So typically for milk or soy, if they're introduced in a form of infant formula, this will be the first few months of life. For solids, it will be probably after six months when food solids are typically introduced. And rarely, this form of infantile FPIES would start in children older than twelve months if they were not exposed to the food. So, for instance, they reacted to oat, and the introduction of wheat was delayed, and then they introduced it when they were twelve or thirteen months. But this is the most common presentation that we see in the allergy

office. Then FPIES to seafood starts later. So we know that we can have children who are five or six or seven that will start reacting to shrimp or to fish that they have eaten before, but they ate it infrequently. And then we also have FPIES that starts in adults. And this is really quite mysterious because those people have eaten the same food for 20, 30 years, and as a young adult or an even older adult, they will start reacting with exactly similar—well, not entirely identical—symptoms, but close enough. So the major difference between adults is that adult FPIES seems to be more common in women, significantly, like a predominance of females, like 70, 80% in all of the case series. And also, the symptoms may start a little bit later. So they start up to six hours after eating the food. And sometimes vomiting is not present. So the most common feature or symptom is this excruciating abdominal pain. And I say excruciating to the point that people describe it as being on the floor, unable to move, like really out of it, but some of them don't really get vomiting or diarrhea. And this is a major difference between the two.

Dr. Mariam Hanna How would you describe it to a patient, the severity of the symptoms to expect if they've had just, like, a severe presentation in the past? Are they a more sensitive patient with FPIES versus the one that's only had a bit of vomiting and just needed some support at home?

Dr. Nowak-Wegrzyn: Yeah, I think it's a great question because we don't have a biomarker to diagnose or to predict severity. But in my practice, when I see an infant who took two bites of a baby cereal or egg or a taste of peanut and ended up in the emergency room needing IV fluids or being admitted, this is severe, and I do worry that the future reactions may be more severe. And this has been supported by the data from our colleagues in Michigan, who analyzed a large cohort of patients. And the only feature of everything that they analyzed that predicted the severity or the need for IV fluids during the challenge was the severity of the FPIES reaction. So I do worry. Now, if somebody ate the full serving and they vomited and became sick, then, I don't know. I'm thinking maybe if they tolerated a small amount—if I introduce a smaller amount, the symptoms will be milder. But there's always this kind of red flag in the back of my head that says, oh, this can be a problem. They really can surprise us.

Dr. Mariam Hanna Okay, now to the more challenging part. How common is it for there to be more than one trigger or another food of concern? How often do we see that?

Dr. Nowak-Wegrzyn: So, probably between—depending on which study you look at, which patient population—between 50% to 75% only react to one food or one food group, because sometimes we, for the purpose of introduction, we group them together in a related food category. So really, multiple food FPIES—and this is consistent across the studies—is less than 10%. So about 20, 30%, or 40%, depending on the study, might have two. So the majority will still have one. So I think it's very important to explain this to the parents. And yet, in the 2017 consensus guidelines, that table where we talk about low, medium, and high-risk foods, many families have looked at that and now are starting to flag other foods that they're too scared to introduce. How do you counsel around that?

Dr. Nowak-Wegrzyn: Well, the table—so that's good, because we are going to rewrite that Bible, as you said, and we're definitely going to remove the table because the table was meant to facilitate the introduction, not to scare people away. And the idea was that you would first introduce the foods from different food groups that you reacted to. And there were some suggestions, and it wasn't meant as a—so it was more of a roadmap than a prescription for specific food introduction. And this changes all the time. In 2017, we didn't really think much about avocado FPIES. And all of a sudden, now, then, avocado has become such a popular weaning food, now we see more avocado FPIES. So the truth is that any food can cause a reaction depending on the—and we still don't understand why this happens, why that particular food that is introduced at that particular age, that point in time, is causing a reaction. I'm sorry, I don't have a good answer to that. Maybe it's a microbiome issue, the maturity of the gut. Your guess is as good as mine. But certainly do not use that table as the absolute prescription for what you can eat or not. And it really has to be modified. Another point, or issue with the table, is that it was really pre-guidelines for early introduction of peanut and earlier introduction of peanut and eggs. So they would say, "Well, let's delay the introduction because those are potentially higher-risk foods." So it's more of an encouragement to empower caregivers to take the next step. And there's some art to managing patients with FPIES, and you start slow and have lower expectations. Introduce one or two, play with the textures, and it really, if they have successful introduction, it empowers them.

Dr. Mariam Hanna That is super important. Okay, I want to know about chronic FPIES. One, is it real, or is it fake news? How often do you actually see it or make this diagnosis of chronic FPIES?

Dr. Nowak-Wegrzyn: So it is real.

Dr. Mariam Hanna Okay, it is real.

Dr. Nowak-Wegrzyn: It is real. The tricky part is that we don't have a biomarker, and the symptoms of chronic FPIES are quite elusive. So I think the real part that I can tell you for sure is real. If you have a baby that is getting really sick when it's being breastfed or well formula-fed or breastfed and is admitted with hemoglobinemia, hypotension, elevated white blood count, etc., and then everything resolves when the baby is put on an elimination diet or an amino acid formula, or like sensibly hydrolyzed. Right. So that's what I am most familiar with. I think what's—so the difficulty is that unless you challenge to prove, to induce the acute symptoms, you don't have a conclusive diagnosis. So it becomes a diagnosis of exclusion. It's an empiric diagnosis. And the typical picture that I see is that they are fine for a few weeks or a few months on the same feeding, and maybe have mild symptoms of reflux or maybe some loose bowel movements. And then it escalates without clear reason, that they start having more clear watery diarrhea, and they start vomiting more, and then they look horrible, and they are admitted, and then we see elevated white blood count, but there's no evidence of infection. There's no virus, there's no bacteria. They may have elevated platelets, they have increased methemoglobin. So all of those sort of classic findings that are nonspecific, yet they have been described with chronic FPIES.

Dr. Mariam Hanna Yeah, I think that's part of the challenge, is that there are some classic findings. They're nonspecific, and they probably lead to some misdiagnosis and also the flip side over-diagnosis in some situations. Okay, let's talk about other diagnostic challenges that you see. I've heard you say biomarkers, like, a bunch of times. So I assume that's one of our diagnostic challenges with this condition. What other challenges do you see?

Dr. Nowak-Wegrzyn: I think that's the biggest one, to be honest with you. In terms of diagnosis, I mean, we agree that if we have diagnostic criteria, we have diagnostic criteria that have those symptoms within four hours after the ingestion. I have repetitive vomiting, and you have no hives or classic allergic symptoms, and then you either have two or more reactions to the same food, or you have this similar reaction to another food, or there are some minor criteria that you can use to support the diagnosis.

But now that we talk about it, I think that atypical FPIES, right? Atypical FPIES. So we have the classic FPIES, no IgE delayed symptoms, and then we have atypical FPIES, classic symptoms of FPIES, delayed vomiting. But they have IgE, right. So you do a skin test or blood test, and sometimes it comes about serendipitously, because they have IgE to other food. We know that one in three kids with FPIES will have a classic IgE allergy to another food, or they have eczema or something. So you do it, and you find this low-grade IgE, and then are they going to be IgE? Are they going to be FPIES? You don't know. So you have to cover both bases, right? Because we don't know. If you have that phenotype that sort of keeps going back and forth between IgE and non-IgE, it really tells you it's a continuum, right?

Dr. Mariam Hanna: It's an intriguing condition for this very reason. Okay. So recently, a colleague and I were discussing how we work up a patient, and we disagreed a little bit. So I want your clarification, or what you would do in a patient that has a pure classic FPIES story in infancy of delayed, protracted vomiting, let's say, with lethargy, like very classic FPIES. Should we be skin testing them, or should we be doing blood work, or nothing?

Dr. Nowak-Wegrzyn: It's not going to be helpful unless there's some question about the presentation. And it depends on how you're going to manage them, because I have to say that I can tell you, I've never seen a positive test to sweet potato, rice, oat, I don't know, carrots or, I don't know, cauliflower. Those fruits, vegetables, cereal grains, I've never…now, it becomes tricky when you start talking about the FPIES, the classic kind of IgE food triggers, and especially if the kid has eczema, which happens in some of those kids. And then especially if you're saying like, oh, they had mild symptoms, maybe I'll attempt something like your ladder, right? Introduce like, small amounts of baked foods at home. I want to know, am I eating? Is there any possibility of the IgE? Because then I would be prescribing them. I would be teaching, telling them about immediate reactions. So those would be like, I think so the reason when I would test at baseline with the skin prick test, I don't usually do the blood test for those, would be milk, egg, peanut, because we're seeing more egg and peanut nowadays, and I think it was fish and shellfish or tree nuts. So if those are typical IgE triggers, I get a little bit more defensive about that, and I want to make sure that I'm not but the guidelines say this is not indicated. You

have to have a reason. So, you know, other reasons would be concomitant IgE-mediated allergy to a different food, history of anaphylaxis, history of wheezing, and eczema, which would all be associated with a higher risk of IgE.

Dr. Mariam Hanna Are we seeing more FPIES in general? Are we seeing more FPIES to specific foods, like peanut or like egg or like avocado?

Dr. Nowak-Wegrzyn: I think so. I mean, the only population-level data we have is from the 2019 study that we collaborated with Ruchi Gupta, and we estimated 0.5% of kids in the US have symptoms, have a diagnosis of FPIES as reported by the parent, and 0.22% of adults, which we report having that diagnosis. The question was, have you ever been diagnosed? And this is a very rare condition. So we were truly amazed by those responses. Of course, this is so much lower than the classic IgE, right? 8% in kids, 10% from that same kind of sampling method. But so 20 years ago, almost nobody heard of FPIES. So my gut feeling, no pun intended, is that we actually are seeing more, but we only have that one time point in time. So I cannot really say we have good evidence. Now, I definitely see more infants referred by pediatricians, and I see milder phenotypes than I used to see ten or fifteen years ago, which suggests to me that maybe there is an increased awareness.

Dr. Mariam Hanna Okay, let's go back to counseling that family that still needs to work on introducing other solids. We talked about the table. We talked about encouragement, empowerment, providing a roadmap. How do you do it?

Dr. Nowak-Wegrzyn: We've published this paper during COVID on how to introduce foods in FPIES, because we felt like there would be a lot of delayed introduction that could be associated with a higher risk of IgE-mediated food allergies and really wanted to provide some practical advice, and I do practice that. So, essentially, the first thing we say, okay, it's mostly one or two foods that the kid would be allergic to. The older they are, the less likely they are to react. The reactions are most of the time milder if you give them smaller amounts. And this may not be really convincing to somebody who reacted to a lick of a food. But then, that's a different story. We can address it separately, but if they had garden variety FPIES and now they are worried about it because they go online and read all kinds of horror stories, it is important to say that also, I would say the majority have mild, moderate—they're non-severe, that the subset of severe FPIES is a subset. It's a small proportion of those who are being diagnosed. And then if you choose the different food group, then you minimize the reaction. So, for instance, if a baby reacted to rice, it's not such a great idea to give them oat as the next food for introduction at home, even though this is a typical baby food, but it's the same food group. So we would go with a vegetable or a fruit or something crazy, like parsnip or something that is totally different, but it's still

appropriate for the age, right, for the feeding skills. And we prescribe ondansetron; it's not going to work for severe reactions, but for most of the mild reactions, it works. We tell them how to rehydrate at home. We explain what are the reasons to go to the emergency room, really? And in my mind, I would not do, let's say—I mean, if they had a horrible reaction in the past and now

they have vomited a couple of times, I would say, yeah, go. But a lot of the time, I'm just saying, just continue rehydrating, and only if they don't stop vomiting after several hours and they are dry. They're crying but not making tears, not making wet diapers. Yeah, then go, because you may need IV fluid. So we prep them, right. We tell them what to do. So it's all about empowerment. So they feel more in control of what happens. They know what to do. And then I just know that they become, with every food, they just become more relaxed and more confident, and they do it.

Dr. Mariam Hanna It's about providing that roadmap. This is perfect. That was a great summary of it. Can you clarify for me when you provide an ondansetron prescription? Is there a particular age where you don't feel comfortable prescribing it, or are you pretty comfortable prescribing it at all ages?

Dr. Nowak-Wegrzyn: Well, I mostly see them when they're older than six months, and that's, like, the official one. I hear from my colleagues that, like heme-onc, they are using ondansetron for younger ages, but I haven't because I really haven't encountered those patients. So, yeah, I'm pretty liberal with it.

Dr. Mariam Hanna Okay, what about for your atypical FPIES? If you've picked up on IgE sensitization, would you prescribe them an epinephrine auto-injector in case they saw more immediate or IgE-type symptoms with accidental exposure?

Dr. Nowak-Wegrzyn: So if they have, as I said, have other food allergies, and if this is, like, a three-millimeter reaction, then I don't. But if it's a clearly positive five, seven millimeters over negative control, etc., then I would consider doing this because I don't know—I mean, unless I do a challenge and really confirm that they're only going to have delayed symptoms. So, yeah.

Dr. Mariam Hanna How about counseling on resolution? What do you typically tell a family as to when we would expect resolution of their child's condition?

Dr. Nowak-Wegrzyn: So this is a great question, and I think there's some confusion about that. It's important for the caregivers to understand that this is a childhood food allergy, and a lot of the children will outgrow it when their immune system and the gut matures enough to digest the food. So a lot of them outgrow it by age three to five. Not all. And the more severe the phenotype to the particular foods, like horrible reaction to trace amounts or multiple food FPIES with severe presentation, those are the patients that may have more protracted courses and may outgrow it when they're teenagers or even adults. I mean, I do have cases of patients who persisted with their FPIES that started in infancy until they were 20 or 27, or there's some who are still reacting to the same food. So it's—with anything, it's not 100% that if you're—I think you're not helping your patients if you're guaranteeing—you cannot guarantee anything. You cannot guarantee that somebody will outgrow IgE-mediated food allergy. So you cannot say, oh, everybody gets better by the age of three. But being honest and just saying, yeah, most kids do, some don't, and we're just going to monitor. But the good news is that most do. So unless there's something really special about that child, then it's empowering, but I think it's

disempowering if you guarantee—you present it in a way that's almost like you guarantee, and then they don't outgrow it by age three, and then they worry even more because everybody outgrows that my child doesn't. What's wrong with my child?

Dr. Mariam Hanna What's wrong with them? Yep, absolutely. Okay, what about for adults? Do you talk about resolution in adults?

Dr. Nowak-Wegrzyn: Some do, but most of them don't. So at least, like, over a three-year period, most of them would still react. So I think if you develop it in adulthood, it's probably going to be more persistent. And we don't understand why people develop this in the first place. But we know now that adults develop IgE-mediated physiology more than we've ever considered in the past, and we need to learn what leads to the breach in oral tolerance. So in infantile FPIES, you don't develop tolerance. You have problems generating the tolerance. In adults, you had tolerance for years, and then all of a sudden, you lose it. So, it just tells you the immune system is dynamic. It's a very dynamic living system that changes. Could it be a virus? Could it be the kind of drugs you're taking? I don't know. Could it be a change in your microbiome? Yeah.

Dr. Mariam Hanna All intriguing theories and so exciting that we still don't know all the answers to do with FPIES. It makes it interesting to see what's happening next. Okay. The Canadians are excited about ladders, and there's no one better to talk to me about ladders. What is your perspective on the use of ladders for reintroduction, for milk and egg FPIES presentations? What are your thoughts on this?

Dr. Nowak-Wegrzyn: So I think that it's reasonable, and I'm doing it for people who have had—for children who had mild symptoms, mild reactions. I would not do ladders in somebody who had serious, severe FPIES, small amount, ended up needing IV fluids in the hospital. I would be wor ried about that because in my mind, they're more likely to react to the baked form of that food. But if you do that ladder in a gradual way, don't give them a muffin the first time they eat it. Just give them one-eighth or one-sixteenth of a muffin and do that. Okay. The next time you give them twice as much, and the next time you give them twice as much. And monitor for the IgE, for the gastrointestinal symptoms. I think it's appropriate. The issue is, how do you balance that kind of fear of reaction versus being proactive, using this proactive approach to management, and not delaying the introduction of foods, right? Like, we're keenly aware of that potential. You know, if you delay the introduction, you may set them up for the IgE-mediated food allergies.

Dr. Mariam Hanna That's what's intriguing about this condition and shared decision-making. I feel like that's the right answer to this question. All right, it's already time to wrap up and ask today's allergist, Dr. Nowak-Wegrzyn, for her top three key messages to impart to patients and physicians on today's topic, FPIES. Dr. Nowak, over to you.

Dr. Nowak-Wegrzyn: All right, so FPIES is real. It's both acute and chronic FPIES. It's not a myth, and it can be an allergic emergency. So it is important to recognize and manage appropriately. It is a form of food allergy for infants; it does go away. So, like other food allergies

that are IgE-mediated, many children will outgrow, will start tolerating the food by age three to five. But some will not, so it's still FPIES. It doesn't mean that there's something horrible. And then, when dealing with infantile FPIES, do not delay the introduction of solids. Really do not restrict the diet unnecessarily. And work with your allergist to come up with the best strategy based on shared decision-making on how to advance your child's diet in a responsible and safe way.

Dr. Mariam Hanna Perfect. Thank you, Dr. Nowak, for joining us on today's episode of The Allergist.

Dr. Nowak-Wegrzyn: Thank you, Mariam. I'm happy to join, and thanks for the invitation.

Dr. Mariam Hanna My pleasure. This podcast is produced by the Canadian Society of Allergy and Clinical Immunology. The Allergist is produced for CSACI by Podcraft Productions. The views expressed by our guests are theirs alone and do not necessarily reflect the views of the Canadian Society. This podcast is not intended to provide any individual medical advice to our listeners. Please visit www.CSACI for show notes and any pertinent links from today's conversation. The "Find an Allergist" app on the website is a useful tool to locate an allergist in your area. If you like the show, please give us a five-star rating and leave a comment wherever you download your podcasts and share it with your networks because we're all about improving your gut reaction. Thank you for listening. Sincerely, The Allergist.