

Early Life Feeding Choices and the Allergic March

Transcript

Editor's Note: This is a transcript of a live webcast presented on July 18, 2023. It has been edited for clarity.

Overview of the Atopic March



Jenifer Lightdale, MD, MPH: I like to start my talks thinking about the epidemiology of the allergic march and here, many of you may have already had some introduction to the allergic

march. There really is a conventional way we think about this where atopic dermatitis—or eczema—is really an entry point to allergic diseases. And you see atopic dermatitis early on in infancy, followed fairly quickly by development of gastrointestinal (GI) and then respiratory allergy comorbidities. And those really can continue to march through your life. So, even as the eczema and the food allergies may start to resolve, you have a lifetime of feeling sensitive to the world with asthma, and perhaps rhinitis or seasonal allergies.

And really our current concept of the allergic march is that things are not quite as step-in-line as we expect, but we still see this early occurrence of the atopic dermatitis along with development of food allergy and then those can really start to interplay, and you'll see other developments of allergen-induced type 2 inflammatory conditions like asthma and seasonal allergies. And then intriguingly, other non-IgE allergic diseases, which do affect us in the GI world (particularly eosinophilic esophagitis [EoE]), so I'll talk more about that.

In terms of epidemiologic data supporting the atopic march, there really are a number of studies, at this point, and these have held up in systematic reviews and meta-analyses showing that people with atopic dermatitis are highly at risk for other inflammatory conditions. And this concept that EoE, as a type 2 inflammatory diagnosis, is something we are thinking about in GI, and this is also highly associated with atopic dermatitis and food allergy and is probably another late allergic march manifestation. So, EoE is getting more interesting.

Why this happens is still something we're all understanding. There are probably a lot of systemic factors, perhaps something about your genomics or your epigenetics, certainly a propensity of the body to have a type 2 inflammatory reaction to things,

and then there are clearly tissue-specific factors about the person themselves. So, that might affect whether it's a local immune response, whether there's barrier dysfunction in the GI tract, and that can lead to what we call dysbiosis. And then also how the environment is playing in. And all of these are interacting with each other to put some people more at risk for this allergic march.

The GI system—of course, as a gastroenterologist, I believe is where it's all happening—and really, when you think about our GI system, it's a remarkable set-up for experiencing the world. Really, the whole gut involves a semipermeable barrier (our gut mucosa) that is designed to allow stuff to be absorbed—in particular, nutrients. But ideally, it's not absorbing pathogens and antigens that live inside the lumen—inside our gut. We really don't want those getting into our bloodstream. Ideally, the gut mucosa is designed to protect against pathogens and antigens, but the whole thing depends on healthy cellular and microbial architecture. And so the gut microbiome becomes very important. If it's healthy, it's helping the semipermeable barrier to allow absorption of nutrients, and then it's also protecting against pathogens. If it's disrupted (in what we call a dysbiotic scenario), that's when you may have inflammation, and also you get loosening of the gut mucosa and the tight junctions, so you get the proverbial leaky gut and more stuff can get into the bloodstream and literally allow, now, more inflammation to start happening. So, this is how the GI system becomes key to all of this.

The other thing we know about the gut is it's really where the immune cells are located. We think about 70% of the immune cells are located within the gut mucosa. So, if you put it all together and you think about your gut microbiome and your immune system and how the gut mucosa (the lining of the gut—the barrier) is really quite porous and designed to allow stuff to get in, you can see how it's all quite complex, and then we also have a number of signaling pathways. All of this has the microbiome playing a role in protecting us, but also in allowing things to get into the gut. Through that, you can get tolerance,

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where you develop tolerance to things or you can be sensitized to potential allergens. You can also get more inflammation going. Really, what it's all about is keeping our gut barrier intact and having good, tight, epithelial junctions.

All of this gut stuff then gets [us to the] key to understanding the allergic march, and if you want to move beyond the allergic march and think about how the microbiome plays in, it's what we can then also start to describe as the food allergy pyramid. On the right side of this slide, you see that the microbiome is really key. If that's not healthy, you get dysbiosis. If you have dysbiosis, you have epithelial barrier dysfunction of the gut, which basically means more stuff is able to leak through. That's the increased permeability. You get the immune system not able to tolerate what's coming in. You get hypersensitized to stuff and, before you know it, you're very dysregulated, and you're on your way to being very sensitive to the world. And this is why, on the left side of the slide, we're talking about gut dysbiosis as something we want to recognize as potentially modifiable. This may be a target for something we need to get better at preventing.

Long-Term Effects of Food Allergy

I'm going to talk quickly about long-term effects of food allergy and, really, the key to recognize about food allergy is something we all have felt, I think both professionally and personally. As I always say, I don't really remember anybody with food allergies when I was first training in medicine in the early 90s, it was rare really, and at this point, we do say it's about 5.8% of children will have some diagnosis of food allergy. And then, when you do have a food allergy, you are worried about it, but more importantly, in pediatrics, the parents are very worried about it. So, parents not only worry that their children have food allergies, but consider them to be severe.

This burden of food allergy as a public health issue is very real. We see that there are more emergency department visits. There are big emotional effects on our patients. Really, parents have to think about food allergy often, and there are studies showing that parents are really afraid of food allergy. And then it does have social effects on children and creates challenges for parents navigating social events for their children. So, how

to go out to restaurants, go to birthday parties, or just be a normal kid. It also has a tremendous financial burden when we have kids with food allergies.

And really, when we put all of this together, what I think we want people to recognize is that the gut microbiome is interacting with the immune system. It's probably the key to us developing immune tolerance or perhaps to being sensitized. That later issue really occurs with gut dysbiosis. That's where you have dysregulation of the immune system which promotes immune hypersensitivity and leads to type 2 inflammatory conditions (many of them often), and food allergy is really an early component of the atopic march with a considerable public health burden. Even though we see food allergy improve over later childhood, it's a signal that the person may be sensitive and have allergy in other ways, and it is taking a toll on the families of children with food allergies.

Nutrition-Related Strategies for Preventing Food Allergy

What can we do about this? I mean, this becomes the big critical question and I think a couple of strategies I want to explore in this next part of this talk really involve nutrition. Because I think many people have looked and explored and believe they understand how nutrition relates to strategies for preventing food allergy.

Breast Milk & Formula

I'm going to start, first, thinking about infants and their nutrition which of course is breast milk and formula. And here I think what we want to highlight is that studies have shown that there are potential protective factors against the progression of the allergic march, and many of them are nutritional factors.

Most certainly, breastfeeding is something that seems to hold up as a potential protective factor against the allergic march. What microbial impact we've had (so what you've seen in terms of exposures) and that I'll show you can be a little bit dependent on what your experiences have been to date. In terms of the gut barrier, we think about where special formulas play in, so I'll talk a little bit about that. Certainly, across all aspects, we're wondering if we can play with the microbiome by introducing

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what I will call good bacteria. I don't mean to be judgmental, but these are probiotics. These are hopefully bacteria that can have a positive impact on our microbiome. And then, in general, the quality of diet can really play into preventing progression of the allergic march.

Speaking first about breast milk, because it's so important. We know that breast milk indisputably is providing optimal nutrition through the first 6 months of life. So that's really important to state and to hold as an absolute firm principle for all that we think about in terms of human breast milk. However, I think it is also important to recognize that its role in allergy prevention has been more difficult to pin down. At this point in various systematic reviews and meta-analyses, I think we're pretty confident that the benefits of breast milk include lower risks of infection, can actually prevent obesity, and can be helpful with certain autoimmune disorders.

But the evidence isn't there yet—or at least our understanding of how human breast milk plays into allergy prevention remains a little bit harder to pin down. And so, when we look at this available data, what we're seeing are variable effects, and we're getting some signals about how breastfeeding plays into atopic disease risk. In particular, we see that exclusive early breastfeeding does appear to reduce atopic dermatitis. So it helps with the eczema, and if the eczema is sort of the entry into this world of the atopic march, that gets very important. The other thing we know about breastfeeding is it's not a one-time thing. It's really about duration, and we see that longer duration of breastfeeding can help and, in particular, it can help with childhood wheezing and asthma. The trickiest thing to really link to breast milk is the food allergy piece, and there really is an inconclusive association, at the moment, with risk for IgE-mediated food allergies. So again, you can promise many things about breast milk, but perhaps not that it's going to prevent food allergy itself.

Some of this variability appears to be related to timing, and I'll start talking about important windows of opportunity for both exposure as well as developing tolerance. So, a very important study came out, now, a couple of years ago, right before the pandemic, that really looked at how cow's milk formula exposure plays into cow's milk allergy, with specific interest in

the timing of that exposure. They called this the ABC Randomized Controlled Trial. It was done in Japan, and what you see is they were able to take babies who were going to breastfeed, and if they had to be exposed to a formula (perhaps because breastfeeding wasn't going very well) in the first 3 days of life, they randomized the babies to either get an amino acid-based formula or to get a regular cow's milk formula. And then they looked to see whether there was cow's milk allergy at age 2 years. And what the data showed fairly conclusively is if you had the amino acid-based formula, you were less likely to have cow's milk allergy at 2 years of age. This is looking at the very first 3 days of life and then looking at what happens at 2 years of life. What we did see, also, is that the cow's milk formula in those first 3 days of life also increased the risk of asthma or recurrent wheeze.

That data really winds up being put also into the context of thinking about continuity and, in particular, what we started to look at is not just whether you get exposed in the first 3 days of life, but also whether you then go back to breastfeeding or whether you continue to have exposures to cow's milk formula. And what's very important about this follow-up study was that you could see that babies who had continuous feeding (so they got some exposure to cow's milk formula right in those first 3 days of life, but then they continued to get some exposure as they continued to breastfeed), those babies actually had the lowest risk of allergy compared to babies who discontinued the cow's milk formula and then may have picked it up again somewhere between 1 and 5 months. So, really, whether there's continuous exposure or not to cow's milk formula—that becomes very important.

And what was also seen here is it may also have a little bit to do with the volume of milk exposed. Again, we're looking at timing: how long were you being given the formula exposure for? And then also what they're looking at is how much you're getting, and what formula you're getting. And what you're seeing is if you had more days of formula ingestion, and you had more formula overall, you actually lower the risk of the cow's milk allergy.

A study that I was involved in that sort of put all this together used a prospective, longitudinal cohort where there was

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documentation of whether formula had been given in the hospital after delivery, then again there was a sense of whether the babies were only formula-fed, only breastfed, or had a combination. And then we were looking whether you exclusively breastfed for 6 months (with absolutely no formula given in those first couple of days). And you really start to see what we call critical windows of opportunity, where a little bit of formula right away with continuous exposure is probably going to be your best bet vs the exclusive breastfeeding for 6 months, and then the exposure to cow's milk after 6 months, often with formula.

I think, across all these studies, what we're starting to really talk about is—regardless of the timing of formula introduction—it's still so important to talk about this formula exposure as supplementary. In the end, there are too many benefits to breast milk not to focus on breast milk as so important, but really to also recognize that if formula must be given in the first couple of days (again usually because breastfeeding is not going well) that's something to recognize as a trigger and that continuously now giving some formula may be helpful for preventing allergy.

In healthy infants, there's really no clear role for doing anything but a standard formula, and really standard cow's milk formula is going to be the preferred choice for healthy infants. And if you're saying, well maybe if we could work with a different formula to prevent allergy: it's pretty clear at this point that soy milk, goat milk, and formula made from other mammalian milk is not going to be helpful.

Microbiome Support

Alright, so what are the other options for preventing food allergy? Here, it's really what can we provide in nutrition that will provide microbiome support (so avoid dysbiosis)? We're going to talk about another window of opportunity. This is the window of opportunity for modifying the microbiome, and we do know that it's all about those first 1,000 days of life—so really, the first couple of years of your life, when you have rapid development and maturation of your metabolic, endocrine, neural and immune pathways that are all involved in microbiome development. When we think about the first 1,000 days of life, we're really getting ahead of the baby being born.

We're thinking about prenatal factors, and maternal microbiome is probably critical—not just GI but also vaginal and skin and basically the maternal microbiome. What's the mode of delivery? And then in terms of postnatal factors, we definitely are interested in antibiotic use, diet, environmental exposures, types and timing of complementary foods, and probiotic uses.

I think a lot of interest is being paid now to these external factors because that seems to be the stuff that we can modify. And what we're also recognizing is that, as the microbiome matures, you're going to have real replacement of, if you will, the neonatal microbiome, which is really heavily *Bifidobacteria* and *Lactobacilli*. And you're going to start to get much more diversity in the adult microbiome. And that's really critical for digesting complementary foods.

Another thing we're really interested in is how nutrition itself supports microbiome development, and here there's been increasing interest, in the last few years, around the milk fat globule membrane (MFGM), which is a lipoprotein structure that surrounds the fat globules in milk. It turns out it's got a lot of different proteins in it that are important for GI, immune, and cognitive development. But to the point of this particular section of the talk, what we also know about these MFGMs is they interact and adhere to *Lactobacilli* and other microbiota. So, it's believed that codelivery of MFGMs—which are very prevalent in breast milk and can be prevalent in all mammalian milks—with the right microbiome (so with the *Lactobacilli* themselves) actually seems to be helpful for seeding the microbiome and basically making sure that the good bacteria are able to get through the harsh GI environment and make sure the microbiome has those *Lactobacilli* healthy as they arrive to become part of the baby's microbiome. So, there are a number of studies now that have thought about how we can really provide that type of nutritional support for the bacteria that we think are good for babies in terms of the microbiome, and those seem to play a role in the brain-immune-gut axis and, again, a number of different studies have been looking at this.

Complementary Foods

What about when to introduce complementary foods? How can we use that to try to prevent food allergy? One of the things that you need to understand, if you start thinking about

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complementary foods, is how that will affect the microbiome. And what's pretty clear is that, once complementary foods are introduced, the microbiome undergoes rapid structural and functional changes. And this is really when [the microbiome] starts to increase in diversity—gets beyond the *Lactobacilli*- and *Bifidobacteria*-predominant strains and into much more adult-like microbiome. It's believed that a microbiome suited for an adult is better for our diet, which is much more diverse than just breast milk and/or formula. Compared with infant diets, adult diets have a lot of carbohydrates; they have fiber, and then the bacterial species that we want in our microbiome have to be capable of degrading all of the different nutrients in our foods as well as glycans: mucin and complex carbohydrates. And so we kind of need our microbiome to be able to work with us because we want to eat a so much better diet than what infants are eating.

Of course, as you're increasing your diet, you're having allergen exposures—foods that might trigger your immune system—and there is increasing evidence that early allergen exposure through complementary foods is probably critical for preventing food allergies. And a lot of this is really based on the results of the LEAP and the EAT studies, but at this point, the evidence looks pretty clear.

Guidelines are now encouraging early introduction of allergenic foods in these critical windows. The baby has to be developmentally ready, but ideally at a moment when the immune system is ready to develop tolerance to it as opposed to later on when it might become more hypersensitive. The 2017 National Institute of Allergy and Infectious Diseases (NIAID) guidelines for peanut introduction do look at risk of food allergies, and if you have no or mild atopic dermatitis and no egg allergy, you might not need to follow this. But if you are at high risk, then we definitely want those allergenic foods being introduced between 4 and 6 months of age, so literally offering infant-safe forms of peanut at 4 months of age. The 2021 North American consensus guidelines are recommending introduction of peanut protein around 4 to 6 months, and egg around 6 months, as part of a diverse diet, and really urging that other potentially allergenic foods should not be delayed.

We really need to be making sure that babies get allergen exposures at 4 to 6 months, which is earlier than a number of guidelines had been in the past and, indeed, may actually run up against guidelines around exclusive breastfeeding. These guidelines are all about avoiding allergy, so they get particularly important if you're in a family with high risk for food allergy (lots of family members who might have allergies or be at risk for type 2 inflammatory conditions like asthma, atopy) or if the babies themselves has any of these conditions—that's when it gets really important.

And really, there's just increasing evidence for earlier introduction of multiple potentially allergenic foods, and I think, at this point, we really consider the most common allergenic foods to be egg, peanut, and cow's milk. But the evidence is there, certainly, for egg and peanut, and although it's lower for cow's milk, it's been sort of the secondary stepsister of trying to prevent allergy. I think we're starting to see that evidence increase.

All of this is really pointing to the potential of this window of opportunity for allergy prevention. Really recognizing that there are these windows of opportunity. The way to have the least amount of allergy is going to be to have the exposure at younger ages, again mostly around 4 to 6 months is where most of the guidelines are ending up. And this gets really important depending on if you're high risk or not. If you are at the most severe risk for allergy, the important thing is not to run away from the allergen. It's actually to say, okay, you're at high risk, so we're going to expose you at 4 months of age.

However, that message is taking a while to get through. This is a 2021 survey showing really a low rate of uptake of this guidance for early allergy introduction in the United States and really suggesting that people are putting it off. If they're worried about a food being allergenic, such as peanut, tree nuts, cow's milk, egg, etc, they are putting off any exposure to it for often even past 1 year of age. And this is probably not surprising. We think many pediatricians are either not aware of the guidelines or are having trouble understanding or applying them. They may feel that they don't have time, in general, in our current healthcare system to do what needs to be done around exposures. But I think a really fascinating thing is that there's

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still concerns. There's real fear around allergy reactions, and I think that you see that in the parents too. And actually, when you put it all together in a survey of primary care providers, 40% of respondents believed that the youngest age for peanut introduction still is 1 year of age, which is not true and really needs to be recognized as something we're going to have to educate each other and educate our families about. Again, we want to get our peanut introduction down into the 4 to 6 months age range.

How do we address myths and misperceptions among parents? I think it's really important to start talking about it. Parental concerns are commonly cited as the barriers to early introduction of allergens, and we need to start talking about this early, at the 2- and at the 4-month well-child visit, so people are prepared; they've heard about this. And really, a key counseling point is that early introduction of allergenic foods as part of the diverse diet should begin at 4 to 6 months of age, ideally with peanut protein, and then not to be afraid of other potential allergens once we see the peanut is well tolerated. We have to be reassuring. Severe allergic reactions are very rare with first ingestion of a food. And then also, to correct the myth around IgE testing, as it's pretty clear that IgE testing is not a good guide. If you have a positive IgE test, or for some reason you've tested that before, that might be a reason to involve an allergist. Certainly, anyone who has an allergic reaction, has IgE, should see an allergist.

Takeaways here are really that nutrition-related strategies for the prevention of food allergy should begin prior to 6 months of age, and it's very important that all who practice pediatrics start to really internalize that because I think we're still afraid of it. It's very important to recognize the evidence for it. In terms of cow's milk allergy, it's really recognizing whether there's exposure to cow's milk, and if there was, then to recognize that actually this is not necessarily going to prompt allergy and, if anything, the right thing to do at that point is to continue to have some exposures to cow's milk, particularly in formulas, as a strategy for preventing food allergy. And to do this all with that counseling that breastfeeding is still important, and so we want to continue to breastfeed but just not to be afraid of exposures to cow's milk. And then to recognize this whole new frontier of really working with our microbiome itself, perhaps

better understanding nutrition like MFGMs as well as different probiotics we might use that could be helpful for getting the microbiome correct.

Food Allergy Management: Evidence-Based Strategies

Evidence-based strategies in food allergy management is sort of where I want to wind up. What we know we need to do is recognize if somebody has a life-threatening allergy and, at that point, we're going to be thinking about allergen avoidance and emergency treatment. Certainly, as a gastroenterologist, if I am worried for IgE, I will send a baby usually for serum tests. If, at that point, there's any concern (or sometimes before), I will involve the allergist. And of course if the allergist is concerned, they are prescribing an epinephrine autoinjector. When we prescribe elimination diets, we want to do them very deliberately. We want to be limiting food combinations with allergic potential. We want to be thinking about optimal nutrition, making sure that we're not putting someone in a position where they could lose the full complement of macro- or micronutrients. There's certainly a lot to learn about food label literacy. Here, I definitely find it very helpful to work with a dietitian, and that gets really important for patients with multiple food allergies. And, at the same time, I don't want to overcall it. I really don't want people unnecessarily eliminating food. So, it has to be done very intentionally.

In terms of working with the hypoallergenic formulas, I think what I really try to stress to people is to recognize that if I am concerned that the baby is having a reaction to the intact cow's milk protein, I really need to focus on the hydrolysis level. I think really the goal should be to be focused on extensive hydrolysis as our ideal for a baby with cow's milk allergy. The extensively hydrolyzed formulas have considerably smaller oligopeptide chains compared to partial hydrolysis; it's really the sensitive formula. They really want to move into the extensively hydrolyzed formula. These are devoid of things that might trigger the immune system (so large allergens), but very importantly, they still are oligopeptide chains. So those small peptide chains actually can increase tolerance. They help induce tolerance, really, and I try to stick with extensively

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hydrolyzed as opposed to amino acid-based formulas as long as the baby is growing and is comfortable. They may not be perfect. They may still have a little bit of stool weirdness or a little bit of eczema, but as long as they're growing and they're comfortable, I want to stick there. I think we used to aim for perfection. We would go to amino acid-based formulas. These are very hypoallergenic, but they actually don't help you induce tolerance. So, trying to get the immune system to a tolerant position gets really important.

There's a lot that's been looked at in terms of adding various probiotics. This is a study looking at adding *Lactobacillus rhamnosus* GG (LGG) to extensively hydrolyzed formula for tolerance induction—not just working with the extensively hydrolyzed formula but adding in LGG. What this study is showing is if you have the LGG in the formula, you really were seeing more tolerance at every time point for cow's milk protein. So, that's important to recognize. And also, what's important about this is that we see that that plays out in terms of also helping, in general, the immune system to calm down. You're less likely to go on and have other allergic manifestations. What this is showing is extensively hydrolyzed casein formula with LGG, comparing that to a rice hydrolyzed formula, a soy formula, the extensively hydrolyzed whey formulas, or amino acid-based formulas. All of those are pretty similar in terms of the risk of allergic manifestations at 3 years of age. That would be like asthma or seasonal allergy or other food allergy. The one that had the least is the combined extensively hydrolyzed formula with the probiotic, and that seems to help you have less inflammatory reactions in general.

And I think to that same point, there's been interest in, "Can we be stepping down formulas?" So, maybe a baby isn't comfortable and isn't growing on an extensively hydrolyzed formula, and we switch them to amino acid-based formula. This was a study that enrolled 60 infants that met that criteria. You had to have IgE-mediated cow's milk allergy to be enrolled in this study. We had to be able to prove that you had an IgE specific to milk. You stayed on the amino acid-based formula for 4 weeks, and then they were randomized to try again to go to the extensively hydrolyzed formula. What you can see is that if you were able to switch, which most of the time they could, it was well tolerated. Those babies were most likely to be able to

tolerate milk at a year of age compared to the ones who were randomized to stay on amino acid-based formula the whole time. So, when to step down? How long to stay on the amino acid-based formula before you step down to the extensively hydrolyzed formula (ideally with a probiotic involved) is an area I think that there's going to be more interest in, especially in light of the last year and all the formula shortages discussion. How long do you have to be on that amino acid-based formula?

Then there's a lot of interest in how we reintroduce foods and moving beyond the hypoallergenic formula to introducing complementary foods. And here, I think, some of the best work really is out of Europe and the United Kingdom, really looking at food ladders. These are home-based strategies for diet advancement. Ideally, you are slowly increasing allergen exposure by moving up the ladder. The bottom of the ladder is really the baked or heat-treated foods, and then you move your way towards less processed products. The example is a cow's milk allergen ladder, which would start with a baked muffin and then you slowly move your way to soft cheese or yogurt. The thought here is that, wherever along the ladder you seem to get to and you can tolerate, maybe you go up 1 rung, let's say from a muffin to yogurt, and you can't handle the yogurt, you should go back down the rung to the muffin and stay there as long as you can. That's helping your immune system to develop tolerance. That's really been largely safe in appropriately selected patients, particularly those with non-IgE-mediated food allergy. But, if you have very high levels of IgE, let's say to milk, you may have more difficulty following a ladder approach. So those are certainly, again, best managed (from my perspective as a gastroenterologist) with an allergist or by an allergist. But these food ladders in the non-IgE world are actually quite useful, and that is the majority of babies with cow's milk allergy.

What about immunotherapy for IgE-mediated food allergy? First thing, it's really important to make sure families understand that it does not cure food allergy in the traditional sense, but it can help reduce sensitization and increase tolerance. And that allows a controlled consumption of small amounts of allergen. So, it may be helpful for getting over that fear factor at a birthday party. It can be helpful for making life more tolerable for the family. A key to immunotherapy is that

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it's not a one-time thing; it's ongoing treatment to maintain tolerance and then it really has to do with what we are trying to get oral immunotherapy to be effective against. So, it's quite useful for peanuts, a little bit less useful for eggs, and the least useful for cow's milk. Although I would say, "Watch this space," because I think we're still learning how to use immunotherapy, and we're going to get better at it.

Conclusions

My key takeaway for this whole talk is to recognize that, along with atopic dermatitis, food allergy is 1 of the first manifestations in the allergic march. Food allergy is not a small thing; it's associated with considerable health, financial, and psychosocial burdens among families and patients. And so we really need to see this as a public health crisis in the infants being prone to food allergy. In terms of trying to prevent it, I think the target of interest is really the gut microbiome. That's why, as a gastroenterologist, I think a lot about this topic. If we can modulate the gut microbiome, we can reduce the risk of allergy development and ideally increase tolerance acquisition; although, we're still working on exactly how we're going to do that. What we do believe in—and we really appreciate that our allergy colleagues showed this in the peanut world, particularly, and now are moving into other nutrients that babies rely on, like milk—is that early introduction of potentially allergenic complementary foods is really what it's all about. When we talk about early, we're talking about during the 4- to 6-month window of opportunity as opposed to waiting, as we have for a number of years, until a year of age or later to introduce potentially allergenic foods. We really want early introduction during the 4- to 6-month window of opportunity, and that's really probably the best way we know right now of significantly reducing the risk of food allergy.

AUDIENCE QUESTIONS

Editor's Note: This is a transcript of live audience questions with the educator's responses from the presentation on July 18, 2023

✦ **How do you reconcile the potential benefits of early and ongoing cow's milk formula feeding and the introduction of potentially allergenic foods between 4 and 6 months with**

World Health Organization (WHO) and other guidelines promoting exclusive breastfeeding through 6 months?

That's the question that everybody is grappling with, and I will tell you, having talked to people who were involved in the WHO guidelines, in particular—and perhaps the American Academy of Pediatrics (AAP) breastfeeding guidelines as well—is the focus for those guidelines was really on breastfeeding duration and also, perhaps, some other secondary outcomes that were not about allergy prevention. I think, if we start to move into the world of allergy prevention, that it becomes important to introduce complementary foods earlier than the WHO guidelines are promoting, and again other guidelines, including the AAP.

If we're focused on allergy prevention, which we particularly want to do in high-risk families—so my recommendation these days is to understand your patient. If your patient is in a high-risk allergy family or perhaps situation—so that might be with family history, sibling history, parent history, but also perhaps that baby's experiences: were they given some cow's milk formula in the first few days of life because of breastfeeding difficulties? And then they got the hang of breastfeeding, but now you're wondering what to do. Do they have eczema gets very important. Do they have other stigmata of allergy? Those are babies for whom we actually want the earlier exposures. At that point, we are starting to think about the rest of their life, and we do want to prevent food allergy because it is a public health burden.

✦ **You mentioned the recommendations for early introduction of peanut, egg and cow's milk. What about other common allergens, such as wheat, soy, and sesame?**

Most of those have been looked at in terms of multiple foods and multiple potential allergens—of course, they're all potential allergens in the baby because the baby is so new, they haven't yet shown us if they're having a reaction. I think that the answer is—peanut becomes the most worrisome from an IgE perspective, so really the emphasis has been on the peanut exposure at 4 months of age and then to not shy away from other allergen exposures. Really, once the baby has demonstrated that they can handle peanut, you then want to be open to other allergens. I think, again, milk is sort of a

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common one; egg is a common one. And then you are moving into the other potentially allergenic foods and, of course, there are 9 very common allergenic foods. Probably, this early exposure plays out for all of them, but the data are a little trickier and haven't been as randomized in terms of how we're doing it. It might be additive, etc. So, "all foods earlier" is sort of the bottom line.

✦ Does giving some formula in the earlier days of life as a supplement to breast milk have any impact on the microbiome?

I think there are studies showing that diet does affect microbiome. Breastfeeding babies have a different microbiome collectively than formula-feeding babies, and soy formula-fed babies will have a different microbiome from cow's milk protein formula-fed babies. The issue with the microbiome is that it does change over very, very fast. It's like a complicated analysis. Let's say you saw a baby and then you checked its microbiome—if you let it go back to its regular diet—2 or 3 days later, the microbiome will be different again. I think it's not just, "Can we change the microbiome?" The question is: how do we keep it healthy? But definitely, diet is the key to changing your microbiome and that even happens for babies.

✦ If cow's milk formula was given in the first few days, are you recommending continued exposure only for those infants at higher risk for allergy (eg, due to family history), or for any baby exposed to formula in the first few days?

I think we're a little far from recommendations. Where we are right now is better understanding why we have been getting these variable results when we were trying to understand milk exposure and allergy, and it's becoming clear that it's not just when the exposure happens; it's whether or not it's a continuous exposure and then whether or not it's a little or a lot. I mean, all of that can play in. So, I think we're a little far from a recommendation.

Personally, at this point, the analyses we're starting to do that don't just take a cross-sectional look at data, but really try to look longitudinally at what has happened for a baby (ie, they had an exposure, that exposure continued or it didn't continue) and then looking at the first few days of life and then the next 6 months or life when most complementary foods are starting to

be introduced. Where I am is this: if the baby had some exposure early on, and now mom is breastfeeding, well, it's really important to recognize that it could be in that baby's interest to continue to have some exposures, on a semi-regular basis, to formula. I mostly practice no fear. I think the parents, for me, are often afraid. They don't want to do wrong, and here you're not doing wrong, if you had an exposure early on, to continue to have some exposures to cow's milk-based formulas.

That's where I am, is trying to really recognize it's a longitudinal discussion and that, in my families—I do see families where other siblings had milk protein allergy—that may be a way to help have that next baby avoid having what their sibling had, which is how I met the family in the first place.

✦ For infants who already have suspected cow's milk allergy, how long do you recommend that they remain on extensively hydrolyzed formula before attempting to reintroduce cow's milk formula?

That's a great question! And again, I feel like we tried to figure this out quickly, often just out of what to do last year during the formula shortages as people were really at home not able to get what they needed. I suspect that tolerance for a baby on an extensively hydrolyzed formula for at least a couple of months. So let's say by 2 months of age you have the baby on the hypoallergenic formula. Probably between 4 and 6 months they are going to be more tolerant. But we don't know exactly how many are fully tolerant and how many still might have a problem. I do think if you can get to 10 to 12 months of age, probably most of them are tolerant by that point. So, it's been at least 4 to 6 months—and probably a little bit more—of continuous exposure to the extensively hydrolyzed formula that has allowed things to calm down and ideally allowed the body to start developing tolerance to exposures. I think it's really important to get those milk exposures (let's say through a ladder approach). By 4 to 6 months, I really want them starting to understand the ladder and to be thinking about it—so baked milk, not to be afraid of that at 6 to 8 months of age. So, we're starting to get those milk exposure going so the body can start to develop tolerance.

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✦ **When re-introducing cow's milk formula, do you do that in steps, such as with partially hydrolyzed formula first, or do you usually switch directly to intact protein cow's milk formula?**

The babies I see in the pediatric GI clinic really had failed the partially hydrolyzed formula. To diagnose a milk protein allergy, if you will, or to treat it, we've got them on the extensively hydrolyzed formulas. There, I'm really making the move—I'm using the ladder approach, and I'm really getting a sense of whether they can tolerate the milk protein. My end goal is, indeed, at a year of age, to be able to get them onto cow's milk. And I do find if I use that ladder approach, usually—and again, they've had at least (I'm making up numbers here) 4 months or so of extensively hydrolyzed formula that I'm building on top of—you often are able to go straight to cow's milk. So, I do find that successful.

✦ **Are there any known differences between the efficacy of whey extensively hydrolyzed formula and casein extensively hydrolyzed formula in promoting tolerance induction?**

Most of the studies that compared the casein to the whey were in the German Infant Nutrition (GINI) study, and their primary outcome was focused more on atopic dermatitis than food allergy itself. The bottom line is there may be some components to whey vs casein. They're probably pretty similar, but in the GINI study, you could see a difference between the whey and the casein. Again, the outcome they were looking at, there was eczema and lifetime incidence of eczema in the population, so take that data for what it's worth. But there's probably a difference between them, and it's been my understanding in the way formulas are made in terms of hydrolyzing. You sort of have to pick your poison. You're either going to work with casein, or you're going to work with whey. The extensively hydrolyzed process does not allow you to have both; you can't have both extensively hydrolyzed casein and extensively hydrolyzed whey in the same can. It just doesn't work. They have to sort of pick one or the other to work with. It's mostly probably about hydrolyzing more than anything else.

✦ **You mentioned that the guidelines are published but are still not picked up by many healthcare professionals. What**

do you think can help get the guidelines across to them simpler and faster?

That is a great question! Well, first off, I want to commend everyone who stayed on this talk for the hour because I think educating ourselves and really each other—going against what really became I think quite entrenched in our thinking about food allergy (which was that it's something we should not challenge a baby until a year of age with potentially allergenic foods). It turns out probably to have been perpetuating this public health crisis we're in with so many people with food allergies. We really want to recognize that, historically, babies were exposed to foods much earlier. We don't want to be afraid to do that, and we want to try to follow the guidelines as much as we can. So, kudos to everyone who listened to the hour and thank you for spreading the word because I think, in the end, this is going to be us teaching each other and, as I said, teaching our patients.

✦ **How do these guidelines change with an early confirmed diagnosis of EoE?**

EoE is certainly something I think that we are recognizing is probably linked to the atopic march. And I think it will help us frankly to diagnose EoE earlier in kids. When we talk about early diagnosis of EoE, I think I try to avoid endoscopy in younger children, but my threshold for perhaps looking—and EoE I should say is clinical, so you have to have the symptoms of some sort of feeding disorder, usually difficulty eating, in young children, and then also you need pathology. You literally need to do an endoscopy, get biopsies, and look under the microscope to count the eosinophils to make the diagnosis. But probably in light of this link between the atopic march and EoE, a child who has milk protein allergy, eczema, asthma, and maybe even allergic rhinitis, let's say by 3 or 4 years of age, and is having difficulty eating, that's a kid we don't want to be missing that they might have EoE.

I'm thinking in my head of a family I've known for a while. I took care of the older sibling, and now I'm taking care of the younger sibling. They both had milk protein allergy and gastroesophageal reflux disease. The younger one, he just had that symptom, so he's entering kindergarten, and the older one, we never did endoscopy, and he outgrew it. But this younger

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one, there's just enough persistence of the symptoms that I said to the mom, I can't reassure us that he does not have EoE. And I chose to do an endoscopy. This was last week, and guess what? He doesn't have EoE, so now we can focus on him eating better. But I don't have to worry that I'm missing something. So, I'm not sure if that quite answered the question, but I think it's for us in the world of GI to recognize that the esophagus may be another tissue target for atopic march that we need to be paying attention to in this population.

✦ Would you like to take an additional moment for any closing thoughts?

I think these are fascinating areas. I don't think we have all the answers yet, but I think, as pediatricians, we should pay attention. I do think allergy has been something that has been happening in front of our eyes, probably a lot to do with the environment, but perhaps also because of things that we can influence as clinicians. I just really thank the audience for taking time to listen and perhaps to really examine some of the things they may have held as total truths. To go back and say, "Wait, maybe we actually need to understand this better." And then, as they say, watch this space because I think much more is going to be coming out over the next 5 to 10 years.

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Abbreviations

AAP	American Academy of Pediatrics
EoE	eosinophilic esophagitis
GI	gastrointestinal
MFGM	milk fat globule membrane
NIAID	National Institute of Allergy and Infectious Diseases
WHO	World Health Organization