

Exploring the Connection Between the Microbiome and Allergy Development

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Overview of Cow's Milk Protein Allergy



Jenifer R. Lightdale, MD, MPH: It's really an honor to be here and to talk about 1 of my favorite topics, which is cow's milk protein allergy and how the microbiome plays into

this. I'm going to start with a simple question just to make sure we're all on the same page: What is cow's milk protein allergy? This is an adverse reaction involving the immune system, so it's the immune response to 1 or more protein fractions in mammalian milk, and our mammal of choice here is the cow. But mammals basically all have milk proteins that are either casein or whey, and those adverse reactions to the proteins can actually affect the gastrointestinal (GI) tract, the skin, the respiratory tract and even other systems in the body. Also, there are some allergies that can cause systemic anaphylaxis.

When we think about the prevalence of cow's milk protein allergy in the United States, we talk of at least 1.9% of US individuals having cow's milk protein allergy, at least as defined by convincing symptoms, and that's where the rubber hits the road—this is really self-report or parent-proxy-report, and I'll talk more about why that is—but cow's milk protein allergy is very common. It's actually the most common food allergy and we do know that prevalence, again depending on how it's defined, is going to range between 1.5%, generally in infants younger than a year, to more than 4% in children as they get older. And it's estimated that about 1.4 million children in the US have cow's milk protein allergy.

Why is it tricky to tell you exactly whether or not somebody's having cow's milk protein allergy? This is because we have different ways of thinking about adverse reactions to foods, and I've got them classified here. You can see adverse food reactions can be toxic—that's food poisoning—but for the most part they are nontoxic. When they're nontoxic, they might not involve the immune system at all. So, non-immune-mediated food intolerances don't involve the immune system. So, when you involve the immune system, it's really about allergy. When you don't involve the immune system, you're dealing with intolerance, and 1 of those intolerances certainly can be

enzymatic—that's sort of a classic. So, lactose intolerance is actually [because] you're missing lactase, the enzyme that digests it, and that has nothing to do with your immune system.

The other way you can have nontoxic reactions is to involve your immune system. So, those [reactions] are when the immune system is being triggered by an allergen—that's technically a food allergy. And there we have our classic immunoglobulin E (IgE)-mediated allergy, which is the way most people think of allergy. There's an antibody to that food trigger—to that protein. You have an immediate reaction, and I'll talk more about what IgE allergies look like in a minute, but the key and really important thing to understand is many allergies actually are not IgE-mediated. So, they are non-IgE-mediated, and there's no antibody to measure. So, there's a food trigger, the immune system is involved, but it's really a clinical diagnosis. We cannot measure IgE to make that decision.

Thinking a little bit more about IgE-mediated cow's milk protein allergy and non-IgE-mediated cow's milk protein allergy—as I said, IgE-mediated cow's milk protein allergy is really your classic allergy. It's within minutes, and some of the symptoms can be hives and sort of localized and more classic, but of course I think the life-threatening concern is that the whole system gets involved, and you have anaphylaxis. You also can have GI symptoms with IgE-mediated allergy, and you also can get respiratory issues, including asthma or even swelling of the bronchus or even of the vocal cords. You can also have cutaneous symptoms. So, here is again where you might have a rash, like hives, you might have atopic dermatitis or even angioedema, just these nonspecific swellings.

Non-IgE-mediated cow's milk protein allergy is really the key condition that I think about with cow's milk protein allergy in infants. So, these are less than a year of age. What's interesting here is it's a delayed [reaction], these are mostly type 2 and 4 allergies (if anyone thinks that way). They are delayed hypersensitivities, so not immediately. They can take 6 hours, 12 hours, even up to 72 hours to really become clear. By that point, by the way, you've usually exposed the person to the



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same food again, especially an infant with a cow's milk protein allergy [who] will have had another feeding of that mammalian milk.

Those allergies are not going to present the same ways, and I get to think about them a lot as a gastroenterologist because many of them present with irritability. Colic is sort of a classic concept where it seems to be something going on in the GI tract. There can be a lot of different GI symptoms. You can have respiratory symptoms and you also can have rash, but again it's that delayed piece of it, and no IgE to measure, that makes it more of a clinical diagnosis.

The Gut Microbiome, Immune System Development, and Food Sensitization

I'm going to switch now to talking about the gut microbiome, the immune system development, and food sensitization because I think a big question we have is why do babies get cow's milk protein allergy? What we know is it really has a lot to do with how the human immune system is developing in the newborn and how that interplays with the microbiome and, of course, between the microbiome, which is all of the organisms that live in your gut, and the human immune system in your gut epithelial barrier.

And what we know is that most of your immune system is actually located in your GI tract. Your body is getting exposed to the world through your GI tract. That's why gastroenterologists have so much fun. And the human immune system is, like I said, separated from everything by the intestinal epithelium, and what we're realizing now is there's a lot of bidirectional interaction between the immune system and what lives in the gut. And what lives in the gut is what we call our microbiome. This is a very important part of us, but it's different from us. It's a bunch of organisms that, again, have been there as long as there has been humankind. We don't fully understand it yet. It's clearly about this interaction between the gut microbiome that is through and/or around the gut epithelium and how it's actually signaling to our immune system. And why is it doing that? We say it's doing that for its own reasons. Every organism that lives in our GI tract wants to live successfully in our GI tract. So, it's telling our immune system that it's okay; it's a friend. But in that process, things can go wrong and that's where we can start to have what we call

dysbiosis, where we don't have a good microbiome—we have dysbiosis, and that definitely contributes to the development of allergic and/or autoimmune diseases. I won't be talking about autoimmune diseases today.

But thinking specifically about this question of food allergy and how to understand what's going on there; what's really important to understand is that the microbiome is developing literally in that first—what we talk about as the first thousand days of life—but really from a newborn to neonate, all the way through toddlerhood, childhood and then to adulthood. Much of your microbiome is actually being established by toddlerhood, really (I think they say) by age 2 to 3, you've basically got your immune system—I mean, your microbiome has been established and how that's interacting with your immune system is already happening. It is a dynamic story. There's lots going on and 1 thing going on is diet is changing, so you really go from a newborn diet to a neonatal diet and then, of course, you start introducing real foods and, by the time you're a year, 18 months, 2 years of age, you're really into regular diets. That's going to be dynamic, and there're also a lot of external factors that are happening. In terms of the microbiome itself, that's changing, probably diet-related, but also as more exposures are happening and perhaps more disrupters are happening.

And what you want to keep in mind is, over those first thousand days of life, you've got this relative abundance of different species and our different phyla of organisms and (mostly) thinking about bacteria. You actually have bacteria, viruses and fungi, all of those are part of your microbiome. But focusing just on the bacteria, you have certain phyla and species that we know are part of a healthy microbiome, and they're going to be changing in terms of their abundance, how much there are of them and also the diversity. And like everything, the more diverse, the better. So, we want many, many different types of organisms in our microbiome, and, ultimately, we want to have a healthy microbiome with lots of diversity there.

Okay, so what contributes to dysbiosis? That's, again, an emerging area, but we can start to think about things as disrupters to developing a good, healthy microbiome. And 1 thing is a cesarean delivery. We know that a cesarean birth baby will have a different microbiome from a vaginal delivery. There



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can be changes in the microbiome or dysbiosis that can be seen when there's prematurity. Antibiotics are really a classic disruptor, so needing to use antibiotics, which can be life-saving—all of these things can be lifesaving, [such as] cesarean deliveries. We obviously want to keep premature infants alive, but we just have to know that all of this can contribute to dysbiosis. Formula feeding vs breastfeeding definitely leads to changes in the microbiome, and formula feeding vs breastfeeding is more likely to contribute to dysbiosis. And then we also know that hospitalization—so not being in a normal environment, but really being in a maybe more sterile environment, such as the NICU—that may contribute also to dysbiosis. So, that's just the beginning. Honestly, the world of understanding what disrupts healthy microbiome development is just starting, and there's so much. But I think it's part of where we are in our developed world to recognize that this is something that happens. We are doing lifesaving things and people are making important choices in their lives and, again, all with the goal of having a healthy infant, but somewhere in there we may have affected the microbiome.

What happens when you do that? First, again, it's important to recognize that standing between your immune system and your microbiome is your gut epithelium and, as long as that gut epithelium is healthy, it's only letting in the stuff that should be let in, and it's keeping out stuff that shouldn't get in. And that includes, by the way, bad bacteria like *Escherichia coli* O157:H7, which causes a hemolytic-uremia syndrome. You don't want to let that in, so a healthy microbiome will keep out the *E coli* that could cause a problem. But, if you have dysbiosis where your microbiome isn't healthy, you do start to see changes in the epithelium, and that can be pathologic toll-like receptor activation, which does change the permeability of the epithelium. You can have overexpression of proinflammatory chemicals. You can have epithelial damage, which basically causes a leaky gut. You get this breakdown of the intestinal barrier. And all of that is just letting more stuff in, and once it's getting in past the epithelial barrier, it's literally getting into your bloodstream, and there you're starting to have things happen. And so, that leaky gut is really about stuff being able to get into the bloodstream, and now all the things in your bloodstream, including your immune system, are now starting to interact with it.

When you have a good healthy intestine, it's not letting in allergens or things that might trigger the immune system. But when you have dysbiosis and intestinal permeability, you actually get uncontrolled entry of allergens, and those can include food antigens. And when those food antigens can get into the bloodstream, and you've got an immune system that's a little bit immature, it's starting to see things that it shouldn't be seeing, and it's starting to have reactions. And it's not sophisticated enough yet to recognize that it's just food, and it doesn't need to have reactions. So, that's basically how you start to have dysbiosis contributing to these increasing issues around food allergies that we've been seeing in our industrialized societies.

Cow's Milk Protein Allergy Management Practices

All right, so that was a lot. I'm going to move more clinically now to think about cow's milk protein allergy and various management practices. And here, hopefully, I'm going to take all of that sort of science, and what's going on, and what we're trying to understand at a basic science level but apply it now in what you're going to experience in the office.

First, really recognizing that cow's milk protein allergy, again, is mostly a non-IgE-mediated phenomenon and so, therein, it's hard sometimes to figure out what's going on using blood tests because you cannot find IgE, and instead you're relying on a clinical report. And we know that both over- and underdiagnosis of cow's milk protein allergy is occurring. So, we certainly have people reporting, and people think that must be an allergy when it might not be. But the flip [side] is also happening where people are reporting, and someone doesn't recognize that what the person's reporting is actually an immune-mediated phenomenon. We do worry about overdiagnosis, and that's been shown to put you at risk for growth faltering, micronutrient deficiencies, and worse, familial quality of life, in that people start restricting when maybe they didn't need to. I would argue that underdiagnosis also can put you at risk for growth faltering if people don't recognize that the issue is this immune-triggered response. So again, not to say that underdiagnosis is nothing, but overdiagnosis, for sure, we want to be on guard against that and be rigorous in making a decision that the diagnosis needs to be managed.



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I think the symptoms that people are reporting are particularly challenging because they are often common in healthy infants. So, infants can have colic or at least seem to be crying and you may call it colic, and whether it is allergy or not is tricky because the infant looks well. What to do with those infants is interesting. And, of course, they're nonspecific and they overlap with other issues, like functional GI disorders—later on, irritable bowel syndrome (IBS), but in an infant, again, [it] could be colic, with a sense that it's localizing to the GI tract. Gastroesophageal reflux disease (GERD) also can overlap a lot with cow's milk protein allergy, and actually guidelines say treat empirically for cow's milk protein allergy if you're wondering about GERD because there's so much overlap and often GERD is being overcalled. So again, getting all this right is tricky and I'm happy to answer questions on that if someone has something specific.

You know, what's a specific symptom? Anaphylaxis. Anaphylaxis is a very specific symptom of cow's milk protein allergy. It does imply that there's IgE, and then you can go and measure IgE levels of cow's milk. But basically, almost all other symptoms are going to be nonspecific and, again, we want to recognize that that's a challenge. In terms of diagnosing cow's milk protein allergy, really the standard is if you think that that is what the baby has, you want to do an elimination diet to take it away, and then you want to try reintroducing. And so we say take it away for 2 to 4 weeks. If they say, "Yeah, that really helped," or "No, it didn't"—either way, try reintroducing the food. Actually, there are the Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines, which really are pushing that reasonable cow's milk protein allergy and how to manage it. In this guideline, they say, try reintroducing at 2 to 4 weeks, and you want to understand if the symptoms come back.

And then, the other thing that's pretty clear is that, to do elimination, you really need to move to an extensively hydrolyzed formula, and I'll show that, but you really need to break down the protein quite a bit, or you need to change mom's diet in a breastfeeding mom to remove milk from her diet completely so at least she's not having breast milk with oligosaccharide pieces from cow's milk protein in them.

Obviously, if symptoms are persisting, you may need to reevaluate. The whole time, please be clinicians and be thinking about what else could be going on. The other thing is, if you

think it's IgE-mediated allergy—so if you have hives or if you're having anything concerning—it is totally appropriate to look for IgE levels, and there you may see that it's cow's milk. You may see an IgE to whey or casein. The key here is that, just because there's a small level, that's not confirmatory, that's just more building your argument towards that you think you're dealing with a cow's milk protein allergy.

Let's talk a little bit about breaking down protein so that it doesn't cause the allergy. These are sort of simple pictures of what are supposed to be complex molecules. An intact cow's milk protein molecule, either of whey or casein, is pretty big, maybe 350 to 450 kDa—quite a big structure. This is just showing like a little chain of pearls. With partial hydrolysis, we break it down so it's now about 10% of that. It's taken the chain of pearls and broken it down into pieces that are about 10% of the size, maybe 30 to 50 kDa. And then, if you get down to extensive hydrolysis, you're really in the 5 to 10 kDa, so it's really one-tenth of that. And amino acids, of course, is all the way down to the amino acids (the building blocks of protein).

The problem we get into with amino acids is they're actually so broken down that it's not teaching the immune system. Our immune system's actually quite dynamic, and it is growing in the neonate. It's becoming more sophisticated. So you want to be super careful, and sometimes you need to be on it, but to use amino acid-based formulas, you use them when you need to, which is when the baby really isn't growing and is really still having symptoms of allergy.

But my practice and what I really try to teach people to do is to focus on extensively hydrolyzed formulas. These should be the mainstay of what you're using for therapeutic elimination diets when you're in a formula-fed situation and you want to pick the right formula for cow's milk protein allergy. It should be an extensively hydrolyzed formula. That's going to treat almost all the babies and, very importantly, also gives their immune system a little bit to work with, so ideally they're inducing tolerance; they're starting to learn to be tolerant. And that's important because we want the baby to get over the allergy. Food allergies are a major cost burden for families. I don't need to tell most of you this. They're quite costly, and in a number of places, for different reasons, there may be out-of-pocket costs. So, you really want to be careful of not sort of perpetuating



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allergy. And we do know extensively hydrolyzed formulas are most cost-effective in general, but they're also most likely to get you over the allergy.

Probiotics in the Management of Cow's Milk Protein Allergy

One thing that's a really interesting world is whether we can work with probiotics, and there's been a lot of interest in, can we treat a dysbiotic situation? Can we actually do something to try to make the microbiome healthier? And so, this is 1 study that really showed that the microbiome is really predictive of [whether] the composition of the microbiome at 3 and 6 months was predictive of whether or not cow's milk protein allergy resolved. In particular, this study looked at *Clostridia* and *Firmicutes*, and what they saw is when there were more of those, you were more likely to have resolution of the cow's milk protein allergy. We do not give probiotics with either of those particular phyla, but this concept really suggests that microbiota manipulation through probiotics might be helpful for developing tolerance. And, indeed, that's been shown in different ways and with very specific probiotics.

Probiotics is a class. People ask me, do I believe in probiotics? It's like asking me do I believe in antibiotics. Of course! What are we trying to treat and what's the best antibiotic to use? And that's the way I think of probiotics.

You really need to recognize that the benefits are going to depend on the bacterial strain that you're using. You really have to be into the strain level, so not just the phyla, not just the species, but down to the strain level. And there's 1 in particular that I'll talk a little bit about, [it's] just there's a lot of data on it, but *Lactobacillus rhamnosus* GG in particular has been shown to have benefits in terms of allergy, diarrhea, integrity of the intestinal epithelial barrier and then it's also been shown to have some respiratory benefits.

And this gets important because it turns out not only can you help allergy by using an extensively hydrolyzed formula, but if you add the probiotic into the formula, you get even better outcomes, at least in terms of long-term outcomes. And here we're particularly interested in inducing tolerance, getting the immune system calmed down, addressing the dysbiosis, getting the immune system not reacting to the cow's milk

protein. And what this is showing, these are the same formula, but the green bar has the probiotic as well as the formula and you can see that formula plus probiotic was actually better at inducing tolerance, getting the baby able to tolerate milk basically at all the age groups. So, same formula, just adding the probiotic in.

And there have been a number of different studies that have tried to understand, again, what adding probiotics in on top of extensively hydrolyzed formulas can do and this was 1 study that really is looking long-term, so not just infancy and what happens there, but understanding over the first few years of life. So, these are basically 3-year-olds that they're looking at in terms of their likelihood of having an atopic reaction (any allergic reaction, so it could be food allergy, it could be asthma, it could be eczema). And they're looking at 3 years, but what's important is the baby at 3 years is not eating the same diet as they were as an infant. So, this is really now looking back. What formula were they on as an infant, and now what's happening at 3 years of age? And what you're seeing is, if you were on an amino acid-based formula (all the way on the right) you actually have the highest risk of having any allergic manifestation at 3 years of age. So again, you're no longer necessarily having that amino acid-based formula at 3 years of age, but that's what you were fed as an infant, you're more likely to have allergy. And that's compared with extensively hydrolyzed whey formulas, soy formulas, and hydrolyzed rice formulas; they all have less chance of having allergy as the amino acid-based formula. But the lowest risk of having any allergic reaction is if, as a baby, you were actually fed not only extensively hydrolyzed casein formula, but it had *Lactobacillus rhamnosus* GG (LGG) in it. So, really the extensively hydrolyzed casein formula alone will not perform as well. It's really that LGG that really helps with this improvement. And so, what they're saying is, relative to other formula types, having not only an extensively hydrolyzed formula but also the LGG is associated with more rapid and durable tolerance.

And, actually, that probably is more cost-effective and may be a good approach to cow's milk protein allergy. There's some nice studies showing that if you did this for 12 months, this is actually a cost-effective way of handling cow's milk protein allergy—or at least trying to mitigate it—and certainly more



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cost-effective than switching the baby to an amino acid-based formula.

Considerations for Your Practice

Alright, so in my last few minutes, I just want to think about basically considerations for your practice and what to do with those babies who you've started on an extensively hydrolyzed formula and, of course, here I'm saying with the LGG because that's the data I'm working with. But basically babies who have cow's milk protein allergy and you're trying to manage them.

One of the things that can happen is you have started them on the formula, and they actually don't do well and there I really use guidelines (the DRACMA guidelines in particular) looking at continued growth faltering and continued symptoms. At that point, you would probably put them on an amino acid-based formula, and the question is, how long do you stay on that amino acid-based formula? And this was the Step-Down Approach for Cow's Milk Allergy (SDACMA) trial where they were looking at, could we step down from amino acid-based formulas to the extensively hydrolyzed formulas? And they actually enrolled 60 infants who had IgE-mediated cow's milk allergy who had been managed with amino acid-based formula. They had that for at least 4 weeks. They gave them a challenge of the extensively hydrolyzed formula, so tried to see if they could handle a little bit more of those proteins in a line, not just amino acid-based formula. If they could, then they randomized them to either continue the amino acid-based formula or to switch. And what they found was that switching was actually well tolerated.

So, what to do with this? I don't know that we're at guidelines yet, but you want to feel empowered to say that a lot of infants who are on amino acid-based formula for cow's milk protein allergy probably can be transitioned after 2 to 4 weeks, just like we've said, to step down, if you will, to the extensively hydrolyzed formulas.

Okay, so why is that? Well, cow's milk protein allergy is a phenomenon. The immune system's maturing; it's dynamic, and most infants are actually going to outgrow it by 3 to 4 years of age. They call it tolerance acquisition. How fast people acquire tolerance will vary by study, but all of them show that by 3 to 4 or 5 years of age, you're likely to be over your allergy.

IgE allergy lasts a little longer. That can take up to 10 years, but for the most part, it is a transient phenomenon. It's something you're going to outgrow.

Well, how do we start bringing milk back into the diet of infants or toddlers who are not having milk? I think there are approaches out there, and most will suggest that reintroduction can start after 6 months or at age 1 year. It can be done at home. You really don't have to worry, with 2 exceptions. One would be if you're worried about severe—the baby has actually shown you that they have anaphylaxis—that 1, I think, be careful suggesting at home. Certainly, at home should only be suggested by the allergist instead of the gastroenterologist. So, I really think, with that baby, be careful. And then also, food protein-induced enterocolitis syndrome (FPIES) (which I'm not going to talk about today), but an infant diagnosed with FPIES, acute FPIES, where they've had hospitalizations, that may not be a home introduction either. But your run-of-the-mill (so to speak) infant who felt better on extensively hydrolyzed formulas or changing mom's diet (taking milk out of her diet), you can start reintroducing the milk after 6 months of age.

There is this milk ladder approach, which is basically starting with theoretically less antigenic foods at small doses—so we bake the foods to denature the protein—and then moving more systematically towards antigenic foods with higher doses of intact proteins, like milk or yogurt. And there's many different versions of this that are available on the internet, so whole countries have really put together guidelines on how to do this, including the United Kingdom and Canada.

I think there can be persistent symptoms. If that happens, I just back down and say, okay, let's keep the milk out. But every 6 months, I'm trying it again. And here, my European friends and the European Society for Paediatric Gastroenterology Hepatology and Nutrition, or ESPGHAN, have very good guidelines on this. Really, after 12 months, you may want to look at IgE levels. Again, those don't necessarily diagnose, but they're important, maybe at that point, to make sure you're not dealing with something else. And we do know that the higher the IgE level is, the longer the allergy will probably hang out. So, if it's a very high level, it's going to be around for a while.



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I'm going to end with some considerations for your practice and it really is all around counseling caregivers (so the parents) and managing it as the provider. The first is really to rigorously diagnose cow's milk protein allergy. It is a clinical diagnosis. It's going to be based on patient reports, but write down exactly what symptoms, make sure you've asked, feel good yourself that you've probed a bit, and then counsel. And if you think it's a worried parent and it's not a real allergy, counsel them about the risks of overdiagnosing.

Positively manage, though. If you think, "Yup, okay, that sounds like a cow's milk protein allergy," then manage it. And there, of course, it's all about following them. You want to be watching growth as the main outcome, I think, that we need to focus on. Don't be afraid to be reintroducing and use dietary counseling to do this and sort of gradually bringing in the milk protein exposure. And again, I happen to usually use a ladder approach. And then, of course, also consider whether you might to go from an amino acid-based formula to an extensively hydrolyzed formula or from extensively hydrolyzed even to intact formula. That could be due to what the family is having to absorb from out-of-pocket costs, but also could be about, unfortunately these days, with some of the shortages we've been dealing with, just to have a back-up plan. And perhaps, also to be engaging and seeing if tolerance has been acquired.

Key Takeaways

Just some key takeaways to this talk really are that cow's milk protein allergy is the most common immune-mediated adverse food reaction that human beings have. And it's really all about our immune system. Our immune system, in turn, is all about our microbiome, and that's really being established in those first thousand days of life. The microbiome is incredibly dynamic, incredibly reflective of a variety of influences, including our diet. And then also recognizing that, in our modern era, there is lots of potential for dysbiosis or an imbalanced microbiome, and that can be a precursor for food allergy, including cow's milk protein allergy, because of how the intestinal barrier has been affected.

In terms of what you should do in terms of management, I think, when you've identified cow's milk protein allergy, you make it better by getting rid of intact cow's milk protein as much

as you can and perhaps considering probiotics, and I would say watch this space as something we're really all trying to understand. And then also, always with a sense of the social determinants of health and really an eye to health equity, to recognize the economic impact of prescribing therapeutic formulas and doing everything you can to make sure, when you can, that you advance the diet away from those. There, you can use this gradual reintroduction concept and, there again, the milk ladder is an approach and a philosophy.

AUDIENCE QUESTIONS

✦ **What are the differences between extensively hydrolyzed casein formula and extensively hydrolyzed whey formula in the context of use for infants with cow's milk protein allergy?**

When you extensively hydrolyze a formula—which, by the way, I am just a gastroenterologist, so this is my understanding. When the decision is made to take a formula or any milk and to hydrolyze it, you start to break it down, and the first thing they do is they have to divide up casein and whey. And you wind up working with 1 or the other. So, you sort of throw out 1 to work with the other. And you have to choose which 1 you're going to work with. And then, from there, you start to break it down. You, being the company that does it or the industrial process that does that. And, of course, it's chemically done or whatever; it's basically done in a biochemistry way. There's no formula that has both extensively hydrolyzed casein and extensively hydrolyzed whey. It would just be, I think, far too complicated. So, they're picking 1 or the other and, from my perspective, either 1 is fine, and they're both out there on the market. And there's reasons that different companies are making different ones. They've gone with it for their own research and development reasons that go beyond this talk. But just to recognize that everybody has to pick 1 or the other to hydrolyze and then, in terms of treating cow's milk protein allergy, there really isn't, from my perspective, 1 better than the other.

✦ **When, if ever, is a clinical diagnosis of cow's milk protein allergy appropriate in the absence of an oral food challenge?**

I think it is a clinical diagnosis, and the way you're going to confirm the diagnosis if you, as the provider, are suspicious, is



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you will suggest elimination. Then, I think it is appropriate, if you want to be rigorous, to say, “And we will try a food challenge in 2 weeks or 4 weeks.” I will tell you, sometimes that just happens sort of organically. Someone wasn’t sure, or it was hard to get the baby off, and the mother who’s excluding milk, she forgot. She went to a party; she ate something, and it can happen a bit organically. So, it can be appropriate to make the diagnosis without necessarily doing that very formal food challenge, but I will tell you the other philosophy these days is that it’s a transient phenomenon, so you don’t want to be too prolonged in how long you’re being so strict with elimination. So, I do think, after 4 weeks, you want to start to reintroduce, and hopefully it will be tolerated. That doesn’t mean that it wasn’t cow’s milk protein allergy in the first place. It just means that that it doesn’t take too long to sort of help the immune system start to understand and calm down a bit.

✦ **In our practice, we test an occult stool for infants we suspect cow’s milk protein allergy in. Can you speak about this? Is it recommended? Pros and cons?**

Right, so cow’s milk protein allergy can be associated with food protein-induced allergic proctocolitis (FPIAP). That’s the very technical definition of allergic colitis, and cow’s milk protein allergy can be associated with that. I don’t use blood in the stool necessarily to make the diagnosis or to refute the diagnosis because food protein-induced symptoms can also be upper tract. They may not involve the colon at all or the rectum at all, and that’s where you get all the GERD. So, positive or negative blood in the stool is just another piece of information that’s helping me make a rigorous assessment of what the family is telling me, to make a decision about whether or not I’m dealing with cow’s milk protein allergy.

✦ **Can you give some guidance on how to determine if a particular probiotic is better than another for babies who are breastfed to help them get over or help in the management of cow’s milk allergy?**

The answer is probiotics, right now in the United States, are not actually considered a food or a drug and they’re not being regulated by the Food & Drug Administration (FDA). So, I think there are a number of probiotics out there that are being studied, and I am relying on data being shown to me in clinical

studies that a particular strain of probiotic works to address a certain condition. And I am very open to that. So, when someone comes to me and says, “Do you like this probiotic?” I say, “Show me the data.” What are we trying to go after? If it’s milk protein allergy, show me that this probiotic that you want to use—and again a patient’s not going to do this, but I will go to the internet and try to understand if there is data. Again, I’m in the world of this, so I’m also trying to keep up with the data. And there are some probiotics that have been well studied. The one we talked about today has been particularly well studied (LGG). It just has a lot of basic science that, for different reasons, has just emerged honestly over about 40 years. So, it’s all basic science that gets you to, okay, that’s how it’s working for allergy, and actually that particular probiotic also works very well for atopic dermatitis or eczema. So, again, you have to really ask, and if a representative comes to the office and says, “Try my probiotic,” then I say, “Great, let me see the studies.” I want to understand what they did, and I want to assess that for myself.

✦ **Keeping with the theme of the microbiome and what can affect the infant’s microbiome, do you have any thoughts on how the mother’s microbiome affects the infant?**

Ooh, wonderful question and I would say, we are sure it does! So, a healthy maternal microbiome is probably the foundation for a healthy start to an infant’s microbiome and, unfortunately, a dysbiotic microbiome in mom probably will mean a dysbiotic microbiome in baby. Now, what to do about it is the world we’re in because my own philosophy is let’s assume everybody has some dysbiosis. How do we all, as a society, get ourselves to as healthy of a microbiome as we can? So, continue to watch this space. It’s such a wonderful area.

✦ **Can the ladder approach be used for any other common allergens, such as egg?**

That’s a wonderful question, and there have been trials. And I personally think yes. So, that is how I will do it: Try to step up from denatured proteins (baked eggs, fried eggs) towards actual basically feeling like something that has a lot of egg protein in it. So, yes, but it’s not as well-defined as the milk ladder.



Exploring the Connection Between the Microbiome and Allergy Development

ABBREVIATIONS

DRACMA	Diagnosis and Rationale for Action against Cow's Milk Allergy
ESPHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
FDA	Food & Drug Administration
FPIAP	food protein-induced allergic proctocolitis
FPIES	food protein-induced enterocolitis syndrome
GERD	gastroesophageal reflux disorder
GI	gastrointestinal
IgE	immunoglobulin E
LGG	<i>Lactobacillus rhamnosus</i> GG
SDACMA	Step-Down Approach for Cow's Milk Allergy

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