Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

Confronting the Allergic March
Transcript

Editor's Note: This is a transcript of a live webcast presented on July 12, 2023. It has been edited for clarity.

Overview of the Allergic March

Alessio Fasano, MD: In order to really frame what we're going to discuss today, I believe that some clarification in terminology is worthwhile, particularly introducing what we mean by allergic march. It's a term that has been used for many other conditions of chronic inflammatory diseases that encompass the history and the progression of a condition; in this case, an allergic disease.

There is now pretty solid evidence that this march involves 3 major districts: the skin, the gastrointestinal (GI) tract and the respiratory tract. So, the sequence that is typical—but not universally occurring in all patients—is you start with the skin manifestation with atopic dermatitis that can move then to food allergy, then allergic asthma, and eventually allergic rhinitis. So, these 3 tracts, skin, GI, and respiratory tract, seem to be sequentially involved. And this encompasses what we're going to review today, meaning this conceptual pathophysiologic framework that will give us the possibility to find biomarkers of march initiation and therefore a target for prevention and treating these allergic diseases.

Now, if we look at the progression of the allergic march in a general population—again general rules with some exceptions—is that, typically, early ages are affected by the skin manifestation and the food allergy manifestation. So, in other words, the skin and the GI tract seem to be the ones that are involved earlier, as discussed before, and you see the peak, around 1 or 2 years of age, of these manifestations (the skin and GI manifestations) to be followed over time by the respiratory tract manifestation in which the allergic asthma and rhinitis seems to be involved.

Now, in getting into the details on the pathogenesis, the sequence of the events seems to be the following:

- We have an insult of the skin with this atopic dermatitis—that is determined by genetic predisposition plus the exposure to environmental factors.
- That leads to destruction of the skin barrier that allows the entrance of allergens that can eventually stimulate the immune response.
- That immune response leads to sensitization to the allergens, either at the epidermis level and/or the GI level, that leads to an immune response typical of allergy (what we call, technically, type 2 inflammation), with the activation of specific immune cells.
- Those immune cells eventually, once activated, can migrate from the original source of the encounter with the allergen to the districts that we discussed before: the GI tract, the lung, the nose and, eventually, the skin, where they start the issue.
- Once they settle in this district, then they may be activated when re-exposed to the same allergen to then lead to the food allergy, the allergic asthma, and the allergic rhinitis that are the conditions that we discussed before.

If we look at the US data that reflect mainly what we see—also with a few exceptions—in terms of regional distribution, you see that the food allergy, asthma, and seasonal allergy—they tend to increase, over time, with age. Food allergy, you see the numbers [increasing], at the 0-5 range and the 6-11 and 12-17, with an overall average of 6% roughly. The same with asthma, which starts low and then goes up over time. The atopic dermatitis [is relatively stable] over the years, and the seasonal allergy, you see goes from 10%, to 21% to 24%, with an average of 19% roughly. All this to say that the diagnosis of allergic disease in kids in these 3 ranges of ages, tends to increase over time.

What Is the Etiology of the Allergic March?

Why? What is the etiology of this allergic march? Once again, in general, allergies are instigated by a specific subgroup of immunoglobulins (the immunoglobulin E [IgE] antibodies). This

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is an overview of the physiology of the immune response of the Th1/Th2 immune response in allergy in which you are sensitizing against an allergen and can eventually induce an IgE-specific immune response. Again, these antigens, they typically get portal entry via mucosal surfaces or the airway to the GI tract and, as I mentioned at the beginning of this discussion, skin penetration that was [historically] not considered part of the equation, now seems to play a more and more substantial role in breaking the tolerance, or the start of this allergic march, and the development of hypersensitivity to specific allergens.

What is the process of IgE-mediated sensitization? Again, the steps have been pretty much figured out. They are summarized in this cartoon. When we have the first exposure to the antigens, they will be managed by specific immune cells, that are called antigen-presenting cells, that can eventually present these antigens to a subgroup of lymphocytes (T cells). They are the CD4-positive T-helper (Th) cells that eventually, when exposed to these antigens, mature in Th2 cell–committed immune cells that produce a specific micromilieu with cytokines that instruct B cells to produce specific antibodies when they mature in plasma cells: the IgE antibodies. These IgE antibodies will eventually circulate and bind mast cells and basophils that eventually now are committed to that specific antigen. When there is a re-exposure (in other words when subjects are re-exposed to the same initial sensitizing allergen), we'll find these mast cells and basophils already primed and ready to release chemical mediators, like histamines and so on and so forth, and that will eventually cause degranulation of mast cells and basophils, with the typical symptoms that come with that.

What are the drivers? How do you start this march? In other words, genetic disposition is necessary, but not sufficient. What else is in play? Epigenetics, meaning that eventually some genes will be put into motion by environmental factors that will lead to inflammation. Allergens, of course, you have to have the exposure to the instigator. They can come from blood, pollutant exposure, or early-life feeding choices. We said the skin barrier dysfunction is becoming more and more tangible in this march from genetic predisposition to clinical outcome, but I think that, again, there is a great deal of attention to an imbalanced microbiome (particularly the gut microbiome, but not only that). Now we have evidence also the skin microbiome can eventually be instrumental in creating the condition to start this clinical march from genetic predisposition to clinical outcome, most likely because of epigenetic pressure, as we will see in a moment.

Dysbiosis as a concept now has gotten more and more attention from the scientific community. In general, the dysbiosis "signature" is the depletion of the protective component of the microbiome, decreased diversity of the microbiome, and the colonization with microbes that seems to be more capable to favor food allergy because they are strongly associated with these conditions.

The level of attention to the microbiome's role in the allergic march is testified to by the number of publications over time. You see from the beginning (2002) to a couple of years ago that the number of publications related to the microbiome and allergy has been skyrocketing, meaning that there's clear attention to the matter, and there is a belief that the microbiome is not just an associative situation but can be causative. So, in other words, it's because of the microbiome that we start this march.

And that really is in line with many other conditions or chronic inflammatory diseases in which the immune system plays a role. In the past, we were convinced that genetic predisposition and exposure to environmental factors were necessarily sufficient to lead to a clinical outcome. We know that this is not the case. We know that there are at least another 3 elements at play, including the ones that we see in allergy march.

One, we have to have a breach of this barrier that prevents these environmental factors, these allergens, from coming into our body. Because, if they don't, of course, there's not going to be an immune response. Gut permeability is the one that's studied the most, but again, as I mentioned, the skin barrier also is an object of a great level of attention coming to the allergy march. Of course, we talk about immune disorders. So, the immune system becomes hyper-belligerent—in this case, skewed toward the Th2 immune response. It's important. And we mentioned already about the microbiome that seems to play a substantial pathogenic role in starting this march.

And again, these elements that I presented, they are highly interconnected. For example, now there is strong evidence

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suggesting that if you have an increased gut permeability, you have increased antigen trafficking, and therefore the immune response becomes hyper-belligerent and vice versa. A state of chronic inflammation can cause increased gut permeability. If you have an increased gut permeability, you have dysbiosis and vice versa and so on and so forth. But the element that I want to really reiterate, that I mentioned already before, is the epigenetic role of the microbiome in determining if, when, why, and how specific genes are put in motion so that you start that march toward the clinical outcome.

Now, why is the gut microbiome the object of a lot of attention, including allergic diseases, that may eventually link pathogenetically dysbiosis to the clinical outcome? Well, because now we have pretty solid evidence of microbes that live in the symbiotic relationship with us and they evolve with us. They are capable of being similarly important for some of our physiological functions. For example, they produce metabolites from prebiotic fibers, like short-chain fatty acids, which are extremely important for physiological, healthy GI function. If balanced, they protect against the colonization of pathogens that can eventually instigate the beginning of the march towards the allergic disease, and they facilitate the antigen-experienced regulatory T-cells (Tregs), which are important for putting a brake on the Th2 immune response that is typical of allergic diseases.

This is a cartoon that summarizes what I just told you. You have, on the left, the healthy situation. On the right, dysbiosis leads to a Th2 immune response if genetically predisposed to do so. So, you have, on the left, a diverse microbiome with production of post-biotics, like short-chain fatty acids. They maintain a healthy barrier, and therefore a controlled antigen trafficking that keeps this in what we call a mucosal state of anergy, as we see in a moment. On the right, we see the pathologic situation in which there's a decrease of microbial diversity, a decrease of production of some metabolites, where others like butyrate increase, and this may eventually lead to the break of the barrier and antigen trafficking that can instigate the immune response that I mentioned to you before that can lead to a Th2 immune response. And recruitment of these immune cells, including mast cells and eosinophils, are the ones that eventually, when re-exposed to the food allergens—they eventually lead to the clinical outcome.

What are the factors that decide if we are in a friendly relationship with the microbiome or we're in dysbiosis? There are many, and they start even prenatally because, of course, we receive the microbiome mainly during delivery. But not only that, now, we know there is also a discussion during pregnancy (particularly the last trimester) between the mom and the fetus in terms of transfer of specific microbiota from mom. Of course, lifestyle, particularly the diet and stress of the maternal components, can really dictate a good engraftment of the microbiota to the baby. And, of course, genetics always is important. Perinatal events, like the modality of delivery. If we have vaginal delivery, we will more likely receive a compatible microbiota compared to Cesarean deliveries, in which we don't have a selected microbiota that can be compatible with our genetics. Gestational age—if there is a preterm birth, that's more risk of a dysbiotic engraftment. And last, but definitely not least, postnatal factors, and we'll go a little bit more in details with that. The feeding mode, breast milk vs formula, geographic region, the household, (again) the maternal diet, complementary food used, antibiotic exposure, infections, and so on and so forth.

Talking about the allergic march at the mucosal level and, in this case, again, the GI tract is the one that's studied the most. If you go from left to right, this pretty much encompasses what is the concept of the march. Number 1, this is physiology. The barrier works well. You are in the symbiotic relationship with the microbiota, antigen trafficking is tightly controlled, and therefore we develop what we call mucosal tolerance, homeostasis—what we call a state of anergy. There are regulatory dendritic cells and macrophages, Tregs and some protective cytokines, like IL-10 and transforming growth factor-β (TGF-β). They are maintained at the status quo.

The problem is when we move from step 1 (normal controlled permeability) to step 2 (minor barrier defects in which the antigen trafficking is not controlled anymore); antigens start to really get into the lamina propria on the other side of the barrier in an uncontrolled fashion. And that really instigates an immune response with an innate immune regulatory defect

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that leads to the production of proinflammatory cytokines that put us in a vicious cycle. Because these cytokines, per se, can increase gut permeability, and therefore, they are in this vicious loop of antigen trafficking, inflammation, and proinflammatory cytokines that increase the permeability even more until we move to step number 4 (break of tolerance and an onset of low-grade inflammation, including type 2 immune response typical of the allergic march).

The problem has been always how you go from step 1 to step 2. So, what really causes these minor barrier defects? Here, we contributed to this gap in knowledge, a couple of decades ago now, with the discovery of this molecule, zonulin, that is the modulator of permeability of many districts, including the GI tract. Dysbiosis is a strong stimulus to activate this pathway that increases gut permeability and starts this march, from genetic disposition to clinical outcome, secondary to an imbalance of the microbiome.

Zonulin has been associated with the events that I showed you before, so in other words, that intestinal permeability is an integral part of food allergy and, again, the structure in between cells (technically called tight junctions) that are modulated by zonulin are the ones that are affected, that leads to this uncontrolled antigen trafficking. Therefore, moving from the panel on the left (that is tolerance) to the panel on the right (that is food allergy)—because you see that you keep at bay food allergens until they are completely digested in a physiological state, but if you have a zonulin-dependent breach of the gut barrier and increased tight junction permeability, now you have these undigested food allergens that can come through. With the mechanism that we discussed before, this may eventually lead to a break in tolerance and the onset of the problem that we discussed.

This is the literature report on zonulin and chronic inflammatory diseases, including asthma and food allergies. They are part of the Th2 immune response that we've been discussing so far.

Overview of Cow's Milk Protein Allergy

And at this point, I want to really zoom in on what is probably the most impactful allergy in childhood: cow's milk protein allergy.

The classical situation that we have in mind, where we talk about cow's milk protein allergy, has been changing over time with new knowledge that comes on board that applies not only to food allergies, including cow's milk protein allergy, but many other Th2 immune responses, including dermatitis and asthma and so on and so forth. So, the World Allergy Organization uses this definition when it comes to cow's milk hypersensitivity—that it is an umbrella term that encompasses different kinds of conditions.

Cow's milk protein allergy is the hypersensitivity reaction caused by immune signaling following exposure to cow's milk protein. The IgE-mediated component of this cow's milk protein allergy is the hypersensitivity reaction to cow's milk protein mediated by IgE. And these are the ones that I showed you that they are IgE that binds to the Fcε receptor on mast cells and basophils, leading to the release of histamine or other inflammatory mediators.

But now there's another group, that we were totally unaware of, that applies not only to cow's milk protein allergy but also to any form of allergy. These are non-IgE-mediated allergies, in this case cow's milk protein allergy. It's a hypersensitivity reaction to protein in cow's milk that is caused by cell-mediated and other non-IgE-mediated mechanisms, leading to a delayed-onset reaction. Now you don't need the IgE mediation anymore—these can be mediated just by the involvement of a cell without production of IgE.

A third element that has nothing to do with allergy is what we call cow's milk intolerance. That's not an allergic hypersensitivity and is not the subject of this discussion today, but just to make clear that you know this and to avoid any kind of confusion. Intolerance and allergic hypersensitivity are 2 different things. One is immune-mediated; the other one is not immune-mediated.

What are the mechanisms of these 3 forms of hypersensitivity? Again, for the IgE-mediated allergy, it's allergic sensitivity

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mediated by IgE. The organ systems involved are pretty much ubiquitous: oral, respiratory, cardiovascular, cutaneous, GI, and so on and so forth. The timing of onset typically is very, very fast. Now, the non-IgE-mediated cow's milk protein allergy is still an immune response. It's mediated by immune cells and not IgE. Usually, symptoms are focused on the GI system. It's delayed, so it's not something rapid that happens in a matter of minutes, and the typical examples are the food protein–induced allergic proctocolitis, food protein–induced enterocolitis syndrome, and food protein–induced enteropathy.

Cow's milk protein intolerance, again, is not an immune-mediated response. Typically, GI symptoms are delayed hours or days, like the non-IgE-mediated cow's milk protein allergy, but, again, this is an intolerance. Typical example, lactose intolerance; it's not an immune response.

What are the symptoms of mild-to-moderate cow's milk protein allergy? Well, it depends if it's IgE-mediated or not. With IgE-mediated, it involves the skin: you have pruritus, erythema, urticaria, angioedema. You can have acute flares. The GI symptoms are typically vomiting, diarrhea, abdominal pain, and colic. And respiratory symptoms can be acute rhinitis and conjunctivitis. The non-IgE-mediated cow's milk protein allergy—they have slightly different symptoms. For example, GI symptoms (the most common) are irritability, because, of course, these kids are very cranky because of the colic; vomiting; food refusal or aversion; diarrhea (or it can go the opposite way to constipation); and stomachache. And if you have an allergic colitis, you can have blood and mucus in the stools in the kids that otherwise are growing and eating well. The skin, there is little difference between the IgE- and non-IgE-mediated, so there's pruritus, erythema, nonspecific rash and moderate, persistent AD.

I want to make clear, and I want to direct your attention to the note. The symptoms of cow's milk protein allergy are exceedingly common in infants without cow's milk protein allergy. So, that means that to make a diagnosis and, therefore an intervention, like an elimination diet, you've got to be really, really sure that you're barking up the right tree. So, in other words, we're talking about cow's milk protein allergy, not other conditions because, again, these are nonspecific. They are very, very frequent in little kids, as symptoms.

That brings me to the algorithm for diagnosis of cow's milk protein allergy in infants. Of course, if we are dealing with an acute, life-threatening situation like anaphylaxis or clear immediate-type reaction (so the kid is exposed to cow's milk and in a matter of minutes will develop symptoms), you do not need to do anything else other than cow's milk protein elimination and then specific IgE testing. There is no other approach but eliminating cow's milk protein right away. With IgE testing, you can find yourself in 2 different categories (ie, positive or negative specific IgE results). That can be the IgE-mediated (ie, positive specific IgE results), and then you go for the therapeutic elimination diet (so with special formulas with no cow's milk protein in there). If, on the other hand, it's IgE-negative, then you need to go to the standardized oral food challenge that we'll review in a moment.

If the starting point is not an acute response to cow's milk or immediate cause-and-effect response to cow's milk exposure, then you need to go for a diagnostic elimination diet, meaning that for 1 to 2 weeks for early or late reactions, or 2 to 4 weeks for GI symptoms, you need to eliminate cow's milk protein from the diet of the child. If you have an improvement of the symptoms, then you go to the standardized oral food challenge. If you do not have symptom improvement (because, as we said, these symptoms are not specific to cow's milk protein allergy), then you rule out cow's milk protein allergy; there's no need for the elimination diet.

What is the frequency of the problem? Well, unfortunately, every single time that we deal with food-related disorders, we really need to rely most of the time on parent-reported outcome. And we see that, based on that, there is a peak of the occurrence of cow's milk protein allergy around 2 years and then it will decrease over time. So, typically, people grow out of this over time, as we discussed before. But the overall average is 2% in all kids, year 1 to 17. But you see the different numbers and how they start low, and then up at 2 years, and then go down again.

What are the risk factors? Family history for allergy. So, in other words, genetics counts. Of course, antibiotic exposure during

pregnancy because, as we said, the microbiome coming from mom is most important. Exposure to complementary foods before the age of 4 months. You know, the GI tract is not mature enough to digest and to maintain that nice barrier function before 4 months, so you increase the risk of antigen trafficking if you introduce solid food too early. And, of course, the presence of atopic dermatitis, because that means that there's been a pre-exposure to antigens, so this kid is eventually more at risk of a second exposure to the GI tract.

A lot of attention now has been based on the breastfeeding extent and duration. So, the importance of how long these babies are breastfed and the duration of the breastfeeding. So, what about all this? I don't have to elaborate too much to this audience that breastfeeding has a tremendous number and variety of advantages in terms of feeding patterns. It definitely is the most impactful among other factors that determine the development of the newborn immune system. This is due to the presence of specific bioactive components in human milk that are immunomodulators, like TGF-β, human growth factor, cytokines, and so on and so forth. And, of course, the breastfeeding ensures the baby has a good engraftment of friendly microbes that are fed the proper prebiotics in the human milk oligosaccharides that are present in breast milk, but also because the breast milk has some probiotics.

The question now is—while these are undisputable advantages, the role of breastfeeding in improving food allergies, and allergies in general, is not totally clear. Recent studies suggest the effect of breastfeeding may be modified by the interaction with other genetic and environmental (particularly dietary) factors that may eventually lead to more of a protective vs neutral kind of effect. The data that we have so far are rather inconclusive, to be totally honest. Of course, exclusive breastfeeding provides optimal infant nutrition and should be encouraged through 4 to 6 months of age, as we typically do. Breastfeeding has not consistently been linked to the prevention of cow's milk protein allergy. But even if we don't have a consistent benefit for prevention, it looks like breastfeeding seems to be protective against atopic dermatitis and may also reduce the risk of wheeze and asthma. Breastfeeding remains, therefore, a key component of optimizing the health for the immune system and gut microbiome for the development that I told you about before.

Interestingly enough, though, is that when we compare the cow's milk protein allergy, either confirmed by oral food challenge or by a skin prick test, in the kids that have cow's milk presented while breastfeeding, the incidence of allergy is much lower than in the ones that avoided it. So, in other words, it looks like, as with peanut allergy, early but continued—that's the other key element, it can't be on and off—cow's milk formula ingestion may reduce the risk of cow's milk protein allergy without interfering with breastfeeding. So, mixed feeding that is continuous seems to be a good way to prevent cow's milk protein allergy.

Now, what about other formulas? Soy formulas made without cow's milk, and other formulas made with other mammals like goats, are definitely not recommended for allergy prevention, because it looks like they carry a similar risk to that of cow's milk protein allergy. What about the hydrolysate formulas? Mixed results there in terms of prevention of food allergies. Differences across individual formulas preclude broad recommendations, and we can't do meta-analysis because of that. For infants at risk for allergic disease, hydrolyzed formulas may be considered on a per-product basis. So, there are different formulas with different compositions.

To summarize, one major risk for cow's milk protein allergy is the imbalance of the microbiome because, epigenetically, they put in motion the genes that start the allergic march, and this can be mediated by several factors: mode of delivery, feeding choice, environmental stuff, and so on and so forth. Breastfeeding—sure it provides optimal infant nutrition—but data to prevent cow's milk protein allergy are inconclusive. Early, ongoing cow's milk formula feeding can reduce the risk of cow's milk protein hypersensitivity without interfering with breastfeeding, and, finally, the data with regard to the effect of hydrolysate formula on cow's milk protein allergy are mixed.

Novel Strategies for Cow's Milk Protein Allergy Management & Induction of Tolerance

I'm going to move on to wrap up our chat here on novel strategies for management and induction of tolerance. Again,

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this is a work in progress, so there are no clear final recommendations, but there are some issues that I believe are worthwhile to review. Dietary avoidance is the conventional management approach for cow's milk protein allergy. In other words, if mom has the capability, continued breastfeeding should be encouraged. For infants receiving formula, intact cow's milk protein formula should be avoided, of course, and extensively hydrolyzed formula is recommended as an alternative. For those eating complementary foods, special attention to adequate calcium intake is recommended because cow's milk– and dairy-free diets are poor in calcium and vitamin D.

There is a lot of discussion about—if mom is breastfeeding and the kid has been diagnosed with cow's milk protein allergy—if mom needs to embrace an elimination diet. In general, it's not necessary because, for the vast majority of kids, breast milk of a woman consuming cow's milk does not contain sufficient allergens to trigger allergy. I know that is a general practice with moms on diets when the kids continue to have symptoms, meaning that this can happen, but it's a rare event.

This slide is just to remind everybody what kind of formula alternatives to cow's milk protein–based formulas we have available. Besides the standard intact-protein formula, we have plant-based protein like soy. Hydrolysate formulas—they're made of cow's milk proteins that have been partially or extensively hydrolyzed, so they are not large enough peptides to induce an immune response anymore. And then the amino acid–based (or what are called elemental) formulas are made with single amino acids. And you see there are advantages or disadvantages of these different options. Of course, the more that you go from the standard formula to amino acid–based elemental formulas, the more the cost increases. But, of course, the allergenicity also decreases. So, the more you go down, the more safe the formula, but it costs more.

Formulas that are not recommended in kids with cow's milk protein allergy, besides the standard cow's milk formula, are formula from goats or other mammals, A2 formula, and so on and so forth. We discussed this already.

American Academy of Pediatrics–recommended substitutions of formulas for IgE-mediated cow's milk protein allergy are the following:

- Less than 6 months of age, they consider extensively hydrolyzed formula or, as a second choice, amino acid–based. That again is more expensive and the palatability is not that good. Kids, they don't like it because it really smells bad, but that's a second choice.
- More than 6 months of age, the extensively hydrolyzed formula is preferred. Sometimes, you can try soy formula, but again, the success of soy formula has mixed outcomes there. And again, as a second choice, amino acid–based formula.
- Non-IgE-mediated cow's milk protein allergy at all ages, you just go with the extensively hydrolyzed formula and amino acid–based as a second choice.

Reintroduction. There's a lot of commotion there, you know. How can we do that? How can we make sure that we don't harm these kids or that they go into anaphylaxis? What is the right time? And so on. Well, in general—but these are rules with a lot of exceptions—most of the kids with cow's milk protein allergy outgrow their allergy (develop tolerance) by, at the latest, age 5 years, and sometimes earlier than that. But the time to tolerance varies. It may be more rapid with non-IgE- vs IgE-mediated cow's milk protein allergy. The guidelines have recommended trialing reintroduction starting with baked goods. So, trialing baked milk in 6- to 12-month intervals to evaluate tolerance.

Increasingly now, there is a focus on various strategies for increasing tolerance by modulating immune response through home reintroduction and/or immunotherapy. But again, now there are data that three-quarters of the kids with cow's milk protein allergy develop tolerance to baked milk—so cooked milk—by age 3 years.

There is the so-called food ladder approach to induce cow's milk protein tolerance. Home-based strategies for dietary advancement that slowly increase allergen exposure. So, they begin always with heavily heat-treated foods (so baked goods), and then progress to cooked foods (like pancakes), to less-processed foods (like soft cheese), and then cow's milk formula.

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The intention, at least on paper, is to help the induction of natural tolerance with this approach. You know, this kind of food ladder approach, it's largely safe in appropriately selected patients with non-IgE-mediated food allergies. And again, the effectiveness of this approach decreases as cow's milk protein–specific IgE levels increase.

This is a typical milk ladder for mild-to-moderate non-IgE-mediated cow's milk protein allergy. You start with cookies—let's say start with 1 and increase the amount to 3. And then, you go to muffins, and you see the amount there. Then to pancakes. They are the softest. And then the cheese that has some undigested cow's milk protein in there. And then you go to yogurt, and finally the complete reassumption of cow's milk or formula containing cow's milk protein. That's the typical recommended ladder. Of course, this has to be done not just in a vacuum, but under the supervision of a healthcare professional. So, in other words, the healthcare provider needs to guide this milk ladder reintroduction that can be done at home.

What about probiotics and cow's milk protein allergy management? This is a huge debate. Of course, you know the probiotics are live microorganisms that, in general, are considered to confer health benefits to people who ingest them. The most used are *Lactobacillus* and *Bifidobacterium*. They are found in large amounts in healthy breastfed infants, and they are associated with reduced antigen trafficking due to intestinal permeability that is improved, as is the immune modulation. And very frequently, cow's milk protein allergy infants have lower levels of these bacteria in the microbiome. Now, there is a series of products out there that have been proved in many studies that the induction of oral tolerance or the acquiring of tolerance to cow's milk protein is accelerated in kids with IgE-mediated cow's milk protein allergy if using extensively hydrolyzed formula fortified with a probiotic, in this case *Lactobacillus rhamnosus* GG (LGG) that you see in the dark orange compared to the yellow bar.

What about immunotherapy for IgE-mediated cow's milk protein? Oral immunotherapy can induce desensitization to cow's milk protein, but will not typically cure the allergy (in other words, sustained nonresponsiveness). It's not routinely recommended in patients with cow's milk protein allergy due to the risk of anaphylaxis and GI adverse events. What are the recommendations for the oral immunotherapy? It's considered for patients with confirmed IgE-mediated cow's milk protein allergy who value the ability to ingest controlled amounts of milk more than the potential risks. So, in other words, they really want it because calcium and vitamin D are considerations. Consider use of omalizumab, an anti-IgE antibody, when starting this oral immunotherapy. Avoid use in patients who cannot tolerate baked milk (for obvious reasons). Remember, this has nothing to do with the food ladder. It's totally different. Food ladders introduce allergens in forms that are likely to be tolerated, while oral immunotherapy is ingesting the allergens in forms known to cause allergic reactions, but in the presence of immune modulator.

To finish up, these are the takeaway messages that I want to leave you with. The allergic march represents the natural history of allergic diseases that starts from atopic dermatitis and potentially progresses to asthma. Gut dysbiosis, skin barrier dysfunction, and genetic and environmental factors contribute to the progression of the allergic march. The extensively hydrolyzed formulas are typically the first-line approach for kids that are formula-fed that are affected by cow's milk protein allergy. And finally, cow's milk protein allergy has conventionally been managed through avoidance and periodic reintroduction to test for tolerance. The food ladder or the immune tolerance can often induce desensitization and/or tolerance.

Audience Questions

Editor's Note: This is a transcript of live audience questions with the educator's responses from the presentation on July 12, 2023

✧ Are both non-IgE-mediated and IgE-mediated food allergies considered part of the allergic march?

Yes, they are. Again, while the IgE-mediated allergies have features like biomarkers, the level of IgE, that you can follow, we don't have that luxury for non-IgE-mediated food allergies, particularly cow's milk protein allergy. So, it is very difficult to follow this march and its components and evolution with non-IgE-mediated allergy, but the essence is the same, yes.

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✧ What can be done to intercept or halt the progression of the march, and would these recommendations differ for infants at high risk for allergy vs those who do not have risk factors for allergy?

There is some stuff that we can control, meaning the mom's lifestyle, for example, when it comes to healthy diet, exercise, and avoidance of exposure to risk factors like smoking, excessive caffeine and alcohol, and so on and so forth. And then there are other elements that, in general, we cannot control. If there's a medically indicated need for a Cesarean delivery, there's not much you can do about it. Or if the kid has a severe infection that requires antibiotics, there is not much you can do about it. Conversely, if you use the Cesarean delivery for planning the vacation of the OB-GYN, that's not a good use of that approach, and definitely not a good approach to be promiscuous in the use of antibiotics in kids when it's not necessary. Remember, in the first 2 years of life, most infections are viral and therefore do not require antibiotic use. For the kids at risk, of course, the early introduction of cow's milk protein consistently, together with breast milk, seems to be an advantage in terms of possibly favoring tolerance and, again, this is not unique to cow's milk protein allergy. We see now also with peanuts, this famous paper [the LEAP study][1] that was published now a while ago in which the group proved that early, rather than delayed introduction (as we used to), is advantageous in favoring tolerance.

✧ Do you recommend the probiotics mentioned for preterm infants?

Preterm infants don't have the chance to reach the full maturation of many functions, including engraftment of the microbiome. There is a lot of discussion out there of the possible use of probiotics in preterm infants to prevent a series of possible negative clinical outcomes, like the allergic march. There are 2 schools of thought here, which happens when we don't have solid evidence quite yet.

The believers say there is absolutely no reason to question the use of probiotics. Worst case scenario, they do nothing; best case scenario, they can be very helpful to establish a more balanced and friendly microbiome in the gut and therefore help prevent negative outcomes, including the start of the allergic march.

The other camp says, "How do you know that?" This, in preterm infants, can be deleterious. If these probiotics, in large amounts (because you need to give large amounts), can go systemic and cause major problems because they can eventually reach the bloodstream of these kids.

I don't have an intellectual answer yet, but I have to say that, because there are no controlled studies that can prove or disprove one of these 2 theories, right now the general acceptance is that even for very low-birth-weight infants, probiotics have been used in experimental settings—so it's not standard of care—to prevent, for example, necrotizing enterocolitis that is a much more complicated and worrisome condition that low birth weight kids may face.

✧ What is your advice to mothers for ongoing formula supplementation, when their baby received cow's milk formula in the first 72 hours of life in the hospital, who wish to continue breastfeeding only? If it's still recommended, how frequently and how much?

If these kids are at risk for cow's milk protein allergy, then exposure to cow's milk protein in the first 72 hours and then interruption and reintroduction is the perfect storm to start the allergic march. I showed you the data that intermittent exposure to cow's milk protein is the highest risk element for development of cow's milk protein allergy. So, I know that this is still debated, but in controlled trials, the continuous exposure to formula with cow's milk protein in it while breastfeeding is probably the best way to go. My recommendation would be: "You feed your baby your breast milk, and at the end, offer some formula." It doesn't need to be a great amount of formula introduced, but it has to be done every day. That would be the best way to minimize the risk that these kids will develop cow's milk protein allergy if it was already introduced to them in the first 72 hours. If there is no family history of cow's milk protein allergies, or any form of allergies, and therefore the risk is relatively low, you may avoid that.

[1]Du Toit G et al. *N Engl J Med*. 2015;372(9):803-813.

Confronting the Allergic March

✧ Instead of utilizing formula and breast milk for preventing cow's milk allergy, why not recommend that mom consume cow's milk and expose baby to the protein that way?

Because, as I mentioned, the passage of cow's milk protein through the breast milk is inconsistent and relatively rare. It is possible, but relatively rare. If we were confident that 100% of mothers consuming cow's milk protein will have the proteins pass in the breast milk, I would say that would be the logical way to go. But that's not the case.

✧ In a child with suspected non-IgE-mediated cow's milk allergy that successfully acquires tolerance to cow's milk formula, is continued cow's milk protein ingestion necessary to maintain that tolerance?

No. I mean, once the tolerance has been acquired, that is a change in the immunologic status, so it's not that you have to consume cow's milk every day to maintain tolerance, meaning that whatever you introduce of cow's milk dairy products, you will be able to tolerate it.

✧ You mentioned that guidelines recommend reintroduction of baked milk after 6 to 12 months of avoidance, but do you ever reintroduce cow's milk formula earlier than that? If so, in which infants?

The guidelines now say if you do give baked products and the baby reacts, you need to wait at least another 6 months to do a second try. That's the bottom line. If you do that earlier, the chance that they will react again is high, and that's the reason why the recommendations have been framed that way. Of course, there are exceptions to the rule and I'm very sympathetic of the fact that there are so many aspects to consider when cow's milk products need to be reintroduced: economic, social, nutritional, and so on and so forth. But first and foremost, we want to make sure that kids are safe, and therefore it may be that waiting for another 6 months can be—I would say—a very conservative approach. I would not recommend to do this any earlier.

✧ Would you like to take an additional moment for any closing thoughts, Dr. Fasano?

My final thoughts are the following. Compared to 20 years ago, the field of food allergies and the allergic march has changed dramatically. Now we have a much better understanding than before. When I started to be a pediatrician, the concept was to expose as late as possible to the instigator, and that that will protect the kids. Now we know that it's just the opposite. Expose as soon as possible if you want to prevent food allergy. If the tolerance is already broken, now we have better tools or regulations to follow to reestablish the tolerance, and I believe that now we have growing evidence that probiotics (to rebalance a dysbiotic microbiome that seems to be instrumental to break tolerance) can be used to regain tolerance faster because, eventually, epigenetically you can slow down or stop the march. I think that we have evolution that we didn't have before and, again, this is something that changed completely the landscape of the way that we handle these conditions.

⊙ *To complete this course and claim credit, click here, or go to: https://pnce.org/Allergic-March*

GI	gastrointestinal
IgE	immunoglobulin E
Th	T helper
TGF-β	transforming growth factor-β
LGG	*Lactobacillus rhamnosus* GG

This activity is supported by an educational grant from **Reckitt | Mead Johnson Nutrition**.

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