Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

COURSE TRANSCRIPT

Preventing the Allergic March in Children: Where Are We?

Overview

The "allergic march" describes the natural history of atopic diseases, which begin early in life and progress over years or decades. **Dr. David Hill** discusses the common manifestations of the allergic march, including atopic dermatitis, food allergy, allergic rhinitis, asthma, and eosinophilic esophagitis. Topics will include the genetic, environmental, and inflammatory contributors to the allergic march as well as current and emerging interventions to slow or prevent the march. Therapeutic interventions that will be covered include atopic dermatitis treatment, prevention of sensitization, and immunotherapy.

Target Audience

This activity was developed for pediatric physicians, nurses, nurse practitioners, dietitians, allergists and other health care providers who have an interest in newborns, infants and toddlers.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Comprehend the immune responses that cause the allergic march
- Discuss successes and shortfalls of current strategies to mitigate allergy in children
- Examine research and future strategies to help mitigate the allergic march in children

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This activity was released on June 11, 2021 and is eligible for credit through June 11, 2023.

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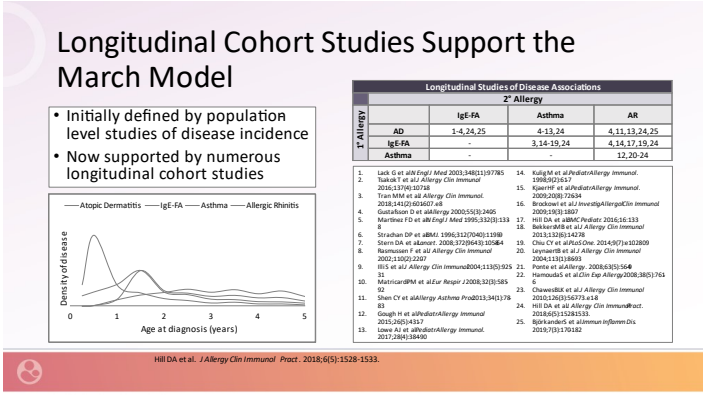
Preventing the Allergic March in Children: Where Are We?

Editor's Note: This is a transcript of an audio webcast presented on May 26, 2021. It has been edited and condensed for clarity.

David Hill, MD, PhD: The learning objectives for today's activities are as follows. First of all, comprehend the immune responses that cause the allergic march. We will also discuss both successes and some shortfalls in terms of current strategies to mitigate allergy in children. And finally, we will apply what we've learned to examine research and future strategies that are in development to mitigate the allergic march in children.

The Allergic (Atopic) March

First of all, I'd just like to give an introduction to the allergic march, which is also known as the atopic march. I use those 2 terms interchangeably. The allergic march itself is an old model that has been in existence for decades, and it describes the natural acquisition or development of allergic manifestations in children, primarily allergic children, over time. The stereotyped progression of the allergic manifestations on a population level are as follows. Typically, they start with atopic dermatitis in infants. Often, then, children with atopic dermatitis will progress to the development of food allergy. And, in this particular case, I'm talking about classic anaphylactic IgE-mediated food allergy. The march then progresses in a subset of children to the development of asthma, and then, again, on a population level, soon thereafter, to allergic rhinitis. And this model is useful not only in understanding the patterns of allergic disease in allergic patients, but also to understanding the underlying mechanisms—both genetic and immune—that result in these diseases and the connections between them.



Slide 1 - Longitudinal Cohort Studies Support the March Model

So first of all, I just want to give a little bit more background on the allergic march itself and how this concept has come into existence. So, as I mentioned, on a population level, meaning when you look at allergic children en masse, the incidence of atopic dermatitis is earlier than the other allergic manifestations (Slide 1). And typically, we see it somewhere in infancy between the age of a few months and a year of life, which is the peak incidence for the atopic dermatitis or eczema. That's followed subsequently by IgE-mediated food allergy and asthma, which both have an incidence somewhere between 1 and 2 years of life. And then finally, allergic rhinitis, which has a slower onset and has a peak incidence somewhere between 2 and 3 years of life.

Now, initially, these observations were made on a population level. And, as such, we couldn't actually measure the relationships between the various manifestations. We couldn't say, for example, in a specific child with atopic dermatitis, what would be their risk of going on to develop food allergy.

However, subsequent studies in longitudinal disease cohorts have now supported not only the concept of the allergic march in children but also allowed us to actually measure those risk

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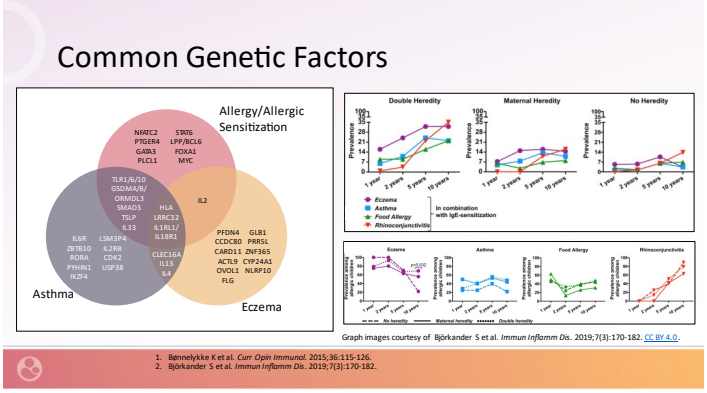
relationships. Here, in Slide 1, I'm just showing a set of really nice studies over the last 2 decades that are all longitudinal birth cohorts that have actually measured the risk relationships between the various allergic manifestations. And so we now know that not only on a population level do we see this pattern, but even in individuals there is risk imparted by development of 1 allergic manifestation and the subsequent development of another.

What Causes the March?

Genetic Factors

In the next stage of this talk, I'd just like to delve into the mechanisms underlying the march itself. And we're going to start with a brief discussion of some of the genetic factors that have been implicated not only in allergy but in the march.



Slide 2 - Common Genetic Factors

So here's a really nice Venn diagram from the review below, which came out in 2015, that talks about some of the risks that have been identified through well-powered GWAS studies looking at allergic outcomes (Slide 2). And as you can see, it's divided up into 3 sections, looking at polymorphisms associated with asthma; allergy and allergic sensitization; and then finally, eczema. And as this audience likely is aware, there are a number of risk loci that have been identified for these various diseases. For example, for eczema, a well-described association is with a gene and a protein called filaggrin or *FLG*. And you can see that in this particular case, filaggrin polymorphisms have been associated with risk of eczema but not with the other allergic manifestations.

In contrast, if I can draw your attention to some of the areas of overlap in the diagram on Slide 2, for example in the purple area that overlaps asthma and allergic sensitization, you can see TSLP and IL-33. These are 2 epithelial-derived proteins that are early indicators of essentially barrier damage, and they've been well described in mouse models—and subsequently in human studies—to be associated with allergic outcomes. So in that particular case, we have a risk loci that is associated with 2 allergic disease states. And then for a subset, we can actually see that there are risk loci that have been associated with all 3 of these allergic disease states. In particular, a number of HLAs, IL-1, and IL-18 receptor signaling.

However, to really put this in context, I want to share another study with the group, [shown on the right side of Slide 2], which came out in 2019.[1] And what the authors did is they took a cohort of children, and they subcohorted them based on whether or not their parents were allergic. And so, under the graph that says double heredity, essentially that means both the mother and the father had an allergic history. Maternal heredity is just the mother with allergic history, and then no heredity means no allergic history. And they looked at allergic outcomes over the course of 10 years, as shown here for eczema, asthma, food allergy, and allergic rhinitis. And what they found was that, indeed there seems to be a role for genetics, as indicated by associations with heredity status, for all of the allergic manifestations.

However, when we look at specific diseases individually, something interesting fell out of this

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analysis.[1] And that was that for eczema, in purple on the left-hand side there, there was a statistically significant difference between double heredity and no heredity, indicating that for eczema in particular—and you can actually see that in the Venn diagram on the left-hand side—there is a high degree of genetic relative risk, if you will, in terms of ultimately developing that disease. There were not significant associations for the other disease outcomes that were studied. However, you can certainly see a trend for asthma, and maybe less so for food allergy. But what's notable is that for allergic rhinoconjunctivitis, actually, even the no heredity group showed a similar Increase in disease incidence over time, suggesting that for that particular outcome in this cohort, genetics played a lesser effect.

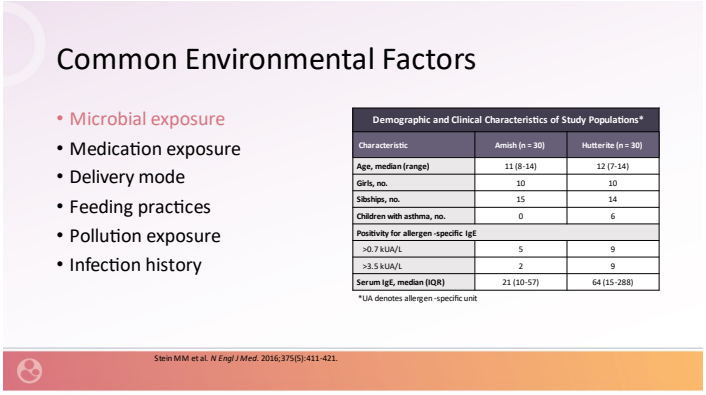
Environmental Factors

So definitely genetics are very, very important, but they're not the only factor. As the audience will be well aware, multiple environmental factors have been shown to associate with different allergic outcomes. We're just going to touch on a few key environmental factors next.

There've been literally hundreds of studies of environmental exposures and allergic outcomes over the last several decades—very nice high-powered studies. But I tried to boil down the major environmental exposures into the following 6 bullet points:

- Microbial exposure
- Medication exposure
- Delivery mode
- Feeding practices
- Pollution exposure
- Infection history

And each of these categories has been shown to influence 1 or more allergic outcomes in children.



Slide 3 - Common Environmental Factors

To give you an example, I'm going to start with microbial exposure. This is a really nice study that was in the *New England Journal of Medicine* in 2016.[2] And what the authors did is they examined 2 groups of children, 1 from Amish background and 1 from the Hutterite backgrounds. And what's interesting about these 2 populations is that they are related to each other genetically. And so, what this analysis allows the authors to do is to control, if you will, for any of the genetic factors that we talked about in the last slide, and to really look primarily at the environment that these children grew up in.

And the authors examined 30 children from each group, and you can see the allergic outcomes in this table here (Slide 4).[2] For example, in the Amish children with an n of 30, there were no children with a diagnosis of asthma. And there were lower sensitization scores, if you will, in terms of allergen-specific IgE or serum IgE levels in total, when compared with the Hutterite children, where you had 6 children with asthma and more of those children had evidence of sensitization as well as higher serum IgE levels.

And the authors hypothesized that this could be due to differences in the child's environments.[2] And there is 1 sort of key difference between these 2 farming groups, and that is that the Amish have maintained very traditional farming practices where they're physically involved in a lot of aspects of the

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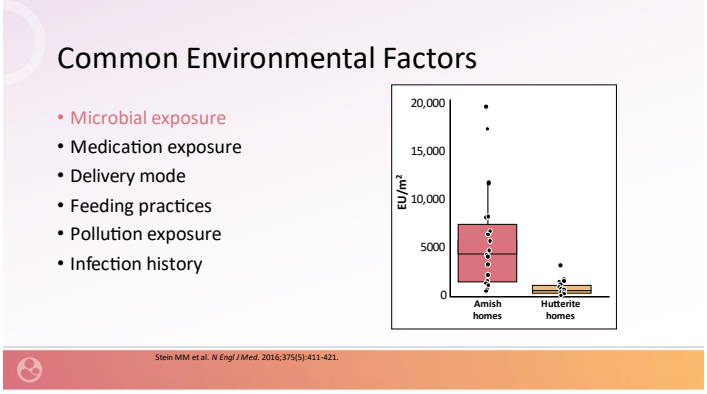
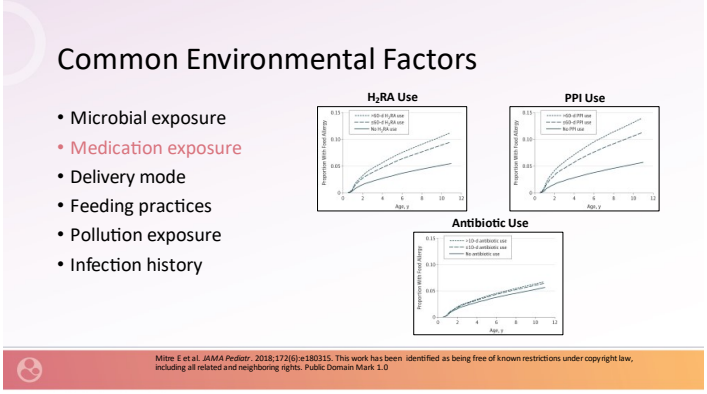
farming itself, and physically involved with the animals to a higher degree than the Hutterite populations, where those groups have actually adopted more modern farming practices.



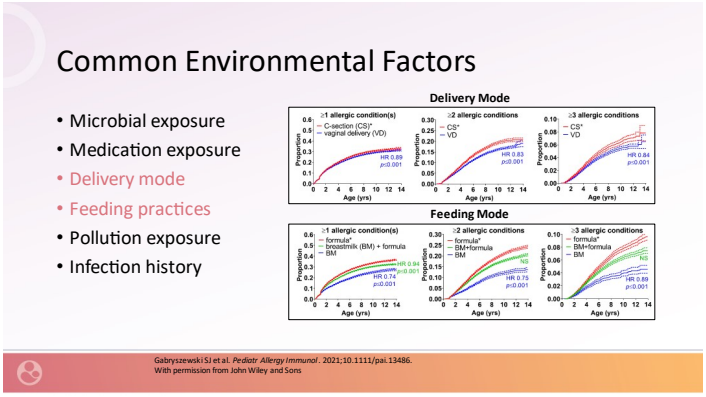
Slide 4 - Common Environmental Factors

And so the authors hypothesized that, potentially, exposure to microbes or microbial components that are associated with traditional farming practices could explain these outcomes.[2] And they tested this by actually looking at endotoxin levels in the homes of these children. What they found was that, indeed, the endotoxin levels were much higher in the dust in Amish homes than they were in the Hutterite homes (Slide 4). Again, suggesting that exposure to microbial signals might be a key environmental modulator for the outcomes of asthma.



Slide 5 - Common Environmental Factors

Next, I want to talk a little bit about medication exposures and we're going to stay on this theme of microbes and the relevance of microbial exposure to allergic outcomes. But in this particular case, we're going to look at 3 different medications that fall into 2 classes that are each thought to manipulate or alter the commensal microbes that either live on our skin or in our gut (Slide 5). And those are medications used for acid suppression. So you can see the H2 receptor antagonists on the upper left and the proton pump inhibitors (PPIs) on the upper right, as well as, of course, antibiotics down below. This article was published in *JAMA Pediatrics* in 2018.[3] What the authors found is that high use of either H_2 receptor antagonists or PPIs, was associated with significantly more likelihood of developing food allergy. And, to a lesser extent, this still significantly similar trend was observed with antibiotic use. So again, now we've got this idea that potentially microbial exposure in the environment is protective, and if we manipulate the microbes that live with us, that potentially we might, on a population level, be increasing the risk of developing allergy.



Slide 6 - Common Environmental Factors

The last environmental component I want to discuss is actually delivery mode and feeding practices (Slide 6). This is a similar study to the one I just showed in *JAMA Pediatrics*. It used, essentially, cohorts of allergic children to look at outcomes.[4] And then it subcohorted those children based on various exposures. So the 2 exposures that the

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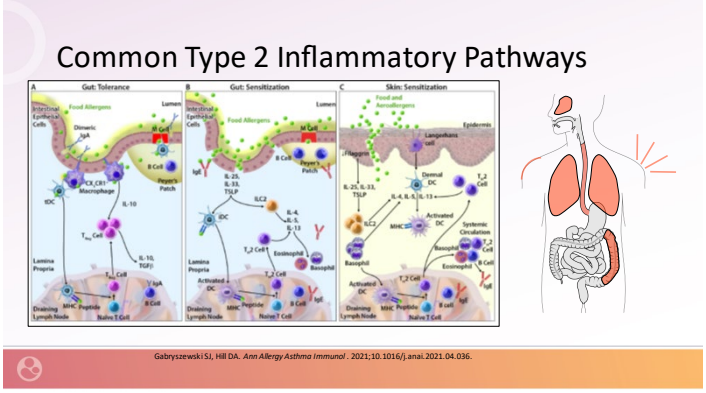
authors used here were delivery mode, meaning either C-section or vaginal delivery, as 1 set of exposures, or feeding mode, meaning either exclusive breast milk feeding, breast milk supplemented with formula, or formula exclusively. Again, the concept here, at least with the delivery mode, is that potentially a different mode of delivery might alter the commensal bacteria that colonize the skin and the gut, so potentially, again, a microbial hypothesis there. And the same thing can be said for feeding mode. It has been shown that the gut microbiome of a child that's breast milk fed is different from that of a formula-fed child; although, there's also the consideration of sort of allergen exposure here, and how that might modify risk of allergy development.

What the authors found is that delivery mode, and in particular delivery by C-section, increases a child's risk of developing not just 1 allergic condition but multiple allergic conditions. So here we're seeing 2 or more or 3 or more allergic conditions as we move from left to right across the graphs. So potentially, C-section is not only predisposing to a single allergic manifestation but actually predisposing to progression on the allergic march. Similar with feeding mode, we see that an infant that was formula-fed, or breast milk-fed with formula supplementation, has a higher risk of developing 1 allergic manifestation. And in terms of 2 or 3 allergic conditions, the exclusively breast milk-fed infants were actually protected.

Type 2 Inflammatory Pathways

The last causal mechanism that I want to talk about is actually the immune system itself. And that's because the branch of the immune system that predisposes people to all of these [atopic] diseases, is common among them. And that is the type 2 immune system or the type 2 branch (Slide 7).



Slide 7 - Common Type 2 Inflammatory Pathways

So what is the type 2 branch? Well, the type 2 branch gets its name from the Th2 cell, which is the classic allergy T cell. You can see an example of it in the middle panel B towards the bottom: it's purple, says Th2 cell, and you can see that that cell actually produces a number of characteristic allergy-type cytokines: IL-4, IL-5, and IL-13. What we know is that in a healthy scenario, a nonallergic scenario on the left-hand side, is that there's a whole lot of mechanisms that help to tolerize the immune system. So, this is actually a diagram on the left of the gut, and you can see that there are a lot of immune cells that are specifically evolved to actually take up food allergens from the gut and present them to the immune system in such a way that the immune system recognizes them as safe, and it actually differentiates Tregs to those antigens to produce IL-10 and dampen any potential immune response.

What happens in allergy, obviously, is that that process goes awry. So the middle panel D is gut sensitization. And then the right panel C is actually skin sensitization. And what I want the audience to note is that there are actually a number of similarities between gut sensitization and skin sensitization. So I'm going to start with the gut. And you can see that in scenarios where the gut barrier is disrupted, whether that be through inflammation or other mechanisms, food antigens can actually

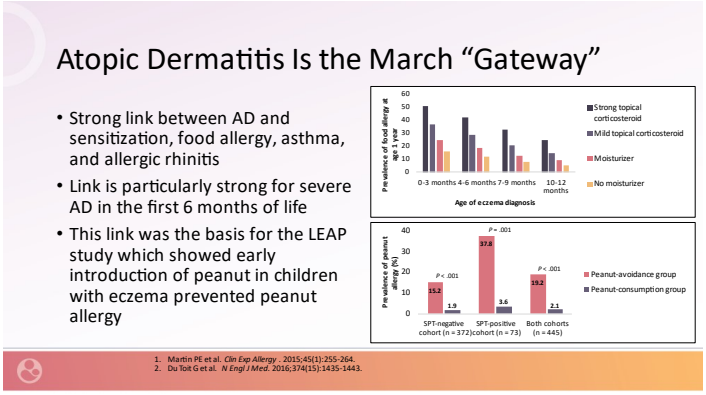
access what's called the lamina propria, underneath the epithelium. And when that happens in the context of damage, a number of key cytokines are produced by that epithelium, specifically IL-25, IL-33, and TSLP.

Now, you remember that those are actually a couple of the genes that were associated with particular allergic outcomes in the genetic studies. When the immune system comes into contact with food allergens in the context of those inflammatory cytokines, 2 things happen. One is, the dendritic cells that take up the antigen become activated. And the other is, a number of innate immune cells, in particular innate lymphoid cells, also become activated to produce those classic type 2 cytokines (IL-4, -5, and -13). The activated dendritic cell can go back to the lymph node where it presents that antigen to a naive T cell. And because of the activated state of that dendritic cell, the T cell that was naive becomes a Th2 cell that can then come back to the mucosa and make your type 2 cytokines.

What's important is that Th2 cell response is not just limited to the gut for 2 reasons. Firstly, the T cell can interact with the cells and cause class switching to IgE. That IgE can then circulate around the body, and that's why we get anaphylaxis to peanut, for example. And also, that Th2 cell itself potentially can leave the gut and cause disease in other locations.

Now, compare the gut sensitization to the skin sensitization panel on the right (Slide 7), you'll actually see a lot of things are similar. We're talking about an epithelium, we're talking about food and aero-allergens that are entering the immune space right underneath the epithelium. That's happening in the context of inflammatory cytokines, IL-25, IL-33, and TSLP, which, again, are producing type 2 cytokines, IL-4, -5, and -13, and essentially pushing the immune system towards an adaptive inflammatory allergic response. Again, those T cells and those IgE molecules can enter the circulation and cause systemic disease.

The take-home message here is that because of the shared immunology that underlies these various conditions, there's opportunity for bleed over, if you will. Sensitization that causes 1 allergic manifestation can also predispose, potentially, to the development of another. And that's why we can get our various allergic manifestations whether they be in the lung or the skin or the sinuses or systemically, with anaphylaxis.



Slide 8 - Atopic Dermatitis Is the March "Gateway"

I want to talk a little bit more about atopic dermatitis. Atopic dermatitis is commonly thought of as the gateway to the allergic march. And the reason for that is exactly the mechanisms that I discussed on the last slide. Because of the unique immunology of the skin, when allergens are exposed to the skin, very often the immune system will recognize them as foreign and mount an allergic response. And we actually see this clinically, there's a very strong link between atopic dermatitis and sensitization, between atopic dermatitis and food allergy, and between atopic dermatitis and asthma and allergic rhinitis. And this link is particularly strong for severe atopic dermatitis in the first 6 months of life. So the study on the right-hand side of Slide 8 nicely shows this.[5] And what the group did was they looked at a group of children who either had no atopic dermatitis or had severe atopic

dermatitis. And the way that they cohorted those children was based on the medication they were using. So, there's potentially some confounders there, but for the sake of this study, think about strong topical corticosteroids as being equivalent to severe eczema, whereas no moisturizer means this child has skin that does not have atopic dermatitis and doesn't need to use moisturizer.

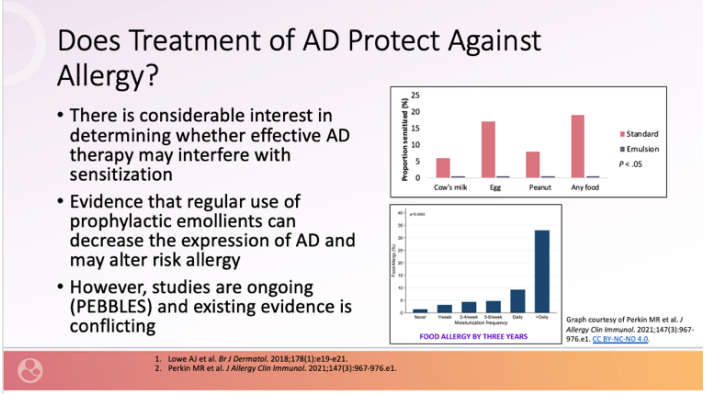
And when you look at the prevalence of food allergy at 1 year of age, the prevalence is much, much higher in those children that were using strong topical corticosteroids equating to severe eczema as compared to those who were using just a little bit of moisturizer, no moisturizer at all, equating to no atopic dermatitis.

And this link was actually the basis for a seminal study in the allergy field known as the LEAP study, which showed that early introduction of peanut in children with eczema actually would prevent peanut allergy.[6] And the whole hypothesis was that since children with eczema are at higher risk for developing food allergy, if we can get them eating allergens, introducing it via the gut and accessing those [tolerance-inducing] immune mechanisms that I talked about 2 slides earlier, that potentially we could prevent the development of peanut allergy. And indeed, that's exactly what the authors saw. You can see that across the entire study, there was a significant reduction in prevalence of peanut allergy in children who were randomized to consume peanut protein.

Can We Prevent the March?

Interfere with the "gateway"

And so this leads me to the question of what can we do to prevent the march itself? And I think the first thing that researchers have started to investigate is whether or not we can interfere with atopic dermatitis as the gateway to prevent the development of allergies.



Slide 9 - Does Treatment of AD Protect Against Allergy?

And so, a lot of these studies are underway, and every time I give this lecture, I look for the latest studies that have come out. And we're still at the stage where a lot of things are ongoing, but I do want to share a couple of key observations with you (Slide 9).

And the first is that there is some limited evidence that regular use of prophylactic emollients can decrease not only the expression of atopic dermatitis—meaning the actual degree of skin inflammation—but also potentially the risk of developing allergy. This is a small study that showed that in children that were using prophylactic emollients, there was actually lower prevalence of allergy, whether it be to cow's milk, egg, peanut, or any food.[7] However, there is also conflicting data.

This is a more recent study. It's a limited analysis of what's called the PEBBLES study, that just came out in the *Journal of Allergy and Clinical Immunology* this year.[8] And they actually found that the prevalence of food allergy was highest in children that were using moisturizer more frequently. So, again, there's a couple of potential confounders there and I think, ultimately, the conclusion at this stage has to be that we don't know whether or not we're going to be able to prevent the development of food allergy or sensitization in general at this stage, but there are a number of studies that should be

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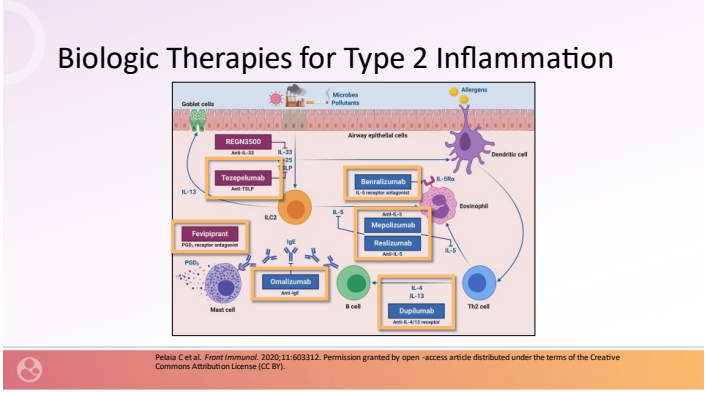
helping us answer that question in the coming years.

Interfere with sensitization

So let's talk a little bit about something that's on the horizon, if you will, and that is whether or not we can interfere with sensitization to allergens with biologics (Slide 10).



Slide 10 - Biologic Therapies for Type 2 Inflammation

As the audience will likely be aware, there have been a whole number of biologic therapies that have come out to target the type 2 allergic immune cascade over the last 10 years—initially with things like omalizumab, the anti-IgE molecule, and subsequently with things that are still just in development and just coming out, for example the anti-TSLP and anti-IL-33 biologics. But what's really exciting about this is we can now, as immunologists and allergists, target specific aspects of this cascade and look at whether or not we're able to modify outcomes. And so I just want to highlight a couple of the molecules or the medications that are either in development or already available. We do have molecules that are targeting IL-33 and TSLP. You'll remember that these are 2 of the early innate alarmin molecules that are produced by the epithelium in the context of damage, predominantly. They are key early signals to the immune system to actually develop an allergic response.

We also have a number of medications that are now approved and in use. These include medications that are targeting the IL-5 signaling pathway. This is most relevant in the context of eosinophils, and so there is potentially more limited scope in terms of the ability to prevent allergies, but there's certainly a lot of use and interest in these medications for eosinophilic asthma, for example.

Of course, we now have a new medication that targets both IL-4 and IL-13 mediated signaling. That's dupilumab. IL-4 being a key heavy-hitting type 2 immune cytokine. It's very important not only for the effector functions of Th2 cells but actually earlier in the differentiation of the Th2 cell itself.

We now have molecules that are designed to interfere with the late stage of the allergic cascade

For example, prostaglandin antagonists, as well as the anti-IgE, omalizumab. So, there are a number of studies underway that are examining the utility of these molecules in the treatment of specific allergic diseases. But for a number of those studies, secondary outcomes include examination of treated or untreated children over time to see whether or not we can interfere with allergy development. There is something to be said for the potential utility of some of the molecules that act higher up in the allergic cascade, for example, anti-TSLP or dupilumab that potentially could interfere with the development of the Th2 cell itself, which really is the key step if you're going to interfere with immunologic memory.

Immunotherapy

And then the last thing I want to touch on is actually immunotherapy, which is the oldest form of immunomodulation that we have in our medication arsenal. Immunotherapy has actually been around for almost 100 years, which is incredible to think about.

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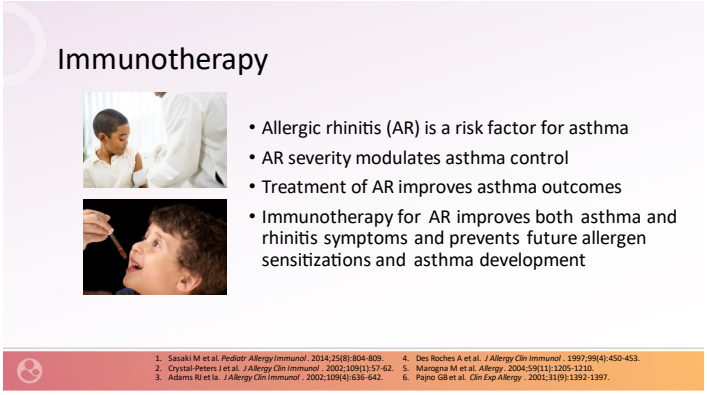


Slide 11 - Immunotherapy

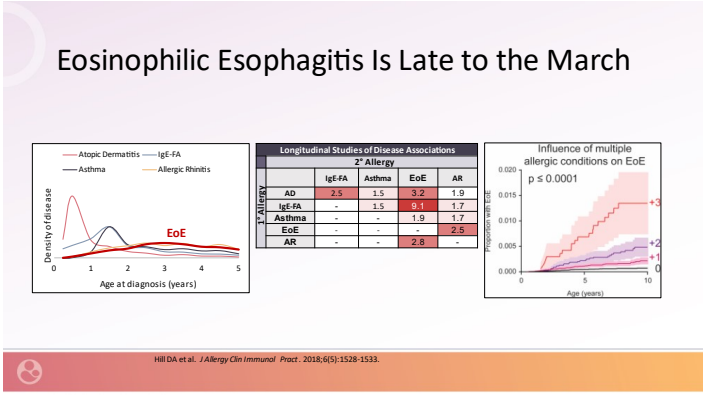
We use it most often in the treatment of severe allergic rhinitis. And this is relevant because allergic rhinitis is actually a risk factor for asthma. And allergic rhinitis severity correlates with worse asthma control. If you treat allergic rhinitis, and you treat it effectively, you can actually improve asthma outcomes. And so this is probably, even though it's one of the older forms of therapy, it's probably one of the best studied in terms of its ability to not only modify the immune system but also modify immune outcomes. And so there is actually evidence that if you were to treat a child with immunotherapy for allergic rhinitis, that treatment will actually improve their asthma and prevent the sensitization of that child to future allergens as well as modify the risk of that child developing asthma in the future.[9,10] And so, in terms of a lot of these things that we've been talking about, and hope that we're going to be able to modify the allergic march, I would say immunotherapy is already an option to do that.

New Concepts in the Allergic March

Eosinophilic Esophagitis

And finally, I just want to close on a couple of new concepts in the allergic march. And these are really ideas that have come into the common discussion in the last 5 years or so. And they're exciting because I think they represent an interest by the field and by investigators in expanding this model and bringing it up to speed with 21st-century immunology and clinical practice.

And the first [new concept] is the addition of a disease process called eosinophilic esophagitis (EoE) to the allergic march model (Slide 12). So, members of the audience may be familiar with eosinophilic esophagitis. It's essentially a food allergy, primarily, that manifests with eosinophilic inflammation of the esophagus. And it's much more indolent than classic food allergy that presents with anaphylaxis within minutes of eating the food in question. EoE on the other hand, actually develops over months and years and can often go undiagnosed for a long period of time. The symptoms are pain and reflux-type symptoms. But if it's not treated, either through food elimination or through swallowed steroids, it can actually predispose individuals to fibrosis and the development of strictures, and ultimately food impactions.



Slide 12 - Eosinophilic Esophagitis Is Late to the March

Now, there's a lot of interest in understanding the fundamental immunology of eosinophilic esophagitis, but there's also interest in understanding how it relates to the other allergic manifestations. And to that end, there was a recent study that looked at the incidence of EoE compared to the other allergic manifestations as well as the risk relationships between EoE and the various

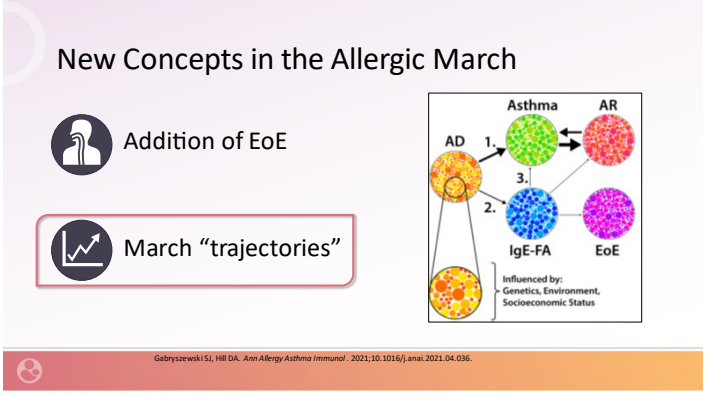
other allergic diseases.[11] And there was reason to suspect that, indeed, there would be a strong relationship here because what we do know about the immunology of EoE is that it seems to be a Th2 cell–driven disease, and of course you can tell from the name that it manifests with type 2-type inflammation.

What I'm showing you on the left-hand side here is a graph of the allergic march, if you will, where I've overlaid eosinophilic esophagitis. And you can actually see that the incidence of EoE is somewhere around 3 years. It's very similar to allergic rhinitis. Keep in mind that there is a delay in diagnosis of EoE for most children, they can go months or even years before they're diagnosed. And so the actual incidence of disease could be earlier than what we're able to observe with this kind of study. However, this kind of study does allow us to measure the actual risk relationships between EoE and the other allergic manifestations. And the way that you read this center graph is, the first allergic disease that was developed is on the left-hand side, and then the second allergic diseases across the top. And so what you can see is that, for example, for a child who has atopic dermatitis, their risk of developing EoE is somewhere around 3.2 times that of a child who doesn't have atopic dermatitis.[11] There was a very, very strong risk relationship between classic IgE-mediated food allergy and EoE, where the risk was almost 9 times that of a child who doesn't have IgE-mediated food allergy.

And then what the authors were also able to show is that there is a cumulative effect of having multiple types of allergy on the risk of developing EoE.[11] This is a Kaplan-Meier curve on the right-hand side, and the way you read it is that for a child with no allergic diseases the risk of developing EoE was low, and that's the zero and the black line. For a child with 1 allergic disease, for example atopic dermatitis, the risk was slightly higher. And you can see that for a child with 2 or even 3 allergic diseases—atopic dermatitis, food allergy, and allergic rhinitis—the risk of developing EoE was the highest. So this is going back to our initial slides discussing the underlying mechanisms of the march itself, is it genetics? I would say probably. Is it environment? Probably. And is it shared immune pathways? Probably.

March "Trajectories"

The second new concept in the allergic march that I'd like to discuss is the concept of allergic march trajectories. This concept actually stemmed directly from clinical care. And I think the audience will immediately recognize that—even though it's nice that on a population level, atopic dermatitis comes first, and then it's followed by food allergy, and then it's followed by asthma—in actual practice, in individuals, that's often not the case. And so what the field is starting to recognize is that we need to take into account is these individual paths, if you will, on the march (Slide 13). Because they might be telling us something really important about either the genetics that underlie a particular outcome, or the environment. And I think now's the time to start doing this because we have the methodologies to do it and to do it well.



Slide 13 - New Concepts in the Allergic March

So just to give you an example, this is a figure from a recent review that describes some of the top

allergic trajectories that exist in 1 cohort of children.[12] And on the left-hand side, you can see atopic dermatitis. Atopic dermatitis is still the most common first allergic manifestation. On the numbers-to-numbers level, atopic dermatitis usually comes first. And it is then followed by 1 of 2 common pathways. The most common pathway is atopic dermatitis to asthma and then asthma to allergic rhinitis. And I like to think of this path, of this trajectory, as the airway allergy trajectory. The child is sensitized via atopic dermatitis to aeroallergens and then develops, aeroallergy.

However, there are other paths. And the second most common path is actually atopic dermatitis to food allergy. This may not be surprising of course, because there's been decades of literature and now the LEAP study that's shown that atopic dermatitis is a huge risk factor for food allergy.[13] But now we can actually start to think about a separate trajectory, which is atopic dermatitis to food allergy. And then I showed you on the last slide that there is a very strong link between classic food allergy, IgE-mediated food allergy, and development of EoE. And then of course, children can take their own paths, right? They can start with food allergy and go to asthma, or they can start with food allergy and go to allergic rhinitis. That's okay too; it's just less common. And why exactly might a child take a particular path? Well, it comes down to the fact that any 1 of these 5 diseases is actually made up of multiple different diseases and different endotypes. Some that might be driven predominantly by genetics, others that might be driven predominantly by environment.

And finally, I think we need to take into account that socioeconomic factors can also influence our perception of disease progressions, whether it be how we diagnose disease or how we treat disease. And so I like this model because it's starting to acknowledge the complexity of the allergic march, but at the same time bring it up to speed with how we're thinking about these various diseases and how they relate to each other.

Key Messages

And so, with that, I'd just like to close by reviewing our learning objectives and summarizing a few of the key messages. First of all, 1 of the objectives was to comprehend the immune responses that caused the allergic march. Well, it turns out that in fact it's complicated. It probably is an interplay of genetics with environment and how those genetic and environmental factors impinge on the type 2 immune system. I think that there's definitely overlap or bleed-over, if you will, between the various allergic manifestations. Meaning that if you develop a sensitization in the skin to an aeroallergen that could feed into both asthma and allergic rhinitis. Similarly, for food allergy, the strong connection between classic food allergy and EoE is real and represents shared immunology.

We also discussed the successes and shortfalls of current strategies to mitigate allergy in children. I think some of the clear successes are early introduction of allergenic foods in the LEAP study and in subsequent studies that have now led to changes in recommendations from the AAP and the AAAAI in terms of when we should be introducing foods and allergenic foods to children, essentially moving that earlier.[14,15] There have been some shortfalls. I think the question still remains as to whether or not, even though intuitively it makes sense, we're going to be able to achieve protection from allergy through early and effective treatment of eczema, for example.

And then, finally, in terms of future research and strategies to help mitigate the allergic march in children, I think the most promising future comes from the biologics. In particular, those biologics that target early and innate sources of cytokines that can

then predispose to the development of Th2 cells. So specifically, anti-TSLP, anti-IL-33, also dupilumab because it targets IL-4 and IL-13 receptor signaling, which is not only important for how Th2 cells function, but it's also important for Th2 cell developments in the first place. And so, if we can interfere with these early, early, signals, I think the chance of us actually blocking the development of allergic memory through the T cell is highest.

Question and Answer

What are your thoughts on formulas developed to expose babies to common allergens starting as early as 4 months?

Dr. Hill: I think the concept behind them is spot on. I mean, we've got decades of evidence now from disease models, predominantly mice, showing that the gut is the immune organ of tolerance. If we are able to expose the immune system in a responsible way to those allergens, the likelihood of promoting tolerance is high. We also now have evidence from a number of translational and clinical trials that have shown that early introduction of foods via the gut protects against actual clinical outcomes. So I think the science is there. And being creative in our modes of food allergen exposure, whether they be through formulas that incorporate various allergenic foods or through supplementation with, for example, a vitamin D drop that also has various food allergens in it, I think that makes a lot of sense. And ultimately we're just going to have to do the trials and do them in a rigorous and controlled randomized manner longitudinally to make sure that we actually prove that it's helpful and certainly that's not harmful in some way.

For an infant who has no allergies themselves but who has parents or siblings with atopic conditions, what do you recommend for parents to try to prevent the development of atopic disease?

Dr. Hill: I take a very pragmatic approach to this. And this is a question that comes up all the time in the clinic, I think, in part, because I am also a researcher who studies this. And so, informed patients will ask these very appropriate questions. And ultimately we need to treat each child as an individual, and we need to treat that child using currently accepted best practices. And the way that I do that with my patients is, first and foremost, if they're infants and they have atopic dermatitis, I do my best to treat that eczema effectively, and to encourage the families and partner with them to develop a care plan, which we're all in agreement on is going to help that child not only be comfortable, but control that skin inflammation to try to reduce the likelihood of sensitization.

The other thing that I do is I follow the recommendations from the AAP and AAAAI in terms of early food introduction,[14,15] and in particular in children with eczema, because that evidence, I think, is very strong. In those children who are at risk, early introduction of allergenic foods is important.

Now, there is certainly evidence, and I presented some today, in terms of the hereditary nature of allergy, but I don't think I would necessarily modify my approach to a child's care based on there being allergic parents. For example, if I were a pediatrician and an infant came in that didn't have eczema and didn't have any allergy but both of the parents were really, really highly allergic, I would still recommend early introduction of allergenic foods. So really my management of a patient would not be modified greatly by whether or not their parents are allergic because I would recommend the same for a child of a nonallergic family.

How do you expect peanut powder oral immunotherapy and other food allergen immunotherapies to impact the development of the allergic march?

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Dr. Hill: I would say if we're talking about food introduction or immunotherapy even, then in my mind it kind of puts me on that second trajectory, the food allergy trajectory. And if you look down the food allergy trajectory it starts with atopic dermatitis, then it goes to classic anaphylactic food allergy, then it ends up in a small subset of children at EoE.

Of course, now you're talking about a scenario. The question was a scenario where a child already has anaphylactic food allergy and is getting oral immunotherapy for that allergy. And in my mind, the maximum opportunity [with using oral immunotherapy] is to potentially prevent the development of EoE.

Now, this is complicated because in some children it's actually been shown that a risk factor of oral immunotherapy for foods is EoE. And that was part of the initial observations that made us cue into the fact that EoE and classic food allergy might be related in terms of their pathology. But the way I tend to think about it is that, in the majority of kids that have classic food allergy, they've not yet developed the immune background that's going to lead to EoE. And so if we're able to tolerize them to their classic food allergen, then potentially we can prevent them ultimately going on to develop EoE, again, in a small subset of children. But then, again, there's also going to be kids who have already developed the immune background for EoE, and therefore when we give them that food, peanut, one of the consequences is going to be EoE manifesting.

What types of infections can impact the development of atopic conditions?

Dr. Hill: I didn't touch on these data, specifically—we just talked about other environmental factors, but 2 things come to mind actually. So, one of them is respiratory viral infections, which are known to be a risk factor for development of asthma.

Now, I would say the causality there is not well worked out. And what I mean by that is, it could be that children who are admitted to the hospital as infants or young children because of the respiratory viral illness, are already predisposed to develop asthma. They would have developed asthma anyway, but because of that underlying predisposition when they got the viral infection, they had slightly more severe respiratory symptoms and they ended up in the hospital.

The other way to look at that, and I think that data support this too, is that there's something about early respiratory infections that actually predispose to the development of asthma. And I think the question is still out on that, but that would be one link that I could make between infection and allergic outcome.

The other one is colonization of the skin, actually. So there's been a number of nice studies that have shown that whether or not a child with eczema has their skin colonized with *Staphylococcus aureus* will actually modify allergic risk as well. And so those would be 2 examples where I can think of—1 being a virus, the other being a bacteria—that patients might come by allergic risk.

For infants who require the use of antibiotics or proton pump inhibitors, how can the risk of future allergy development be mitigated?

Dr. Hill: This is another question that commonly comes up, and the answer is, I think, relatively straightforward but also potentially not completely satisfying. The answer is, when children truly need those medicines, we should use them. Antibiotics, obviously, are life-saving medications that saved and do save thousands of lives every year. However, there are times when antibiotics are over prescribed. The classic scenario in pediatrics is the viral otitis media. And sometimes it can be very hard to tell if an otitis is bacterial or viral, but there are

now better diagnostic pathways that pediatricians can use to help to come to those decisions. But the key is, when the antibiotics are needed, they're needed. And what we should try to do is reduce unnecessary exposure to those medicines.

Now, with something like the reflux meds, [there may be] additional opportunities to reduce use of those medicines. They tend to be one of the most prescribed medicines in pediatrics for reflux; they're used to treat everything from not eating to nondescript gastrointestinal pain. And so I think there is potentially an opportunity to reduce our use of those medications, and the way that I would approach it is essentially make sure that they're truly indicated in the first place, and then follow up with the patient and see whether or not there's been a clinical response. Because if there hasn't been a clinical response to that medicine in 6 to 8 weeks, the likelihood of there being a clinical response in the future is lower. What we need to try to avoid is children just staying on those medicines for years, potentially with little therapeutic benefit.

Now, in terms of things you can actually do, if children are on those medicines, unfortunately, I can't give you any evidence to support one thing or another. People could speculate about use of probiotics, etc, etc. But ultimately, unfortunately, the evidence in terms of allergic outcomes for those interventions is insufficient for me to be able to give a broad recommendation. So I would focus on making sure we're using the medications appropriately, that we're doing therapeutic trials, and then we're discontinuing those medications, in particular the acid-blocking agents, if we don't see a therapeutic response.

Are there safe ways to increase the microbial or dust endotoxin exposure of infants to help for that asthma and other atopic conditions?

Dr. Hill: I think let kids be kids. I think that's a very safe way to do it. So I've got a 4- and 8-year-old, and my 4-year-old comes home with just completely dirty knees and hands, and during COVID, is putting them in his mouth and all kinds of things, and I just kind of smile and part of me says, "Gosh, I really want to throw him in the tub right away." And the other part of me says, "That's part of being a kid." I think that the way to safely increase exposure to microbes is let kids be kids and not be overly anxious to reduce their exposure to just normal kids' stuff.

The other thing is there have been some nice studies that have shown that actually having a pet in early childhood can be helpful in preventing allergies. I think it's probably a combination of both microbial exposure and also allergen exposure. But the studies are there, and they show that having a dog in early childhood prevents against developments of allergies later on. So that's another potential way to do it.

For a 2- or 3-month-old infant who presents with severe atopic dermatitis, how do you counsel parents regarding the future risk of allergy development?

Dr. Hill: There are specific numbers that you can give people. For example, the study that I showed you is available online, and it's available on our lab's website, and you can actually pull that table and tell a parent exactly the risk that the child would have, if you apply that population level data to that child. The way I tend to approach it in practice is to be a little bit less about the numbers, to be honest. And the reason for that is because population-level data is great, but individuals are individuals, and kids are kids, right? And so there's no way for me to actually say to a child or to a family, "Bobby's risk of developing asthma is 3 times that of somebody who doesn't have eczema." Because they don't actually know that.

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What I tend to say is, "Lots of studies have shown that children with eczema are at higher risk of developing food allergy, respiratory allergy, and asthma." And so what I would like to do for both that child's comfort and to mitigate future risk of developing allergy is to treat that eczema. To treat it safely, to treat it effectively, consistent with practice parameters, and we're going to essentially get a double win out of that. We're going to help that child be more comfortable and potentially reduce their risk of developing future allergies. So that's the way I approach it. The numbers are out there, you can find them on my lab's website. We have a PDF that we made that pediatricians can download, an allergist can download, but the way that I personally approach it in my own practice is not to go by the numbers and instead focus on making connection with the family, partnering with them to come up with a therapeutic plan that everybody's on board with, and then instituting that plan.

Dr. Hill, do you have any brief thoughts before we conclude?

Dr. Hill: I would just thank everybody again, for being interested in this topic. It's one that's highly relevant to pediatrics; it's also highly relevant to adult medicine. And I would just like people to come away with the knowledge in addition to the work that's already been done, that there's a lot of new things happening in this field. And so to stay tuned to the journals. People can also follow various labs on Twitter, our lab is on there, and we try to be responsible in terms of getting information out there not only to patients and patient advocates but also to clinicians and providers.

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Abbreviations

AAAAI	American Academy of Allergy, Asthma & Immunology	**IL**	Interleukin
AAP	American Academy of Pediatric	**PPI**	Proton pump inhibitor
EoE	Eosinophilic esophagitis	**Treg**	Regulatory T cell
HLA	Human leukocyte antigen		

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