Can Phenotyping Help Guide Management of Asthma, Atopic Dermatitis, and Food Allergy?

✦ Course Transcript ✦

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David R. Stukus, MD: I'm going to talk about phenotyping, which is something that I utilize every single day for just about every single patient that walks through my doors. And really part of what I love about being an allergy specialist is a good understanding of the underlying pathophysiology, what's going on underneath the surface. And we're going to talk about some of these key concepts to help you start phenotyping your patients and, most importantly, understand why it matters.

Before we get into some of the details and even examples of how to use phenotyping and things like that, I think we just need to acknowledge that this isn't necessarily easy to do. I think that there's overall a lack of awareness in regard to what phenotyping is and how to implement that into clinical practice. I think it's going to take time for people to understand some of the big concepts and then really to start to practice with it. And in the setting—sometimes in the primary care setting especially—of seeing 30 patients a day, it's a valid argument to say who has time for this? But hopefully, with the conversation we're going to have and some of the discussion points, you'll recognize that phenotyping does play a role, and I think if you can recognize the value in it and think through some sort of baby steps and practical ways that you can implement this into practice with those patients that you're seeing, hopefully you'll see that it's not only important because it's going to impact the treatment decisions and their prognosis and things along those lines, but hopefully you're going to find that it's enjoyable as well. And it gives you just a higher sense of satisfaction and deeper understanding of what's going on with that individual patient in your practice at that time.

It always helps to start with some definitions and when we think about endotypes, endotypes are sort of like data. What's the underlying immunologic or inflammatory metabolic pathophysiology process going on? What are the chemicals involved? What are the signals? What are the mediators? Things like that. Whereas phenotyping is a bit more of a step above that. It's almost like a 10,000-foot view whereas endotyping is more an in the dirt. And phenotypes are more of a set of observable characteristics resulting from the interaction of one's genotype, their genetic predisposition, with the environment. And I'll offer some examples as we go through this, but phenotypes really are when you have those patients in your office and you recognize certain characteristics that go along with that. That's what we're talking about when it comes to phenotyping, not necessarily having that endotyping in front of you or available at that time. And hopefully, this makes more sense.

Asthma, allergic rhinitis, atopic dermatitis, food allergy, these represent some of the most common chronic conditions affecting children across the United States, across the world. Roughly 30% of children have allergic rhinitis, 20% have asthma, 5% to 8% have food allergies and, on the surface, we know that people with asthma have shared characteristics. We know that they have underlying inflammation in their lower airways and they have hyper-reactive airways with bronchial hyper-responsiveness. That's asthma, recurrent episodes of basically hyperactivity over time. But not all asthma is the same, as we'll talk about soon. Just because somebody has asthma doesn't mean that they have the same type of asthma. Same with allergic rhinitis. Are we talking about somebody who has perennial allergic rhinitis to cat and dog dander, dust mites or is it more seasonal allergic rhinitis? Those are actually different entities. And the same thing with food allergies. We'll talk about atopic dermatitis as well.

Underlying all of these, we now know that there's different pathophysiology. Just because people have asthma doesn't mean that they have the same types of inflammation which is going to impact their response to treatment and ultimately it's going to impact their prognosis. The better you understand these concepts of phenotyping, hopefully you'll start to tease out those very key differences amongst those

patients that you're seeing on a regular basis and some examples that hopefully offer even more information for you.

We can use the family history and the history of early onset, severe eczema and other allergic conditions to help identify those patients that have allergies. We always want to clarify and offer an accurate diagnosis to begin with. For instance, we know that chronic nasal congestion and clear rhinorrhea are very common symptoms amongst infants and toddlers. Do all of those have allergic rhinitis? Absolutely not. Are those the main symptoms that occur with allergic rhinitis? Absolutely. How do we tease out those that are from recurrent viral infections or due to irritant exposure vs those that are actually allergic? We want to clarify the diagnosis because the way we treat those are extremely different as well as the prognosis and how we impact that. And then ultimately, those patients that we have that start off with persistent atopic dermatitis, then develop environmental allergies or food allergy and asthma, they're the ones that are going to have probably lifelong allergic conditions and more persistent allergy as well. There's some key reasons to sort of put these concepts into place whenever we're starting at that initial diagnosis even. But, of course, the absence of risk factors does not mean that one cannot develop allergies. It is a very complex interaction between our genetic predisposition and early life exposures that really determine who develops allergies and who doesn't. Just because you lack risk factors doesn't mean you can't have allergies, so we don't want to ignore that in somebody who doesn't have these risk factors either.

Biomarkers are a nice tool that we can use to get a better sense of the immune response to what's going on from a pathophysiologic standpoint or other signs of inflammation and things like that. And when we think about inflammation, I always think about what type of inflammation. We have our T-helper cells and there's generally 2 different pathways, so we have T-helper 1, T-helper 2, T_H1, T_H2. For autoimmune conditions, this is more of a T_H1 profile, so there's a lot of inflammation going on with people who have lupus and rheumatoid arthritis and things like that. Whereas with allergic conditions, this is more of a T_H2 profile and what that means is that we have different mediators involved. When it comes to T_H1, this is going to be more interferon gamma, interleukin 2 and this is more neutrophil dominant whereas T_H2 or allergy, we're going to use interleukins 4, 5, 10 and 13 and this is going to be more eosinophil dominant. Both have inflammation going on, but these have very different sort of end cell types and inflammatory mediators involved.

When it comes to allergic inflammation, there's a couple of key mediators. We have the IgE antibody which is often bound to those mast cells which are present throughout all tissues throughout the body. Also, the basophils in the circulation and we have eosinophils which end up at the end targets causing inflammation. And with allergic inflammation, of course, it can involve the skin, the respiratory tract, both upper and lower as well, and then when it comes to IgE recruitment and production, interleukins 4 and 13 are major mediators and with the eosinophils, interleukin 5. And this is going to be really important when we talk about treatment with biologics which is very exciting because now we can put our phenotyping hats on together and identify specific targets of the immune system when we identify those candidates that may benefit from treatment with a biologic. And that's why these concepts are very important.

How do we tie these biomarkers with the clinical characteristics to get to a phenotype? Well, when it comes to asthma, as I mentioned already, it's not the same. We can have 20 different types of asthma and there's really no one size fits all best approach to say just because somebody has asthma doesn't mean we should treat them all the same. Do they have intermittent asthma or is it more chronic? Is it mild, moderate or severe? We're all very familiar with the ways of grading the severity. How well controlled are they? Are they having exacerbations or just mild symptoms? Are they having infrequent symptoms or frequent symptoms? What age did they have the onset of their asthma? And all of these different factors are going to tell you the type of asthma that they have which is going to change their prognosis. We know that 40% of all toddlers are going to have wheezing at some point, but not all of those are going to go on to develop asthma. Can we predict those that will likely develop asthma? Well, we can through

the asthma predictive index and we know that those that have the presence of eczema, family history of asthma, they have sensitization to aeroallergens, eosinophilia, those are the ones that are more likely to have persistent asthma as opposed to transient wheezing. It's also going to change how they're going to respond to therapy as well.

When we think about our patients with asthma, I think it's important to really think through, is this more of a T_H1 or T_H2 inflammation? T_H1 inflammation is mostly associated with adult-onset asthma, those who are smokers and those that lack allergies. It's really hard to have a ton of comorbid allergic conditions, but not and a T_H1 profile. Whereas those with more T_H2 inflammation have those allergic or atopic comorbidities. They have peripheral eosinophilia, I already mentioned the role of the eosinophils, and this is where we can measure biomarkers. Not just the peripheral eosinophilia, but also exhaled nitric oxide, which is a good representation of the eosinophilia in the lower respiratory tract. And this is something that can be measured in the office setting with a very simple tool that can be combined with spirometry. Fhile we're measuring lung function, we can also measure whether or not they have eosinophilic inflammation because that may change the phenotyping and the type of asthma that they have.

When it comes to different types of asthma, it's important to think through, again, is it type 2 inflammation? If so, that tends to respond a lot better to inhaled corticosteroids. There's different phenotypes that we can be considering. There's different types of therapy that we can target with biologics and things like that. Whereas if it's more of a type 2 low or T_H1-predominant asthma, that's where we may not want to give them a high dose of inhaled corticosteroids because their neutrophil-predominant inflammation may not respond very well to that. That's where we may want to go more towards long-acting muscarinic antagonists or bronchodilators or other approaches to help open up their airways or treat their inflammation and different types of biologics. So again, this is just exemplifying why it's important to learn how to phenotype and start phenotyping our patients with asthma and other allergic conditions.

When it comes to atopic dermatitis, if you just look at the surface, there's a lot of shared characteristics where we see that inflammation and we see those eczematous patches that often occur in the antecubital fossa, popliteal fossa. They can occur on the cheeks, on the face. But there's different types of atopic dermatitis when you actually look under the skin, the types of mutations involved and types of inflammation, things like that. So again, just because 2 people have eczema or atopic dermatitis doesn't mean they have the same type and that doesn't mean that they're going to have the same prognosis or that they're going to have the same response to therapy. And we can start to tease that out as well.

We can really characterize atopic dermatitis phenotypes by the age of onset. The majority of children with atopic dermatitis are going to present in infancy or the first 2 years of life, but not everybody will. If they present later in life, that should be the first clue that this is a different type of atopic dermatitis than I typically see and that allergic phenotype. What part of the body is involved? What do the lesions actually look like? The age of onset can be used to really think through some of the clinical features and differential diagnosis, especially if it presents in adolescence or adulthood. That's a very different type of atopic dermatitis as opposed to those that present in infancy.

Where is it affecting them? The atopic dermatitis really that's focused on the scalp and the face and the neck but is sparing the body is very different than the infant-onset T_H2 type atopic dermatitis that often goes along with allergic comorbidities. Hands and feet can be affected as well. You can have dyshidrotic eczema. You can have nummular eczema and then really this is the morphology of it, of is it that eczema that they scratch more and more. You get that thick lichenification which is very different than eczema that kind of just resolves with some minimal topical corticosteroids and things like that. Just some concepts to kind of consider of this isn't obviously a time for a deep dive into atopic dermatitis, but you get the sense now that hopefully there are different types, just like there is with asthma.

Now, oral food allergies. This is really interesting and this is where we're starting which is where we were with asthma say 15, 20 years ago. This is where we are with food allergy now and we're starting to identify these different phenotypes. A couple of key examples: We know that 75% of children who are allergic to cow's milk or hen's egg can tolerate those same allergens when it's baked into foods, it's prepared in the oven because they're reacting to this 3-dimensional epitope formation that gets unraveled at high temperatures. So that's really great in formation to know. They have a milder form. They're also more likely to outgrow their milk and egg allergy at a younger age compared to somebody who can't tolerate the baked form. That's 1 example of how we're using phenotyping. We're also understanding more and more about threshold doses and there are patients of ours out there so that you can have 100 children with a peanut allergy, but they can all have different thresholds that would cause a reaction, let alone severity of reaction, which tends to reproduce itself over time. And we're getting better at identifying that by these oral food challenges and some threshold dosing and things like that.

This is sort of where the field is going and we should not be telling everybody that just because they have a diagnosis of food allergy that they're all at the same risk for causing a reaction, let alone the same risk for having severity of reaction. And this is the nuance of where we are in regard to management.

Proper diagnosis is always paramount, so we want to make sure that when we diagnose food allergy that we're getting it right. There's another module in which I discuss all the pitfalls of panel testing and using IgE tests as screening tests. We want to use those IgE tests properly to clarify the diagnosis and provide accurate diagnosis because unnecessary avoidance of foods is a real problem and it's not a benign recommendation to tell people to take food out of their diet unless there's a really good reason.

We are seeing more and more biologics being developed for the treatment of asthma, atopic dermatitis and allergic conditions than at any point in history. These are very exciting times. Biologics are interesting because they target very specific parts of the immune system and we're going to talk about why the most important thing for phenotyping is to understand which biologic is right for your patient. But it's also important to understand that biologics are very different than what we currently have available. When we talk about corticosteroids, for instance, I often will tell families, especially if they have steroid phobia or hesitancy, I can make sure that your child never wheezes again when they asthma if I give them a high enough dose of prednisone to take every day, but you're not going to like me very much because it has terrible side effects and we'll be dealing with brittle bones and stomach ulcers and cataracts and adrenal insufficiency and things like that. Whereas, with biologics, because they are so specific, if we can identify and properly target that part of the immune system that's causing those issues, we have much less side effects to worry about and it's just so specific for each patient.

The other thing to consider is when do we even think about biologics for our patients. Well, there is cost involved. When each of these treatments cost $1,000 to $3,000, if not more, per treatment, we want to identify the right patient and typically, when it comes to something like asthma, if they've failed medical therapy, meaning that they've been adherent with a good regimen of whatever is indicated for their type of asthma and they continue to have exacerbations, particularly if they have emergency room utilization or they're being hospitalized for their asthma, those are ideal candidates for biologics because they've been shown that they can decrease those exacerbations. Whereas if you have a patient who's nonadherent and they just cough or wheeze when they try to play sports, probably not the best candidate in regard to biologics. For atopic dermatitis, this can be extremely debilitating and if they're doing good skin care and using the right topical anti-inflammatory medications and have persistent disease that's impacting their quality of life and their sleep and they're miserable all the time, those are the patients that we should be thinking about biologics for atopic dermatitis. And now, of course, we have an FDA-approved indication for using a biologic to treat food allergy. That's a fun conversation we get to have with families now as well. These are things to consider when you have those patients in your office that just aren't doing well, especially those with truly

persistent and severe disease despite all of our best efforts with medical therapy.

As far as what to do in your office setting to kind of get these patients ready to be seen, well I think it depends on access to specialists. If you have a good relationship with allergists, immunologists, pulmonologists, dermatologists in your area, just identifying those children to refer to them sooner rather than later is a great first step. That's the best thing you can do to help your patients, especially since most of you probably won't be prescribing biologics in primary care. Other than that, I don't think it's necessary to start doing any of the evaluation. I don't think that you have to start measuring peripheral blood eosinophil levels and things along those lines. If you happen to have it, you can use that to your advantage to help phenotype and identify those patients, but other than just referring, if you can, I think that's the best thing that you can do to help your patients.

Where does this lead us? Well, now we live in the age of biologics. When it comes to biologics available for asthma, we absolutely have to be accurately phenotyping our patients. There are different biologics that are available. Some of them target IgE, some target the interleukin 4, 13 shared receptor, some of them target underlying epithelial factors and some of them target interleukin 5. If we're going to use a biologic that targets interleukin 5 in somebody with a T_H2 low asthma or T_H1 inflammation, they're not going to benefit from that, and these biologics come at a very high cost. They cost thousands of dollars, but they can work extremely well, especially for our patients who have severe, persistent asthma despite our best medical therapy. Those that are having severe exacerbations. Biologics are a game-changer in regard to treatment, but we have to identify the best candidate for each biologic. And there's different biomarkers that we can use for that in regard to eosinophils, in regard to elevated IgE. Whereas something like tezepelumab, we don't need to have any biomarkers because that's targeting more of the structural proteins and epithelium involved in asthma.

For those of you who are prescribing biologics, hopefully you're using a lot of these tools and a lot of these have criteria right in their prescribing information. For those of you who don't prescribe biologics, I think it's important to identify your patients that have truly severe disease that would benefit from it and then refer to a specialist in your area that can hopefully identify and accurately prescribe these for them.

We also have options when it comes to atopic dermatitis and the same rules apply. We're at the point now where we can identify those with refractory or severe disease, use our understanding of phenotyping to identify the best biologic for them, and this is an evolving space. We're having more and more options available, especially when it comes to the small molecule inhibitors, such as JAK inhibitors and things like that. I encourage all of you to stay on top of this as much as possible. This is an evolving landscape but it's very exciting for all our patients. But again, it just reinforces the absolute need to understand how to phenotype our patients when prescribing therapy.

Another great way is if you're not quite sure if your patient has allergies or food allergy or asthma or where they're going, we know that infant-onset atopic dermatitis is highly associated with T_H2 inflammation. This is often the first outward sign of that patient, that baby in front of you, saying pay attention to me, I'm the person who's likely going to develop allergies as I get older. For instance, let's say you have a patient who has had recurrent episodes of cough and/or wheeze associated with upper respiratory infections and you're not quite sure if it's asthma or not, well if that same patient had terrible atopic dermatitis or they still do, that should be a very big clue that, yes, this is likely asthma until proven otherwise. That's one way that we can use these as predictive factors and, also, from a diagnostic standpoint as well.

When it comes to food allergy, we sort of talked about the different phenotypes, but there's different types of food allergy as well. We have the classic IgE-mediated hypersensitivity which cause rapid onset eye swelling and anaphylaxis. We have non-IgE-mediated food allergy, such as food protein-induced enterocolitis syndrome. Those are very different phenomena and management is very different, risk is very different. We have pollen food allergy syndrome,

so patients who have allergic rhinitis caused by seasonal pollen. Sometimes, if they eat fresh fruits or vegetables, they will experience itching inside their mouth and throat, not because they're allergic to those fruits or vegetables, but because they share homologous proteins with the pollen that's actually causing their allergy symptoms. That's a very different type of food allergy than somebody who has anaphylaxis after eating a peanut. And I already talked about how we're starting to really identify these different phenotypes and this just is another example of how we can help patients, because they're very different, based upon what type of food allergy they have.

In regard to integrating phenotyping into your practice, this is something that I was trained in during my fellowship, and I've been in clinical practice for 16 years. I do this naturally. It happens with every single patient that I see. I'm already thinking about the pathophysiology based upon their clinical history. What types of triggers do they have? What types of symptoms do they have? What's the most likely diagnosis? I utilize biomarkers and I think through that. How can any of you get to that level as well? Well, it takes practice. I encourage you just to start thinking about these concepts, especially for asthma. I think that's one of the best ways that you can really provide individualized care and help those patients that have persistent disease or that aren't well controlled. And just being thoughtful about some of these different risk factors and biomarkers that could be employed or just treating that child as what's the overall gestalt of who they are. Let's not just treat their asthma, let's treat the entire individual. If they also have atopic dermatitis, environmental allergies, that's a different type of asthma than somebody that just has asthma without the other conditions as well.

Some of the key takeaways I think that we want to focus on is really thinking about, especially with biologics, that we want to choose the right target and we can't do that without phenotyping and use of biomarkers. We want to think about the right patient. What's their disease severity? Adherence is a big problem as well, or nonadherence, I should say. We always want to think through before we escalate therapy, are our patients taking the medications as prescribed and, if not, how can we help them with that. And then shared decision-making. This is the right path for what might be the right treatment for 1 person might not be the right treatment for another, based upon their preferences and values. And then, following everybody up. If we think that we've accurately identified a good treatment option for somebody, let's make sure we have a good follow-up plan in place and outcomes measures. How do we know it's working? How do we know if we want to continue on this path? When do we want to revisit this? When do we want to reconsider? And so on and so forth.

Phenotyping patients can really provide individualized treatment options as we're thinking about the top takeaways. Their clues are everywhere. This was just a very brief introduction to it, but if you start paying attention and it's kind of fun, actually, if you get used to it and it really is providing the best care for our patients and hopefully the best outcomes as well. And I hope that this was very helpful for you. Thank you very much for your participation.