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Understanding Asthma Immunology, Phenotypes, & Biomarkers

Announcer:
Welcome to CME on ReachMD. This activity, titled “Understanding Asthma Immunology, Phenotypes, and Biomarkers,” is brought to you by CHEST. This educational activity is supported by an educational grant from GlaxoSmithKline and an educational grant from Genentech, a member of the Roche Group.

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Here’s your host, Dr. Sandhya Khurana, Professor of the Depart of Medicine Pulmonary Diseases and Critical Care at the University of Rochester Medical Center.

Dr. Khurana:
As a disease with significant heterogeneity, asthma is best managed when we take a personalized approach to its evaluation and management. But in order to do that, we must first understand its immunology, the phenotypes and biomarkers, all of which will be the subject of today’s discussion.

This is CME on ReachMD, and I’m Dr. Sandhya Khurana. Here with me is Dr. Monica Kraft, Professor and Chair of the Department of Medicine at the University of Arizona and Deputy Director of the Asthma and Airway Disease Research Center at this institution.

Dr. Kraft, welcome to the program.

Dr. Kraft:
Thank you so much for having me.

Dr. Khurana:
So let’s begin with an overview of current understanding of asthma pathobiology, which has evolved significantly over the recent years. Dr. Kraft, can you share some of the recent findings?

Dr. Kraft:
Absolutely. One, I think it’s an amazing time to be caring for patients with asthma because our understanding of the disease has evolved very dramatically, really over the last, I would say, couple of decades to the point where we now have treatments that we can offer patients that target specific inflammatory pathways. That’s very exciting in that we have a lot to offer our patients that we really didn’t have before – the concept of understanding what type of asthma a patient has. And so one easy way to think of it is we have 2 major buckets, and we call those type 2 and non-type 2 asthma. And so, when we think about type 2, we think about allergy; we think about eosinophils. And there are many different kinds of type 2 asthma, so it’s not just 1 entity either. And it’s not only a Th2 or T helper 2 disease because we know that innate lymphoid cells also have a role in this type of type 2 asthma. And still, when I say type 2, I’m referring to specific cytokines or a specific type of inflammation, that include specific cytokines such as interleukin 4 and 13 and interleukin 5 as examples,. The non-type 2 we would think about things like Th1 type of inflammation, Th17, very neutrophil-predominant disease, interleukin 6, others, so there’s a whole different type of inflammation that we see in non-T2. And in fact, asthma

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can exist in either, so our charge as clinicians is to figure out what kind of asthma a patient has. With this construct in mind this is the start, and then we can move forward from there and discuss how to determine our approach in the clinical arena.

Dr. Khurana:
That's great. It sounds very complex, obviously, and it's really hard to wrap our mind around some of this pathobiology. And we're hearing so much about phenotypes and endotypes. What is a phenotype, and what is an endotype? What has helped us understand this heterogeneity in asthma better?

Dr. Kraft:
Great question. This is what I do every day when I'm seeing patients, but it's a different mindset to understand that not all asthma is created equal, it's not all the same, and so, to figure it out, we first start out with this concept of phenotypes, which are basically observable characteristics, such as age of onset, lung function, exacerbation history, family history,. Aspirin sensitive asthma is another phenotype, and asthma caused by specific triggers such as exercised-induced asthma and menses-induced asthma. The goal is to determine the endotype, which is the mechanism that's driving or the biological pathway that's driving that phenotype.
Now, the challenge about this is there are many endotypes that can exist within a phenotype, so we often have several potential endotypes that we think about. For instance, type 2 asthma, a good way to think about it is allergic and eosinophilic. Now, they're not necessarily one in the same, so we might want to be interested in age of onset. Early-onset might suggest more of an IL-4/13-dominant or driven asthma. Later onset asthma that is associated with eosinophils may also be more IL-5-driven with less allergy. So, 4/13 really drive IgE-mediated allergic inflammation. IL-5 drives eosinophil maturation and survival. Think about other triggers such as I mentioned: exercise induced, aspirin sensitive asthma would be others. And the presence of sinus disease, nasal polyps, also help differentiate the type of asthma, but that's all under this type 2 bucket. And so examples would be in the clinical arena that might help would be able to do things such as using biomarkers, such as blood eosinophils, exhaled nitric oxide, IgE, lung function, all those things that we can do to really better understand and put the history together with the biomarkers that we have available to us to determine what kind of inflammation is driving a particular patient's asthma.

Dr. Khurana:
This is great. There are multiple endotypes that can give us the same phenotype or observable characteristic, and it's really teasing out those more granular endotypes that really help us determine the pathway involved and then pave the way for future treatments. In terms of severe asthma itself, what were some of the phenotypes or the cluster analysis work that you can share with us that has been pivotal in our understanding?

Dr. Kraft:
So, in addition to these phenotypes that I mentioned, which would be sort of early-onset allergic, you have the later-onset with lots of eosinophils, sinus disease, less allergy, exercise-induced asthma, aspirin-sensitive asthma or aspirin-exacerbated respiratory disease—those are examples of phenotypes—but there are also clusters that the Severe Asthma Research Program has identified, and they went ahead and recruited a large number of patients with and without asthma, looked at all of the characteristics that we think about, and really, probably the major ones were age of onset, lung function, and the presence of bronchodilator reversibility. And they did an unsupervised cluster analysis and identified 5 clusters that overlap with some of the phenotypes we discussed: early onset asthma associated with atopy and IgE, later onset asthma not associated with atopy and another that mimics COPD. So, even within an unsupervised cluster analysis, you can see different clusters ranging from very young, low healthcare utilization, steroid-responsive to very eosinophilic, presence of nasal polyps, no allergy to fixed airflow limitation, presence of eosinophils, high healthcare utilization - a spectrum of asthma across these 5 clusters.

Now, obesity is interesting in that it can create its own phenotype that is more IL-6-driven and is associated with metabolic syndrome, sometimes type 2 diabetes and high serum IL-6 levels, and so that would be considered a non-type 2 asthma phenotype. And we didn't talk about the non-type 2 phenotypes as much, and so I'd like to do that for a minute. Obesity-induced asthma would be considered one of them. Also, there's an infection-induced phenotype. We all have seen these patients who have had upper respiratory and even lower respiratory infections that are left with paroxysmal wheezing that really looks a lot like asthma as it develops into a chronic illness, Infection-induced asthma that tends to have more of a neutrophilic type of inflammation. Other non-type 2 phenotypes include asthma associated with exposure to environmental irritants and pollutants which is associated with neutrophilic inflammation. For example in Phoenix, Arizona the air quality can be very poor in the summer. There can be high levels of particulates and ground-level ozone. Patients have a very difficult time leaving their homes during the summer months because of these environmental issues due to worsening asthma.

So, back to the obesity question, I think obesity can create a separate phenotype, but it can also make type 2 asthma worse. As such, Anne Dixon has been very instrumental in really moving this field forward, and so she showed that if obesity occurs later in life associated with asthma, bariatric surgery can be very beneficial. However, if obesity has been present a long time, especially in an

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early-onset scenario with allergy, it is less likely bariatric surgery is able to really change the course of asthma. So obesity can do a lot of different things with regard to asthma pathobiology.

Dr. Khurana:
Yes, that is so fascinating. For those just joining us, this is CME on ReachMD. I'm Dr. Sandhya Khurana, and today I'm speaking with Dr. Monica Kraft about some important updates to our molecular understandings of asthma.

So, Dr. Kraft, let's focus on the subject of biomarkers. I know you mentioned them briefly earlier. If you could elaborate on what is currently clinically available and perhaps some research tools that we hope to see utilized in the near future?

Dr. Kraft:
I think we have a couple of biomarkers that we can use that give us a sense as to what kind of inflammation is driving a patient's asthma, and then we've got some on the horizon, so that's exciting. So I think the blood eosinophil is the most common that we think about, and if the count is elevated—usually, we like to see levels above 150, ideally 250–300 and up—really gives us a sense that eosinophils are driving the asthma. Now, with that we have to remember that eosinophils have a circadian rhythm, so it depends on when they are drawn. Also, the presence of medications, such as oral steroids and high-dose inhaled steroids, can impact the value, so we've got to keep that in mind when measuring.

And so the take-home there would be to make sure you measure them more than once, and so the guidelines really suggest at least 3 times to get a good sense of how they vary, and I often… Depending on if the patient's asthma status changes, I will order it. Especially if they're coming in for an exacerbation, I'd like to see if, in fact, blood eosinophils are elevated before they start their prednisone as an example.
And so along those lines in the type 2 arena, exhaled—a fraction of exhaled nitric oxide, or FeNo, is also a valuable biomarker not used as... It's not as widespread as I would like to see it used. It is more indicative of IL-13-driven inflammation, or that's at least the hypothesis. It can suggest untreated inflammation or response to particular biologics where IL-13 is inhibited, as examples. It can also be decreased by oral steroids and by inhaled steroids. In some patients it can be used as a measure of adherence. In others it really is a measure of untreated inflammation. And so I like to measure it basically at every visit for my patients with severe asthma because, again, I need to get a sense of how often it's elevated, Together with the blood EOS I think can be very helpful.

Now, of course, in the T2 space, if you want to know if allergy is driving the asthma, certainly IgE is a biomarker that helps us with that, but really allergen-specific IgE is what I prefer to use. Now, I'm not an allergist, so I usually use the blood tests the RAST testing, I order allergen-specific IgE, and then I'll get a total IgE with that as well. We know that total IgE really can be associated with asthma, and the higher the level there is some loose correlation with asthma,. I use total IgE if I'm ever going to be considering therapy that inhibits IgE directly, like omalizumab, but the allergen-specific IgE gives me a little bit more granular data on what types of allergens may be in fact driving that person's asthma.

There are a couple of others on the horizon that I think are interesting to note. Eosinophil peroxidase, which is a granule that is from an activated eosinophil, can actually be measured by a throat swab or nasal swab. This biomarker is being investigated by the Mayo Clinic-Scottsdale Group, and they hope to create a point-of-care biomarker for activated eosinophils in the clinic. And as part of our PrecISE Severe Asthma Network we'll be validating this nasal swab in 800 patients, so it would be great to come back and talk about whether that can be a very useful point-of-care biomarker. We'll know a patient's eosinophil status right there in the clinic. We won't have to wait for patients to go to the lab, so that's a nice—a nice option. Urinary bromotyrosine is also an up and coming biomarker. Bromotyrosine is indicative of eosinophilic inflammation and can be measured in urine, and that's another biomarker that's being investigated, this one by the Cleveland Clinic group, It will also be incorporated into PrecISE, so we've got 2 on the horizon that we're looking to validate.

Induced sputum is a great way of looking at airway inflammation. It's just not as feasible in the clinical arena, so that's not used as often. We generally use it in the research setting. And periostin used to be a very, I would say, a high-profile biomarker that's IL-13-driven, but due to the fact that it is not useful in children and adolescents because it's also produced by bone and growth can affect it. It is not as robust a biomarker as we hoped it would be, so it has fallen out of favor.

So at this point the biomarkers we use the most would be blood eosinophils, exhaled nitric oxide, total IgE and allergen-specific IgE with the idea of measuring certainly the blood eosinophils and the FeNo at multiple events. I usually get a total IgE and allergen-specific usually on initial evaluation, and between all of those, that can give me a very nice sense of whether T2 inflammation is driving a patient's asthma and really helps me with therapeutic choices as well.

Dr. Khurana:
Thank you so much, Monica. That is fascinating, and it really lays a great groundwork for our understanding of biomarkers and how to

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use them. If you'll just allow me to pick your brain and share a patient's story with you, and see if you could walk us through how you would apply phenotyping in somebody like this patient in clinical practice. So I have a 42-year-old female who has uncontrolled asthma, early-onset, and she has had frequent exacerbations despite regular use of an inhaled steroid and a long-acting beta agonist. If you were seeing somebody like that in your clinic, what would your first few steps be in trying to understand her immunobiology a little bit better?

Dr. Kraft:
Sure. That's a great question. These are the kind of referrals I receive frequently. The patients aren't reading the textbook so to speak. They're not responding to ICS-LABA, which for many asthmatic patients works very well—the combination works very well—but not for everybody. I think before we jump into phenotyping, we also—I also like to look at comorbid conditions because I think that adds to medication burden and can actually make—cause patients to be somewhat steroid-resistant. So, certainly severe sinus disease, nasal polyps or any association with exacerbation with aspirin are important characteristics you would like to determine. You'd certainly want to have your ENT colleagues involved, especially in the setting of nasal polyps, make sure they're on a good sinus regimen of nasal rinses, intranasal steroids, perhaps azelastine, antihistamines, etc., so you'd want to make sure that's covered.

I also think about gastroesophageal reflux disease, both acid and nonacid. And patients may not have overt symptoms of GERD. What I have noticed is, those who do I often see a nice response to muscarinic antagonists interestingly because I think they have high vagal tone. That's just a little bit of an aside. Therefore, GERD can exacerbate asthma and can also cause upper airway dysfunction and vocal cord dysfunction, so it is really important to identify whether GERD is present. And sometimes that will take impedance testing because the patient's surrogate may be airway symptoms and not typical GI symptoms, so always need to sort of think about that.

And then obstructive sleep apnea—again, through vagal mechanisms can exacerbate asthma as well, and so that needs to be treated. And with obesity also being an important factor to consider in asthma, obesity and OSA certainly go together, so you want to make sure all those entities are treated.
Certainly, if patients are smoking, and 20–40% of asthmatics smoke can contribute to a steroid-resistant state.
So those are examples of comorbid conditions you want to certainly make sure are addressed being treated because they are present in asthma and can add to medication burden.

I always get pulmonary function tests, and I want to make sure that I'm dealing—what kind of airflow limitation am I dealing with. I'm usually interested in knowing not only spirometry; I like a full set of pulmonary function tests. I like to look at lung volumes, look for any concerns about small airway disease as well, which you can often glean by full PFTs, and so get a sense for that in addition to a really good history about exacerbation pattern, triggers, the role of allergy and sort of age of onset, all those characteristics we've been discussing, and then, of course, moving on to using the biomarkers we just discussed, so certainly blood eosinophils, exhaled nitric oxide and IgE.

I'm always amazed at how rare the biomarkers are used. Oftentimes patients might come to me with a CBC but not a differential. FeNo is really not done very often, at least in the referrals I've been seeing, which are both in and out of state. So again, they can be very useful to assist you in understanding what kind of asthma this patient—a patient has, so I would absolutely measure exhaled nitric oxide, blood eosinophils, total IgE and allergen specific IgE and then put the history, comorbid conditions and biomarkers together to come up with a treatment plan at that point.

Dr. Khurana:
Those were great insights, Dr. Kraft. Thank you so much for enlightening us. We're almost out of time, so I'm just going to open the floor for what your call to action would be going forward as it relates to understanding asthma mechanisms and the heterogeneity, the phenotyping going forward.

Dr. Kraft:
Absolutely. And thank you again for this opportunity to talk about the patients that we both see. I know you do a lot of this as well, Sandhya, and you're right there with me on all the areas that we've discussed today- that includes an appreciation of the heterogeneity of asthma, that if patients are not responding to ICS-LABA combination, they should be referred to determine what driving their asthma if they're not responding to standard guideline-based asthma medications. Before referring, think about using blood eosionphils, exhaled nitric oxide and IgE to try to understand a patient's asthma as much as you can, and then if you still need help, then certainly refer on to an asthma center where physicians like Sandhya and I do this every day.

Dr. Khurana:
Thank you so much, Monica. And with that call to action in mind, I want to thank you very much for joining us today and sharing your time and your expertise with our audience. Thank you again.

Dr. Kraft:

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Thank you.

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