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Pediatric Severe Asthma

Announcer:
Welcome to CME on ReachMD. This activity, focusing on pediatric severe asthma, 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 Medicine at the University of Rochester and Director of the Mary Parkes Center for Asthma, Allergy, and Pulmonary Care.

Dr. Khurana:
Much like the manifestations of severe asthma seen in our adult patients, pediatric severe asthma is associated with significant morbidity and lung function decline, but there are many important differences between adult and pediatric asthma as well, and on today's program we'll be taking a look at how these distinctions inform our management approach for young patients.

This is CME on ReachMD, and I'm Dr. Sandhya Khurana. Joining me to talk about some key considerations for treating severe asthma in children is Dr. Deepa Rastogi, a pediatric pulmonologist at the Children's National Research Institute and Associate Professor of Pediatrics, Genomics and Precision Medicine at the George Washington School of Medicine and Health Sciences.

Deepa, welcome to the program.

Dr. Rastogi:
Thank you, Dr. Khurana. It's a pleasure to talk about severe asthma in children with you today.

Dr. Khurana:
So let's start with some background for our audience, Dr. Rastogi. Just how prevalent is severe asthma in children, and how does this differ in terms of manifestations and impact from severe asthma in adults?

Dr. Rastogi:
The national prevalence of asthma in children is about 10%, but that's talking about all-comers. There are substantial differences between the populations that are affected. African-Americans and Hispanics tend to be particularly more afflicted by asthma where the prevalence may reach as high as 25%. And what's remarkable in these populations, the disease burden, the severity of disease tends to be higher in these children as well, so substantial socioeconomic disparities exist for pediatric asthma.

Dr. Khurana:
It's clearly a huge burden. What is known about determinants of severe asthma in childhood in terms of gene and environment interaction?

Dr. Rastogi:

What we know about asthma generally is that it's a multifactorial disease. Over the past couple of decades now, lots of those genome-wide association studies that have been done to essentially identify the genetic component have identified this gene called ORMDL3 in the context of childhood asthma.

Now, having identified this gene, it's still very much a theoretical research concept. There may be genetic predisposition, but what we understand best is the role of environment, and from that perspective it's been extensively investigated.

Indoor allergens—you know, pests, like roaches or mice. Pets also contribute, so having a dog, cat, gerbil, hamster, anything that's hairy that sheds dander. And then from the outdoor perspective, in addition to pollen, which has been most consistently associated with allergies and asthma, there's a whole lot more recognition of the contribution of ozone and traffic-related airway pollution where the particles may not necessarily be allergens but may be irritants to the airway.

The other thing that I would like to highlight is recent research that has identified the contribution of school environment. We recognize that children spend the vast majority of their waking hours in schools, and there have been some very good studies that have identified the role of industrial-strength cleaners that are used in schools that may also be contributing to development as well as worsening of asthma in children.

Dr. Khurana:
Thank you, Deepa. Are there other factors that you think, when you see young patients who have uncontrolled or difficult-to-control asthma, that could be contributing?

Dr. Rastogi:
Yes. So, one of the reasons why I think we've not been able to define the exact disease burden of severe asthma in children is because of the contribution of what we call masqueraders of severe asthma in children. For instance, when children are very young, their breathing pipes may be soft or what we call malacia. Particularly with lower airway malacia, such as trachea malacia or bronchomalacia, the wheeze may be very similar to what one would expect with asthma. Those children will get diagnosed with asthma, but since they don't have asthma, they won't respond to the medication. When they won't respond to the medication, that then starts fitting into the definition of severe asthma. So again, it's very important to keep this caveat in mind what is known as all that wheezes is not asthma.

The second thing that may contribute to wheezing is GE reflux disease. I think there's enough literature to suggest that this should be something that a practitioner should at least consider, particularly when they are dealing with children who may not be responding to asthma medications.

And lastly, obstructive sleep apnea or sleep-disordered breathing is now recognized to be a major contributor to poorly controlled asthma. Nocturnal symptoms due to asthma are actually worsened when a child has sleep-disordered breathing, so again, addressing that would be an important aspect to management of severe asthma in children.

Dr. Khurana:
Now, we usually think of asthma in children as allergic, but I know that there's been increasing appreciation of heterogeneity in pediatric asthma as well. What can you tell us about the different phenotypes and endotypes of severe asthma in childhood?

Dr. Rastogi:
Yeah, again, we turn to our adult colleagues for these terms. Endotype is such an excellent new term in the realm of asthma, and we're extending that into the pediatric population where, again, for the longest we believe that asthma is an allergic disease, and for a large part it still is. I think we also look for allergies more often in children. But what the Severe Asthma Research Program in the adult population and to some extent in the pediatric population highlighted for us were a subset of patients who do not pan out to be allergic. So now I'm speaking about children where we've looked for the masqueraders; we've looked for allergies. They are clearly fitting the definition of asthma, but they do not have an allergic phenotype. So I think this is possibly one of the hottest areas of investigation currently in pediatric asthma.

The 2 specific contributors or triggers to nonallergic asthma that we understand best thus far are that associated with obesity, so obesity-related asthma, and the second group is asthma among children where it's associated with upper respiratory infections, which again tends to overlap with allergic asthma, but this exacerbation or this severe asthma is occurring in a child who's otherwise nonallergic. That is being very well-defined as a distinct phenotype or endotype in children in the context of nonallergic asthma.

Dr. Khurana:
Thank you. This is great information. Those who are just joining us, this is CME on ReachMD. I'm Dr. Sandhya Khurana, and today I'm speaking with Dr. Deepa Rastogi about severe asthma in our pediatric patients.

So, Dr. Rastogi, let's take the great foundation you've laid out for us and apply that to clinical evaluation for patients and their initial management. What does that process look like in your practice?

Dr. Rastogi:
I'd like to prefix this by saying, as a pediatric pulmonologist, I obviously have the luxury of doing detailed testing on the patients that we see in our clinic, but what I'd encourage practitioners to think about and thereby access is pulmonary function testing. Most importantly, because there may be a tendency for individuals to modify their lifestyle to their disease severity, and when we ask them about their disease burden, they may tell us that they're doing well, when we do their lung function testing, on that we may identify lung function deficits. This becomes particularly important because lung function deficits in childhood are associated with disease burden during childhood and morbidity as adults.

The relatively newer pulmonary function that is available is the fractional exhaled nitric oxide, or FeNO, and the information that FeNO adds is actually complementary to the other pulmonary function testing because it gives us information on the presence of allergic inflammation in the airways. So, identifying the pattern of inflammation in the airway plays a key role in us determining what kinds of medications we'll give these children.

The second part of that highlighting the importance of identifying allergic inflammation is identifying what these children are allergic to. One of the ways that we look for allergic sensitization is to look for eosinophilia. And specifically for sensitization we can then do testing even in the blood or on the skin to common indoor and outdoor allergens. So this information together, looking for presence of airway allergic inflammation and systemic allergic sensitization, that helps us classify these children into allergic or nonallergic asthma, and by looking at the pulmonary function testing, we are able to say what deficit of lung function are these children living with, which brings us to our next point, which is the importance of team based and multidisciplinary approach.

There are several centers now in the US where the allergists and pulmonologists are working together. For practitioners who may be taking care of children with severe asthma or may not have the luxury of this kind of testing and would want to phenotype their patient better, I would encourage them to look for this multidisciplinary asthma center near them and send the children there. We run one of these kinds here in Washington, D.C., and it's primarily a consultative center where we do the evaluation and a lot of children will be classified and will be placed on the right medication and then sent back to the pediatrician to be continued on the care that we deem to be effective in these children. These centers are very good in phenotyping these children.

Dr. Khurana:
Great. Thank you. And where is the field at in terms of advanced therapies and targeted therapies in pediatric severe asthma?

Dr. Rastogi:
You know, we've been lucky. Unlike some adult medications which take decades to come down to children, several of these asthma medications were almost simultaneously tested in the pediatric population as well. These medications fall in the category of biologics, so they modify a biological pathway. The one that has been best understood and most used thus far is omalizumab, or XOLAIR, which is an anti-IgE antibody. That was the first biologic to be used for asthma both in adults and in children, and in children it's been used now for almost 15 years, consistently effective. There's a clear algorithm on calculating the selection criteria which the practitioners can look on the XOLAIR website, and the medication is dosed accordingly.

The relatively newer medications are targeted sort of more upstream at this eosinophilic inflammation that we were talking about, so eosinophilia which is best linked to allergic sensitization. And here we have anti-IL-5 and anti-IL-5 receptor antibodies. So without delving too much into detail, these medications have also been found to be extremely effective in children, and there are several good review articles on these medications as well. And along the same lines, dupilumab is actually a dual antibody, anti-IL-4, IL-13. So just like IL-5, IL-4 and IL-13 are cytokines in allergic inflammation produced by T-cells and others, this medication, dupilumab, specifically targets both IL-4 and IL-13.

Since omalizumab has been around for the longest, it's approved for children over the age of 6 years; mepolizumab, which is anti-IL-5, was also approved for over 6 years; but others are approved for older children over the age of 12 or 18. And obviously that limits who we can extend it to in the pediatric population, but we also recognize that frequently children who fit the bill of severe asthma per the definition tend to be adolescents or older children, so having these medications gives us more in our armamentarium to take care of severe asthma in childhood.

Dr. Khurana:
So, Dr. Rastogi, before we wrap up, if you could share with us some of the urgent unmet needs you feel in pediatric severe asthma exists and what can we do or can be done to better address these gaps.

Dr. Rastogi:

We started off by discussing severe asthma, and unlike what we know in the adult population, just because we have had several large cohort studies that have looked at severe asthma clearly defined as severe asthma in the adult population—we need more of those in children. Just as in the adult world we've been able to endotype severe asthma so beautifully, we need to do the same in children.
So this lack of understanding of phenotypes and endotypes in children does limit our ability to manage these children better.

The second thing, again acknowledging the importance of allergic asthma in children, I think the time is ripe to identify nonallergic asthma in children, so again, I think primarily a major thing that we'll ask of the practitioners is to consider the existence of nonallergic asthma in children and then for the researchers to really delve deeper into what may be the underlying mechanisms for nonallergic asthma in children. One of the major unmet needs I think is also acknowledging that irreversible changes may start early in children and that research that is going on primarily in the adult population can easily be extended in the pediatric population, primarily with the goal to actually prevent the worsening of reversible airflow obstruction into the irreversible airflow obstruction.

Dr. Khurana:
You've certainly given us a lot to think about as well. We've come to the end of our program today, but I want to thank you very much, Dr. Rastogi, for speaking with us about the current state of severe asthma in childhood. It was a pleasure.

Dr. Rastogi:
Thank you so much. Lovely speaking to you today and discussing all these different aspects of severe asthma in children. Thank you for your time.

Announer:
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