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Recognizing Patient Needs Across the Heterogeneous Spectrum of Severe Asthma

Announcer:
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This medical industry feature, titled "Recognizing Patient Needs Across the Heterogenous Spectrum of Severe Asthma" is sponsored by Amgen & AstraZeneca. This program is intended for physicians.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is ReachMD, and I'm your host, Dr. Jennifer Caudle. Joining me to consider factors contributing to patient needs in severe asthma care is Dr. Michael Wechsler, a Professor of Medicine and Director of the Cohen Family Asthma Institute at National Jewish Health in Denver, Colorado. Dr. Wechsler, welcome to the program.

Dr. Wechsler:
Thank you so much for having me today.

Dr. Caudle:
Well, we're excited that you're here. So let's start with some perspective on severe asthma. Dr. Wechsler, how many patients are classified as severely asthmatic, and what's the threshold for that designation?

Dr. Wechsler:
Right. So it's important to know that of all asthma patients, approximately 5 to 10% suffer from severe asthma.[1] Guidance from the GINA and ATS, ERS guidelines, or the Global Initiative for Asthma and American Thoracic Society, European Respiratory Society guidelines that were published in the American Journal of Respiratory and Critical Care Medicine, they defined severe asthma as asthma that is uncontrolled despite adherence with optimized high-dose inhaled corticosteroids in addition to another asthma controller medication, or that requires high-dose treatment to remain controlled. These patients may also require added biologic therapies or oral corticosteroids.[2,3]

But before making a diagnosis of severe asthma, we should investigate and rule out the most common reasons why patients continue to experience symptoms while on asthma medication.[2] One of them continues to be poor inhaler technique, and that can affect up to 80% of patients at home.[4]

Other problems include poor medication adherence,[5] also an incorrect diagnosis of asthma, with symptoms due to alternative conditions such as, laryngeal obstruction, or cardiac failure, or deconditioning.[2] All those can mimic asthma as well. Also, comorbidities and complicated conditions including rhinosinusitis, gastroesophageal reflux, obesity, and obstructive sleep apnea[6] can all complicate asthma management.

Lastly, ongoing exposure to sensitizing or irritant agents in the home or work environment[2] can also play an important role in terms of making asthma worse. And so all those things need to be addressed in patients with severe asthma.

Dr. Caudle:
Thanks, Dr. Wechsler. And if we zero in on uncontrolled asthma, how do we define that?

Dr. Wechsler:

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So when asthma is uncontrolled, it means that asthma symptoms persist despite treatment. So even with advances in treatment, 20 to 50% of patients with severe asthma still have uncontrolled disease.[7] And if we take a look at the American Thoracic Society and European Respiratory Society joint guidelines, uncontrolled severe asthma is defined as having at least one of the following characteristics.[3]

First, poor asthma symptom control, which can be defined as an asthma control questionnaire score greater than 1.5, or an asthma control test score less than 20, or being quoted as not well controlled based on the GINA guidelines.[3]

Second, frequent exacerbations, with "frequent" being defined as more than one exacerbation requiring corticosteroids in the prior year.[3]

Third, at least one serious exacerbation in the prior year, meaning either a hospitalization or an ICU stay due to asthma[3]

And lastly, anyone who has persistent airflow limitation, which is defined as having FEV1, or forced expiratory volume in one second, as less than 80% of predicted.[3]

So all of those are key features of how we define patients with severe uncontrolled asthma.

Dr. Caudle:
And if we stay focused on severe, uncontrolled asthma, Dr. Wechsler, can you tell us about the overall burden it can have on a patient's life?

Dr. Wechsler:
Of course. Despite recent advances in treatment, many patients with severe asthma remain uncontrolled.[8-10] And it's well known that poorly controlled asthmatics have frequent symptoms and exacerbations, in addition to decreased quality of life,[11] increased oral corticosteroid use[12] either intermittently or chronically, and increased healthcare resource utilization.[6,12] In fact, approximately 12 to 27% of patients with severe asthma may be hospitalized for exacerbations[8,10,13] and increased oral steroid use can also lead to adverse events and comorbidities.[2,14-16] And of those severe asthma patients represent a relatively small fraction of those with asthma.[1] One analysis found that severe asthma patients represent approximately 40% of the total asthma-related direct costs, including frequent hospitalization and emergency room visits.[17]

Another set of data show that among U.S patients with severe asthma, approximately 20% may have two or more exacerbations per year that require systemic steroids or oral corticosteroids.[7] And up to 50% of severe asthma patients may have poor asthma symptom control based on the Asthma Control Test.[7]

The last impact I'd like to point out is that uncontrolled asthma patients have a higher frequency for emergency room visits and hospitalization do an asthma attack.[7,18]

Dr. Caudle:
For those of you who are just joining us, this is ReachMD, and I'm your host, Dr. Jennifer Caudle. And today I'm joined by Dr. Michael Wechsler to help identify patient needs across the spectrum of severe asthma.

So Dr. Wechsler, let's dive deeper into airway inflammation and asthma. How is this characterized?

Dr. Wechsler:
So it's important to know that the airway inflammation asthma underlies its disease characteristics, as well as its severity, and serves as a real target for treatment.[19] As a reminder, inflammation in asthma is both heterogeneous and dynamic.[19] There are numerous cell types, there are numerous mediators, there are numerous immune pathways that drive all the multiple inflammatory pathways in asthma.[19] And the pathways are likely different in individual patients and can vary over time, but these pathways may be active at the same time within a patient, so they may not be mutually exclusive.[19]

And if we take a look at the types of asthma inflammation, a frequently used categorization is type 2, or T2, and non-T2 inflammation.[19] However, in some patients, the end product of airway inflammation will be a mixture of both categories with either T2 or the non-T2 being dominant. T2 inflammation is characterized by predominance of allergic or eosinophilic inflammation, whereas non-T2 is marked by neutrophilic cellular infiltrate or infiltrate of a few cells also called pauci granulocytic inflammation.[19]

The last thing I'd like to mention is that T2 pathways have been the recent focus for the development of novel treatments, especially biologics.[19]

Dr. Caudle:

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And as I understand it, the airway epithelium is now a well-established contributor to these inflammatory pathways of asthma. Is that correct?

Dr. Wechsler:
Yes, since the airway epithelium is the first continuous line of defense against inhaled insults,[20] it plays an important role in asthma pathophysiology, regardless of whether a patient has type 2 high or non-type 2 mediated inflammation that drives a patient's asthma or biomarker profile.[20-24]

That being said, the epithelium is a common source of inflammation. Epithelial cytokines, such as TSLP, or thymic stromal lymphopoietin, IL-33, and IL-25 are all rapidly released in response to insults. And these initiate multiple inflammatory cascades.[22,23]

Of course, the airway epithelium is also affected in turn. In asthma, the airway epithelium is significantly changed in several ways. For instance, goblet cell hyperplasia, and increased mucus production can lead to airway blockage,[21,22] or epithelial tight junction number and integrity are decreased, which allows external insults to penetrate the airway wall,[20,21] or increased epithelial thickness also results in airway narrowing.[21,22,24] And lastly, subepithelial inflammation in fibrosis can lead to fixed airway obstruction.[21,24] All of these features play a role in the inflammatory cascade that's mediated by the epithelium.

Dr. Caudle:
Well, with all that being said, Dr. Wechsler, can you tell us more about the inflammation within the epithelium that occurs in response to airway insults?

Dr. Wechsler:
Sure. Environmental exposures at the epithelium trigger the release of several different epithelial cytokines, including TSLP, which is a key epithelial cytokine in asthma.[25] And these cytokines can then initiate multiple downstream inflammatory pathways that drive an individual's asthma symptoms.[25]

Dr. Caudle:
Now, earlier, you mentioned different categories of asthma. Are there biomarkers that help classify patients into these categories, and given the heterogeneity of asthma inflammation, are current methods of asthma characterization sufficient?

Dr. Wechsler:
Yeah, it's a great question. So to help inform clinical decision making for severe asthma, a limited number of biomarkers are currently utilized. These include peripheral blood eosinophils, specific and total IGE, and exhaled nitric oxide.[19] These three biomarkers also reflect the characteristics of the underlying inflammatory profile, and in particular, whether type 2 inflammation may be present.[19] In addition, blood eosinophil count is a key predictor of a patient's phenotype and response to therapy.[19] In fact, research has shown that patients with higher blood eosinophil levels, greater than 300 cells per microliter, tend to have a better response to certain treatments.[26]

However, as I mentioned before, a patient's inflammatory profile may change over time.[19, 27-29] In one study that evaluated phenotype stability based on sputum sampling, approximately 50% patients with asthma changed their biomarker profile after one year follow up.[27] This study underscores the dynamic nature of asthma, inflammation and the potential limitations of placing patients into specific categories.

Dr. Caudle:
And I take it that this potential for biomarker profiles to shift over time complicates our aims at reducing asthma exacerbations?

Dr. Wechsler:
Absolutely. Even with currently available therapies, there continue to be challenges in managing patients with severe uncontrolled asthma.

And despite subspecialist care and biologic treatment for 12 months or more[9], approximately 60% of asthma patients receiving biologics had breakthrough exacerbations in a year.[9] Again, suboptimal response to treatment in severe asthma can lead to poor control with an increased risk of asthma exacerbations and increased healthcare utilization, the need for additional treatments such as systemic corticosteroids, which can have their own adverse effects and decreased quality of life.[2,6,11,12,14-16]

Dr. Caudle:
Well with those insights in mind, I'd like to thank my guest, Dr. Michael Wechsler, for helping us better recognize patient needs across the severe asthma spectrum. Dr. Wechsler, it was great speaking with you today.

Dr. Wechsler:

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Thank you so much. Thank you for inviting me to talk about this really important topic.

Announcer:
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