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SMART Asthma Care: A Way to Address Exacerbations and Inflammation

Announcer Open:
You're listening to *Deep Breaths: Updates from CHEST* on ReachMD. This non-CME education was brought to you by CHEST and was sponsored by AstraZeneca. Your host is Dr. Demondes Haynes, who's a Professor of Medicine in the Division of Pulmonary and Critical Care at the University of Mississippi Medical Center in Jackson.

Dr. Haynes:
Welcome to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Demondes Haynes, and joining me today to discuss how single maintenance and reliever therapy can help alleviate the burden of exacerbations in our asthma patients are Drs. Njira Lugogo and Neil Skolnik. Dr. Lugogo is a Clinical Professor of Internal Medicine in the Division of Pulmonary and Critical Care Medicine at the University of Michigan Health. Njira, thanks for being here today.

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

Dr. Haynes:
And Dr. Skolnik is a Professor of Family and Community Medicine at the Sidney Kimmel Medical College of Thomas Jefferson University and the Associate Director of the Family Medicine Residency Program at Jefferson Health Abington. It's great to have you with us as well, Neil.

Dr. Skolnik:
It's a pleasure to be here, Demondes.

Dr. Haynes:
So let's start with you, Neil, by discussing the state of asthma in the United States. How are we doing with regard to our treatment of asthma?

Dr. Skolnik:
Demondes, you know, we're not doing quite as well as I think we usually feel like we are. I remember back in the early 2000s when combination therapy with ICS/LABA came out, it felt like a godsend. People felt much better, and they had much better symptom control. But that feeling, although it was a lot better than it was, isn't fully realized. And according to CDC data, over half of the patients in the United States actually are not well controlled.

Dr. Haynes:
And if we focus specifically on exacerbations, Neil, how are we doing with regards to that?

Dr. Skolnik:
Well, that's where it gets really tough. Recently, I had the opportunity to look back at CDC data published in the MMWR as measured by ER visits and deaths per year over the last 20 to 30 years. And if you look at that data on the emergency room visit rate, in 1992, 58 people per 10,000 visited the ER with asthma exacerbations. Move ahead to 2018, it had only gone from 58 per 10,000 down to 52 per 10,000. Not as much better as we would have thought. If you look at mortality in 1990, there were 4,800 deaths from asthma in the United States. In 2000, it was approximately 4,500. And just 3 years ago in 2020, it was 4,100. Now, yes, the population has grown over that time, so proportionately there are less deaths, but it's not as good as we would have hoped.

Dr. Haynes:
Turning to you now, Njira, do you have any thoughts on why that might be the case?

Dr. Lugogo:
I think it's probably a rather complex issue. But by nature, if we really wanted to take the most simplistic approach to this, we would need to examine how we manage asthma and what kind of priorities we've put in terms of asthma management. And by that, I mean that we focused on control, which is generally reporting less symptoms and not using your rescue inhaler quite as much. However, we haven't really developed very good strategies for risk mitigation. And what we see is a lot of exacerbations. And those are high-risk events where people have attacks that require acute care and often oral steroids.

And we now have an appreciation in the last 20 years that inflammation and bronchoconstriction happen at the same time. And therefore, when these acute episodes occur, we have both inflammation and constriction. And thereby, we need to really treat both of those factors that are occurring at the same time.

And for many patients, there may be a window of opportunity when they begin to deteriorate but before they require acute care or oral corticosteroids where we could potentially intervene by dealing with the inflammatory symptoms by giving higher doses of anti-inflammatory therapy to reduce exacerbation. So we've learned a lot and we have a lot of drugs, but the implementation part of our care is lagging behind the access to new strategies to manage asthma.

Dr. Haynes:
For those just tuning in, you're listening to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Demondes Haynes, and I'm speaking with Drs. Njira Lugogo and Neil Skolnik about the burden of exacerbations in our patients with asthma.

So if we switch gears a bit, Njira, and focus on single maintenance and reliever therapy, or SMART therapy for short, can you tell us how this approach can help address inflammation and decrease exacerbations?

Dr. Lugogo:
I really do think that this is the new way that we are going to move forward in managing our patients, and it requires a bit of a paradigm shift in that in the past, we divided maintenance treatments from rescue treatments; our rescue treatments were predominantly focused on bronchodilation. But now, we appreciate that acute symptoms are caused by bronchoconstriction and inflammation. And so what we are aiming to do with SMART therapy is really treat our patients with the same maintenance therapy and reliever therapy using a single inhaler. Now remember that inhaler has to contain formoterol since formoterol is the only rapid-onset reliever that's a long-acting beta agonist. And so this formoterol-containing strategy combined with ICS in a single inhaler can be used by all patients twice a day and when they have acute symptoms for rescue as a means of targeting both inflammation and constriction at the same time. And based on the data we have, it's a way of reducing exacerbations quite significantly, dealing with that rising inflammation that occurs when patients are acutely ill and experiencing worsening asthma symptoms and developing asthma exacerbations.

Dr. Haynes:
Now, Neil, SMART therapy is not an FDA-approved form of therapy in the United States. So is there anything new on the horizon?

Dr. Skolnik:
Yeah, Demondes. And this has created quite an issue because even in the NAEPP guidelines from 2020, and we'll talk about this in one of our subsequent podcasts, SMART therapy is recommended, but it's recommended because of the robust evidence base that says it works. But the problem is it's not FDA approved in the United States. And while some of my subspecialty colleagues are comfortable using therapy that is off label, many of my primary care colleagues are not as comfortable with that. So it's presented this dilemma where we have therapy that has a robust evidence base of efficacy at decreasing exacerbations, but it's not FDA authorized for use in the United States.

Recognizing that, a new therapy that has been looked at and studied for reliever therapy was looked at in a very large trial of over 3,000 patients. And that trial was called the MANDALA trial. And that was published in the *New England Journal of Medicine*. This was a multinational, phase 3, double-blind, randomized, event-driven trial that evaluated the efficacy and safety of albuterol-budesonide, and that's abbreviated in the paper BDA, as compared with albuterol alone as rescue medication in patients with uncontrolled, moderate-to-severe asthma who were receiving ICS maintenance therapies. And those maintenance therapies were continued throughout the trial and the decision about what therapy was decided by the patient's clinician. So there were over 3,100 patients in the trial. There were three arms: a high-dose budesonide-albuterol, a lower-dose budesonide-albuterol, versus albuterol alone, all on top of that controller ICS therapy.

What the MANDALA trial showed, very well conducted, is that the risk of severe asthma exacerbations was significantly lower by 26 percent in the higher-dose combination group than in the albuterol-alone group. So that was a hazard ratio of 0.74; it was statistically

significant with a P value equal to 0.001. That medication then went to the FDA for approval and was approved earlier this year.

So it's now going to be available for us to use exactly as Njira was talking about as reliever therapy that does what we've known for years to be important—and we've implemented this with controller therapy—addressing inflammation and bronchoconstriction at the same time. Until SMART therapy that Njira talked about, we didn't think of that with regard to rescue therapy. And now fortunately here in the United States, we'll have albuterol-budesonide available to address that window of opportunity that occurs prior to an exacerbation when patients start using their albuterol little more, start feeling not as good, their peak flow goes down, and that exacerbation may be coming. And it turns out that the use of an anti-inflammatory along with a SABA decreases the likelihood of going on to develop a full-blown exacerbation.

Dr. Haynes:
With that in mind, let's come back to you, Njira, for our final question today. How do you think budesonide-albuterol should be used? And which patients are good candidates for this approach?

Dr. Lugogo:
The approval for budesonide-albuterol was for the prevention of asthma attacks. And so it is available for adults of over the age of 18 to be used as a rescue strategy across the asthma severity spectrum.

On the GINA 1 to 2 patients, those were people we previously gave SABA only who gave bronchodilators to and said, "Use it if you have symptoms or use it before exercise." We now appreciate that many of those people have inflammation; they just happen to go through long periods of relatively limited symptoms, but they are still at risk for attacks. And so that particular population would benefit from pairing budesonide with albuterol on ICS with a SABA.

On the more severe end of the spectrum, the GINA 3s to 5s, those would be patients on combination ICS/LABA plus potentially adding a long-acting antimuscarinic. Those particular patients have perhaps enough anti-inflammatory therapy when they are well, but when they're sick and develop worsening inflammation, that requires treatment. And particularly for patients that cannot access formoterol-containing compounds and therefore cannot undergo SMART therapy, ICS SABA is a perfect solution for rescue therapy. And so that's a population that I think will be quite benefited by this new algorithm and treatment strategy.

Dr. Haynes:
Well, with those final comments in mind, I want to thank my guests, Drs. Njira Lugogo and Neil Skolnik, for joining me to discuss SMART therapy as a way to address exacerbations in our patients with asthma. Dr. Lugogo, Dr. Skolnik, it was great having you both on the program today.

Dr. Skolnik:
My pleasure.

Dr. Lugogo:
Thank you for having me.

Announcer Close:
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