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www.reachmd.com  
info@reachmd.com  
(866) 423-7849

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## Identifying and Treating Severe Asthma Patients with Biologics

### Dr. Turck:

With more biologic options available than ever before, the challenge in severe asthma isn't availability; it's precision. So how can we identify the right patient at the right moment to intervene?

Welcome to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and joining me in this discussion is Dr. Brittany Duchene. She's a pulmonary and critical care physician and an Assistant Professor in Medicine at the University of Vermont in Burlington. Dr. Duchene, thanks for being here today.

### Dr. Duchene:

Thrilled to be here. Thank you for the invite.

### Dr. Turck:

Well, to start us off, when you're evaluating a patient with difficult-to-control asthma, how do you distinguish true progression to severe asthma from uncontrollable disease driven by modifiable factors?

### Dr. Duchene:

This is a really important question. And in fact, I run a severe asthma clinic out of UVM, and up to 20 percent of the patients I see actually don't even have asthma; they end up having some other comorbidity that's mimicking asthma. So it's really crucial to be confident that you are treating the correct disease for obvious reasons. When you are confident in your diagnosis, try to avoid triggers that patients will have. They're oftentimes environmental triggers, but they could also be related to exercise or even really robust emotional states can trigger asthma. So trying to limit those as best as you can is really critical.

As you alluded to, the other very important factor in good asthma control is mitigating those comorbidities that worsen asthma. And there's a lot of them—acid reflux, sinus disease, obesity, depression, anxiety, and even pregnancy can worsen asthma. And so it's a very important step prior to even considering pharmacotherapy as to whether you can target and treat those comorbid conditions. And then once you've done all of that really hard work and your patient has tried their very best—ensuring that if they are on an inhaler, they're using it appropriately and as prescribed—but essentially if all of these things seem to be reasonably targeted, a moderate persistent asthma patient is going to have daily symptoms. They may even have nighttime symptoms that awaken them up to four times in a month and with some limitation of activity. And this is using the NHLBI severity classification guidelines that are present.

With severe asthma, on the other hand, you're going to have symptoms throughout the day with the need for multiple doses of rescue inhaler, whatever that looks like. And they oftentimes will have at least weekly awakenings at nighttime with pretty significant limitation in their daily activities.

### Dr. Turck:

So then once you confirm that a patient has severe asthma, what clinical indicators most strongly signal that it's time to transition to a biologic?

### Dr. Duchene:

The most obvious patient to me is the patient who is relying on oral corticosteroids. Patients that are on chronic steroids orally are at really high risk of some pretty terrible side effects—weight gain, high blood pressure, diabetes, and osteoporosis. And these are, generally, younger patients. So having a 50-year-old who's on 10 milligrams of, say, prednisone daily is going to have some terrible side effects in 10 to 20 years from now if they remain on that. So those I classify as my top-tier patient that I want to liberate from those oral

steroids. And honestly, when they're on the chronic steroids, you don't need to really phenotype or classify them to get approved for biologic therapy because there are chronic steroid indications for some biologic medications.

The other patient would be someone who's having frequent exacerbations, so if they're having two or more exacerbations in a year and clearly having symptoms that are limiting their daily activity, that's going to be an important person to target for biologic therapy.

And then the third tier that I think of would be the patient who is significantly symptomatic despite being on all sorts of inhaler therapies. And they may not be necessarily exacerbating, but they have clear eosinophilic disease. They're on really high-dose inhaled steroids—maybe they're on two inhaled steroids—they're maxing out their SMART therapy inhaler regimen, and they're just really having a hard time.

**Dr. Turck:**

Now, biomarkers are playing a growing role in guiding therapy. So how do you integrate measures like eosinophils, FeNO, and IgE into your decision-making?

**Dr. Duchene:**

Yeah, I love this question, and I love phenotyping asthma. The more that we learn about asthma, the more complicated it seems to get and the more subsets of these two big endotypes we see: T2-high or T2-low asthma. And there's several phenotypes, meaning how this patient presents to you within each of those two main endotypes, and those are determined by the mechanism of action of their asthma.

So if you're able to really nail down what is driving their bronchoconstriction and their airway inflammation, we're practicing precision medicine at this point, right? You know, "I see that you have a really elevated IgE, and you're very atopic. You're getting a lot of symptoms related to your clinical allergies. So then maybe targeting the IgE is going to be the ticket to improving your asthma." As compared to a patient who is profoundly eosinophilic and is having a ton of mucus production but it's not really allergy driven, you may end up choosing more of an IL-4, IL-5, or IL-13 type of biologic target to help that patient.

These are really great options for our T2-high patients; our T2-low patients unfortunately don't have as many great interventional options as far as biologics are concerned, but there are alarmin-targeting biologics, such as the TSLP biologics, and I know there's IL-33 biologics that are in the works right now that can be beneficial for these patients. So I think it's profoundly important to phenotype these folks and practice precision medicine with them.

**Dr. Turck:**

For those just tuning in, this is *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Brittany Duchene about how we can recognize which of our patients with severe asthma may benefit from biologic therapy.

So let's shift to timing now, Dr. Duchene. What does the latest evidence tell us about the benefits of initiating biologics earlier in the disease course rather than waiting until later stages?

**Dr. Duchene:**

Yeah, so I think there's relatively convincing evidence right now that shows targeting really severe asthmatics with biologic therapies seems to reduce their risk significantly for future morbidity and mortality related to their asthma. So that in itself is a pretty heavy outcome. And so I think when I see a truly severe asthmatic who clearly is having a lot of issues, I don't have a really high threshold for starting these medications. And these are very well tolerated with a low side effect profile. So the risk far outweighs the benefit of allowing these folks to go untreated and have this inflammatory cascade just flourish.

The one other thing that we're very interested in doing with biologic therapy, which isn't necessarily proved yet in science, but we do think that there's probably some decreased airway remodeling that happens when you treat asthma sooner effectively. We know that if you exacerbate a lot, that ongoing inflammation in the lung can cause airway remodeling and can lead to more of a chronic obstructive pattern, particularly on PFTs. A lot of this is being researched currently and is a really interesting area of study for this. But I think targeting our severe asthmatics earlier, as opposed to later, will reduce their potential for worse morbidity and mortality moving forward and hopefully prevent that airway remodeling that we dread.

**Dr. Turck:**

I know we talked a little bit about biomarkers earlier. Are there any other specific patient characteristics that help you anticipate a stronger response to biologic therapy?

**Dr. Duchene:**

Yeah, I think it is a little intuitive. If you have patients that have the type of disease phenotype that responds strongly to inhaled steroids or oral steroids, they're probably going to respond very robustly to our biologic therapies that target airway inflammation. And so those would be our T2-high patients, particularly those with really high eosinophil levels. As you know, most of these biologic targets are really

targeting the downstream effects of the eosinophils, so IL-4, IL-5, and IL-13. So those patients tend to respond very robustly to this. That's not to say that others don't. I certainly have patients who are truly type 2 low; however, they did require chronic steroids, and I was able to liberate them from steroids even though the mechanism of action of most of these biologics are more eosinophilic based. So there is certainly a role for them in our T2-low patients.

The other group that can be a big challenge are those that have had asthma since they were like four years old. A lot of times by the time I see them in clinic, if they've had asthma for that long, they can have airway remodeling. And I think that's equivalent to if you have lung inflammation and then subsequent pulmonary fibrosis, you can't fix the fibrosis that is formed. So in the airway itself, you can reverse inflammation. You can't reverse the airway remodeling, which is essentially fibrosis of the airway itself.

**Dr. Turck:**

And lastly, Dr. Duchene, how do you approach shared decision-making with patients when considering biologics, and what factors tend to matter most to them?

**Dr. Duchene:**

This is one of the most important conversations you're going to have in discussing whether you should start a biologic agent with your patient. There's a lot to think about, you know? I mentioned that it's a very easy drug to give and to take; it's well tolerated. There's not monitoring levels or blood work you have to do.

But this is a chronic medication, and currently, we don't have good data to support how we get people off of these medications if their asthma's in remission. There's not great guidance on how to then see if we can peel back the biologics. There's certainly been anecdotal and case report literature showing a return of a really crazy asthma exacerbation after stopping these medications. That's probably not the rule for everyone. So have a really upfront conversation about that with your patient and just be clear that, "Hey, there's the potential that you're on this for life," and if you're 25, that seems like a lot.

And I always certainly talk about the potential side effects, even though they are pretty rare and mild, like injection site irritation. There's this thought of parasitic infections or unusual opportunistic infections because you're blocking the eosinophilic pathway. So I tend to ask if they do a lot of traveling; do you eat undercooked pork if you're down in South America, or do you go swimming in African rivers? I've had one person say, yes, they do those things. So I just screen them for a parasitic infection prior to starting them.

Then really the last point in the shared decision-making of this is going to be setting expectations for what they can expect. Typically, these aren't medications that you start immediately and all of a sudden you feel better. Generally, we recommend a four- to five-month trial period to see if the effects are really appropriate for that medication and things to look for. We should expect decrease in exacerbations. We should expect a decrease in the need for steroids, both inhaled and orally given. And hopefully, their daily limitations are improved as well.

**Dr. Turck:**

Well, with those final comments in mind, I want to thank my guest, Dr. Brittany Duchene, for joining me to share her insights on identifying and treating patients with severe asthma with biologics at the right time. Dr. Duchene, it was great having you on the program.

**Dr. Duchene:**

Appreciate it. Thank you so much.

**Dr. Turck:**

For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit *Clinician's Roundtable* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.