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

Lessons From the Clinic: Managing Challenging CSU Cases

Announcer:
You're listening to *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to O*n the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. I'm Dr. Charles Turck, and joining me to explore how we can navigate challenging cases of chronic spontaneous urticaria, also known as CSU, is Dr. Matthew Zirwas. He's an American Board of Dermatology certified physician with DOCS Dermatology in Bexley, Ohio. Dr. Zirwas, thanks so much for being here today.

Dr. Zirwas:
Oh, I am thrilled to be on here, and I am thrilled to be on with a Dr. Turck. I totally feel like I am in an episode of Scrubs right now. This is perfect. Perfect.

Dr. Turck:
I'm looking forward to getting started. Before we go into the details, Dr. Zirwas, let's start with the big picture. What makes a CSU case challenging to navigate from your perspective?

Dr. Zirwas:
Oh, the worst part by far is that every patient thinks that they have an allergy. So they come in convinced that there is some food, and if they just figure out which food to avoid, they will be fine. And that's probably my favorite thing about the disease: having figured out through lots of trial and error of how to convince them.

Dr. Turck:
Any tips that you can share related to that? How you do convince people of that?

Dr. Zirwas:
Yes, and it is like magic. I call it medical jujitsu. We've got really good data to support what I'm about to say.

So my spiel to a patient is, "So, oh my gosh, I know this seems so much like a food allergy because it totally gets better and worse depending on what you eat. But what you've got, CSU, is actually an autoimmune disease, so it's your immune system attacking itself. But we know that diet plays a huge role in how your immune system works. And so what you're eating is going to affect how actively your immune system's attacking itself. And, in particular, there are different things that can be a problem in different people. So for some people, there are foods that are high in histamine, and if you eat those foods, it'll trigger it. There are other people where there are foods that are high in things called salicylates, and that'll trigger it. But even if you completely avoided everything—if all you did was drink water and eat rice—your hives might get a little better, but they wouldn't go away. So your diet is making your hives better and worse, but it is not causing them."

Dr. Turck:
With Maui Derm NP+PA Summer 2026, you spoke about a patient whose CSU cleared up on remibrutinib except for persistent facial dermatitis, which resolved after patch testing and allergen avoidance. Would you tell us a bit more about that case, like what tipped you off?

Dr. Zirwas:
Yeah. So it's one of the things that, whenever we're dealing with reasonably common stuff, remember that multiple diagnoses are not

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like, "Oh my God, that is crazy." So it was somebody with a fairly typical CSU who went on the remibrutinib and did great. But then, she had this facial component that would not resolve, and the facial component didn't behave like hives. The lesions weren't moving around. They weren't evanescent. They didn't have the typical morphology of hives. So although the patient understandably thought it was still the same thing, from my perspective, and I think from most derms or allergists' perspective, we would've looked at that and been like, "Okay, this is not like residual hives. There is something else going on here."

It's one of the things I used to teach residents when I was a residency director. When something doesn't behave the way you expect it to behave, always keep in mind that maybe this isn't what I thought it was. Don't just think, "Treatment failed. That drug doesn't work on everybody. It didn't work on you." That's probably what happened, but in cases like this, is there something I'm missing? Was I wrong whenever I made the initial diagnosis? And in this case, we were right when we made the original diagnosis, but there was a second diagnosis that we just couldn't tell until we got rid of the first diagnosis.

Dr. Turck:
Zooming out for a moment, how would you tell whether a patient's CSU just isn't responding to treatment or if another condition is involved? And which other conditions should clinicians keep in mind when evaluating patients?

Dr. Zirwas:
Oh, fantastic question. So we had a really good study on this come out earlier this year, because one of the big questions historically has been, how much workup should we do for these people? When I was a resident, we were doing full body CT scans, every lab you could imagine, the whole thing, and then the data came out and said, "Eh, you pretty much never find an answer doing that."

And we now know the right questions. There are some red flag questions that, if you ask these and they're negative, they don't need any workup at all. So are you having any fevers? Are you having joint pains, muscle pains, or bone pain? So any of those now put you into the autoinflammatory syndromes that can present with hive-like lesions and systemic symptoms.

The second thing that we need to ask about is the specifics of the hives. And the way that I ask is… A hive shouldn't last for more than 24 hours. But if you ask a patient, "Well, do your hives last more than 24 hours?" "Yes, they never go away." What I do is literally point to one particular hive, and I'll say, "Okay, if we took a picture of that exact hive, and in 24 hours we took a picture of that exact spot again, would that exact hive still look the same, or would that one have gone away but there might be three others right around it?" "Oh, that one would've gone away, but there'd be the other." "Okay, so your hives do not last more than 24 hours." Number two, do the hives burn more than they itch? And number three, when they resolve, do they leave any little, bluish or purplish marks? Any of those three make us think about urticarial vasculitis.

Now, if you don't take a decent history and if you don't actually look at the lesions, then yeah, you could call anything hives, right? So I've seen, particularly, erythema multiforme called hives, and I've seen hives called erythema multiforme. Those are probably the biggest two. Maybe drug rash, viral exanthem. But again, those are much more likely to be acute rather than chronic. And they really aren't the same if you've asked the right questions and taken a good look at the lesions. There's not a lot of diagnostic dilemma whenever we're dealing with CSU.

Dr. Turck:
For those just joining us, this is *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Matthew Zirwas about complex cases of CSU.

So, Dr. Zirwas, let's say a patient does have another condition alongside their CSU. How does that shape or change your overall treatment approach?

Dr. Zirwas:
It really depends what that other condition is. So let's say they've got something like atopic dermatitis or asthma. And people with atopic conditions, in my experience, are more likely to get hives. With CSU, I think they just have more unstable mast cells. And if they've got a comorbid condition that I can kill two birds with one stone, then I'm going to give them a drug like dupilumab that will treat both.

If they have a significant component of chronic inducible urticaria, so, dermographism, cold urticaria, things where a physical stimuli are triggering mast cell degranulation, then I'm more likely to give them remibrutinib, which is indicated now for dermographism, and I'd extend that out to other chronic inducible urticarias and CSU.

And if they've got asthma or food allergies, then I'm really going to think about omalizumab.

Now, the other place where this comes in is if they've got other autoimmune diseases. So if they've got rheumatoid arthritis, inflammatory bowel disease, or something like that, then I may end up pointing them towards a JAK inhibitor, because with the data that we do have, JAK inhibitors are not indicated for chronic spontaneous urticaria, but we've got a few case series out there that say that

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JAK inhibitors are actually quite effective for CSU.

Dr. Turck:
Now, on the other hand, when a patient is only dealing with CSU, but they're having an incomplete response to antihistamines and omalizumab, how do you decide what comes next?

Dr. Zirwas:
Oh, great question. So first, just because we haven't mentioned it yet, when we talk about antihistamines and CSU, the most important thing is really going high on the dose. So you want give people four times the normal dose of a 24-hour non-sedating antihistamine. You can do that once a day, or you can divide it up into half of that dose twice a day. And you're going to continue that along with whatever else you're going to do.

I know you asked, what if they don't respond adequately to antihistamines and omalizumab? I'm going to broaden that out to be, what if they don't respond adequately to antihistamines? Because really, we should not be thinking of omalizumab as our first-line agent. We've got three first-line agents that all have very similar efficacy. We have no head-to-head trials to say that one is better or safer than the others. And so it really comes down to patient preference.

So the way that I will phrase it to patients is, "Hey, we've got three different things that we could put you on. First, I'm going to ask you a few questions to figure out which is going to be the best one to put you on to try first." And I sometimes will actually phrase this to patients like I am setting them up on a blind date. And so, in my head, there's a component that a patient with urticaria, CSU, is kind of saying to me, "Hey, I'm new to CSUville. I don't know anybody. Do you know any cute drugs you could set me up with?" You wouldn't then be like, "That's it. You're new to town. I don't need to know anything about you. Here's who you should go out with." No, you're going to ask them some questions, like, does it matter what religion they are? Does it matter if they want to have kids? Do you care if they've been divorced before? What do you care about?

So whenever I'm talking about CSU with a patient, question number one is, would you rather have a pill or a shot? So a pill you have to take twice a day, every day. Now, the good part about the pill is it is by far the fastest thing that we have got. A lot of people tell me that their itch gets better the first day that they take it. Most people are dramatically better in the first week. But you're going to have to remember to take a pill twice a day.

Now, on the other hand, we could give you a shot. The shot you won't have to do as often, maybe once every two weeks, maybe once a month. So you don't have to remember to take it every day, but it's going to take longer for the shot to work. Which one would you rather try first? And most patients have an opinion then. If they say, "I want to do a pill," fine, I'm going to do remibrutinib. If they say, "Oh, I'd rather not have to take a pill twice a day, I want do the shot." Okay, great.

We got two different shots we could give you. They both work about the same. They're both extremely, extremely safe. With one of them you're going to have to take the shot every two weeks. With the other one, you're going to have to take a shot once a month. But you probably have to come into the office at least for the first few shots if we give you the once-a-month one, whereas the once every two weeks one, you just take it home. Does one of those sound a lot better than the other?

And then, if they give me an answer, they're great. If they don't give me an answer, and if there's no other reason—if they have no comorbidities that make me pick one drug over another—and they have no preferences on pill versus shot or more frequent shots that you do at home or less frequent shots that you come into the office for, if they don't care about any of that, then my first-line drug is remibrutinib.

And it is purely because it works the fastest. It's not that, oh my God, speed of onset is the only thing that matters. No, everything matters. But all of these drugs, they work in about two-thirds of patients—all three of them. So about one in three patients that you start on any of these drugs are not going to do great. In remibrutinib, I'm going to know in a month. So if you're not dramatically better in a month, if you're not dramatically better in two weeks, it's probably not going to be the drug for you. But certainly, if you're not doing dramatically better in a month, it's not the drug for you, and then I can switch you over to one of the biologics. On the other hand, if I start one of the biologics, I have to give it three to four months before I decide whether it's working or not.

Dr. Turck:
And there have been several recent updates in CSU presented at meetings such as EADV and Fall Clinical. Before we wrap up our discussion today, are there any emerging data or treatment developments in CSU that you think are particularly important for clinicians to be aware of?

Dr. Zirwas:
The thing that is interesting that is coming is a drug in particular called barzo. And I cannot pronounce it to save my life. Barzoliv-lu-lab.

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But barzo is a c-Kit drug, so it binds to the c-Kit receptor on mast cells and literally kills the mast cells. I'm an investigator in these trials, and it is stunningly effective. Like, stunning. The preliminary data didn't really back this up, which kind of surprised me, but I think whenever we get the full data, I think it's going to show that it is by far the most effective of the drugs that we have in terms of putting people into a completely hive-free state.

The other thing that's really good about it is, once we get rid of all their mast cells, if we have an interruption in therapy—three months, six months, and typically my experience has been about six months—we can stop the drug, and the hives don't come back.

Now, the downside with barzolvolimab is that it causes hypopigmentation of the hair and the skin. And I've seen that pretty commonly. I'm still waiting for the data to come out to see if it's, like, 30 percent of patients or 80 percent of patients. So far, it appears to be the case that, whenever you stop the drug, that completely reverses, and your melanocytes start making melanin again pretty darn quickly. But that's kind of the unique adverse event associated with the barzolvolimab.

Dr. Turck:
Well, with those key takeaways in mind, I want to thank my guest, Dr. Matthew Zerwas, for sharing his insights on diagnosing and treating complex CSU cases. Dr. Zirwas, it was great having you on the program.

Dr. Zirwas:
Thank you, Dr. Turck. It was a ball being on here. I love getting to pontificate away about CSU.

Announcer:
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