Diagnosis, Management, and Updates on Chronic Spontaneous Urticaria (Supported by Novartis)

Adam Friedman, MD, FAAD, interviewed by Sabrina Shearer, MD, FAAD

SABRINA SHEARER, MD, FAAD: Welcome back to another episode of Dialogues in Dermatology. I'm Sabrina Shearer, assistant professor of dermatology at Duke University and the Durham Veterans Affairs Medical Center and I'm super excited to be joined today by Dr. Adam Friedman. Dr. Friedman is chair and professor of dermatology at George Washington University School of Medicine and Health Science where he also serves as the director of dermatology residency program director of Translational Research and director of the supportive Onco Dermatology Program. Dr. Friedman has a wide range of clinical and research interests and has been an active leader within the American Academy of Dermatology throughout his career. He's joining us today to share his clinical pearls on the diagnosis and management of chronic spontaneous urticaria. Dr. Friedman, thank you for being here.

ADAM FRIEDMAN, MD, FAAD:
My pleasure. Thanks for having me.

SABRINA SHEARER, MD, FAAD:
Wonderful. So just to make sure that we're all on the same page, let's start out with the basics. Can you review the differences between acute and chronic urticaria and also inducible and spontaneous urticaria?

ADAM FRIEDMAN, MD, FAAD:
Absolutely. So yeah, I think defining a disease is of the utmost importance, especially one that sadly has not really been under the warm and embrace of dermatology for all too long. So the first dividing fork in the road when we think about urticaria will be acute versus chronic, and this is really defined by time. Acute urticaria will last less than six weeks. Why six weeks? I have no idea. And I think sixes come up a lot in dermatology in terms of when we check labs sometimes when it comes to defining disease, but arbitrarily it's six weeks. And the mantra I want you to remember is food, drug, or bug when it comes to acute urticaria, which affects roughly about 80% of the global population at least once in their lifetime, you could probably narrow it down to one of those three broad categories and it was actually a pretty decent chance you might actually figure it out.

My personal belief, I think infection plays probably the biggest driver of this, but it should not last longer than six weeks. That's the key point. Now, when you go beyond the six week mark, and that might be developing urticaria every day for six weeks straight, I believe that it doesn't have to be consecutive. You could have kind of blasts of it for a couple weeks,Remission, itcomes back all greater than six weeks, I think is part of that definition. And then you fall into the world of chronic urticaria, whereas opposed to that food, drug or bug mantra, often we have no idea why it is happening. That is where terms idiopathic certainly can come in, but even that term has changed a little bit. But I think the best way to think about it, this is immune driven just like so many of our primary inflammatory skin diseases where we know what's happening but there's not a clear root cause, which is a term our CSU patients use a lot.

We do understand what is actually happening. Now getting to chronic urticaria, as you alluded to, there are kind of two broad categories there. There's what's now called chronic spontaneous urticaria and then chronic inducible urticaria or CindU for short. That's probably the easiest one to review. It's inferring that some external trigger is setting off the urticaria usually within minutes of that exposure, most commonly dermatographia, which is by scratching the skin, you induce a histamine release from mast cell degranulation and you can have a lot of fun drawing things on people's skin to really highlight that. I want to say though, it's important that while these are two categories, you can have both. So if you have a patient with chronic spontaneous urticaria, which we'll get into, you should also be checking for inducible forms, most notably dermatographia. But then you get think about cold, heat, pressure, or delayed pressure, which doesn't occur within minutes, usually occurs an hour or two after that.

Chronic pressure, vibratory sunlight induced even from increasing body temperature, so exercise or what's called cholinergic urticaria, there's some really easy things you can do at the bedside to figure that out. Using an ice cube for cold, I sometimes have patients do jumping jacks or if there's time maybe run up and down the hallway to raise their body temperature. The sunlight or photo urticaria or photo induced urticaria, the common byline is I was just outside, I had it and now I'm here and it's gone. That also goes with cold too if it's in the dead of winter. So the story, but also the ability to induce as the bedside can help. But I find that those tend to be a little more recalcitrant to treatments. We'll talk about treatments, they tend to be a little longer lasting, but there there's a direct correlation between external trigger and why it's happening.

Now, chronic spontaneous urticaria, there should be no clear trigger, formerly known as chronic idiopathic urticaria. The name changed over the years to highlight that maybe we do have a better understanding of maybe some underpinnings of disease, and that's where the spontaneous piece comes in because idiopathic infers, we have no clue it's happening, but we have no idea. We have a better understanding. And recent developments in the pathophysiology kind of have broken this down into two endotypes, notably type one auto allergic, which is associated with IgE antibodies to an auto antigen. This is probably the more common type. And then type two B, which is more resistant, longer lasting. This is autoantibodies to a variety of things, could be directly to the high affinity Fc epsilon receptor, could be to IgE. This tends to be a little trickier when it comes to management and there are ways to distinguish them. There are tests you can do though they're not often readily available. But I think for the purposes of this podcast, I think it's just important to be aware that there are these two endotypes under the umbrella of CSU, and that's why we've moved away from the chronic idiopathic urticaria nomenclature.

SABRINA SHEARER, MD, FAAD:
Even having a little bit more of an explanation., even aving that autoimmune etiology in place, I feel like doesn't really always give patients that answer that they're looking for.

ADAM FRIEDMAN, MD, FAAD:
They want that answer so badly, right? They're like, if we just figure this out, it all goes away. And they may have also been set up for failure in that respect because someone may have told them, oh, if you just go to the dermatology, they do a biopsy, you'll know exactly what caused this and you have to walk that back very gently on a tightrope.

SABRINA SHEARER, MD, FAAD:
Yeah. So tell us a little bit about the patients that are referred to you. What has their story been like up to this point?

ADAM FRIEDMAN, MD, FAAD:
Yeah, the journey is real and many have probably struggled for a long time. There's something unique about chronic spontaneous urticaria compared to all the really fun to us, horrible for our patients chronic inflammatory diseases in that it can come on within nanoseconds. That unpredictability, I think adds to the burn of disease and may also contribute to that finding and

hunting down the white whale of underlying causes or radiology. But often they've been struggling for a while. They have bounced around to maybe it be primary care, infectious disease, rheumatology is a big one, allergy is another one. And that speaks to what I mentioned before about not really having a set home. Certainly allergy immunology is probably a more appropriate home than some of the other ones that I mentioned if we're really talking about chronic spontaneous urticaria. But I think that when you go to these different specialists, it infers something.

So if you're going to allergists, you think that this is an allergy where it is not. And so some of these referrals will come from those different specialties, whether it be needs of biopsy, whether it be needs patch testing, whether it be, I don't really know what to do, we've already tried antihistamines and that's all I know what to do. So I think that there are a lot of different stories that kind of funnel into a nice tall glass of frustration. Even misdiagnosis I think is certainly a big one. Even when the management strategy starts off correctly, it's more of a start rather than a finish in terms of not even necessarily using the right dosing event antihistamines, which we'll talk about really not having a wherewithal of using off-label therapies for which really that's the majority of the things we do for chronic spontaneous urticaria though that is changing, which is really exciting.

Also, I think a unifying feature is the impact and experience with respect to quality of life, and I think you have to be prepared to sit down and hear the trials and tribulations. I think that's one of the ways to really best partner with these patients. It also will engender trust when you tell them you don't need a biopsy or no, no, you don't need a million labs or Yes, I got the giant stack of labs you already had, and no, I'm not going to go over each individual one for 15 minutes because there is not typically an underlying etiology that you can define based on labs. So I think partnering with the patient allows you then to redirect the definition and will also save you a lot of time when it comes to trying to course correct. But yeah, it is definitely a struggle and I think it really starts with it not being established where these patients are really supposed to go.

SABRINA SHEARER, MD, FAAD:
Yeah, absolutely. And you alluded to this a little bit with patients getting tons and tons of lab work a lot of times before they even reach you, but if you are seeing a patient and you're

making that new diagnosis of urticaria for the first time, what's your initial workup? Are you getting any lab work?

ADAM FRIEDMAN, MD, FAAD:
It really depends. So I've been saying this a lot recently, which I'm not really sure why given, Hamilton's been out for a while, but I love the kind of Aaron Burr mentality lab less talk more- kind of a playoff of that - in terms of you could really get to the diagnosis based on the history. You can get to it by just talking to the patient and it's really pointed questions with respect to not just saying, Hey, how long has this been going on for? Because that may be interpreted differently than how you mean it. Because if we're defining chronic spontaneous urticaria as lasting longer than six weeks, if we're defining urticaria in general by a single individual lesion does not last longer than 24, maybe at most 36 hours, then we need to define that. So if you point at a spot say, will that be there tomorrow?

Will that spot last longer than 24 hours? That's very different than saying, how long has this been going on for? Because those plaques, those hemi arcuate or wheal and flares, which I don't think always follow that kind of classic textbook description, they will keep coming and going. So overall, it's been going on for a long time, but you really wanted to find the ephemeral nature of each individual lesion. So I think it's a lot to do with the questions. And then in terms of review of systems, I think it is important to get into it because there are comorbidities. I want to be clear that a comorbidity is not necessarily a cause and those comorbidities can range from autoimmune diseases. Obviously autoimmune thyroid disease is a common one. I think there is some maybe connection between H. pylori, but it's not a hundred percent clear.

There can be comorbidities of just having a chronic inflammatory skin disease as we know just like with psoriasis and atopic dermatitis. So I think it's important to gather that information to then guide your workup based on the unique profile of the patient versus hey, all CSU patients get these labs. If you look to the guidelines, they do recommend doing some basic tests like CBC, maybe a CMP. I don't really get the whole ESR CRP, which is in the guidelines. Those are nonspecific markers of inflammation, but I guess it tells you if there's systemic inflammation. So maybe that's useful just because of the connectivity with respect to the comorbidities of thyroid disease and CSUI will sometimes check if there's something in the review of system suggestive of thyroid disease because if you find let's say antithyroid globulin antibody and the patient feels otherwise, well, what do you do with it?

And if you ask an endocrinologist, they say absolutely nothing because you treat the patient, not the lab. So I really try to reserve these tests more if there's something, the story rather than, oh, you got CSU, we're checking all these things. That doesn't necessarily go along with the European or CUADAI guidelines, but that's just been kind of my take. And then not so much with CSU and angioedema, which you can have overlapping, but if you had just angioedema alone, because sometimes those patients come in and they're told they have hives, but it's really angioedema. I will check complement levels C4,C1 esterase inhibitor function, because it's just angioedema. We want to kind of figure out is even being acquired, is this related to some underlying autoimmune disease? Myeloproliferative disorder? Is this Quincke's Edema, hereditary angioedema? So that might be a reason why I would check those, but that would be angioedema alone, not with urticaria. Okay.

SABRINA SHEARER, MD, FAAD:
And as far as longitudinal screening with those patients, then, are you mostly repeating a review of systems periodically and then going from there? Yeah,

ADAM FRIEDMAN, MD, FAAD:
Exactly. Yeah, I mean there are tests and especially going back to the autoimmune nature of that type 1 and type 2B, there are tests out there, they're not commonly used. There's the autologous serum skin test, which really indicates autoreactive mast cell activation, basal activation test, which I sometimes get because that could be an indicator at least based on the literature, if someone's going to be less responsive to antihistamines. And then I mentioned thyroid OTO antibodies, I might get that if someone is giving me some sign that, yeah, that's weird at this point I'm gaining weight, I'm really intolerant to cold. Or if it's early on where they're getting too much thyroid hormone being released, and it's almost the polar opposite of that. So I really more rely on the patient's story rather than just automatically checking. But the other two tests I mentioned, they're actually part of the suggestive criteria to really call someone a type 2B, but those aren't typical tests you order. Getting a total IgE I think could be helpful when you're thinking about some of the more advanced therapies as a predictor, whether someone will have a good response. But in general, I want to say I don't have a standard workup for every patient. It's more based on the patient themselves.

SABRINA SHEARER, MD, FAAD:

Gotcha. So let's move on then to how are you treating these patients? What's the best strategy or your initial treatment strategy for patients with chronic urticaria?

ADAM FRIEDMAN, MD, FAAD:

Yeah, so I think given the fact that you have a lot of overlap between CindU and CSU giving some good education about preventing those triggers, or let's say for example someone with CSU is being exposed to a direct mast cell degranulator, so we know for example, NSAID are direct mast cell degranulator, so non-biologic mast cell degranulation, we will have a conversation about that or if it's relevant to the patient. But I think the mantra is you should have a need for speed when it comes to up titrating your approach. What I mean by this is our first line is going to be second generation non-sedating, not really non-sedating. Many of them are sedating H1 antihistamines. So these include cetirizine, loratidine, fexofenadine, which I find to be the least sedating of all of them. Loratidine and Levocetirizine, which I think is the most potent of these, but also can be the most sedating.

By the time they've come to me and probably any of you, they probably have tried at least one of these, the standard dosing on the box, and based on the guidelines both here and in the Europe, it is recommended to go up to four-fold the recommended dosing of these. The recommended timing of this varies, and I favor more the EU approach, which is they come in, you double the dose, the standard dosing of any one of these within a week if it's going to do something in my opinion, you'll know, which that's one of the things I like about the speed of onset with respect to the disease, but also with medication. And so I will give the patient a sliding scale. I'll say, in a week's time, if you've doubled down and you are not seeing significant improvement, you're going to add another one, same deal.

Try that for a week or so and I will communicate via our portal, which makes it easier than having them come in with higher regularity, which makes it, it's difficult. Obviously our schedules are very, very full. And then again, if they are getting some improvement but not enough, then a week goes by, they're going to go up to the fourfold recommended dosing. Now the guidelines suggests we should not mix and match these that you pick one and stick with it. I don't always again follow that because if someone is more sensitive to the second generation antihistamines, meaning they get more sedated from them, I might do fexofenadine in the morning and maybe cetirizine in the evening or levocetirizine in the evening. I really do not like diphenhydramine. It is short acting. It is very sedating, but sometimes at night, that's not a bad thing.

But I really do prefer those second generations over the first generation ones that are sedating and they work, they cross the blood-brain barrier, but I think they have their limitations. Along with that up titration, the literature has bounced around with the kind of adjunctive therapies as part of your first line. These included leukotriene receptor antagonists like montelukast. There was a period where their recommendation was yes, include these with your second generations. Then they fell out of favor and now they're back in favor again. The limited studies show that combining them with the second generation H1 antihistamines may add a little extra benefit, but it's not tremendous. I think it's worth trying, but I wouldn't hang your hat on it. In a similar fashion, H2 blockers, famotidine ranitidine were in favor. Actually, there was a point where they talked about the triple threat, which was your H1 antihistamines brine receptor antagonists and H2 blockers.

Now, at least in this moment, H2blockers are frowned upon limited data. They say, just don't even bother. Something that we can all uniformly agree on is that topical steroids do nothing, and we really should avoid systemic steroids. There was actually a study comparing levocetirizine as monotherapy and levocetirizine plus systemic steroids, and the two groups had equivalent outcomes. The other thing with systemic steroids for getting all the fun side effects that come along with them, you often get a rebound reaction like with atopic dermatitis. So they love you initially, but then as they come off of it, it comes back with a vengeance and that's when they post a negative Yelp review about you. So that's kind of like the starting place. And the other thing I'll throw out there is vitamin D. There are some evidence that higher dose vitamin D, like between 2 and 5,000 international units a day bind with second generation H1 antihistamines may boost their effect. And to me it's like one of those, well, why not, right? It's low hanging fruit, people are vitamin D anyway. So I do often talk about that with patients as well. But that's going to be my kind of first line, but we're going to max that out at most within four weeks from when I first saw them.

SABRINA SHEARER, MD, FAAD:
You mentioned them that it's pretty quick onset as far as when the response happens. How good of a response are we talking with the antihistamines? Are we talking like 50% total clearance?

ADAM FRIEDMAN, MD, FAAD:

Yeah, I mean, I think there are patients who clear, I don't want to kick the antihistamines in the shins, but I would say on average 50% of people will not have an acceptable response. I think that's the way to think about it. I think 50% of patients with CSU will not get where they need to be. And just like the FPFs call for treat to clearance, that's the same deal with these international societies is we are treating to clearance and we're not even considering pulling anything away until they're clear for about six months from that point of when they are clear. So yeah, I definitely have patients who I'm actually shocked who are doing great. I had recently a patient with cholinergic urticaria (CindU) mind you, but just on threefold, the recommended dosing of antihistamines and really focusing and taking them about 30 minutes before working out done, never got it again. So I think it is highly variable, and that's where that basophil activation test might be useful to determine whether or not they will work the way we want them to. But about half of CSU patients will not respond the way we want, and that's when we're then going to go to our second and then ultimately our third line options as well.

SABRINA SHEARER, MD, FAAD:
And so what is your second line option? What's next?

ADAM FRIEDMAN, MD, FAAD:
Well, we don't really have many on label options. It's going to be omalizumab, which is a anti-IgE therapy. So monoclonalantibody to IgE when it came out. No doubt, a game changer in the world of CSU and I would argue still somewhat of a game changer. The game has changed with respect to how we use it. So when it first came out, everyone was super excited and then they learned that (1) it came in a little vial that you'd have to kind of stir up because it was so viscous to then be able to draw up and inject it in the office. And the reason you were rejecting the office was because of this black box warning that really had no applicability to CSU, and this was the risk of anaphylaxis, which has only even to date been seen in the asthma pipeline and in asthma patients, which is great news.

And because of that great news, the label has changed in that now you have a actual syringe that the patient can self-inject. It doesn't have to be you, but 2), after the patient being observed for three injections, which would be day zero, day 30, day 60, because it's going to be given every four weeks, the patient could then do it from home, which makes it a lot easier because it's not so simple to have patients sit around for two hours after every visit, and that's going to be every month. So it's become easier to use. I don't think that was vocalized very well. I don't think

the derm community was made aware of this major change, which I think is certainly helpful. But I think that's a great medication. That said, from the data we have now, instead of 50% of patients don't respond, adding this into the mix, maybe it goes down to about maybe 30 or 28% of patients who don't get an adequate response to omalizumab.

So I think it definitely has made a big difference, but there's still a good cohort of patients who don't respond the way we want them to really then pushing us to put on our off-label hats, which I think we're really great at wearing. We look awesome in that off-label hat, and that's where maybe augmenting the dose. So the dosing is 300 milligrams every four weeks. Maybe it's doing one 50 every two weeks, maybe it's doing 450 milligrams subcutaneously. Obviously off label makes it a little harder to get it, but we've done it. It's been published on. But then the other systemic options are pretty broad. So Cyclosporine probably has the most evidence in terms of its immediate efficacy. The problem is you can't stay on cyclosporine forever. So actually there was a recent paper out of Europe talking about whether or not a patient is doing well on cyclosporine after six months of use, get them off of it.

So if it's in writing, we got to certainly consider it. Mycophenolate Mofetil got to stay in the sun thanks to the NYU group. Nick Soter, who longstanding faculty member group champion of CSU, did several small studies looking at mycophenolate mofetil, kind of like a soft immunosuppressant, and I certainly have used it in my practice. Methotrexate, oldie, but goodie, certainly very familiar in the world of dermatology, has some decent efficacy. And we even have data in pediatric patients in the atopic dermatitis world, thanks to folks like Amy Paller. So can feel pretty comfortable using that. I don't really use so much azathioprine, but there is some data. Same with hydroxyurea, other drugs in terms of targeting neutrophils, which can play a role in the pathophysiology, Dapsone and Colchicine have some evidence. And then last but not least, there is some data shown that narrowband UVB can be helpful.

It's more impractical about getting a patient to come in three times a week, which is not always so easy. But then obviously we play around with other things that we have in our toolkit, whether it be dupilumab, which is up and coming and is being studied and may have an indication relatively soon, messing around with JAK inhibitors, which is so easy to do nowadays, thanks to all the indications of dermatology and all the wonderful samples we get. But I think that my take home point is be creative because we literally have one FDA approved advanced therapy currently. We have antihistamines, but there's a good percent of patients who will not respond

the way we want. And so we need to then put our thinking caps on and of course get creative to get these patients clear.

SABRINA SHEARER, MD, FAAD:
Yeah, absolutely. And I think one thing that patients always want to know, maybe in addition to all of these things is: what about my diet? So what are your thoughts on low histamine or pseudo allergen-free diets, and is there any evidence to support those changes?

ADAM FRIEDMAN, MD, FAAD:
Yeah, so it's funny, I was asked by Vivian Shiwho runs a session at the annual AAD meeting coming up in March on diet and skin disease. And so I've had the opportunity to speak on acne and rosacea and that, that's easy. She asked me to speak on CSU, and I'm like, really? The whole point we're supposed to say that there is that underlying cause, diet is not part of it, and now I have to give a 20 minute talk on diet and CSU. So if you're listening, Vivian, thank you so much for that awesome opportunity. Funny thing is there actually is some data on this. It's these challenges that force us to go on PubMed and actually look, and there are a couple studies, the categories you mentioned, some of them. So the pseudo allergen-free diets, in essence, is a restrictive diet protocol where you pull things out of your diet to see if it makes a difference.

That is pretty low evidence and it sounds honestly horrible, and I wouldn't wish that on anybody. So I don't think the evidence really supports pseudo allergen-free diets, low histamine diets, though there is just some evidence. I mean, none of the evidence is extraordinary, but there is some evidence. And the idea here is you're avoiding histamine rich foods. This includes aged cheeses, fermented foods, salted fish, wine unfortunately. But there is some evidence supporting its use even there's been a couple studies with Mediterranean diet kind of replacing a haphazard diet, which a really focused diet, Mediterranean diet, which has some supporting evidence. I would say histamine-free or reducing histamine rich foods and the Mediterranean diet probably have the best evidence where pseudo allergen-free diets, which is a restrictive diet, doesn't really have supportive evidence, but it's all relative. We're talking about a handful of studies, but if you're twisting my arm to to pick one, it would certainly be the histamine rich food avoidance, which really seems to play a role, which makes sense, right? Because if you're already releasing too much histamine from the mast cells and now you're introducing exogenous histamine, probably not a good thing. So from a linear perspective, it makes sense to me.

SABRINA SHEARER, MD, FAAD:

Yeah. Great. Well, this has been super helpful. Did you have any last words of advice for our listeners?

ADAM FRIEDMAN, MD, FAAD:

Yeah, I mean, I think the future's bright for CSU and this really should be under our umbrella, and I think it will be, especially when industry starts to get interested and you have a pipeline, I mentioned dupilumab will hopefully have the indication soon. It's already approved in Japan. We have small molecule inhibitors like Bruton's kinase inhibitors that should also be hitting the shelves hopefully in the next year or so, and actually many more that are in phase two and early phase three. So I find that when you have a disease state that is really tricky that we don't have a lot of things for, and all of a sudden you get a lot of tension and a spotlight things to emerging therapies, then people start to take notice and really take ownership over it. So I think it's important to recognize this is not just a nuisance. This is a chronic immune driven disease that really drives patients crazy and uniquely drives them crazy compared to many of the other conditions we manage. And so I think it's really important to have your finger on the pulse of where we are with our understanding of disease, diagnosis, and ultimately management.

SABRINA SHEARER, MD, FAAD:

Wonderful. Well, this has been a super informative conversation, and these are patients that really need us, so I'm glad that you shared your pearls to help us treat them. Thank you so much for being here, Dr. Friedman, and thank you all for tuning into another episode of Dialogues in Dermatology.