Dr. Mariam Hanna: Hello, I'm Dr. Mariam Hanna, and this is The Allergist, a show that separates myth from medicine, deciphering allergies and understanding the immune system. With fall approaching, I'm gearing up for a spike in venom stings and consults. Imagine it, the season's end. Insects buzzing like they're at their final feast, and some poor human accidentally crashes the party. Naturally, the bugs take it personally. This isn't exactly scientific, but I'm claiming creative license. Blame it on that late-night rewatch I just had of a Bee Movie. If Jerry Seinfeld can give bees a voice, I can give them a motive. I had a patient recently decline venom immunotherapy. He had been stung with a significant systemic reaction, including hypotension and vomiting. Positive testing to honeybee and yellow jacket, normal tryptase, dealing with another chronic health condition. The kicker here: he declined immunotherapy. It's a decision I don't often hear. Given the efficacy of immunotherapy here, I was prepared to speak about the pros and cons of immunotherapy to yellow jacket and to honeybee. He straight out declined, epinephrine auto-injector in hand. He'll come back for retesting, and if he changes his mind in the interim, he has my number. It's a story that challenges the allergist. Today's guest is going to review venom immunotherapy with us. From the challenges of diagnosis to treatments and what's coming next. It's my distinct pleasure to introduce Dr. Golden. Dr. Golden is an associate professor of medicine at Johns Hopkins. He directed a research program on insect allergy and anaphylaxis at Johns Hopkins for 30 years and has published numerous research articles and review articles on this very topic. Dr. Golden is currently enjoying his golden years of retirement after establishing a busy private practice in Baltimore and serving as the allergy division chief in Baltimore, where he developed the allergy and immunology teaching program for medical residents. He continues to contribute as a member of the Joint Task Force on practice parameters and in chapters, reviews, editorial boards, and invited lectures. Dr. Golden, welcome to the podcast.

Dr. David Golden: Oh, thank you. Thank you so much for inviting me

Dr. Mariam Hanna:-Can you start first by, let's get the basics out of the way. Let's explain what venom allergies are and how they differ from other types of allergies that we see in the clinic.

Dr. David Golden: Okay. Allergies are allergies. We usually mean immediate hypersensitivity reactions, and that is caused by, in some people, the development of allergic antibodies to something. You have to be exposed. You can't be allergic. Actually, you can have an allergic reaction on the first sting. Like every allergy, you have to be exposed. Some people develop allergic antibodies, and then they're armed, unfortunately, for a reaction the next time or any future time that they get stung. The same venom protein exposures will trigger those antibodies to cause the release of histamine and other factors into the system that cause the itching in hives, trouble breathing, dizziness, shock, or worse, reactions that constitute this kind of allergic reaction. So allergies can differ because of the exposure. So, a local reaction to a food might mean a stomach reaction, but a local reaction to a sting might mean your arm gets swollen. So, it's different. And the pattern of reaction can be different. But in general, there's either a sting causing a normal reaction or a local reaction that's abnormal. So that's usually something we call a large local reaction. We can describe that a bit more, or systemic reaction. So that's the

whole system. If you get stung on your finger and your arm swells up, that's a local reaction. actually. If you get stung on your finger and your face swells up, that's a systemic reaction. It had to go through your system to get to your face. And systemic reactions can be anaphylactic. So that's going to involve another system, the throat, or breathing, or dizziness, or circulation, or blood pressure. Or non-anaphylactic, like just breaking out in hives all over and having a swollen face is pretty scary and might get many people worried enough to go for venom immunotherapy, although apparently not your patient. And yet that's something we would call a mild reaction because it was systemic, but it wasn't anaphylactic. So that's the range of allergic reactions we see to stings.

Dr. Mariam Hanna: Okay, so stepping away from the range, what about the different types of venom allergies that we have? What are the most common types that we should be prepared to see in our clinics?

Dr. David Golden: All right, well, first off, this is stinging insects and not biting insects. Biting insects almost never cause systemic or anaphylactic reactions. It actually happens from mosquitoes. Estelle Simons actually, many years ago, described "skeeter syndrome" of multiple large swellings, allergic reactions locally on the body in children. But anaphylaxis was really, really rare. Stinging insects typically are the ones that cause anaphylaxis, and there are three main families: bees, wasps, or vespids is the general name or entomologic name, and ants. So stinging ants in the southeastern U.S. are a scourge and a much more frequent cause of sting allergy than the flying Hymenoptera. They are Hymenoptera. They do sting. It's not their bite; it's their sting that causes the anaphylaxis. There is venom in them, they're not related to other stinging ants, like in Australia, the jack jumper ants, for which there is a venom immunotherapy. So there are stinging ants in different parts of the world. The bees are bees. Bumblebees are bees, but they're a very infrequent cause of allergic reactions, sometimes in greenhouse workers. And wasps, a broad family, include the yellow jackets and hornets that are closely related, very closely related. And the paper wasps, Polistes wasps, that are related, but more distantly, with about 50% cross-reactivity when we talk about that.

Dr. Mariam Hanna: Perfect. Let's compare a little bit. A large local reaction from an insect bite, as you said, not a sting. Are they related in any way to increasing your chance of a venomous allergy?

Dr. David Golden: No.

Dr. Mariam Hanna: No. Okay.

Dr. David Golden: That's as short as that.

Dr. Mariam Hanna: That is the best consult that I get, so that's perfect.

Dr. David Golden: So then having allergies...

Dr. Mariam Hanna: Yeah.

Dr. David Golden: Having asthma or allergies or having atopy in general. Atopy in general. And having positive tests to anything else does not increase the risk of venom allergy. It's not an atopic disease, and it's not usually familial, although it can be, and I've certainly seen that. But 95% of the people we see with sting anaphylaxis have no family history.

Dr. Mariam Hanna: Perfect. So then let's take it one step further. What about large local reactions with stings? Do those increase your likelihood of having a systemic reaction?

Dr. David Golden: Absolute risk versus relative risk? Do they increase it? Yes. How much do they increase the risk? Not so much. And that's a catch. And that's where how much does it mean to me or to you or to your patient? And those are three different things. And that's why it's the kind of question and answer that gets us into shared decision-making with patients that all we can do is say, well, we think your risk is pretty low, but you may or may not be happy with me telling you that you have a two or 3% chance of needing an EpiPen for your next reaction. On the other hand, the population risk is one to one and a half percent, so it's double the risk, but it's still not that much different. And we definitely don't give epinephrine injectors—I'm getting ahead of myself—but to anyone with a positive test, that's a whole other question.

Dr. Mariam Hanna: It is, and we're going to dig right into that, but I'm going to bring you back. Okay, so then what about the patient that gets a diffuse cutaneous rash, hives from a sting? Are these the patients that we should be worried about for systemic reactions or not?

Dr. David Golden: Not usually. Like people with large local reactions, which are allergy-related, those people usually have a positive test, but we consider them low risk for having a systemic or particularly for an anaphylactic reaction. We've known since studies at Hopkins in the '80s that children with cutaneous systemic reactions, meaning skin only and none of the airway or circulation, children with those reactions, which—that was an important study because they noticed—Ken Schuberth and Marty Valentine noticed that of all the children that were being referred to them to our study program for systemic reactions, 60% had only the skin-only cutaneous reactions. So that raised the question of, well, are they going to get worse or not? Because if not, maybe they don't really, really need venom immunotherapy. A study was published in New England Journal in 1990. No, they don't get worse. I mean, they can, but it turns out it's like 1%, which again, is about the population—a little more than the population risk in children. It's never been formally proven in adults, but the evidence that is published adds up to about the same thing. So it took until the updated practice parameters 2016–17 for us to change the recommendation in adults from saying, adults, yes, they should get venom immunotherapy, to adults, no, they should not get venom immunotherapy if they've only ever had a skin reaction.

Dr. Mariam Hanna: Yes. And that practice shift I was well aware of because that represented before I got into practice and after I got into practice that this shift happened. Okay, I like to talk about this a lot before we actually start talking about current methods to diagnose venom

immunotherapy, because before we even decide as to what we're going to test them with, like, should they even be tested, I think is often the first part to get through in our histories. So current methods that you utilize in practice for diagnosing venom allergies, which ones will you routinely do on your patients that you suspect have had a systemic reaction or have a true indication for getting t esting. Who would you test, Dr. Golden?

Dr. David Golden: All right, so we're assuming I'm convinced from a good and detailed history that we should move ahead with testing. Okay, because that's test number one: the history.

Dr. Mariam Hanna: Exactly.

Dr. David Golden: Okay. Given, I'm a traditionalist, so I would go with skin testing. I think to this day it has a slightly better sensitivity than serum IgE testing for venom. The gap has narrowed, but it has never really closed. I think it has greater clinical correlation, and there is evidence to support that. But the real answer is that neither test is perfect, and they are often complementary. So we're moving toward a future. We're just starting work on the next update of the insect sting allergy parameter. And I wouldn't be surprised if we decide to recommend that both testing modalities should be used. Whatever you start with is fine. I prefer to start with skin testing. There are reasons that in practice, actually, there are logistical issues. Venoms are not always available for testing. The supply issues—for those who've been in practice more than ten years—supply issues were a huge problem, to the point where there was no venom at all for a year or two in Canada, I believe.

Dr. Mariam Hanna: Absolutely.

Dr. David Golden: Uh-huh. So there are a lot of reasons that come into this besides just saying, well, which one's a better test? Whichever one you choose to do first is fine, but whatever is negative, you maybe should consider doing the other modality to be sure. Because there is evidence that things can be positive on one and negative on the other, or positive on either test, and negative the next time you do the same test for that matter. Not that it goes from very strong to negative, but there are a lot of people who are positive but not strongly, and another time they're, I guess it just is below the level of detection. So one problem with serum IgE testing these days is that the accuracy of the labs has improved, and they're now reporting down to 0.1 kilounits per liter as positive, and it's positive. It does detect IgE, but what's the clinical significance of that IgE? All of the published literature on the clinical validation of skin test, of serum IgE testing, was based on a cutoff of 0.35. So there's actually no data on the 0.1 to 0.35 range. And we actually do know that when you do this, meaning you use a lower limit of detection, what you're detecting is a lot more people with asymptomatic sensitization. This is the part—the bugaboo—of testing for any allergen is that there are tons of people who are positive on testing and have no reaction at all, and many of them have very low levels of IgE. And that's a lot of what you detect when you. On the other hand, if the patient has a history of anaphylaxis to a sting and they're positive at 0.17, okay, they need venom immunotherapy. Yes, it's positive. Right. So again, history, history, skin test or serum IgE, and then consider doing the other test just to round out your testing until you're sure you've detected everything you need to detect.

Dr. Mariam Hanna: Are you using a lot of component testing to venoms in practice now?

Dr. David Golden: So, to take one small step back, one of the reasons a lot of people are doing serum IgE testing first is because we may end up talking about who should also have a serum tryptase level drawn. And if you are doing that, then you're drawing blood anyway. So I recognize the other practical reason that the serum IgE testing is often the first step. Component-resolved diagnosis isn't the same. So we've heard a lot about that with food allergies, for example, where the question is, does it increase the sensitivity of our testing? And the answer is not usually, actually, although I can give you an example of where it does with venom. And does it tell us more about the kind of reaction someone's going to have? It may with foods. But, so far that's not been shown with venoms at all—that the pattern of sensitization has anything to do with the reaction. That was a big disappointment. We thought we'd find large local reactors and systemic reactors. So far, not true, although I have not seen it systematically examined. Interesting question. So its main utility is to separate the cross-reaction from the real dual sensitization to honeybee and yellowjackets. A lot of our patients, up to half of ours, are positive for both honeybee and yellowjacket. They may have only had a reaction to one of them, but they may have been stung by more than one kind over the years, and now we don't know if they're really allergic to one or the other or both. Component testing can tell us that.

Dr. Mariam Hanna: That would have been my patient right at the beginning. This positive to honeybee as well as yellowjacket, one sting. And which is it? Or are you desensitizing him to both? So this is where component testing really would have helped as the second round of testing.

Dr. David Golden: Oh, it almost certainly would answer that question. It has some other uses. I alluded to a moment ago that Api m 10 is a honeybee allergen that is relatively underrepresented in some of the commercial venoms. So, it can be missed, first of all, in testing. And number two, it can be not very effective in venom immunotherapy. Someone can be on honeybee immunotherapy and still react to honeybee because there's not enough Api m 10 in the venom. So we can't solve that problem yet, but we can detect that patient.

Dr. Mariam Hanna: I'm intrigued by this topic because our testing is advancing, and our treatments are, but they're starting to advance as well. And it's a very similar story to what we are hearing happening on the flip side, in the food allergy world, as an example. Okay, let's go into venom immunotherapy a little bit. How do you counsel patients as to the effect, this treatment, the expected effect of the treatment that you are prescribing them?

Dr. David Golden: It works. It's the most effective form of immunotherapy we know of. There's no other immunotherapy that can say it's up to 98% plus effective. But then we get into the nitty-gritty details, and that gets a little fuzzy. Nevertheless, first of all, what's our threshold? What do we mean by "it works"? So if someone's on immunotherapy for grass and they have half as many sneezes, it's been highly successful. But we're talking about eliminating the systemic reaction. If the patient gets one hive, it's a treatment failure. So, when we talk about a

success rate of 98%, that's remarkable. The patients who do have reactions are almost always way less severe than their original reaction. So we can almost think of this as a 100% success rate. Now, what are the exceptions? The exceptions are, a lot of those studies were done with mixed vespid venom. So that's using a higher venom antigen load. If you give single venom therapy, with just yellow jacket, I'm going to estimate it's 92% effective instead of 98%. And again, the failures are not such bad failures, but still, the key is honeybee. And honeybee is about 80% effective. And couldn't it be better than that? So, a future guideline, I hope, will match the European guideline in allowing that for beekeepers and people with known honeybee anaphylaxis and frequent exposure, they should really be on a double dose of 200 micrograms. They don't have to be 80% protected. They could be 90% protected.

Dr. Mariam Hanna: Oh, that's interesting. I'll have to tell you my beekeeper stories. We collect so many stories with venom allergy. Actually, there's never a boring story to how you got that sting. Okay, I deal a lot with pediatrics, and I think one of the biggest things is putting a child on shots, because to this day, there is no other route. So should venom immunotherapy be as readily approached in the pediatric population as it is for adults?

Dr. David Golden: Short answer, yes. Again, patient selection is important.

Dr. David Golden: So two questions. My colleagues at Hopkins asked the question, will they get worse? So that's why we know this is... The cutaneous reactors have a not zero, but very low frequency of getting worse. That can be really reassuring. Some parents and families are going to still, I won't say demand, but say that they really want the immunotherapy. They want the security. And that's a quality of life issue. And that's actually an accepted indication to grant immunotherapy. Others will say, no, that's not so bad. I'm not so worried. We don't want them to have a major impairment or quality of life—the family or the child. Those with moderate to severe reactions. So, we published that study in New England Journal in 2004. The ten to twenty-year follow-up of the children who did and didn't get venom immunotherapy, there were those who declined, even though they had the parents, I guess, declined. And now those are in their late teens or mid-twenties. And we followed up on that. And it's obviously hard to capture the large population twenty years later. But we found enough to get a statistically significant result that of those children who had had that moderate to severe systemic reaction, anaphylaxis, that 32% reacted when they got stung again ten to twenty years later. That's not nothing. That's still ten times more than the population risk.

Dr. Mariam Hanna: Wow. Okay. Your thoughts on new and emerging treatments for venom allergies that you find promising or that are coming down the pipeline? Is there going to be SLIT? Is there a patch?

Dr. David Golden: Nope. There was a single study of SLIT, an Italian study that was pretty good, actually, and showed efficacy for large local reactions. But that's efficacy, and I have no doubt that it could work. It was accompanied by an editorial saying, this is outrageous, it's unethical, and we should not be doing SLIT for venom because it's dangerous. And I can understand that knee-jerk reaction. But again, I'm going to say we don't know. We don't know what we don't

know. But there's nothing in the pipeline, unfortunately, to tell you that there's going to be an alternative in the near future. Not true. There will be, I believe, a BTK inhibitor approved for chronic urticaria. There is strong evidence, and now inhuman evidence from Melanin Dispenza, that it can reduce the severity and increase the tolerated dose in a peanut challenge from two days of treatment. So, there are situations, certainly for desensitization procedures, for going to a party and not being sure what you're going to eat, that there might be a treatment that somebody could take that we're getting to the point where we recognize that what I just said about venom, our standard was 100% eliminating the systemic reaction. Not a single hive, right? That's not our standard anymore for anaphylaxis. Interesting how it's changed. Now we're pretty happy if we can make it less severe, so that a higher threshold dose can be achieved now with new and upcoming medications.

Dr. Mariam Hanna: Right. And a lower target for immunotherapy even.

Dr. David Golden: Yes.

Dr. Mariam Hanna: All right. What will the new practice parameters have?

Dr. David Golden: I mentioned one or two about the order of testing and complementary or combined testing, about 200 micrograms for beekeepers or similarly exposed honeybee anaphylactic patients, and component-resolved testing because everything I said before is actually not in the practice parameter. It was not available at the time. What won't it say? It won't have to—well, it depends on what happens between now and then. It won't have to update the testing for tryptase and the role of mast cell disorders because we updated that in the 2024 published anaphylaxis practice parameter update, including venom-specific recommendations. Likewise, things about treatment-related, diagnosis-related that cross over so that some things don't have to be redone that otherwise would have been done.

Dr. Mariam Hanna: I have to tell you, I had double physician parents who wanted to become beekeepers, come with their children, and they wanted them tested for honeybee allergy and prescribed epinephrine auto-injectors. And they were really disappointed with all of my answers from this encounter because not only did we not test, we did not prescribe epinephrine auto-injectors. And we said, this is like they're going to be at slightly higher risk if they keep getting stung more and more. But that doesn't mean that they're going to anaphylax. Is that right? Or should they empirically have one in their first aid kit?

Dr. David Golden: Well, you know, I just a few days ago spoke to the Eastern Apicultural Society, a huge meeting of, I think, every beekeeper east of the Mississippi. I don't know if there were any Canadians there. This is one of the things that comes up, and it made me dig out some studies. There's actually a systematic review and meta-analysis of studies of beekeepers. Frequent exposure is a risk factor, just being stung. If you've been stung—anyone who's been stung in the past summer—if you've been stung this summer, you have a 40% chance that you have a positive test for venom-specific IgE, which is twice the population average. If you do have IgE and you're asymptomatic, that's all very nice, but what is your risk of a future reaction?

There are only two published studies. One says 17%, one says 5%. Either way, now we're getting into five times the population average.

Dr. David Golden: And I would have said the same things that you did. I still wonder if they're going to go see someone else or the pediatrician and get an epinephrine injector anyway. If they're really that... Well, if...

Dr. Mariam Hanna: Their risk post a sting is 5% to 17% in the future year. Is that a case to have one in the first aid kit?

Dr. David Golden: Oh, wait, wait. Will they likely be stung in the next year? That's the only way that statistic is...

Dr. Mariam Hanna: Well, just a minute. Will the children be active with the hives, or will they just be the children of beekeepers?

Dr. David Golden: Different. That's not working with the bees. If they're working with the bees, they're going to get stung, I'll grant you that. And then I'd have to... This gets to the question, and I've been asked before by people who wanted adults who want to take up beekeeping and want to be tested first. And if they're positive, they may want to even ask you about venom immunotherapy. And this gets into the same recommendation that we advise against all of that. But we do know the statistics that I've just been quoting, that sensitization is common. That sensitization does carry a somewhat increased risk. Frequent exposure is going to continue to amplify that risk to a certain extent. Many beekeepers have systemic reactions, but they just shrug it off because what happens is they self-immunize. But then they lose that immunity in the winter. So the first sting in the spring, they get a reaction, hopefully not too severe, and then they're okay for the rest of the season because they're... And you know, if they do get two or three stings every couple of weeks, year-round, 100 to 150 stings a year, year-round, they can self-immunize. That's a thing.

Dr. Mariam Hanna: That's so neat. I didn't know that.

Dr. David Golden: But they have to not let up in the winter.

Dr. Mariam Hanna: Right?

Dr. David Golden: Right. Okay, so what about the children? That's a really tough one because it does put us in a tough position. We know the recommendations. We also know the statistics. We also know that nothing's impossible. Children, fortunately, also are the ones that tend to have the mildest reactions, but that's still just statistics. We do know of severe cases because they do get the publicity. The risk is never zero. So all you can do is have that discussion. This is shared decision-making. And if what you're saying doesn't dissuade them from their fear, which is really what it comes down to, then you can say, first of all, testing is useless because it's negative today, and then you get stung tomorrow, and next week it's positive. So, if what they're

asking is, should they have an epinephrine injector? That's different. Yes, I think every beekeeper should have epinephrine injectors or epinephrine treatment available in the areas of the hives. They may have a visitor. They may have someone that didn't even know they were allergic, as long as they are educated in the basic recognition of anaphylaxis.

Dr. Mariam Hanna: I sneakily asked my patient that if I said no and didn't prescribe them, if they would seek a second opinion and get somebody else to prescribe because they're all doctors around them. And they said yes. And I'm like, I'll save you this step. It's okay. As long as we've had our discussion.

Dr. David Golden: That's right. If they get the picture and they still make their choice, this is patient values and preferences, right? And if their quality of life will be improved with this understanding and having the epinephrine injector, fine. If they want to be tested, you know what? It's not going to change anything. They're already scared to death. They already have the epinephrine injector. But if it's positive, well, they want venom immunotherapy. And how do you feel about that?

Dr. Mariam Hanna: No, that doesn't make sense.

Dr. David Golden: That's not indicated.

Dr. Mariam Hanna: Okay. All right, time to wrap up.

Dr. David Golden: Already?

Dr. Mariam Hanna: Things have flown by today. It's all the buzz. And I want to ask today's allergist, Dr. David Golden, for his top three key messages to impart to patients and physicians on today's topic—venom allergies. Dr. Golden, over to you.

Dr. David Golden: Oh, well, there are so many messages there, aren't there? But you know what? Probably what I deal with, in general, misperceptions, myths, obstacles to proper care. First of all, sting anaphylaxis is not a fluke. Okay? Patients are amazing. "Oh, I've been stung a million times with no reaction. This time, I couldn't breathe. But it's a fluke. It'll never happen again." Not true. And it'll go away. It's been ten or twenty years since that last reaction. Doesn't matter. The risk can remain for a lifetime, even in the absence of any sting reaction. Okay, that's takeaway number one: never underestimate the risk of anaphylaxis.

Let's see. Number two. On the other hand, it's a myth that the next one will kill you or that they always get worse. That is true for some, or may be true for some allergens. It is not true for insect stings. The chance of things getting worse is less than 3%, and in some studies, less than 1% in children and adults.

Okay, takeaway number three. Venom immunotherapy does exist. You now know more than 95% of American—I won't speak for Canadian—primary care providers, who don't know that

venom immunotherapy even exists. They, fortunately, are better than they used to be about prescribing epinephrine treatment. But then they tell the patients, "Don't bother seeing an allergist. There's nothing else they can do." After 40 years on the market, venom immunotherapy is invisible to non-allergists. It's amazing. People find it on the Internet, but they don't find it from their primary care doctors or emergency room physicians, at least not in the U.S. So, we just need to get that word out. It's just unbelievably not there yet, and it doesn't have to be that difficult. We rapidly spread it out to six or eight weeks and even twelve weeks when we get out to four-plus years. For the long term or so, it should be more readily available and more readily accepted.

Dr. Mariam Hanna: Perfect. Thank you, Dr. Golden, for joining us on today's episode of The Allergist.

Dr. David Golden: Thank you so much for having me.

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