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.

I had this appointment yesterday. The visit was for something completely different, as it usually is. The appointment was over. I was standing up and nearly at the door. "Can I get some Epi refills for him?" A pause. "He'll need about..." Then she starts counting in the air. "Six, please." Then no words, just a look in her eyes.

This look always has so many layers. It's "I'm scared, and I'm trying to be brave, and I'm terrified because he could die from this." You hopefully can't read my thoughts in that moment. I usually smile. I print the prescription. For families who've lived with allergies for years, they pretend it's routine. It never really is. It's a transaction that has layers too. Do you know when to use it? Do you know how to use it? Will you actually use it? Where will you go afterwards? I hand her the paper, and then I walk into the next room. And then I do this dance all over again.

Epinephrine sits at the center of what we do. We prescribe it every day, we teach it every day, we trust it with our patients' lives. Yet we still wrestle with the same questions: when should it be given? Why is it still underused? Will new delivery systems change anything? Will they change everything, maybe?

Today we're talking about epinephrine. We're talking about the science, we're talking about the devices, and we're talking about the future, which is all actually exciting in this field. Our guest is one of the leading voices in this space. Dr. Jay Lieberman is a professor of pediatrics at the University of Tennessee. He serves as the interim division chief of allergy and immunology at Le Bonheur Children's Hospital. He's a program director for the allergy and immunology fellowship program. He previously chaired the food allergy committee for the American College of Allergy, Asthma, and Immunology, and he currently serves as co-chair of the Joint Task Force on Practice Parameters. He's an associate editor for Annals of Allergy, Asthma, and Immunology, and he also serves in leadership roles with the American College of Allergy, Asthma, and Immunology, the ACAAI, and he serves in leadership roles at the American Board of Allergy and Immunology as well. That's a lot of allergy and immunology that just happened in the last 10 seconds there. Dr. Lieberman, thank you for saying yes, and welcome to the podcast.

Dr. Jay Lieberman

Thank you so much. It's great to be here.

Dr. Mariam Hanna

We've hashed out epinephrine in previous episodes and some of our listeners may have heard about it, but we're going to take a slightly different angle or slice into this conversation today. We'll start with epinephrine at this day and age, it remains the cornerstone for the foreseeable future for anaphylaxis management. What makes epinephrine uniquely effective and why are we not talking about any other medications to replace it yet?

Dr. Jay Lieberman

As many of the listeners obviously know, epinephrine does things in the body that we want to happen during an allergic reaction. By activating the adrenergic receptors, specifically alpha-1, beta-1, and beta-2, it counteracts everything bad that happens during an allergic reaction. It increases vascular resistance or increases blood pressure by the alpha receptor. It increases inotropy and chronotropy, so it increases how fast your heart rate goes as well as how strong it contracts. These are good things. Epinephrine also, via the beta-2 receptor, leads to bronchodilation. It used to be used for asthma. All of these things are perfect. These are exactly the things that we would like to happen during a severe allergic reaction. Interestingly, at very high doses, whether that's occurring physiologically or not we don't really know, but at high doses it also stabilizes mast cells. It checks all boxes for what you would want to happen during an allergic reaction.

Dr. Mariam Hanna

Why has no other medication been able to replace it or replicate it? Why are we still only talking about epinephrine? We'll talk about all the different routes, but why still just only epinephrine?

Dr. Jay Lieberman

I think part of that is just because what we've used, we know it works and we've already got products. But it's really fascinating if you look at really good studies of anaphylaxis. For example, the early sting challenge studies done in the late '70s and early 1980s, what's fascinating is in true anaphylactic distributive shock where there's a drop in blood pressure immediately and epinephrine doesn't work, in those patients norepinephrine actually helped them. Norepinephrine doesn't activate beta-2, so you don't get bronchodilation, but for sting anaphylaxis, maybe it would be better because it does better to restore blood pressure. In that regard, maybe norepinephrine could be better than epi in true hypotensive shock.

On the flip side, for food allergy, really good studies out of the UK in fatal anaphylaxis cohorts suggested that bronchoconstriction may be a leading cause of death in food allergic reactions, so perhaps adding on a bronchodilator on top of epinephrine might help. But when you look at all cases, epi still checks the boxes that you want as one medication, probably is still the best.

Dr. Mariam Hanna

And misconceptions are abundant in the world of epinephrine. We're going to take a moment to talk about misconceptions, and I think a lot of allergists listening will feel validated because they deal with this. But what are some of the big misconceptions that you hear about still amongst healthcare professionals out there to do with epinephrine?

Dr. Jay Lieberman

I think there's tons. Probably the biggest misconception is that it's dangerous or it's a medication of last resort. I think there are so many reasons for this. One is that forever we've only had it as

an injection. And for whatever reason, injections have scared people. If it's an injection, it must be more strong than just...

Dr. Mariam Hanna

Has a mystique around it.

Dr. Jay Lieberman

It's weird. I can just pop some diphenhydramine liquid or pill, that's not going to harm me in any way. But if I have to inject it, it must be really severe. Then there's the social aspect, and I always bring this up in talks, the movie Pulp Fiction. I think people have in their mind this thing where I'm going to just jab somebody and it's going to reverse their, cause their heart to explode or something like that. There's just this social stigma with it that goes along with it that we've been trying to counteract for years.

From the lay public and from the non-allergist, that's the biggest misconception that it's not safe, that it's last resort, it's super strong, and we only use it in certain scenarios. What's fascinating on the allergist side, I think the misconceptions are that we really know a lot about it in the sense of, oh yeah, it definitely works, and we know the dosing that's to be used. In reality, we're probably underdosing epinephrine delivery with the devices that we have available to us when you look at really good studies and trying to figure out what's the right dose.

Dr. Mariam Hanna

Part of the medication of last resort I'm hearing is both from healthcare professionals as well as from patients that come in and they say, "How much time does this buy me?" Can we make a comment towards that, please, as well?

Dr. Jay Lieberman

There are layers and nuances to that question. The "how much time does this buy me?" kind of thing is not where we want to be as far as a treatment paradigm because we don't want it to be viewed as, "This is going to work for a minute and you have to go right to the emergency room."

As a part of that, as you and many of the listeners may know, the most recent North American or at least practice parameter guidelines for anaphylaxis say if you take epinephrine and the reaction is fully resolved, the patient is better, there is no other issues, you don't actually have to activate emergency medical services because we don't want there to be a barrier to the use of epinephrine saying, "Oh, if I have to go to the emergency room, I'm not going to use it."

But we also want to take this stigma away, like you said, of, "Oh, it's only going to buy me a couple minutes because it's going to be like, oh, I'm better and then it's going to wear off." The tail of the epinephrine curve, when you give it, actually lasts a lot longer than we think, that probably is working for hours, honestly.

Dr. Mariam Hanna

And for hours. Okay. And then sometimes when we talk too much about the epinephrine discussion and use of epinephrine, what we're overly focused on is get the medication in, and we're still having trouble with recognition of anaphylaxis. Dr. Lieberman, I've recently sat through many talks about the definition of anaphylaxis, various societies and associations that have varying definitions depending on the age and presentation. Was it sting or is it food? And then once a definition is more than one sentence, I've already gotten confused, so how are my patients going to get this? Can we talk about that a little bit?

Dr. Jay Lieberman

I'm confused, too. I've been on guideline panels trying to create new definitions and new criteria, and I'm still confused. There has been a push by some people to say we need to just get rid of the term anaphylaxis almost and just say allergic reaction and then maybe there's a spectrum of that, but I don't know if that clears it up.

There's a lot of confusion. One big part of it is that we don't have any biomarker. For a heart attack, we have a biomarker. You come in with chest pain, I can do a workup and say, "Oh yeah, this is happening." Whereas tryptase being our best biomarker, it's not perfect by any means.

Lacking a biomarker, we're just stuck with these clinical criteria and everyone can argue. In the end, what I tell my patients regarding this is I don't care what the symptoms are. I don't care what anyone calls it. If you are concerned, or you're concerned about your child having an allergic reaction that is worrisome to you, I'd rather you just give epinephrine. Who cares what that symptom is, because we know now that epinephrine, in the doses we use, is very safe.

Dr. Mariam Hanna

Perfect. And the reason for the timeliness of all these discussions obviously is to do with new routes of administration of epinephrine. We talked about needle has a barrier to usage, and for anybody that's considering allergy and immunology, they need to watch Pulp Fiction and understand what the reference is made specifically about because you will quote it, and so will the parents and the patients that are in the room of the appropriate age. But let's talk about the new nasal epinephrine and others coming down the pipeline here. What's available for data on their use to begin with?

Dr. Jay Lieberman

Obviously we've had intramuscular epinephrine for years, and that's both via auto-injector, which is the one we give to patients, and then syringe and needle. Those two routes do have different pharmacokinetics. The syringe and needle gets into the blood a little slower and has a slower peak, whereas the auto-injector gets in pretty quickly, has a quick peak, and then tails off a little quicker than the syringe and needle.

Regulatory agencies, knowing that we have been using those for years, have used those almost as a standard of okay, the bar, the standard of care. And therefore, newer routes have had to say if we can mimic those routes, meaning bracket between those routes, then the regulatory

agencies have said that is good enough to lead to approval for the treatment of acute allergic reactions or anaphylaxis.

Newer routes have been studied for years. The first route being studied actually early on by Dr. Simons in Canada was the sublingual route, and that unfortunately never got to market. Other routes now being studied include intranasal, for which we now have approved products in North America, as well as sublingual via sublingual film, sublingual tablets, and other nasal preparations such as dry powders.

Dr. Mariam Hanna

Okay. And before we veer too far off, why is an auto-injector delivery faster or different than a needle and syringe? Does the nurse not push hard enough on the plunger, or what's the mechanics here? Walk me through that, please.

Dr. Jay Lieberman

One thing I do with my trainees and residents sometimes is I'll take an auto-injector and activate it in clinic on the sides of the auto-injector and just have it it is a very rapid injection. We used to say hold for like 10 seconds and now we say hold for 3 seconds. Honestly, that delivery is done within a second. It is very rapid, very powerful, and they've done pig models where they showed how deep it goes into the fascia. That's very different than just syringe and needle and a slower push, even if you push fast.

Dr. Mariam Hanna

Okay, so even if you push fast. And then I've also seen discussions about like you mentioned specifically with sting anaphylaxis, the response in terms of diastolic blood pressure for nasal versus intramuscular or with an auto-injector. Can we talk about that, because it is bracketed but one is different than the other?

Dr. Jay Lieberman

The bracketing is based on the pharmacokinetics, meaning just how much epinephrine gets into the bloodstream, is it comparable to the intramuscular routes that we currently have? Now, the pharmacodynamics is a little different in the sense of the regulatory agencies want to see it very similar or the same, it's not required bracketing.

And what we have found out, like you pointed out, is that at least in healthy volunteers, who are not having an allergic reaction, that the intramuscular route leads to almost a drop in diastolic in most patients on average. Where it will increase heart rate a little bit, increase systolic blood pressure a little bit, the diastolic goes down. The thought of that is that it's activating receptors in the muscle that leads to some vasodilation actually within the muscle itself, and that's what leads to the diastolic changes. It's unclear, but that's the theory.

Because intranasal doesn't get delivered to the muscle, what you see, and actually you see this with sublingual as well, you see actually an increase in diastolic with the non-injectable forms,

which theoretically is definitely something you would want to see from a product treating anaphylaxis.

Dr. Mariam Hanna

Okay. And at the time of our recording, sublingual is not approved, but the pharmacodynamic data is out there. How do those compare? Because now I'm going to be nasal versus sublingual, and how do those go neck and neck, please?

Dr. Jay Lieberman

We don't have obviously intranasal versus sublingual. The product that's farthest along is a sublingual film, and that pharmacokinetic and pharmacodynamic data, while not compared directly to intranasal, does look more similar to intranasal than intramuscular, in the sense of like you see that diastolic change similar to intranasal rather than intramuscular.

And so it's hard to compare, you're talking apples and oranges, but overall in my mind at least, I view the sublingual more similarly to the intranasal than the intramuscular.

Dr. Mariam Hanna

Okay. And could there be harm or danger in that slightly different pharmacodynamic? I mean, we're riding on decades of knowledge as to what happens to our patients acutely in anaphylaxis, and now we're going through some modeling in otherwise healthy individuals.

Dr. Jay Lieberman

That's a great question. Obviously, we don't know the answer to that. It depends on who you ask, to be honest with you. In my mind, I think there's no downside and we can talk about that in the sense of whatever you use is the best epinephrine, whatever you're willing to use.

But what we do know is the regulatory agencies, at least in America for the intranasal product, required a post-marketing study. And so they do have data that has been published in close to 1,000 individuals undergoing an allergic reaction in an allergist's office and getting the epinephrine intranasally, and the outcomes from that. And so far, the outcomes have been pretty similar honestly to auto-injector data as best we can tell.

Dr. Mariam Hanna

Okay. I don't want to put a negative slant on this, but listen, people die when they use epinephrine sometimes and it makes the news. Someone like me thinks the first death using a new route will stop everybody and say, "Did this work?" Can I get your thoughts on that, please?

Dr. Jay Lieberman

You are speaking my language. This is my concern as well because what we know from intramuscular epi, the way we've been using it, auto-injectors, there are still deaths even if they use it. In addition, about 10% or so need a second dose. It's not foolproof, it's not perfect. That

one study that I mentioned with the intranasal route had an almost exact same number needing a second dose.

So that's where I say so far at least it appears clinically we should see similar results. And I totally agree there unfortunately probably will be a death reported of somebody who had a reaction, used the intranasal product, and succumbed to the anaphylaxis. And I don't think we need to go crazy with that, investigate it, understand it, but it is likely to occur.

Dr. Mariam Hanna

And the hope with the new needle-free routes is that we change the rates of first-dose administration in the community. Has that happened? Will that happen?

Dr. Jay Lieberman

That's the million-dollar question. We don't have data of that yet that I'm aware of at least. Hopefully we will see some. It's hard to track because how do you know if they used it early, is it ED cohorts and did you have intranasal versus intramuscular and how likely were you to use it?

The reality is I just sit down with my patients as a clinician and I say, "Here's this, here's this device. Which are you or your kid more willing to use?" because I don't care beyond that right now. If you are willing to use it and use it quickly, that's what I want you to have. And so that's how I view it, and we'll see if data, as they come out, change that.

Dr. Mariam Hanna

And Dr. Lieberman, you and I live on different sides of the 49th parallel. We're not going to discuss politics on this episode whatsoever. However, I want to know how it's been going over the past couple years with nasal epinephrine. Have patients been ready to take it up? I mean, we've anticipated and projected what the mindset of the community will be and what the mindset of the prescriber will be. How's that playing out on your side?

Dr. Jay Lieberman

I can speak to my own practice. I offer it to any patient who is, it's on their formulary. It's not for example, it's not on some Medicaids near my states, and so it's not offered to those patients. But when I offer it, it's not 100% uptake. Some patients will say, "Look, I've seen my kid get better with the injectable. I feel just more comfortable using that until there's more data." And that's fine. I say, "Perfect, we're going to refill your auto-injector. No problem."

And then there's that group of patients that will just say, "Yes. Oh my god, do you think this works, doctor?" I say, "As best we know it's going to work," and they're quick to uptake it. I've had a few patients definitely use it in the field. Anecdotally, they have told me, "Wow, this was great. Worked quickly. I love it." I haven't had a failure yet in my hands, but that's a small sample size. So the uptake's been across the board. I think more favorable than not in my own personal hands, but it's definitely a spectrum.

Dr. Mariam Hanna

Okay. And let's talk about clinicians and challenges that we foresee for our clinicians when it comes to education, prescribing, and appropriate use. Is everybody going to be popping nasal epinephrine for their seasonal allergies now in Canada, or what are we going to expect here is going to happen, please?

Dr. Jay Lieberman

With the provider angle, there's definitely clinicians who are not willing to use it. They don't believe PK, PD data, they want to see more clinical data, and that's fine. There's nothing wrong with that, whatever they're comfortable with. So I do see that on the clinician side.

As far as use for other conditions, it's fascinating. Like I truly believe epinephrine in the doses we use is very safe, like I've said before. There are data coming out that it can treat, for example, acute urticaria, which is not surprising. Probably not going to be needed as an acute urticaria treatment in the future, but it could work. So it would work for all these other conditions probably. I don't think we'll get there in the real world, but yes, it could be used.

Dr. Mariam Hanna

And then the technical education about how to use this product. I've sat in some sessions where they're like, "And you don't squirt it in the air before squirting it in your nose, because there goes your dose." And then I keep visualizing how am I going to teach parents to headlock their child to administer a nasal dose. Can we talk about how you walk people through this education on how to use it? Again, I don't have it physically in my office to prescribe to patients yet, but I'm troubleshooting these issues in my mind, as you can see.

Dr. Jay Lieberman

Just kind of the logistics are it is a one-time use, there's no priming like you talked about. It's a pretty simple device. One good thing about the device is it's been used for other conditions such as opioid overdose. And it works in patients who are non-responsive. Someone else can just take it, put it in the nose, and it gets absorbed based on data from or extrapolation from opioid overdose, for example. So that's one good part about it.

Second good part about it is that it's pretty quick. You don't have to hold people down, but your point with the kids is very well taken. How are you going to hold them down? If the kid is that opposed to an intranasal device, then clearly you may want to discuss an intramuscular device. However, you get the same problem, holding that kid down. It's no different whether you have the auto-injector or the intranasal device. I do feel that when I present it to most families, they're happy to see it. They don't have any, "Oh my god, my kid will never do this," kind of thing.

Dr. Mariam Hanna

No, fair enough. And the only reason I ask is that sublingual epinephrine got stalled on the mechanics of opening the package. I'm like, "Oh boy, so what can go wrong with the nasal one?" is kind of where my mind went when that happened. Okay, we digress.

Dr. Jay Lieberman

Well, that's a good point. Along those lines, one feedback was some people have been concerned that it's too easy to activate. There's not a safety to block activation of it. So that's one feedback that I have gotten from clinicians and patients.

Dr. Mariam Hanna

No, fair enough. See, this was a productive comment. All right, good. How should allergists and other healthcare providers think about switching patients between epinephrine products? Is there going to be an avalanche of people at the allergist's door now that we have this new route available, or can this be discussions had with their primary care providers or at their next appointment?

Dr. Jay Lieberman

Typically in our world it's at the next appointment is how we've been doing it. Not many primary care providers in our area or in the US that I've heard of are really doing this and prescribing it.

For me personally, it's just a discussion, like I said. I show my patients the devices that are available for prescription and I say whichever one you or your child is willing to use is the one that I think we should pursue and then worry about cost and all that later. That comes into it, obviously, you can't deny that. But I want them to have what they will use, and whatever that is, I'm all for.

Dr. Mariam Hanna

Okay. What's on the horizon as we look in epinephrine? You said sublingual, you said powder potentially. Any other things on the horizon for epinephrine anaphylaxis management?

Dr. Jay Lieberman

Those alternate routes are probably the farthest along with the sublingual film being a little further than sublingual tablets, which are being studied as well. The other thing being discussed is like I talked about the dosing, or are we underdosing?

You said you had Dr. Paul Turner on before who did a really nice study in adolescents showing we're probably underdosing, meaning the 500-microgram dose is probably better than the 300 in most adolescents, and that doesn't even include obese adults, which we have a lot of in the United States. So the reality is is it worth looking at dosing again, which some people are thinking, and bringing at least the 500 microgram to the United States one day as a consideration. So that's the other consideration going on right now.

Dr. Mariam Hanna

Do you anticipate changes with more disease-modifying therapies like oral immunotherapy for food allergy? Are we going to tell our patients less and less use epinephrine and maybe just pop an antihistamine, but not that bad diphenhydramine one?

Dr. Jay Lieberman

I personally don't see that occurring. First of all, it's an amazing time to be in food allergy with all the revolutionary therapies going on right now. Most therapies continue to have an avoidance arm to the therapy. There are obviously some therapies where you get to free eating. But that's a minority I think of overall patients.

The second part of that is how confident do you ever feel that patient is no longer at risk for a life-threatening reaction? Can you ever feel confident enough to say, "Ah, you don't need your epinephrine." I think for the majority of patients, we're not going to get there for a while. So you'll still have epinephrine. I don't think it'll be a lot of patients not getting epinephrine who are on therapy.

Dr. Mariam Hanna

Fabulous. Thank you, Dr. Lieberman, for joining us on today's episode of The Allergist.

Dr. Jay Lieberman

Thank you very much. I appreciate it.