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. A child has to hear a word 500 times before they can start using it in everyday speech. I think that's how I feel about anaphylaxis and epinephrine. You have to explain it, walk someone through it, answer their questions on it before they're uncomfortably comfortable and start using it appropriately. After all, it is a needle. I think the same holds true for us physicians. You have to witness it, treat it, appreciate the variety in how it can present before you really truly get it. In fact, you'll hold onto a few of these stories as you go through your career. The child that was hypotensive and needed multiple doses of epinephrine, the time you hesitated, the one where the caregiver swung the autoinjector and the needle bent, or perhaps it's the terrified one that screamed at the prospect of needing to use epinephrine and curled up in the furthest corner of the room, hiding from everyone with their knees held closely to their chest in between sobs, coughs, and screams.

These days, the future of allergy management is exciting with treatments and studies showing up every week while we're detangling it. For some, we haven't yet had the magic wand that could prevent anaphylaxis or perhaps just get rid of that needle. Now this too could be changing, which is why it's finally time for us to really dig deep into this topic.

It's my absolute pleasure to introduce today's guest. Dr. Paul Turner is a pediatric allergist and clinical immunologist. He serves as a reader and honorary consultant at Imperial College London and clinical professor at the University of Sydney. His research focuses on the mechanisms of severe allergic reactions, particularly to food. Dr. Turner also leads the Food Allergy Desensitization Program at St. Mary's Hospital, London. In addition to his clinical research roles, Dr. Turner chairs the World Allergy Organization's Anaphylaxis Committee and advises on global allergen risk assessment initiatives. He's deeply involved in education and advocacy, driving projects like nationwide allergy action plans to improve the safety of children with life-threatening allergies. Dr. Turner, thanks for taking time to join us today, and welcome to the podcast.

Dr. Paul Turner:
Pleasure to be here.

Dr. Mariam Hanna:
Dr. Turner, we're going to start with the basics, and it's basic and not basic at the same time. We really need to kind of hammer out this definition of anaphylaxis. So for us, can you define anaphylaxis?

Dr. Paul Turner:
Not easily. That's the problem. And this is the whole problem. So we've a nice definition that we use in the UK where anaphylaxis is when there is a problem with the A, B, and C or A, B, or C, I should say: the airway problem, or a breathing problem, or a circulatory problem. And we call the C consciousness because people who aren't healthcare professionals understand

consciousness better than circulation. And it's when there's an allergic reaction happening that's causing a problem with an A, B, or C. And when we teach families and patients over here in the UK, we talk about an A, B, C issue, an air, breathing, or consciousness issue, and they seem to get that, but clearly, some people struggle with that and they need more precise terminology or criteria to consider whether something's anaphylaxis or not. And

Dr. Mariam Hanna:
What's unique about your way of describing it is that you're not talking about hives and lots of hives and many hives.

Dr. Paul Turner:
Yeah, well absolutely. I mean, the hives is a bit of a red herring, really a furphy, because we know that one in 10 really severe reactions, probably one in 10 deaths due to anaphylaxis, you don't get hives, you don't get the skin involvement. And certainly, the anaphylaxis reactions I see—and I see about five or six a week here in clinical practice—often the skin stuff comes after the breathing issues. And so actually, it's really key that people don't get bogged down on the skin stuff because sometimes you don't get the skin stuff.

Dr. Mariam Hanna:
So with that definition in mind, then, why is epinephrine used in the management of anaphylaxis?

Dr. Paul Turner:
So essentially what epi does is it counteracts a lot of the effects of these mediators at the level of the blood vessel. So through alpha-1-mediated vasoconstriction, it's against the vasodilatation that anaphylaxis mediators cause. Through beta-1 receptors, we think it has a positive effect on how forceful the heart pumps and how fast the heart pumps—so what we call positive inotropy and positive chronotropy. And so that puts up your cardiac output.

And at beta-2 receptors in the lungs and in the airways, it causes bronchodilation, counteracting the sort of asthma-type features of anaphylaxis. There are also these adrenal receptors on mast cells. So unlike any other drug, they actually help stabilize mast cell degranulation and stop it from occurring. So they can prevent progression in that way, which no other drug can do easily.

And that's why when someone's having anaphylaxis, it's all about using the first-line treatment, which is epinephrine, and everything else comes second because nothing else stops the reaction in its tracks, whereas the epinephrine will do so.

Now, things are a little bit more complicated here because we have good data from Europe, and I think most people would agree from the US now, that the majority of people, when they have anaphylaxis, they don't use their epinephrine. And so, for instance, there was a lovely study done in the UK where 80% of teenagers having anaphylaxis, they didn't use their EpiPens or other devices, they didn't do what they were meant to do, and they just came back and told us about it a year later.

And then if you look in the European Anaphylaxis Registry, which has probably more than 5,000 anaphylaxis reactions collected now, only about 14-15% of those receive epinephrine. And so these data tell us that 80% plus of people having anaphylaxis, they don't do what they're meant to do, but they get better anyway. So just like you and me, if we cut ourselves, we don't suddenly need to rush to hospital for sutures. You put a bit of pressure on it, maybe occasionally put a bit of an aster strip on it or a plaster on it, and that's all you need. And it's the same with anaphylaxis. The body tries to sort itself out. The body tries to make itself better. And we've seen that in the research that we've been doing. And our current theory is that just like some people can't clot their blood properly—we call them, they've got hemophilia—anaphylaxis, equivalence of hemophilia, some people can't sort themselves out when they have anaphylaxis, and they're the cases who end up getting stuck in intensive care or worse, even dying.

Dr. Mariam Hanna:
So some people can sort themselves out and that represents the majority, some cannot. They get much, much sicker and need additional support. So what data do we present or do we have for the use of epinephrine kind of very broadly, or at least the recommendation is to currently use it wherever you think there's anaphylaxis occurring. So what data is presented for that? Because that's the data that

Dr. Paul Turner:
Becomes, what do we know about it? Yeah.

Dr. Mariam Hanna:
Questioned when we're coming up with a new device or a new way of addressing this.

Dr. Paul Turner:
We don't need to complicate things. Epinephrine works. The problem we have is that sometimes some people need a hell of a lot of it, and they need more than you can give with just one or two doses through an autoinjector. And we know that there's a very narrow window for epinephrine use. And if you give too little, it doesn't do the job. If you give too much, it can kill you. We've had some tragic cases in the UK of people who actually—they weren't even having anaphylaxis, but they got misdiagnosed as having anaphylaxis, got given too much adrenaline, and they died because of the adrenaline overdose and not because of the allergic non-anaphylaxis reaction they were having. So adrenaline, you've got to use it safely. And the intramuscular route is very safe for sure, we know that.

But if you are having a really bad reaction, a couple of doses by an injection into a muscle isn't going to do it, and you need an infusion. And we've got some really good data from animal models using dogs where actually giving a very low-dose intravenous infusion of adrenaline, of epinephrine, works wonders, and it's much better than bolus dosing, whether it's bolus dosing by injection into a muscle or subcutaneously or even intravenous dosing down a cannula.

All those can have a very negative effect on the heart, whereas a low-dose continuous infusion works really well.

Dr. Mariam Hanna:
How quickly does epinephrine work intramuscularly if it's going to work?

Dr. Paul Turner:
It's a hard question. People get better on their own. And so this is one of the problems, for instance, with the new intranasal forms of epinephrine coming through that people sort of go, ah, look, people get better. But actually, eight out of 10 people will get better on their own without doing anything. There's good data to show that now. And so when someone turns around, for instance, the only study on intranasal epi that I've seen so far to look at clinical effectiveness, it was done in a Japanese center—15 kids having a food challenge, eight of them had, to my mind, anaphylaxis. And on the basis of 80% of them who would've gotten better anyway, we've got 1.2 Japanese children who have so far responded to intranasal epi.

And I'm not sure that's enough for me, for instance, to be able to turn around and go, yeah, let's all start prescribing intranasal epinephrine. We need more clinical data. If you look at how quickly it takes the epinephrine to get absorbed following an injection into the muscle, in most people it happens within five minutes or so. But actually, for some people, it can take 15 or 20 minutes for that to happen. And we don't always see a difference in response.

So there are some people I've got where they've taken 15 or 20 minutes to respond clinically, but they have quite high levels of epinephrine within five minutes when we've tested them. And we've seen the opposite as well. And that's why, at my end, I really don't think you can use how much epi is in the blood as a readout on whether you are a quick responder or slow responder, or whether you've had enough epinephrine or not enough epinephrine. You've got to be guided by the clinical consequences, the clinical effect.

Dr. Mariam Hanna:
So if clinical effect is so important, how does nasal epinephrine get approved? What data did they have to demonstrate to show effect, because these patients were not acutely undergoing anaphylaxis that tested?

Dr. Paul Turner:
Yeah, yeah. So the current forms of epinephrine, whether it's intranasal or sublingual, the companies developing these forms have been told by the regulators that if they can show a similar blood level as what you get with EpiPen, then they will get approved on the grounds of what we call bioequivalence. And it's bioequivalence of pharmacokinetic data—PK data—which basically means how much epi is in the blood.

And I'm okay with that if it's an injection, because we know how the injections work and EpiPen is an injection. And so if you are making a competitor device to EpiPen that's also an intramuscular injection or an injection into subcutaneous tissue, which essentially EpiPen would be in people with large BMI, then actually fair enough. But if you're studying a device that

administers epinephrine into the nose or sublingually or some other compartment, I don't think you can use that PK data.

We've shown in our study, funded by the UK government over in the UK, that the level of epi in the blood does not correlate very well to what your heart is doing. And sometimes, if you have too high level, it can actually cause something called negative tropy. So it can have an effect at inhibitory adrenal receptors, and it causes your stroke volume to go down, which is not a good idea if you're having anaphylaxis. We did a study where we had eight people having anaphylaxis due to peanuts, and these guys were completely barking mad in that they actually came back six or seven times to have anaphylaxis events with us over the course of a year or two.

And so eight of them had anaphylaxis on two occasions, and on one occasion we gave them epinephrine with a needle syringe, one dose, and the other occasion we just watched them to see if they would get better. And epinephrine, when we gave them epinephrine, it didn't make the heart pump any harder. It put up the heart rate, but it didn't make the heart pump harder, which is what you see in people not having anaphylaxis when they self-inject.

And so it raises the question of, well, does epinephrine have an inotropic effect in people having anaphylaxis? And more importantly, can we just jump with data on people who are not having anaphylaxis and say, well, clearly it's going to be the same when they are having anaphylaxis? And I think the answer is no. And that's why I think the bottom line is you've got to have the clinical data.

Dr. Mariam Hanna:
Lemme turn it a little bit around on you. Do you see a gap currently where eight out of the 10 patients that are undergoing anaphylaxis will not use anything? Do you see it as a gap? It's better than nothing, we would hope.

Dr. Paul Turner:
It's a hard one. And so it is trying to get the message out there that any A, B, C involvement, any A, B, C feature that might be caused by a food allergen or a venom sting or something—that's anaphylaxis. If you wait until you are blue in the lips and you are choking and you can't breathe, you've got a high chance that you might not make it.

And so it's trying to get these people to understand that they don't need to be scared of using epi and getting these people to understand when to use it at the first sign of anaphylaxis. Don't wait until you're irrecoverable. And I'd love to turn around one day and say, use your intranasal device or take a sublingual tablet or puff or whatever it may be. But we're not there.

Dr. Mariam Hanna:
You're not there.

Dr. Paul Turner:
Not yet there.

Dr. Mariam Hanna:
Okay. Are there absolute populations that should not be used in the context of shared decision-making? Paul, we may present these options to patients. Are there patients where you're like, absolutely no, these should not be offered a needle-free, something that we have less experience and kept?

Dr. Paul Turner:
I don't think so. I mean, I really hope these needle-free options work well, and they should work well. It looks like these companies have overcome the local vasoconstrictor effects of epinephrine so that there is absorption and it's not just the blood vessels going and closing off so that nothing gets in. And you see that clearly from the PK data, the pharmacokinetics data that they've generated.

But you've got to know it's going to work. Got to. We need the data, we need proof of clinical effect. And until we've got that, as far as I'm concerned, all these other forms are just going to be like an antihistamine. If you really need it, don't use it. I want you to know that you are getting the stuff that you really do need, which is intramuscular in the first instance. And if you don't really need it, then fine, take it. Certainly not going to do any harm.

Dr. Mariam Hanna:
Do you think that the needle will swing the opposite end and say, at some point, we need to be concerned about safety because of overuse or abuse of epinephrine? If it's so easy to give a spray?

Dr. Paul Turner:
I think we need to be concerned about people going, that hasn't worked. Use another dose, use another dose, use another dose, and they've got 10 doses, and actually they're not. If it doesn't work with the first dose or second dose, then what's next down the line? Likewise, at my end, I dunno what I would do if I'm using intranasal epi in someone and I've given two doses and they're not better. Do I switch over to IM or should I switch 'em over to an IV low-dose infusion?

We still need to work that out, and we can't work that out until we've got some clinical experience with this. And that's why we really need the studies now to help guide us on when to call it, when to switch route. Are we going to go from intranasal to IM, or are we going to go from intranasal straight to low-dose IV infusion? We just need that clinical data.

And I was really surprised when the FDA's advisory committee turned around and said, it's not ethical to get that data. We do hundreds and thousands of food challenges every single day across the world. I can't think of anywhere more ethical or safer than when our kids are having allergic reactions in hospital under expert supervision. We look to see if the intranasal works or not.

And I would argue it's actually not ethical to prescribe these alternative routes of epinephrine until we know that they are safe and effective. They certainly seem to be safe from the studies. They're safe in people not having anaphylaxis, but do they work? And that's what we really need to know.

Dr. Mariam Hanna:
And close on the heels of nasal epinephrine, sublingual epinephrine is likely to come. What are your thoughts on this now? Pandora's box is like being jammed right open with multiple options. Are we going to see the same kind of PK data being presented in otherwise well individuals?

Dr. Paul Turner:
Well, we already are, and I think the FDA's got it wrong. We've just published in *JACI,* our big journal of allergy and clinical immunology, a rebuttal that actually the regulators have got it wrong. You can't use this PK equivalence as the basis for approval. It's a bit of a Pandora's box because the data's not really there for EpiPen.

I guess maybe they're worried that if they open it and say no, we need evidence of clinical efficacy, they might turn around and go, well, where's the evidence of clinical efficacy for EpiPen? Now, I don't think that's what we're trying to push for at the beginning, to say, show me that. Then we can argue. I think we've seen enough patients get better from EpiPen, particularly those of us who do research where we watch 'em have reactions as opposed to just seeing them when they pitch up to emergency, to know that EpiPens and other similar autoinjectors can work.

We know that, but we also know they don't always work. One in three deaths that we have in the UK due to food anaphylaxis—these people administer their autoinjectors correctly in a timely manner, yet they still end up dying. And it's because if you are having a really bad anaphylaxis reaction, you need more than one or two drops. It's a drop in the ocean, and you need an ocean of epinephrine given safely with a lot of fluids to help stabilize the circulation, to volume, so that epinephrine can sort of circulate around the body to where it's needed.

And so I think it would be absolutely indefensible as an allergist, if I was asked to represent or give an expert opinion on an allergist who had changed his patient or her patient over to intranasal or sublingual at the moment and said, you don't need your injectors anymore. I think it would be impossible to defend if a patient then died of anaphylaxis in the community. It may have been they would've died even if they had their autoinjectors because, as I said, one in three die despite that. But I think it would be indefensible because there's no efficacy data other than these 1.2 Japanese children, and I'm not prescribing my patients something that's only been shown to work in 1.2 children.

Dr. Mariam Hanna:
A stern warning. Okay, switching it up on you for a second. Can the use of epinephrine

prophylactically prevent an allergic reaction? I think what I'm thinking of is the thought of overuse or abuse due to ease of use. Can I just use it and go to the party and not worry?

Dr. Paul Turner:
Yeah, yeah, absolutely. So there's no data that prophylactic epinephrine, at least by injection, helps. There's at least one case report in the literature of someone who used their EpiPen for a non-anaphylaxis reaction who then went on to die of anaphylaxis about 40 minutes later. So it certainly doesn't always work, particularly IM like a bolus.

The reason that I'm being a bit cautious with my words is that I'm now aware of some people in specialist centers, when they have a patient who is at risk of anaphylaxis to chemotherapy or biologicals, something like that, and they don't have a choice, they actually are now doing immunotherapy or giving the chemotherapy under cover of a low-dose epinephrine infusion very carefully. And that seems to work.

One of the interesting things that I've discussed with colleagues, both this side of the pond and your side of the pond, is there's a tendency to use epinephrine earlier in the USA and Canada. And we've seen that in particular with the studies about PALFORZIA, the product for peanut immunotherapy, because most of those clinical trials were done both in America and also outside America. And we've looked at that data and absolutely there's more epinephrine use in the States than there is outside in Europe, but we're not seeing a favorable safety signal.

We're not seeing less severe anaphylaxis happening. We are not seeing any changes in morbidity or hospitalizations after food challenge or delayed discharge after food challenge or so on and so forth. So I think the bottom line is it's getting the balance right, isn't it? I would rather people overuse than underuse for sure, but at the same time, I don't want people to think they need to use EPI for every single reaction they're possibly having, irrespective of whether it's anaphylaxis, because then we're over-medicalizing a condition.

And particularly if that medicine is associated with fear of use because it's an injection, then we are giving the impression that a diagnosis of food allergy is worse than a life sentence. Life sentence—you serve life, but then you get released afterwards. Whereas food allergy—you've got it the whole of your life. Life means life. And we've got to help these people live with their food allergies safely.

And we don't want people to be thinking that every single time they get that itchy mouth, where they think they've eaten something they're allergic to, that it's going to progress. And then if they don't use their autoinjector, they're going to end up, if they're lucky, in intensive care with a tube down their throat. We've got to make sure people use epinephrine when they need to, but we've also got to be very clear about when they don't need to because I think that's the way to increase appropriate, safe use of epinephrine.

And I think we are getting there. The data that we've looked at shows that in the USA, in Spain, in the UK, even in Australia, where apparently you've got this epidemic happening, the death rate from food anaphylaxis is going down. So we are improving things. We are. It's a very rare outcome, and it's becoming rarer over the last 20 years. But we've got to understand how to continue that trend. What is it that we're doing that seems to be working, and try and focus on that to make life even better for people affected by severe allergies.

Dr. Mariam Hanna:
Alright. Alright. Now that is a good ending. Time to wrap up and ask today's allergist, Dr. Paul Turner, for his top three key messages to impart to patients and physicians on today's topic, epinephrine/adrenaline. Dr. Turner, over to you.

Dr. Paul Turner:
I think the first one is that epinephrine can work really well. It's just sometimes you need lots of it. So if you think you've got an A, B, C symptom or feature, here's your epi. If two doses don't do the trick, you need to make sure an ambulance is on the way. These are the people who need to be rushed to hospital and in hospital rapidly get an IV epinephrine infusion.

At the moment, I just don't think we've got any evidence that these alternatives to intramuscular injection in the community setting are effective. And I'm not going to be prescribing any of them until there's good data to show that they work in people having allergic reactions.

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

Dr. Paul Turner:
It's been a pleasure.

Dr. Mariam Hanna:
This podcast is produced by the Canadian Society of Allergy and Clinical Immunology. *The Allergist* is produced for CSACI by PodCraft Productions. The views expressed by our guests are theirs alone and do not necessarily reflect the views of the Canadian Society.

This podcast is not intended to provide any individual medical advice to our listeners. Please visit www.csaci.ca for show notes and any pertinent links from today's conversation. The *Find an Allergist* app on the website is a useful tool to locate an allergist in your area.

If you like the show, please give us a five-star rating and leave a comment wherever you download your podcast and share it with your networks, because we've got to get teaching on the A's, B's, and C's. Thank you for listening.

Sincerely, *The Allergist.*