



Dr. Stukus: Hello, and welcome to Conversations from the World of Allergy, a podcast produced by the American Academy of Allergy, Asthma & Immunology. I'm your host Dave Stukus. I am a board certified allergist and immunologist and serve as the social media medical editor for the Academy. Our podcast series will use different formats to interview thought leaders from the world of allergy and immunology. This podcast is not intended to provide any individual medical advice to our listeners. We do hope that our conversations provide evidence based information. Any questions pertaining to one's own health should always be discussed with their personal physician. The Find an Allergist <http://allergist.aaaai.org/find/> search engine on the academy website is a useful tool to locate a listing of board certified allergists in your area. Finally, use of this audio program is subject to the American Academy of Allergy, Asthma & Immunology terms of use agreement which you can find at www.aaaai.org. Today's edition of our Conversations from the World of Allergy podcast series has been accredited for continuing medical education credit. The American Academy of Allergy, Asthma & Immunology is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Information about credit claiming for this and other episodes can be found at <https://education.aaaai.org/podcasts/podcasts>. Credit claiming will be available for one year from the episode's original release date. Today we are very pleased to welcome Dr. Lieberman who is an associate professor of internal medicine at the University of Tennessee Health Science Center in the Bonheur Children's Hospital in Memphis, Tennessee. Dr. Lieberman has had a very accomplished and productive research and academic career focused on food allergy and anaphylaxis. He is a current member of the Joint Task Force for Practice Parameters, a coauthor of the most recent 2015 anaphylaxis practice parameter update, and an associate editor for the Annals of Allergy, Asthma, and Immunology. Today Dr. Lieberman has joined us and will be discussing anaphylaxis which is a very important topic not only for allergists and their patients but for medical professionals across all disciplines. I personally have nothing to disclose, and Dr. Lieberman discloses relationships with Kaleo and Aquestive Therapeutics, and their materials, products, relating to epinephrine. Dr. Lieberman thank you so much for taking the time to join us, and welcome to the show.

Dr. Lieberman: Thanks a lot Dr. Stukus, and thanks for having me.

Dr. Stukus: Oh, it's our pleasure. So this is going to be a great conversation. I know there's a lot of questions surrounding anaphylaxis, but let's just start with the actual term anaphylaxis which can be really confusing for both patients as well as medical professionals. Can you tell us what this term actually means?

Dr. Lieberman: Yeah. I can understand the confusion. It's confusing even for specialists within anaphylaxis. So I think to understand it a little bit we do have to go a little bit into the history. I hope it doesn't bore the listener too much, but we have to understand where the term came from, and it was initially coined by Paul Portier and Charles Richet when they were studying toxin from the sea anemone

and trying to develop an antidote, and what they found is instead of developing an antidote they made the dogs they were studying more responsive to the toxin, they made them hyperresponsive, and so what they coined is a term instead of developing prophylaxis or protection to the toxin they developed something they called anaphylaxis, and so that was the first time that term was actually used, anaphylaxis the opposite of prophylaxis or protection, and that was in the early 1900s. So since then the term has been used to kind of describe various forms of a hypersensitivity reaction, and therein somewhat lies the problem of not understanding what it is because we don't have a very, very specific definition for anaphylaxis. So over the past hundred years the term has been altered and changed depending on kind of consensus definitions or criteria, and it remains today still a clinical diagnosis. So the definition is different depending on the society or the group of experts that makes the definition. In its easiest form most people would describe it as an acute allergic or hypersensitivity reaction that can be serious and can lead to death, and that is a catchall term, but it's probably the easiest way to describe it.

Dr. Stukus: Oh, well that's really fascinating. So it sounds-- and it's really interesting to hear you describe how sort of this vague, catchall term, and it can be applied however you like, and I think we'll get into some of the clinical criteria very soon, but let's go back to something you mentioned because you mentioned that it can be life threatening or cause death. There's a lot of people out there that really equate this word anaphylaxis meaning you're going to die, but is that true, and are there different severities of anaphylaxis?

Dr. Lieberman: Yes. There's definitely different severities, and usually I think you're right, when people think anaphylaxis they think oh my gosh if I have anaphylaxis I can die, and while that's true it's not that common, and there are different grades of it like you say. The problem is there's not one accepted criteria or grading system throughout a single country or even through the world, so there's various grading systems, and usually the experts who come up with the grading systems develop either a five stage or a three stage grading system with one being a mild reaction, sometimes that can be a local severe or systemic allergic reaction but it may only involve one organ system for example like hives and swelling due to an allergen may be a stage one anaphylaxis in some criteria where others would require two organ systems to be truly an anaphylaxis event, but no matter which one you look at they all have the similar idea of stage one being a more mild form of anaphylaxis, and the higher the stage whether it be a three stage or a five stage grading system, three or five stage would be a much more severe reaction and some would include death as the final stage.

Dr. Stukus: And so it sounds like in general terms if anybody were to use the term anaphylaxis or to do it as a diagnosis that you really can't apply that same degree of severity from one person to the next. Does that sound fair?

Dr. Lieberman: Oh, I would completely agree with that, and it just further adds to all the confusion.

Dr. Stukus: Yeah. No, absolutely. Now you mentioned some of the specific symptoms. Can you take some time and actually describe for us the symptoms that are occurring during anaphylaxis and kind of what's happening inside the body that's causing those symptoms, and then after that I'll pick your brain about the signals and mediators that are involved as well.

Dr. Lieberman: Yeah. Absolutely. So clearly no matter which kind of cohort of anaphylaxis you look at, the most common finding or symptom or sign of anaphylaxis is going to involve the skin, and typically that's going to be described as hives or in medical terminology as urticaria, and that is often associated with swelling or angioedema. So hives and swelling are clearly the most common well presenting finding of anaphylaxis, and then come the other findings, and they can be in really almost any organ system to be honest, the other common ones being gastrointestinal, and unfortunately there's not one finding that's always involved. You can have vomiting, you can have severe abdominal pain or cramping, you can have diarrhea. Then there's the respiratory system and that can be starting from the upper respiratory so runny nose, congestion, like any type of an allergic finding that you would expect to see even with pollen for example, down to the lower airways to wheezing, bronchoconstriction, and the swelling can involve the airways as well which can be scary to some patients. The other organ systems would be the cardiovascular system, so at its utmost form anaphylaxis leads to shock, and it's pretty much the quintessential distributive shock meaning you have overt hypotension, leaking of the vessels and capillaries so that you can't maintain blood pressure, and so it really can lead to protean manifestations throughout the entire body.

Dr. Stukus: Yeah. That's really fascinating that this one condition can encompass so many different organ systems. So why is that? What are some of the chemicals and mediators that are impacting these different organ systems and how does that sort of work on a cellular level?

Dr. Lieberman: Yeah. So I think we know at least some of the mediators and some of the pathways, and the most well described and understood pathway with an anaphylaxis involves mast cells and basal cells, and in its most classic form that would be IGE mediated, so meaning there is an allergen out there such as a food protein, a protein within venom from a flying insect for example, or a medication that will in a susceptible personal it will bind these allergic antibodies, these IGE antibodies that can be sitting on mast cells or basal cells, and when that happens the mast cells and basal cells get excited. They will release numerous contents, and the one that's pretty much the most well described and studied is histamine, and so histamine has various effects throughout the body, and it's easiest to think about it as the mediator because we know a lot of its effects such as a blood vessel's vasodilation leading to the swelling can lead to the hypotension in its most severe form, and the lungs histamine can lead to bronchoconstriction which leads to wheezing and difficulty breathing, and the GI system histamine can lead to contraction of smooth muscle and therefore the cramping or abdominal pain or vomiting or diarrhea that can occur with it. It's not so simple as histamine's the only mediator and that's going to explain everything within anaphylaxis although it's a good model to explain a lot of the findings. There are clearly various other mediators both within mast and basal cells, and outside of mast cells and basal cells. So for example outside of them we know there's activation of the complement pathway as well as activation of the kinin and kininogen pathway, the contact system. So there are various other aspects of the immune system being activated although the mast cell basal cell kind of model and picture is probably the most well understood to and the easiest to under-- both well researched and the most easy to understand.

Dr. Stukus: Now I like how you describe that these mast cells and basal cells kind of get excited especially if it's an IGE or allergic reaction that causes them to unload their contents. Can you give us a

sense of like timing of onset? So if somebody has a food allergy and they accidentally eat their food will those same cells get excited a day or two later, or is this going to happen much more rapidly?

Dr. Lieberman: Yeah. What a great question, and so most of what we know suggests that using that pathway, the IGE mediated pathway, it's kind of known in immunology as the immediate type hypersensitive, and immediate type typically meaning seconds and minutes up to hours. So whether would happen in a classic reaction would be if the food is ingested the symptoms will typically occur if it's a local symptom such as itching in the mouth within seconds to minutes, if the food then gets digested and has to travel to other parts of the body you would see that in minutes to maybe up to an hour or two, but with other forms of anaphylaxis it could be even quicker. So for example if you're stung that is injected directly into the body so the reaction may even occur even quicker than up to an hour. There's one kind of well quoted study that looked anaphylaxis and the time to onset of severe symptoms, and it was quickest for iatrogenic or medication induced, or if it was for example an allergy shot given that caused the reaction, that was the quickest and that was within minutes, and then venom was next within 15 to 20 minutes, and then foods a little longer, 30 to 45 minutes to the onset of the severe symptoms.

Dr. Stukus: So people really need to focus on a timeframe within hours not days.

Dr. Lieberman: Yes, and I tell all my patients it's if you're experiencing for example hives and it's a day later it's very rarely going to be the allergen or anaphylactic event. The only caveat to that I would say is we do know there is something called biphasic anaphylaxis so that's where you would have the initial reaction which is severe and the symptoms completely resolve with treatment, and then they come back hours to even a day later, so it would be a recurrence of that one time event. That's pretty rare as far as anaphylactic events go, but that would be the only caveat to if you have symptoms a day later probably is not going to be anaphylaxis.

Dr. Stukus: Got you. So you mentioned this biphasic occurrence where you have anaphylaxis, it resolves and comes back again as a pretty rare phenomenon, but how about anaphylaxis in general. Is this something that is pretty common, and can it effect anybody of any age, children, and adults?

Dr. Lieberman: Definitely can affect anyone of any age. There's study that tried to pinpoint how prevalent it is. I usually quote that if you live in the United States or North America a lifetime prevalence of probably somewhere between one or two percent. So one in 50 to one in 100 people who are born in the North America probably will experience anaphylaxis sometime within their life.

Dr. Stukus: Wow. Is there any way to identify those people as soon as they're born so that they can kind of be on the lookout?

Dr. Lieberman: I wish. If I could develop that man I'd probably be a rich man.

Dr. Stukus: Yeah. We'll have you back on if you ever do.

Dr. Lieberman: Exactly.

Dr. Stukus: You already mentioned some of them, but I'd love to have you kind of summarize and recap about the most common causes of anaphylaxis because I think there's a lot of misconceptions from both medical professionals and patients as well. So what do people need to be aware of?

Dr. Lieberman: Yeah. So common causes of anaphylaxis and the most common cause of it you would see would be foods, drugs, and insects such as venoms from a fire ant or a wasp or a yellow jacket for example. Now it does depend on your age group, and this is true whether you live in Europe or North America, that children who experience anaphylaxis almost it's always going to be due to a food, and that the younger they are that becomes almost a hundred percent. So if you look at case series or cohorts of anaphylaxis whether it be Europe or North America, and you look at children under the two years of age, almost a hundred percent of causes are do to food, almost. Now as people get older, adolescence you start introducing other causes such as venom, such as medications, and interestingly in the adult and geriatric population foods go way down as causes and usually the most common cause if identified is a drug. Now in adults also in many case series the most common cause is not identified, so we call it idiopathic, and when I'm talking to patients I use the idea saying we're idiots and that's why we call it idiopathic because we can't figure out what the cause is, but idiopathic anaphylaxis is definitely a common cause amongst older adults and geriatric population.

Dr. Stukus: Now if I may kind of these are some big sort of areas, do all foods cause anaphylaxis or are there select foods that are more likely going to call anaphylaxis.

Dr. Lieberman: Yeah. There's definitely select foods. There's some geographic variance in the foods depending on where you live and which foods are common, but clearly we know that in younger infants milk, egg, nuts-- including peanut-- seafood are common triggers. In some younger infants soy and wheat are also included. So the classic what we call the big eight allergens, and that's somewhat based on cases of anaphylaxis, what are the common triggers, and also what are common foods as well, and then now it's important because in our country the FDA has required labeling of the big eight allergens in food products so those would be the milk, egg, wheat, soy, peanut, tree nut, fish, and shellfish, and so that would be the most common triggers. Sesame is another one that's starting to be more common and we're seeing more in North America especially, and so those would be the major food allergens. So for example when a patient comes to me and they're telling me my kid has allergic reactions to red dye, I'll typically say, "That's probably not going to be a true allergy," but I'm more likely to entertain the idea that if the kid reacts to peanut or cashew it's going to be more likely to be a true trigger rather than some very rare food such as like I say red dye is a common one that gets brought up to me and then-- sorry-- with the insects it would be things like yellow jacket, bee, wasp, and then if you live in the right part of the country fire ants.

Dr. Stukus: Okay. So we're not really talking about like mosquitoes or spiders or things like that.

Dr. Lieberman: Yeah. So very rarely is it described that mosquitoes or spiders lead to anaphylaxis, and I often have to tell patients that it's a common response to develop itching, swelling, etc., from mosquito bites, it's very, very, very uncommon to develop a systemic or severe or life-threatening type of allergy to that.

Dr. Stukus: Oh, great. And then with medications or-- I mean this is a broad range of different things we're talking about-- or is it more antibiotics or is it more people who are undergoing surgeries? Can you comment more on that?

Dr. Lieberman: Yeah. So exactly, those are probably two of the largest groups of medications that are implicated in anaphylaxis. So on the inpatient side it's around the time of surgery, and so there a lot of anesthetic agents that are associated with anaphylaxis in that setting. On the outpatient setting we see referrals and cases and cohorts described of anaphylaxis more commonly to antibiotics. Now that being said, any medication pretty much can cause anaphylaxis but those would be the two larger groups that you see more often.

Dr. Stukus: Okay. Now that you've described some of the more common causes, can you also comment on routes of exposure in regards to triggering anaphylaxis and likelihoods? There's always a lot of concern of if you have an allergy to a food or medication or say a venom or something like that just being in the same room or inhaling it, is that the same risk, or rubbing on the skin, is it's actually injected in the body or eaten?

Dr. Lieberman: Yeah. We see it all the time, and so the idea, the science is is you have to have the protein interact with the body. So we think at least as best we know the protein has to interact with that IGE antibody, the allergic antibody, to lead to all the downstream events. So when we think of the protein it's hard for most proteins to be aerosolized, so meaning if I open up that bag of peanuts and I try to detect peanut protein in the air there's very, very little, and if there's any it settles on the ground very quickly because the protein just falls to the ground. So true anaphylactic reactions to aerosolized proteins in the form of foods is pretty rare, but the route of exposure can be anything theoretically as long as the protein is exposed to the body, and the way it's exposed may-- as we talked about earlier-- may lead to how severe or quickly the symptoms will onset. So if I take peanut protein in a peanut allergic patient, and I would never do this, but if I injected it I.V. into somebody that would lead to a very quick, very severe reaction obviously. So it's the protein that matters. It's just very rare for food proteins to be aerosolized in everyday regular activities.

Dr. Stukus: Okay. That's great. And the same thing with like medications? Do we have the same risk from all the medications that we can rub on the skin for various reasons, is that the same risk as if it were injected or ingested?

Dr. Lieberman: Yeah. It's pretty rare for topical medications to lead to a systemic reaction. It would have to be a breakdown in the skin to allow that molecule to be able to be exposed in high enough amounts to lead to that severe reaction.

Dr. Stukus: Okay. Great. Yeah, you've done a fantastic job of really breaking down the common causes of anaphylaxis as well as what's going on inside the body. What do we know in regards to the recognition from medical professionals? Is this something that emergency room physicians or emergency responders recognize very easily, or does this seem to be misdiagnosed on a regular basis?

Dr. Lieberman: I think it's been a constant trouble and effort to try to improve recognition of anaphylaxis, and there's been various criteria to establish to try to help say anaphylaxis may be present or is likely to be present if there are various scenarios or clinical criteria, and with the idea being that if these are there it's reasonable to treat this case as anaphylaxis. It's very hard on the frontline for emergency room doctors also who see a lot of people coming in, and for example if they come in just with hives and swelling it's very hard right at that moment for the emergency room doctor to try to figure out is this anaphylaxis and therefore is this life threatening and do I need to treat this aggressively, or is this typical hives and swelling and it's not going to progress. So it's very hard for them. Now the clinical criteria that was established in the United States from the National Institutes of Allergy and Infectious Disease use clinical criteria to try to say if these are present anaphylaxis is probably there, and those criteria are pretty good at saying if they're present anaphylaxis may be there, but those criteria are not perfect because if those criteria are met very often it may be something else. So it's not ideal unfortunately.

Dr. Stukus: Now do you have any tips on, you know, what do you tell patients or other providers when you're providing education? Is there some easy way to distinguish or err on the side of caution?

Dr. Lieberman: Yeah. So I personally say there are two main things obviously is if you know you're at risk for anaphylaxis because you have an allergy to X, Y or Z, the obvious thing to say is avoid it, don't get into situations if possible where you'll have the event. Now sometimes that is not possible or you don't even know the cause, in which case I say if the symptoms are concerning to you at all and you're worried then err on the side of caution like you were saying and treat it, and that would get into the treatment that I think we'll talk about, but obviously the treatment is-- first line treatment is epinephrine. So I always say err on the side of caution, treat it as anaphylaxis and in the worst case scenario you've over treated but there's very little downside to that.

Dr. Stukus: And have you actually seen patients have anaphylaxis with your own eyes?

Dr. Lieberman: Absolutely. And it can be frightening when it's a severe case.

Dr. Stukus: And in your experience does it tend to be the same sort of situation with every patient or have you found that it's highly variable based upon a whole bunch of factors?

Dr. Lieberman: Highly variable, and some patients they're feeling fine and then two minutes later they are covered in hives and they're having trouble breathing and they look a little shaky and diaphoretic, and you can tell that in just in the general sense well something is wrong going on here, and then some patients will have a little slower progression, they'll have a few hives develop and then they may vomit and then they say they're feeling bad, and so it's a little slower, but all of them, you know, and you take it all into account we need to be a little bit probably even for myself be a little more aggressive in managing it and probably not waiting for it to get to the next step.

Dr. Stukus: Now I think that speaks volumes that somebody as experienced as yourself and, you know, you witness this, and you understand this better than anybody and yet it's so highly variable of what you're seeing. I understand why it's a daunting thing for people to diagnose clinically. Now you talked

about the clinical criteria, but is there an easy test that anybody can order? Is there a blood test or any other diagnostic tests that can prove that this is anaphylaxis either while it's happening or after the fact?

Dr. Lieberman: Yeah. So this is kind of in some ways the holy grail for anaphylaxis. We don't have a good diagnostic test, right? I think in a perfect world we'd have a point of care test that you can run and get back within a minute or two and to say, "This is an allergic reaction that could be severe or could be life threatening, and we need to treat it as such." So the most common test people will use is something called a serum tryptase. This is something that is released from mast cells and will increase in the bloodstream during allergic reactions. The problem is it's not always elevated in patients having allergic reactions. Dogma says that it's not going to be elevated in cases for example of food induced anaphylaxis. It doesn't increase in the bloodstream right away, it takes on average 60 to 90 minutes to reach its peak and to be highly elevated. The other problem is it can be elevated in patients but not above kind of the lab cutoff of an elevated level. So most labs use an elevated level for example of 11.4, but you can have a patient with a baseline of 2 and if they go from 2 to 10 that's probably clinically relevant, but if you just use the standard marker of what's elevated based on the labs it would say that it's not elevated. So a serum tryptase is a thing we often tell patients to say if you present with symptoms of anaphylaxis at the emergency room it may be we're checking while if possible and I'll often give patients a prescription to say please draw a serum tryptase if I present with symptoms that it's concerning for anaphylaxis, and I'll compare that to their baseline when they're not having symptoms to see if do I believe that this is a mast cell mediated event, but it's not an ideal test unfortunately.

Dr. Stukus: Is there some timeframe in which the tryptase is more accurate as opposed to not accurate?

Dr. Lieberman: Yeah. Probably in most series when you actually measure it from the time of onset, probably starts to rise above elevated levels at about 30 minutes, peaks around 90 minutes, and then is gone 120 to maybe 150 minutes after that in most patients. So it's definitely time sensitive which makes it even harder.

Dr. Stukus: Sure. So not very helpful if you're seeing somebody the next day or a week later.

Dr. Lieberman: No, but I'll tell you, you know, there's always cases that may be different, so I tell trainees and other physicians that it's worth checking, because I've checked in a patient a day later and was off the charts a day after the initial presentation because it can be helpful even 24 hours later. I just would not expect it to be elevated.

Dr. Stukus: Okay. And you spent a lot of time talking about how histamine is a major player in a lot of what's going on throughout the body during anaphylaxis. Is that something we can easily measure?

Dr. Lieberman: Histamine peaks sooner, so maybe 20 to 30 minutes after the incident. It's a little harder to measure as well. So it becomes clinically less relevant or clinically less-- it's harder to measure and use as a marker. Some people have reported the use of a 24 hour urine histamine metabolite so you can measure a histamine metabolite in the urine, but you'd have to collect that over 24 hours and then

measure. So I don't find that personally clinically helpful most of the time although it can be measure, just not typically used.

Dr.Stukus: Oh. Got you. Okay. Now let's go back to a really important concept that you introduced previously. Tell us how should we be treating anaphylaxis?

Dr. Lieberman: Yeah. So treatment in every guideline no matter where you live or when it was published is going to be the same. First line treatment is epinephrine, and it's mainly the only therapy. All other therapies are adjuvant therapies. So we always counsel patients to say if you're at risk you need to have epinephrine available in some form, and unfortunately as of right now the only way we can deliver epinephrine is parenterally or through, you know, we have to inject it. So typically we inject it into the muscle. So we recommend intramuscular injection of epinephrine, and to repeat that if the symptoms are not improved, and it can be repeated in five minutes or ten minutes. It doesn't really matter. There's no contraindication to delivering epinephrine I.M., and we're using doses that are much lower than what we use for, for example, you know, CPR and resuscitation. So I always just make sure patients understand that that the therapy is in epinephrine, there's no downside to using it. If after using the epinephrine you want to treat with antihistamines that's fine, but that is not the primary treatment for anaphylaxis.

Dr.Stukus: What about steroids?

Dr. Lieberman: Steroids once again are also not the primary treatment. There will be, you know, this has been looked at in various reviews, and there doesn't seem to be any therapeutic benefit to steroids. That being said, I know how medicine is practiced and I can't deny that if I were in the emergency room and someone comes in looking like they're in anaphylaxis the idea of throwing the kitchen sink at them seems very appealing. So they're often used but there's very little evidence to say they have any role in treatment of anaphylaxis.

Dr.Stukus: Now does it matter what the trigger is for anaphylaxis in regards to epinephrine? Like does it work better if it's caused by venom versus food or anything like that?

Dr. Lieberman: Yeah. We don't know that for sure to be honest with you. There are some case series looking at for example patients who died due to their anaphylaxis, and one of the things about them is when, for example, in some of the case series when they looked at patients who died of food induced anaphylaxis there was some suggestion that asthma was a risk factor and bronchoconstriction led to the fatality and therefore treatment with a short-acting beta agonist or a bronchodilator may be beneficial to do in addition to the epinephrine, but there's no-- we don't know if epinephrine works better in one cause of anaphylaxis versus the other.

Dr.Stukus: So always better just to use it regardless, correct?

Dr. Lieberman: Absolutely.

Dr. Stukus: And can you tell us why it's so effective? What's special about epinephrine compared to antihistamines or steroids or things like that in regards to anaphylaxis?

Dr. Lieberman: Yeah. So the way I tell it to patients is epinephrine is essentially a natural hormone, right? So it's a shot of adrenaline, and I tell my patients especially younger ones that feeling you get before a big game or before a big test that you are having probably an increase, a release of adrenaline or epinephrine. What it does is it counteracts all the negative effects that we think are harmful with anaphylaxis meaning so if bronchoconstriction is one of the major causes of death with anaphylaxis epinephrine reverses that bronchoconstriction. It bronchodilates, and actually used to be used in asthma. So epinephrine it counteracts the vasodilation or the drop in blood pressure, it constricts blood vessels, so it counteracts that part of it. It increases the heart rate and how hard the heart is beating, so it increases circulation. So it really counteracts all of the life threatening aspects of anaphylaxis.

Dr. Stukus: How fast does it work?

Dr. Lieberman: Onset is within minutes, but the problem is it's also gone within minutes. So that's why it's important that if we feel like you've got a dose of epinephrine and after even a minute or two we feel like you know what you're no better, there's no real downside of giving a second dose of epinephrine at the doses we're talking about.

Dr. Stukus: Okay. And is there one particular-- you mentioned using it in the muscle-- is there one particular muscle that's recommended compared to others?

Dr. Lieberman: Yeah. So right now all recommendations are to give it into the outer thigh muscle, the vastus lateralis muscle. Now that's based on one study that showed that the absorption of epinephrine was higher if you gave it through the thigh than if you gave it through the elbow. There's not much data beyond that to agree with that or say that there's even a better way that we haven't tried yet but based on that study all guidelines currently agree that epinephrine should be administered in the outer thigh muscle.

Dr. Stukus: Okay. Now you mentioned safety and that's why we want to use it because it's not going to cause major side effects, but I know there's a lot of fear surrounding use of epinephrine from both medical professionals as well as patients. Part of it has to do with it being a needle and an injection but also concerned about side effects. Can you comment on some of the common misconceptions that you hear, and then also kind of bust those myths and tell us what the truth actually is?

Dr. Lieberman: Yeah. I think my favorite misconception all thanks to Quentin Tarantino is that epinephrine has to be injected right into the heart, right? From Pulp Fiction. So epinephrine, it's going to get throughout your system honestly no matter where you inject it, and in severe cases of anaphylaxis actually it's recommended that epinephrine be given by an I.V. drip, so straight into the bloodstream. So it's not dangerous to be given in any form or in any way, and we know that because we do give I.V. epinephrine, that obviously should be monitored, but I think that's the most common misconception is oh I have to inject it in a certain place. The other misconception is that it's going to lead to something that they

can't even imagine like oh my heart's going to burst or my heart's going to beat so fast I'm going to have a heart attack or something like that, and there's no evidence to that whatsoever. At the doses we use the physiologic changes really aren't huge. It's really just reversing any negative effects from the anaphylaxis.

Dr. Stukus: And when we advise patients to seek emergency care after they give epinephrine is that because it's a dangerous thing to use or because the needle is huge, or what are the reasons that we recommend they be monitored?

Dr. Lieberman: Yeah, and that stems mainly from if the reaction is severe and you felt your child or yourself that you needed epinephrine then you need to be monitored to make sure that the symptoms are not going to progress, right? Because your epinephrine even if you have a two pack of auto-injectable epinephrine, that is quick onset like we talked about the quick off. So within minutes that has already worn off. So the idea of being evaluated is mainly to say let's make sure that this is truly resolving, let's make sure your blood pressure is okay, your oxygen levels are okay, and it has nothing absolutely to do with this because we're worried that epinephrine has any side effects.

Dr. Stukus: Have you ever injected yourself accidentally or on purpose with an epinephrine auto-injector?

Dr. Lieberman: I will admit to doing it on purpose on numerous occasions, mainly when I have pediatric patients or adolescent patients who when the thought of injecting themselves with epinephrine scares the, for example, I'll walk into the room with an epinephrine auto-injector in my hand and literally I've had kids go physically walk to the corner because they are now scared of it, and so in patients like that I will actually self-inject epinephrine on occasion to show them look, it's no big deal, it doesn't hurt, nothing's happening to me, my heart isn't beating out of my chest, and it's not a dangerous thing.

Dr. Stukus: Well what does it feel like?

Dr. Lieberman: You want to know the truth, I don't really feel anything when I do it. I've got other people who have done it also, healthy people, they say they get a little bit jittery. I've never really felt that jitteriness. I've hooked myself up to a monitor too also, and there's a minimal change in blood pressure or heartrate that, yeah, I don't think is worrisome at all.

Dr. Stukus: Okay. And once again for our listeners we don't recommend that you try this at home. This is purely Dr. Lieberman's experience. I accidentally injected myself one time. I thought it was a training device, but it was a live device, and it was weird, I didn't feel anything either. I was kind of excited actually because I had always wanted to do it so, but no, you're right, it's really kind of underwhelming to be honest with you.

Dr. Lieberman: You couldn't immediately have leaped over tall buildings.

Dr. Stukus: No. I should have tried, however. Now let's go back to aftercare or management and prevention and things like that. So which patients should be prescribed an epinephrine auto-injector? Is there some rule of thumb or is there any guidance in that realm?

Dr. Lieberman: Yeah. I mean I think it's a little bit practitioner dependent, but I mean any patient who we truly believe is at risk for anaphylaxis, is at risk for a severe life threatening reaction, should have epinephrine available on hand, and like I said unfortunately in current times that means an auto-injectable epinephrine, and there are some rare cases in which patients would have a vile, and I've even seen on YouTube people making up their own epinephrine injection kits that they then carry. That's obviously not recommended from a safety aspect, but I think anyone who has potential for a life threatening reaction should have epinephrine available.

Dr. Stukus: Okay. And let's go back a little bit to the fatalities from anaphylaxis. Do we have any idea in regards to how common it is for someone to die from anaphylaxis?

Dr. Lieberman: Yeah. There's a lot of different reports. Well here's the one thing I'll say. It's very rare that someone dies from anaphylaxis, and it's also very rare even if you have a known allergy, for example, a known food allergy you are much more likely to die obviously from a car accident, and so what I tell patients to say is that you are taking as much risk getting into the car every day as you are going into a restaurant. So you just take the proper precautions. We don't get into a car, drive 100 miles an hour down a crowded street without a seatbelt. We drive close to the speed limit or under the speed limit, we wear a seatbelt, and so if you have a food allergy for example you read labels, you ask the waiter at the restaurant about the dish you're ordering, you carry your epinephrine and have that available, you take the proper precautions, and if you do that you can really minimize your risk.

Dr. Stukus: This has been a fascinating conversation on many levels, but to kind of summarize this is a good point to do so. You mentioned that anaphylaxis is a heterogenous condition, it can have variable presentations including severity, some being very mild, some being more severe. You've also mentioned that fatalities are rare, but it's also common. So up to one in a hundred are at risk to develop it at some point in their lifetime. Does everybody have the same risk for dying from it, or have we learned anything from prior cases and the literature in regards to some common themes that places some people at greater risk from dying from anaphylaxis compared to others?

Dr. Lieberman: Yeah. There's a couple of things that come up, and in the food allergy world it appears that if you have underlying asthma, and we have talked briefly about it before, but if you have underlying asthma that seems to be a pretty decent risk factor for more severe reactions, and then risk taking behavior as we know is a risk factor, right? And so this is commonly seen in adolescence. They don't want to carry their epinephrine with them, they don't want to tell other people at the party that they're allergic to things so maybe they'll eat something and take a little more risk than they should have. So asthma I think is a risk factor based on my reading of the literature, risk taking behaviors obviously, and then the route of exposure. So inpatient or perioperative anaphylaxis if something is given I.V. like I talked about before it's probably more likely to lead to a more severe reaction.

Dr. Stukus: Okay. Now can anybody ever outgrow their risk for anaphylaxis, or does it magically go away over time in people?

Dr. Lieberman: Yeah. I mean it's such a great question because we don't really know. People we know outgrow some food allergies for example, and we know that labeling-- if you're labeled with penicillin allergy for example we know people outgrow that. The question is were these patients truly allergic to begin with, and the testing just got improved over time, and we know that for example milk and egg allergy are outgrown much more commonly than other allergies like peanut and seafood allergy, but usually if you're allergic to something a lot of the times that's going to be lifelong, and the risk theoretically then would be lifelong.

Dr. Stukus: Okay. Now I just have a couple more questions that as we were talking here it dawned upon me that I'd love to get your opinion on some of the more esoteric and rare forms of anaphylaxis. If you could just briefly comment on say red meat anaphylaxis or exercise induced anaphylaxis. What are your thoughts on those?

Dr. Lieberman: Yeah. So the red meat anaphylaxis is a great story that's evolved over the last 20 years in which as best we know the idea is that patients who have a history of tick exposures, and not all patients who have a history of tick bites, but in some certain patients who are for whatever reason at risk for it who get bitten by ticks develop antibodies to a certain chemical called alpha-gal, it's a sugar that sits on the protein in mammalian meats, and for whatever reason, it's not quite clear yet, this is the one exception with anaphylaxis in which for food allergy that you eat the food and the symptoms don't typically occur within minutes rather they occur within hours, with an average onset for most patients around four to six hours. So it's the one case in which we say this is a delayed anaphylaxis with food allergy. And then for the exercise anaphylaxis that's an evolving area of understanding because we know there's different types of exercise induced anaphylaxis, so some patients who can just go out running can get covered in hives, develop shortness of breath and have true anaphylaxis whereas others who require cofactors, and the common ones implicated include foods such as wheat, and the other common cofactor include medications such as NSAIDs or aspirin, and so when you add the two together, the NSAIDs and the exercise, you can reproduce symptoms in these patients, but if you do one without the other you can't reproduce symptoms. So the exercise induced anaphylaxis is in the nice evolving area of research where we're starting to understand it a little bit better.

Dr. Stukus: Oh boy. That's fascinating. So along those lines, the last question I have for you is especially for the medical professionals who are listening to our conversation, are there areas surrounding anaphylaxis diagnosis or management that you feel we need to improve upon whether it's out in practice or in regards to research and better understanding?

Dr. Lieberman: There's a lot that we need for research. I think for me the holy grail would be one diagnostic marker or criteria. Ideally you would have a physiologic marker that you could do or a test that you could say "this is anaphylaxis," and for practitioners I think we all need to understand that epinephrine is not dangerous, we need to use it earlier within reactions and not be scared of it. I think some of that would improve if we had non-injectable forms of epinephrine. I think for whatever reason that barrier of

injecting a medicine is one that both patients and practitioners have, and if you had a non-injectable form I'd hope that that barrier would be overcome, and in presentation to recognize it as an entity more often even if the patient doesn't have a life threatening case.

Dr. Stukus: Oh, that's great. Dr. Lieberman I really can't thank you enough for your time and for joining us today. This was an outstanding conversation. We've covered a lot of ground, and I know that this can be very useful for those who are listening in, but before we say goodbye is there anything else you'd like to add?

Dr. Lieberman: I just wanted to say thanks for having me on. It was enjoyable.

Dr. Stukus: Yeah. It was our pleasure. We hope you enjoyed today's episode. Information about credit claiming for this and other episodes can be found at <https://education.aaaai.org/podcasts/podcasts>. Credit claiming will be available for one year from the episode's original release date. Please visit <http://www.AAAAI.org> for show notes and any pertinent links from today's conversation. If you like the show please take a moment to subscribe to our podcasts through iTunes, Spotify, or Google Play so you can receive new episodes in the future. Thank you again for listening.