



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'm 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. For today's episode, we are extremely pleased to welcome Dr. Aleena Banerji to today's episode. Dr. Banerji is an Associate Professor of Medicine at Harvard Medical School and serves as the Clinical Director of the Allergy and Clinical Immunology Unit and Director of the Drug Allergy Program at Massachusetts General Hospital. Through her extensive clinical and translational research and well over 100 peer reviewed manuscripts, Dr. Banerji has earned an international reputation as a leading expert in drug allergy. Dr. Banerji served as one of the chief editors for the October, 2020 issue in *The Journal of Allergy and Clinical Immunology: In Practice* dedicated to the practical guidance for the evaluation and management of drug hypersensitivity and also served as coauthor for the recent Academy Drug Hypersensitivity Work Group Report, which is the topic of today's episode. <https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/Practical-Guidance-for-the-Evaluation-and-Management-of-Drug-Hypersensitivity-2020.pdf> That was a mouthful. <laughs> And with that, neither Dr. Banerji nor I have any relevant relationships to disclose. So with that, Dr. Banerji thank you so much for joining us today, we're going to have a great conversation and welcome to our podcast.

Dr. Banerji: Hi Dave. Thank you for the invitation, I'm really excited to talk about this project and drug allergy in general.

Dr. Stukus: Yeah, it's refreshing to hear somebody so excited to talk about drug allergy. And I'd actually like to start there if that's okay. So tell us a little bit more about yourself and your personal career and

interest in this area. Can you think back to what first led to focus on drug allergy and what do you continue to find so rewarding and interesting about this area?

Dr. Banjeri: So it's certainly an area that I am very passionate about and when I think back to my career, what I remember most is in residency, we didn't really have a big allergy group and I just remember a few cases in the ICU where patients had a penicillin allergy label and we would need to give something that was a beta-lactam. And I do remember just hoping that an allergic reaction didn't occur. Certainly there were times where we had to use broad spectrum antibiotics and now we know as an allergist, that's not optimal. And so I think when I started my fellowship I learned that we could answer these questions and we could do more than just hope that a reaction didn't occur. And so I think it really opened my eyes as a fellow and got me excited and I knew that I could impact patient care.

Dr. Stukus: And we're going to talk a lot about ways that we can do that now. And that's wonderful. And so did you have that experience throughout your training as well of just seeing the positive ramifications of taking that label off of somebody's electronic record, did that sort of stimulate some interest as well?

Dr. Banjeri: Absolutely. It was not just the antibiotics and removing the labels, but when we saw cancer patients and we were able to help them stay on the best treatment, that also really made me excited about this area.

Dr. Stukus: I'm glad you mentioned that because so often I think people just think of drug allergy as penicillin, but really we're talking about any type of medication or treatment that people receive for a whole host of conditions. So that's great. Now we're going to spend the bulk of today's discussion focusing on the Academy's Work Group Report that you coauthored in October, 2020 surrounding concepts related to the evaluation and management of drug hypersensitivity. But before we get into those details, can you give us an overview of the entire drug allergy issue published last October in the Journal of Allergy and Clinical Immunology: In Practice?

Dr. Banjeri: Yeah, this was a huge multiyear effort honestly and it was led by myself along with Dr. Ana Broyles at the Children's Hospital in Boston and Dr. Mariana Castells at Brigham and Women's Hospital. And it was really meant to be a practical guidance for our allergy colleagues and when you look at it, you'll see that there are a number of authors, individuals who are experts in their own areas and every single of them really contributed to getting this document to where it was. But the document itself is really two main sections, the first is a general section that reviews the broad approach to the evaluation and management of really any patient presenting to the office. And the second section is very drug specific or drug class specific and includes clinical symptoms of that specific drug or drug class, it includes published data on non-irritating skin test concentration as well as published data on desensitization protocols if those are relevant. And so it's really aimed at being just an everyday tool for allergists to use in their office and it covers adult and pediatric patients.

Dr. Stukus: And it's a wonderful resource, we'll put the link on the show notes and things like that and we encourage everybody to look at it for all the details. But I just want to go back for one second, so you mentioned that this was two years in process and putting this together, I don't know if people realize this

when they read an issue, but you started planning for this back at a time when we weren't wearing masks and we were hugging strangers and shaking hands and <laughs> going about our business and then it was published in October, 2020. So did you have to invite authors and coordinate and focus on the editing and then make sure that everything was consistent as it was being written and laid out or tell us a little bit more about that process?

Dr. Banjeri: Yeah, it was several years that I think actually dated now back to maybe five years ago where we sought out colleagues and experts and they submitted a summary and believe it or not, over that several year period of time we had to reach out to the authors to update their sections a couple of times because it took us so long to put everything together, make sure it was updated. And then even the last year was spent making everything look even, clean, readable and updated.

Dr. Stukus: Well on behalf of all of our readers thank you very much for all the work that you put into it. Now what was the impetus for putting together a new Academy Work Group Report on this topic, how does that even come about?

Dr. Banjeri: It's a great question and I was thinking back to that when you asked me to talk today and I really think this was a combination of two things, one we knew that this was a huge knowledge gap area in the field, but also this was actually a combination of a quad AAAAI presidential initiative by Dr. Tom Fleisher and he had really been focused on expanding the scope of practice around 2016 when this project started, so I have to give him as well as his colleagues on the board at the time a lot of credit for supporting this effort.

Dr. Stukus: I like that you use the term scope of practice. So in your opinion or the opinion of your fellow experts who put this together, what role should allergists have in addressing drug hypersensitivity reactions both within the community and in hospital settings?

Dr. Banjeri: Among physicians I truly believe that allergists played the most important role in addressing drug allergies in the community and hospital setting. And in fact I might actually go one step further and say that I think a lot of our non-allergy physician colleagues have not been trained to address drug allergies and probably don't really have the interest or passion in addressing drug allergies and so I think allergists need to own this.

Dr. Stukus: And can any allergist serve in this role, if you're in private practice out in a community or does it have to be somebody like yourself that's at a major academic institution?

Dr. Banjeri: This can be every single allergist and I think-- when I talk about drug allergies, other than pointing out that allergists are the key physicians in evaluating drug allergies, I think allergists are the most well versed, we always take a history, history, history and then allergists know how to take that history and convert it into, "Was it a side effect, was it an intolerance, does the patient really have to avoid the drug or not?" And even though simple things can happen in a matter of minutes just by evaluating the history with tools that allergists have learned all along in their career.

Dr. Stukus: That's great. Can you give us some background regarding the importance of properly diagnosing drug hypersensitivity? As you mentioned, history, history, history, but how common is actual drug hypersensitivity versus sort of labels of drug allergy and what ramifications does that label have for an individual patient?

Dr. Banjeri: Drug allergies unfortunately are much too common and even the idea that someone is allergic may not actually be what's listed in the chart, so people might list heartburn from aspirin and so then nobody gives them the aspirin. We also know that at least ten percent of the United States population self-reports a penicillin allergy and we actually know from the literature that less than one percent of these individuals are truly allergic to penicillin. But when that penicillin allergy label for example sits on that chart, broad spectrum antibiotics are used that leads to antimicrobial resistance, C. diff, a lot of negative outcomes that don't really need to occur because we know in a lot of cases that allergy label is not actually the truth and that patient is not truly allergic.

Dr. Banjeri: And am I correct in that in addition to just broad spectrum antibiotics and antimicrobial resistance, does this increase cost of care overall or even contribute to increased length of stay when people are hospitalized for whatever reason?

Dr. Banjeri: It actually does and there are several publications including from my own colleagues at Mass General that exactly support that data where there's longer hospital stays, worse outcomes, broad spectrum antibiotics lead to antimicrobial resistance and higher costs of care.

Dr. Stukus: Lots of great reasons to try to avoid that unnecessary label especially when it's incorrect. I'd like to go back to medical school or even undergrad for those of us who majored in molecular biology or biochemistry, can you walk us through the traditionally used, all right everybody's going to shudder when I say these words, Gell and Coombs classification <laughs> of drug hypersensitivity reactions? We all know what the pictures are like and we all know that that section of reading it over and over again, but what's the Gell and Coombs classification? And then also where are folks such as yourself really thinking these days about how we should classify drug reactions?

Dr. Banjeri: Yeah, it brings us back to the days of Janeway and Janeway immunology which I think we all have a copy of that book somewhere <inaudible 00:12:19>, we all have a copy. <laughs> So Gell and Coombs is important because while it's important to categorize the reaction, as allergists categorizing the reaction then helps you decide how to manage that reaction and I think that's why it's important. And so the very, very basics that I think are probably important is type one is thought to be that typical IgE mediated allergy where you have hives or swelling or anaphylaxis. Type two is often thought to be the antibody dependent reaction and an example might be hemolytic anemia. Type three is the classic immune complex mediated reaction and the classic example we always talk about is serum sickness. And then the type four is more of a delayed type hypersensitivity. And a classic example of that is something like contact dermatitis, but it also includes some of the more severe drug reactions that we talk about including Stevens-Johnson's DRESS and so on. And again it really helps us if we categorize it figure out what do we do next for that patient's reaction.

Dr. Stukus: And is the conversation still including discussion of type one, type two, type three, type four hypersensitivity or is there a different way of thinking about the way we classify these reactions?

Dr. Banjeri: I think it's more thinking whether it's allergic IgE, non allergic, non IgE and then delayed and I think some of that classification gets a little bit complicated when we think about what we're trying to manage with that patient's reaction.

Dr. Stukus: An area of common misconception that I hear from referring providers is that the term quote, unquote "allergy" means that you're going to have anaphylaxis next time you get it. So if somebody does have delayed type four hypersensitivity, can they then have anaphylaxis next time they get it or does it seem to stay within whatever mechanism initially caused their reaction?

Dr. Banjeri: That's a great question and I would say that we don't think anaphylaxis would occur, that's not the type of immune system process that is occurring. And oftentimes we avoid the drug, so we don't even know if you gave the drug again if that same reaction would occur specifically with Stevens-Johnson or DRESS and we can certainly reassure the individual that anaphylaxis should not happen based on that prior delayed type hypersensitivity reaction.

Dr. Stukus: And not to go too far off topic, but it's very current right now because your group has done magnificent work with suspected allergic reactions to the COVID vaccines and you're finding that you can often give it again regardless of what happened the first time and for reasons we don't fully understand, they do fine. Is that what you're experiencing?

Dr. Banjeri: It is and I think it's such an important topic and such an important question because especially with the delayed reaction, so individuals having reactions after four hours, we do not see that skin testing really has much value, again because it's not an immediate reaction and that almost all of those individuals do fine with that second dose and we're talking about the mRNA vaccines where you need a second dose.

Dr. Stukus: Yeah, and to go back to what you said, so often you get the label, we just never give it again, so we never know what happens. And I think we're going to talk a lot about ways that we can sort of manage that as we go through this. So I'll plant that seed for our listeners as we move into the specifics here. Speaking of, there is a ton of ground to cover regarding the report that you put out for specific types of drug hypersensitivity reactions and different drugs and things like that and that unfortunately falls way outside the scope of what we can talk about today, we only have an hour, we don't have all day, although I'd love to keep you all day. But start us off with thinking about some general factors that seem to place people at higher risk to experience a true drug hypersensitivity reaction. Can we identify those folks sort of at the outset?

Dr. Banjeri: I think it's hard to know ahead of time and the risk factors are not necessarily that well studied. But we certainly know that age could play a role, gender, maybe more common in females which we're also seeing with the vaccine reactions. There is a lot of emerging literature on certain genetic polymorphisms and also maybe some drug related factors. We know that an IV route may be more

immunogenetic than oral. So just some little tidbits of what might place someone at higher risk, but there's no absolute risk factor.

Dr. Stukus: Okay. Let's make this as practical and as real as possible and if we can imagine that we're in the clinic setting or an inpatient consultation and we have that patient who's in front of us right now and they were referred to us or they're seeking evaluation for a suspected reaction to a medication. What's the most important part of our evaluation and how should we focus on that aspect?

Dr. Banjeri: I think it's always going to be history, history, history, isn't that we call medical school 101, the first thing that we ever learned, you can't graduate medical school without it? I think it really is the history and it's interesting because I think things have changed with time and even more so this past year where there's so much telemedicine and electronic medical record use to the point where, I'm sure you've had this experience, I've had patients tell me to just look in the chart. I'll ask a question and they say, "Well it's my chart, just look in there." And it really still is just about the history.

Dr. Stukus: Are there specific details that you try to tease out when you're taking that history?

Dr. Banjeri: Yes, there's some very specific questions and these are things that we talk a lot about with our fellows, things like, "What was the timing of the reaction, was it immediate, was it delayed? Was the reaction more than ten years ago? Did the reaction occur with the first dose or did it happen after several doses?" Or for example, "Did the rash happen ten days after you completed the antibiotics? What was the nature of the reaction, was it a maculopapular rash, was it itchy, were there hives, was there any blistering or skin desquamation?" And then also, "Did the reaction need treatment, did it resolve on its own? Did you need to go to the emergency room? Did you need epinephrine?" I think all of those are very, very good questions to go through when you're asking a patient about their drug allergy history.

Dr. Stukus: How do you personally do this in clinical practice, have you just done this for so long that you just know that, "These are the questions I need to ask," in some order or do you have a standardized checklist or what do you do when you teach fellows for instance?

Dr. Banjeri: When I teach fellows, we have a slide that we go through at the beginning of the year that goes through these exact questions and I think it almost has become second nature at this point and it kind of just comes as we're talking to the patient and we go through those questions. But the hard part is that most patients don't know the answers to those questions and so at the end of the day, the most important things really are, "How long ago did it happen?" which the patient will remember, if there was blistering, that sometimes patients will easily be able to tell you. And then did they have to go the emergency room or need epinephrine. I think those basics even if the reaction as a long time ago, patients are able to provide that history and so I think those questions add a lot of value.

Dr. Stukus: I love that you focused on the questions we need to ask, but then on the receiving end of it, what do you do with the information, are you assessing risk at all times and does that change the algorithm in your mind? Give us some insight into the inner workings of Dr. Banerji's mind when it comes to evaluation of drug allergy.

<laughter>

Dr. Banjeri: <inaudible 00:20:12> on the drug allergy. I think those questions in my mind are really trying to help me decide, first was it a side effect or an intolerance where I don't need to worry that much versus was this a true allergy and if it is, does that patient have to avoid it or can I use skin testing or drug challenges or desensitization to help that patient either today or in the future receive that drug and clear that drug allergy from their list. And so it's really just trying to categorize in my mind, not necessarily exactly Gell and Coombs, but can I remove that allergy or what can I do today to potentially remove that allergy from the patient's chart.

Dr. Stukus: So you're using the history and the responses to then help determine next steps, is that what I'm hearing?

Dr. Banjeri: Exactly.

Dr. Stukus: Ah, okay. What about, you mentioned side effects and intolerance, what are some of the more common answers that you hear for those questions that really helps you have more reassurance that this wasn't a true drug allergy?

Dr. Banjeri: I think for example as I mentioned, bleeding or heartburn from aspirin, where we know that it's an expected side effect. And I'll have to tell you, a favorite of mine is iodine allergy, right, I mean we all see it listed and it's often in the context of someone having a reaction to IV contrast or to shellfish. And we all know you can't be allergic to iodine. And so there are things like that that even to this day when you have an electronic medical record, you should be able to clarify that individuals can't be allergic to iodine. So I think things like that where we have a lot of knowledge on what's a side effect, what's an expected side effect. So for example with the vaccines, you know you're going to get muscle aches and fatigue, maybe a fever and so there shouldn't be an allergy that becomes listed because of those side effects which were anticipated.

Dr. Stukus: So even when patient says, "I had an allergic reaction," to something, we have to use our thinking caps to determine, "Oh, is this actually an allergy or is it one of the more predictable side effects?"

Dr. Banjeri: Exactly, completely agree.

Dr. Stukus: And what about, how do you handle gastrointestinal manifestations, you know, a lot of people if they diarrhea or cramping or even if they get yeast infections when they take antibiotics for instance, how do you classify those in your mind?

Dr. Banjeri: That's a hard one and I would classify it as an intolerance. But the challenge is patients will often say that those symptoms were so severe that they would never take the medication again. And so what I usually do in those cases is I will list it, I will clearly put that it's an intolerance and I will add as much detail as I can so that the next time someone is looking at the chart, it's very clear that there's no

absolute contraindication. And so if that drug has a high benefit, it's a conversation with the patient explaining, "You had a reaction which you may have again, but we can manage those symptoms and it's not severe, it's not a life threatening type of allergic reaction and oftentimes those symptoms aren't necessarily going to occur again." And I think trying to go through those things today so that I can have the best documentation on the chart as possible is going to be really helpful in five years or ten years if and when that patient needs that drug again.

Dr. Stukus: And do you communicate that to the patient as well to hopefully increase their understanding should they encounter another person who's prescribing that medication?

Dr. Banjeri: Yes, and I think that's such an important part of the clinical allergy evaluation is to explain to the patient when it's a side effect and an intolerance versus an allergy. And they may not leave with the same belief that I have, but at least we've tried and gone through it because they will probably hear the same thing multiple times down the road.

Dr. Stukus: I've proposed tattoos for those where we remove the label of drug allergy, but our institution has not been in favor of that thus far.

Dr. Banjeri: Yeah, good luck with that one.

<laughter>

Dr. Stukus: All right, so history, history, history. I believe you said history is important. So moving on, the next standard part of medical school 101 is the physical exam, but how helpful is the physical exam in somebody who had a suspected drug allergy reaction 20 years ago? Of course we're still going to go through this, but does it actually give us any clues or offer any insight?

Dr. Banjeri: Unfortunately it doesn't. There's nothing usually present on an exam at all at that point especially when it was a long time ago. But what I will say is if you're getting called on the phone or inpatient consult that there's an inactive reaction that they want you to come evaluate, pictures are going to be a thousand words and they're so valuable. But the other side of this is in this new era of telemedicine trying to help decide who needs an in person visit or who needs a virtual visit, I'll tell you that a lot of our allergic rhinitis patients, we say, "Come in, in person visit," but if the main reason is a drug allergy consult then we will set up a telemedicine visit or a virtual visit because the physical exam is less important in that moment in really getting the history, which you can do through a virtual telemedicine visit.

Dr. Stukus: And then the pictures as you mentioned now we can upload those through the electronic medical record and people can send them or they can scroll through their photo library on their phone and upload it any time.

Dr. Banjeri: Yeah, they're so helpful if you can capture it in the moment and I know we tend to do this a lot on the inpatient side and then when we see the patient in the office a few weeks or a few months later, that picture really helps.

Dr. Stukus: Are there any laboratory tests that may be useful? And I know we're covering a wide swath of potential different types of drug allergy reactions, but if there are how do you decide which ones to order and when?

Dr. Banjeri: It's similar to the physical exam, labs in the moment when there's no reaction or no active symptoms aren't necessarily that helpful. But certain things that you can think about in the moment, so say you are called about a patient having a reaction is you could consider a tryptase if you're thinking about an anaphylactic reaction, but that tryptase has to be drawn within a couple of hours of the reaction and you have to remember that if it's negative it doesn't rule out allergy, but it's certainly helpful if it's high. And then maybe for some of the immune mediated reaction, complement studies such as C3 or C4 might be helpful, an eosinophil level might be helpful, but otherwise we don't really have great blood tests, there's no IgE test for drugs like we have for food allergies that really have great sensitivity and specificity. So I think that is certainly an area where we need a lot more work in the field of drug allergy.

Dr. Stukus: And if you order any of these studies, complement studies, tryptase, are any of them diagnostic that says, "Yes, absolutely this patient is having a drug allergy reaction or is it just one piece of the puzzle that has to be interpreted accordingly?"

Dr. Banerji: I think one piece of the puzzle exactly how I would describe it where it may or may not help get to the etiology of the patient's symptoms, but if the eosinophil level is high it certainly adds support to a potential reaction to a medication or a potential allergic reaction being ongoing, not necessarily classic IgE, but an allergic type immune mediated reaction.

Dr. Stukus: Well what about skin testing, when should that be considered as part of the evaluation?

Dr. Banerji: Skin testing is such a big part of drug allergy, but what I would say and what's a lot of documentation in this guidance is skin testing really uses just a non-irritating concentration. So you apply it to the skin and if it's negative, it doesn't necessarily rule out allergy, it's helpful when it's positive. And again, skin tests are really helpful when we're talking about the IgE mediated type of reactions and so they can be helpful in some cases, but you just have to remember we're using non-irritating concentrations and that if they're negative, it doesn't rule out allergy and we really do have to think about graded challenges or drug challenges, which would be the gold standard when there's a negative skin test.

Dr. Stukus: What do you mean by non-irritating concentrations? What would happen if you just put undiluted medication for a skin prick or an intradermal test, would everybody have some sort of response or tell us a bit more about that?

Dr. Banerji: The way that we think about non-irritating skin test concentrations are if you were to take a group of people who were not allergic, would they have a positive skin test to a certain concentration? So if you took a full concentration dose of a certain drug and you just tested people, would it be falsely positive? And that's what you're trying to identify and so what you really want to make sure is that if you tested people who were not allergic, would you get a false positive and making sure that that doesn't happen with the concentration that you're using and that it really is positive only in individuals who are allergic. So it's an art of medicine trying to make sure that you're using these non-irritating concentrations and that's partly why this document is so helpful is there's a lot of literature on this and so we try to put it all in one place where allergists could just look quickly and find that non-irritating skin test concentration that was supported by the literature rather than having to think through what should they use, which publication should they look at because there are many publications on these topics.

Dr. Stukus: I'm going to pause here because that's not fair. When I was a fellow in training 15 years ago I would spend hours going through the literatures trying to find <laughs> one or two protocols for these skin testing concentrations and now you're saying it's all in one place?

Dr. Banerji: Yeah, and that's the art of medicine and point of this whole document. I completely agree and again that goes back to why I was so passionate about this is that as a fellow we were all doing the same thing, we would go look and then you'd find five publications saying five different things, right?

Dr. Stukus: Yes.

<laughter>

Dr. Banerji: <inaudible 00:30:37>. Hopefully we solve that issue to the extent that we can, but obviously we're going to have update this document periodically as new literature comes out because this is not a truth as of now, it's what we knew last year and we may learn more, there may be other drugs, there may be new principles that we learn, new science and so we're going to hopefully continue to update this regularly.

Dr. Stukus: Yeah. And so as you mentioned we can't go through all the protocols, but we have a great resource for people to go and look for specific medications and how to dilute them and use them. But what are some of those general principles you just mentioned regarding the skin testing as part of a drug allergy evaluation? We covered using non-irritating concentrations, but is there a general, you start with intradermals, you start with skin prick testing, when do you stop, tell us a little bit more?

Dr. Banerji: So we always start with skin prick tests and then progress to intradermals and we wait that 15 or 20 minutes that you would with any skin test. And you essentially would keep going until you've gotten to the last concentration unless it was positive and at that point you stop and you believe that it's a true positive when you're using non-irritating skin test concentrations. But if you've gone through all the steps based on the literature and you have now negative skin testing, that's when you may want to consider doing a challenge or a drug challenge or an oral challenge and that's often what we use as the gold standard to rule out drug allergy. But you do have to be cautious when you're using drug challenges

because you don't want to use it in someone that might have had recent anaphylaxis and so there are a lot of caveats to when you use a drug challenge or not. But the goal with skin testing is to go through the steps 15 to 20 minutes each and go through each step in the literature that gets you to the final concentration that's still non-irritating.

Dr. Stukus: And how do you know if it's positive? We've all seen the-- you do an intradermal and you get the redness without a significant wheal, how do you determine is it positive or negative, are we looking for no response whatsoever, is there sort of a sliding scale that we should use?

Dr. Banerji: We compare to it the histamine, so just like we do for food testing or environmental testing, you always have your saline and histamine controls and depending on where you look in the literature, you're looking for something that's three to five millimeters larger than the histamine.

Dr. Stukus: And would that be for both the skin prick and intradermal?

Dr. Banerji: Correct.

Dr. Stukus: Okay. How often do you grab an unsuspecting medical student or somebody else to serve as a control subject?

Dr. Banerji: We often repeat the skin test on the patient if the result doesn't fit with the clinical picture. And it's interesting how many times when you duplicate the exact same skin test in the same person, you may get a different result.

Dr. Stukus: From technique, from the person applying the test or just over time or any other thoughts on that?

Dr. Banerji: You know, it's not necessarily over time because you'll do it the same day, if you get a positive that you truly don't believe and you repeat it maybe on the other arm and it's negative, it might be technique, it might be how it was injected, things like that that we do encourage individuals or physicians to repeat skin tests if you get a result that's not necessarily 100 percent consistent with the history. And then also make sure that you made the dilutions properly, that you're <inaudible 00:34:07> using a non-irritated skin test concentration and so on.

Dr. Stukus: And would it matter if the medication being used was out of date or something like that?

Dr. Banerji: It typically doesn't because if you're using a medication that's out of date, if anything it's degraded, we're not looking for a medication to be effective, we're actually just looking for a non-irritating skin test concentration. So in general we don't like to use expired medications and I wouldn't recommend using expired medications, but it shouldn't impact the result of skin testing if you're using something that's a few days out from being expired.

Dr. Stukus: That's a great point, thank you. Let's go back to drug challenges because you mentioned that-- okay so we have the patient history, history, history, physical exam may or may not be helpful, no real laboratory test unless you're in the acute setting and then skin testing for those who have a history consistent with those immediate type of allergic reactions. Let's say that's negative, how and when do we do a drug challenge, what does that look like?

Dr. Banerji: So drug challenges are really defined as a gold standard and it really should be the individuals that have a low risk history, you don't want to be challenging someone who had anaphylaxis to a drug a month ago even if skin testing is negative, it's hard to put someone through that risk if the benefit isn't high. But an important point about drug challenges and I think probably the most important point is we generally advise only using one or two steps for the drug challenges because multistep drug challenges could falsely induce tolerance whereas we know that one or two steps wouldn't necessarily do that and really does clear that allergy. And so drug challenges are often used when someone has a remote history of allergy, true low likelihood of allergy and skin testing was negative if skin testing is relevant. Certainly, things like aspirin and NSAIDs there is no non-irritating skin test concentration, so you may proceed with a drug challenge without skin testing. But again these are in individuals who have low likelihood of true allergy.

Dr. Stukus: So find somebody who's not likely going to have anaphylaxis right in front of you.

Dr. Banerji: Yes. That's great advice.

Dr. Stukus: <laughs> So we have tools to determine risk, we should use them. Are there protocols as well for these different challenges? Let me extrapolate a bit further and then I'll let you talk. Somebody had anaphylaxis to an IV formulation of a medication years ago, they haven't received it since, your skin testing is all negative, do you have to give the same treatment through an IV or can they take it orally or how do you handle that situation?

Dr. Banerji: Depending on the medication. So for example beta-lactams, there is a lot of information out there about cephalosporins that share side chains. So you could actually use an oral cephalosporin that shares a side chain with something that's intravenous and that could then make your challenge in the office much simpler. There are certainly rare cases where IV is the only option and in those cases, you could just proceed with the skin testing and clear it and at least in the chart document negative skin testing and if that patient was ever in a situation where they had to have that drug and it's only intravenous then they could perform the test dose or the drug challenge at that time on the inpatient side when they have that drug. So even in those cases, it's important to try to finish the skin testing or potentially use an alternative that's oral that has a similar structure.

Dr. Stukus: You're making me think of patients experiencing suspected reactions during operations, so intraoperative anaphylaxis and it sounds like that would a situation potentially where you'd say, "Look, we're not going to give it to you on a regular basis, but we're going to communicate with those and if you have to receive this again, here's how to give it." Does that sound appropriate?

Dr. Banerji: That's exactly an example of this where we can't necessarily give sedatives or anesthetics in the office and then we will test, clear the skin test, say it's negative and then advise giving it in the operating room as a challenge or a test dose exactly like you described.

Dr. Stukus: Let's go back to our patient and let's say that our evaluation suggests, "Yes, you have experienced an immediate drug hypersensitivity reaction and we feel that you're at risk should you get it again," do they absolutely have to avoid that medication again, what about drugs with similar chemical structures? You mentioned before about sort of giving things again to see what happens, but what do you do when it is that IgE mediated history?

Dr. Banerji: I think it depends if it was last week or a month ago versus 20 years ago and if it was recent, I think it's harder to skin test and challenge someone if the reaction was two weeks or four weeks ago. But if the reaction was 20 years ago, I think even with anaphylaxis, we feel a lot more comfortable skin test challenging and so on and certainly using other drugs with similar chemical structures is perfectly okay.

Dr. Stukus: Okay. You know, we've all been walking around with this thought of, "Well you can't do any skin testing for at least four or six weeks after an acute allergic reaction because of potential anergy and false negatives, is there evidence to support that or is that just kind of made up?"

<laughter>

Dr. Banerji: No, it's not made up. There was literature in venom allergy actually and that's where the idea of false negativity within that four to six weeks. But in our hands, we've actually seen something similar with plantain allergy where in some of the patients if we're testing within two to four weeks of a severe reaction, you get a false negative skin test and so we do advise waiting for four to six weeks if possible. But then there's also the other side that if you wait too long you're again going to get a false negative and so ideally trying to evaluate someone after six weeks or after four weeks, but within six to twelve months. Again, that doesn't always happen because the reaction could have already been 20 years ago. For example with anesthesia, we ideally recommend that four week to six-month timeframe to really be able to capture the true positives.

Dr. Stukus: Okay. When should somebody think about drug desensitization and what does that entail?

Dr. Banerji: Drug desensitization should really be considered when a patient is felt to be truly allergic and also when you have no reasonable alternative. And general principles of drug desensitization are diluting that drug one to a thousand or so where you start with something very dilute and then you essentially double or triple the amount of drug that you're administering every 15 to 20 minutes, so it's a very mathematical process where you're giving something very dilute and increasing the amount until you get to the full dose. But it is a complicated process and often does have to be done on the inpatient side depending on the resources available and you need a pharmacist, you need a good RN team, so it does take a lot of work, but there are cases where there are no good alternatives and that drug really is first

line and provides better outcomes and so you do have to think about using a drug desensitization in those cases.

Dr. Stukus: Does that cure them of their allergy or do they have to continue to receive it within some interval in order to remain desensitized?

Dr. Banerji: Generally if it's been about five half lives then the patient is no longer tolerant. And so if you give a chemotherapeutic today or an antibiotic course today through drug desensitization, once it's been five half lives, so a few days, a couple of weeks, the patient is no longer tolerant and if they need the medication again, you'd have to go through the drug desensitization process. But if it was aspirin and you desensitized them today and the individual stays on it every day, then they can just continue taking it every day until there's a break and they had to stop their aspirin for some reason, then you'd have to desensitize them again.

Dr. Stukus: All right, let's go back to our individual patient. We've taken a detailed history and everything they've told us suggests that they have never actually experienced a true drug allergy reaction and they most likely had no side effects or maybe they even reported an allergy because their father reported having an allergy or another sibling or things like that. Can we then just simply remove the drug allergy label from their medical record and tell them they can get it again without doing any testing or evaluation or dose challenges or anything like, are we actually allowed to do that?

Dr. Banerji: Absolutely, yes. This is so important and if we leave the listeners today with nothing else, this is the most important point is that you as the allergist or the physician, when you feel that that patient is not allergic, please, please, please remove it from the allergy list, nobody else is going to do it. And the patient may even sometimes get confused and so it's our job really to update that electronic medical record and remove that allergy when we feel they're not allergic.

Dr. Stukus: What do you say, you know, we're largely consultants, so when you send that communication back to the referring physician or provider, what do you say, what language do you use when you tell them, "Oh, I didn't have to do anything, this patient's not allergic?"

Dr. Banerji: I think you have to be careful with your language because you don't want to make the other physician who might have added it to the chart feel like they don't know information. And so I think we often will describe very carefully the symptoms, what the patient described and explain why it's not an allergy, why it might be an intolerance, why we feel as allergists it's not an allergy. Because if you don't explain it, I think there will be a lot of misinformation or misinterpretation of the note and so I think it's important for us to explain why we think it's not an allergy and why we think it might be an intolerance or a side effect.

Dr. Stukus: And maybe even provide a link to the JACI: In Practice Drug Allergy Supplement and say, "Here's some additional reading."

Dr. Banerji: I'm going to start doing that, I love that idea.

Dr. Stukus: <laughs> My institution at Nationwide Children's Hospital, we have approximately 12 to 13,000 different employees who rotate through that can easily place a drug allergy on somebody's electronic medical record, it's impossible to educate all those folks. And there's 12 people in our division <laughs> so there's about 12 people that feel comfortable removing those allergies from the chart. Do you have similar experiences at your institution, is this a widespread problem where these labels get thrown on there and nobody takes them off?

Dr. Banerji: It is, it is such a big problem and especially because a lot of it is not true allergy, it's not even that we are able to just work on what's allergic, there are so many things in the chart listed in the allergy section that are inaccurate and there's no easy solution other than kind of starting to chip away at it. But I would hope that in the next few years with technology and with what we can do with electronic medical records, there is a way to clean out, you know, if tinnitus is written for aspirin as a common example or if fatigue is written, that there are ways for the symptom to automatically update itself without everyone manually having to edit those things.

Dr. Stukus: That would be great. After our evaluation and when we have our results whether it's just by the history or any testing that is done, can you discuss the importance of shared decision making in the evaluation process and management of drug hypersensitivity reactions, is it one size fits all or do we have to have a conversation with that patient in front of us?

Dr. Banerji: Oh this is such an important aspect and I think we do have to help the patient understand what just happened, right? So when you skin test it's nice because there's objective information there that there was no allergy when it's negative. But there are many times where, not many times, but rare cases where we'll have gone through the evaluation, we'll explain to the patient that they don't have that penicillin allergy and then we'll see them two years later and the penicillin allergy was added back. And so I think the patient really needs to understand what the evaluation was, why we think they're not allergic and for them to understand, "We are taking this off of your chart," so they understand because you don't want them going to the next doctor and saying, "Oh I had a penicillin allergy when I was ten years old." So I think it's shared decision making is so important because the patient needs to understand what we're doing.

Dr. Stukus: And then as far as getting the medication again if they do have a true-- if we deem them to be truly allergic for whatever reason whether it's a mediated delayed onset, is there still a role to discuss with them, "Hey, we have options here. We can certainly try again if you are willing to accept that risk or if that's important to you?"

Dr. Banerji: Yes, and I think that's another part of the shared decision making that's really important and certainly in this vaccine era that we're talking about where we don't necessarily understand if a reaction is reproducible and so there are times where it might be slightly higher risk, but the benefit is so high that you may proceed with doing a challenge, et cetera based on shared decision making with that patient.

Dr. Stukus: Great. What are some of the more large scale efforts to de-label a penicillin allergy for instance, what does that entail, what does that look like, is it changes to the EMR, is it more standardized

protocols for patients admitted to certain inpatient units that have that history or things along those lines? What's being done at your institution and beyond?

Dr. Banerji: I'm really lucky to work with Dr. Kim Blumenthal who is very passionate about this area and has done a lot of work de-labeling penicillin allergies, I think it's one of her life's mission for it no longer to exist. But the ideas are to have very simple protocols, very simple algorithms that could be put into place by, as you're saying, not just the allergist, so all of our physician colleagues or nurse practitioners or other healthcare professionals who can take someone who has a rash, list it to penicillin 50 years ago and simply do a quick one or two step challenge and clear that allergy or pathways that differentiate what's an intolerance from an allergy and I think it's really important, but I think that's what large scale efforts would look like.

Dr. Stukus: I didn't hear you mention permanent tattoos though.

Dr. Banerji: <laughs> Not yet.

Dr. Stukus: All right, not yet, not yet, so you're saying there's a chance. Now other than the In Practice supplement that we've been talking about today or I should say issue, I'm sorry, in October 2020, where can listeners find additional information to support these concepts that we've discussed here?

Dr. Banerji: There's certainly a lot of literature out there, I think JACI: In Practice has numerous publications, many of which were used to reference the information that's in the guidance. There's also a lot of information on the AAAAI website that I've certainly used, there's difficult questions that are posted and the answers there. And then I think something that you and I have learned a lot about is Twitter, I think there's a lot of information there and that's always fun to post questions and get answers and something I'm learning about, but I think Twitter's another option.

Dr. Stukus: Oh great. What would you say to an allergist or really any medical professional who says, "All right, great. Great episode, love everything that you gave, but I don't have the time for this stuff, I'm seeing 40 patients a day with rhinitis, it's the springtime, I'm busy, phones are ringing off the hooks," what would you say to them in their efforts to address drug allergy in their clinical practice?

Dr. Banerji: I would say that, "You already know how to do this, it can take you minutes. And honestly if the allergist won't do it, no one else will do it and we really are impacting at the population health level." And then hopefully this drug allergy guidance document will keep everything simple and it's at your fingertips and will make this process very easy.

Dr. Stukus: That's great, a call to arms for our colleagues in allergy, I love it. Before we depart, I'd like to ask you to take out your crystal ball, this is always sort of a uh-oh moment, but if you could predict what the future may look like or give us your wish list regarding our ability to evaluate and/or treat drug allergy reactions, what thoughts do you have, what would you love to see come to fruition in the next five to ten years or beyond?

Dr. Banerji: It's a great question, I'm not sure about the tattoos yet. But ways that the electronic medical record could be cleaned up without it being manual which we had gotten to talking about a little bit earlier. But also just better tools in the field of drug allergy, we don't have great tools, we have skin testing using non-irritating concentrations, it's not really a great tool. And also a lot more in the area of pharmacogenomics, understanding risk factors. I think there's just a lot of work that we need to do beyond just, "What are the symptoms? Here's what you could use for skin testing," and then maybe challenge or desensitize. I think we need a lot more in the area, in the whole field of drug allergy.

Dr. Stukus: Yeah. Well I hope that we see that. Anything in the pipeline that you're aware, you know, basophil activation test or things along those lines?

Dr. Banerji: I think there's lots of small emerging projects and literature in those areas, but I think we need a lot more.

Dr. Stukus: Excellent. Well Dr. Banerji, I can't thank you enough for spending time to go through this important document and really give us perspective and some important concepts that are really helpful for all of us as we evaluate patients with suspected drug allergy reactions and I think that this is going to be very helpful for a lot of our listeners. Before we depart, is there anything else you'd like to add?

Dr. Banerji: Just thank you. I appreciate this opportunity, I hope that the listeners learned something new today and that they find this drug allergy guidance document a really useful tool just in their day-to-day practice and management of patients with drug allergies, so thank you.

Dr. Stukus: Oh, it's our pleasure, thank you very much. We hope you enjoyed listening to 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 www.aaaai.org for show notes and any pertinent links including the Journal issue that we discussed today from today's conversation. If you like the show, please take a moment to subscribe to our podcast through Apple Podcasts, Google Podcasts or Spotify, so you can receive new episodes in the future. Thank you again for listening.