Dr. Mariam Hanna:
Hello, I'm Dr. Mariam Hanna and this is The Allergist, a show that separates myth from medicine, deciphering allergies and understanding the immune system. Allow me to share with you my super simplified antibiotic allergy counseling to explain to patients the mechanism of their rash. Are you ready? It was either the bug, the drug, or an ill-fated interaction between the bug and drug. Oftentimes a simple oral challenge done in office is all that's needed. Contrast this to other drug allergy stories we hear. A patient diagnosed with lymphoma was prescribed Rituximab, a treatment that could offer the best chance of remission, but during the first infusion, within minutes, the patient developed an intense burning sensation in the chest. Their face became flushed, elevated heart rate and breathing became a struggle. The infusion was stopped immediately and the patient was treated. Next time more pre-medication. The same story. The third time, a longer course of steroid, antihistamines, H1 blocker, and a slower infusion rate. Landed in the hospital, admitted, fever, changes on blood work and another reaction.
The medication was this patient's lifeline and yet their body was rejecting it. The fear in the room is often palpable at this point. Now, what? Complex drug allergy and desensitization is really not for the faint of heart. The process I think of as a delicate balance of pre-medication and conducting a drug in a controlled manner. It kind of reminds me of the Mickey Mouse clip from Fantasia where he's conducting the buckets and the mops in an orchestrated manner. She may not be Bach, but today's allergist will conduct us along the path to understanding and managing drug allergies.
Allow me to introduce Dr. Christine Song. She's an Assistant Clinical Professor in the Department of Allergy and Clinical Immunology at the University of Toronto, where she's also the residency program director. She is the drug allergy lead at St. Michael's Hospital with expertise in assessing and managing all types of drug hypersensitivity reactions in both inpatient and outpatient setting and developing novel desensitization protocols whenever necessary to help patients get their first line of care. And with that Dr. Song, thank you so much for taking time out of your busy schedule to join us today and welcome to the podcast.

Dr. Christine Song:
Wow. Thank you so much for having me. I was really excited when you invited me to be on here with you and I love, love, love that case that you just presented because I think it just is so good at highlighting the importance of properly addressing these situations.

Dr. Mariam Hanna:
So let's start by explaining what a drug allergy is and how it differs from other types of adverse drug reactions that we really don't manage in the allergy clinic.

Dr. Christine Song:
Yeah, absolutely. I mean, I think we all know that medications can cause a whole slew of different adverse reactions, but the ones that we have expertise in assessing and the ones we can perhaps do something about are the ones that we think of as these immunologic reactions. So for example, a medication might have a side effect. A first-generation antihistamine, might make someone really sleepy. That's not really an allergy per se. Whereas if a patient takes a

medication, they develop a rash or a fever or other organ involvement, something that implies that the immune system has seen this drug as something bad. Those are usually the ones that we are interested in assessing. There are a few other really severe adverse drug reactions that aren't just sort of a mild side effect, but unfortunately those are very difficult to predict. Those idiosyncratic reactions like fluoroquinolones causing tendon ruptures and statins causing other issues with the liver or the muscles. But it's really, the ones that allergists tend to see are the ones that come with rashes plus perhaps other organ systems involved.

Dr. Mariam Hanna:
We are here to help with rash decisions. I always say. Why are there some that are more likely to cause allergies versus others? Is it just we prescribe them more often or are they more amenable to causing these IgE type symptoms or type IV, type reactions?

Dr. Christine Song:
Yeah, I am pretty sure it's a combination of those penicillins and beta-lactams being so commonly prescribed or something like cefazolin being used fairly ubiquitously for preoperative antibiotic sort of prophylaxis. But there is something to be said about the drugs themselves as well. Hard to know about the IgE mediated ones, but certainly some drugs for instance, can actually cause direct mast cell degranulation, even independent of these allergic antibodies. So things like fluoroquinolones and vancomycin, for example, contrast dye, IV iron. So those are also common referrals. I think especially for the T-cell or those delayed type reactions, those ones actually probably there is something to be said about the drug. We know that there are certain HLA predispositions to having reactions to a number of those drugs. And there's lots of different models of how some of these drugs cause those reactions, whether it's the drug binds to our own proteins and stimulates that immune response or sometimes the drug itself can actually directly stimulate the T-cell receptor or affect that sort of HLA T-cell receptor kind of interaction.
So there's definitely certain drugs that are more likely to cause that, especially with certain HLA types. So the answer to your question is multifactorial. And then lastly I'd say there are certain other drugs. I do tend to see this in those sort of combo antibiotics. So your Amoxicillin clavulanate or your Sulfamethoxazole trimethoprim, there's something about those ones as well that seem to be a bit more likely to cause reactions.

Dr. Mariam Hanna:
Okay. Let's walk through just the basics of immune mechanism for our immediate reactions versus the delayed drug allergies. I heard you say it in big picture already, but let's reconfirm what those are or the difference here.

Dr. Christine Song:
So probably the most common one would be what we call based on the Gell and Coombs classification. If people remember their basic immunology, those are the T-cell reactions. And again, that can manifest in a number of different ways. It could be a sort of measles looking rash that comes up days to maybe even a week or later after starting the drug. It can sometimes be a bit difficult to differentiate from hives. So often people will say, oh, I had hives with the drug. But

when you actually see photos or get into the details, it's probably more of what we call this maculopapular, morbilliform measles type rash. So it can be fairly benign or it can actually be quite severe. It can be associated with a fever, which is always a bit more of a red flag. It can be associated with mucosal blistering, skin blistering very worrisome. For Stevens-Johnson syndrome, toxic epidermal necrolysis.
It can be associated with pustules. There's lots of other manifestations that the type IV delayed reactions can present with. And then there can be a whole slew of other organ systems being involved as well. So liver, kidney, lungs. So whenever we see someone with that sort of measles type looking rash that we suspect could be from the drug, we don't just stop at the skin. We try to make sure that there's no other involvement there. And then there are a few other much less common types of reactions, at least in adults. And you might see this more in kids, but these sort of serum sickness-like reactions where they might get a hive-like rash, but it's more burning, more inflammatory. They get joint pain, fever. And again, those ones tend to come on a bit more delayed sometimes even after the patient has stopped taking the drug. So they took the week of the drug and five days after completing the course they present with this. So those are the most common ones that we tend to see.

Dr. Mariam Hanna:
Because of the timeline involved, how do you work through that with families in the office? How do you work through the story?

Dr. Christine Song:
Yeah, absolutely. So I always want to know, they were well until what happened? If they had some sort of infection, what was that infection? Because if someone had some sort of a viral infection or bacterial infection and they went on the antibiotic and then got the rash, that's very different than someone was just getting this antibiotic prophylactically for a dental procedure. I have no other reason to think that they had some other underlying viral illness. So it's really the person was well until what? So what were the drugs prescribed for?
I have to get a sense of what were all of the drugs. Right. So often we're referred a patient and they think it was the obvious antibiotic, but it turned out that they were also taking a whole bunch of other pain medications that we can't totally rule out until we do further testing. So really patient was well until when, what were the drugs that they received, including anything that was over the counter. And exact timelines and dates are so important, it's so helpful. And details and timelines, we often will actually draw out a chart because it's sometimes hard to just think about lists of dates, but we actually try to make a drug timeline, symptom timeline.

Dr. Mariam Hanna:
That's a very handy tool, actually a visual for the patient as well as for us to look at these reactions. How reliable is skin testing? I guess one of the things is can we trust a negative skin test? Are we always worried with positive testing? Right. So what is the reliability of these tests, especially as we get into the non-standardized drugs?

Dr. Christine Song:

So the skin test is one piece of it, but the clinical history is perhaps more important. So if a skin test is negative, but I have a very convincing history of an anaphylactic reaction, I have no other explanation, would I challenge that patient? Again, that's a lot of shared decision making. It's well what drug are we dealing with? Do they need that drug? Is it just as easy to avoid it? But I will say that I very rarely get a positive skin test for drugs when it comes to those immediate reactions with the exception of Cefazolin, that one is and Rocuronium sometimes. But when I do the skin testing, I actually more recently have found the delayed interpretations to be more helpful. So when someone has a history of what sounds like a delayed type type IV T-cell mediated reaction, then I'm either left with is it safe to just re-challenge this patient depending on what type of reaction they had?
Should I do an intradermal skin test with the culprit drugs? But instead of just challenging them with the drug on the same day as the skin test because T-cells take a lot longer to activate, reactivate, do I get them to kind of monitor the skin test site? We bring them back in a week or two to then consider if we're going to do a drug challenge, almost like using the skin testing, almost like a TB skin test. It's immunologically the same idea. And then there's also patch testing. So for patients who have acute generalized exanthematous pustulosis or patients who have had DRESS like drug reaction with eosinophilia systemic symptoms. If the culprit drug is unclear, so in adults, patients are often started on 10 drugs all at once and then they get the reaction. And based on that detailed timeline, we just don't know which drug. Then I find that type of delayed intradermal or patch testing can be really helpful.

Dr. Mariam Hanna:
Okay. Let's go back to intradermal. Would you do intradermal? So I see a lot of pediatric patients and so you said serum sickness, way more common in our pediatric population. Would you consider an intradermal test with that kind of story with a delayed read?

Dr. Christine Song:
So I think in the last 10 years, the pediatric allergists have been able to get away with a lot of just direct challenges. It's very rare to do these skin tests. And I would also, again, it goes back to that shared decision making. Right. Because when I'm thinking of the adults that I'm doing this kind of testing on, they're often patients who are likely to need these drugs again fairly soon. They have a lot of medical comorbidities and just saying that they're allergic to five different antibiotics is just not going to be practical. Right. As opposed to in kids often when they do get a medication that leads to the reaction, I feel like usually it's not so many different culprit drugs that you're looking at. It's not like they started five different things like the Vanco, the subtracts and the pip tazo and the Meropenem all at the same time with their statin and everything else. I feel like if you're weighing the risks and benefits or pros and cons, I would imagine that in kids usually could be like, well, how likely are they to need this particular drug in the next five years? And then maybe we can consider re-challenging a number of years out. Whereas with a lot of our adult patients, we don't really have that luxury because you just know they're going to be back in hospital eight months later with another infection.

Dr. Mariam Hanna:

Okay. We've mentioned shared decision making a number of times already. Once a drug allergy is highly confirmed or highly suspected, what are the key things you're trying to cover with them?

Dr. Christine Song:
So let's say you have a patient who comes in with 10 things listed as their medication allergies. What I try to do is I try to prioritize, okay, which of these are actually going to be really important? And it's usually going to be the aspirin and the penicillin. And then sometimes we're, and usually we rule out all of the different contraindications to skin testing and challenging. And often we are able to de-label some of those and patients are very happy with that. But sometimes we're then left with this list of other things that are remaining.
I always ask them, "Is this something that you want us to pursue? We can." And some patients, it's interesting, some people are like, "You know what, I'd rather not get the sulfa drug challenge. I don't really need that." And I think, yeah, if you don't need it, then that's okay. Right. There's always some inherent risk whenever we challenge someone. So it's really weighing out the individual risks and benefits for each patient. If it's truly a drug that they will never need, then we don't have to worry about it. Right. And we just advise, still consider yourself allergic.

Dr. Mariam Hanna:
Okay. Let's just briefly talk about counseling that you provide around rates of resolution for our IgE mediated reactions.

Dr. Christine Song:
To see if they've outgrown it, you mean? Yeah. Sometimes if there was some rash and there was a little bit of difficulty breathing, but I wasn't sure if I was anxious or if I was really having a hard time breathing. This is a very common story. Right. So that's very different than the patient who has a cardiac respiratory arrest witnessed by anesthesia. They put them on an epinephrine infusion because it all happened in the OR. So even when you look at those immediate reactions, it's hard to give you one straight answer. For those perioperative ones, I just tell them to consider themselves allergic forever just because those reactions were so bad.

Dr. Mariam Hanna:
Because of the severity of the reaction.

Dr. Christine Song:
Yeah.

Dr. Mariam Hanna:
No, fair. And so I think even important to say that there is a spectrum that ones we will reassess and ones we will say, this reaction was concerning enough that I would just consider lifelong avoidance as the strategy here. No, that's appropriate.

Dr. Christine Song:
Exactly.

Dr. Mariam Hanna:
NSAID allergy. What about NSAID allergies? Something different,-

Dr. Christine Song:
Oh, I have a very distinct approach for NSAID allergies and the residents who work with me know this, but I mean, as you know, most reactions to the NSAIDs are usually not IgE mediated. Most of them will react to virtually most of the COX-1 inhibiting NSAIDs if they've reacted to one. But I always think of NSAIDs as often being very dose dependent. So usually when these patients come to us, it's like they took two ibuprofen gel caps and then had a wicked reaction. So I think there is something about the liquid gel caps and that fast release plus usually they're taking a higher dose. The way that I look at this is I say, look, the most important thing for most people is not so much the NSAID piece. For most people it's are they going to be able to take 160 milligrams of aspirin if they present with symptoms that are concerning for coronary artery, like an acute coronary event or for a suspected stroke, at least in our adult population. Right. And also for women who plan to be pregnant at some point in their life, I also really like to prioritize that aspirin at 160 milligrams or less because there are lots of indications in pregnancy for which 160 milligrams of aspirin is recommended. So for the aspirin challenges, I usually split them up over two separate days because if a patient gets 80 milligrams and let's say you wait a period of time and then give them 160 milligrams and then they react, it's not really clear to me if they would've tolerated just 160 or if they've reacted because I've exceeded say, arbitrarily 200 milligrams, that might've been their provoking dose. So that's different than desensitization. So a desensitization is really the assumption that they're allergic. It's not a test, it's not a test dose, it's not a greater challenge. A desensitization is the assumption or the confirmation that they are truly allergic to this drug and instead of giving them the drug, you start at a dose that's usually like one 10 thousandth of the usual dose and then you give them increasing amounts and it can take hours and often has to be done in a critical care setting. So very resource intense. So if you can prevent the poor pregnant patient who needs aspirin for their preeclampsia, if you can prevent them from having to do this whole prolonged aspirin desensitization in ICU while they're pregnant, to me that's a win. So that's why I usually we'll encourage people to do the challenge if they're willing.

Dr. Mariam Hanna:
All right. With increasing number of de-labeling for drug allergy, are you finding that you're doing less desensitization or we're utilizing this tool now just as much as ever?

Dr. Christine Song:
I would say that that's a tricky one. Just from personal experience, I would say we are probably able to de-label more people because it used to be that if you reacted to let's say one drug, you were assumed to be allergic to anything remotely related to it. So then it used to be common practice that if they needed something else remotely related that they would just get desensitized to it. So for drugs that just are not common, but they're something that patients really need, a patient was reacting to her urso, like her ursodeoxycholic acid for her primary biliary cirrhosis. So we had to desensitize them. We end up doing a lot of chemotherapy

desensitizations because they often do have, again, very true IgE mediated reaction, skin test positive, so lots of chemo desensitizations. We recently had a patient who had an acute generalized exanthematous pustulosis to her Imatinib, which she really needed for her GIST tumor.
And so we were able to do a desensitization for that. Being Toronto and the higher immigrant population and managing a lot of cases of TB here, we end up doing a lot of desensitizations for TB meds, even for patients who've had really severe reactions like DRESS, which historically has often been a contraindication to doing desensitization, but there have been some reports. And so we figure if it's been published and successful somewhere and the patient really has no other option, then we'll try it. So yeah, less desensitization of some of those other common drug allergies, but perhaps more of these sort of unique situations.

Dr. Mariam Hanna:
Okay. There's no right or wrong answer here, but pre-medication, how do you approach pre-medicating for desensitization? As a fellow, I worked with many different allergists and I quickly learned that they each had their own pre-medication cocktail that they would want you to spew out. Is there a standard one?

Dr. Christine Song:
It's funny because I mean you probably know there's really no evidence for the pre-medication, but that's not to say that it's not still appropriate in many situations. I actually don't have any one particular protocol because I think it really depends on the drug you're talking about and what's been published on it. So for example, for a lot of the chemo desensitizations, standard pretreatment would be a lot of dexamethasone, antihistamines, corticosteroids, montelukast, and even aspirin if they don't have a prior history of flushing, and that's standard for some of the chemo's. There really is no particular regimen. So usually when I'm making a recommendation back to the referring physician, they usually have their own standard pre-medication protocols that they'll use for said drug. And so I don't even specify, I just say pre-medication as per your protocol, because I don't really have any evidence to suggest any better pre-medication protocol.
But the area where I think people sometimes get confused is I have seen where sometimes a referring doctor will say, "They got desensitized." And I'm like, "What? They didn't get desensitized." And what they meant was they got the desensitization protocol pre-medications. So that's where I see some of these sort of errors come up where that can be very misleading. And yeah, same thing, contrast style. Every radiology department has their protocols. I don't get too wrapped up in the pre-medication specifics because I just don't think I have any evidence to back any protocol up over another.

Dr. Mariam Hanna:
And there's wisdom in admitting that as well. What practical tips would you have for healthcare providers to help patients get to the right diagnosis?

Dr. Christine Song:

Yeah, so absolutely photos are key. I would say also just some details about what the medications in question were and an idea. I recognize that when we get the referral, the whole point of them coming to us is so that we can kind of delve into the details, but giving some idea of what the reaction was can be very helpful. I'm just going to give one example that I think illustrates this. I was referring a patient for a query, penicillin allergy, and all it said was penicillin allergy on there. There was no detail and the patient had no idea. I asked her, "Do you know where you got this label from?" She had no idea. And so I had to dig through connecting Ontario where we have access to some of the other local hospitals charts, and she was admitted with jaundice for drug induced liver injury from Clavulin.
And so just again, this idea that you can have such a potentially life-threatening reaction and not have any details about it when you're first seeing the patient, the patient might not know about it, that I find I think some detail would be very helpful, if you have that available of course. Yeah, and then I think also one of the things that I do for my patients when I see them is I always try to write things down for them. So whether patients go to the emerge or their family doctor or walk-in clinic, I think if there's a suspicion that they've had a reaction to a specific drug, some patients are very good about knowing which drug that actually was. And some patients say, "I don't know, I had this horrible reaction. They said it might've been a drug, but I'm not sure which drug." So I think just having something written down for the patient I think is always really helpful.

Dr. Mariam Hanna:
Fantastic. And very practical. All right, time to wrap up and ask today's allergist Dr. Christine Song for her top three key messages to impart to patients and physicians on today's topic, drug allergies. Dr. Song, over to you.

Dr. Christine Song:
Yes. Of course in your final take three, it's hard because you feel like you've talked about everything. So if I had three sort of final points, number one is if you've suspect that your patient has had a drug allergic type of reaction, by all means there are people like us who assess this and can make some recommendations. So the first step is please refer these patients because there's often testing and recommendations that can be provided. Number two, as we had just alluded to some details about the reaction and are really quite critical. And then I would say for the third point as well, just I think updating that allergy list is really important.
So we often will assess a lot of patients and we can de-label some of their allergies or sometimes we cover in our assessment that there's actually, oh, we were referred this patient for a particular allergy, but there was actually another allergy that came up in conversation. So what we really try to outline that back to the referring doctors. So just that updating the EMR and making it clear which ones have actually already been addressed so that these allergy labels don't continue to follow them and or so it's really clear for future providers to know which medications actually are safe for the patient and which ones to still avoid.

Dr. Mariam Hanna:
Perfect. Thank you so much Dr. Song for joining us today on today's episode of The Allergist.

Dr. Christine Song:
Thank you so much for having me. It's so great to be here.

Dr. Mariam Hanna:
This podcast is produced by the Canadian Society of Allergy and Clinical Immunology. The Allergist is produced for CSACI by Podcraft Productions. The views expressed by our guests are theirs alone and do not necessarily reflect the views of the Canadian Society. This podcast is not intended to provide any individual medical advice to our listeners. Please visit www.csaci.ca for show notes and any pertinent links from today's conversation. The find an allergist app on the website is a useful tool to locate an allergist in your area. If you like the show, please give us a five-star rating and leave a comment wherever you download your podcasts and share it with your networks because details, details, details, labels, and a photo. Thank you for listening. Sincerely, The Allergist.