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.

In 1928, Dr. Alexander Fleming is noted to have returned from a holiday to find mold growing on a Petri dish of staphylococcus bacteria. The mold seemed to prevent the bacteria from growing around it. Many of us recognize this story as the discovery of one of the most essential antibiotics known to mankind, the discovery of penicillin.

Amoxicillin really did change the face of medicine and continues to be a really handy medication for most of our common upper respiratory infections, from ears to throat, to chest, to sinuses. This drug really does work wonderfully with these bugs, and if you treat kids, you've also discovered it tastes delicious, whether suspension or chewable tablets, making administration to young and old, easy-peasy. Fast-forward a couple years from 1928 and I bet you if you looked hard enough, you would find the era of, you guessed it, penicillin allergy, the most commonly reported drug allergy.

So that's what's going to be our story this time. It's siblings. The referral came and it just said, "Rule out penicillin allergy." The siblings were scheduled to come in together for evaluation and sorting through this important condition is going to change their lives. I tell you, turns out these kids have never even actually had amoxicillin. They had a grandparent and an aunt who carry this label, and as such, the family was so fearful of having this medication ever prescribed. The more I think we've come far in our specialty, the more I'm shocked by how long it takes for us to play our broken game of telephone and implement evidence-based robust guidance into the right hands.

So today we're going to dig deep into the label of penicillin allergy and support you with evidence and data to help tackle and de-label the most common drug allergy we have with Dr. Ana Copaescu. Dr. Copaescu is an allergy and immunology internal medicine specialist at the McGill University Health Center in Montreal, Canada. She is a clinician scientist at the Research Institute of the McGill University Health Center with publications in allergy immunology, particularly drug allergy, severe drug reactions, and antimicrobial stewardship. Dr. Copaescu, who also has a healthcare protest outside her very doors this afternoon, so we're going to ignore the honking in the background, joins us today and thank you so much for taking the time out of your busy schedule to join us. Welcome to the podcast.

Dr. Ana-Maria Copaescu:
Thank you very much. I'm so excited to be here.

Dr. Mariam Hanna:
I'm excited as well. Let's dig deep and not cause a protest today. How common is penicillin allergy actually? What's the number you like to quote people?

Dr. Ana-Maria Copaescu:

Penicillin allergy is actually quite common. We're talking about more than 10% of the Canadian population that can report a penicillin allergy, but among these, actually less than 1% are truly allergic. These numbers can actually be a bit more increased in hospitalized patients where we talk about up to 25% of our patients that could have a beta-lactam or a penicillin allergy label.

Dr. Mariam Hanna:
Wow, that's really common. So then what are the most common ways that people present or get labeled with this penicillin allergy? What happens to them?

Dr. Ana-Maria Copaescu:
So actually when patients present to our clinics with a penicillin allergy, the most common symptoms are going to be skin rashes such as urticaria or maculopapular rashes followed by sometimes angioedema, which is the swelling of the deeper tissues of the skin, but they can also report respiratory and gastrointestinal symptoms such as vomiting and diarrhea.

Dr. Mariam Hanna:
Has there ever been worse than that? Has there ever been fatalities associated with a penicillin allergy?

Dr. Ana-Maria Copaescu:
When we look at anaphylaxis rates, these have historically been described anywhere from 0.7% to 10% for penicillin, and these have been observed in all age groups. Now you've asked specifically about fatalities. STEM studies indicated that penicillin has shown to cause fatal anaphylaxis at a rate of 0.002% in the general population. So yes, unfortunately there have been case reports of fatal anaphylaxis related to penicillin.

Dr. Mariam Hanna:
But it is incredibly rare with many zero points and lots of zeros after that before you gave me a number. I like that it's reassuring. So how common are other non IgE-mediated reactions like serum sickness-like reactions or more concerning reactions that we talk about DRESS or SJS with penicillin?

Dr. Ana-Maria Copaescu:
So all of these reactions can be associated with penicillin and as you've mentioned, serum sickness for example, it's something that is rarely described among our patient population. So the symptoms can start several days after the patient has taken the penicillin. When we look at types of medications that cause serum sickness, yes, penicillin is considered a common cause and can represent up to 4% of all adverse drug reactions associated with penicillin. So the actual numbers are difficult to describe. Then when we look at the severe cutaneous drug reactions, Stevens-Johnson is a rare condition. We're talking about five to six cases per million per year, and then in about 30% of these cases, penicillin can be a factor. Similarly, DRESS, if we look at numbers, once again, 74% of the cases associated with DRESS were associated with antibiotics and then about 20% beta-lactams.

Dr. Mariam Hanna:
Those were very important statistics I think for us to keep in perspective when we see patients or when we worry about penicillin allergy. Now Dr. C., for one reason or another, it seems like you're quite passionate about penicillin allergy. So I must ask what were key drivers to this passion into penicillin or drug allergy? What key moments really improved your understanding or made you say, "I want to know more. I want to research more into this condition"?

Dr. Ana-Maria Copaescu:
So depending on the different definitions, we see that the patients that carry what we call a low risk allergy represent a large portion of the patients that we see in our daily clinics. Also, we are incredibly fortunate to note by having various studies that drug challenges performed by allergies are extremely safe, particularly in the pediatric populations where direct oral challenges have proven to be very safe. So if we also put together with all of that, the resource and logistical difficulties of performing skin testing, when we look at all of these combined, well, it makes us want to think, "Is there something else that we could do for penicillin, something decisive, something that could tell us, okay, well this is the management that we should do for low risk penicillin allergies"?

Dr. Mariam Hanna:
So in July 2023, just a couple of months ago, under the wonderful direction of Dr C., the PALACE study was published representing the first international randomized study to look at reducing the burden of penicillin allergy and Dr. C., I can't summarize it better than you, so you're going to have to tell me. What were key takeaways from the PALACE study?

Dr. Ana-Maria Copaescu:
So the PALACE study is the first international randomized study to look at the burden of penicillin allergy and see if the simple test dose procedure after careful assessment of course can be used to remove a patient's penicillin reported allergy compared to traditional skin or scratch testing. So in this multicenter trial across six outpatient specialized centers, we included 382 low-risk patients and these were defined using the PEN-FAST score. These patients were randomly assigned to either oral challenge with penicillin, that was our intervention arm or penicillin skin testing followed by oral challenge, and those that had a previously negative skin test. So that was the standard of care arm. The primary outcome here was a physician verified positive immune mediated oral penicillin challenge, and we managed to show that this was not different when we looked at the intervention group compared to the control group, one case in each arm. So the oral penicillin, the direct oral penicillin challenge was non-inferior to the current standard of care.

Dr. Mariam Hanna:
So it was safe to go straight to giving them a dose of the medication and monitor. You mentioned the PEN-FAST criteria. Can you walk us through what those criteria are?

Dr. Ana-Maria Copaescu:

So in patients that have a reported penicillin allergy, these are the first three letters of the score, PEN. There are four allergy history criteria that can be used. So the F stands for five or the time since the reaction of less than five years. A stands for anaphylaxis or angioedema. S is for severe cutaneous adverse reactions, and T is for treatment and whether any pharmacological treatment or unknown treatment was required for the reaction. A score of less than three from the initial validation study by Professor Jason Trubiano was associated with a very high negative predictive value.

Dr. Mariam Hanna:
So if they received any treatment for a reaction that happened under five years, so if we've seen them rapidly, they'd already get two points and then it would have to be like any kind of symptom that's concerning or a rash, specifically a rash.

Dr. Ana-Maria Copaescu:
So a rash specifically would not give them an extra point. It would have to be something that is compatible with anaphylaxis or angioedema or a very severe cutaneous adverse reaction in order for them to receive an extra point.

Dr. Mariam Hanna:
Okay. So a bad rash doesn't give them an extra point?

Dr. Ana-Maria Copaescu:
Not necessarily. And then you're going to tell me what is a bad rash right?

Dr. Mariam Hanna:
Well this is what comes to the office, right?

Dr. Ana-Maria Copaescu:
Definitely. So the description is very important and the patients will report different types of rashes and that's when it's important to take into consideration the severity of the rash and if there were any severity criteria involved there as well.

Dr. Mariam Hanna:
Okay. So this study that you mentioned, enrolling more than 300 patients, was an adult study. So can we extrapolate this data to pediatrics? We do that all the time with kids, but do you think it's safe to say from what you've seen with the adult study that we should be applying this rule in pediatrics?

Dr. Ana-Maria Copaescu:
So this is a wonderful question. Collaboration with Dr. Ben-Shoshan and Dr. Jason Trubiano, we actually try to validate the PEN-FAST score in a large Canadian prospective pediatric cohort. And this previously validated tool in an adult population was actually not useful for risk stratification in children younger than 12 years. So we think that the criteria included in the PEN-FAST that we just discussed might not provide adequate information in the pediatric

population when we compare it with the adult population. So this also highlights once again that children are not little adults and clinical decision rules need to be derived specifically and validated in that target population.

Dr. Mariam Hanna:
Okay. So it sounds like part two of another kind of validation criteria might come at some point, maybe.

Dr. Ana-Maria Copaescu:
Hopefully. Or the safety of direct oral challenge in low risk pediatric population has been shown with various publications in the past as well.

Dr. Mariam Hanna:
So maybe they don't even need criteria. We're just satisfied with the fact that they're an extremely low risk population in general. Okay, well that's good. Okay. So then in these adults, a lot of the times they don't remember the story. Where no story can be found, how do we apply the PEN-FAST criteria?

Dr. Ana-Maria Copaescu:
So we're very reassured when somebody doesn't know. So the unknown history is one of the most commonly reported reactions in our patients in general. So in the initial PEN-FAST validation study, a patient reported penicillin allergy was defined as non-immune mediated, immune-mediated, or unknown. So that was part of the definition. And among the more than 600 patients included, 96 actually had an unknown history. However, in this particular trial, when the allergy history could not be confirmed the patient was excluded from the randomization. But we do understand that the majority of times an unknown history, an unclear history can be reassuring or can make us think that the patient has a low risk history.

Dr. Mariam Hanna:
That works for me. If they don't remember, that's actually reassuring. Okay, that's a great pearl. Let's go to a different, slightly different population again. So not done in this study, but can we extrapolate this into the pregnant population that may require some antibiotic prophylaxis or antibiotic use during pregnancy?

Dr. Ana-Maria Copaescu:
So yes, this has been done in the past, so we're fortunate our colleague, Dr. Raymond Mak from British Columbia actually demonstrated the safety of direct oral challenge to amoxicillin in pregnant patients using the PEN-FAST as a risk stratification tool. Of course there are several other studies that have underlined how safe and how effective direct oral challenge is in the obstetric population. And it makes us understand that as you mentioned, pregnancy does not modify a person's risk of having an allergic reaction and it should not be a barrier to performing direct oral challenge in well stratified patients.

Dr. Mariam Hanna:

Okay. It sounds like there's a lot of low risk penicillin allergy floating around everywhere and maybe some de-labeling needs to happen. How aggressive can we get? Can we start considering de-labeling patients during an acute illness? So somebody comes in with a terrible ear infection, low risk sounding story for a true penicillin allergy. Can we just give them their first dose and observe them during an acute illness?

Dr. Ana-Maria Copaescu:
That is a wonderful question and it leads to a risk benefit discussion with our patients. So obviously we want to offer the best treatment and the best management options. If they do report an unknown reaction as we previously mentioned, or a very low risk reaction, it could actually be beneficial for them to start their antibiotic course using a penicillin based antibiotic if that is the best management for them. Obviously in an acute setting, as you've mentioned, particularly in the pediatric population, if they have a viral infection, it could be a bit tricky, right? Because if they develop a skin condition, we will probably say, oh, it's the second time they had a reaction to penicillin, which is not necessarily beneficial. That's why it's always a risk benefit discussion to have either with our adult patient or with the parent's child in order to understand that, "Yes, the majority of times it will go well, we'll have the best antibiotic to treat your infection, but if you do develop a skin reaction, we'll have to reassess you in the allergy clinic afterwards".

Dr. Mariam Hanna:
Dr. Copaescu, I was trying to stump you with a hard question. You navigated through that one seamlessly. Okay, let me try another one. I have trouble with serum sickness-like reactions and how to counsel patients, particularly young patients that may present with difficulty in moving a joint with a diffuse rash that looks almost purpuric in its resolution and they're young, and this potentially could be a long label. Where have we come along with these SSLR reactions? This was not included in the PALACE trial, but I'm curious to get your up-to-date information as to how we should counsel and how we should manage in clinics.

Dr. Ana-Maria Copaescu:
So as you already mentioned, even in the original adult validation of the PEN-FAST, having a serum sickness-like reaction was excluded, such as other manifestations such as organ related manifestations, acute interstitial nephritis, or drug induced liver injury, were all phenotypes excluded from the PEN-FAST. So we actually don't have probably enough numbers in the adult population, but when we talk about our pediatric population, we're fortunate to have a recent cohort actually published by Dr. Ben-Shoshan of 75 patients that had suspected serum sickness-like reaction. Only five presented non-severe reaction demonstrating that it's probably safe to re-challenge these patients.
So once again, it leads us to this discussion, right? Having a consent, informed consent with our adult patients or with the parents and a risk benefit discussion. So an adult who presents a very typical serum sickness-like reaction that requires a hospital stay prolonged treatment needs to understand that skin testing has not been proven as an investigative tool and that direct oral challenge can carry the risk of disease reactivation. Once again, it leads us to sitting down with our patient and deciding if it is something that we want to re-challenge or we might offer the

reintroduction of other beta-lactams with avoiding that specific penicillin that might've caused a reaction.

Dr. Mariam Hanna:
Perfect. Okay. I can't let you go without giving you a couple myths to bust. I feel like you're the right person to bust these myths. Okay? So here's the first one. Are you ready? Okay, straight up. If you have a family history of penicillin allergy, does this increase your personal risk of having an allergy to this medication?

Dr. Ana-Maria Copaescu:
So that's a wonderful one. So there is-

Dr. Mariam Hanna:
You're being polite. You're being polite. You got to bust this one, you got to just rip into it. What do you think?

Dr. Ana-Maria Copaescu:
So there's no predictable pattern to family transmission of penicillin allergy. So a patient does not need to avoid penicillin if a family member is allergic to penicillin or drugs in the penicillin family. However, this could be a bit difficult. We already addressed the severe cutaneous adverse reactions and there have been some HLA associations described, but this could be the topic of a whole new podcast, but in general-

Dr. Mariam Hanna:
That sounds like a different episode. All right, you heard it from Dr. Copaescu, in general, a family history of possible penicillin allergies, probably that guy's not even allergic, and you should probably be fine to try it and speak with your doctor to always provide you the best advice for your own healthcare. Okay, time to wrap up today's episode and ask today's allergist, Dr. Ana Copaescu, her top three key messages to impart to patients and physicians on today's topic, penicillin allergy. Dr. Copaescu, over to you.

Dr. Ana-Maria Copaescu:
So first of all, drug allergy labels are not for life, and this is something you've mentioned in the beginning. So all patients with a penicillin allergy label should have clinical evaluation that includes medical history. So the drug allergy history alone can be used to remove allergy labeled sometimes, particularly when the reactions are compatible with side effects. Second takeaway as discussed for low risk phenotypes, penicillin allergy removal can be performed safely with a direct oral challenge, not necessarily requiring a specialist skin testing. So in this context, we hope that our trial will lead to penicillin drug allergy removal in various settings around the world and performed by various healthcare professionals safely in low risk patients with adequate training and resources. And finally, after the labeling, it is recommended for patients to be provided with risk regarding future reactions to medications in the future. And any patient who presents a reaction or compatible with an allergy or not, should be instructed to document the reaction and seek evaluation by an allergy immunologist.

Dr. Mariam Hanna:
Sounds like official recommendations from our top author, Dr. Copaescu. The economic and health impact of these recommendations really ought to make healthcare providers and policymakers rethink and sit up and take notice of these needless labels of penicillin allergy. Thank you Dr. Copaescu for continuing to shed light on this important condition and joining us today on today's episode of The Allergist.

Dr. Ana-Maria Copaescu:
Thank you very much.

Dr. Mariam Hanna:
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