



Penicillin Allergies: Over-diagnosed and Under-addressed with Kimberly G. Blumenthal, MD, MSc, FAAAAI

Dr. Davis Stukus: Hello, and welcome to "Conversations from the World of Allergy", a podcast produced by the American Academy of Allergy, Asthma and Immunology. I'm your host, Dave Stukus. I'm a board-certified allergist and immunologist, and serve as a social media and 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 <http://www.AAAAI.org>. Today's edition of our "Conversations from the World of Allergy" podcast series focuses on penicillin allergy. We are going to discuss timely information to help patients, the general public, and healthcare professionals better understand how to diagnose and clarify reported penicillin allergies. We are extremely pleased to welcome Dr. Kim Blumenthal, who is an assistant professor of medicine at Massachusetts General Hospital in Boston. Dr. Blumenthal is the current chair of the Adverse Reactions to Drugs, Biologicals and Latex Committee of the Academy. With over 50 peer-reviewed publications, Dr. Blumenthal is a widely recognized expert in drug hypersensitivity, and her development of novel penicillin allergy stewardship programs designed to help clarify self-reported penicillin allergies. Today, Dr. Blumenthal has graciously agreed to join us to discuss the impact of over-reporting penicillin allergies. Dr. Blumenthal, thank you so much for taking the time to join us today, and welcome to the show.

Dr. Kimberly Blumenthal: Thank you for having me.

Dr. Davis Stukus: Let's start with some basic information. Can you give us some examples of what would include a penicillin or a beta-lactam antibiotic, and also what types of common infections are they used to treat?

Dr. Kimberly Blumenthal: Yeah, so beta-lactam antibiotics are a broad class of antibiotics that all share this common chemical structure called a beta-lactam ring, and it's crucial to their efficacy in being able to kill bacteria. But within that group of beta-lactam antibiotics, we have other drug classes. The penicillins are one of them, and a very large group of them. The cephalosporins are another drug class, and then this class of beta-lactam antibiotics also includes carbapenem and monobactam antibiotics. Those are less commonly used. So penicillin, actually the penicillins, include about 15 chemically related drugs, and so this is commonly considered penicillin, ampicillin, amoxicillin. Sometimes amoxicillin is put with another

antibiotic called clavulanic acid, and that's called Augmentin. There's also methicillin. And all of these drugs are used a lot for ear infections, throat infections, sinus infections, and then also dental infections as well as dental prophylaxis, like if you have to take an antibiotic before you go see a dentist, and then also surgical prophylaxis. A lot of surgical operations require these types of drugs before the operation. The cephalosporin group is really a big, big group that also includes some things that we've commonly heard of, including Keflex, which is cephalexin; also Cefaclor. So anything really that started with a C-E-F or C-E-P-H is probably a cephalosporin antibiotic, and it's related to the penicillins, and those drugs are really useful orally as well as, if you have a bad infection in the hospital, very useful for intravenous antibiotics. The cephalosporins are actually one of the most common used antibiotics in the hospital today.

Dr. Davis Stukus: Wow, so it sounds like this is a very important class of antibiotics that we need to have at our disposal.

Dr. Kimberly Blumenthal: Yes, it really is. So part of the problem is that when you have any allergy to any one of them, it's often really confusing for all medical providers to know which ones you can and cannot have, and it's really the tried-and-true, oldest class of antibiotics we have. Penicillin was first used in the 1940s. So they've been around a long time; they have a really good, benign sort of side-effect profile; and they're still currently used for a whole host of infections.

Dr. Davis Stukus: What percentage of people will self-report as having a penicillin allergy, and then how many of those are actually allergic?

Dr. Kimberly Blumenthal: Today in the United States, about one in ten Americans have a penicillin allergy listed on their record; and then if we look at a more sick population-- maybe if we look at a hospitalized population at any hospital across America-- up to 15 percent will have a penicillin allergy on their record. When allergists have assessed these patients, talking to them further about the allergy history, maybe doing some tests, we actually find that upwards of 90 percent are not allergic. Maybe more near 95 percent are not allergic.

Dr. Davis Stukus: Wow. So really, what you're describing are millions, millions of people that are walking around thinking that they have a penicillin allergy but they actually don't have one. Is that correct?

Dr. Kimberly Blumenthal: Yeah. We have estimated at least 30 million Americans report an allergy to penicillin, and most of them will not be allergic, and part of this might have to do with what we're calling an allergy because intolerances or side-effects are often put in what we unfortunately call the Allergy section of the electronic health record. And so somebody who might have an intolerance to penicillin is listed as an allergy, but without proper documentation, anyone with an allergy, intolerance or side-effect to penicillin might not get a penicillin or related drug when they need it.

Dr. Davis Stukus: What kind of problems come up when someone has a penicillin allergy listed on their chart, as you mentioned, if they're not actually allergic to it? In other words, what's the big deal?

Dr. Kimberly Blumenthal: I think this is a really good point, because part of healthcare and part of our prescribing is really, why the Allergy section exists, is really just to protect our patients from unsafe medical practices. So if we know you're allergic to one medication and we go to prescribe a medication that is the same or similar, the prescribers will get an alert, and we'll hopefully interrupt the prescribing of that medication for safety purposes. And while that structure is really necessary for a whole host of reasons, that structure is kind of what caused the problem of over-labeled, unverified penicillin allergy in America, and what we know now is just having this report of a penicillin allergy leads to the use of more broad-spectrum, sometimes less effective drugs that are used for infections. So when you could have used a penicillin, or could have used a cephalosporin, or should have used a penicillin or cephalosporin, you're actually given something that kills the good, the bad, and the ugly bacteria, it's more likely to cause toxic side-effects, and we have done a number of studies recently, some of which I've conducted actually, that have shown that if you're having a surgery and you go to the operating room and have a penicillin allergy on your record, you're not likely to receive the drug cefazolin, which is a cephalosporin, and that decision not to give you cefazolin actually increases your risk of having a surgical site infection, and that's a really morbid thing for a patient to have to struggle with. Also really costly to the healthcare system. Also when we think about public health, we think about resistant superbugs, and we know that giving these broad-spectrum drugs instead of the penicillins and relatives increases the risk of you having colonization or infection with MRSA-- that's methicillin-resistant Staph aureus-- and also the bad diarrheal disease, C. diff colitis. And so we did a study using United Kingdom large data sets, and actually found that having a penicillin allergy label resulted in 69 percent increased risk of MRSA and 26 percent increased risk of C. diff, and that was actually over a period of six years only after that penicillin allergy label. So it doesn't seem like a big deal to have a penicillin allergy on your record. It seems like it's there to protect you from badness happening to you in the healthcare system. But in fact, when we look at individual patients and populations, it seems to be the harms are outweighing the benefits to having that labeled incorrectly.

Dr. Davis Stukus: Wow, that's really scary. You're describing where patients are actually becoming more sick and more susceptible to some of these really difficult-to-treat infections, which can not only make them sick but lead to more complications down the road. So it sounds like it is a very big deal.

Dr. Kimberly Blumenthal: Yeah, it just shouldn't be taken lightly when you're documenting an allergy on your record, and for some allergies and some medication allergies, it's not known to be such a big deal, but in the case of antibiotics, there is this progression that if something is an allergy, you will go for something different, right? And so that something different in most cases of infection ends up resulting in increased toxicities, increased side-effects and resistant C. diff, which is terrible, these superbug colonizations. So it's really one of those things where just questioning what the allergy is on the part of the patient or the provider could end up improving the quality and safety of medical care we give.

Dr. Davis Stukus: You mentioned that 90 or 95 percent or so of people that report having a penicillin allergy don't actually have one. Can you help us better understand some of the reasons why they're so frequently over-reported?

Dr. Kimberly Blumenthal: Absolutely. So it's always been our most common reported drug allergy, but that really is just because it's the most common drug. It was prescribed since the 1940s, and so we've had a lot of time to accumulate a lot of the population with a penicillin allergy. But one of the main reasons why allergies are not all confirmed is that we're talking about different things when we're talking about an allergy. So a lot of people might have an intolerance or a side-effect, or they might have gotten, for example, diarrhea or nausea from penicillin. They might have gotten a yeast infection after penicillin, or headache or fatigue, and these are all these things that, depending on their severity, warrant documentation in our electronic health record, but do not pose contraindications to receiving penicillins or their relatives. And so part of it is what we're talking about when we're talking about allergies. There's also a couple smaller groups where when children are given penicillins, which they're commonly given because of the guidelines for ear infections and strep throat infections-- when a child is given a penicillin antibiotic-- children can just get rashes with viral infections or with bacterial infections, and so sometimes if the child is also on a penicillin or a cephalosporin, it becomes challenging to distinguish on the part of the pediatrician and on the part of the parent whether the rash was from the drug or from the infection. So the right thing is being done initially considered allergy, but what ends up happening is those children then become aged, and they come see me in my adult clinic, and no one's questioned it for their entire life, and instead of questioning that five years or so after it occurred, it's just carried through to adulthood, and other alternative antibiotics have been given in the meantime. And then finally, those who have a true allergy to penicillin-- so a true allergy that is immediate-- which is an IGE allergy, which typically includes hives or swelling, shortness of breath, anaphylaxis-- the severe, immediate symptoms to penicillin-- those patients, after a period of not being exposed to penicillin, because tolerant actually of penicillin. So patients who had a skin test that were positive were followed over time, and after a period of ten years, most of them weren't allergic anymore. So really because of the idea that not all things we're calling allergy is allergy, so this misdiagnosis in childhood, and also this mechanism problem, which is that even if you had a true allergy, it might not always persist-- that kind of creates that huge differential between who reports an allergy and who is allergic.

Dr. Davis Stukus: That sounds very complicated. It sounds like there are a lot of challenges here. Thank you for describing that. As an aside, I recently learned that at my institution, there are 12 thousand different individuals that work here that have the ability of listing an antibiotic allergy on somebody's electronic medical record, and it's just impossible to help educate everybody and get everybody on the same page. So I don't know if you have any idea of similar numbers at your institution, but it's a rampant problem.

Dr. Kimberly Blumenthal: Right. I think many different practices have different workflows on who enters allergies, and if it happens-- a lot of times it happens that whatever the patient reports, whatever's reported, gets entered, without sort of the thought of, "How is this going to impact the patient?" It's just sort of a documentation flow rather than a critical assessment of how to enter the allergy or the intolerance or the side-effect, and what implications it would have and how detailed to make it. So it's very challenging to reach everyone who's entering, editing allergy information in the health record.

Dr. Davis Stukus: You've described a lot of the challenge involved in over-diagnosis and misdiagnosis, but can you help us think through some tips to really help determine if somebody's prior symptoms while taking penicillin or penicillin-like antibiotics were due to an allergy or maybe some other reason?

Dr. Kimberly Blumenthal: Absolutely. I think that it is useful to think about rashes and cutaneous symptoms. So if there was a rash, then it might have been an allergy, but then I like to think about the circumstances around the reaction. Was there a viral infection, a bacterial infection that was known? Maybe more than one drug was given to the patient, and so there could be a possibility that only one drug rather than all of the drugs caused the reaction, as well as is there another explanation for the symptoms altogether? Once we get that sort of clarified and the circumstances around that original reaction-- which often is entirely unknown, so that's challenging to begin with. So sometimes despite having this conversation and trying to probe, we don't get many details. But the more details we can get, the better, and then kind of focusing down on the symptoms that occurred. For the skin symptoms that we might have, thinking about whether it was itching, rash, swelling, redness, and then thinking about, in addition to skin, was there another system involved? So, often the severe reactions will include the skin but also something else, like shortness of breath or wheezing or feeling lightheaded, chest tightness-- and so all of those types of signs would be more concerning to me that there might be an immediate IGE allergic reaction. All of those types of reactions should be evaluated by those that have some specialty expertise because trying a penicillin or related drug again. And then if something seems like maybe it didn't involve the skin, it wasn't very severe, maybe it's more of a side-effect or an intolerance. Now those types of reactions can really be judged in a conversation between a patient and a primary care doctor on whether it's worthwhile to try again. They might not be predictable. So just because you had a bad headache in the setting of amoxicillin for one infection a few years ago doesn't mean you're going to have that same bad headache today. So I think that intolerance and side-effect reactions don't need allergy expert expertise to be able to decide whether or not it's safe to try again.

Dr. Davis Stukus: That's great. It's really helpful to really think through the different symptoms and timing of onset and that approach. Now, in your opinion, what are some aspects that you hear from a patient that say immediately-- red flag should go up and, "Yes, this is most likely, or much more concerning that a true allergy is present"?

Dr. Kimberly Blumenthal: I think about two kind of concerning groups of true allergies. The first we talked about a little bit briefly-- these sort of immediate IGE reactions, anything that sounded like potentially anaphylaxis, anything that involved two or more of our organ systems-- so if you had a runny nose and a rash, or you had cough and a rash, or something gastrointestinal with a rash-- those would all be concerning to me for an anaphylaxis or IGE reaction. And then I try to get the sense a little bit about the severity, because not everything IGE progressed to anaphylaxis requiring, for example, an epinephrine pen and hospitalization. So asking about whether the symptoms were severe enough that they called the doctor, just discontinued the medication, were any treatments offered, was there an urgent care visit, an emergency room visit, a hospitalization that required an IV be placed or used-- and so all of those types of details, if we can get at them, we can really get at severity as well. So all of those types of kinds of warning signs make me think, "Oh, this really sounds like a potential allergy that requires formal testing before trying again." And then there's another group of reactions that can happen to a lot of drugs,

and particularly the antibiotics, and the beta-lactams can all be culprits for these types of reactions, and those are skin reactions that are very severe. So if there was a rash, I often want to ask a few more details to make sure that I feel confident that the reaction wasn't a severe cutaneous adverse reaction, and severe cutaneous adverse reactions include the reaction that-- Stevens-Johnson syndrome, toxic epidermal necrolysis, as well as DRESS reaction, which is drug reaction with eosinophilia and systemic symptoms-- so a lot of sort of alphabet soup there, but all of those reactions are actually really severe and can't be tested through our traditional allergy tests, and need more caution with the prescribing of those same drugs or potentially structurally related drugs. So I ask a lot about blistering of the skin, lesions that were in a mucosal surface-- so in the inside of the mouth, eye involvement, genitalia-- and then I ask a lot about organ involvement, particularly if the kidneys or the liver had testing that showed dysfunction is important. And so those are sort of some other types of warning signs, not for those immediate reactions, but so that I can feel confident moving forward that there was no sign of a severe cutaneous adverse reaction.

Dr. Davis Stukus: That's really helpful to hear you explain, and I think that also highlights that some of these true allergic reactions to penicillin and other drugs can really be severe and even life-threatening in some situations. So yes, those are some aspects that would certainly raise a red flag. Now, let's switch gears a little bit. I see children all the time who have a penicillin allergy listed on their electronic medical record because their parents have a reported penicillin allergy or a history of a reaction to it. So help us understand-- can a penicillin allergy actually be inherited, and do those children actually need to avoid it?

Dr. Kimberly Blumenthal: That is one of our common misconceptions about penicillin allergy is that it runs in families. I also see a lot of patients who report a first-degree relative has a penicillin allergy so they thought also that they had a penicillin allergy. That's just a common misconception, with the exception of those severe cutaneous adverse reactions that I mentioned-- the Stevens-Johnson syndrome, DRESS syndrome. Those types of reactions can have a genetic component, but to date we don't really know what that genetic component is for penicillin-related severe cutaneous adverse reactions. But generally speaking, this is not familial, and it really matters if the patient in front of you, the child in front of you, had a reaction, and if they haven't been exposed to it before, no precautions need to be taken to prescribe amoxicillin or ampicillin or a penicillin for that patient. I think if there's a heightened degree of anxiety on the part of the mom because she's seen every one of her kids have a reaction, you could always do the first dose under observation in a medical practice, but there shouldn't be any increased risk for one patient just because first-degree relatives also had an allergic reaction.

Dr. Davis Stukus: Thank you for clarifying that, and I agree it's an extremely common misconception. Let's build upon what you mentioned just now, because you talked about giving the first dose in the office. So for all these patients that have different symptoms that occur, or if it's unclear if they have side-effects or a true penicillin allergy, what types of test do we have at our disposal that really can help determine the most accurate diagnosis?

Dr. Kimberly Blumenthal: One of the best tests we have is actually to give back amoxicillin and observe for signs and symptoms of an allergic reaction, and that we call an amoxicillin challenge, or a penicillin drug challenge, and that is remarkably useful in many different scenarios, not just the rule-out of a very,

very low risk for ever having a penicillin allergy that's just described, but for patients that you're not sure that the symptoms that they described are allergic or an intolerance or it was a very mild reaction. Simply giving back amoxicillin-- and sometimes this is done in two steps or a few steps just to be able to monitor patients safely and to have a secure, safe environment for the family members and the patient to feel like if they were to have a reaction that they could be attended to-- but we also have for the IGE-sounding allergies and for any patient that is sounding like they might have had a true allergy, we can use a skin test, and the primary skin test reagent for penicillin allergy has been available for just almost ten years now as an FDA-approved product, and we can use that as well as diluted penicillin to do a skin test with results that are available in 45 minutes, and doing the skin test in patients prior to the amoxicillin challenge really does increase your safety and your security in the evaluation. So after a negative skin test, we know with 95 percent certainty that there's no allergic reaction, no penicillin allergy. And then to get that extra 5 percent, we still do an amoxicillin challenge, where we give back amoxicillin and we observe for signs and symptoms, just like for the patients who are very, very low risk, and doing that together then has a negative predictive value-- so you're not allergic to penicillin-- of 100 percent for an immediate reaction, but there's still a possibility of having a delayed reaction that night. Some sort of mild rash might develop that night or the next day, or maybe with the first long course of penicillin or amoxicillin.

Dr. Davis Stukus: So it sounds like just administering again when the history especially is not concerning for a severe or immediate-onset reaction, and then we also have skin testing available at our disposal. To build upon that, can you talk a little bit about the fascinating approach that you've taken at your hospital to really address and help reduce unnecessary labeling of penicillin allergy?

Dr. Kimberly Blumenthal: Yeah, absolutely. So we have different approaches depending on where the patient is located. So the approach to a hospitalized patient is different than an approach to an outpatient or ambulatory patient. In the inpatient hospital setting, what we really care about, from the allergy and the infectious disease perspective, is that the patient gets the right drug and gets it safely, and not all patients who have an allergy to penicillin on their record need to have a penicillin skin test in the hospital. We also in our studies found that penicillin skin testing in hospitalized patients can be really cumbersome, it can be hard. You show up to do a skin test and the patient has a lot of other appointments that day. They're going to radiology or they're on oxygen or they're eating their lunch and they don't want to be bothered. So there were so many different factors that made the inpatient setting, the hospitalized patient, hard to do skin testing, but so important for that specific infection to use the right drugs. So we implemented guidelines that use test doses. We use sort of this drug challenge approach, where, depending on the patient's allergy history, we start a lot of beta-lactam antibiotics by test doses, or sometimes full doses; and then in rare circumstances where a penicillin or very close relative is needed, we do still do penicillin skin testing in the hospital. So it's been able to sort of target what-- the penicillin skin testing we do in the hospital, as well as make sure that there aren't barriers to receiving first-line indicated beta-lactams in our hospital. And we did that at Mass General Hospital, the hospital I work at, and then we were able to spread that throughout the healthcare system that Mass General is part of. So we're now doing the same approach for all hospitalized patients at two academic medical centers and three community hospitals in one large healthcare system. And so it's worked for hospitals that had allergy access immediately, and also a couple community hospitals that didn't have allergy access immediately. And so that's really

important because while Boston is flush with allergists, there are many places throughout America where it's not the-- doesn't feel the same way, and where allergy access is a problem. And so there's a way to sort of collaborate with the community sites so that they can get-- hospitalized patients get the right drug at the right time in the inpatient setting, and then on their discharge, if they need penicillin skin testing or allergy evaluation, that happens as an outpatient.

Dr. Davis Stukus: That's amazing. Congratulations on that, on all of your hard work and efforts along that realm. As you mentioned at the beginning, with millions of Americans having this label of penicillin allergy, this type of approach really can hopefully address for as many patients as we possibly can. How long have you been working on that?

Dr. Kimberly Blumenthal: Since 2012.

Dr. Davis Stukus: Wow, okay.

Dr. Kimberly Blumenthal: Yeah. To be exact. So our first guideline approach for hospitalized patients was piloted in 2012, and we have been-- like most quality improvement kind of studies, we've modified things for our hospital; we had to modify things for our new electronic health record; we modified things to make sure that all of the allergy group at the two academic sites felt comfortable with our approach; and then we modified for places that-- for these other hospitals that didn't have access at all to an allergist inpatient. And so there's been many different modification-then-study, modification-then-study time periods between then and now.

Dr. Davis Stukus: Really, again, amazing work. Congratulations.

Dr. Kimberly Blumenthal: Thank you.

Dr. Davis Stukus: As we sort of wrap up our conversation, which has just been filled with great information that hopefully our listeners will gain a lot more understanding from, in your opinion, where is the biggest breakdown in the general understanding, not only among patients but also medical professionals, surrounding penicillin allergies?

Dr. Kimberly Blumenthal: I think that the biggest problem is thinking that the allergies that are entered are permanent, and this really is important in penicillin allergy, but important in many other allergies too. I really like the idea that patients and providers should think of an allergy list-- a medication allergy list-- that evolves like a medication list. So things can be added, things can be edited, and things can be deleted over time, and that that is the appropriate life of an allergy list. In reality, what we really see is that an allergy list just grows over time. It starts out with nothing in childhood and then just things are added, added, added, added, added, until we see, unfortunately, sick and elderly hospitalized patients with allergies that have been up to 50 long. And so I would encourage patients to think about whether allergies are appropriately documented, adequately documented. I would encourage any-- all primary care providers and any provider that clicks a button that says "Allergies Reviewed", that they actually think about what kind of information is in that allergy that they're saying that they reviewed, and to think

about whether more detail might save the patient from unnecessary avoidance of a good drug for an infection.

Dr. Davis Stukus: I've never heard anybody describe it in the way you just did, and I really love it, of the allergy list being this evolving list that should be really discussed in detail and changed over time. I'm sure that not only myself but many of our listeners will adopt that and hopefully will so-- will do so. Dr. Blumenthal, thank you again for taking the time to be with us today. This really was a great conversation, and we can't thank you enough for taking the time. Before we depart, is there anything else that you'd like to add?

Dr. Kimberly Blumenthal: No. I think for any providers that are unfamiliar with this topic but interested in getting-- doing more penicillin allergy evaluation and helping with this, there's a new study review that was just published in the Journal of the American Medical Association that was endorsed by three professional societies, including the AAAAI as well as two infectious disease societies, pharmacy societies, called the IDSA and SHEA organizations, and this publication is a review of penicillin allergy evaluation and management, but also includes toolkits for unfamiliar providers to be able to do some of these evaluations yourself-- so a history tool, an amoxicillin challenge tool-- and so I would say if this is of interest, to check that out.

<https://jamanetwork.com/journals/jama/fullarticle/2720732?guestAccessKey=cbc3185b-59df-4aa5-a4ca-92f84185ac7a>

Dr. Davis Stukus: Thank you for mentioning that, and as you mentioned, it's really hot off the press at the time that we're recording this, and we will be able to put that as a link in our show notes. That's great. We hope you enjoyed listening to today's episode. Please visit <http://www.AAAAI.org> for show notes and any pertinent links from today's conversation. If you like the show, please take a moment to subscribe to our podcast through iTunes or Google play so that you can receive new episodes in the future. Thank you, again, for listening.