

## PedsCases Podcast Scripts

This is a text version of a podcast from [PedsCases.com](http://PedsCases.com) on “**Beta-lactam allergy in the paediatric population- CPS podcast.**” These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at [www.pedsCases.com/podcasts](http://www.pedsCases.com/podcasts).

### **Beta-lactam allergy in the paediatric population- CPS podcast**

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#### **Introduction:**

Hello, my name is Larissa Shapka and I'm a paediatric resident at the University of Toronto. This podcast was produced by PedsCases and the Canadian Paediatric Society (CPS). The goal of this podcast is to summarize the CPS practice point titled “Beta-lactam allergy in the paediatric population.” The podcast was developed with Dr. Elissa Abrams, one of the authors of the practice point and the President of the Allergy Section of the CPS. She is also an Assistant Professor in the Department of Pediatrics and Child Health, Section of Allergy and Immunology, at the University of Manitoba, and an Associate Member of the Department of Pediatrics, Division of Allergy and Immunology, at the University of British Columbia. To view the complete CPS practice point, please visit [www.cps.ca](http://www.cps.ca). The script for this podcast can be accessed at [www.pedsCases.com](http://www.pedsCases.com).

Beta-lactam allergies are the most commonly reported medication allergy. However, the vast majority of these are not true IgE-mediated allergic reactions. The mislabeling of these reactions is not benign and has been associated with negative outcomes, so it is important to have a practical approach to this topic. The CPS practice point provides guidance on how to stratify and manage patients based on their risk of a true beta-lactam allergy.

#### **Objectives:**

By the end of this podcast, listeners should be able to:

1. Classify different types of drug reactions.
2. Identify negative impacts of erroneously labeled beta-lactam allergies.
3. Describe factors influencing cross-reactivity between classes of beta-lactam antibiotics.
4. Outline an algorithmic approach to assessing patients with a possible beta-lactam allergy.
5. Identify patients who are at low risk for a penicillin allergy.
6. List indications for referral to paediatric allergist for assessment of possible beta-lactam allergy.

Please note that this podcast will not focus on the acute management of an allergic reaction.

We will begin with a clinical case to provide some context and return to it throughout the podcast to apply what we learn. Let's get started.

**Case:**

You are assessing Emily, a 6-year-old girl with pharyngitis. She has a positive rapid antigen detection test for group A streptococcus, so you plan on prescribing a course of amoxicillin for this infection. As you discuss the plan with Emily's mother, she tells you that Emily is allergic to penicillin medications. "Help" you think to yourself. "What are my next steps in this situation?"

**Background:****Definition and classification of drug reactions:**

Let's begin by reviewing some terminology. According to the World Health Organization, a drug allergy is an immunologically mediated hypersensitivity reaction. Hypersensitivity reactions can be classified by the Gell and Coombs system, which divides reactions into four different types based on their underlying immune mechanism.

- **Type I** immune reactions are IgE-mediated. They are immediate, with onset of symptoms within minutes to 2 hours of exposure. Clinical presentation includes urticaria or angioedema, respiratory distress, GI symptoms, hypotension, or anaphylaxis.
- **Type II** reactions are cytotoxic in nature. These typically occur 10 hours to weeks after drug exposure, and examples include drug-induced anemia and thrombocytopenia.
- **Type III** reactions involve immune complex deposition in tissues. Symptom onset is 1 to 3 weeks after exposure to the medication. Examples include serum sickness-like reactions which can present with fever, urticaria, or arthritis/arthralgias. Many vasculitides are also type III reactions.
- **Type IV** reactions are mediated by T-cells (not antibodies) and occur 2 to 14 days after exposure to the offending drug. Type IV reactions include Stevens-Johnson syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). Maculopapular rash can also be a presentation of Type IV hypersensitivity reaction. It is important to note that while in adults, about 5% of maculopapular rashes associated with beta-lactam exposure are thought to be true Type IV reactions, this is not the case in children. Instead, most maculopapular rashes in pediatrics are due to infection, and should not preclude further use of antibiotics.

Clinically, immunologic drug reactions are often classified as immediate or delayed, based on whether symptom onset occurs within, or after, 1 hour of drug exposure. Notably, the only type of drug reaction in the immediate category would be IgE-mediated. The purpose of this classification is to clearly identify IgE-mediated reactions, given the potential for escalation of symptoms to life-threatening anaphylaxis with subsequent exposures.

Remember that because exposure is needed before sensitization can occur, symptoms of an IgE-mediated reaction are unlikely to present after first exposure to an allergen. In the context of our discussion today, this means that symptoms should not develop after the first dose of a course of antibiotics. Instead, symptoms usually are expected to occur during the latter days of antibiotic treatment. When they do develop, onset would still be expected within one hour of the last dose administration.

**Epidemiology:**

Due to the potential for anaphylaxis, IgE-mediated reactions are often very concerning for patients, caregivers, and health care providers. However, anaphylactic reactions to penicillins are rare, occurring in less than 1% of cases.

What puts patients at risk for developing a beta-lactam allergy? Parenteral, long-term, and high dose antibiotic therapy have all been described as risk factors. Family history of a beta-lactam allergy has not been implicated.

In North America and Europe, 5 to 8% of children have been labelled as having a beta-lactam allergy. However, of those assessed by an allergist, 94 to 96% tolerated beta-lactam challenges. So, why does misdiagnosis happen? One contributing factor may be misclassification of symptoms. Common side effects of antibiotics, as well as symptoms of concurrent illnesses are often mistaken for an allergic reaction. Similarly, an antibiotic and a pathogen may happen to interact in a way that mimics the presentation of true allergic reaction. Another factor may be lack of reassessment. In patients with a true IgE-mediated allergy, circulating beta-lactam specific antibodies can naturally decrease overtime. Once diagnosed though, many children carry forward the label of an allergy and avoid penicillin for life, without subsequent reassessment.

### **Implications of mislabeling:**

We've spent some time taking about why inaccurate beta-lactam allergy labelling may occur, but why does it matter? Erroneous penicillin allergy labelling has actually been associated with poorer clinical outcomes. Alternative antibiotics used to treat infections in these patients are often less desirable, and have been linked to longer hospital admissions, higher rates of admission to ICU and re-admission to hospital, as well as increased mortality.

Not only does this have negative implications for the individual patient, there are also larger-scale impacts. One of these is the increased cost to the health care system for these admissions. Importantly, the use of broad-spectrum antibiotic therapy also contributes to antibiotic resistance. Programs that have been implemented to de-label erroneous penicillin allergies have been shown to counteract these trends. Negative implications are not just limited to patients with an inaccurately labelled beta-lactam allergy. Many patients with true IgE-mediated penicillin allergies have been instructed to avoid other beta-lactam antibiotics, including all cephalosporins. This is thought to be unnecessary in more than 97% of cases. Given all of this, it is important to approach labelling and counselling of beta-lactam allergies in a deliberate manner.

### **Beta-lactam antibiotics:**

Now let's review beta-lactam antibiotics. As the name suggests, beta-lactam antibiotics are grouped together based on their shared molecular structure of a beta-lactam ring. They include the following classes: penicillins, cephalosporins, carbapenems, monobactams. The medications differ based on the R group attached to the acyl side chain. Allergenic potential may develop when the beta-lactam ring opens up and links with nearby proteins in the blood.

An important question that comes up is the potential for cross-reactivity among beta-lactam antibiotics in allergic individuals. Within the penicillin class, cross-reactivity is caused by the similarities in both the beta-lactam ring as well as the side chains. When a patient has a true penicillin allergy, all medications in the penicillin class should be avoided.

In terms of cross-reactivity between the penicillin and cephalosporin classes, estimates have greatly changed with time. In the past, it was felt that there was a 10 to 20% chance of concomitant cephalosporin allergy, thus penicillin allergic patients were advised to avoid all cephalosporins. This is now viewed as overly restrictive, and evidence has shown that the common beta-lactam ring is rarely implicated in cross-reactivity. Instead, it is side chain similarities between penicillins and cephalosporins that are responsible. The current rate of

cross-reactivity between these classes is now believed to be less than 2%. Given that incidence of true penicillin allergy is under 10% of those self-reporting a penicillin allergy, this would translate to a cross-reactivity rate of less than 1% of patients with self-reported and unconfirmed allergy.

The current recommendations from the CPS are that patients with a suspected IgE-mediated penicillin allergy should avoid cephalosporins with a similar side chain. However, cephalosporins with dissimilar side chains can be prescribed. Please refer to Table 2 in the CPS practice point or to the appendix in the PedsCases podcast script to see which penicillins and cephalosporins share similar side chains.

Now that we have covered some background information about drug allergies and beta-lactam antibiotics, we will move on to discussing an approach to a patient with a possible beta-lactam allergy.

### **Assessment of possible allergy:**

Your assessment of a patient with possible beta-lactam allergy starts with a detailed history. This will guide risk stratification, and determination of need for further assessment, including referral to an allergist, skin testing, or an oral challenge.

### **History:**

The following key questions should be asked on history after a possible drug reaction:

1. Which medication was prescribed, and what was the indication for it?
2. How many courses of the medication did the patient receive? Have they received any related medications?
3. How many doses were administered before the onset of the reaction?
4. How long did it take for symptoms to develop after the dose was taken?
5. Were any concurrent medications taken?
6. What were the characteristics of the reaction? This includes a description of any skin symptoms and photographs if possible.
7. Was the medication stopped?
8. How was the reaction managed? Was medical attention sought?
9. How long did symptoms last?
10. Were there any symptoms suggestive of a systemic non-immediate immunologic reaction such as unexplained fever, arthritis/arthralgia, lymphadenopathy, skin exfoliation, or mucous membrane involvement?
11. Were any symptoms consistent with a severe cutaneous adverse drug reaction (e.g., SJS, DRESS or AGEP)?
12. Has the same medication been taken again? If so, did a reaction occur?

### **Skin testing:**

International guidelines recommend epicutaneous and intradermal testing as part of the workup of a suspected IgE-mediated allergy. However, the utility of these tests varies between adults and children. Skin testing is less likely to be useful in children due to poor negative and positive predictive values. A recent study revealed that 94% of children with a positive oral challenge for penicillin had a negative skin test. Additionally, the positive predictive value for penicillin allergy in children is only around 40%. Therefore, skin testing is not a useful screen for a penicillin allergy, unless there is a history of a convincing allergic reaction. It is also important to know

that skin testing is specific to the standardized reagent used, such as penicillin itself, so even when it is done, it does not rule out an allergy to other members of the same antibiotic class with different side chains (such as amoxicillin).

Provocative drug challenge:

An oral drug challenge is the gold standard test to rule out an IgE-mediated allergy, and would be indicated in situations where there is low clinical suspicion for a true allergy. Skin testing is not a pre-requisite for a provocative drug challenge. In fact, data indicates it may be as reliable to go directly to an oral challenge without skin testing. Contraindications for a provocative drug challenge include a history of recent anaphylaxis, or systemic non-immediate immunologic reaction such as serum sickness-like reaction, SJS, DRESS, or drug-induced hemolytic anemia.

When performed, oral drug challenges should use the specific beta-lactam in question, and not another group member with a different side chain. There is variation in how different centres perform oral challenges, with some administering a single dose challenge and others doing graded dosing in two steps.

Case:

Now let's return to our case.

You start to collect more details from Emily's mother about the nature of her previous reaction to penicillins. You find out that Emily had a reaction to amoxicillin a couple of years ago after it was prescribed for an ear infection. The symptoms included a rash on her torso, which her mother describes as "tiny red bumps." She thinks the rash developed a couple of days into the course of antibiotics and lasted for a few days but doesn't remember any specific timing in relation to a dose administration. Emily did not have any hives, lip or throat swelling, difficulty breathing, vomiting, diarrhea, or dizziness. She did not require any emergency medical attention. Her mother does not remember blistering inside the mouth, peeling skin, joint pain or swelling, or ongoing fevers as part of the reaction. Emily's parents brought her to her primary care provider after and were told she may be allergic to amoxicillin and should stop taking it. Emily has avoided all penicillin medication since. She has not been seen by an allergist. Her mother is worried about the potential for further allergic reactions and is requesting you prescribe a different type of antibiotic.

**Identifying patients at low risk for penicillin allergy and principles of management:**

The CPS practice point outlines an algorithmic approach to assessing a possible penicillin allergy. In this podcast, we will discuss some overarching principles guiding the management of possible beta-lactam allergies and the decision-making process. Please refer to Figure 3 in the practice point or to the appendix in the PedsCases podcast script to see the very helpful flowchart outlined by CPS to identify low-risk patients.

Children with a suspected penicillin reaction who have since tolerated the medication are not allergic. Penicillin can be prescribed again.

On the other end of the spectrum, patients diagnosed with a penicillin allergy by an allergist should be considered to be allergic. However, an allergist should reassess them in 5 years, as they may outgrow the allergy.

Many cases, however, will be less clear-cut. In these instances, further information is needed to determine the likelihood of a penicillin allergy – for instance, the onset, type, and duration of

symptoms experienced during the reaction. You should try to determine whether the previous adverse exposure resulted in acute or delayed symptoms.

If there are concerns about a potential IgE-mediated allergy, indicated by (a) acute onset of symptoms within 2 hours of dose administration, (b) signs of urticaria or angioedema, wheeze, dyspnea, throat tightness/swelling, voice change, dizziness, syncope, hypotension, or vomiting or diarrhea, *and* (c) symptom resolution within 24 hours of discontinuing the antibiotic, then penicillin allergy is possible.

Children with suspected IgE-mediated reaction should be referred to an allergist for further assessment. They should avoid all penicillins as well as cephalosporins with similar side chains. Cephalosporins with dissimilar side chains can be prescribed. In certain circumstances in which the medical team would like to have the option of using a particular cephalosporin with a similar side chain, a provocative challenge can be discussed with an allergist.

Delayed symptoms can also be indicative of a possible penicillin allergy in some cases. Children with severe systemic or cutaneous delayed reactions after penicillin should be referred to an allergist for assessment and counselling. Symptoms of severe systemic or cutaneous adverse reactions include mucous membrane involvement, skin desquamation, arthritis/arthralgia, lymphadenopathy, ongoing unexplained fever, or evidence of renal or liver involvement. In these cases, the specific antibiotic in question should be avoided. In regard to use of other penicillins or cephalosporins with similar side chains, the decision should be made based on a risk/benefit analysis. There is no strong evidence to indicate cross-reactivity in severe delayed allergic reactions, but some organizations suggest avoiding cephalosporins with similar side chains.

In cases where there were delayed symptoms, but no symptoms indicative of severe systemic or cutaneous reactions, the child should be considered at a low risk for allergy. Children at low risk of having a true penicillin allergy, including those with mild delayed exanthems, can have the medication prescribed again. One can consider giving a single test dose of amoxicillin (15mg/kg) with a 1-hour observation period to provide reassurance and confirm no allergy is present. Other beta-lactam antibiotics (including cephalosporins with similar and dissimilar side chains, carbapenems, and monobactams) can be prescribed without monitoring.

If inadequate details are available or symptoms do not clearly fit into acute or delayed timeline, then penicillin allergy is possible, and the child should be treated as such. Medication re-exposure should be avoided and patients should be referred to an allergist.

### **Case:**

Based on the history of Emily's rash after amoxicillin, you believe that she is at low risk of having a penicillin allergy. You explain to her mother that she did not have any acute symptoms that would be concerning for a true allergic reaction, and no delayed symptoms that make you worried for any other severe drug reaction. Instead, you suspect that the rash could have been due to a virus. Given this, you feel that amoxicillin is still the most appropriate choice to treat her group A streptococcus pharyngitis. You suggest a supervised test dose, which her mother is in agreement with. You also educate Emily and her family that as long as she doesn't have further symptoms, there is no need to avoid penicillins in the future.

### **Key points:**

Before we leave, let's review a few key points:

1. Reported beta-lactam allergies are common, but most cases are not a true drug allergy.
2. Erroneous labeling of beta-lactam allergies can have adverse effects.

3. The history of the reaction will help you determine if a patient is at low or high risk of having a beta-lactam allergy. Key distinguishing factors include onset, type, and duration of symptoms, as well as any subsequent exposures.
4. If symptoms are not consistent with an IgE-mediated allergy or severe systemic or cutaneous drug reaction, the patient is at low risk for penicillin allergy, and can receive penicillins.
5. If an IgE-mediated allergy to penicillin is suspected, penicillins should be avoided, as well as cephalosporins with similar side chains. The patient should be assessed by an allergist.
6. Children with severe systemic or cutaneous drug reaction should avoid re-exposure and be assessed by an allergist.
7. After a beta-lactam allergy has been diagnosed by an allergist, patients should be reassessed in 5 years as they may outgrow it.

That concludes this podcast reviewing the Canadian Paediatric Society practice point on “Beta-lactam allergy in the paediatric population.” We hope you found this episode helpful. Thank you very much for listening!

**References:**

Wong T, Atkinson A, Jong G, Rieder MJ, Chan E, Abrams E. Canadian Paediatric Society, Allergy Section Executive. Beta-lactam allergy in the paediatric population. January 30, 2020.

**Appendix:**

**Referenced supplemental tables and figures from CPS practice point:**

**Table 2. Chemical structures of 7-position side chains of penicillins and cephalosporins**

Similar side-chain cross-reactivity within group		
Group 1	Group 2	Group 3
cefoxitin cephalothin cephaloridine penicillin g	cefaclor cephradine cephalexin cefadroxil cefatrizine cefprozil amoxicillin ampicillin	cefepime ceftizoxime cefpime cefotaxime cefpodoxime ceftriaxone cefetamet cefteram

**Table 3. Chemical structures of 3-position side chains of cephalosporins**

Similar side-chain cross-reactivity within group					
Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
cefadroxil cephalexin cephradine	cefmetazole cefoperazone cefotetan cefamandole	cefotaxime cephalothin cephapirin	ceftibuten ceftizoxime	cefuroxime cefoxitin	cefdinir cefixime

**Figure 3. Algorithm to identify paediatric patients at low risk for penicillin allergy**

