



## BETA-LACTAM ALLERGY: EVALUATION OF ALLERGY AND EMPIRIC ANTIBIOTIC SELECTION IN PATIENTS WITH A REPORTED ALLERGY

Up to 15% of hospitalized patients report an allergy to penicillin. However, it is estimated that the label of a “penicillin allergy” is either inaccurate or not indicative of a true IgE-mediated reaction in up to 90% of patients. Often, penicillin “allergies” are miscategorized due to family history, non-allergic adverse reactions or confounders related to the patient’s underlying illness, or historical childhood events. Furthermore, IgE mediated penicillin allergy wanes over time, with 80% of patients penicillin-tolerant 10 years after the reported reaction. Being labelled as penicillin allergic results in dramatic shifts in antibiotic use, with more frequent use of vancomycin, fluoroquinolones, and clindamycin. These alternative agents, as compared to beta-lactam therapy, may be associated with increased toxicity (kidney injury with vancomycin), collateral damage (*C. difficile* infection with fluoroquinolones and clindamycin), clinical failure, increased risk of surgical site infection, increased length of stay, and mortality. The incorrect labelling of a sizable proportion of patients with a penicillin allergy adversely affects patient outcomes, which makes it imperative to identify mislabeled patients.

While a detailed medication history by itself may identify erroneous “allergies”, it may not be effective in patients unable to provide a reliable history or with limited medical record at that institution. Penicillin skin testing (PST) with the PRE-PEN® skin test antigen, which is FDA indicated for the assessment of penicillin allergy along with Penicillin G, has a 97-99% negative predictive value. Approximately 95% of patients with a reported penicillin allergy have a negative penicillin skin test and can be safely prescribed penicillins. Inpatient use of PST by a variety of clinicians (pharmacists, Infectious Diseases fellows, other physicians) and in a variety of settings (Emergency Department, Intensive Care Units, general inpatient floors) has led to significant improvements in antibiotic use, specifically in regards to reducing unnecessary use of vancomycin, fluoroquinolones, carbapenems, and aztreonam.

This is a guideline for beta-lactam allergy evaluation in the inpatient setting at Michigan Medicine for patients who report a history of allergy to a beta-lactam antibiotic. This guideline is designed for patients who specifically have a penicillin and/or cephalosporin allergy history. It outlines the following:

- Steps to perform a **beta-lactam medication history** review to clarify the reaction (allergy vs. intolerance), and for allergies, identify tolerance of beta-lactam antibiotics after the reported adverse drug reaction event. In a pilot at Michigan Medicine, a significant number of patients were able to have their allergy removed based on such a review.
- Guidance for optimal **initial antimicrobial therapy selection** based on risk stratification if the beta-lactam allergy cannot be removed based on the above medication review.
- Guidance for **when to place a consult for the beta-lactam evaluation team**, and what testing that team may perform.

- The primary inpatient team should review all beta-lactam allergies with the patient and update the allergy label whenever additional relevant information is obtained
- The primary team may perform a **beta-lactam medication history review** to clarify the reaction (allergy vs. intolerance), and for allergies, identify tolerance of beta-lactam antibiotics after the reported adverse drug reaction event.
  - a) If the reaction was consistent with intolerance (non-allergic adverse reactions (fatigue, chills, headaches, and isolated GI symptoms such as nausea, vomiting, diarrhea, and abdominal pain) to any beta-lactam or family history of allergy, then the allergy history should be updated to note that the reaction was consistent with intolerance or family history, not an allergy, and that the patient can safely receive beta-lactams.
  - b) If the allergy occurred to amoxicillin or ampicillin, then the allergy can ONLY be removed if the patient subsequently tolerated an antibiotic containing amoxicillin or ampicillin. If alternative penicillin agents were tolerated in a patient with a history of an amoxicillin/ampicillin reaction, then the patient's medication allergy history should be updated with dates and name of the penicillin based antibiotic tolerated. However, the penicillin allergy label cannot be completely removed as some patients may be mono-sensitized to aminopenicillins (i.e., amoxicillin and ampicillin)
  - c) If the allergy occurred to a penicillin-based antibiotic other than amoxicillin or ampicillin, then the allergy label can be removed if ANY penicillin-based antibiotic was subsequently tolerated by the patient.
  - d) If the allergy occurred to amoxicillin/clavulanic acid, then the allergy label can ONLY be removed if the patient tolerated amoxicillin/clavulanic acid. See b and c above regarding ability to delabel/update based on past tolerance of penicillins. Any other penicillin antibiotic course tolerated should be updated on the patient's medication allergy record, but as some patients may be mono-sensitized to clavulanate, the clavulanate allergy label cannot be removed.
  - e) If the allergy occurred to a cephalosporin, carbapenem, or aztreonam, then the allergy can only be removed if the tolerated course contained that exact agent. If alternative beta-lactam agents (including other cephalosporins) were tolerated in a patient with a history of a cephalosporin reaction, then the patient's medication allergy history should be updated with dates and name of the beta-lactam antibiotic(s) tolerated but the cephalosporin allergy label cannot be completely removed.
  - f) The allergy record should be updated as appropriate (NOTE: Pharmacists have the independent authority to document in the MiChart Allergy record). The medication allergy label should be updated to include the name of the medication and dates of administration. The primary team should be notified of the change. In addition, the beta-lactam evaluation team should be notified in all cases of a change to an allergy label. The beta-lactam evaluation team will provide patient education, notify the patient's primary care physician, other providers, and outpatient pharmacy, as appropriate. The patient may be given a wallet-sized medication beta-lactam allergy card with the updated information if appropriate.

- If the beta-lactam allergy cannot be removed based on the above medication review, **initial antimicrobial therapy choices can be made by using this guidance:**
  - First, risk stratify the patient's reaction based on the history into one of four categories defined below
    - **Low-risk:** Pruritus without rash, remote (>10 years) unknown reaction, mild rash (any rash that self-resolves without additional medical intervention (i.e., mild maculopapular rash) with no other symptoms, patient denies allergy but is on record
    - **Medium-risk:** Urticaria/hives with no other symptoms, severe rash with no other symptoms (IF responses to questions in 'Contraindications' below are all 'no'). Severe rash defined as: rash that requires medical intervention (corticosteroids, anti-histamines) and/or requires ER visit or hospitalization.
    - **High-risk;** any of the following: Respiratory symptoms (chest tightness, bronchospasm, wheezing, cough), angioedema (swelling, throat tightness) cardiovascular symptoms (hypotension, dizzy/lightheadedness, syncope/passing out, arrhythmia), anaphylaxis
    - **Contraindications to Allergy Evaluation and Removal:** Organ damage (kidney, liver), Drug Induced Immune-Mediated Anemia/Thrombocytopenia/Leukopenia, Rash with mucosal lesions (Stevens-Johnson Syndrome/Toxic Epidermal Necrosis), Rash with pustules (acute generalized exanthematous pustulosis), Rash with eosinophils and organ injury (DRESS – drug rash eosinophilia and systemic symptoms), Rash with joint pain, fever, and myalgia (Serum Sickness)
      - The following is a set of screening questions that may help elicit contraindications to testing. If the adverse drug event involved a **severe** rash (see above definition), please ask the following:
        - Did you notice any joint or muscle pains with the rash?
        - Did you notice any ulcers/lesions in the mouth or genitals?
        - Where you told that your kidneys/liver were damaged by the drug?
        - Did the drug cause your blood counts to be affected (Red Cells, White Cells, Platelets)?
        - Any 'yes' to the above would constitute a reaction consistent with a "Contraindication" categorization
  - Once the patient's reaction risk is stratified, empiric antibiotic selection can be made based on the following:
    - **Low- medium risk penicillin allergy: Cephalosporins may be utilized. Penicillins should generally (see NOTE below) be avoided.**
    - **Low- medium risk cephalosporin allergy: Penicillins may be utilized. For alternative cephalosporins, if the exact cephalosporin agent is known, then using a cephalosporin with dissimilar side chains (Appendix) would be acceptable. For example, ceftazidime can be prescribed to a patient with a low-risk allergy to cephalexin. The exact cephalosporin and those agents that share side chains (Appendix) should generally be avoided (see NOTE below). Aztreonam or a carbapenem are safe to use in all instances.**
    - **High-risk penicillin, cephalosporin, or carbapenem allergy: Aztreonam may be utilized (except if ceftazidime or ceftiderocol is the documented drug allergy)**

- In the setting of **“Contraindications to Allergy Evaluation and Allergy”**: Avoid penicillins, cephalosporins, and carbapenems. Aztreonam may be utilized except if ceftazidime or cefiderocol is the documented drug allergy. Beta-lactams may be utilized if endorsed by allergy consult. *Also note that drug-induced liver injury and acute interstitial nephritis are thought to be drug-specific, so agents in another class (cefazolin if AIN developed to nafcillin, for example) may be considered depending on the clinical scenario, without allergy consultation. In addition, serum sickness is almost always associated with cefaclor but appears to be uncommon with other beta-lactams, which are likely safe to use (without allergy consultation).*

- NOTE: The main purpose of this protocol is to increase the utilization of beta-lactam antibiotics and reduce the use of alternative antibiotics in the appropriate clinical circumstances. However, deviation from the above recommendations may be appropriate based on the particular clinical scenario. A careful discussion of the risks and benefits should be performed in this setting.
- The allergy record should be updated with any new information regarding tolerance/intolerance of beta-lactam agents. At a minimum, the medication allergy label should be updated to include the name of the medication and dates of administration. The beta-lactam evaluation team should be notified in all cases of a change to an allergy label. The beta-lactam evaluation team will provide patient education, notify the patient’s primary care physician, other providers, and outpatient pharmacy, as appropriate. The patient will may given a wallet-sized medication beta-lactam allergy card with the updated information if appropriate.

- In patients where the above steps do not enable optimal antimicrobial therapy, **consulting the beta-lactam evaluation team should be considered.**

- NOTE: Pharmacists have the authority to order consults to the beta-lactam evaluation team. “Per policy, no cosign required” should be chosen as the ordering mode and the attending on service as the ordering provider. The attending on service should be notified of the placement of the order.
- The beta-lactam evaluation team will consist of dedicated members who are trained and supervised by Allergy. The specific testing/procedure/challenge protocols and details will be consistent with those utilized and endorsed by Allergy, and include the use of the following procedures, depending on the scenario:
  - Direct full dose challenge
  - Test dose challenge
  - Penicillin skin testing
  - Desensitization
- Barriers to beta-lactam allergy evaluation should be considered before consulting the team, and include the following:
  - Patient currently experiencing an allergic reaction.
  - Discharge is imminent
  - Patients in the ICU must be off vasopressors for at least 24 hours
  - Patients who received an anti-histamine in the preceding 3 days. Re-evaluate patient after the 3-day window has lapsed.

**Appendix: Cross-Reactivity Between Cephalosporins (only necessary when determining risk of cephalosporin-> cephalosporin cross-reactivity)**

See bolded recommendations on pages 3-4. Combinations with an 'X' (red boxes) share R1 side chains, and therefore are at a higher risk of cross-reactivity. Combinations without an 'X', or those not listed, do NOT share R1 side chains and exhibit a decreased risk of cross-reactivity. For example, cefazolin does not share a R1 side chain with any cephalosporin and can be safely prescribed in a patient with a mild-moderate allergy to any other cephalosporin. However, cephalexin shares an R1 side chain with cefadroxil, and so should be avoided in a patient with a mild-moderate cefadroxil allergy.  
Note: both the matrix and the table present the same information, just in different formats. Derived from Blumenthal KG, et al. Lancet 2019;393:183-198

	Cefaclor	Cefadroxil	Cefprozil	Cephalexin	Cefepime	Ceftriaxone	Cefotaxime	Cefpodoxime	Ceftazidime	Cefiderocol	Aztreonam
Cefaclor		X	X	X							
Cefadroxil	X		X	X							
Cefprozil	X	X		X							
Cephalexin	X	X	X								
Cefepime						X	X	X			
Ceftriaxone					X		X	X			
Cefotaxime					X	X		X			
Cefpodoxime					X	X	X				
Ceftazidime										X	X
Cefiderocol									X		X
Aztreonam									X	X	

<b>Clinically relevant cross-reactivity:</b>
Shared R1 Side Chain: Cefaclor, Cefadroxil, Cefprozil, Cephalexin
Shared R1 Side Chain: Cefepime, Ceftriaxone, Cefotaxime, Cefpodoxime
Shared R1 Side Chain: Ceftazidime, Aztreonam, Cefiderocol

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The recommendations in this guide are meant to serve as treatment guidelines for use at Michigan Medicine facilities. If you are an individual experiencing a medical emergency, call 911 immediately. These guidelines should not replace a provider's professional medical advice based on clinical judgment, or be used in lieu of an Infectious Diseases consultation when necessary. As a result of ongoing research, practice guidelines may from time to time change. The authors of these guidelines have made all attempts to ensure the accuracy based on current information, however, due to ongoing research, users of these guidelines are strongly encouraged to confirm the information contained within them through an independent source.

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