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

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.

- 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 pharmacist on 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.
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, cefazolin 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 ceferodecto 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.
Appendix: Cross-Reactivity Between Cephalosporins
(Derived from Blumenthal KG, et al. Lancet 2019;393:183-198) Combinations with an ‘X’ (red boxes) share side chains, and therefore are at a higher risk of cross-reactivity. Combinations without an ‘X’, or those not listed, do NOT share side chains and exhibit a decreased risk of cross-reactivity. For example, cefazolin does not share a side chain with any cephalosporin, and therefore exhibits a decreased risk of cross-reactivity with any cephalosporin. Some examples of cephalosporins that do not share side chains with any other beta-lactam: Cefazolin, Cefdinir, Ceftaroline. Note: both the matrix and the table present the same information, just in different formats.

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

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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