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BETA-LACTAM ALLERGY
EVALUATION, ANTIBIOTIC SELECTION, AND BETA-LACTAM ALLERGY EVALUATION SERVICE CONSULTATION 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, and 80% of patients are 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, are 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 effects patient outcomes, which makes it imperative to identify mislabeled patients.**

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 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 identify tolerance of beta-lactam antibiotics after a reported allergic reaction.

- 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.

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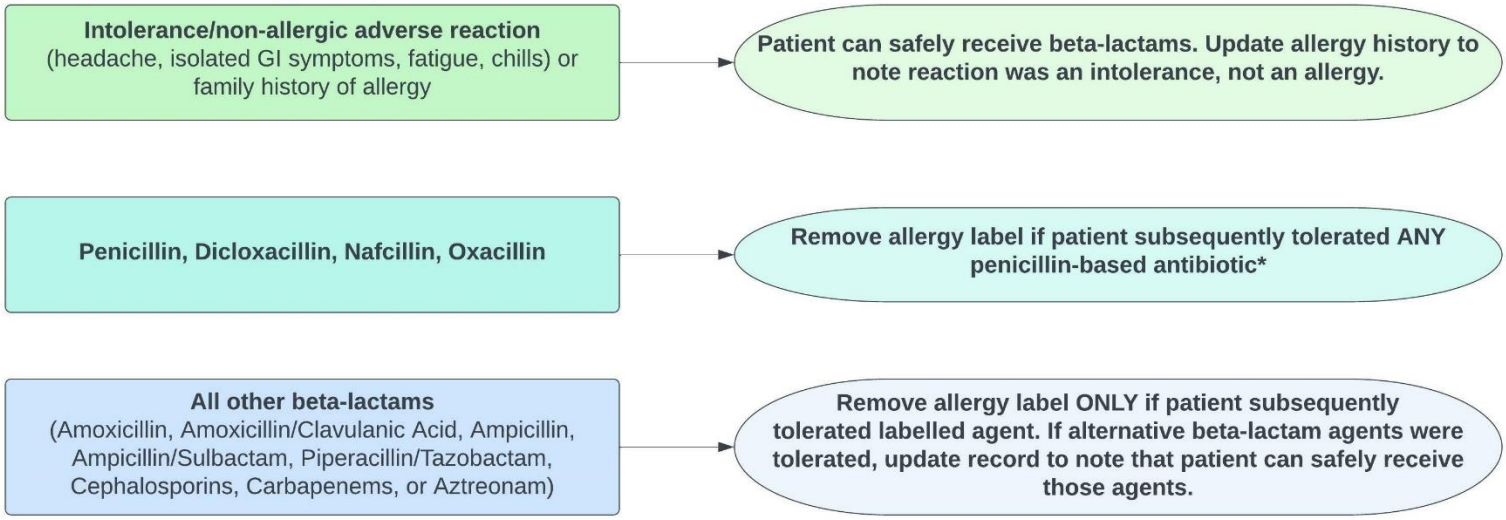
The primary team may perform a **beta-lactam medication history review** to clarify the reaction (allergy vs. intolerance), and for allergies, identify whether patients have tolerated beta-lactam antibiotics after the reported adverse drug reaction. The primary inpatient team should review all beta-lactam allergies with the patient and update the allergy label whenever additional relevant information is obtained.

When conducting a beta-lactam medication history review, inquire:	
When did the reaction occur?	(If the adverse drug reaction involved a severe rash) *Did you have any joint/muscle symptoms, ulcers/lesions in mouth or genitals, kidney/liver damage, or any impact to blood counts?*
What was the nature of the reaction (e.g., itching, rash, hives, shortness of breath, wheezing, swelling, syncope)?	
Which antibiotics have you tolerated since the reaction?	

Drug Allergy Label	**Update Allergy Record**

Advanced-practice practitioners, medical assistants, nurses, pharmacists, and physicians have the independent authority to document in the MiChart Allergy record



- * 'Penicillin-based antibiotic' refers to Amoxicillin, Amoxicillin/Clavulanic Acid, Ampicillin, Ampicillin/Sulbactam, Dicloxacillin, Nafcillin, Oxacillin, Penicillin, and Piperacillin/Tazobactam
- When documenting tolerance of agents, ideally include both the name of the medication and dates of administration.
- ***The beta-lactam evaluation team should be consulted in all cases of a change to an existing allergy label.***

If the beta-lactam allergy cannot be removed based on the above medication review, **antimicrobial therapy choices** can be made by using this guidance:

Allergy Risk Stratification	Appropriate Antibiotic Selection
Low- Risk Allergy: • Remote (>10 years) unknown reaction • Patient denies allergy but is on record • Pruritis without rash • Urticaria/hives with no other symptoms • Mild to severe rash* with no other symptoms **If severe rash, ask: Did you have any joint/muscle symptoms, ulcers/lesions in mouth or genitals, kidney/liver damage, or any known impact to blood counts? Any 'yes' would constitute a reaction consistent with a **severe non-IgE Allergy*** **High-Risk Allergy:** • Anaphylaxis, respiratory symptoms, angioedema/swelling, cardiovascular symptoms (syncope/passing out, arrhythmia) **Severe non-IgE Allergy** *(see also footnote #)*: • 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)	**Low Risk Penicillin Allergy**: Any cephalosporin may be utilized **Low-Risk Cephalosporin Allergy**: Any penicillin may be utilized. May also use cephalosporins with dissimilar side chains. Below groups share side chains: Group A: Cefaclor, Cefadroxil, Cefprozil, Cephalexin Group B: Cefepime, Ceftriaxone, Cefotaxime, Cefpodoxime Group C: Ceftazidime, Cefiderocol *Cross-reactivity matrix with same information available in Appendix.* **High Risk Penicillin Allergy:** May use cephalosporins with dissimilar side chains. May use any carbapenem. The only cephalosporins that have identical side chains with a penicillin are ***Cefaclor***, ***Cefadroxil***, and ***Cephalexin***. <u>All other cephalosporins (for example, cefazolin) do not share identical side chains and can be used*.</u> *Cross-reactivity matrix with same information available in Appendix.* **High-Risk Cephalosporin Allergy**: May use any carbapenem. Avoid penicillins and cephalosporins. **Avoid penicillins, cephalosporins, and carbapenems.** **Aztreonam** may be utilized **except** if ceftazidime or cefiderocol is the allergy.

- *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.*
- *Specifically, Cefaclor, Cefadroxil, and Cephalexin share identical side chains with Amoxicillin/Ampicillin. Other Penicillins (such as Oxacillin and Piperacillin) do not share identical side chains with any cephalosporin. As such, patients with a <u>confident</u> history of a high-risk allergy to a penicillin <u>other than ampicillin/amoxicillin</u> can receive any cephalosporin.
- #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. 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.
- 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 consulted in all cases of a change to an existing allergy label.***

The **Beta-Lactam Allergy Evaluation Service (BLAES)** consists of dedicated members who are trained and supervised by Allergy.

BLAES should be consulted:

- **If the beta-lactam allergy is currently impacting optimal antimicrobial therapy (patient is receiving vancomycin, aztreonam, clindamycin, fluoroquinolone, carbapenem because of the allergy)**
- **If the beta-lactam allergy is likely to impact care in the future. For example, a patient prior to surgery, transplant, or who is at risk for infection.**
- **To arrange outpatient referral for beta-lactam allergy evaluation**
- **Whenever a change has been made to a patient's existing beta-lactam allergy record, or to evaluate whether a patient can be de-labelled.**

In all cases of a change to the patient's allergy record, 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.

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:

Direct de-labelling (based on medication history review and patient interview)	*Graded-dose challenge*
Direct oral or intravenous challenge	*Skin testing followed by drug challenge*

Most patients (>75%) with penicillin allergies do not require penicillin skin testing. In experience thus far, 99% of patients undergoing skin testing and/or direct challenges have tested negative and been safely de-labelled.

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Appendix: Clinically Relevant Cross-Reactivity to Inform Antimicrobial Choices in Patients with Low-High-Risk Allergy

Combinations with an 'X' (red boxes) are at a higher risk of cross-reactivity. E.g., cefazolin can be prescribed to a patient with a low-to-high-risk allergy to penicillin. However, cephalexin should be avoided in a patient with a high-risk penicillin allergy (Derived from Blumenthal KG, et al. Lancet 2019;393:183-198)

	Amoxicillin ± Clavulanate	Ampicillin ± Sulbactam	Aztreonam	Cefaclor	Cefadroxil	Cefazolin	Cefepime	Cefiderocol	Cefotaxime	Cefoxitin	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime ± Avibactam	Ceftolozane/ Tazobactam	Ceftriaxone	Cefuroxime	Cephalexin	Ertapenem	Imipenem ± Relebactam	Meropenem ± Varbor	Oxacillin/ Nafcillin	Penicillin	Piperacillin/ Tazobactam
Amoxicillin ± Clav		X		X	X													X				X	X	X
Ampicillin ± Sulbact	X			X	X													X				X	X	X
Aztreonam								X						X										
Cefaclor	X	X			X							X						X				X	X	X
Cefadroxil	X	X		X								X						X				X	X	X
Cefazolin																								
Cefepime									X		X					X								
Cefiderocol			X											X										
Cefotaxime							X				X					X								
Cefoxitin																								
Cefpodoxime							X		X							X								
Cefprozil				X	X													X						
Ceftaroline																								
Ceftazidime ± Avi			X					X																
Ceftolozane/Tazo																								
Ceftriaxone							X		X		X													
Cefuroxime																								
Cephalexin	X	X		X	X							X										X	X	X
Ertapenem																				X	X			
Imipenem ± Rele																			X		X			
Meropenem ± Vabor																			X	X				
Oxacillin/Nafcillin	X	X		X	X													X					X	X
Penicillin	X	X		X	X													X				X		X
Piperacillin/Tazo	X	X		X	X													X				X	X	

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Revision History:

03/2020: Added cefiderocol
07/2021: Revised background and inpatient process
05/2022: Revised risk stratification, expanded cross-reactivity matrix, and added clarifications for patient candidates
12/2022: Revised risk stratification, added cross-reactivity information to table