Beta-lactam Allergy Guideline

Background:

The prevalence of penicillin allergies in the Unites States (US) has been estimated to be between 8 and 15%. Cephalosporin allergies are less frequent and are reported in approximately 1% of the US population. However, >97% of patients reporting a penicillin allergy are not truly allergic when assessed by skin testing and direct amoxicillin challenge. Among patients with a low severity penicillin allergy, over 95% can tolerate penicillin. This is due to the fact that most penicillin allergies are documented after the occurrence of delayed benign rashes that do not necessarily recur on re-exposure, intolerances due to penicillin, or other symptoms unrelated to an allergy such as urticaria due to a viral infection. Moreover, over 80% of patients with true IgE-mediated penicillin allergy outgrow their allergy after 10 years due to waning sensitization.

Overuse of second line agents such as fluoroquinolones due to over-cautious avoidance of a wide range beta-lactams can have significant negative consequences, including adverse drug reactions, *Clostridioides difficile* super-infection, and antimicrobial resistance.

The purpose of this guideline is to guide clinicians in prescribing antibiotics for inpatients with reported allergic reactions to penicillin or cephalosporin antibiotics by allowing these patients to receive more narrow-spectrum, more effective, less toxic, and/or less costly antibiotic.

Appendices:

Appendix 1: Patient allergy assessment tool (consider utilizing this tool when discussing allergy with your patient)
Appendix 2: Determining type of reaction and action plan
Appendix 3: Cross-reactivity matrix for antibiotics on formulary at CHI Memorial
Appendix 4: Test Dose Procedure

Appendix 1:

Patient allergy assessment tool

1) What is the name of the antibiotic you are allergic to?

2) Please describe the details of the reaction.

3) Was it immediate or a few days after taking it?

4) When did your allergy occur?
    a. < 1 year ago, 1-10 years ago, >10 years ago

5) How was the reaction managed and what happened?

6) Have you taken any other antibiotics since (amoxicillin, augmentin, keflex, ceftin etc.)?

Appendix 2:

Type of reaction and Action Plan

<table>
<tr><th colspan="3">Dermatological</th><th colspan="2">Respiratory or Systemic</th><th colspan="2">Unknown Reaction</th></tr>
<tr><th colspan="2">Clinical manifestation</th><th>Severity or Allergy type</th><th>Clinical manifestation</th><th>Severity or Allergy type</th><th>Clinical manifestation</th><th>Severity or Allergy type</th></tr>
<tr><td colspan="2">Childhood rash</td><td>Unlikely to be significant</td><td>Laryngeal Involvement (“throat tightness”, “hoarse voice”)</td><td>Severe</td><td>Unknown reaction ≤ 10 years ago</td><td>Unknown</td></tr>
<tr><td rowspan="2">Diffuse rash or localized rash/swelling with no other symptoms</td><td>>10 years ago or unknown</td><td>Non-severe</td><td rowspan="2">Respiratory compromise (“shortness of breath”)</td><td rowspan="2">Severe</td><td rowspan="2">Unknown reaction >10 years or family history</td><td rowspan="2">Unlikely to be significant</td></tr>
<tr><td>≤ 10 years ago</td><td>Non-severe</td></tr>
<tr><td colspan="2">Angioedema (“lip, facial, or tongue swelling”)</td><td>Severe</td><td>Anaphylaxis, unexplained collapse</td><td>Severe</td><td colspan="2">Renal</td></tr>
<tr><td colspan="2">Generalized swelling (outside of angioedema)</td><td>Severe</td><td colspan="2">Hematological</td><td>Severe renal injury, failure, or AIN</td><td>Potential immune mediated</td></tr>
<tr><td colspan="2">Urticaria (“wheals and hives”)</td><td>Non-severe</td><td rowspan="3">Low platelets, neutrophils, hemoglobin, eosinophilia</td><td rowspan="3">Potential immune mediated</td><td>Mild renal impairment</td><td>Unlikely immune mediated</td></tr>
<tr><td colspan="2">Mucosal ulceration (“mouth, eye, or genital ulcers”)</td><td>Severe</td><td>Severe liver injury, failure</td><td>Potential immune mediated</td></tr>
<tr><td colspan="2">Pustular, blistering or desquamating rash (“skin shedding”)</td><td>Severe</td><td>Mild hepatic enzyme elevation</td><td>Unlikely immune mediated</td></tr>
<tr><th colspan="4">Reaction Risk (Color Coded) & Action Plan</th><th colspan="2">Gastrointestinal or Neurological</th></tr>
<tr><td colspan="4">Appropriate for oral re-challenge or direct de-labeling</td><td>Low Risk</td><td>GI symptoms (nausea, vomiting, diarrhea)</td><td>Unlikely immune mediated</td></tr>
<tr><td colspan="4">Appropriate for oral re-challenge or using full dose beta-lactam with dissimilar side chain (Appendix 3)</td><td>Low Risk</td><td rowspan="2">Mild neurological symptoms (headache, depression, mood disorder)</td><td rowspan="2">Unlikely immune mediated</td></tr>
<tr><td colspan="4">May be appropriate for test dose of beta-lactams with dissimilar side chains* or penicillin skin test</td><td>Moderate risk</td></tr>
<tr><td colspan="4">Not appropriate for allergy testing</td><td>High risk</td><td>Severe neurological manifestation (seizures, psychosis)</td><td>Unknown or unclear mechanism</td></tr>
</table>

*If moderate risk penicillin reaction, can consider test dose of cefazolin, 3rd, 4th, 5th generation cephalosporins or carbapenem.

If moderate risk cephalosporin reaction, can consider test dose of cephalosporins with dissimilar side chains (Appendix 3), penicillin (if reaction to 3rd, 4th, or 5th generation cephalosporin), or carbapenem.

Aztreonam full dose can be administered unless reaction was to ceftazidime

Adapted from Devchand *et al*. 2018

Appendix 3:

Cross-reactivity matrix

	Penicillin	Amoxicillin	Ampicillin	Piperacillin	Cefazolin	Cefadroxil	Cefoxitin	Cefuroxime	Ceftriaxone	Ceftazidime	Cefepime	Ceftaroline	Ceftolozane
Penicillin	=						*						
Amoxicillin		=	*	*		*							
Ampicillin		*	=	*		*							
Piperacillin		*	*	=		*							
Cefazolin					=								
Cefadroxil		*	*	*		=							
Cefoxitin	*						=	*					
Cefuroxime							*	=	*	*	*		*
Ceftriaxone								*	=	*	*		*
Ceftazidime								*	*	=	*		*
Cefepime								*	*	*	=		*
Ceftaroline												=	
Ceftolozane								*	*	*	*		=

A box with (*) Indicates that the two antibiotics share a similar or identical side chain and that there is a risk of cross-reactivity between them. Empty boxes indicate a lack of side-chain similarity and a lower risk for cross-reactivity. Cefazolin and Ceftaroline have dissimilar side chains to all other penicillins and cephalosporins.

Appendix 4:

Test Dose Procedure

Note: This procedure is NOT meant to be used for patients with Type II-IV reactions including SJS/TEN, DRESS/DISH, serum sickness, drug-induced cytopenias, other significant laboratory abnormalities such as nephrotoxicity or delayed reactions

1) Utilize Appendix 2 to identify appropriate candidates for the test dose
2) Review patient's current medications to ensure no antihistamines, famotidine, high dose steroids were given in the last 24 hours as these may mask an allergic reaction
3) Obtain patient's verbal consent prior to procedure
4) Drug order & monitoring
    a. Oral rechallenge for de-labeling
        i. Single dose penicillin VK 250mg (if reported allergy penicillin) or amoxicillin 250mg (if reported allergy amoxicillin or ampicillin)
        ii. Perform observation every 30 mins for 1 hour post oral challenge
    b. Test dose of beta-lactam that you intend to use
        i. Give patient 1/10th of full standard treatment dose (ex: for ceftriaxone (standard dose: 1-2g), formulate 1g dose in 50mL of normal saline and give 1st 5 mins of dose ~160mg)
        ii. Monitor for 30 minutes. If the patient remains asymptomatic, give the full dose.
        iii. Monitor patient for 60 more minutes to ensure no reaction
        iv. Subsequent doses can be given as per hospital's standard protocol
5) Profile Anaphylaxis & Acute Drug Hypersensitivity Protocol MCT to be available during the test dose procedure
6) If no evidence of reaction, ASP Team to document results of the procedure in the progress notes, remove allergy from medical record and inform patient of the allergy removal

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