

**Aim:** To optimize use of beta-lactam antibiotics in patients with beta-lactam allergy labels.

Patient with **PENICILLIN** allergy label

**EXCLUSION CRITERIA**  
None

**Discuss with Infectious Disease** if allergy label to: carbapenem, aztreonam, or multiple classes of beta-lactams (e.g. penicillin and cephalosporin).

- Evaluate reported allergy and severity (**Table 1**) by obtaining information on:
  - Previous evaluation by an allergist for penicillin allergy.
  - Name of penicillin(s) to which the allergy label applies.
  - Reaction details (e.g. see **Table 4** or rash type examples).
  - Timing/onset of reaction: Immediate/acute ( $\leq 24$  hrs of penicillin dosing), delayed ( $> 24$  hrs of penicillin dosing).
  - Treatment of reaction: None/antibiotic continued, antibiotic discontinued, antihistamines, steroids, epinephrine, hospitalization/ED.
  - Tolerance of culprit penicillin and other beta-lactams before and after course that caused the reaction.
- Update EMR with information above.

See **Figure 1** for rates of overall cross-reactivity of beta-lactam antibiotics, mechanisms of cross-reactivity, and knowledge gaps.

### Severe Type II-IV reactions (delayed)

- Stevens-Johnson syndrome (SJS).
- Toxic epidermal necrolysis (TEN).
- Drug reaction with eosinophilia and systemic symptoms (DRESS).
- Acute generalized exanthematous pustulosis (AGEP).
- Generalized bullous fixed drug eruption (GBFDE).
- Linear IgA bullous dermatosis.
- Severe**<sup>†</sup> maculopapular rash.
- Drug-induced autoimmune disease (bullous pemphigoid, pemphigus vulgaris, drug-induced lupus).
- Serum sickness.
- Blood disorders (hemolytic anemia, agranulocytosis, thrombocytopenia).
- Drug-induced liver injury, nephritis, pneumonitis, meningitis, pancreatitis, vasculitis.
- Drug fever.

- Avoid all** beta-lactam (BL) antibiotics.
- Use** non-BL antibiotics by microbial coverage (e.g. vancomycin, fluoroquinolones, clindamycin).
- Refer** to allergist.

### Severe Type I reactions (immediate)

- Anaphylaxis (**Table 2**).
- Skin:** Acute urticaria (hives), angioedema, flushing/redness.
- CV:** Hypotension, syncope.
- GI:** Repetitive vomiting, abdominal cramping.
- Musculoskeletal:** Hypotonia.
- Respiratory:** Dyspnea, wheezing, hypoxia, repetitive coughing, stridor, aphonia, dysphonia.

- Avoid** penicillins.
- Can** administer cephalosporins with **dissimilar** side chains (**Table 3**) **normally** without additional precautions.
- Can** administer carbapenems **normally** without additional precautions.
- Can** administer non-BL antibiotics by microbial coverage (e.g. vancomycin, fluoroquinolones, clindamycin) (generally less effective than BLs).
- Refer** to allergist.

### Non-severe reactions

- Mild/moderate**<sup>†</sup> maculopapular rash.
- Isolated pruritus without rash.
- Delayed** urticaria\* with pruritus and without other systemic symptoms.
- Patient denies allergy but is on record.

- Evaluate eligibility for penicillin allergy delabeling (if 3 months to < 18 years of age).**
- Can** administer cephalosporins with **similar** or **dissimilar** side chains (**Table 3**) **normally** without precautions.

\***Delayed urticaria:** Onset at  $>24$  hours of penicillin dosing, or after 2 doses, whichever is longer.

**<sup>†</sup>Classification of maculopapular rash:**  
**Severe:** Widespread rash that may become confluent and develop into erythroderma;  $>1$ -wk duration, with systemic involvement (e.g., fever, eosinophilia); rarely, with minimal vesicles or pustules.  
**Moderate:** More or less widespread rash;  $>1$ -wk duration, without systemic involvement.  
**Mild:** More or less widespread rash;  $<1$ -wk duration, without systemic involvement.

### Reactions inconsistent with allergy

- Isolated intolerances: diarrhea, nausea, vomiting (not repetitive), mild abdominal pain, headache, fatigue, vaginitis.
- Family history of allergy to penicillin.
- Patient tolerated culprit penicillin after allergy label.

- Evaluate eligibility for penicillin allergy delabeling (if 3 months to < 18 years of age).**
- Can** administer penicillin or cephalosporin of choice without precautions.

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Patient with **CEPHALOSPORIN** allergy label

**EXCLUSION CRITERIA**  
None

**Discuss with Infectious Disease** if allergy label to: carbapenem, aztreonam, or multiple classes of beta-lactams (e.g. penicillin and cephalosporin).

- Evaluate reported allergy and severity (**Table 1**) by obtaining information on:
  - Previous evaluation by an allergist for cephalosporin allergy.
  - Name of cephalosporin(s) to which the allergy label applies.
  - Reaction details (e.g. see **Table 4** for rash type examples).
  - Timing/onset of reaction: Immediate/acute ( $\leq 24$  hrs of cephalosporin dosing), delayed ( $> 24$  hrs of cephalosporin dosing).
  - Treatment of reaction: None/antibiotic continued, antibiotic discontinued, antihistamines, steroids, epinephrine, hospitalization/ED.
  - Tolerance of culprit cephalosporin and other beta-lactams before and after course that caused the reaction.
- Update EMR with information above.

See **Figure 1** for rates of overall cross-reactivity of beta-lactam antibiotics, mechanisms of cross-reactivity, and knowledge gaps.

**Severe Type II-IV reactions (delayed)**

**Severe Type I reactions (immediate)**

**Non-severe reactions**

**Reactions inconsistent with allergy**

- Stevens-Johnson syndrome (SJS).
- Toxic epidermal necrolysis (TEN).
- Drug reaction with eosinophilia and systemic symptoms (DRESS).
- Acute generalized exanthematous pustulosis (AGEP).
- Generalized bullous fixed drug eruption (GBFDE).
- Linear IgA bullous dermatosis.
- Severe**<sup>†</sup> maculopapular rash.
- Drug-induced autoimmune disease. (bullous pemphigoid, pemphigus vulgaris, drug-induced lupus).
- Serum sickness.
- Blood disorders (hemolytic anemia, agranulocytosis, thrombocytopenia).
- Drug-induced liver injury, nephritis, pneumonitis, meningitis, pancreatitis, vasculitis.
- Drug fever.

- Avoid** all beta-lactam (BL) antibiotics.
- Use** non-BL antibiotics by microbial coverage (e.g. vancomycin, fluoroquinolones, clindamycin).
- Refer** to allergist.

- Anaphylaxis (**Table 2**).
- Skin: Acute** urticaria (hives), angioedema, flushing/redness.
- CV:** Hypotension, syncope.
- GI:** Repetitive vomiting, abdominal cramping.
- Musculoskeletal:** Hypotonia.
- Respiratory:** Dyspnea, wheezing, hypoxia, repetitive coughing, stridor, aphonia, dysphonia.

- Avoid** penicillins and cephalosporins.
- Can** administer carbapenems **normally** without additional precautions.
- Can** administer non-BL antibiotics by microbial coverage (e.g. vancomycin, fluoroquinolones, clindamycin).
- Refer** to allergist.

- Mild/moderate**<sup>†</sup> maculopapular rash.
- Isolated pruritus without rash.
- Delayed** urticaria\* with pruritus and without other systemic symptoms.
- Patient denies allergy but is on record.

- Avoid** cephalosporins with similar side chains (**Table 3**).
- Can** administer cephalosporins or penicillins with **dissimilar** side chains (**Table 3**) **normally** without precautions.

\***Delayed urticaria:** Onset at  $>24$  hours of cephalosporin dosing, or after 2 doses, whichever is longer.

<sup>†</sup>**Classification of maculopapular rash:**  
**Severe:** Widespread rash that may become confluent and develop into erythroderma;  $>1$ -wk duration, with systemic involvement (e.g., fever, eosinophilia); rarely, with minimal vesicles or pustules.  
**Moderate:** More or less widespread rash;  $>1$ -wk duration, without systemic involvement.  
**Mild:** More or less widespread rash;  $<1$ -wk duration, without systemic involvement.

- Isolated intolerances: diarrhea, nausea, vomiting (not repetitive), mild abdominal pain, headache, fatigue, vaginitis.
- Family history of allergy to penicillin.
- Patient tolerated culprit cephalosporin after allergy label.

- Can** administer penicillin or cephalosporin of choice.

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**Table 1. Immune-Mediated Antibiotic Hypersensitivity Reactions**

Type	Description	Pathogenesis	Onset of Reaction	Typical Clinical Findings
<b>I (Immediate)</b>	IgE-mediated hypersensitivity	Antibiotic-specific IgE binds to mast cells and basophils. Subsequent antibiotic exposure leads to mast cell and basophil degranulation	Minutes to an hour (can also be considered within 6 hours of exposure)	Anaphylaxis, urticaria (hives), angioedema, <b>repetitive</b> vomiting, SOB, wheezing, chest pain, palpitations, syncope, cardiac arrest
<b>II (Delayed)</b>	IgG-mediated hypersensitivity	Antibiotic binds to WBC, RBC, or platelet and acts as antigen leading to antibody mediated cell destruction	Days to weeks	Hemolytic anemia, thrombocytopenia, neutropenia
<b>III (Delayed)</b>	Immune-complex mediated hypersensitivity	Antibiotic and IgG/IgM bind to form immune complex activate complement	Days to weeks	Serum sickness (fever, urticarial, arthralgia, lymphadenopathy), drug fever, vasculitis
<b>IV (Delayed)</b>	Cell-mediated hypersensitivity	Antigen specific T-cell activation	Days to weeks	Pustules, vesicles, desquamation, exfoliative exanthema, contact dermatitis, maculopapular rash, DRESS, SJS, TEN, AGEP, acute interstitial nephritis, drug-induced liver injury,

**AGEP:** acute generalized exanthematous pustulosis. **DRESS:** drug rash with eosinophilia and systemic symptoms. **RBC:** red blood cell. **WBC:** white blood cell. **SJS:** Stevens-Johnson Syndrome. **SOB:** shortness of breath. **TEN:** toxic epidermal necrolysis.

**Table 2. Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled:**

- Acute onset\* of an illness with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND ≥ 1 of the following:**
  - Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
  - Reduced blood pressure\*\* or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
  - Severe gastrointestinal symptoms (e.g. severe crampy abdominal pain, repetitive vomiting)
- Acute onset of hypotension\* or bronchospasm or laryngeal involvement (stridor, vocal changes, odynophagia) even in the absence of typical skin involvement**

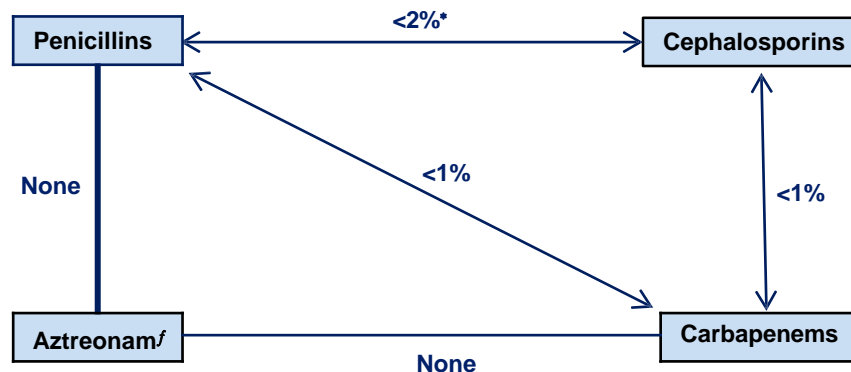
\*Minutes to several hours from exposure. Most immediate reactions occur within the 1st hour following drug administration.

\*\*Hypotension defined as systolic blood pressure (mm Hg):

- < 12 months of age: < 70
- 1-10 years of age: < 70 + (2 × age in years)
- > 10 years of age: < 90.

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**Figure 1. Rates of Overall Cross-Reactivity of Beta-Lactam Antibiotics**



\*Cross-reactivity rate **excludes** shared group aminopenicillins (ampicillin, amoxicillin) and cephalosporins.

<sup>f</sup>Aztreonam has no shared cross-reactivity with other BLs, except for ceftazidime and cefiderocol, which share a similar R1 side chain with aztreonam.

#### Mechanisms of cross-reactivity:

- Cross-reactivity between BL antibiotics is possible through:
  - a. A side chain (R1 or R2 group);
  - b. The core BL ring (very rare);
  - c. The adjacent thiazolidine (penicillin), and/or
  - d. The dihydrothiazine (cephalosporin) ring
- Cephalosporins have both an R1 and R2 group. Penicillins have only an R1 group.
- Despite varied mechanisms of cross-reactivity, true **cross-reactivity** between BL antibiotics in **Ig-E mediated** reactions is largely based on **similarity of R1 side chain**.
- It is possible to have **coexisting** and **independent** hypersensitivity reactions to different BL antibiotics that cannot be explained by side chain similarity.

#### IgE vs. non-IgE mediated hypersensitivity reactions:

- Although cross-reactivity between BL antibiotics in **IgE-mediated** hypersensitivity reactions is primarily based on the R-group side chains, there is uncertainty regarding **severe non-IgE-mediated** reactions, such as severe cutaneous adverse reactions (SCARs). It is generally recommended to avoid all BLs in patients with a history of SCAR to a BL. More studies are needed to determine the safety of using alternative BLs in these patients.

#### Knowledge gaps:

- Cross reactivity of beta-lactamase inhibitors (e.g. avibactam, clavulanate, relebactam, tazobactam, sulbactam) is **not well-established**.
- Cross reactivity of oxacillin, nafcillin, and piperacillin with other penicillins is **not well-established**.
- Cross reactivity among carbapenems (ertapenem, imipenem, meropenem) is **not well-established**.

BETA LACTAM CLASS AND ANTIBIOTIC		PCN					1 <sup>st</sup>			2 <sup>nd</sup>			3 <sup>rd</sup>					4 <sup>th</sup>	5 <sup>th</sup>			CARB			MB		
		Oxacillin	Penicillin G/V	Piperacillin	Ampicillin	Amoxicillin	Cefadroxil	Cephalexin	Cefazolin	Cefoxitin	Cefuroxime	Cefprozil	Cefdinir	Cefixime	Ceftriaxone	Cefotaxime	Cefpodoxime	Ceftazidime	Cefepime	Ceftaroline	Ceftolozane	Cefiderocol	Ertapenem	Imipenem	Meropenem	Aztreonam	
PCN	Oxacillin	•	U	U	U	U																					
	Penicillin G/V	U	•	U	•	•	•				•																
	Piperacillin	U	U	•	U	U																					
	Ampicillin	U	•	U	•	•	×				•																
	Amoxicillin	U	•	U	•	•	×	•			×																
1 <sup>st</sup>	Cefadroxil		•		•	×	•	×			×																
	Cephalexin		•		×	•	×	•			•																
	Cefazolin								•																		
2 <sup>nd</sup>	Cefoxitin								•																		
	Cefuroxime								•				•	•	•	•	•	•									
	Cefprozil		•		•	×	×	•			•																
3 <sup>rd</sup>	Cefdinir											•															
	Cefixime								•		•	•	•	•	•	•	•	•									
	Ceftriaxone								•		•	•	×	×	•	×	•	•	•								
	Cefotaxime								•		•	•	×	×	•	×	•	•	•								
	Cefpodoxime								•		•	•	×	×	•	•	×	•	•								
	Ceftazidime								•		•	•	•	•	•	•	•	•	•	•	×						×
4 <sup>th</sup>	Cefepime							•				•	×	×	×	•	•	•	•								
5 <sup>th</sup>	Ceftaroline												•	•	•	•	•	•	•	•							
	Ceftolozane											•	•	•	•	•	•	•	•	•	•						
	Cefiderocol																×				•						×
CARB	Ertapenem																					•	•	•			
	Imipenem																					•	•	•			
	Meropenem																					•	•	•			
MB	Aztreonam																×										×

**Table 3.** Potential risk of cross-reactivity between beta-lactam antibiotics based on R1 side chain similarity. R1 side chain similarity is the most well-established determinant of cross-reactivity among BL antibiotics in IgE-mediated hypersensitivity reactions.

1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, etc. refer to generation of cephalosporins.

PCN: penicillins  
 CARB: carbapenems  
 MB: monobactam

- × Identical or highly similar side chain (higher risk of cross-reactivity)
- Less similar side chain (lower risk of cross-reactivity)
- U Unclear risk of cross reactivity
- Dissimilar side chain (lowest risk of cross-reactivity)

Disclaimer: This guideline is designed for general use with most patients; each clinician should use their own independent judgment to meet the needs of each individual patient. This guideline is not a substitute for professional medical advice, diagnosis or treatment.

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**Table 4. Examples of Rash Types**

<p><b>Macular papular rash</b></p> 	<ul style="list-style-type: none"> <li>• Typically non-severe skin reaction</li> <li>• Tiny red dots covering a large area of the body, may feel rough to the touch.</li> <li>• Appears after 2—3 days (or later) of antibiotic administration (delayed reaction).</li> <li>• Can be treated through, does not contraindicate future antibiotic use.</li> <li>• May not recur with future drug administration.</li> </ul>
<p><b>Urticaria (hives)</b></p> 	<ul style="list-style-type: none"> <li>• Itchy, red bumps with white centers (look like new mosquito bites).</li> <li>• Typically appear within 6 hours of antibiotic administration (but can be a delayed reaction too).</li> <li>• Bumps disappear after a few hours and new ones may appear.</li> </ul>
<p><b>Severe skin drug reaction (exfoliating dermatitis)</b></p> 	<ul style="list-style-type: none"> <li>• Skin peeling or blistering with mucosal (eyes, mouth, genital) involvement</li> <li>• Develops after several days of antibiotics.</li> <li>• Examples: Stevens-Johnson syndrome, Toxic Epidermal necrolysis (TEN)</li> <li>• Requires hospitalization</li> </ul>
<p><b>Erythema multiforme</b></p> 	<ul style="list-style-type: none"> <li>• Rings containing a “bull’s-eye”</li> <li>• Appears after 2-3 days of antibiotic administration (delayed reaction)</li> </ul>

Images used with permission from the following references:

- [penicillin-allergy-algorithm-with-pictures.pdf \(hopkinsmedicine.org\)](https://www.hopkinsmedicine.org/health/conditions-and-diseases/penicillin-allergy-algorithm-with-pictures)
- Atlas of Dermatological Conditions in Populations of African Ancestry. CMYA Donkor, J Aryee-Boi, IR Osazuwa, FK Afflu, AF Alexis. Springer Cham 2021

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## Work group

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