CLINICAL GUIDELINE

BETA-LACTAM ALLERGY GUIDELINE: Inpatient and outpatient

Age < 25 years of age

Children's MINNESOTA

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

EXCLUSION CRITERIA
None

Patient with PENICILLIN allergy label

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 **page 6** for rash type examples).
  - Timing/onset of reaction: Immediate/acute (≤ 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).
- Generized bullous fixed drug eruption (GBFDE).
- Linear IgA bullous dermatosis.
- **Severe**† 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.
- **MSK**: Hypotonia.
- **Resp**: 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**† 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.

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.

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

†__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.

CLINICAL GUIDELINE

BETA-LACTAM ALLERGY GUIDELINE: Inpatient and outpatient

Age < 25 years of age

Children's MINNESOTA

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

EXCLUSION CRITERIA
None

Patient with CEPHALOSPORIN allergy label

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 **page 6** for rash type examples).
  - Timing/onset of reaction: Immediate/acute (≤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)

- Stevens-Johnson syndrome (SJS).
- Toxic epidermal necrolysis (TEN).
- Drug reaction with eosinophilia and systemic symptoms (DRESS).
- Acute generalized exanthematous pustulosis (AGEP).
- Generized bullous fixed drug eruption (GBFDE).
- Linear IgA bullous dermatosis.
- **Severe**† 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.
- **MSK**: Hypotonia.
- **Resp**: 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.

Non-severe reactions

- **Mild/moderate**† 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.

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 cephalosporin after allergy label.

- **Can** administer penicillin or cephalosporin of choice.

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

†**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.

CLINICAL GUIDELINE

BETA-LACTAM ALLERGY GUIDELINE: Inpatient and outpatient

Age < 25 years of age

Children's MINNESOTA

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

Table 1. Immune-Mediated Antibiotic Hypersensitivity Reactions

Type	Description	Pathogenesis	Onset of Reaction	Typical Clinical Findings
I (Immediate)	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, repetitive vomiting, SOB, wheezing, chest pain, palpitations, syncope, cardiac arrest
II (Delayed)	IgG-mediated hypersensitivity	Antibiotic binds to WBC, RBC, or platelet and acts as antigen leading to antibody medicated cell destruction	Days to weeks	Hemolytic anemia, thrombocytopenia, neutropenia
III (Delayed)	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
IV (Delayed)	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:

1. **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:**
   a. Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   b. Reduced blood pressure** or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
   c. Severe gastrointestinal symptoms (e.g. severe crampy abdominal pain, repetitive vomiting)
2. **Acute onset of hypotension* or bronchospasm or laryngeal involvement (stridor, vocal changes, odynophagia) even in the absence of typical skin involvement**

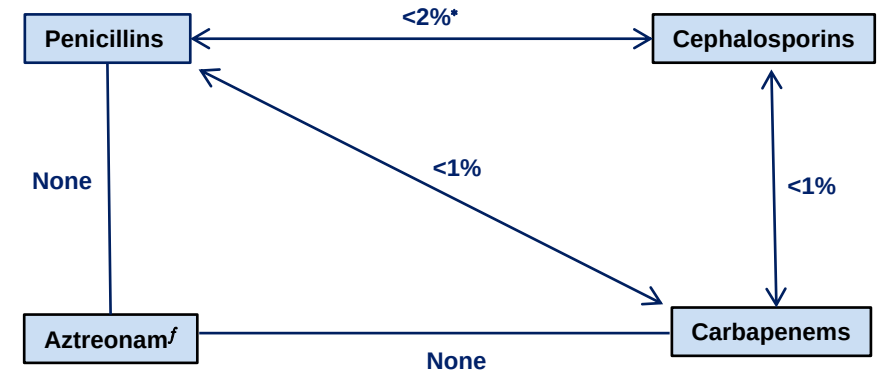
*Minutes to several hours from exposure. Most immediate reactions occur within the 1st hour following drug administration.
**Hypotension defined as systolic blood pressure (mm Hg):
- < 12 months of age: < 70
- 1-10 years of age: < 70 + (2 × age in years)
- > 10 years of age: < 90.

BETA-LACTAM ALLERGY GUIDELINE: Inpatient and outpatient

Age < 25 years of age

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

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



*Cross-reactivity rate excludes shared group aminopenicillins (ampicillin, amoxicillin) and cephalosporins.
[f]Aztreonam has no shared cross-reactivity with other β-lactams, with the exception of ceftazidime and cefiderocol, which share a similar R1 side change with aztreonam.

Mechanisms of cross-reactivity:

- Cross-reactivity between beta-lactam antibiotics is possible through: a) a side chain (R1 or R2 group); b) the core β-lactam 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 beta-lactam antibiotics is **largely based on similarity of R1 side chain.**
- It is possible to have **coexisting** and **independent** hypersensitivity reactions to different beta-lactam antibiotics that cannot be explained by side chain similarity.

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**.

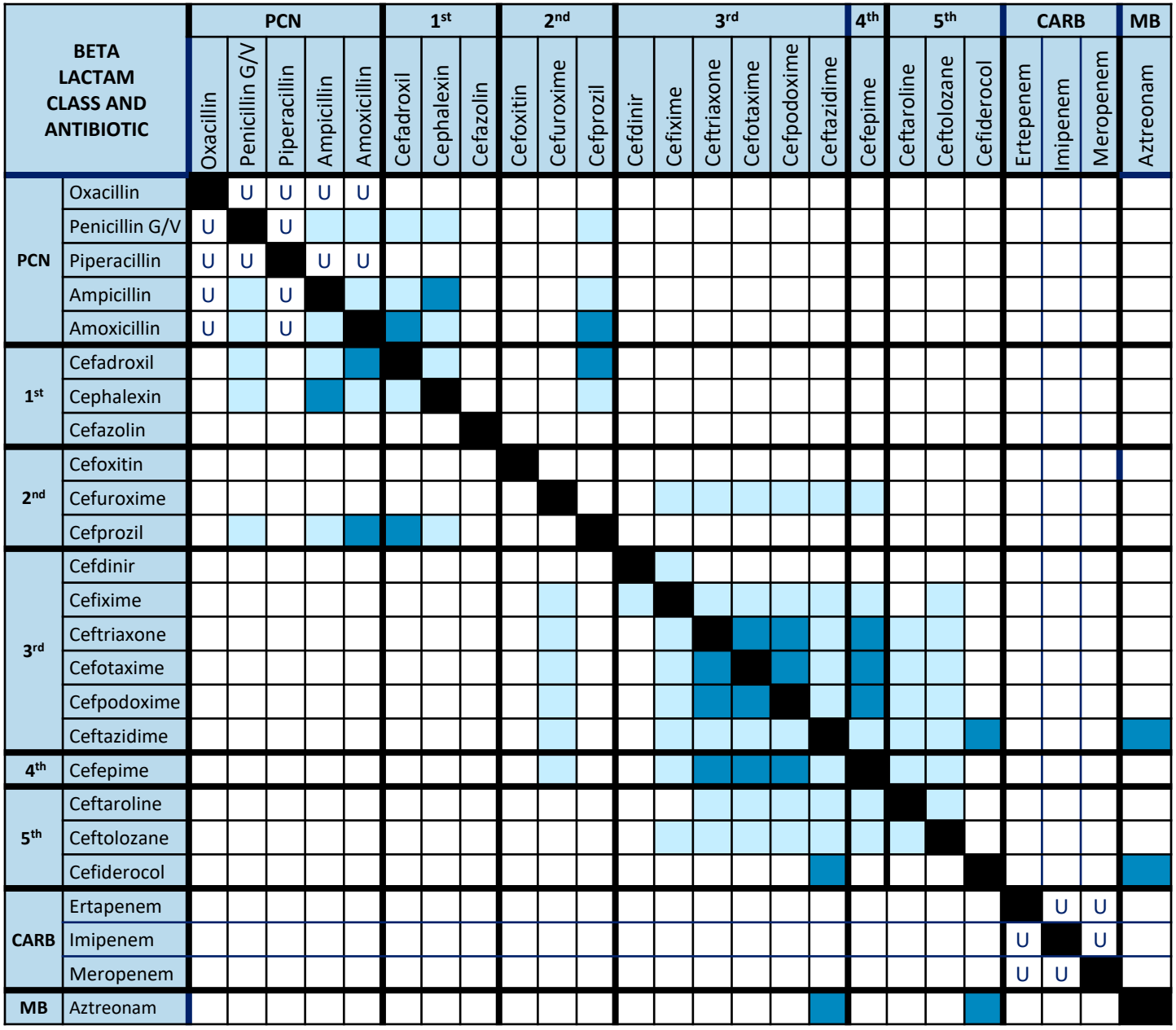


Table 3. Potential risk of cross-reactivity between beta-lactam antibiotics based on R1 side chain similarity. R1 side chain similarity is the most well-established determinant of cross-reactivity among beta-lactams.

1st, 2nd, 3rd, etc. refer to generation of cephalosporins.

PCN: penicillins
CARB: carbapenems
MB: monobactam

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.

BETA-LACTAM ALLERGY GUIDELINE: Inpatient and outpatient

Age < 25 years of age

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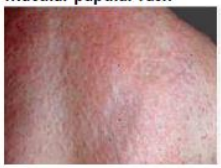
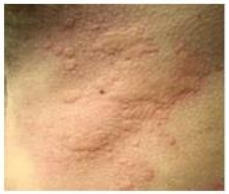
Examples of Rash Types

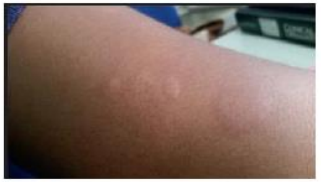
Macular papular rash



- Typically non-severe skin reaction
- Tiny red dots covering a large area of the body, may feel rough to the touch.
- Appears after 2—3 days (or later) of antibiotic administration (delayed reaction).
- Can be treated through, does not contraindicate future antibiotic use.
- May not recur with future drug administration.

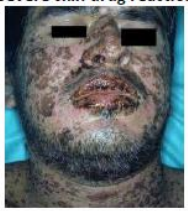
Urticaria (hives)





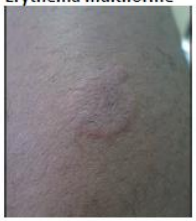
- Itchy, red bumps with white centers (look like new mosquito bites).
- Typically appear within 6 hours of antibiotic administration (but can be a delayed reaction too).
- Bumps disappear after a few hours and new ones may appear.

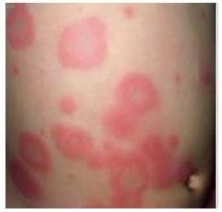
Severe skin drug reaction (exfoliating dermatitis)

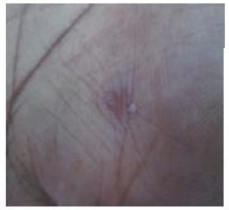


- Skin peeling or blistering with mucosal (eyes, mouth, genital) involvement
- Develops after several days of antibiotics.
- Examples: Stevens-Johnson syndrome, Toxic Epidermal necrolysis (TEN)
- Requires hospitalization

Erythema multiforme







- Rings containing a "bull's-eye"
- Appears after 2-3 days of antibiotic administration (delayed reaction)

Images used with permission from the following references:

- penicillin-allergy-algorithm-with-pictures.pdf (hopkinsmedicine.org)
- 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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