



Guidance for Managing Patients with Allergies to β -Lactam Antibiotics Other than Penicillins

Key Points

Background

- Cross-reactivity between penicillins, cephalosporins, and carbapenems are rare and typically not a class effect, but reactions more commonly occur between agents with similar side chains
- Careful evaluation of antibiotic allergy and prior tolerance history is *essential* to optimal treatment
- Alterations in antibiotic prescribing due to reported beta-lactam allergy results in higher costs, increased risk of antibiotic resistance, and worsened patient outcomes

Evaluation of Beta-Lactam Allergy

- Obtain a detailed history of allergic reaction, including nature of the reaction and timing in relation to the agent
 - Do NOT accept “penicillins” or “cephalosporins” as an allergy; obtain the specific medication received including approximate date and timeframe after administration
- Classify type and severity of the reaction paying attention to document any IgE-mediated symptoms (e.g., anaphylaxis, hives, angioedema, etc.)
- Evaluate prior tolerance of beta-lactam antibiotics utilizing patient interview and/or the electronic medical record

Recommendations for Challenging Patients Reporting Allergies to Beta-Lactam Antibiotics other than Penicillins. See **Figure 2**

Follow-Up

- Document tolerance or intolerance in the patient’s allergy history
- Consider referring to allergy clinic for skin testing

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Overview of Beta-Lactam Allergic Reactions

Table 1: Gell and Coombs Classification of Allergic Reactions

Type	Descriptor	Pathophysiology	Presentation	Typical Onset
I	IgE-mediated	Allergen binds to preformed IgE on basophils or mast cells, resulting in release of inflammatory mediators.	Anaphylaxis, hypotension, angioedema, urticaria, shortness of breath, chest tightness	Within 30 min to <2 hours
II	Cytotoxic	Cell destruction occurs because of cell-associated antigen that initiates cytolysis by antigen-specific antibody (IgG or IgM). Most often involves blood elements.	Drug induced hemolytic anemia, thrombocytopenia, granulocytopenia	Typically >72 h to weeks
III	Immune complex	Antigen-antibody complexes form and deposit on blood vessel walls and activate complement. Result is a serum sickness-like syndrome.	Fever, rash, lymphadenopathy with arthralgia	>72 h to weeks
IV	Cell-mediated (delayed)	Antigens cause activation of T lymphocytes, which release cytokines and recruit effector cells (e.g., macrophages, eosinophils).	Delayed maculopapular rash, allergic contact dermatitis, acute interstitial nephritis, drug induced hepatitis, SCARs (DRESS, AGEP, SJS, TEN)	>72 h

Abbreviations: SCAR (Severe Cutaneous Adverse Reaction), DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms), AGEP (Acute Generalized Exanthematous Pustulosis), SJS (Stevens Johnson Syndrome), TEN (Toxic Epidermal Necrolysis)

Beta-Lactam Allergy Overview and Management

Beta-Lactam Cross Reactivity

- Cross-reactivity between penicillins, cephalosporins, and/or carbapenems is typically not due to a class effect, but an allergic reaction to antibiotics with similar side chains
- **Figure 1** shows penicillins, cephalosporins, and carbapenems with similar side chains and the potential for cross-reactivity
 - The exact risk of cross-reaction between each pair is undefined and likely varies amongst pairs
 - Although avoiding beta-lactams with similar side chains was previously recommended, new literature indicates challenging patients in a controlled manner is safe for specific clinical scenarios.
- Penicillins and Cephalosporins Clinical Studies^{1,2}
 - 252 patients with immediate hypersensitivity (IgE mediated) to a penicillin underwent cephalosporin skin and ImmunoCAP testing
 - 95 (38%) reacted to a cephalosporin with similar side chain to the penicillin (cefaclor, cephalixin, cefadroxil, cefamandole)
 - Only 4 (1.5%) patients reacted to cephalosporins with a dissimilar side chain (ceftriaxone, cefuroxime, cefotaxime)
 - 214 patients with delayed hypersensitivity (T-cell mediated) to penicillin underwent skin testing with 6 beta-lactams, 3 with similar side chains to penicillin and 3 with dissimilar side chains
 - Cross reactivity was found in 40 (19%) of the patients overall. All reactions were due to the 3 cephalosporins with similar side chains to the penicillin derivatives; no reactions were due to the 3 cephalosporins with dissimilar side chains
 - Cephalixin and cefaclor have similar side chains to ampicillin and resulted in positive skin tests in 18% and 14% of patients, respectively
 - Cefadroxil has a similar side chain to amoxicillin and resulted in positive skin tests in 8% of patients
 - *When patients experience allergic reactions to a dissimilar beta-lactam, this likely represents a second allergic reaction, not cross-reactivity*

- Penicillins and Carbapenems Clinical Studies^{3,4}
 - Two studies evaluated penicillin allergic patients with a history of immediate hypersensitivity and/or delayed hypersensitivity reactions
 - 416 patients were skin tested and received IV challenges against imipenem, meropenem, and ertapenem
 - No patients with penicillin allergies reacted to either the skin test or IV challenge
 - Data supports that carbapenem use is safe in patients with a known penicillin allergy

Figure 1: Beta-Lactam Cross-Reactivity

Beta-Lactam Cross Reactivity		PCNs					1st Gen CPNs			2nd Gen CPNs			3rd Gen CPNs					4th Gen CPN	Advanced CPNs			CARB		MONO	
		Penicillin G/V	Oxacillin	Amoxicillin	Ampicillin	Piperacillin	Cefadroxil	Cephalexin	Cefazolin	Cefaclor	Cefoxitin	Cefprozil	Cefuroxime	Cefdinir	Cefotaxime	Cefpodoxime	Ceftazidime	Ceftriaxone	Cefepime	Ceftaroline	Ceftolazone	Cefiderocol	Ertapenem	Meropenem	Aztreonam
PCNs	Penicillin G/V																								
	Oxacillin																								
	Amoxicillin																								
	Ampicillin																								
	Piperacillin																								
1st Gen CPNs	Cefadroxil																								
	Cephalexin																								
	Cefazolin																								
2nd Gen CPNs	Cefaclor																								
	Cefoxitin																								
	Cefprozil																								
	Cefuroxime																								
3rd Gen CPNs	Cefdinir																								
	Cefotaxime																								
	Cefpodoxime																								
	Ceftazidime																								
	Ceftriaxone																								
4th Gen CPN	Cefepime																								
Advanced CPNs	Ceftaroline																								
	Ceftolazone																								
	Cefiderocol																								
CARB	Ertapenem																								
	Meropenem																								
MONO	Aztreonam																								

NO STRUCTURAL SIMILARITY Cross reaction unlikely, no R1 or R2 side chain similarity

LOW STRUCTURAL SIMILARITY Cross reaction less likely, similar R1 or R2 side chain

HIGH STRUCTURAL SIMILARITY Cross reaction likely, identical R1 or R2 side chain

PCNs = penicillins

CPNs = cephalosporins

CARB = carbapenems

MONO = monobactams

Diagnosis

How to Obtain a Detailed Assessment of Allergic Reaction

Information collected should include the following:

1. Source of the reported allergy history (patient, family member, healthcare professional, etc.)
2. Specific agent prescribed and infection treated
3. Dose and route of medication
4. Signs and symptoms experienced along with timing of onset of the reaction in relationship to the administration and first initiation of the medication
5. Whether or not the reaction necessitated urgent medical evaluation
6. Treatment given for the reaction and response
7. Whether or not the patient has taken the medication again since the prior reaction (consider discussing brand and generic names in addition to combination antibiotics)
8. Whether or not any recurrent signs or symptoms occurred with subsequent drug exposure
9. Concurrent medications at the time that the reaction occurred and if any of these were newly started
10. Other previously tolerated antimicrobial agents

When to Refer for Skin Testing

Skin testing for penicillin or any beta-lactam allergy is an outpatient procedure and requires referral to Allergy/Immunology clinic. Below are patients to consider for referral.

1. History concerning for recent (<10 years) IgE-mediated reaction more than itching and rash. This includes immediate onset urticaria (hives), angioedema, bronchospasm, immediate emesis, or diarrhea and/or change in blood pressure.
2. Patient considered high-risk for reaction based on underlying medical diseases including poorly controlled respiratory or cardiac disease or pregnancy.
3. Patient at high risk of needing frequent antibiotics to treat infections or planned perioperative antibiotic use. This includes but is not limited to patients on immunosuppressive drugs or have underlying immunodeficiencies (i.e. transplant and oncology patients).
4. Patient who failed an antibiotic challenge.
5. Patients not comfortable with any form of antibiotic challenge.

When to Administer Beta-Lactam via Desensitization [Protocol](#)

1. Severe IgE-mediated reaction and need for similar beta-lactam antibiotic to treat infection.
2. Patient considered high risk due to severe illness or pregnancy.
3. Unable to complete a comprehensive inpatient allergy evaluation including the ability to perform skin testing because of current medication use or inability to obtain skin testing reactions.

Note: If considering, recommend consulting Allergy and/or Infectious Diseases services. Desensitization protocols are different than graded challenges.

- They must be administered in an ICU setting due to frequent monitoring
 - Desensitization does not entirely eliminate the risk of anaphylaxis
- Administration of a desensitization protocol does not allow for removal of the patient's listed allergy
- Interruption in therapy requires re-administration of the desensitization protocol

Beta-Lactam Allergy Management Algorithm

1. Obtain allergic reaction history, determine classification (Table 1) and severity of reaction
 - a. This guidance document is intended for use in an adult patient population
2. Evaluate prior antibiotic tolerance history
 - a. Review allergy documentation in EPIC to determine if previously tolerated beta-lactams are noted
 - b. Review previously prescribed antibiotics using the [Medications tab](#) in the [Chart Review section](#)

- i. For ease of viewing, apply filter by therapeutic class and choose “antibiotics”
 - ii. See Appendix A for additional information
3. See **Figure 2** for management recommendations in patients WITH or WITHOUT prior tolerance history

Follow-Up Documentation Recommendations

Nursing Communication

- Following the completion of a graded challenge, nursing will document the outcome of the graded challenge per the order set instructions **AND** contact the care team pharmacist to process orders for full doses of therapy and complete the Beta-Lactam Allergy Documentation consult
 - If the patient tolerates the graded challenge, please document in the allergy comment section:
 - The antibiotic name, date administered, and that the patient tolerated the graded challenge without any adverse events
 - If the patient did not tolerate the graded challenge, please document in the allergy comment section:
 - The antibiotic name, date administered, the reaction the patient had to the graded challenge, timing of the reaction in relation to the first dose, and any rescue medications administered that were required to treat the reaction

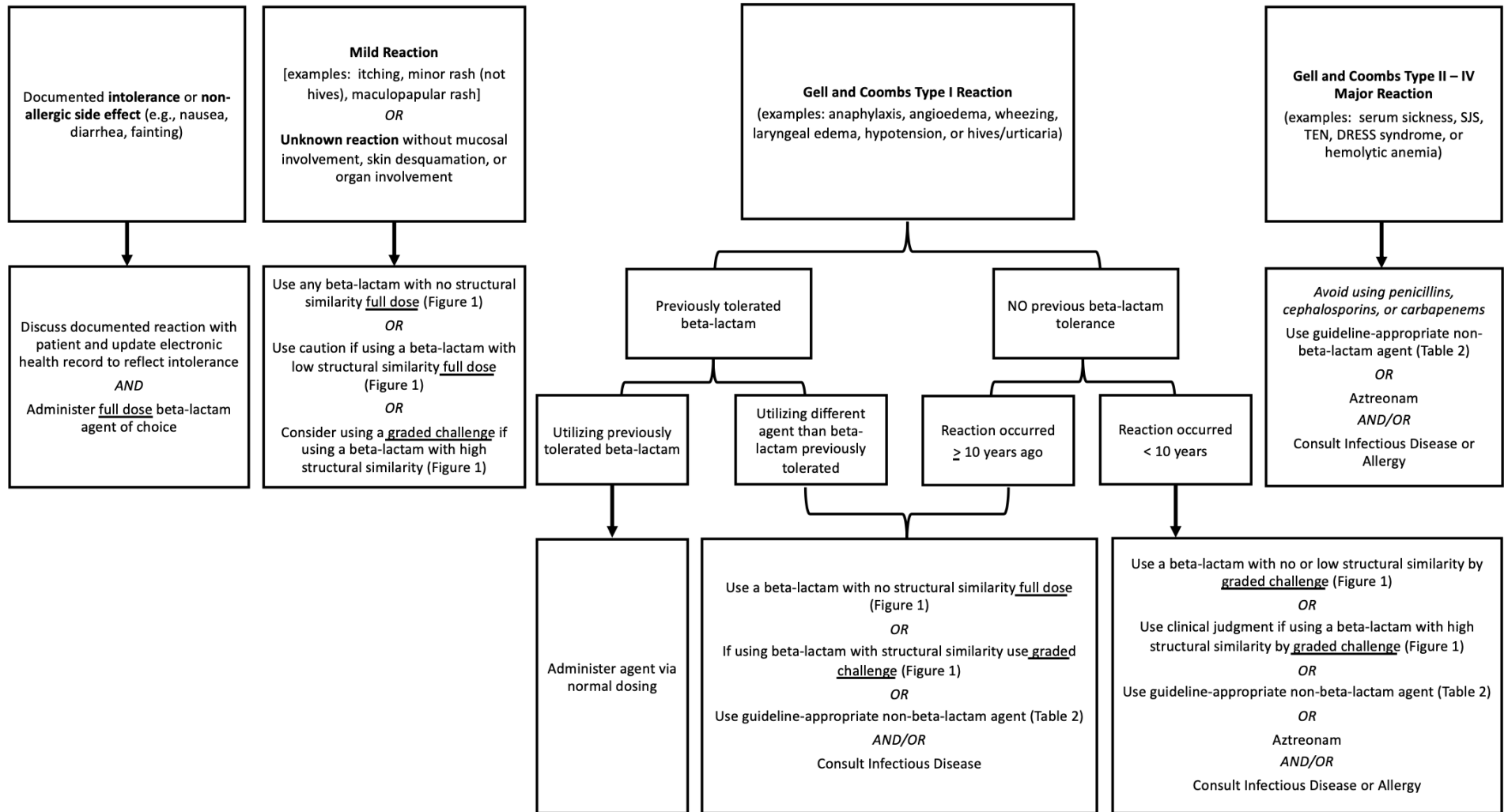
Pharmacy Consult – Beta-Lactam Allergy Documentation

- Providers can consult pharmacy to update a patient’s beta-lactam allergy in the electronic health record
 - By consulting pharmacy, there will be a formal note posted to the chart in addition to an update of the allergy field in the electronic health record
- If a consult is placed, the pharmacist will document using the below iVent

The screenshot shows the 'New i-Vent' form. At the top, there is a header with fields for Type (Consult), Subtype (Beta-Lactam Allergy Documentation), Status (Open), Significance (Medium), Value (50.00), Time spent (20min), Response (Accepted), and Outcomes (Optimized Therapy). Below this, there are sections for 'Associated Orders' and 'Associated Users'. The 'Documentation' section contains a text area with the following text: 'Beta-Lactam Allergy Update Consult. Adult Willow (MRN:05000040) was assessed by *** for review of beta-lactam allergy. Based on review, {Select appropriate option:37746}'. The form also includes a rich text editor toolbar with options for font style, size, color, and text alignment.

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- After completion of the iVent and posting the note to the chart, pharmacy will document in the comment section of the beta-lactam allergy using the “.rxbetalactamallergyupdate” smart phrase
 - Note that an allergy may be de-labeled (deleted) as a result, but the comment should still be placed within the allergy before deleting the entry for visibility on why the allergy was removed. This is especially important when patients are readmitted with a history of allergies.

Figure 2: Recommendations for Challenging Non-Penicillin Beta-Lactam Allergic Patients⁺



⁺If patient has a penicillin allergy, refer to the [Penicillin Allergy Guidance document](#). This guidance should only be utilized in the specified adult patient population above. In pregnant patients with beta-lactam allergies, recommend consulting Infectious Diseases or Allergy/Immunology service.

IV Graded Challenge (or Test Dose) Process

Dosing Recommendations

- Utilize the “Graded Challenge” order set and select the agent required for treatment
 1. Time 0 minutes: administer 1/100th therapeutic dose
 2. Time 30 minutes: administer 1/10th therapeutic dose
 3. Time 60 minutes: administer full therapeutic dose

Background

- Graded challenges are a method of cautiously administering a drug when the risk of allergic reaction is low
- Graded challenges are not desensitization and should be used as directed in **Figure 2**
- Patients who tolerate a graded challenge have demonstrated they are not allergic to the drug used
- Once a patient passes a graded challenge, normal dosing can be performed with current and subsequent use, as long as no new reaction develops
 - When a patient passes a graded challenge, document as listed above in the “Follow-Up Documentation Recommendations” section
 - A patient is considered to have “passed” the graded challenge if they do not develop a Type I hypersensitivity reaction (e.g. urticaria, angioedema, exanthem, wheezing, hypoxia, hypotension, anaphylaxis)
- If challenge is passed, any listed allergy to that medication should be deleted from the medical record
- If a patient subsequently develops the following reactions, an allergy should be added back to the medical record:
 - Target or bullous lesions, pustulosis, mucosal erosions
 - Widespread dark erythema, painful skin
 - Elevated liver enzymes or impaired renal function, directly related to the antibiotic

Administration Recommendations

- Graded challenge can be conducted in any inpatient units, or the emergency department, when staffing is sufficient for monitoring
- Patients on beta-blockers can have impaired responses to epinephrine; if a patient is on a beta-blocker and the use of the beta-lactam antibiotic is not urgent, the next dose of beta-blocker should be held and challenge scheduled for the following morning prior to any subsequent beta-blocker dosing
- Do not pre-treat with antihistamines or glucocorticoids
- Nursing Instructions
 - Monitor patients for symptoms of allergic reaction between each dose change
 - Obtain vitals at baseline and prior to each drug administration
 - Allergy kit should be stored at the bedside throughout procedure
 - Kit contains epinephrine, diphenhydramine, and hydrocortisone
 - Administer rescue medications in the setting of an allergic reaction (according to CP_RX 14)
 - Contact primary team immediately if reaction develops

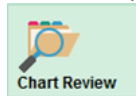
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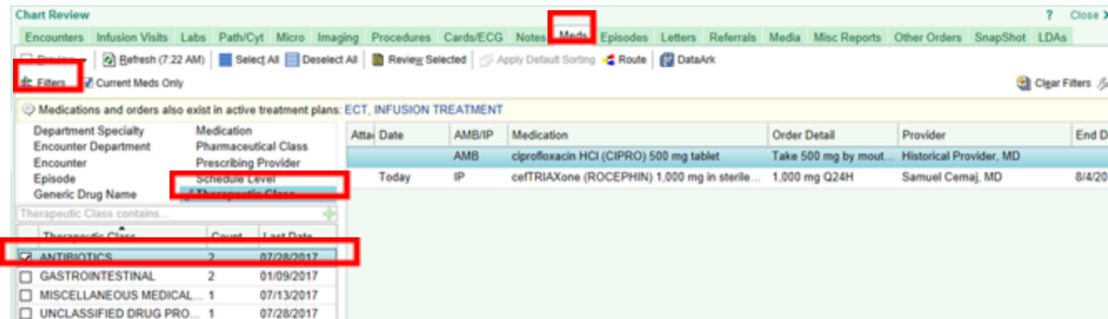
Appendix A

Evaluating past antibiotic tolerance in EPIC medical record.

1. Select “Chart Review” on the left panel of the patient’s electronic medical record



2. Select the “Meds” tab in the chart review section
3. Apply a “Filter” in the selection plane below the medications tab
4. Select the “Therapeutic Class” filter followed by the class “Antibiotics”
 1. Select “Pharmaceutical Class” and choose “Penicillins,” “Cephalosporins,” or “Carbapenems”



The results will show both inpatient (IP) and outpatient (AMB) antibiotics a patient was prescribed at Nebraska Medicine or with affiliated providers.

Table 2: Examples of Non-Beta-Lactam Agents; Follow [ASP Guidance](#) based on suspected type of infection

• Aminoglycoside (e.g., gentamicin, tobramycin, or amikacin)
• Anti-MRSA agents (e.g., vancomycin, daptomycin, or linezolid)
• Clindamycin
• Fluoroquinolones (e.g., levofloxacin, ciprofloxacin ^{NF})
• Macrolides (e.g., azithromycin, clarithromycin)
• Sulfamethoxazole-trimethoprim
• Tetracyclines (e.g., doxycycline, minocycline)

Selected References

1. Romano A, Valluzzi RL, Caruso C, Maggioletti M, Quaratino D, Gaeta F. Cross-Reactivity and Tolerability of Cephalosporins in Patients with IgE-Mediated Hypersensitivity to Penicillins. J Allergy Clin Immunol Pract 2018; 6(5): 1662-72.
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4. Romano A, Gaeta F, Valluzzi RL, et al. Absence of cross-reactivity to carbapenems in patients with delayed hypersensitivity to penicillins. Allergy 2013; 68(12): 1618-21.
5. Khan DA, Banerji A, Blumenthal KG, et al. Drug Allergy: A 2022 Practice Parameter Update. Ann Allergy Asthma Immunol. 2022.