Nebraska Medicine
SERIOUS MEDICINE. EXTRAORDINARY CARE.

Penicillin Allergy Guidance Document

Key Points

Background

- Careful evaluation of antibiotic allergy and prior tolerance history is *essential* to providing optimal treatment
- The true incidence of penicillin hypersensitivity amongst patients in the United States is less than 1%
- Alterations in antibiotic prescribing due to reported penicillin allergy has been shown to result in higher costs, increased risk of antibiotic resistance, and worse patient outcomes
- Cross-reactivity between truly penicillin allergic patients and later generation cephalosporins and/or carbapenems is rare

Evaluation of Penicillin Allergy

- Obtain a detailed history of allergic reaction
- Classify the type and severity of the reaction paying particular attention to any IgE-mediated reactions (e.g., anaphylaxis, hives, angioedema, etc.) (Table 1)
- Evaluate prior tolerance of beta-lactam antibiotics utilizing patient interview or the electronic medical record

Recommendations for Challenging Penicillin Allergic Patients

See Figure 1

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[1]

Type	Descriptor	Pathophysiology	Presentation	Typical Onset
I	IgE mediated	Allergen binds to 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)

Penicillin Allergy Overview and Management

Epidemiology

- Penicillin allergy is common with a reported prevalence of 8% of patients in the United States [2]
- The true incidence of penicillin allergy amongst those with a reported allergy is less than 10%[3]
- In a study conducted at Nebraska Medicine in 2015, beta-lactam allergy accounted for 45.7% of documented antibiotic allergies[4]
    - Majority classified as cutaneous reactions or undocumented (rash 19.1%, hives 20.2%, or undocumented 17.6%)
    - Only 11.2% of allergic reactions documented were classified as severe IgE mediated (anaphylaxis 3.3% and angioedema 7.9%)

Statement of the Problem

- Prescribing broad spectrum antibiotic agents in patients with reported penicillin allergy can lead to higher costs, increased risk of antibiotic resistance, and worse patient outcomes[2,5,6]
- Careful evaluation of antibiotic allergy and prior tolerance history is *essential* to provide optimal treatment

Incidence of Cross-Reactivity

- Early studies reported inflated cross-reactivity rates between penicillin and cephalosporin agents due to cephalosporin contamination with benzylpenicillin[7]
- Cross-reactivity between penicillin and cephalosporin agents is usually caused by side chain recognition[7]

Table 2: Beta-Lactam Cross-Reactivity in Penicillin Allergic Patients

Drug Class and Available Formulary Agents	Estimated Cross-Reactivity[3,7]	Recommendations for Challenge in Penicillin Allergic Patients
1st Generation Cephalosporin (cefazolin, cephalexin)	1.9 – 7.9%	• Results are influenced by two large trials conducted when early cephalosporin agents were contaminated with penicillin • Inconsistent definitions of allergic reaction resulting in overestimation of cross-reactivity • Patients allergic to ampicillin should avoid cephalosporins with identical R-group side chains (cephalexin and cefaclor[NF])
2nd Generation Cephalosporin (cefuroxime, cefoxitin)	1.9%	• Patients allergic to penicillin G should avoid using cephalosporins with identical R-group side chains (cefoxitin) • Patients allergic to amoxicillin should avoid cephalosporins with identical R-group side chains (cefadroxil[NF] and cefprozil[NF])
3rd Generation Cephalosporin (ceftriaxone, ceftazidime)	0.7%	• Generally considered safe
Advanced (4th/5th) Generation Cephalosporin (cefepime, ceftolozane-tazobactam, ceftaroline[NF])	N/A	• Minimal data available • Generally considered safe
Carbapenem (meropenem, ertapenem)	1%	• Risk profile similar to general population (no increased risk of reaction)
Monobactam (aztreonam)	< 1%	• Cross-reactivity is highly unlikely • Patients allergic to ceftazidime should avoid aztreonam due to side chain similarity

NF = non-formulary at Nebraska Medicine

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 initiation of the medication (see Appendix B for severity classification)
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

Consider referring a patient for penicillin skin testing if they meet any of the criteria below[8]

- History of penicillin allergy more than 10 years ago
- Requires frequent antibiotic use
- Immunosuppressed state (e.g., solid organ transplant patient or patient undergoing chemotherapy)
- Planning for elective surgery
- Multiple antibiotic allergies
- Anaphylaxis when beta-lactam agent was administered concurrently with multiple other agents

Penicillin Allergy Management Algorithm

1. Obtain allergic reaction history, determine classification (Table 1) and severity of reaction
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 medication tab in the chart review section
        i. For ease of viewing, apply filter by therapeutic class and chose “antibiotics”
        ii. See Appendix A for additional information
3. See Figure 1 for management recommendations in patients WITH or WITHOUT prior tolerance history

Follow-Up Documentation Recommendations

- If patients have tolerated the antibiotic for which they describe an allergy, delete the allergy within the electronic medical record and treat patients according to institutional guidelines
- If full-dose or graded challenge is tolerated (per Figure 1), document in penicillin allergy section within the comments of the allergy (drug name and date of tolerance)

Figure 1: Recommendations for Challenging Penicillin Allergic Patients

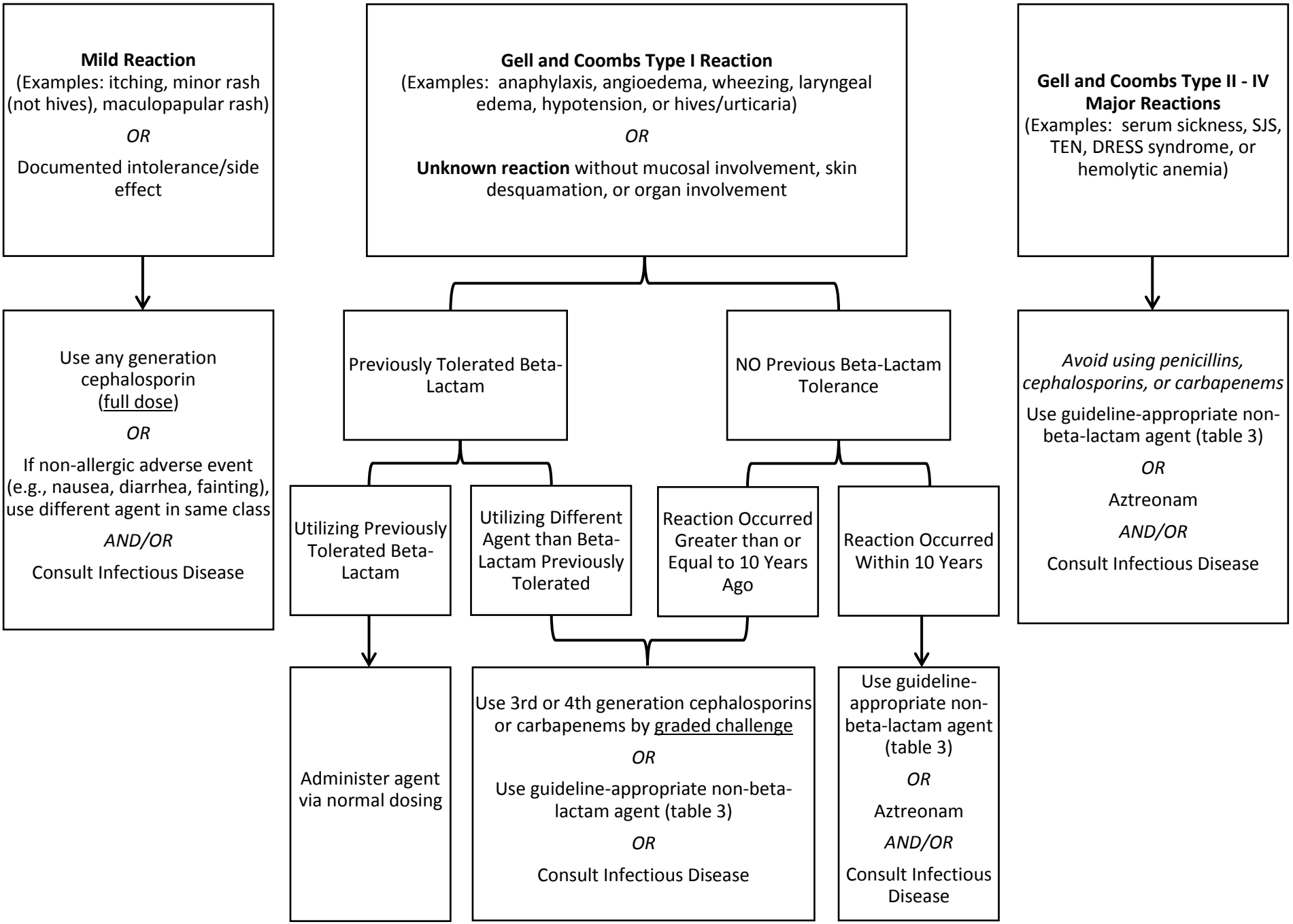


Table 3: Examples of Non-Beta-Lactam Agents

• 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 or clarithromycin)
• Sulfamethoxazole-trimethoprim
• Tetracyclines (e.g., doxycycline, minocycline)

Graded Challenge (or Test Dose Procedure)

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 1
- Patients who tolerate a graded challenge prove they are not allergic to the drug used
- Once a patient passes a graded challenge, normal dosing can be performed with subsequent use, as long as no new reaction has developed
    - When a patient passes a graded challenge, document this within the allergy section of EPIC in the comments of the related medication allergy
- If challenge is passed to same medication listed as an allergy, their allergy designation should be deleted from the electronic medical record

Dosing Recommendations

- Utilize the "Graded Challenge" order set and select the 3rd/4th generation cephalosporin or carbapenem 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

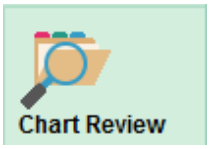
Monitoring Recommendations

- Beta-blockers can blunt the effects of epinephrine. If patient is on a beta-blocker, next dose should be held and challenge scheduled for the following morning prior to first dose of day.
- Monitor patients for symptoms of allergic reaction between each concentration change
- Obtain vitals at baseline and prior to each drug administration
- Recommend allergy kit to be stored at the bedside throughout procedure
    - Kit should contain epinephrine, diphenhydramine and hydrocortisone
    - Only administer these medications in the setting of an allergic reaction (see CP_RX 14)
    - Do not pre-treat with antihistamines or glucocorticoids
- Contact primary team immediately if reaction develops
- Graded challenge can be conducted on all inpatient units, progressive care, and/or intensive care unit

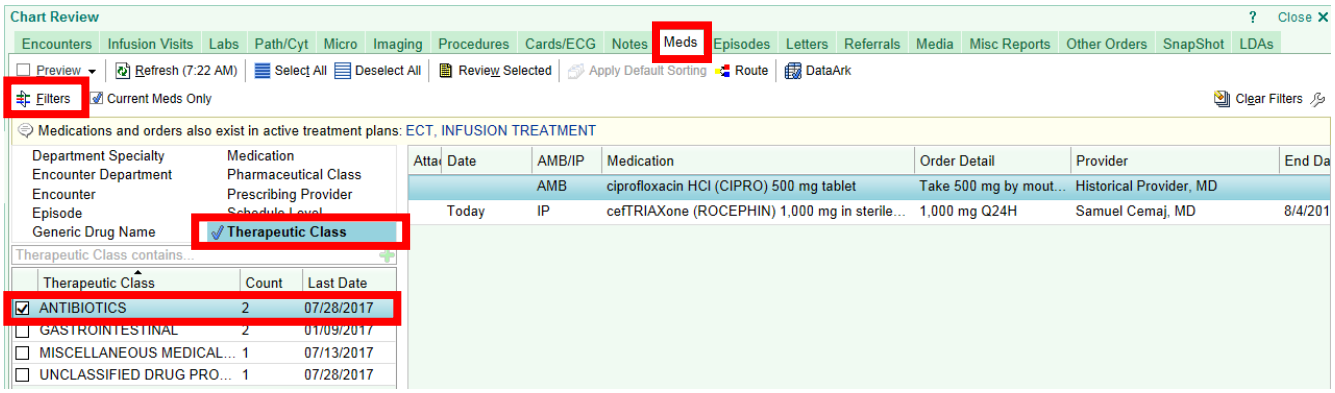
Appendix A

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"



Appendix B

Table 4: World Allergy Organization Immunotherapy Systemic Reaction Grading System[9]

Grade	Characteristics
1	*Signs or symptoms of **one** organ system present* Cutaneous • Generalized pruritus, urticaria, flushing, or sensation of heat or warmth • Angioedema (not laryngeal, tongue or uvular) Upper Respiratory • Rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) • Throat-clearing (itchy throat) • Cough perceived to come from the upper airway, not the lung, larynx, or trachea Conjunctival • Conjunctival erythema, pruritus or tearing Other • Nausea, metallic taste, or headache
2	*Signs or symptoms of **more than one** organ system present* (see above in addition to the following criteria) Lower Respiratory • Asthma: cough, wheezing, shortness of breath (e.g., less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) Gastrointestinal • Abdominal cramps, vomiting, or diarrhea Other • Uterine cramps
3	Lower respiratory • Asthma (e.g., 40% PEF or FEV1 drop, NOT responding to an inhaled bronchodilator) Upper respiratory • Laryngeal, uvula or tongue edema with or without stridor
4	Lower or Upper Respiratory • Respiratory failure with or without loss of consciousness Cardiovascular • Hypotension with or without loss of consciousness
5	Death

References

[1]Solensky R, Khan DA, Bernstein IL, et al. Drug Allergy: An Updated Practice Parameter. Ann Allergy Asthma Immunol 2010; 105: 273e1-78.
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[6] Su T, Broekhuizen BDL, Verheij TJM, Rockmann H. The impact of penicillin allergy labels on antibiotic and health care use in primary care: a retrospective cohort study. Clin Transl Allergy 2017; 7: 18-25.
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[9] Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol 2010; 125: 569-74.