Penicillin Allergy Guidance Document

Key Points

- Cross-reactivity between penicillins and cefazolin, later generation cephalosporins and/or carbapenems is rare
- 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%, despite approximately 10% reporting it in their history
- 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

Evaluation of Penicillin Allergy

- Obtain a detailed history of allergic reaction including nature of the reaction and timing in relation to the agent
- 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 2 and Figure 3

Follow-Up

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

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]

Figure 1: Beta-Lactam Cross-Reactivity

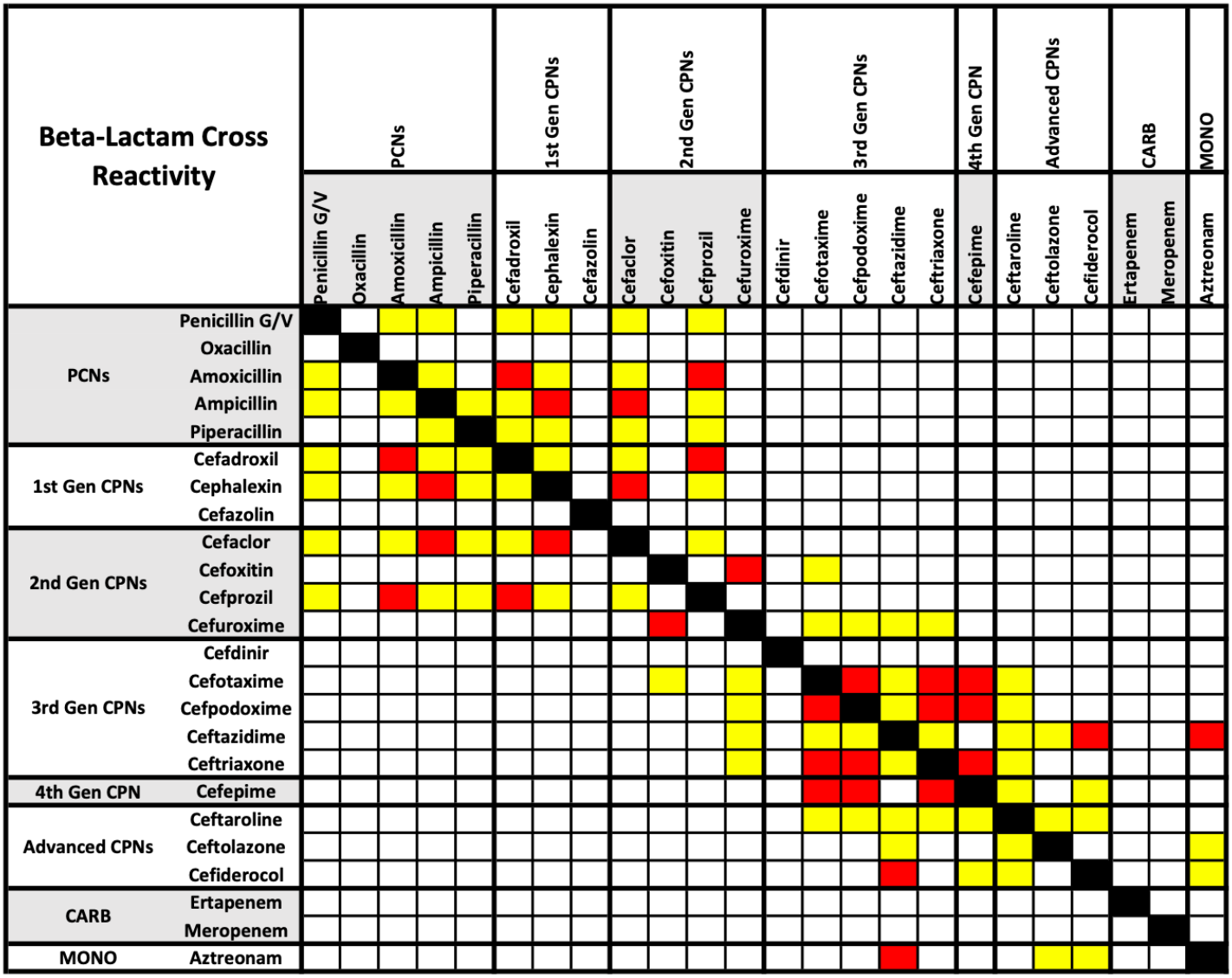


Table 2: Beta-Lactam Cross-Reactivity in Penicillin Allergic Patients

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 have also resulted in overestimation of cross-reactivity • Patients should generally avoid cephalosporins with identical R-group side chains to which they are allergic (ampicillin and cephalexin or amoxicillin and cefadroxil) • Cefazolin has no known cross-reactivity, although allergies do exist
2nd Generation Cephalosporin (cefuroxime, cefoxitin)	1.9%	• Patients allergic to amoxicillin should generally avoid cephalosporins with identical R-group side chains (i.e., cefprozil)
3rd Generation Cephalosporin (ceftriaxone, ceftazidime, ceftazidime-avibactam)	0.7%	• Generally considered safe • Limited data on newer combination agents
Advanced (4th/5th) Generation Cephalosporin (cefepime, ceftolozane-tazobactam, ceftobiprole[NF], 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
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 or Administer a Desensitization

Consider referring a patient for penicillin skin testing if:

- History of anaphylaxis or a recent (< 10 years) IgE-mediated reaction (e.g., immediate onset urticaria, angioedema, bronchospasm)
  - Note: penicillin skin testing is not usually indicated for patients with low-risk, non-IgE-mediated reactions

Consider administering a desensitization if:

- Severe IgE-mediated reaction or acutely ill/pregnant AND need for beta-lactam agent

Penicillin Allergy Management Algorithm

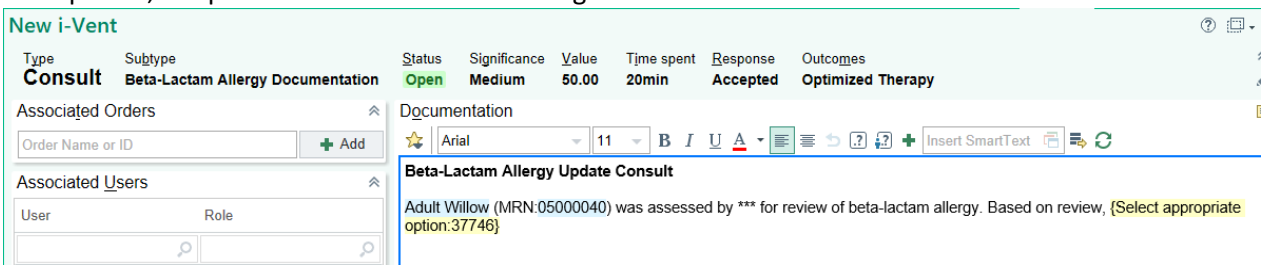
1. Obtain allergic reaction history, determine classification (Table 1) and severity of reaction
   a. This guidance document is intended for use in an adult patient population
2. Evaluate prior antibiotic tolerance history
   a. Review allergy documentation in EPIC to determine if previously tolerated beta-lactams are noted
   b. Review previously prescribed antibiotics using the 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 2 and 3 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

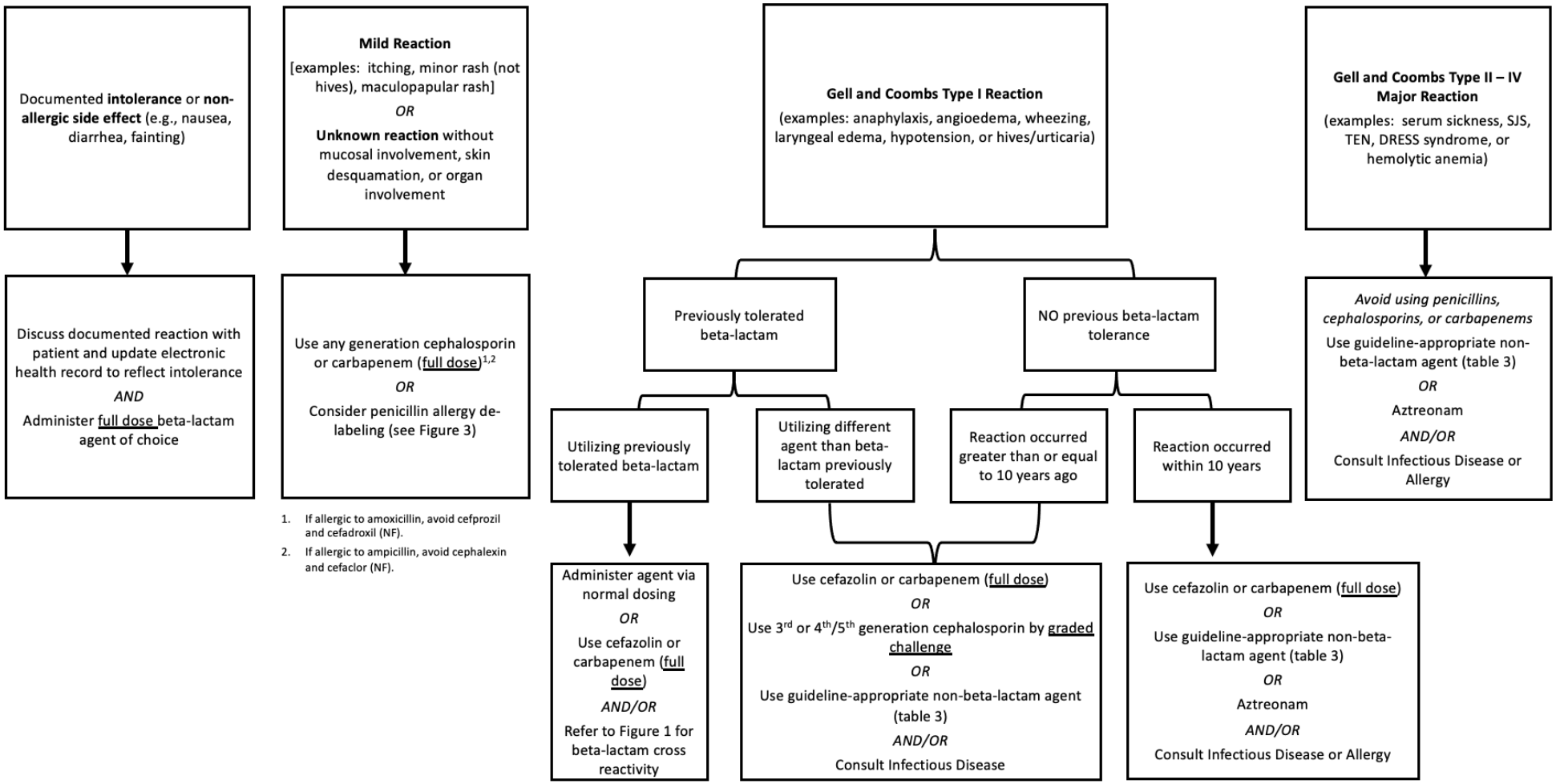
Pharmacy Consult – Beta-Lactam Allergy Documentation

- 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**
  - 

- 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 of this process, but a comment in the EHR should still be placed within the allergy profile before deleting the entry for visibility on why the allergy was removed. This is especially important for when patients are readmitted with a history of allergies.

Figure 2: Recommendations for Antibiotic Challenges in Patients Allergic to Penicillin[+]



[+]This guidance should only be utilized in the specified adult patient population above. In pregnant patients with penicillin allergies, recommend consulting Infectious Diseases service or contacting Allergy/Immunology for current recommendations.

Figure 3: Penicillin Allergy De-Labeling via Oral Amoxicillin Challenge

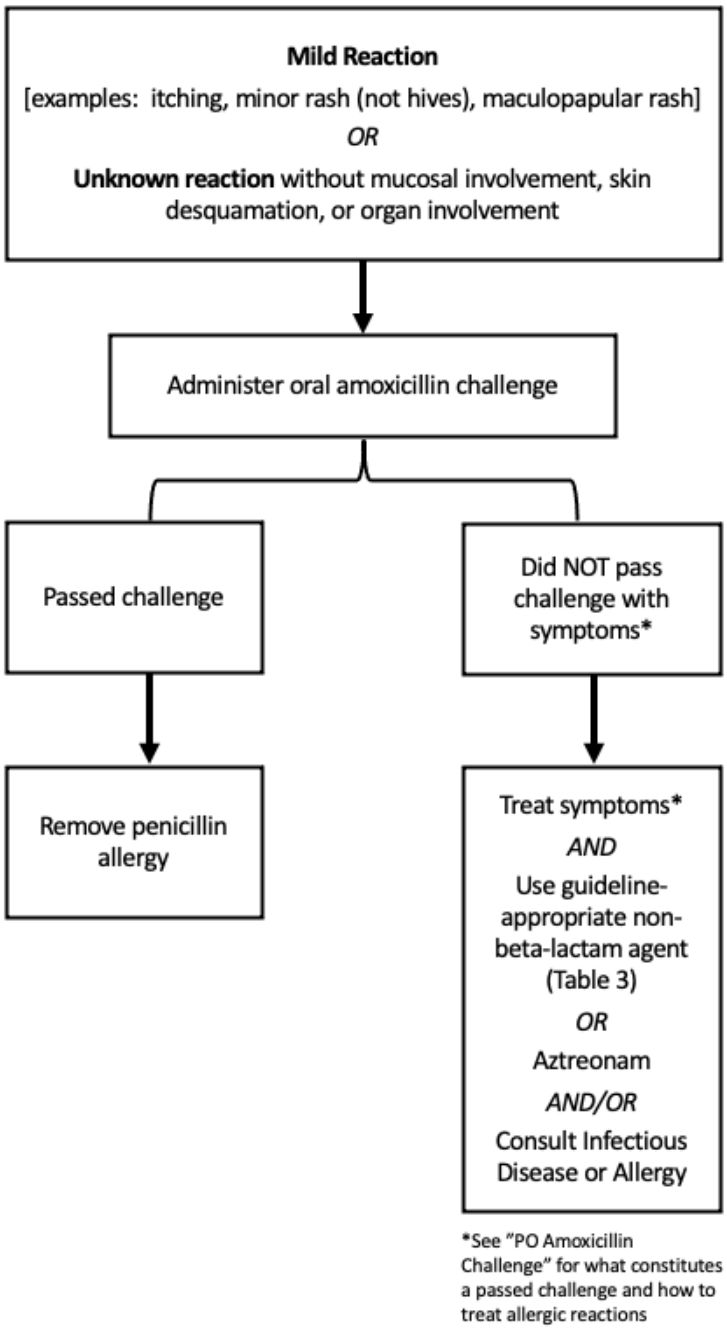


Table 3: Examples of Non-Beta-Lactam Agents

• 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)

IV 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 2 and 3
- 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, the 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

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

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

PO Amoxicillin Challenge (or Test Dose Procedure)

Background

- Direct oral amoxicillin challenges are recommended in patients with low-risk (see Figure 2 and Figure 3) penicillin reaction history without history of skin testing. It allows rapid, safe, and effective de-labeling of penicillin allergies
- Direct oral challenges are not desensitization and should be used as directed in Figure 2 and 3

- Once a patient passes a direct oral challenge, normal dosing of the agent (oral or intravenous) can be performed in current and subsequent use
    - 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)
- Patients who pass a direct oral challenge, should have this documented as listed above in the "Follow-Up Documentation Recommendations" section and the listed allergy should be deleted from the record
- If a patient subsequently develops the following reactions, the 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

Dosing Recommendations

- Utilize the "Graded Challenge" order set and select the oral amoxicillin agent

1. Time 0 minutes: administer amoxicillin 25 mg dose
2. Time 30 minutes: administer amoxicillin 250 mg dose
3. Time 60 minutes: challenge completed and if tolerated the doses in Steps 1 and 2, administer full therapeutic dose of required antimicrobial agent

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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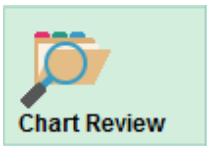
Reviewed November 2022: Antimicrobial Stewardship Program

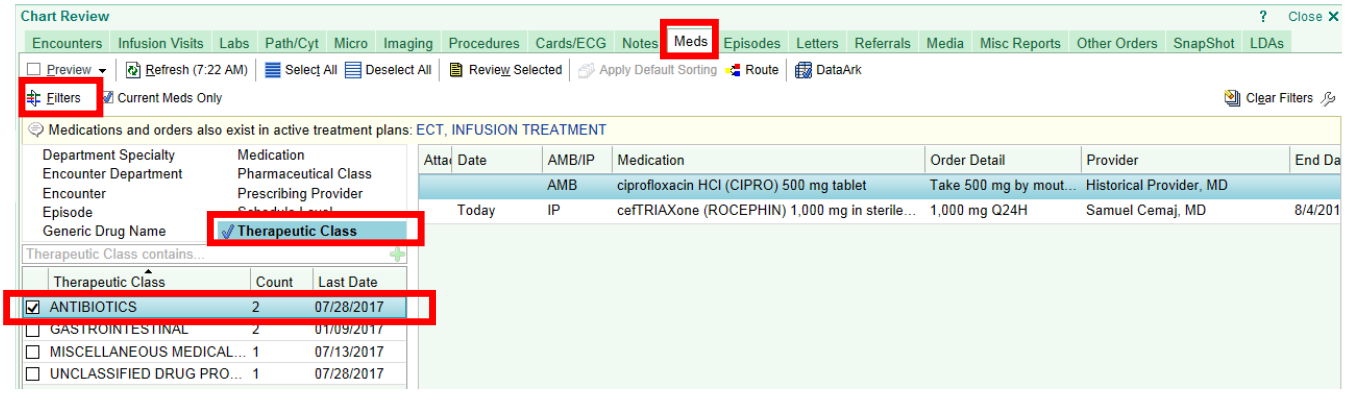
Appendix A

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"



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

References

[1]Khan DA, Banerji A, Blumenthal KG, et al. Drug Allergy: A 2022 Practice Parameter Update. Ann Allergy Asthma Immunol. 2022.

[2] Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. Curr Allergy Asthma Rep 2014; 14: 476-83.

[3] Pichichero ME. A Review of Evidence Supporting the American Academy of Pediatrics Recommendation for Prescribing Cephalosporin Antibiotics for Penicillin-Allergic Patients. Pediatrics 2005; 115: 1048-57.

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[5] van Dijk SM, Gardarsdottir H, Wassenberg MW, Oosterheert JJ, de Groot MC5, Rockmann H. The High Impact of Penicillin Allergy Registration in Hospitalized Patients. J Allergy Clin Immunol Pract 2016;4(5):926-31.

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[7] Romano A, Gaeta F, Poves MFA, Valluzzi RL. Cross-reactivity among beta-lactams. Curr Allergy Asthma Resp 2016; 16: 24-36.