

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 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

Disclaimer: This resource is intended for non-commercial educational and quality improvement purposes. Outside entities may utilize for these purposes but must acknowledge the source. The guidance is intended to assist practitioners in managing a clinical situation but is not mandatory. The interprofessional group of authors have made considerable efforts to ensure the information upon which they are based is accurate and up to date. Any treatments have some inherent risk. Recommendations are meant to improve quality of patient care yet should not replace clinical judgment. Variations, taking individual circumstances into account, may be appropriate. The authors and institution accept no responsibility for any inaccuracies, information perceived as misleading, or the success of treatment.

Overview of Beta-lactam Allergic Reactions

Table 1: Gell and Coombs Classification of Allergic Reactions¹

| 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 allergies⁴
 - 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 benzylpenicillin⁷
- Cross-reactivity between penicillin and cephalosporin agents is usually caused by side chain recognition⁷

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 | Black | | | | | | | | | | | | | | | | | | | | | | | | |
| | Oxacillin | | Black | | | | | | | | | | | | | | | | | | | | | | | |
| | Amoxicillin | | | Black | | | Red | | | | Red | | | | | | | | | | | | | | | |
| | Ampicillin | | | | Black | | Red | | | Red | | | | | | | | | | | | | | | | |
| 1st Gen CPNs | Piperacillin | | | | Black | | | | | | | | | | | | | | | | | | | | | |
| | Cefadroxil | | | Red | | Black | | | | | Red | | | | | | | | | | | | | | | |
| | Cephalexin | | | | Red | | Black | | | Red | | | | | | | | | | | | | | | | |
| 2nd Gen CPNs | Cefazolin | | | | | | Black | | | | | | | | | | | | | | | | | | | |
| | Cefaclor | | | Red | | Red | | Black | | | | | | | | | | | | | | | | | | |
| | Cefoxitin | | | | | | | | Black | | | | | | | | | | | | | | | | | |
| | Cefprozil | | | Red | | Red | | | | Black | | | | | | | | | | | | | | | | |
| 3rd Gen CPNs | Cefuroxime | | | | | | | | Red | Black | | | | | | | | | | | | | | | | |
| | Cefdinir | | | | | | | | | | Black | | | | | | | | | | | | | | | |
| | Cefotaxime | | | | | | | | | | | Black | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red |
| | Cefpodoxime | | | | | | | | | | | | Black | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red |
| | Ceftazidime | | | | | | | | | | | | | Black | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red |
| 4th Gen CPN | Ceftriaxone | | | | | | | | | | | | | Black | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red |
| Advanced CPNs | Cefepime | | | | | | | | | | | | | | Black | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red |
| | Ceftaroline | | | | | | | | | | | | | | | | | | | Black | Red | Red | Red | Red | Red | Red |
| | Ceftolazone | | | | | | | | | | | | | | | | | | | | | Black | Red | Red | Red | Red |
| CARB | Cefiderocol | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Ertapenem | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Meropenem | | | | | | | | | | | | | | | | | | | | | | | | | |
| MONO | Aztreonam | | | | | | | | | | | | | | | | | | | | | | | | | |

CAUTION Cross reaction less likely, Similar R1 or R2 side chain
AVOID Cross reaction likely, identical R1 or R2 side chain

PCNs = penicillins CARB = carbapenems
 CPNs = cephalosporins MONO = monobactams

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% | <ul style="list-style-type: none"> • 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% | <ul style="list-style-type: none"> • Patients allergic to penicillin G should avoid using cephalosporins with identical R-group side chains • Patients allergic to amoxicillin should avoid cephalosporins with identical R-group side chains (cefadroxil and cefprozil) |
| 3rd Generation Cephalosporin (ceftriaxone, ceftazidime) | 0.7% | <ul style="list-style-type: none"> • Generally considered safe |
| Advanced (4th/5th) Generation Cephalosporin (cefepime, ceftolozane-tazobactam, ceftazidime-avibactam, ceftaroline ^{NF}) | N/A | <ul style="list-style-type: none"> • Minimal data available • Generally considered safe |
| Carbapenem (meropenem, ertapenem) | 1% | <ul style="list-style-type: none"> • Risk profile similar to general population (no increased risk of reaction) |
| Monobactam (aztreonam) | < 1% | <ul style="list-style-type: none"> • 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

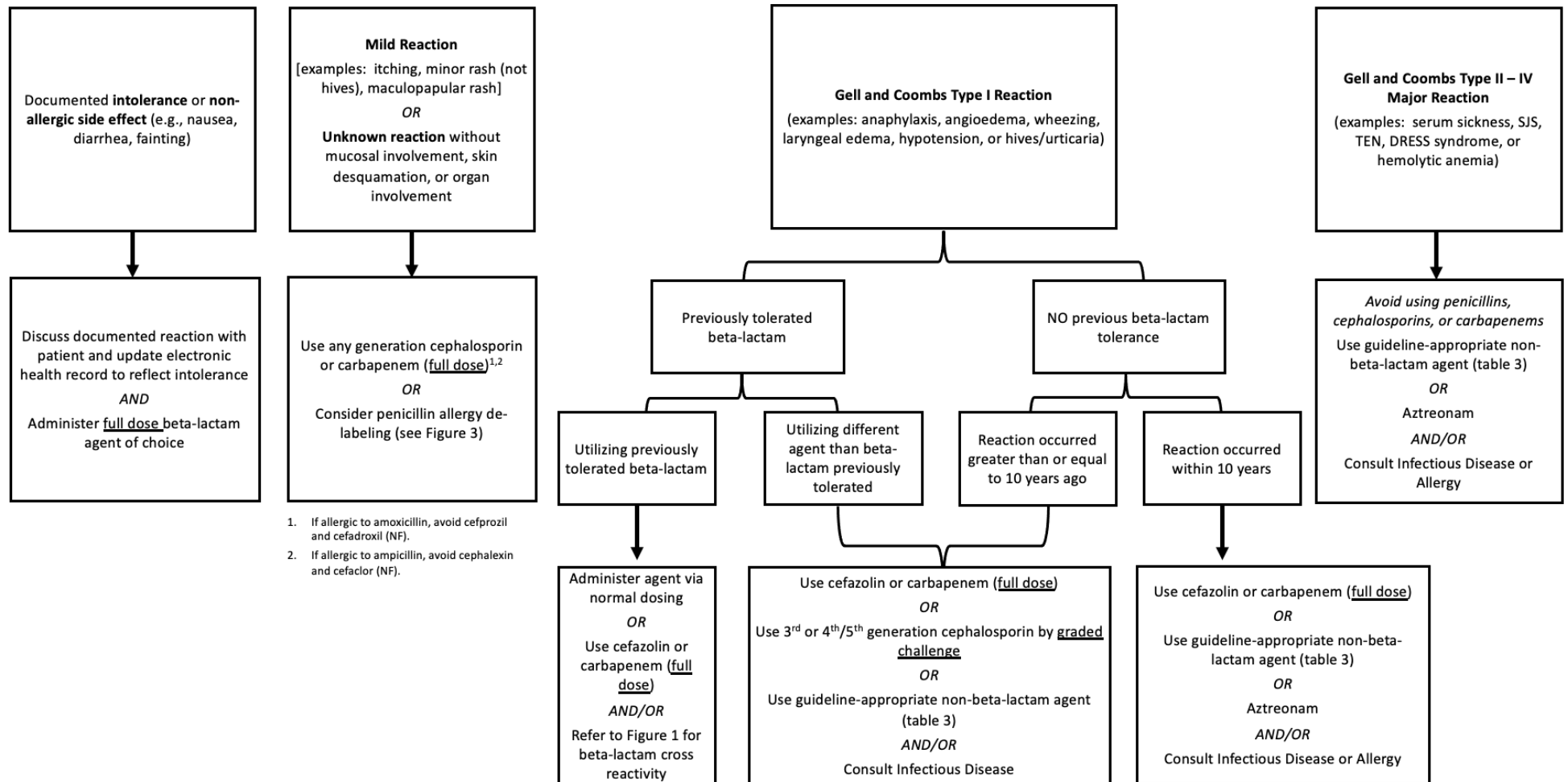
Penicillin Allergy Management Algorithm

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

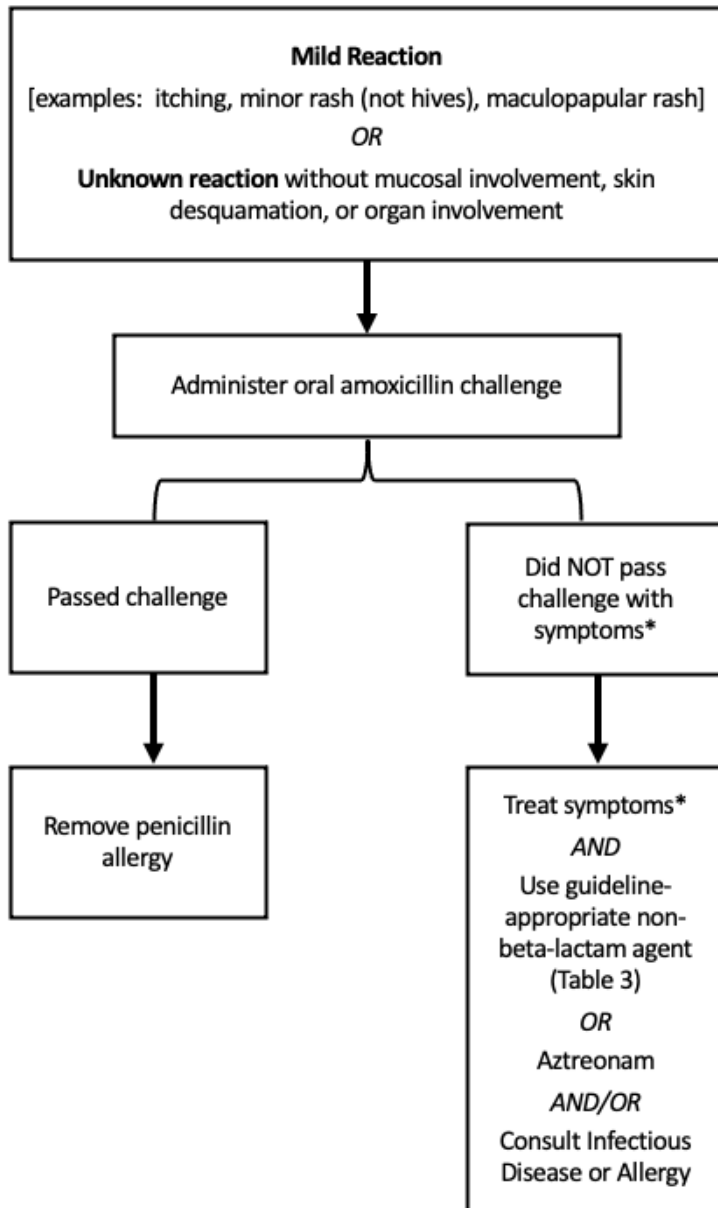
- Please note this documentation section is still being updated within our OneChart team. An updated guidance document will be posted once the OneChart updates are finalized.
- If patients tolerate the antibiotic for which they noted an allergy, the allergy can be deleted from the electronic medical record and documented
- If full-dose or graded challenge is tolerated (per Figure 2 and 3), RN or PharmD will document that patient tolerated/passed the challenge in the electronic medical record
- If full-dose or graded challenge is not tolerated (per Figure 2 and 3), RN or PharmD will document that patient did not tolerate/pass challenge (list reaction that occurred)

Figure 2: Recommendations for Challenging Penicillin Allergic Patients⁺



⁺This guidance should only be utilized in the specified adult patient population above. In pregnant patients with penicillin allergies, recommend consulting Infectious Disease or Allergy.

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



*See "PO Amoxicillin Challenge" for what constitutes a passed challenge and how to treat allergic reactions

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 the emergency department and on all inpatient units, progressive care, and/or intensive care unit
- Patients on beta-blockers can have impaired responses to epinephrine and if a patient is on a beta-blocker, next dose of this agent 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 concentration change
 - Obtain vitals at baseline and prior to each drug administration
 - Allergy kit to be stored at the bedside throughout procedure
 - Kit contains epinephrine, diphenhydramine and hydrocortisone
 - Administer 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 the emergency department and on all inpatient units, progressive care, and/or intensive care unit
- Patients on beta-blockers can have impaired responses to epinephrine and if a patient is on a beta-blocker, next dose of this agent 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 concentration change
 - Obtain vitals at baseline and prior to each drug administration
 - Allergy kit to be stored at the bedside throughout procedure
 - Kit contains epinephrine, diphenhydramine and hydrocortisone
 - Administer medications in the setting of an allergic reaction (according to CP_RX 14)
 - Contact primary team immediately if reaction develops

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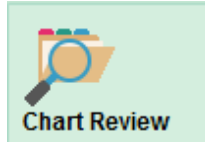
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Reviewed November 2022: Antimicrobial Stewardship Program

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 screenshot shows the EPIC Chart Review interface. The 'Meds' tab is selected in the top navigation bar. Below the navigation bar, there are several utility buttons: 'Preview', 'Refresh (7:22 AM)', 'Select All', 'Deselect All', 'Review Selected', 'Apply Default Sorting', 'Route', and 'DataArk'. A 'Filters' button is highlighted with a red box. Below the filters, there is a section for 'Medications and orders also exist in active treatment plans: ECT, INFUSION TREATMENT'. A table of medications is displayed with columns: 'Attai Date', 'AMB/IP', 'Medication', 'Order Detail', 'Provider', and 'End Da'. Two rows are visible: one for 'ciprofloxacin HCl (CIPRO) 500 mg tablet' and another for 'cefTRIAxone (ROCEPHIN) 1,000 mg in sterile...'. Below the medication table, there is a 'Therapeutic Class' filter section. A table shows the selected 'ANTIBIOTICS' class with a count of 2 and a last date of 07/28/2017. Other classes like 'GASTROINTESTINAL', 'MISCELLANEOUS MEDICAL...', and 'UNCLASSIFIED DRUG PRO...' are also listed but not selected. Red boxes highlight the 'Filters' button, the 'Therapeutic Class' filter, and the 'ANTIBIOTICS' row in the filter table.

| Department Specialty | Medication | Attai Date | AMB/IP | Medication | Order Detail | Provider | End Da |
|----------------------|----------------------|------------|--------|---|---------------|------------------|---------|
| Encounter Department | Pharmaceutical Class | | | | | | |
| Encounter | Prescribing Provider | | | | | | |
| Episode | | Today | IP | cefTRIAxone (ROCEPHIN) 1,000 mg in sterile... | 1,000 mg Q24H | Samuel Cemaj, MD | 8/4/201 |
| Generic Drug Name | | | | | | | |

| Therapeutic Class | Count | Last Date |
|---|-------|------------|
| <input checked="" type="checkbox"/> ANTIBIOTICS | 2 | 07/28/2017 |
| <input type="checkbox"/> GASTROINTESTINAL | 2 | 01/09/2017 |
| <input type="checkbox"/> MISCELLANEOUS MEDICAL... | 1 | 07/13/2017 |
| <input type="checkbox"/> UNCLASSIFIED DRUG PRO... | 1 | 07/28/2017 |

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

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