I. PURPOSE

To guide clinicians in prescribing antibiotics for pediatric and adult inpatients with known or suspected history of allergic reactions to penicillin or cephalosporin antibiotics.

Inclusion/Exclusion

Location:
This guideline is for use on inpatient units. It is not for use in perioperative units, obstetrics units, neonatal units, or emergency departments. Perioperative unit refers to pre-operative holding areas, operating rooms, and the post-anesthesia care unit. Please page the on-call Allergy Fellow if assistance is needed with beta-lactam antibiotic allergy evaluation in these settings. This guideline would apply to post-operative patients admitted to an inpatient unit after surgery.

Population:
This guideline is for patients with documented allergy to penicillin OR cephalosporin antibiotics. If patient has documented allergies to penicillin AND cephalosporin antibiotic, please page the on-call Allergy Fellow for assistance with using this guideline.

Test Dose:
The Test Dose that is described in this guideline is a safe procedure that can be performed by primary teams on inpatient units. Allergy consultation is not needed when the Test Dose is used as part of the Inpatient Beta-Lactam Allergy Guideline. Allergy approval is needed for the Test Dose to be performed for medications other than beta-lactam antibiotics. With Allergy approval, the Test Dose can be performed by primary teams on acute and transitional care units for medications other than beta-lactam antibiotics outside of the Inpatient Beta-Lactam Allergy Guideline.

On-call Allergy Fellow Adult Pager: 443-0463
On-call Allergy Fellow Pediatric Pager: 443-0004

II. BACKGROUND

Most patients with a reported penicillin allergy are not actually allergic [1,2]. Furthermore, cross-reactivity rates between different beta-lactam antibiotics are low, and patients with true penicillin allergy can still safely receive many cephalosporins and carbapenems [12-15].

Inappropriate antibiotic use in patients with a beta-lactam allergy due to over-cautious avoidance of a wide range of beta-lactams has significant negative impact. Inpatients with reported penicillin allergy have longer hospital stays, receive more fluoroquinolones, clindamycin, and vancomycin, and have more Clostridium difficile, methicillin-resistant Staphylococcus aureus (MRSA), and vancomycin-resistant enterococcus (VRE) infections [3].
A beta-lactam allergy guideline with recommendations for which antibiotics are safe to prescribe in patients with beta-lactam allergy can improve patient care by allowing these patients to receive more effective, less toxic, and/or less costly antibiotics [4].

**Background for Penicillin (PCN) Allergy Pathway**

1. Penicillin skin testing is a validated tool for evaluating penicillin allergy, with a high negative predictive value [10-15]. Currently, it is recommended that a negative skin test to penicillin is followed by a test dose procedure, because minor determinants (breakdown products of penicillin) are not available for skin testing [11].

2. Patients with penicillin allergy can still safely receive many cephalosporins and carbapenems [12-15]. Studies suggest that the risk of an allergic reaction to a 1st-generation cephalosporin in penicillin-allergic patients is increased by approximately 0.5% [13]. Penicillin-allergic patients are even less likely to react to later generation cephalosporins and carbapenems, with studies suggesting that cross-reactivity between penicillin and later generation cephalosporins less than 1% [13,14,15].

3. Patients confirmed to be selectively allergic to aminopenicillins (amoxicillin or ampicillin) but who tolerate Penicillin G should avoid cephalosporins with identical R group side chains. Cephalexin (Keflex) is the only cephalosporin on UCSF formulary with identical R group side chains to aminopenicillins. Please page the on-call Allergy Fellow (adult pager 443-0463, pediatric pager 443-0004) for assistance determining cross-reactivity between aminopenicillins and cephalosporins not on UCSF formulary.

**Background for Cephalosporin Allergy Pathway**

1. The allergic determinants of cephalosporins can be derived from the beta-lactam structure. However, cross-reactivity between penicillins and cephalosporins, and between different cephalosporins, is mainly dependent on the R-group side chain structures of these antibiotics. Some 1st-generation and 2nd-generation cephalosporins have a similar side chain to aminopenicillins. For later generation cephalosporins with side chains that differ completely from those of penicillins, there is minimal risk for cross-reactivity [13,14].

2. Inpatients will not receive skin testing to cephalosporins because cephalosporin skin testing has a poor negative predictive value [7,8].

3. Considering the similarity and dissimilarity of side chains is useful for determining cross-reactivity between cephalosporins. Cephalosporins with unique side chains from the cephalosporin that reportedly caused the initial reaction are less likely to cross-react and cause a reaction ([Appendix 5]) [7,8,13,14].

**Definitions**

**Beta-lactam antibiotics:** antibiotics whose chemical structure consists of a core beta-lactam ring with side chains – penicillins, cephalosporins, monobactams, carbapenems
Side chains: component of chemical structure of beta-lactam antibiotics; side chains can be identical/similar or unique between certain beta-lactam antibiotics

Adverse drug reaction: any adverse event due to pharmacologic effects of the drug

Allergic reaction: adverse drug reaction mediated by IgE activation of allergy cells (mast cells, basophils)

Type II-IV reaction: adverse drug reaction mediated by cells and proteins of the immune system but not involving IgE activation of allergy cells

III. STEPS

A. Step 1. Review medication administration history in APeX to see if patient tolerated beta-lactam antibiotic(s) in the past. Step-by-step suggestions for reviewing medication administration history in APeX are provided in Appendix 6.

B. Step 2. Review the history of the adverse reaction for ALL agents in the pharmaceutical class of beta-lactam antibiotics listed in APeX with the patient to determine the type of reaction and recommended management (Appendix 1). Update the documented adverse reaction in APeX with the patient-reported history.

C. Step 3. If appropriate, follow the Penicillin Allergy Pathway (Appendix 2) or Cephalosporin Allergy Pathway (Appendix 3). If the Penicillin Allergy Pathway or Cephalosporin Allergy Pathway suggests a Test Dose, follow directions for the Test Dose Procedure (Appendix 4). Please page the on-call Allergy Fellow (adult pager 443-0463, pediatric pager 443-0004) with the patient’s name/MRN if you have questions. If patient has documented allergy to penicillin AND cephalosporin antibiotic, please consult Allergy for assistance with using this guideline.

D. Note: It is always an option to use an alternative antibiotic agent. Use of penicillin and/or cephalosporin pathway should not delay care of an active infection. An alternative antibiotic per the primary team or Infectious Disease service should be administered to treat active infection until the patient’s listed beta-lactam allergies have been addressed.
IV. REFERENCES

13. Pichichero ME. Use of selected cephalosporins in penicillin-allergic patients: a paradigm shift. *Diagnostic Microbiology and Infectious Disease* 2006;57:13S-18S.


V. APPENDICES

Appendix 1: Determining the Type of Reaction and Recommended Management

Appendix 2: Penicillin Allergy Pathway

Appendix 3: Cephalosporin Allergy Pathway

Appendix 4: Test Dose Procedure Steps

Appendix 5: Cross-reactivity matrix of cephalosporin antibiotics on formulary at UCSF

Appendix 6: Reviewing APeX for History of Beta-Lactam Administration
**Appendix 1: Determining the Type of Reaction and Recommended Management**

*SJS/TEN = Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis
†DRESS/DISH = Drug Rash Eosinophilia and Systemic Symptoms / Drug-Induced Systemic Hypersensitivity

<table>
<thead>
<tr>
<th>Minor Reaction</th>
<th>Other Type II-IV Reaction</th>
<th>Severe Type II-IV Reaction</th>
<th>Higher Risk for Allergic Reaction</th>
<th>Lower Risk for Allergic Reaction</th>
</tr>
</thead>
</table>
| 1. Nausea or vomiting only  
2. Diarrhea only  
3. Minor laboratory abnormalities  
4. Local injection reactions | 1. Drug-induced cytopenias  
2. Other significant laboratory abnormalities (i.e., nephrotoxicity) | 1. Lesions or ulcers involving the mucus membranes; skin desquamation (suggests SJS/TEN*)  
2. Rash, fever, and lymph node, liver, and/or kidney involvement (suggests DRESS/DISH†)  
3. Fever, urticarial rash, arthritis (suggests Serum Sickness) | 1. Hives/urticaria  
2. Angioedema (swelling)  
3. Laryngeal edema  
4. Wheezing / Dyspnea  
5. Hypotension  
6. Treatment with epinephrine  
7. Intubation  
8. Patient unable to give any history due to medical condition. | 1. Itching only  
2. Mild, delayed rash (not hives) without internal organ involvement  
3. APEX lists allergy, but patient and/or caregiver do not recall any details about the reaction. |

Does not preclude consideration of using, with appropriate monitoring, beta-lactam antibiotic(s) in question

Management can be per the primary team. If assistance is necessary, please consult Infectious Disease.

Avoid using penicillin, cephalosporin, and carbapenem. If there is a strong clinical indication for a penicillin, cephalosporin, or carbapenem, please consult Allergy and Infectious Disease.

Follow Penicillin Allergy Pathway or Cephalosporin Allergy Pathway
Appendix 2: Penicillin Allergy Pathway

Guideline for prescribing beta-lactam antibiotics in patients with listed penicillin allergy. If patient has documented allergy to penicillin AND cephalosporin antibiotic, please consult Allergy for assistance using this guideline.

**Severe Type II-IV Reaction**
1. Lesions or ulcers involving the mucus membranes; skin desquamation (suggests SJS/TEN†)
2. Rash, fever, and lymph node, liver, and/or kidney involvement (suggests DRESS/DISH†)
3. Fever, urticarial rash, arthritis (suggests Serum Sickness)

**Higher Risk for Allergic Reaction**
1. Hives/urticaria
2. Angioedema (swelling)
3. Laryngeal edema
4. Wheezing / Dyspnea
5. Hypotension
6. Treatment with epinephrine
7. Intubation
8. Patient unable to give any history due to medical condition.

**Lower Risk for Allergic Reaction**
1. Itching only
2. Mild, delayed rash (not hives) without internal organ involvement
3. APeX lists allergy, but patient and/or caregiver do not recall any details about the reaction.

**Avoid using penicillin, cephalosporin, or carbapenem. If there is a strong clinical indication for a penicillin, cephalosporin, or carbapenem, please consult Allergy and Infectious Disease.**

**OK to administer full dose:**
-- Aztreonam

**OK to administer using Test Dose procedure:**
-- Cefazolin
-- 3rd/4th/5th generation cephalosporin
-- Carbapenem

**If ID consult determines that a penicillin or 1st/2nd generation cephalosporin (other than cefazolin) is the preferred therapy, consult Allergy for possible inpatient penicillin skin testing.**

Place Discharge Referral to Penicillin Testing Clinic for penicillin skin testing if penicillin testing was not performed during hospitalization.

**1. If full dose of a penicillin antibiotic tolerated, remove penicillin from the allergy list.**

**2. Document results of cephalosporin and/or carbapenem test dose procedure (tolerated or not tolerated) in the penicillin allergy comments.**
Appendix 3: Cephalosporin Allergy Pathway

Guideline for prescribing beta-lactam antibiotics in patients with listed cephalosporin allergy. If patient has documented allergy to penicillin AND cephalosporin antibiotic or if patient has documented allergy to 1st/2nd AND 3rd/4th/5th generation cephalosporin antibiotic, please consult Allergy for assistance with using this guideline.

### Severe Type II-IV Reaction
1. Lesions or ulcers involving the mucus membranes; skin desquamation (suggests SJS/TEN*)
2. Rash, fever, and lymph node, liver, and/or kidney involvement (suggests DRESS/DISH†)
3. Fever, urticarial rash, arthritis (suggests Serum Sickness)

### Higher Risk for Allergic Reaction
1. Hives/urticaria
2. Angioedema (swelling)
3. Laryngeal edema
4. Wheezing / Dyspnea
5. Hypotension
6. Treatment with epinephrine
7. Intubation
8. Patient unable to give any history due to medical condition.

Original reaction was to 1st/2nd generation cephalosporin

### Lower Risk for Allergic Reaction
1. Itching only
2. Mild, delayed rash (not hives) without internal organ involvement
3. APEx allergy; but patient and/or caregiver do not recall any details about the reaction.

Original reaction was to 3rd/4th/5th generation cephalosporin

**Avoid using penicillin, cephalosporin, or carbapenem. If there is a strong clinical indication for a penicillin, cephalosporin, or carbapenem, please consult Allergy and Infectious Disease.**

**OK to administer full dose:**
-- Aztreonam

**OK to administer using Test Dose procedure:**
-- 3rd/4th/5th generation cephalosporins with dissimilar side chains (Appendix 5)
  -- Carbapenems

**If ID consult determines that a penicillin or 1st/2nd generation cephalosporin is needed, consult Allergy for possible inpatient penicillin skin testing.**

Place Discharge Referral to Penicillin Testing Clinic if penicillin skin testing was not performed during hospitalization.

**OK to administer full dose:**
-- Cephalosporins with dissimilar side chains (Appendix 5)
  -- Carbapenems
  -- Aztreonam

**OK to administer using Test Dose procedure:**
-- Penicillin antibiotics
  -- 1st/2nd generation cephalosporins with dissimilar side chains (Appendix 5)
  -- Carbapenems

**If ID consult determines that a 3rd/4th/5th generation cephalosporin is needed, consult Allergy.**

Place Discharge Referral to Penicillin Testing Clinic if allergy evaluation was not performed during hospitalization.

**OK to administer full dose:**
-- Carbapenems

**OK to administer using Test Dose procedure:**
-- Cephalosporins with similar side chains (Appendix 5)

Place Discharge Referral to Penicillin Testing Clinic if allergy evaluation was not performed during hospitalization.

Document results of test dose procedure (beta-lactam antibiotic tolerated or not tolerated) in the beta-lactam allergy comments.
Severe Type II-IV Reaction
1. Lesions or ulcers involving the mucus membranes; skin desquamation (suggests DRESS/DISH)
2. Rash, fever, and lymph node, liver, and/or kidney involvement (suggests SJS/TEN)
3. Fever, urticarial rash, arthritis (suggests Serum Sickness)

Avoid using penicillin, cephalosporin, or carbapenem. If there is a strong clinical indication for a penicillin, cephalosporin, or carbapenem, please consult Allergy and Infectious Disease.

Higher Risk for Allergic Reaction
1. Hives/urticaria
2. Angioedema (swelling)
3. Laryngeal edema
4. Wheezing/Dyspnea
5. Hypotension
6. Treatment with epinephrine
7. Intubation
8. Patient unable to give any history due to medical condition

Original reaction was to 1st/2nd generation cephalosporin

OK to administer full dose:
-- Aztreonam

OK to administer using Test Dose procedure:
-- 3rd/4th/5th generation cephalosporins with dissimilar side chains (Appendix 5)
-- Carbapenems

If ID consult determines that a penicillin or 1st/2nd generation cephalosporin is needed, consult Allergy for possible inpatient penicillin skin testing.

Place Discharge Referral to Penicillin Testing Clinic if penicillin skin testing was not performed during hospitalization.

Lower Risk for Allergic Reaction
1. Itching only
2. Mild, delayed rash (not hives) without internal organ involvement
3. APEX lists allergy, but patient and/or caregiver do not recall any details about the reaction.

Original reaction was to 3rd/4th/5th generation cephalosporin

OK to administer full dose:
-- Cephalosporins with dissimilar side chains (Appendix 5)
-- Carbapenems
-- Aztreonam

OK to administer using Test Dose procedure:
-- Penicillin antibiotics
-- 1st/2nd generation cephalosporins with dissimilar side chains (Appendix 5)
-- Carbapenems

If ID consult determines that a 3rd/4th/5th generation cephalosporin is needed, consult Allergy.

Place Discharge Referral to Penicillin Testing Clinic if allergy evaluation was not performed during hospitalization.

Document results of test dose procedure (beta-lactam antibiotic tolerated or not tolerated) in the beta-lactam allergy comments.
Appendix 4: Test Dose Procedure

The ‘Adult Drug Test Dose Allergy Evaluation’ or ‘Pediatric Drug Test Dose Allergy Evaluation’ order sets available in APeX include the necessary orders for the Test Dose Procedure. If the primary team has questions or concerns after reading Appendix 4, please page the on-call Allergy fellow (adult pager 443-0463, pediatric pager 443-0004).

During the Test Dose Procedure, the patient receives a test dose (1/10th of full standard treatment dose). After 30 minutes, if the patient remains asymptomatic, the patient receives the full dose. The patient is monitored for 60 more minutes to ensure that he/she tolerates the medication. Appropriate precautions are necessary throughout the procedure and are outlined below.

If a patient tolerates a medication administered using the Test Dose Procedure, it confirms that the patient can tolerate the drug without developing an allergic reaction (i.e., a Type I, IgE-mediated immediate hypersensitivity reaction). The primary team can order ongoing antibiotic therapy using standard scheduled doses of this medication.

If a reaction occurs as a consequence of the Test Dose Procedure, follow the Action Plan for RN table and page the on-call Allergy fellow (adult pager 443-0463, pediatric pager 443-0004). Order a tryptase level within 1-2 hours after a possible allergic reaction.

Please document the results (medication tolerated or not tolerated) in the allergy section of APeX after the Test Dose Procedure is completed (as per Appendix 2 and 3).

Test Dose Procedure steps:
1. If possible, hold beta-blockers and ACE inhibitors for 24 hours before administering the Test Dose.
   a. Beta-blockers can impair the effectiveness of epinephrine should it be required in the event of anaphylaxis. If beta-blockers have been administered within the last 24 hours, glucagon must be readily available to reverse the effects of beta-blockers in the event that epinephrine is needed to treat anaphylaxis.
   b. ACE inhibitors can increase the severity of an allergic reaction if a patient is allergic.
   c. Beta-blockers and ACE inhibitors do not mask an allergic reaction, so even if a patient is on a beta-blocker and/or ACE inhibitor, if they do not have a reaction during the Test Dose Procedure, it means that they are not allergic to the medication in question.
   d. ADULT PATIENTS: If beta-blocker and/or ACE inhibitors have already been given, please order glucagon in the “Rescue Medications” panel. Call the on-call Allergy fellow (adult pager 443-0463) if assistance is needed with deciding when and how to proceed with the Test Dose.
   e. PEDIATRIC PATIENTS: If beta-blocker and/or ACE inhibitors have already been given, consult Pediatric Allergy (pager 443-0004) before ordering the test dose.
2. Write for the following rescue medications to be immediately available on the floor during the Test Dose Procedure:
   a. Adult patient:
      b. Epinephrine 0.3 mg (1 mg/ml dilution) IM
Inpatient Beta-lactam Allergy
Guideline

AI/ASP/Pharmaceutical Services
P & T approved: Feb 14 2018
Updated: 12/09/2018, 12/01/2019

Prepared by Iris M. Otani, MD
Most recent update: Jan 10, 2020

- 12 -
| Anaphylaxis / Severe | • throat swelling  
|                     | • hives over > 50% body  
|                     | • SpO2 < 90%, cough/wheezing/dyspnea that does NOT respond to albuterol  
|                     | • hypotension (SBP < 90 mmHg) ± tachycardia  
|                     | • loss of consciousness  
|                     | • repeated vomiting  
|                   | • Stop infusion and check vital signs  
|                   | • Give epinephrine 0.3 mg IM  
|                   |   • Give glucagon if patient has taken beta-blockers in the last 24 hours  
|                   | • Call rapid response or code team  
|                   | • Notify primary team and/or on-call Allergy fellow (adult pager 443-0463, pediatric pager 443-0004)  
| Moderate | • swelling of a body part that doesn’t involve the throat  
|         | • cough/wheezing/dyspnea that responds to albuterol, SpO2 > 90%  
| Mild | • itching, flushing  
|      | • hives < 50% of body  
|      | • eye redness/itching/tearing  
|      | • sneezing, runny nose, congestion  
|      | • nausea  
|       | • Stop infusion and check vital signs  
|       | • Give diphenhydramine  
|       | • Give hydrocortisone if no resolution 10 minutes after giving diphenhydramine  
|       | • Give albuterol for cough/wheezing/dyspnea with SpO2 > 90%  
|       | • Notify primary team and/or on-call Allergy fellow (adult pager 443-0463, pediatric pager 443-0004)  
| Subjective | Subjective symptoms other than symptoms listed above.  
|   | • Stop infusion and check vital signs  
|   | • Notify primary team and/or on-call Allergy fellow (adult pager 443-0463, pediatric pager 443-0004) for guidance  

Anaphylaxis / Severe signs include: throat swelling, hives over 50% of the body, SpO2 < 90%, cough/wheezing/dyspnea that does NOT respond to albuterol, hypotension (SBP < 90 mmHg) ± tachycardia, loss of consciousness, and repeated vomiting. In such cases, it is crucial to stop the infusion and check vital signs. Epinephrine 0.3 mg IM should be given, along with glucagon if the patient has taken beta-blockers in the last 24 hours. Rapid response or code team should be notified, along with the primary team and allergy fellow (adult pager 443-0463, pediatric pager 443-0004).

Moderate signs include swelling of a body part that doesn’t involve the throat and cough/wheezing/dyspnea that responds to albuterol with SpO2 > 90%. In these cases, diphenhydramine should be given with hydrocortisone if no resolution after 10 minutes of giving diphenhydramine. Albuterol can be given for cough/wheezing/dyspnea with SpO2 > 90%. The primary team and allergy fellow (adult pager 443-0463, pediatric pager 443-0004) should be notified.

Mild signs include itching, flushing, hives < 50% of the body, eye redness/itching/tearing, sneezing, runny nose, congestion, and nausea. If these symptoms occur, diphenhydramine should be given and hydrocortisone if no resolution 10 minutes after giving diphenhydramine. Albuterol can be given for cough/wheezing/dyspnea with SpO2 > 90%. The primary team and allergy fellow (adult pager 443-0463, pediatric pager 443-0004) should be notified.

Subjective symptoms include all symptoms not listed above. If these symptoms occur, it is important to stop the infusion and check vital signs. The primary team and allergy fellow (adult pager 443-0463, pediatric pager 443-0004) should be notified for guidance.
Appendix 5: Cross-reactivity matrix of cephalosporin antibiotics on formulary at UCSF

This matrix describes the risk of cross-reactivity between two cephalosporin antibiotics. In this chart, only agents on formulary at UCSF Medical Center are included. A box with a (☠) symbol indicates that the two cephalosporin antibiotics share a similar or identical side chain, and that there is a risk for cross-reactivity between them. Empty boxes indicate a lack of side-chain similarity and a lower risk for cross-reactivity. **Cefazolin (1st) and ceftaroline (5th)** have dissimilar side chains to all other cephalosporins (including cephalosporins not on formulary at UCSF). [13,14,16-20]

<table>
<thead>
<tr>
<th>Generation</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
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<td>1st</td>
<td>Cefazolin</td>
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Please page the on-call Allergy Fellow (adult pager 443-0463, pediatric pager 443-0004) for assistance determining cross-reactivity of beta-lactam antibiotics not on formulary at UCSF Medical Center.
Appendix 6: Reviewing APeX for History of Beta-Lactam Administration

1. Select Chart Review
2. Select 'Meds' tab

3. Deselect 'Current Meds Only'

4. Select 'Filters'

5. Select 'Pharmaceutical Class'

Beta-lactams are listed in alphabetical order under 'Pharmaceutical Class' as:
- CARBAPENEMS
- CEPHALOSPORINS - 1ST GENERATION
- CEPHALOSPORINS - 2ND GENERATION
- CEPHALOSPORINS - 3RD GENERATION
- CEPHALOSPORINS - 1ST GENERATION PENICILLINS

6. Click on the beta-lactams to see which medications patient has received in that class.

7. Click on a medication to see details in the Preview pane.
Outpatient:
--Ask patient if he/she remembers taking the medication and if he/she remembers having a reaction to the medication. Go to Appendix 1.

Inpatient:
--See below. Also ask patient if he/she remembers taking the medication and if he/she remembers having a reaction to the medication. Go to Appendix 1.

1. Click on a medication to see details in the Preview pane.

2. Find ‘Most Recent Administration’ to check if patient received full dose(s) of medication in question.

3. Click on ‘Full Administration Report’ for complete medication administration history.

4. Review notes from around administration date to see if there are any mention of a reaction to the medication in question.

Desensitization:
Desensitization is a specialized allergy procedure that allows administration of antibiotics that a patient is allergic to. If an antibiotic has been administered via desensitization, a patient will still be allergic to that antibiotic and cannot receive it in the future.

A medication administered via desensitization will have:
1. the word ‘desensitization’ in the title line
2. additional ‘Admin Instructions’