Treatment of Patients with Reported Allergies to Beta-Lactam Antibiotics – Adult – Inpatient Clinical Practice Guideline

Note: Active Table of Contents – Click to follow link

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Executive Summary

Guideline Overview

This guideline provides information on evaluating patient-reported beta lactam allergies to facilitate optimized antibiotic selection to improve outcomes, to reduce risk of multiple-drug resistant pathogens, to reduce length of stay, and to reduce cost.

Key Revisions (2016 Periodic Review)

Addition of new clinical evidence supporting extremely low rates of cross-reactivity between penicillins, cephalosporins, and carbapenems in patients reporting an allergy to a beta lactam outside that class.

Key Practice Recommendations

1. Reported beta lactam allergies should be extensively investigated including an evaluation of beta lactam antibiotics that the patient has received and tolerated (or not tolerated).
2. Antibiotic selection should be based on allergy evaluation and possibility of cross reactivity.
3. Penicillin skin testing and graded challenges may be considered in patients with specific characteristics for whom beta lactam antibiotics are needed.

Companion Documents

None

Scope

Disease Condition: This clinical practice guideline is designed to lease prescribers through the evaluation, ordering, processing, and administering of beta-lactam antibiotics in patients with reported beta-lactam allergies.

Clinical Specialty: All medical specialties

Intended Users: Physicians, Advanced Practice Providers, Nurses, and Pharmacists

Objective

The clinical practice guideline is intended to provide a standardized process for the evaluation of beta lactam antibiotic allergies or intolerances and the subsequent selection of antibiotics with respect to the evaluation.

Target Population

Adult patients with reported beta-lactam allergies for whom the use of beta-lactam antibiotics may be desired.

Interventions and Practices Considered

The clinical interventions and practices recommended in this guideline are intended for patients with reported beta lactam allergies receiving antibiotic therapy. Practices include evaluation of reported allergies, prescribing of beta lactam antibiotics in patients with a reported allergy, utilization of oral and intravenous graded challenges, and penicillin skin testing.

Major Outcomes Considered

- Utilization of oral and intravenous graded challenges
- Utilization of penicillin skin testing

Methodology

Methods Used to Collect/Select the Evidence

Electronic database searches (i.e. PUBMED) were conducted and workgroup members to collect evidence for review; for the 2016 revision, clinical evidence dating back to January 2014 was reviewed. Additionally, hand searches were performed within selected evidence for other relevant resources. Expert opinion, clinical experience, and regard for patient safety/experience were also considered during discussions of the evidence.

Methods Used to Formulate the Recommendations

All recommendations endorsed or developed by the guideline workgroup were reviewed and approved by other stakeholders or committees.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:
Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[1]

Rating Scheme for the Strength of the Evidence/Strength of the Recommendations:
See Appendix A for the rating scheme used within this document.

Recognition of Potential Health Care Disparities
No potential disparities identified.

Definitions

1. Gell and Coombs classification allergic drug reactions[2-9]
    - 1.1. Type 1: IgE-mediated – most common Type 1 reaction
        - 1.1.1. Immediate reactions (onset less than one hour after drug administration): systemic manifestations of anaphylaxis
            - 1.1.1.1. Urticaria (hives), pruritus, bronchospasm, laryngeal edema, hypotension, and/or cardiac arrhythmias
            - 1.1.1.2. Life-threatening
            - 1.1.1.3. Tested by minor determinant of penicillin skin test
            - 1.1.1.4. Immediate reactions occurring greater than one hour after infusion, or during sustained therapy, even in the presence of urticaria, are rare
        - 1.1.2. Accelerated reactions (onset one to 72 hours after drug administration) – less common Type 1 reaction
            - 1.1.2.1. Urticaria, angioedema, laryngeal edema, wheezing
            - 1.1.2.2. Rarely life-threatening
            - 1.1.2.3. Determined by penicillin skin test
        - 1.1.3. Usually associated with beta-lactam antibiotics
    - 1.2. Type 2: Cytotoxic/antibody-mediated (IgG-,IgM-complement mediated)
        - 1.2.1. Hemolysis, thrombocytopenia, neutropenia, or interstitial nephritis
        - 1.2.2. Usually associated with quinidine, methyldopa, and penicillins
        - 1.2.3. IgG and IgM antibodies do not induce allergic reactions
            - 1.2.3.1. Only IgE binds to mast cells and basophils to produce allergic reactions
    - 1.3. Type 3: Immune complex (IgG, IgM immune complexes)
        - 1.3.1. Serum sickness or vasculitis
        - 1.3.2. Fever, rash, urticaria, lymphadenopathy, and arthralgias
        - 1.3.3. Usually associated with antisera, penicillin, sulfonamides, and phenytoin
    - 1.4. Type 4: Cellular immune-mediated/delayed hypersensitivity reaction
        - 1.4.1. Contact dermatitis
            - 1.4.1.1. Example: health care workers involved in the manufacturing and dispensing of offending agents
        - 1.4.2. Delayed non-urticarial rashes caused by aminopenicillins and drug reaction with eosinophilia and systemic symptoms syndrome (DRESS)
    - 1.5. Unknown mechanism: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug reaction, pulmonary infiltrates (nitrofurantoin), autoimmune disease (vasculitis, rheumatoid arthritis, lupus), drug fever, drug-induced hypersensitivity syndrome (antiepileptics)
        - 1.5.1. Penicillin skin testing will not detect these type of reactions
        - 1.5.2. Desensitization or reexposure should not be performed due to the risk of reactivation of the reaction
2. Rashes
    - 2.1. Urticaria (IgE-mediated) rashes are an intensely pruritic, circumscribed, raised, and erythematous eruption with central pallor.
        - 2.1.1. Usually occur within minutes to hours of receiving offending agent, but may occur up to 72 hours after administering.[10]
    - 2.2. Macular papular or morbilliform rashes (non-IgE-mediated) begin in dependent areas and generalize, often with associated mucous membrane erythema, and are pruritic.
        - 2.2.1. Usually occur more than 72 hours after receiving offending agent.
3. Graded Challenge: A graded challenge is cautiously administering a medication to a patient who is unlikely to be allergic to it. It does not entail modification of the immune response (unlike desensitization).[6,9]
4. Desensitization: Induction of a temporary state of unresponsiveness to a drug that initially caused an IgE-mediated hypersensitivity reaction; the tolerant state is lost 24 to 36 hours after discontinuation of the drug.[11]

5. Beta-lactams may share common side chains (Table 1).[6,9,12,13]
   5.1. Cefazolin does not share a common side chain with any other beta-lactams

Table 1. FDA-approved Beta-lactam Antibiotics with Similar Side Chains[a]

Agent	Agents with Similar Side Chains				
Amoxicillin	Ampicillin	Cefaclor	Cefadroxil[c]	Cefprozil[c]	Cephalexin
Ampicillin	Amoxicillin	Cefaclor[c]	Cefadroxil	Cefprozil	Cephalexin[c]
Aztreonam[b]	Ceftazidime[c]	Ceftolozane			
Cefaclor	Amoxicillin	Ampicillin[c]	Cefadroxil	Cefprozil	Cephalexin[c]
Cefadroxil	Amoxicillin[c]	Ampicillin	Cefaclor	Cefprozil[c]	Cephalexin
Cefdinir	Cefixime[d]				
Cefditoren	Cefepime[c]	Cefotaxime[c]	Cefpodoxime[c]	Ceftriaxone[c]	
Cefepime	Cefditoren[c]	Cefotaxime[c]	Cefpodoxime[c]	Ceftriaxone[c]	Ceftaroline
Cefixime	Cefdinir[d]				
Cefotaxime	Cefditoren[c]	Cefepime[c]	Cefpodoxime[c]	Ceftriaxone[c]	Ceftaroline
Cefoxitin	Cefuroxime[d]	Penicillin G			
Cefpodoxime	Cefditoren[c]	Cefepime[c]	Cefotaxime[c]	Ceftriaxone[c]	Ceftaroline
Cefprozil	Amoxicillin[c]	Ampicillin	Cefaclor	Cefadroxil[c]	Cephalexin
Ceftaroline	Cefepime	Cefotaxime	Cefpodoxime	Ceftriaxone	Ceftazidime
Ceftazidime	Aztreonam[c]	Ceftolozane			
Ceftolozane	Aztreonam	Ceftazidime			
Ceftriaxone	Cefditoren[c]	Cefepime[c]	Cefotaxime[c]	Cefpodoxime[c]	Ceftaroline
Cefuroxime	Cefoxitin[d]				
Cephalexin	Amoxicillin	Ampicillin[c]	Cefaclor[c]	Cefadroxil	Cefprozil
Penicillin G	Cefoxitin				

[a]Agents not listed are either not approved for use in the United States (ceftizoxime, ceftibiprole) or do not share common side chains (e.g. piperacillin, ticarcillin, nafcillin, dicloxacillin)
[b]Aztreonam cross-reacts with ceftazidime and ceftolozane, with which it shares an identical side-chain
[c]Identical R1 side chain
[d]Identical R2 side chain

Introduction

The reported penicillin allergy rate for inpatients and outpatients is 10%.[2-4,14,15] Of these patients, 80% to 90% will not have positive penicillin skin testing, which test for IgE-mediated reactions only.[5,6] The patient may state they are allergic to a medication, but the reaction could be an adverse drug reaction (e.g. GI intolerance) or attributed to the disease being treated (e.g. rash caused by viral infection while on amoxicillin).[5] The positive penicillin skin test also decreases 10% annually after a penicillin allergic reaction and 78% of penicillin allergic patients have negative skin tests after ten years of avoidance.[16]

Since beta-lactam antibiotics share a common beta ring, there is a risk of cross-reactivity.[2-10,12,14-31] Indeed, patients with a history of penicillin allergy are three times more likely to have an adverse reaction to any additional antibiotics (including cephalosporins and sulfa).[17,32] An explanation for not having higher cross-reactivity is that the alpha rings between the different classes vary. Penicillins have a thiazolidine ring, cephalosporins have a dihydrothiazine ring, carbapenems have a modified thiazolidine ring, and monobactams are missing the alpha ring.[3,4,8,15] Common side chains also contribute to cross-reactivity.[4,6,9,10,12,20] The degree of cross-reactivity appears to be greater among the same class of antibiotics than between classes.[9,20] The greatest risk of cross-reactivity is among penicillins.[9,12,20,21] The penicillins and monobactams have an R1 side chain while the cephalosporins and carbapenems have both an R1 and R2 side chain.[3,5,19,20] For the majority of cephalosporins, the R1 side chain is more clinically relevant for cross-reactivity than the R2 side chain as the R2 side chain acts as a leaving group during carrier protein conjugation and therefore it cannot contribute to the epitope for IgE binding.[25]

Prior to 1980, the cross-reactivity between penicillins and cephalosporins was reported to be 10% to 20%. This was probably due to the fact that the cephalosporins used at the time, cephalothin and cephaloridine, share a similar side chain with benzyl penicillin (Table 1).[6] Also during this time, some cephalosporins were contaminated

with trace amounts of penicillin.[6,26] Since 1980, reaction rates in penicillin-history positive and skin-test positive patients who received cephalosporins decreased to between 1% and 4%.[3,6,12,21] A review of cross-reactivity and postmarketing studies of second- and third-generation cephalosporins revealed no increase in allergic reactions in those patients with a history of penicillin allergy.[17] If a patient is penicillin-history positive, but skin-test negative they are at no increased risk of cephalosporin cross-reactivity.[15,21] If patients with a history of penicillin allergies are not skin tested, the risk of a reaction when given a second- or third-generation cephalosporin is less than 1%, but some of these reactions may be anaphylaxis.[9] Generally, cross reactivity between penicillins and cephalosporins is higher among penicillins and first generation cephalosporins.[33] A meta-analysis found that penicillin-allergic patients have increased cross reactivity to first-generation cephalosporins (excluding cefazolin) but no increased cross reactivity to second- or third-generation cephalosporins.[34] However, as cefazolin has a unique side chain, cross reactivity potential with other beta-lactams is low.[11]

Cephalosporins cause immune-mediated reactions in 1% to 3% of patients without a history of a penicillin allergy.[4] Cross reactivity of cephalosporins is mediated by cephalosporin side chains and not the beta-lactam ring.[35]

The estimated cross-reactivity between carbapenems and other beta-lactams is variable. None of the currently available carbapenems have a similar side chain to any penicillin or cephalosporin antibiotic. Retrospective studies show a cross-reactivity rate of about 9% to 11%.[23,24,36] These retrospective studies are limited as penicillin allergies were not verified with skin testing, allergic reactions were not limited to IgE-mediated reactions, and clinical data was taken from chart documentation.[23,25,30] Additionally, a systematic review reveals a very low incidence of proven penicillin IgE-mediated cross reactivity with cephalosporins and carbapenems at 0.5% (1/221 patients).[37]

Prospective studies demonstrate a cross-reactivity rate of 1% to 47%.[38-41] The study showing a 47% cross-reactivity rate was a positive skin test to imipenem or its metabolites performed in nineteen penicillin skin-test positive patients; none of the patients received systemic imipenem.[38] Three other prospective studies showed cross-reactivity rates of 0.9% to 1%. These studies included penicillin skin-test positive patients who received a carbapenem skin test, but not any carbapenem metabolites. Patients who were carbapenem skin test negative then received a systemic carbapenem via a graded challenge. None of the patients had an allergic reaction to the systemic carbapenem.[39-41]

Newer prospective clinical data demonstrate that in patients with a positive penicillin skin test there was no cross reactivity to aztreonam or carbapenem challenges.[42] Additionally, a large retrospective review found that patients with a claimed penicillin allergy versus those with no claimed penicillin allergy had no increased rate of carbapenem hypersensitivity.[43]

Aztreonam cross-reactivity with other beta-lactams does not exist, excepting ceftazidime, and it may be used safely in beta-lactam allergic patients.[8-10,15,30] Despite side-chain homology between aztreonam and ceftazidime, aztreonam is generally tolerated in patients with beta-lactam sensitivity and cross sensitivity with ceftazidime is rare.[11,35]

Penicillin is the only drug class with a valid skin test. Degradation products of other antibiotics are not known or not commercially available. Under physiologic conditions, penicillin degrades to reactive intermediates that act as haptens. These haptens bind to self-proteins and elicit an immune response. Approximately 95% of penicillin degrades to the penicilloyl moiety which is the major determinant. The rest degrades to penicilloate and penicillanyl moieties which are the minor determinants.[9,10,28,44]

A graded challenge is used when there is an indication for the antibiotic and based on the patient's reaction history, there is a low pretest probability of an immediate drug allergy (e.g. reaction happened in the distant past, delayed onset cutaneous reaction, vague allergy history without IgE-mediated symptoms).[9] A graded challenge does not desensitize the patient to the antibiotic, but verifies that a patient will not experience an immediate adverse reaction to the antibiotic.[9] A graded challenge involves progressively increasing the dose of the antibiotic until a full dose is reached. Graded challenges involve fewer doses and are of shorter duration than desensitization protocols.[9] Smaller doses are used so if an allergic reaction is provoked, it should be minor and easily treated.[9,44] If an allergic reaction develops during the graded challenge, the antibiotic should only be administered via desensitization.[9] Graded challenges may be performed in an outpatient setting without intravenous access as long as severe allergic reactions can be treated.[9] Patients who tolerate the graded challenge are considered not to be allergic to the antibiotic and the patient's allergies should be updated to reflect

this. These patients are not at an increased risk for future reactions compared with the general population.[9] Graded challenges should not be performed in patients who have a history consistent with a severe non-IgE-mediated reaction (e.g. hemolysis, Stevens-Johnson syndrome, toxic epidermal necrolysis).[2,9]

Switching to another class of antibiotics due to a reported patient allergy may adversely affect patient care.[5,18,19] Alternative agents may be less effective, cause more adverse effects (e.g. *C. difficile* infection), treat too broadly (contributing to increased resistance), and be more expensive.[45,46] Patients with a listed penicillin "allergy" on admission to a hospital have increased length of stay, increased occurrence of *C. difficile* infection, and increased incidence of MRSA and VRE.[47] The use of a clinical guideline increases utilization of beta-lactam antibiotics in patients with reported penicillin or cephalosporin allergy.[48]

Recommendations

Antibiotic Ordering (refer to *Figure 2*)

1. When a beta-lactam antibiotic is indicated, it should be determined if the patient has any medication allergies. (*UW Health Strong Recommendation, High Quality of Evidence*)
2. The beta-lactam antibiotic may be ordered, processed, and administered if the patient does not have an allergy to beta-lactam antibiotics. (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
3. In the case of a reported allergy:
   - 3.1. A health care professional should investigate and determine the type and severity of the reaction.[9] (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
   - 3.2. Additional information to investigate a medication allergy includes:[9,15]
     - Patient's age at the time of the reaction as concomitant viral rash at time of beta-lactam administration is more common in childhood
     - Patient's recall of the reaction or who informed them of it
     - Time of onset of the reaction after beginning the penicillin (e.g. after one dose or several days of repeated dosing)
       - Nearly all Type I (IgE-mediated) reactions occur within 72 hours of drug administration.[10,49]
     - Signs/symptoms of the reaction
       - Was an antidote or treatment given?
       - Did it require a visit to emergency room?
       - Was there a loss of consciousness?
     - Route of administration (oral or IV)
     - Indication for medication
     - Concurrent medications
     - Did the reaction abate after the medication was discontinued?
     - Had the patient taken other medications in the same or related class before or after the reaction?
       - If yes, was there any sort of reaction?
   - 3.3. Documentation of a reported allergy or intolerance should be as specific as to which drug led to the reported reaction (e.g. amoxicillin, cephalexin, cefazolin, etc.) as it can be determined and avoid entering "penicillin" as a class reaction. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)
   - 3.4. A beta-lactam antibiotic may be utilized if the patient has received that class of beta-lactam in the past without a reaction.[9] (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
     - 3.4.1. Physicians and/or pharmacists should review the medical record and potentially call the patient's home pharmacy to investigate previous antibiotic use.
   - 3.5. **If the patient has <u>NOT</u> received an antibiotic in the same class in the past, the type of reaction should be ascertained**. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)
     - 3.5.1. If it is determined that the reaction was actually a side effect (e.g. GI intolerance including nausea or diarrhea), the original beta-lactam antibiotic may be ordered, processed, and administered. (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)
     - 3.5.2. **If the type of reaction is unable to be ascertained from the patient, family or medical record**:
       - 3.5.2.1. Prescribe beta-lactam antibiotic from different class based on class of beta-lactam allergy.[9] (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)
         - 3.5.2.1.1. The prescribed beta-lactam antibiotic should also have a different side chain (see *Table 1*) than antibiotic the patient is allergic to due to increased reactivity.[3,9,12,19,20] (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)

3.5.2.1.1.1. A graded challenge (see *Graded Challenges*) may be used if the reaction happened recently.[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.2.1.2. Penicillin-allergic patients may be prescribed a cephalosporin (first line) or a carbapenem (second line).[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.2.1.3. Cephalosporin-allergic patients may be prescribed a penicillin (first line) or a carbapenem (second line).[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.2.1.4. Carbapenem-allergic patients may be prescribed either a penicillin or a cephalosporin (either first line).[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.2.1.5. Aztreonam-allergic patients may be prescribed either a penicillin or a cephalosporin (either first line) or a carbapenem (second line).[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.2.2. If use of beta-lactam from same class is desired, consult Allergy for recommendations. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.3. **If the reaction is determined to have been a non-severe, non-IgE mediated reaction that occurred <u>AFTER</u> 72 hours:**

3.5.3.1. Prescribe beta-lactam antibiotic from different class based on class of beta-lactam allergy.[9] (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)

3.5.3.1.1. Prescribed beta-lactam antibiotic should also have a different side chain (see *Table 1*) than antibiotic the patient is allergic to due to increased reactivity.[3,9,12,19,20] (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)

3.5.3.1.1.1. A graded challenge (see *Graded Challenges*) may be used if the reaction happened recently.[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.3.1.2. Penicillin-allergic patients may be prescribed a cephalosporin (first line) or a carbapenem (second line).[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.3.1.3. Cephalosporin-allergic patients may be prescribed a penicillin (first line) or a carbapenem (second line).[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.3.1.4. Carbapenem-allergic patients may be prescribed either a penicillin or a cephalosporin (either first line).[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.3.1.5. Aztreonam-allergic patients may be prescribed either a penicillin or a cephalosporin (either first line) or a carbapenem (second line).[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.3.2. If use of beta-lactam from same class is desired, consult Allergy for recommendations. (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)

3.5.4. **If the reaction is determined to have been a possible IgE-mediated reaction occurring <u>WITHIN</u> 72 hours (i.e. rash <u>+</u> hives) :**

3.5.4.1. Prescribe beta-lactam antibiotic from different class via graded challenge (see *Graded Challenges*) based on class of beta-lactam allergy.[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.4.1.1. Prescribed beta-lactam antibiotic should also have a different side chain (see *Table 1*) than antibiotic the patient is allergic to due to increased reactivity.[3,9,12,19,20] (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)

3.5.4.1.2. Penicillin-allergic patients may be prescribed a cephalosporin (first line) or a carbapenem (second line).[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.4.1.3. Cephalosporin-allergic patients may be prescribed a penicillin (first line) or a carbapenem (second line).[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.4.1.4. Carbapenem-allergic patients may be prescribed either a penicillin or a cephalosporin (either first line).[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.4.1.5. Aztreonam-allergic patients may be prescribed either a penicillin or a cephalosporin (either first line) or a carbapenem (second line).[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.4.2. If use of beta-lactam from same class is desired, consult Allergy for recommendations. (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)

3.5.5. **If the reaction is determined to have been an IgE-mediated reaction occurring <u>WITHIN</u> 24 hours (i.e. immediate urticarial, angioedema, anaphylaxis):**

3.5.5.1. <u>First Line:</u> use non-beta lactam antibiotic.[9] (*UW Health Strong Recommendation, High Quality of Evidence*)

3.5.5.1.1. If no alternatives are available, aztreonam may be considered for Gram-negative infections.[9] (*UW Health Strong Recommendation, Moderate Quality of Evidence*)

3.5.5.1.2. Do not use aztreonam in ceftazidime-allergic patients.[9] (*UW Health Strong Recommendation, Moderate Quality of Evidence*)

3.5.5.2. <u>Second Line (and therapy requires beta-lactam)</u>

3.5.5.2.1. If use of penicillin antibiotic planned, consult Allergy for penicillin skin testing (see *Penicillin Skin Testing*) and/or desensitization.[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.5.2.2. If use of cephalosporin or carbapenem antibiotic planned, consult Allergy for desensitization.[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

3.5.6. **If the reaction is determined to have been a severe, non-IgE mediated reaction (e.g. hemolysis, Stevens Johnson Syndrome, toxic epidermal necrolysis)**:

3.5.6.1. Use non-beta-lactam antibiotic.[9] (*UW Health Strong Recommendation, High Quality of Evidence*)

3.5.6.1.1. If no alternatives are available, aztreonam may be considered for Gram-negative infections.[9] (*UW Health Strong Recommendation, Moderate Quality of Evidence*)

3.5.6.1.2. Do not use aztreonam in ceftazidime-allergic patients.[9] (*UW Health Strong Recommendation, Moderate Quality of Evidence*)

<u>Penicillin Skin Testing</u>

1. Penicillin skin testing is an option for patients with a possible IgE-mediated reactions to penicillin.[9]
   1.1. There is no commercially available skin test for cephalosporins, carbapenems, or monobactams.[9]
   1.2. For patients with multiple non-beta-lactam allergies, and an unknown or vague history of penicillin allergy, penicillin skin testing by the Allergy department should be encouraged. (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)
2. The risk of having an adverse reaction to a penicillin skin test is less than 1% and the reaction is usually only urticaria.[9]
3. Patients with a history of severe, non-IgE mediated reactions should not be skin tested.[9] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)
4. Perform penicillin skin testing with both major and minor determinants when possible.[9] (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
   4.1. An oral challenge should be included, when feasible, to increase sensitivity.[49] (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)
5. Prior to conducting skin testing, patients should be instructed to hold antihistamines, beta-blockers, and tricyclic antidepressants. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)
6. Patients with negative penicillin skin test results are at a small risk of IgE-mediated reaction and can receive penicillin via a graded challenge (see *Graded Challenges*) if the risk of reaction is felt to be low.[9] (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
7. Patients with negative penicillin skin test results can safely receive cephalosporin and carbapenem antibiotics. [9] (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
8. If the penicillin skin test is positive, the patient should not receive penicillins or a beta-lactam antibiotic with a similar side chain.[9] (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
   8.1. These patients should be desensitized when an alternative class of antibiotics may not be substituted (e.g. treatment of syphilis during pregnancy).[2-5,9,12,14,16] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

<u>Graded Challenges</u>

1. Performed in patients who have a low pretest probability of an immediate allergic reaction.[11] (*UW Health Weak/conditional Recommendation, Moderate Quality of Evidence*)

2. Prescribers should be contacted prior to initiating graded challenge. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)
3. Patients do not need to increase their level of care during the graded challenge.[9] (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)
    3.1. Patients must be able to report symptoms and use their call light. .
    3.2. Providers should be contacted if the patient develops any sign of an allergic reaction (examples: hives, clearing of throat, coughing, dyspnea, abdominal pain, uneasiness) for up to 60 minutes after the full dose is administered. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)
        3.2.1. Medications used to treat allergic reactions will be ordered prior to the graded challenge and are available in the unit crash cart or Acudose cabinet.
4. Oral graded challenge[9] (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)
    4.1. Used if oral therapy is desired
    4.2. Procedure: give 10% of dose, then in 60 minutes give full dose.
5. Intravenous graded challenge[9] (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)
    5.1. Used if intravenous therapy is desired
    5.2. Procedure: give 1% of dose, then in 30 to 60 minutes give 10% of dose, then in 30 to 60 minutes give full dose.
6. If the patient has no signs of an allergic reaction, they should be monitored for adverse reactions for up to 60 minutes after the full dose has been administered.[9,31] (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)
    6.1. Further monitoring is patient-specific and at the discretion of the provider, as delayed non-immune mediated reactions can occur days after administration.[9]
7. If the patient has signs and/or symptoms of an allergic reaction, do not give additional doses before discussing with provider next steps in the graded challenge and further monitoring.
8. If a severe reaction develops during the graded challenge and it is determined the patient needs the antibiotic, Allergy should be consulted for desensitization.[9] (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)
    8.1. Graded challenges and desensitization should not be performed if there is a history of a severe non-IgE mediated reaction (e.g. hemolysis, Stevens Johnson Syndrome, toxic epidermal necrolysis), due to the risk of reactivation.[9] (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)
9. The results of the graded challenge should be documented in the patient's allergy record. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)
    9.1. The allergy should not be deleted from the patient's medical record for ease in tracking the results of the graded challenge. (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)
    9.2. Updates to the allergy records should include the specific drug used in the graded challenge (e.g. amoxicillin, cephalexin, cefazolin). (*UW Health Strong Recommendation, Very Low Quality of Evidence*)
10. Patients should have beta blockers discontinued prior to the graded challenge, if possible, to prevent resistance to treatment if a severe adverse reaction occurs.[5,14,16] (*UW Health Weak/conditional Recommendation, Very Low Quality of Evidence*)
11. Do not pretreat patients with glucocorticoids or antihistamines as these can mask the signs of allergic reactions.[9,50] (*UW Health Weak/conditional Recommendation, Moderate Quality of Evidence*)

UW Health Implementation

Potential Benefits and Harms of Implementation

- Standardizing the treatment of patients with beta-lactam allergies lessens complications associated with inadequate or inappropriate therapy.
- Standardizing the ordering of antibiotics for beta-lactam allergic patients, will lead to more consistent patient care.
- Accurately determining patient's antibiotic allergies through interviews, penicillin skin tests, and graded challenges, make future care more efficient.
- Avoiding switching to another antibiotic unnecessarily decreases adverse events, increases efficiency, lowers antimicrobial resistance, and saves money.
- Potential of allergic reactions when performing penicillin skin tests, graded challenges, or switching antibiotics within the same class.

Pertinent UW Health Policies and Procedures

- UWHC Clinical Policy 7.60 Medication Reconciliation

Patient Resources

None

Guideline Metrics

- Utilization of graded challenge order sets

Implementation Plan/Clinical Tools

1. Guideline will be posted on uConnect in a dedicated location for Clinical Practice Guidelines.
2. Release of the guideline will be advertised in the Physician/APP Briefing newsletter.
3. Content and hyperlinks within clinical tools, documents, or Health Link related to the guideline recommendations will be reviewed for consistency and modified as appropriate.

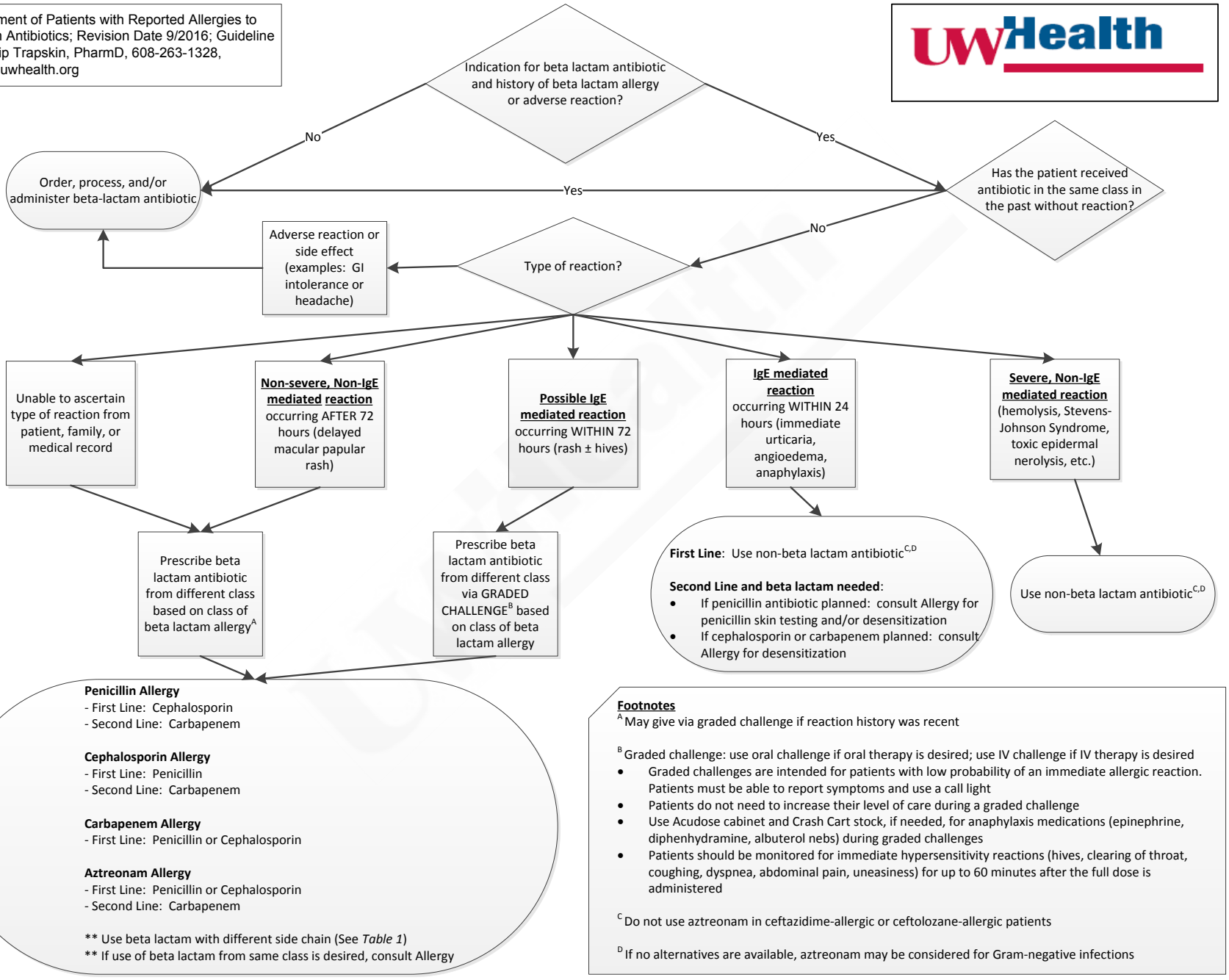
Order Set
IP – Beta-lactam Graded Challenge – Adult – Supplemental [5987]

Disclaimer

Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Figure 1. Beta-Lactam Allergy Practice Parameter Algorithm

From: Treatment of Patients with Reported Allergies to Beta-Lactam Antibiotics; Revision Date 9/2016; Guideline Contact Philip Trapskin, PharmD, 608-263-1328, PTrapskin@uwhealth.org



Footnotes

[A] May give via graded challenge if reaction history was recent

[B] Graded challenge: use oral challenge if oral therapy is desired; use IV challenge if IV therapy is desired

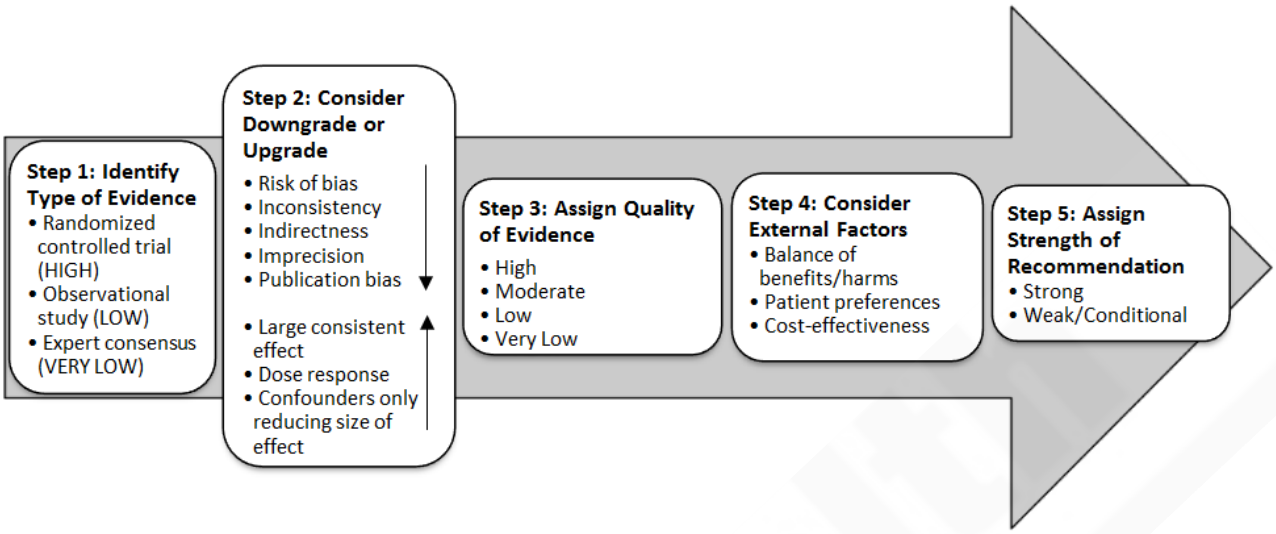
- Graded challenges are intended for patients with low probability of an immediate allergic reaction. Patients must be able to report symptoms and use a call light
- Patients do not need to increase their level of care during a graded challenge
- Use Acudose cabinet and Crash Cart stock, if needed, for anaphylaxis medications (epinephrine, diphenhydramine, albuterol nebs) during graded challenges
- Patients should be monitored for immediate hypersensitivity reactions (hives, clearing of throat, coughing, dyspnea, abdominal pain, uneasiness) for up to 60 minutes after the full dose is administered

[C] Do not use aztreonam in ceftazidime-allergic or ceftolozane-allergic patients

[D] If no alternatives are available, aztreonam may be considered for Gram-negative infections

Appendix A. Evidence Grading Scheme

Figure 1. GRADE Methodology adapted by UW Health[1]



GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

Strong	The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.
Weak/conditional	Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.

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