RUSH UNIVERSITY MEDICAL CENTER

Treatment of Adult Patients with Reported Allergies to β-Lactam Antibiotics

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1) Definitions

A) β-lactam antibiotics: consist of all antibiotics containing a β-lactam ring. This includes the following:
   i) Penicillin and penicillin derivatives (e.g., penicillin, piperacillin, amoxicillin)
   ii) Cephalosporins (e.g., ceftriaxone)
   iii) Monobactams (e.g., aztreonam)
   iv) Carbapenems (e.g., meropenem)

B) The different types of drug hypersensitivity reactions are classified as follows by the Gell and Coombs classification.[1,2]
   i) Type I: IgE-mediated –Type I reaction occurs when IgE specific for penicillin or β-lactam drugs binds to mast cells and basophils to produce allergic reactions-via release of mediators such as histamine
      (1) Immediate reactions (onset <1 hour after drug administration): systemic manifestations of anaphylaxis
         (a) Urticaria (hives), pruritus, bronchospasm, laryngeal edema, hypotension, and/or cardiac arrhythmias
         (b) Life-threatening
         (c) Tested for by a penicillin skin test
         (d) Immediate reactions occurring greater than one hour after infusion, or during sustained therapy, even in the presence of urticaria, are rare
      (2) Accelerated reactions (onset 1-72 hours after drug administration) – less common Type I reaction
         (a) Urticaria, angioedema, laryngeal edema, wheezing
         (b) Rarely life-threatening
         (c) Determined by penicillin skin test
      (3) Biphasic reactions – occur immediately and reoccur within 8-12 hours with the same characteristics as the original reaction to the antibiotic such as urticaria,etc.[3]
      (4) Usually associated with β-lactam antibiotics
   ii) Type II: Cytotoxic/antibody-mediated (IgG-,IgM-complement-mediated)
      (1) Hemolysis, thrombocytopenia, neutropenia, or interstitial nephritis
      (2) Usually associated with quinidine, methyldopa and penicillins
      (3) IgG and IgM antibodies do not induce allergic reactions
      (4) Penicillin skin testing will not detect these type of reactions
      (5) Rapid induction of tolerance should not be performed due to the risk of reactivation of a more severe reaction
   iii) Type III: Immune complex (IgG, IgM immune complexes)
      (1) Serum sickness or vasculitis
      (2) Fever, rash, urticaria, lymphadenopathy, and arthralgias
      (3) Usually associated with antisera, penicillin, sulfonamides and phenytoin
      (4) Penicillin skin testing will not detect these type of reactions
      (5) Rapid induction of tolerance should not be performed due to the risk of reactivation of a more severe reaction
   iv) Type IV: Cellular immune-mediated/delayed hypersensitivity reaction
      (1) Contact dermatitis
         (a) Example: health care workers involved in the manufacturing and dispensing of offending agents (e.g., latex)
      (2) Delayed non-urticarial rashes caused by aminopenicillins and drug reaction with eosinophilia and systemic symptoms syndrome (DRESS)
      (3) Penicillin skin testing will not detect these type of reactions
      (4) Rapid induction of tolerance should not be performed due to the risk of reactivation of a more severe reaction
   v) Unknown mechanism: Erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), fixed drug reaction, pulmonary infiltrates (nitrofurantoin), autoimmune disease (vasculitis, rheumatoid arthritis, lupus), drug fever, drug-induced hypersensitivity syndrome (antiepileptics)
      (1) Penicillin skin testing will not detect these type of reactions
      (2) Rapid induction of tolerance should not be performed due to the risk of reactivation of a more severe reaction

C) Types of rashes include:
   i) Urticaria (hives) are IgE-mediated rashes that are intensely pruritic, circumscribed, raised and erythematous eruptions that can be confluent
      (1) Usually occur within minutes to hours of receiving offending agent, but may occur up to 72 hours after administering[4]
   ii) Macular papular or morbilliform rashes are non-IgE-mediated and begin in dependent areas and generalize, often with associated mucous membrane erythema, and are pruritic

(1) Usually occur > 72 hours after receiving offending agent

D) 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 (i.e., rapid induction of drug tolerance)[2]

E) Rapid Induction of drug tolerance (desensitization): An induction of drug tolerance that creates a temporary state in a patient allowing safe treatment with an antigenic drug[2]

F) Penicillin skin testing: Skin prick and intradermal testing to the major determinant (penicilloyl-polylysine or PRE-PEN®) and diluted penicillin G (substitutes for the two minor determinants) to assess an IgE response to penicillin
   i) This should be considered before administration of cephalosporins or carbapenems in patients with a history of penicillin allergy[2]

G) Cross-reactivity of β-lactam antibiotics: In those with an allergic reaction to a β-lactam antibiotic, IgE can recognize specific β-lactams or similar/identical side chains increasing the probability of an allergic reaction to another β-lactam[2,5]
   i) β-lactams may share common R1 and R2 side chains (**Table 1**) and recent evidence points to a similar or identical R1 side chain as being the major contributor to cross-reactivity[2,6-8]
      (1) The cross-reactivity rate between penicillins and cephalosporins has been estimated as < 1% for those who have not been penicillin skin tested, and as < 2% for those who are penicillin skin test positive[2]
         (a) In those who have not been penicillin skin tested, the risk of a severe reaction following administration of a cephalosporin is estimated to be 0.1%[2]
      (2) The cross-reactivity rate between penicillins and carbapenems is estimated as <1%[2]
      (3) Cefazolin does not share a common side chain with any other β-lactams[2]
      (4) Aztreonam has the exact same R1 side chain as ceftazidime

Table 1. FDA-Approved β-lactam Antibiotics with Similar Side Chains[a]

Agent	Agents with Similar Side Chains				
Amoxicillin	Ampicillin	Cefaclor	Cefadroxil[1]	Cefprozil[1]	Cephalexin
Ampicillin	Amoxicillin	Cefaclor[1]	Cefadroxil	Cefprozil	Cephalexin[1]
Aztreonam[b]	Ceftazidime[1]	Ceftolozane			
Cefaclor	Amoxicillin	Ampicillin[1]	Cefadroxil	Cefprozil	Cephalexin[1]
Cefadroxil	Amoxicillin[1]	Ampicillin	Cefaclor	Cefprozil[1]	Cephalexin[2]
Cefdinir	Cefixime[2]				
Cefditoren	Cefepime[1]	Cefotaxime[1]	Cefpodoxime[1]	Ceftriaxone[1]	
Cefepime	Cefditoren[1]	Cefotaxime[1]	Cefpodoxime[1]	Ceftriaxone[1]	Ceftaroline
Cefixime	Cefdinir[2]				
Cefotaxime	Cefditoren[1]	Cefepime[1]	Cefpodoxime[1]	Ceftriaxone[1]	Ceftaroline
Cefoxitin	Cefuroxime[2]	Penicillin G			
Cefpodoxime	Cefditoren[1]	Cefepime[1]	Cefotaxime[1]	Ceftriaxone[1]	Ceftaroline
Cefprozil	Amoxicillin[1]	Ampicillin	Cefaclor	Cefadroxil[1]	Cephalexin
Ceftaroline	Cefepime	Cefotaxime	Cefpodoxime	Ceftriaxone	Ceftazidime
Ceftazidime	Aztreonam[1]	Ceftolozane			
Ceftolozane	Aztreonam	Ceftazidime			
Ceftriaxone	Cefditoren[1]	Cefepime[1]	Cefotaxime[1]	Cefpodoxime[1]	Ceftaroline
Cefuroxime	Cefoxitin[2]				
Cephalexin	Amoxicillin	Ampicillin[1]	Cefaclor[1]	Cefadroxil[2]	Cefprozil
Penicillin G, V	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, meropenem)
[b]Aztreonam cross-reacts with ceftazidime, with which it shares an identical side-chain
[1]Identical R1 side chain
[2]Identical R2 side chain

2) Introduction

Approximately 10% of inpatients and outpatients report a penicillin allergy.[9] Of these patients, 80-90% will not have a positive penicillin skin test, a test for IgE-mediated reactions only.[10] The patient may state they are allergic to a medication, but the reaction could be an adverse drug reaction (e.g., gastrointestinal intolerance) or attributed to the disease being treated (e.g., rash caused by viral infection while on amoxicillin).[11] If the patient has a positive penicillin skin test the reactivity decreases 10% annually after a penicillin allergic reaction and 78% of penicillin allergic patients have negative skin tests after 10 years of avoidance.[12,13] In addition, resensitization after treatment with oral penicillin is rare, and therefore penicillin skin testing does not need to be reperformed after a patient has tolerated at least one treatment course with oral penicillin.[2] Repeat penicillin skin testing may be considered in patients who have successfully received a course of intravenous penicillin, as resensitization after intravenous treatment is higher than that for oral treatment. On the other hand, resensitization once an IgE specific response to a β-lactam antibiotic is cleared is very rare and not affected by repeated or periodic use of penicillins.[14]

Since β-lactam antibiotics share common structures, there is a risk of cross-reactivity.[2,5,15] Indeed, patients with a history of penicillin allergy are three times more likely to report an adverse reaction to any additional antibiotics (including cephalosporins and sulfa).[16,17] An explanation for not having higher cross-reactivity is that the alpha rings between the different classes vary, allowing for different antigenic determinants to be created when the agents bind to carrier proteins in the systemic circulation (haptenization).[18,19] Penicillins have a thiazolidine ring, cephalosporins have a dihydrothiazine ring, carbapenems have a modified thiazolidine ring, and monobactams are missing the alpha ring. Common side chains also contribute to cross-reactivity.[2] The degree of cross-reactivity appears to be greater among the same class of antibiotics than between classes.[2,20] The greatest risk of cross-reactivity is among penicillins.[2,20-22] The penicillins and monobactams have an R1 side chain while the cephalosporins and carbapenems have both an R1 and R2 side chain. 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.[23] The similarity of R1 side chains between agents is considered the major predictor of cross-reactivity between the β-lactam antibiotics.[2,19]

Prior to 1980, the cross-reactivity between penicillins and cephalosporins was reported to be 10-20%. 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.[2] Also during this time, some cephalosporins were contaminated with trace amounts of penicillin.[2] Since 1980, reaction rates in penicillin history-positive and skin test-positive patients who received cephalosporins decreased to between 1.1 and 4.4%.[2,10,21,22] 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.[16] If a patient is penicillin history-positive, but skin test-negative, they are at no increased risk of cephalosporin cross-reactivity.[21,24] 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 <1%, but some of these reactions may be anaphylaxis.[2] In those who are penicillin skin test positive, the rate of cross-reactivity between a penicillin and cephalosporin is <2%.[2] For patients who are penicillin skin test-positive, treatment options include the administration of a non-β-lactam antibiotic, administration of a cephalosporin via graded challenge, or administration of a cephalosporin via rapid induction of drug tolerance (desensitization).[2] If penicillin skin testing cannot be performed on a patient with a type I hypersensitivity reaction, a cephalosporin may need to be administered via graded challenge or rapid induction of drug tolerance.[2]

The estimated cross-reactivity between carbapenems and other β-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 9-11%.[25-27] These retrospective studies are limited as penicillin allergies were not verified with skin testing, non-validated carbapenem skin tests were performed, challenges with the agents were not performed, allergic reactions were not limited to IgE-mediated reactions, and clinical data was taken from chart documentation.[28-30] Prospective studies demonstrate a cross-reactivity rate of 0.9-47.4%.[31-34] The study showing a 47.4% cross-reactivity rate is considered flawed as it 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.[31] Three other prospective studies showed cross-reactivity rates of 0.9-1%.[32-34] 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. Patients who are penicillin skin test-negative may safely receive a carbapenem. Patients who are penicillin skin test-positive or who have reported a Type I hypersensitivity reaction to a penicillin and who have not been skin tested should receive a carbapenem via graded challenge.[2]

Monobactams, such as aztreonam, are less immunogenic because they lack an alpha ring and therefore are more stable to conjugation by carrier proteins, creating less antigenic determinants for IgE to recognize.[35] Aztreonam cross-reactivity with other β-lactams has not been observed, excepting ceftazidime (they have identical R1 side chains), and it may be used safely in β-lactam allergic patients.[2,4]

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 (penicilloyl-polylysine a.k.a. PRE-PEN®). The rest degrades to penicilloate and penicillanyl moieties which are the minor determinants.[2,36] A penicillin skin test consists of four components: the major determinant (PRE-PEN®), diluted penicillin G (substitutes for the minor determinants), a histamine positive control, and a saline negative control. A skin prick test is performed first and if negative then intradermal dilutional testing is performed followed by a challenge with oral amoxicillin. When performed in this fashion the penicillin skin test has a negative predictive value (NPV) of 97-99%.[36]

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).[2] A graded challenge does not induce drug tolerance (desensitize) to the antibiotic, but verifies that a patient will not experience an immediate adverse reaction to the antibiotic. 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 rapid induction of drug tolerance protocols. Smaller doses are used, so if an allergic reaction is provoked it should be minor and easily treated.[37] If an allergic reaction develops during the graded challenge, the antibiotic should only be administered via rapid induction of drug tolerance. Graded challenges may be performed in an outpatient setting without intravenous access as long as severe allergic reactions can be treated.[2] 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. Graded challenges should not be performed in patients who have a history consistent with a severe non-IgE-mediated reaction (e.g. hemolysis, SJS, TEN).[2,38]

A rapid induction of drug tolerance creates a temporary state in a patient allowing for safe treatment with an antigenic drug.[38] Increasing doses of a drug are administered starting at very small doses to exhaust the mast cells of inflammatory mediators without inducing an anaphylactic reaction.

Switching to another class of antibiotics due to a reported patient allergy may adversely affect patient care.[11,39-43] Alternative agents may be less effective, cause more adverse effects (e.g., *Clostridium difficile*), treat too broadly (contributing to increased resistance) and be more expensive. To optimize antibiotic selection in adult patients with possible β-lactam allergies and avoid negative consequences of antibiotic switching, this clinical practice guideline will outline steps to consider in the situation of using β-lactams in patients with potential or known β-lactam allergies.

3) Recommendations

A) Antibiotic Ordering (**Figure 1**)

i) When a β-lactam antibiotic is indicated, it should be determined if the patient has any medication allergies

ii) The β-lactam antibiotic may be ordered, processed, and administered if the patient does not have an allergy to β-lactam antibiotics

iii) In the case of a reported allergy:

(1) A health care professional should investigate and determine the type and severity of the reaction[2]

(a) The allergy should be entered in the medical record Allergies/Contraindications tab under comments using the following dot phrase "**.PENICILLIN**"

(b) Information to investigate a medication allergy includes:[2,24]

(i) Patient's age at the time of the reaction

1. Concomitant viral rash at time of β-lactam administration is more common in childhood

(ii) Patient's recall of the reaction or who informed them of it

(iii) Time of onset of the reaction after beginning the penicillin (e.g., after 1 dose or several days)

1. Nearly all Type I (IgE-mediated) reactions occur within 72 hours of drug administration[4,44]

(iv) Signs/symptoms of the reaction:

1. Was an antidote/treatment given?
2. Did it require a visit to emergency room?
3. Was there a loss of consciousness?

(v) Route of administration (oral or IV)

(vi) Indication for medication

(vii) Concurrent medications

(viii) Did the reaction abate after the medication was discontinued?

(ix) Had the patient taken other medications in the same or related class before or after the reaction

1. If yes, was there any sort of reaction?

(2) A β-lactam antibiotic may be utilized if the patient has received that class of β-lactam in the past without a reaction[2]

(a) Physicians and/or pharmacists should review the medical record and potentially call the patient's home pharmacy to investigate previous antibiotic use

(3) If the patient has NOT received an antibiotic in the same class in the past, the type of reaction should be ascertained

(a) If it is determined that the reaction was actually a <u>side effect</u> (e.g. gastrointestinal intolerance including nausea or diarrhea), the original β-lactam antibiotic may be ordered, processed, and administered

(b) If the type of reaction is <u>questionable</u> or is <u>unable to be ascertained</u> from the patient, family, caregiver or medical record:

(i) *An effort should be made to rule out any signs or symptoms of angioedema, anaphylaxis, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) and this should be documented in the patient's allergy history*. If the patient is penicillin allergic, penicillin skin testing should be considered if possible

(ii) Prescribe β-lactam antibiotic from different class based on class of β-lactam allergy[2]

1. The prescribed β-lactam antibiotic should also have a different side chain (see **Table 1**) than the antibiotic the patient is allergic to due to increased reactivity[2,10,20,22,40]
   a. A GRADED CHALLENGE (see section 3.C.) may be used if the reaction happened recently[2]
2. Penicillin-allergic patients may be prescribed a cephalosporin (first line) or a carbapenem (second line)[2]
3. Cephalosporin-allergic patients may be prescribed a penicillin (first line) or a carbapenem (second line)[2]
4. Carbapenem-allergic patients may be prescribed either a penicillin or a cephalosporin (either first line)[2]
5. Aztreonam allergic patients may be prescribed either a penicillin or a cephalosporin as first line therapy or a carbapenem as second line therapy[2]

(iii) If use of a β-lactam from the same class is desired, consult Allergy for recommendations

(c) If a <u>non-severe, non-IgE-mediated reaction</u> that occurred <u>AFTER</u> 72 hours is found:

(i) If patient is penicillin allergic, penicillin skin testing should be considered if possible

(ii) Prescribe β-lactam antibiotic from a different class based on the class of β-lactam allergy[2]
1. The prescribed β-lactam antibiotic should also have a different side chain (see **Table 1**) than the antibiotic the patient is allergic to due to increased reactivity [2,10,20,22,40]
   a. A GRADED CHALLENGE (see section 3.C. below) may be used if the reaction happened recently[2]
2. Penicillin-allergic patients may be prescribed a cephalosporin (first line) or a carbapenem (second line)[2]
3. Cephalosporin-allergic patients may be prescribed a penicillin (first line) or a carbapenem (second line)[2]
4. Carbapenem-allergic patients may be prescribed either a penicillin or a cephalosporin (either first line)[2]
5. Aztreonam allergic patients may be prescribed either a penicillin or a cephalosporin as first line therapy or a carbapenem as second line therapy[2]

(iii) If use of a β-lactam from the same class is desired, consult Allergy for recommendations.

(d) If a <u>possible IgE-mediated reaction</u> occurring <u>WITHIN</u> 72 hours is found (i.e., rash <u>+</u> hives):
(i) If patient is penicillin allergic, penicillin skin testing should be considered if possible
(ii) Prescribe β-lactam antibiotic from a different class via GRADED CHALLENGE (see section 3.C.) based on the class of β-lactam allergy[2]
1. Prescribed β-lactam antibiotic should also have a different side chain (see **Table 1**) than the antibiotic the patient is allergic to due to increased reactivity[2,10,20,22,40]
2. Penicillin-allergic patients may be prescribed a cephalosporin (first line) or a carbapenem (second line)[2]
3. Cephalosporin-allergic patients may be prescribed a penicillin (first line) or a carbapenem (second line)[2]
4. Carbapenem-allergic patients may be prescribed either a penicillin or a cephalosporin (either first line)[2]
5. Aztreonam allergic patients may be prescribed either a penicillin or a cephalosporin as first line therapy or a carbapenem as second line therapy[2]

(iii) If use of β-lactam from same class is desired, consult Allergy for recommendations

(e) If an <u>IgE-mediated reaction</u> occurring <u>WITHIN</u> 24 hours is found (i.e. immediate urticarial, angioedema, anaphylaxis):
(i) If patient is penicillin allergic, penicillin skin testing (see section 3.B.) should be considered if possible
(ii) First Line: use non-β-lactam antibiotic[2]
1. If no alternatives are available, aztreonam may be considered for Gram-negative infections[2]
   a. Do not use aztreonam in ceftazidime-allergic patients[2]

(iii) Second Line (and need β-lactam):
1. If use of a penicillin antibiotic is planned: consult Allergy for PENICILLIN SKIN TESTING (see section 3.B. below) and/or RAPID INDUCTION OF DRUG TOLERANCE (see section 3.D.)[2]
2. If use of cephalosporin or carbapenem antibiotic planned: consult Allergy for a RAPID INDUCTION OF DRUG TOLERANCE (see section 3.D.)[2]

(f) If a <u>severe, non-IgE-mediated reaction</u> (e.g. hemolysis, SJS, TEN) is found:
(i) Use a non-β-lactam antibiotic[2]

iv) If a patient with a reported β-lactam allergy successfully receives a β-lactam antibiotic, their allergy history should be updated to reflect this in the medical record Allergies/Contraindications tab under comments using the following dot phrase "**.PENICILLINFOLLOWUP**"

B) Penicillin Skin Testing

i) Penicillin skin testing by the Allergy department should be considered for all patients with a possible IgE-mediated reaction to a penicillin antibiotic[2]
(1) Even if a patient successfully receives a β-lactam antibiotic from a different class, it is still useful to perform a penicillin skin test to either confirm or delabel the allergy, improving future clinical decisions with respect to the administration of antibiotics
(2) There are no commercially available skin tests for cephalosporins, carbapenems and monobactams[2]

ii) *Penicillin skin testing must be performed prior to a rapid induction of drug tolerance to a penicillin in order to ensure the patient is truly allergic before expending more time and resources*

iii) The risk of having an adverse reaction to a penicillin skin test is <1% and the reaction is usually only urticaria[2]
iv) Patients with a history of severe, non-IgE-mediated reactions should not be skin tested[2]

v) Perform penicillin skin testing with both major and minor determinants when possible[2]
   (1) An oral challenge should be included, when feasible, to increase sensitivity[44]
vi) Prior to conducting skin testing, patients should be instructed to hold antihistamines, β-blockers, and tricyclic antidepressants
vii) Patients with negative penicillin skin test results are at a small risk of IgE-mediated reaction and can receive penicillin via GRADED CHALLENGE (see section 3.C.) if the risk of reaction is felt to be low.[2]
viii) Patients with negative penicillin skin test results can safely receive cephalosporin and carbapenem antibiotics[2]
ix) If the penicillin skin test is positive, the patient should not receive penicillins or a β-lactam antibiotic with a similar side chain (**Table 1**)[2]
   (1) These patients should undergo a RAPID INDUCTION OF DRUG TOLERANCE (see section 3.D.) when an alternative class of antibiotics may not be substituted (e.g., treatment of syphilis during pregnancy)[2,38]
x) After the penicillin skin test is performed, a healthcare provider should update the allergy history to reflect the date and result of the skin test in the medical record Allergies/Contraindications tab under comments using the following dot phrase "**.PENICILLINSKINTEST**"

C) Graded Challenge
i) Performed in patients who have a low pretest probability of an immediate allergic reaction
ii) Prescribers and the Allergy department should be contacted prior to initiating a graded challenge
   (1) For ICU, ED, Heme/Onc or BMT patients, if the Allergy department is not readily available to assist with a graded challenge, one may be performed without their immediate involvement, as long as an effort is made to contact them prior to initiation of the challenge and a formal consult is requested so the patient can be followed after the challenge
iii) Patients do not need to increase their level of care during the graded challenge[2]
   (1) Providers will give the patient their call light and tell them to raise an alert if they experience signs of an allergic reaction (including the following: new onset runny nose, itching, congestion, mild nausea/discomfort, hives, full body flushing, chest pain, shortness of breath, wheezing, hypotension, and/or confusion)
      (a) Medications used to treat allergic reactions will be ordered prior to the graded challenge and are available in the unit crash cart or Pyxis cabinet
   (2) A provider will check on the patient's vitals (heart rate, respiratory rate, and blood pressure) prior to beginning the first graded challenge dose (time 0) and every 60 minutes thereafter until the procedure is completed[2,45]
      (a) Further monitoring is patient specific and at the discretion of the provider, as delayed non-immune mediations reactions can occur days after administration[2]

iv) <u>Oral graded challenge</u>:
   (1) Used if oral therapy is desired
   (2) Order set 90093: Beta-Lactam Graded Challenge Module (for all floors)
   (3) Procedure: Give 10% of dose, and then in 60 minutes give remainder of dose[2]
   (4) Oral graded challenge procedure total time is120 min, with 3 vitals checks

v) <u>Intravenous graded challenge</u>:
   (1) Used if intravenous therapy is desired
   (2) Order set 90093: Beta-Lactam Graded Challenge Module (for all floors)
   (3) Procedure: Give 1% of dose, then in 30-60 minutes give 10% of dose, then in 30-60 minutes give remainder of dose[2]
   (4) Intravenous graded challenge procedure total time is180 min, with 4 vitals checks

vi) If the patient has signs and/or symptoms of an allergic reaction, discuss with provider next steps in the graded challenge and further monitoring
vii) If a severe reaction develops during the graded challenge and it is determined the patient needs the antibiotic, Allergy should be consulted for RAPID INDUCTION OF DRUG TOLERANCE (see section 3.D.)[2]
   (1) Graded challenges and rapid induction of drug tolerance should not be performed if there is a history of a severe non-IgE-mediated reaction (e.g. hemolysis, SJS, TEN), due to the risk of reactivation[2]
viii) The results of the graded challenge should be documented in the medical record Allergies/Contraindications tab under comments using the following dot phrase "**.PENICILLINGRADE**"

(1) The allergy should not be deleted from the patient's medical record for ease in tracking the results of the graded challenge

ix) Patients should have β-blockers discontinued prior to the graded challenge, if possible, to prevent resistance to treatment if a severe adverse reaction occurs[11,46]

x) Do not pretreat patients with glucocorticoids or antihistamines as these can mask the signs of allergic reactions[2,47]

D) Rapid Induction of Drug Tolerance (Desensitization)

i) Allergy must be consulted before attempting a rapid induction of drug tolerance

ii) Penicillin skin testing must be performed prior to a rapid induction of drug tolerance to a penicillin in order to ensure the patient is truly allergic before expending more time and resources

iii) The guidelines for a rapid induction of drug tolerance can be found under Clinical Resources: Pharmacy: Inpatient Medminder: Clinical Guidelines: Anti-infective Guidelines: Antimicrobial Desensitization

iv) After a rapid induction of drug tolerance is performed the allergy history should be updated in the medical record Allergies/Contraindications tab under comments using the following dot phrase "**.PENICILLINDESENS**"

4) Summary Points

A) An accurate and thorough allergy history is key to guiding therapy in patients with reported β-lactam allergies

B) Cross-reactivity is only associated with Type I IgE-mediated reactions and is associated with similar or identical R1 side chains[2,6-8]

i) The risk of cross-reactivity between penicillins and cephalosporins is <1% in those with reported allergies, and <2% in those with confirmed penicillin allergies[2]

(1) In penicillin allergic patients who have not been skin tested, the risk of a severe reaction following administration of a cephalosporin is estimated to be 0.1%[2]

ii) The risk of cross-reactivity between penicillins and carbapenems is <1%[2]

C) Cefazolin is the only cephalosporin with a unique R1 side chain

D) Cross-reactivity with aztreonam is low and it may be used safely in patients allergic to all β-lactams except ceftazidime, as they share an identical R1 side-chain[2,4]

E) Penicillin skin tests can be used to reliably rule out Type I IgE-mediated reactions with a NPV of 97-99%[36]

F) Graded challenges can be used to cautiously administer a medication to a patient who is unlikely to be allergic to it[2]

G) A rapid induction of drug tolerance can be used to create a temporary state in a patient allowing for safe treatment with an antigenic drug[2]

5) Disclaimer

A) This Clinical Practice Guideline provides an evidence-based approach for the inpatient antibiotic treatment of patients with reported β-lactam allergies. It is understood that occasionally patients will not match the conditions considered in this guideline.

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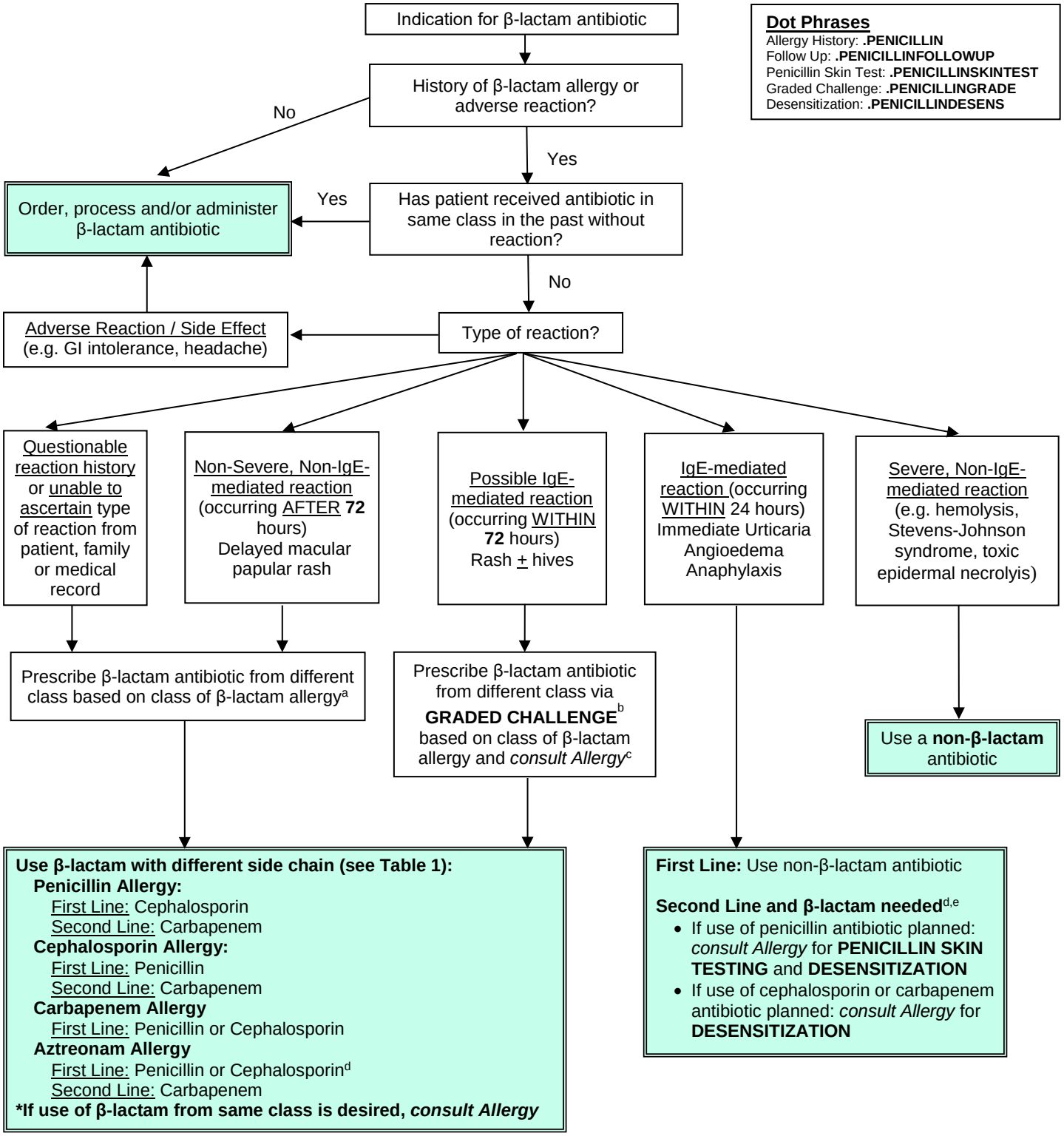
Figure 1. **β-Lactam Allergy Practice Parameter Algorithm** (Adapted from UW Health)



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

- Order set 90093, Beta-Lactam Graded Challenge Module (for all floors)
- *Allergy* must be consulted before performing a graded challenge, except for ICU, ED, Heme/Onc or BMT patients[c]
- Use Pyxis cabinet and Crash Cart stock, if needed, for anaphylaxis medications (epinephrine, diphenhydramine, methylprednisolone) during graded challenges
- Patients do not need to increase their level of care during a graded challenge
- The patient will use their call light to alert the provider to an allergic reaction
- A provider will check on the patient's vitals (HR, RR, BP) prior to beginning the first dose (time 0) and every 60 minutes thereafter until the procedure is completed

[c]For ICU, ED, Heme/Onc or BMT patients, if *Allergy* is not available to assist with a graded challenge, one may be performed without their immediate involvement.

[d]Do not use aztreonam in ceftazidime allergic patients

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