APPENDIX J: UWHC Guidelines For the Use of Beta-Lactam Antibiotics in Patients with Reported Allergies to Penicillin

Please address questions, comments, and suggestions regarding this guideline to Lee Vermeulen, MS, RPh, FCCP, Director, Center for Drug Policy at 608/262-7537.

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A. Principles and Background
The reported penicillin allergy rate for inpatients and outpatients is 10%.1-5 Of these patients, 80-90% will not have positive penicillin skin testing, which test for IgE-mediated reactions only.6,7

The patient may state they are allergic to a medication, but the reaction could be an adverse drug reaction (i.e. GI intolerance) or attributed to the disease being treated (i.e., rash caused by viral infection while on amoxicillin).6 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 10 years of avoidance.8

The different types of allergic drug reactions are classified as follows by the Gell and Coombs classification.2-4,6,7,9-11

1.0 Type 1: IgE-mediated
1.1 Immediate reactions (onset <1 hour after drug administration): systemic manifestations of anaphylaxis
   1.1.1 Urticaria (hives), pruritus, bronchospasm, laryngeal edema, hypotension, and/or cardiac arrhythmias
   1.1.2 Life-threatening
   1.1.3 Tested by minor determinant of penicillin skin test
   1.1.4 Immediate reactions occurring greater than one hour after infusion, or during sustained therapy, even in the presence of urticaria, are rare
1.2 Accelerated reactions (onset 1-72 hours after drug administration)
   1.2.1 Urticaria, angioedema, laryngeal edema, wheezing
   1.2.2 Rarely life-threatening
   1.2.3 Determined by penicillin skin test
1.3 Usually associated with beta-lactam antibiotics

2.0 Type 2: Cytotoxic/antibody-mediated (IgG-, IgM- complement-mediated)
2.1 Hemolysis, thrombocytopenia, neutropenia, or interstitial nephritis
2.2 Usually associated with quinidine, methyldopa and penicillins
2.3 IgG and IgM antibodies don’t induce allergic reactions
   2.3.1 Only IgE binds to mast cells and basophils to produce allergic reactions

3.0 Type 3: Immune complex (IgG, IgM immune complexes)
3.1 Serum sickness
3.2 Fever, rash, urticaria, lymphadenopathy, and arthralgias
3.3 Usually associated with antisera, penicillin, sulfonamides and phenytoin
4.0 Type 4: Cellular immune-mediated/delayed hypersensitivity reaction

4.1 Contact dermatitis
  4.1.1 Example: health care workers involved in the manufacturing and dispensing of offending agents

4.2 Delayed nonurticarial rashes caused by aminopenicillins

5.0 Unknown mechanism: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug reaction, pulmonary infiltrates (nitrofurantoin), autoimmune disease (vasculitis, lupus), drug fever, drug-induced hypersensitivity syndrome (antiepileptics)

5.1 Penicillin skin testing will not detect these type of reactions

5.2 Desensitization should not be performed due to the risk of reactivate of the reaction

Switching to another class of antibiotics due to a reported patient allergy may adversely affect patient care due to the different antibiotic:

- Being less effective
- Having more adverse effects
- Being more broad-spectrum, leading to increased resistance
- Being more expensive

Since beta-lactam antibiotics share a common beta ring, there is a risk of cross-reactivity. 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. Some of the antibiotics share common side chains (see section D) which also may contribute to cross-reactivity. This degree of cross-reactivity appears to be greater amongst the same class of antibiotics than between classes. The greatest risk of cross-reactivity is amongst penicillins.

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. Also during this time, some cephalosporins were contaminated with trace amounts of penicillin. Since 1980, reaction rates in penicillin history-positive and skin test-positive patients who received cephalosporins decreased to between 1.1 and 4.4%. 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. If a patient is penicillin history-positive, but skin test-negative, they are at no increased risk of cephalosporin cross-reactivity. If patients with a history of penicillin allergies aren’t skin tested, the risk of a reaction when given a second or third generation cephalosporin is about 1%, but most of these reactions are anaphylaxis.

The estimated cross-reactivity between carbapenems and other beta-lactams varies depending on the type of study. Retrospective studies show a cross-reactivity rate of about 9-11%. Issues with these retrospective studies were they didn’t verify the penicillin allergies with skin testing, they didn’t limit the definition for allergic reactions to IgE mediated reactions, and they based their results on chart documentation. Prospective studies had a cross-reactivity rate of 0.9-47.4%. The study showing a 47.4% 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. Three other prospective studies showed cross-reactivity rates of 0.9-1%. 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 the patients had an allergic reaction to the systemic carbapenem. Cross-reactivity
with aztreonam and other beta-lactams, except ceftazidime (see Section D), is low and it may be used safely in beta-lactam allergic patients.5,11,21 Also, 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).8,22

Penicillin is the only drug class with a valid skin test. Degradation products of other antibiotics are not known or commercially available. Under physiologic conditions, penicillin degrades to reactive intermediates that act as haptenoids. These haptenoids 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. The risk of having an adverse reaction to a penicillin skin test is <1% and the reaction is usually only urticaria. Prior to conducting skin testing, patients should be instructed to hold antihistamines, beta-blockers and tricyclic antidepressants. Penicillin skin testing has a high negative predictive value since 97-99% of patients with a negative skin test to both the major and minor determinants will not have an immediate type 1 reaction. Skin test-negative patients may safely receive penicillin. Skin test-positive patients should avoid all penicillin compounds. These patient’s should be desensitized when an alternative class of antibiotics may not be substituted (i.e.: treatment of syphilis during pregnancy) 2-5,7,11,16

B. Objectives
1.0 To develop a guideline for prescribers and pharmacists to help with ordering and processing beta-lactam antibiotics in penicillin-allergic patients.

C. Guideline
1.0 When an order for a beta-lactam antibiotic is initiated it should be determined if the patient has any medication allergies.
1.1 The order may be processed if the patient does not have an allergy to beta-lactam antibiotics.
1.2 In the case of a reported allergy:
   1.2.1 The prescriber or pharmacist should investigate and determine the type and severity of the reaction (see Section F).
   1.2.2 If a rash is described, the health care professional should ascertain the characteristics of the rash. Types of rashes include:
      1.2.2.1 Urticaria (IgE-mediated) rashes are an intensely pruritic, circumscribed, raised and erythematous eruption with central pallor.
      1.2.2.2 Maculopapular or morbilliform rashes (non-IgE-mediated) begin in dependent areas and generalize, often with associated mucous membrane erythema, and are pruritic.
   1.2.3 An order for that class of beta-lactam may be processed if:
      1.2.3.1 The patient has received that class of beta-lactam in the past without a reaction.
      1.2.3.2 The patient or family does not recall the reaction.
      1.2.3.3 A non-severe, non-IgE-mediated reaction is described and the prescribed beta-lactam and the beta-lactam the patient is allergic to have different side chains. (see section D)
      1.2.3.4 The health care professional can ascertain that the rash is non-urticarial and the prescribed beta-lactam and the beta-lactam the patient is allergic to have different side chains. (see section D)
      1.2.3.5 A graded challenge may be tried if some concern about cross-reactivity exists. (see section E)
1.2.3.5.1. Prescriber should be contacted prior to initiating graded challenge
1.2.3.5.2. Anaphylaxis treatment medications should be available
1.2.4. The pharmacist should contact the prescriber if:
   1.2.4.1. The type of rash cannot be ascertained, in which case it should be assumed to be urticarial (IgG mediated).\textsuperscript{11}
   1.2.4.2. The patient's history is positive for an IgE-mediated (type 1) reaction.
   1.2.4.3. The reaction is a severe, non-IgE-mediated reaction.
1.2.5. The prescriber and pharmacist should determine the next course of action:

1.2.5.1. Use an antibiotic from another class.
1.2.5.2. Initiate a graded challenge (see section E) if the risk of reaction is felt to be low.
1.2.5.3. Penicillin skin testing.
   1.2.5.3.1. Patients with a history of severe, non-IgE mediated reactions should not be skin tested.

D. Side Chains

1.0 If the order is for a beta-lactam antibiotic that has the same side chain as the antibiotic the patient is allergic to, the prescriber should be contacted for another antibiotic choice due to increased risk of cross-reactivity. Cefazolin does not share a common side chain with any other beta-lactams. The following table lists beta-lactams with common side chains:

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<tr>
<th>Agent</th>
<th>Amoxicillin</th>
<th>Ampicillin</th>
<th>Cefaclor</th>
<th>Cefadroxil</th>
<th>Cefprozil</th>
<th>Cephalexin</th>
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E. Graded Challenge

1.0 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. Since lower doses are initially used, if an allergic reaction happens, hopefully it will be minor and easily treated. Patient's should have beta-blockers discontinued to prevent treatment resistant anaphylaxis if it occurs.

Procedure: give 1%, then 10%, then 100% of therapeutic dose at 30 minute intervals if no reaction develops at each dosage increment.

1.1.1 If a reaction develops, the patient should be desensitized
1.2 Anaphylaxis medications should be available
1.2.1 Epinephrine 0.2-0.5 mg IM or SC Q5 minutes as needed
   1.2.1.1 Pediatrics: 0.01 mg/kg (maximum 0.3mg)
1.2.2 Diphenhydramine 25-50 mg IV
   1.2.2.1 Pediatrics: 1-2 mg/kg
1.2.3 Albuterol 2.5-5 mg nebulized

F. Patient Interview

1.0 Potential questions to ask a patient/family member when investigating a medication
allergy include:
1.1 Patient’s age at the time of the reaction
1.2 Patient’s recall of the reaction or who informed them of it
1.3 Time of onset of the reaction after beginning the penicillin (e.g., after 1 dose or
several days)
1.4 Signs/symptoms of the reaction
   1.4.1 Was an antidote given
   1.4.2 Did it require a visit to emergency room
   1.4.3 Was there a loss of consciousness
1.5 Route of administration (oral or IV)
1.6 Indication for penicillin (or cephalosporin)
1.7 Concurrent medications
1.8 Did the reaction abate after the penicillin (or cephalosporin) was discontinued
1.9 Had the patient taken other penicillins (or cephalosporins) before or after the
reaction
   1.9.1 If yes, what was the outcome

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patients in internal medicine wards of a general tertiary care hospital. Clin Exp Allergy


Order for beta-lactam antibiotic

Penicillin allergy?

No

Implement order

Yes

Patient received an antibiotic in that class in the past without reaction?

No

May try graded challenge if unsure

Yes

Type of reaction?

Patient and/or family do not know/recall reaction

Non-severe, non-IgE mediated reaction
Delaye d maculopapular rash
Itching
GI intolerance

Severe, non-IgE mediated reaction
Hemolysis
Stevens Johnson Syndrome
Toxic epidural necrolysis

IgE mediated (type I reaction)
Urticaria (hives)
Angioedema
Anaphylaxis

Contact prescriber to use alternative agent

Contact prescriber to:
1) Use alternative agent
2) Do penicillin skin test
3) Do graded challenge if felt to be low risk of cross-reactivity