Beta-Lactam Use in Penicillin Allergic Patients
Clinical Guideline

**RECOMMENDATIONS:**

1. Penicillin Anaphylaxis (Type-1 IgE Mediated hypersensitivity)
   a. May use Cephalosporins and Carbapenems
2. Penicillin Reactions that are not IgE Mediated and non-life-threatening (i.e. rash)
   a. May use Cephalosporins and Carbapenems

**Background of Clinical Issue Addressed:** Cephalosporins were introduced into the U.S. market in 1964 and soon followed case reports of hypersensitivity reactions, some occurring in patients with a history of penicillin allergy. Cephalosporins share a similar beta-lactam chemical structure with penicillins, thus the concept of cross-reactivity was proposed. A meta-analysis of this issue, published in 1978, revealed 8.1 % of patients with prior penicillin allergy subsequently develop cephalosporin allergy compared to only 1.9% without a prior penicillin allergy. This 8.1 % cephalosporin allergy rate is the basis for the widely cited (and rounded up) 10% cross-reactivity rate. However, major concerns such as lack of a definition of allergy and the fact that cephalosporins used during this time period were known to have been contaminated with penicillin during the manufacturing process raise doubt as to the validity of this data. Self-reported beta-lactam allergies compromise up to 20% of hospitalized patients, however, 80% to 90% of these patients have a negative penicillin skin test. 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.

**Summary of Recent Studies: Cephalosporin Use in Penicillin allergic and non-allergic patients**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Baseline Allergy Incidence</th>
<th>Male Patients</th>
<th>Female Patients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macy et al. 2009</td>
<td>Cephalosporins</td>
<td>0.60 %</td>
<td>1.08 %</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Conclusions: The baseline rate of allergy to cephalosporins is ~1%

<table>
<thead>
<tr>
<th>Reference</th>
<th>Antibiotic Class</th>
<th>PCN Skin Test (+)</th>
<th>PCN Skin Test (-)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macy et al. 2002</td>
<td>New Cephalosporin Allergy</td>
<td>1/42 (2.4%)</td>
<td>0/80 (0%)</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>New Non-beta-lactam Allergy</td>
<td>8/74 (10.8%)</td>
<td>8/116 (6.9%)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Conclusions: Cephalosporins are used more safely than non-cephalosporins
Cross reactivity is not supported

<table>
<thead>
<tr>
<th>Reference</th>
<th>Antibiotic Class</th>
<th>History of Penicillin Allergy</th>
<th>Unadjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apter et al. 2006</td>
<td>New Cephalosporin Allergy</td>
<td>43/3877 (1.1%)</td>
<td>10.0 (7.4 – 13.6)</td>
</tr>
<tr>
<td></td>
<td>New Sulfonamide Allergy</td>
<td>10/630 (1.6%)</td>
<td>7.2 (3.8 – 13.5)</td>
</tr>
</tbody>
</table>

Conclusions: Absolute risk of anaphylaxis in penicillin allergic is vanishingly small at 0.001%
Cross-reactivity is not supported
Macy et al. 2011 | Cephalosporins | 1/169 (0.6%) | 28/819 (1.2%)

Conclusions: Regardless of sex or penicillin skin testing results, new cephalosporin allergy rates are no different than other commonly used antibiotics.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Antibiotics Class</th>
<th>PCN Skin Test (+)</th>
<th>PCN Skin Test (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmed et al. 2012</td>
<td>New Cephalosporin Allergy</td>
<td>0/21 (0%)</td>
<td>1/151 (0.7%)</td>
</tr>
</tbody>
</table>

Appendix 1

The University of Miami UHealth Tower’s Assessment of Cephalosporin Use in Penicillin Allergic Patients

Introduction:

Healthcare professionals frequently encounter patients who report an allergy to penicillin. Self-reported beta-lactam allergies compromise up to 20% of hospitalized patients. However, 80% to 90% of these patients have a negative penicillin skin test. In some cases, patients interpret a side effect as an allergy and will report it as such in a subsequent visit. Depending on the provider’s belief of cross-reactivity between penicillins and other beta-lactam antibiotics, the selection of antimicrobial therapy may result in the avoidance of a beta-lactam antibiotic. In turn, this may lead to the use of suboptimal, inappropriately narrow or unnecessarily broad spectrum antibiotics. For example, using vancomycin for methicillin-susceptible Staphylococcus aureus (MSSA) bacteremia, where beta-lactam antibiotics have been demonstrated to be superior to vancomycin.

Beta-lactam antibiotics are the first line treatment for many infections; they cover a wide range of microorganisms, including gram-negative and gram-positive bacteria, and are well tolerated by most patients. Cephalosporins have a reported incidence of nonsevere adverse reaction manifesting as skin rash in only 1% to 3% of treated patients. The first cephalosporin, cephalothin, was introduced into the United States market in 1964. Shortly after, studies in the 1960s and 1970s began to report cross-reactivity rates of 8-18%. As a result, the popular belief became that patients with a history of a penicillin allergy have about a 10% risk of an adverse reaction if given a cephalosporin. The results of these studies may have been confounded because in some studies the patient’s penicillin allergy was not confirmed by a penicillin skin test. Additionally, these early studies included first generation cephalosporins, such as cefamandole that are no longer in the market and share a similar side chain to benzyl penicillin. Moreover, in the 1980s manufacturers used the Acremonium fungus to produce both penicillins and cephalosporins which may have led to the presence of cross-contamination. Cephalosporins used today no longer contain trace amounts of penicillin due to different manufacturing processes.

Recent observational studies have found cross-reactivity rates between 0.17% and 0.7%. In a prospective study, the rate of cross-reactivity among participants with a positive penicillin skin test was 6%. These incidences of cross-reactivity between penicillins and cephalosporins is attributed more to the similarities of the side chains versus the beta-lactam ring. In particular, the aminopenicillins, amoxicillin and ampicillin, have the same R-group side chains as several first- and second-generation cephalosporins (Figure 2). The highest observed cross reactivity rate (27%) is with cefadroxil, which has the same R-group side chain as amoxicillin.

Due to the low incidence of true penicillin allergies, the patient’s allergic event must be carefully assessed before choosing an alternative to a beta-lactam agent. Additionally, identifying the time from the
reaction is valuable information because penicillin specific IgE antibodies diminish over time. Thus, patients who experienced a reaction years ago are less likely to have an allergic reaction compared to patients with a recent reaction. Approximately 50% of patients with IgE-mediated penicillin allergy lose their sensitivity 5 years after reacting, and this percentage increases to approximately 80% in 10 years.4 However, in general patients with true penicillin allergy are at are an increased risk of an allergic reaction when given any antibiotic.

A thorough interview of the patient’s allergy is a helpful strategy to evaluate what antimicrobials the patient can safely receive. Factors to consider include, but are not limited to the specific drug that the patient received, approximate date and type of reaction experienced, temporal relationship between the drug administered and allergic reaction, concomitant drugs at the time of the reaction, and their history of antimicrobial use. Thus, in an effort to optimize antibiotic therapy for patients, a retrospective review was conducted to determine if there was consistency with published literature.

Methods:

This observational retrospective chart review was conducted at an academic teaching hospital that serves the adult population. The inclusion criteria included patients with a documented penicillin allergy that were 18 years of age or older and had received at least one β-lactam agent (Figure 1/541+9685741). A Meditech© report was utilized to identify patients admitted from January 1, 2017 through October 28, 2018 which had a penicillin allergy documented. An electronic chart review of each patient was completed to determine sex, age, penicillin allergic reaction(s), and history of β-lactam therapy. The patient-reported allergic reactions were categorized into type-1 hypersensitivity, unknown, or other. In the cases where the patients reported more than one allergic reaction to penicillin, the most severe reaction was collected for data collection. A detailed list of each reported allergic reaction to penicillin and corresponding incidences per patient are presented in Table 1. The University of Miami Institutional Review Board (IRB) granted exemption for non-human subject research.

The primary objective of this study was to identify the percentage of patients that had an allergic reaction following the administration of a β-lactam antibiotic. The definition of not having an allergic reaction in the study was predetermined in advance as a patient that tolerated 2 or more doses of a single β-lactam antibiotic. A secondary objective included identifying the percentage of patients that received a β-lactam antibiotic (2 or more doses) from each drug class. Patients may have received 2 or more doses from more than one drug class. Thus, the categorization of the β-lactam drug classes and cephalosporin generations are mutually exclusive including, penicillins, the first four cephalosporin generations, and carbapenems. Another secondary objective was the percentage of patients that experienced an allergic reaction following a one-time dose of a β-lactam antibiotic and further classified by drug class. In order to identify if an allergic reaction occurred provider progress notes were reviewed for any unlisted drug allergy, adverse reactions or the reasoning behind the discontinuation of the β-lactam antibiotic. Additionally, medications used to treat an allergic reaction; including, diphenhydramine, ranitidine, famotidine, methylprednisolone, and hydrocortisone were identified and evaluated for their use to treat an allergic reaction caused by the one-time dose of the β-lactam antibiotic. The doses of β-lactam agents were classified by drug class and cephalosporin generations to further evaluate the risk of cross-reactivity in regards to the similarities of the penicillins and cephalosporins side chain. The safety endpoint included the percentage of patients with a baseline type-1 hypersensitivity allergic reaction to penicillin that received 2 or more doses of a single β-lactam antibiotic categorized into mutually exclusive β-lactam drug classes and cephalosporin generations. From clinical experience, it has been noted that prescribers may potentially be more hesitant to order a β-lactam agent if the patient expresses having experienced a type-1 hypersensitivity reaction. Consequently, the individual administrations from each drug class and/or cephalosporin generation
were obtained for evaluation of potential cross-reactivity. Finally, descriptive statistics were utilized to present the primary, secondary and safety outcomes.

**Results:**

Of the 243 charts reviewed, 176 individuals met the inclusion criteria. A total of 67 patients were excluded from the study due to no history of beta-lactam therapy. Table 2 describes the patient characteristics. The median age was 69 with a range of 21 to 102 years of age. The majority of patients (59%) were females. Patients had a variety of baseline clinical reactions reported to penicillin exposure with the most prevalent being rash which was further categorized into the broader category of type-1 hypersensitivity allergic reaction (59%). Other baseline allergic reactions included unknown (29%) and other (12%). Table 1 outlines in detail the patient reported clinical reactions to penicillin found in each of the 3 “type of allergic reaction” categories. The majority of patients received 2 or more doses of a single β-lactam agent (160 patients) and the remaining patients received a one-time dose of a β-lactam agent (16 patients).

One hundred sixty patients received 2 or more doses of a single beta-lactam agent; as a result, based on the definition for the absence of an allergic reaction, the percentage of patients that had an allergic reaction was 0% (Table 3). After reviewing prescriber documentation and medications used to treat an allergic reaction, it was determined that the percentage of patients that had an allergic reaction after a one-time dose of a beta-lactam was 0% (Table 3). Of the patients that received 2 or more doses, the majority received a 4th generation cephalosporin (50%), carbapenems (38%), and 3rd generation cephalosporin (28%). The percent of patients that received from the other drug classes/generations included penicillins (18%), a 1st generation cephalosporin (16%), and a 2nd generation cephalosporin (1%). Additionally, the percentage of patients that received a one-time resembles closely the drug class distribution from the patients that received 2 or more doses in that the majority were given 3rd generation (81%) and 4th generation (12%) cephalosporins. However, in this case the administration of penicillins, 1st generation cephalosporin and carbapenems was each 6%. Figure 1 and 2 depict the percentage of patients distributed by drug class and cephalosporin generations. Additionally, no 2nd generation cephalosporins were administered. The percent per category calculated for each drug class and cephalosporin generation was calculated as mutually exclusive.

Of the 160 patients that received 2 or more doses of a beta-lactam antibiotic, 94 reported a baseline type-1 hypersensitivity reaction. These patients are a subgroup of the patients that received 2 or more doses, thus as mentioned above, the percentage of patients that experienced an allergic reaction were 0%. The most commonly administered antibiotics were a 4th generation cephalosporin (49%), carbapenems (41%) and 3rd generation cephalosporins (27%). The other administrations were compromised of penicillins (17%), 1st generation (15%) and 2nd generation (1%) cephalosporins. The percentages were calculated as mutually exclusive based on each individual drug class and cephalosporin generation, Figure 3 depicts the percent distribution.
References: