

Cephalosporins in Penicillin Allergic Patients

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Many times when I order a cephalosporin on Epic, a pop-up box will ask me if I'm sure I would like to order a beta lactam in a patient with a penicillin allergy. Each time I pause and re-examine what the patient's allergy is and whether there is truly a risk in administering cephalosporins to penicillin-allergic patients. Thankfully there are many published articles addressing this specific question.

Classic teaching sites a roughly 10% risk (range of 8 to 18%) of adverse reaction in penicillin-allergic patients given cephalosporins. These numbers are based largely on studies performed in the 1960s and 1970s. Since then many articles have argued that these risks are exaggerated. In avoiding all cephalosporins in penicillin-allergic patients, providers would be prescribing possibly second or third line antibiotics that may be less effective in treatment of specific infectious diseases. This can lead to increased risk of developing antibiotic resistance. Patients may also be placed at unnecessary risk for potentially more dangerous side effects.

In discussing this topic, there are a number of topics to address. Firstly, the concept of a reported allergy versus that of a true allergy is important to discern. A true allergic reaction is IgE mediated. This can be verified with skin testing and radioallergosorbent tests. Campagna 2012 in the Journal of Emergency Medicine reviewed 27 articles that address cephalosporin cross-reactivity in penicillin allergic patients. In many of the studies, patients with reported penicillin allergy underwent skin testing to verify true allergy and it was noted that anywhere **between 3 and 13 percent of patients had a true reaction**. In a study published by Solensky 2012, fifty eight patients with reported penicillin allergy underwent skin testing. Fifty three tested negative and were given ten day penicillin challenge with no adverse effects. This confirms that the number of patients with true penicillin allergy is much smaller than those reporting an allergy.

Where does the classic teaching come from? Assem and Vickers challenged penicillin allergic patients with a first generation cephalosporin (cephaloridine) with a reaction reported in 12.5% of patients. This value correlates well with classic teaching. There are some arguments that the first generation cephalosporin used in this study is obtained from the same manufacturer as the penicillin which could increase cross contamination during the manufacturing process and there is a chance of the medications were manufactured in the same *Acremonium* fungus. However, there are many other similar studies that collaborate with this roughly 10% cross-reactivity.

Macy and Burchette conducted a six year observational study of 249 patients of which 83 had confirmed penicillin allergy. The observational study documented all antibiotics used and any reactions to antibiotics. Of the 42 penicillin allergic patients given cephalosporins, only one had an adverse reaction. The observational study showed reaction rate in penicillin allergic patients was lower for cephalosporins than non beta-lactam antibiotics ($p=0.005$). It was also noted that cephalosporins have fewer adverse reactions overall independent of penicillin allergy ($p=0.005$).

There are a number of limitations to the type of studies done on this topic. First, many of the sample sizes were less than fifty patients. Additionally, most studies were retrospective cohort studies that are limited by recall bias. Patients with allergic reactions to one antibiotic may then remember better whether they had a reaction to another.

Two meta-analyses (Pinchichero and Casey, Anne and Resiman) give interesting insight into the distinction between first versus second and third generation cephalosporins. The studies show that the odds ratio for a cross-reactivity with first generation cephalosporins is 4.8 with a confidence interval of 3.7 to 6.2. This equates to an incidence of 1-10%. The odds ratio for cross reactivity with second and third generation cephalosporins is 1.1 with a confidence interval of 0.6 to 2.1 which suggests no clinical correlation.

From this compilation of articles, we know that the true incidence of penicillin allergy in those with reported penicillin allergy is less than 10%. Despite this, taking a careful and good allergy history is important for deciding antibiotic coverage in patients with infectious disease. **Patients with hypersensitivity to penicillin are predisposed to hypersensitivity in general**. Therefore, penicillin allergic patients have increased risk of adverse reactions to any medication and this may not be related to cross reactivity at all. With a history of penicillin allergy, care should be given in general in prescribing antibiotics regardless of the class of antibiotics.

Overall the cross reactivity is overstated. In patients with reported penicillin allergy, the cross reactivity is **1%** and in those with confirmed penicillin allergy, it is **2.55%**. However, with even a 1% cross reactivity, I

would shy away from first and some second generation cephalosporins. So what makes the difference between first generation versus most second, third, and fourth generation cephalosporins? Through laboratory studies, the cross reactivity of cephalosporins with penicillins is found to be attributable to the **R1 side chain off the beta-lactam ring** rather than the beta-lactam ring itself. Many first and second generation cephalosporins share the same R1 side chain found on amoxicillin and ampicillin, including: cefadroxil, cephalexin, cefatirizine, cephadrine, cefaclor, and cefprozil. Therefore, risk of cross-reactivity is real for these cephalosporins in penicillin-allergic patients. **However, in most second and all third and fourth generation cephalosporins, the risk is unfounded.** There is no cross-reactivity in these medications and they should be used when warranted without hesitation.

Citations / Further Reading:

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