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Management of Beta-Lactam Allergies: Risk of Cross-reactivity

Ten to 15% percent of patients in the United States report a penicillin allergy.[1] These patients are often labeled as penicillin-allergic without further evaluation, leading to avoidance of penicillin, as well as cephalosporins, carbapenems, and monobactams due to concerns about potential cross-reactivity. A common clinical question is whether patients with a true, type I, immunoglobulin E (IgE)-mediated reaction to a specific beta-lactam can tolerate other beta-lactams. This newsletter describes the risks of cross-reactivity between penicillins, cephalosporins, carbapenems, and monobactams.

How much risk of allergic reaction is too high?

In general, the risk of cross-reactivity between penicillin and other beta-lactams is quite low. Among patients who report a penicillin allergy (but have not undergone confirmatory testing) between 0% and 8.1% will react if given a cephalosporin.[2-8] The large range in risk observed in previous studies stems from significant limitations in study design, including open fashion administration as opposed to single- or double-blinded methods, as well as lack of the control groups needed to identify patients with multiple drug allergy syndrome. Therefore, the risk listed in the package inserts for cephalosporins of 10% is likely an overestimation. For example, in patients with skin-test proven allergy to penicillin, the overall reaction rate to cephalosporins is 3.4%, and in patients with no reported allergy to penicillin, true anaphylactic reactions from cephalosporins are extremely rare, with an risk estimated of 0.00011% to 0.1%.[9, 10]

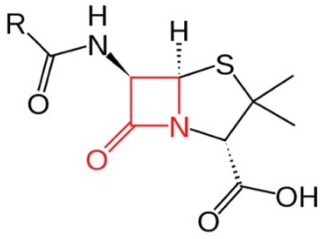
How to differentiate a true beta-lactam allergy from an intolerance?

Allergies to antibiotics are often confused with medication intolerance. It is important to differentiate between the two because a previous intolerance to a medication does not contraindicate future use. True IgE-mediated reactions classically begin within one hour of administration and manifest as anaphylaxis, angioedema, bronchospasm, urticaria (hives), and/or hypotension.[11] Other, non-IgE-mediated, reactions are delayed in onset and typically occur days to weeks after administration and involve a non-severe cutaneous reaction. Classic intolerances to penicillin include nausea, vomiting, and diarrhea. In patients with delayed-onset reactions not accompanied by systemic symptoms or blistering or exfoliation of the skin or mucous membranes, it is reasonable to consider treatment with the same or other beta-lactams in the future.

Antigenic components of beta-lactams:

In clinical practice, penicillin allergies are encountered most often; however, patients also report allergies to other beta-lactams. There are two structural components of beta-lactams that are linked to allergic reactions: 1) the beta-lactam ring and 2) the R-group side chain (**Figure 1**). This fact is important to note because a detailed allergy history identifying which specific agents caused the reaction may help determine which structure caused the allergic reaction.

Figure 1. Beta-lactam ring (shown in red) and R-group side chain



For example, a patient reporting hives reaction to penicillin, but who has tolerated a cephalosporin in the past has proven not to be allergic to the beta-lactam ring. This patient, however, may still be at risk for severe reaction to the R-group side chain. In such case, it would be appropriate to prescribe cephalosporins that have a different R-group side chain than the offending agent

(penicillin). **Table 1** outlines the cross-reactivity of beta-lactams based on structural similarities.[12]

Table 1. Cross-Reactivity Between Penicillins and Cephalosporins

Allergy	Agents to AVOID due to cross-reactivity between side chains
amoxicillin	ampicillin, cefadroxil, cephalexin, cefaclor
ampicillin	amoxicillin, cefadroxil, cephalexin, cefaclor
aztreonam	ceftazidime
cefaclor	amoxicillin, ampicillin, cefadroxil, cephalexin
cefadroxil	amoxicillin, ampicillin, cephalexin, cefaclor
cefdinir	cefixime
cefepime	cefotaxime, cefpodoxime,
cefixime	cefdinir
cefotaxime	cefepime, cefpodoxime, ceftriaxone
cefoxitin	penicillin G, cefuroxime
cefpodoxime	cefepime, cefotaxime, ceftriaxone
ceftazidime	aztreonam
ceftriaxone	cefepime, cefpodoxime, cefotaxime
cefuroxime	cefoxitin
cephalexin	amoxicillin, ampicillin, cefadroxil, cefaclor
penicillin G	cefoxitin

For example, amoxicillin and cephalexin have identical side chains; therefore, patients with IgE-mediated reactions against cephalexin should avoid amoxicillin, ampicillin, cefadroxil, and cefaclor. However, if they were previously challenged and tolerated a cephalosporin such as cefazolin, they may receive penicillin or ceftriaxone. In addition, they may receive other beta-lactams that are not listed in this table, such as cefazolin or piperacillin-tazobactam since there are no side chain similarities. Pharmacists can help prescribing clinicians determine if a patient has previously tolerated cephalosporins and other beta lactams by evaluating their past antibiotic administrations from prior admissions when no reactions were documented and then confirming no reaction with the patient.

Cross-Reactivity of Carbapenems:

Carbapenems share one common structural component with penicillins and cephalosporins: the beta-lactam ring. Historically, the rates of carbapenem cross-reactivity with penicillin-allergic patients were believed to be high. However, more recent evidence has shown that individuals with confirmed sensitivity to penicillin by skin tests reacted less than 1% of the time when challenged with carbapenems.[13-16] Carbapenems should not be preferentially used over cephalosporins based solely on the potential for cross-reactivity, unless there is a concern about a prior cephalosporin reaction and/or a particular side chain.

Cross-Reactivity of Monobactams (Aztreonam):

Aztreonam is the only available monobactam. It has a monocyclic beta-lactam structure. *In vitro* as well as skin testing studies demonstrated no immunologic cross-reactivity between penicillin and aztreonam.[17, 18] Similarly, aztreonam challenges in patients with positive penicillin skin tests revealed no reactions.[18] Therefore, patients with a history of penicillin allergy may safely receive aztreonam.[19] In contrast, patients reporting an IgE-mediated reaction to ceftazidime should not be challenged with aztreonam as the two agents have identical side chains.[18, 20]

DASON Resources:

We recommend that all patients reporting an allergy to penicillin or other beta-lactams have a detailed allergy history documented. The April 2015 DASON Newsletter describes strategies to investigate allergy history and improve allergy documentation as a means to "de-label" patients that are not truly allergic. DASON has also developed a beta-lactam allergy assessment toolkit including a patient questionnaire that your liaison pharmacist can help implement at your institution. Also, the June 2016 DASON continuing education webinar includes discussion of implementing a pharmacy-led allergy assessment protocol as well as penicillin skin testing at Duke University Hospital.

Take Home Points:

- Only 10% to 15% of patients reporting beta-lactam allergies are truly allergic.
- The true cross-reactivity between penicillins and cephalosporins, carbapenems, and monobactams is quite low.
- Cross-reactivity between beta-lactams occurs either due to the structural similarities in the beta-lactam ring or the R-group side chains.

- Patients with non-immunologic adverse events to penicillin may receive penicillins, cephalosporins, or carbapenems.
- Patients with true type I, IgE-mediated beta-lactam allergy to one agent, but tolerance to another beta-lactam, should avoid agents with similar side chains, but may receive other cephalosporins with different side chains, carbapenems, and monobactams.

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