SHC ASP

Beta-lactam Allergy and Cross-Reactivity

Situation: New information is available regarding the use of cephalosporins in penicillin allergic patients necessitating a reappraisal of cephalosporin prescribing in patients with IgE mediated penicillin allergy.

Background:

- Ten percent of the population state they have a penicillin allergy whereas the true incidence is ~1%. Labelling a patient penicillin allergic often results in the use of less effective alternative agents and is associated with increased antimicrobial resistance including C. difficile infection, increased ICU admissions, prolonged hospitalization and increased healthcare costs.[1,4,5]
- The beta-lactam ring is not thought to be the major antigenic structure in penicillin but rather the R1 side chain. Early generation cephalosporins were created with modification to the R1 side chain and later generations had modification to both the R1 and R2 group.[8] Furthermore, the cephalosporin breaks into several pieces that preserve the R1 and R2 side chains making them the likely antigenic components.[2]
- Data with the earliest generation cephalosporins overstate a cross-allergenicity based on studies with cephalosporins that were contaminated with trace amounts of penicillins during the manufacturing process and that used a poor definition of "penicillin allergy".[1,7] The cephalosporins used in early studies also had identical or similar R1 groups to aminopenicillins, many of which are no longer commercially available. A more informative summary of patients with cephalosporin challenge after positive penicillin skin testing is included below.[11]

Table 4
Cephalosporin challenges in patients with history of penicillin allergy and positive penicillin skin testing

Study	No. of Patients	No. of Reactions (%)	Cephalosporin Skin Testing	Reaction(s) to
Girard,[117] 1968	23	2 (8.7)	No	Cephaloridine
Assem and Vickers,[84] 1974	3	3 (100)	No	Cephaloridine
Warrington et al,[118] 1978	3	0	Yes	
Solley et al,[32] 1982	27	0	No	
Saxon et al,[119] 1987	62	1 (1.6)	No	Not noted
Blanca et al,[120] 1989	16	2 (12.5)	No	Cefamandole
Shepherd and Burton,[121] 1993	9	0	No	
Audicana et al,[90] 1994	12		Yes	
Pichichero and Pichichero,[122] 1998	39	2 (5.1)	No	Cefaclor (other cephalosporin not indicated)
Novalbos et al,[123] 2001	23	0	Yes	
Macy and Burchette,[48] 2002	42	1 (2.4)	No	Cefixime
Romano et al,[124] 2004	75	0	Yes	
Greenberger and Klemens,[125] 2005	6	0	No	
Park et al,[3] 2010	85	2 (2.4)	No	Cefazolin and cephalexin
Ahmed et al,[126] 2012	21	0	No	
TOTAL	446	13 (2.9)		

- A meta-analysis including 9 articles published between 1960 to 2005 found a significant increase in allergic reactions to cephalothin, cephaloridine, and cephalexin, and all first generation cephalosporins plus cefamandole, with no increase in reaction to other second (cefprozil, cefuroxime) or third generation cephalosporins (ceftazidime, ceftriaxone).[12]
- In a prospective study of 644 penicillin skin test positive children, the cross-reactivity to a cephalosporin was dependent on the generation of the cephalosporin and side chain similarity and ranged from 23.9% for first and second generation cephalosporins to 0.3% for third and fourth generation cephalosporins.[2]
- Patients with a history of penicillin allergy have an elevated risk of allergic reaction and may develop a new cephalosporin allergy.[8] In a review of 1684 patients with positive penicillin skin tests, there was no difference in rates of new onset cephalosporin allergies compared to new onset non-beta-lactam allergies and there was greater risk of developing a new sulfonamide allergy.[14]
- A recent population based study found that life threatening reactions to cephalosporins are rare events and most are benign rashes. In a study of 949,323 patients exposed to 1,389,538 cephalosporin courses, anaphylaxis only occurred after 0.00002% of oral and 0.00016% of intravenous exposures. Cephalosporin-induced anaphylaxis was 2.9 times more common

in patients with penicillin allergy compared to no drug allergy although this did not reach statistical significance (p=0.13) [1,6,11]

- Many of the recently published studies and reviews on the subject all similarly conclude that cross reactivity is directed toward the side chains and does not cross all generations of cephalosporin classes allowing for several safe cephalosporin options in patients who are penicillin allergic.[1-2,6-9] A review of 27 studies published between 1950 and 2012 found the overall rates of cross reactivity between penicillin and cephalosporins with similar side chains is 2.5% and cross reactivity between penicillin and all cephalosporins is 1% (see attachment).[7] Cross reactivity between penicillins and third and fourth generation cephalosporins is negligible. [2,7]
- The American Academy of Pediatrics sinusitis guidelines has endorsed the use of select second and third generation cephalosporins in patient with type 1 allergic reactions stating: *Patients with a history of a serious type 1 immediate or accelerated (anaphylactoid) reaction to amoxicillin can also safely be treated with cefdinir, cefuroxime, or cefpodoxime.*[10]
- Additionally, studies have found lower rates of new cephalosporin allergy in patients with a history of cephalosporin allergy compared to patients with a prior history of penicillin allergy.[11] Allergies to cephalosporins are usually side chain specific and it is recommended that a cephalosporin with a dissimilar side chain be used.[13] Some experts recommend a 2-step to 3-step graded challenge.[9]
- Penicillins and carbapenems only share a similar beta lactam ring. Prospective studies of carbapenems demonstrate that cross reactivity is unlikely or absent between penicillins or cephalosporins.[2,8,9]
- Monobactams do not cross react with penicillins and most cephalosporins except for ceftazidime as they share a similar side chain.[2,9]

Assessment:

- Beta-lactams are the drug of choice for empiric and definitive treatment for most infections. A designation of beta-lactam allergy carries unintended consequences including the use of alternative second line agents which may compromise patient care. Updating our allergy protocol to maximize the safe use of beta-lactams aligns with our antimicrobial stewardship goals.
- Cross reactivity between penicillins and most second and all third and fourth generation cephalosporins is negligible. Formulary second through fifth generation cephalosporins can be used safely in patients with a history of an IgE-mediated reaction to penicillin. First generations with similar side chains should be avoided (see table 1).
- Cephalosporins with dissimilar side chains may be used with graded challenge in patients with cephalosporin allergies (see table 2). This should be left to expert opinion.
- Carbapenems can safely be used in all patients with a penicillin or cephalosporin allergy.
- Aztreonam can safely be used in all patients with a penicillin or cephalosporin allergy with the exception of ceftazidime as they share a similar side chain.

Recommendation:

- Allow use of formulary 2nd through 5th generation cephalosporins (except cefoxitin) in all patients with a penicillin allergy.
- Modify Cerner allergy alerts to align with allergy recommendations as listed above (excluding allergies within the cephalosporin class).
- Update Policy 43008, Cephalosporin Administration to Penicillin-Allergic Patients. Expand the policy to include guidance for other beta-lactam antibiotics.
- Educate pharmacy, nursing and physicians regarding practice changes.

Table 1. Penicillins and Monobactams with similar side chains

Antibiotic	**β-lactam with Similar Side Chain** *(italicized=not available)*
Penicillin G	*cephalothin, cefamandole,* cefoxitin
Ampicillin or Amoxicillin	Cephalexin, cefadroxil, cefaclor, *cephradine, cephaloglycin, loracarbef, cefatrizine,* cefprozil, *cefamandole, cefonicid*
Aztreonam	Ceftazidime

Table 2. Cephalosporins with identical R1 side chains (derivation from reference 2, table 3)

Antibiotic	**β-lactam with Identical Side Chain**
Group 1	cefaclor, cephalexin, cefoxitin (similar)
Group 2	cefadroxil, cefprozil
Group 3	cefepime, cefotaxime, ceftriaxone, cefpodoxime, cefixime (similar), cefdinir (similar)
Dissimilar	cefazolin, cefotetan, cefuroxime, ceftaroline

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