

Date: 01/2022

From: System Antimicrobial Stewardship Steering

Intention: Informational

**Policy 43008: Penicillin, Cephalosporin, Carbapenem and Aztreonam
Administration to Beta-lactam Allergic Patients**

Situation: The last major update to [Policy 43008](#) allowing 2nd through 5th generation cephalosporin (except cefoxitin) administration in patients with penicillin allergy was in 2017; new data is available supporting use of cefazolin in patients with Type 1 (IgE mediated) penicillin allergy and the [policy](#) has been updated.

Background: Theoretical cross reactivity occurs between agents with the same R1 side chains¹:

	Cephalosporin with same side chain
Penicillin	None (<i>cefoxitin similar</i>)
Ampicillin	Cephalexin, Cefaclor ^{NF}
Amoxicillin	Cefadroxil, Cefprozil ^{NF}

NF: Non-formulary

- Penicillin and cefoxitin do not share an identical side chain¹⁻³. Older papers classify them as similar seemingly based on in vitro data³⁻⁵. More recent publications do not list them as such¹.
- Cefazolin has a completely dissimilar side chain from all penicillins.
- A study published in 2018 evaluated N=252 patient with immediate IgE mediated hypersensitivity to a penicillin-based antibiotic who underwent cephalosporin skin and immunoCAP testing.⁶
 - Patients reacting to cephalosporins with similar or the same side chains: 37% (95/252)
 - Patients reacting to cephalosporins with dissimilar side chains: 1.5% (4/252)
- A recent population based study evaluated the association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing, specifically looking at the proportion of cephalosporin use. Alerts were removed in Kaiser Permanente Southern California locations but retained in Northern California, which served as the control.
 - Antibiotic use was measured during pre- & post-intervention periods from 2017-2018.⁷
 - Over 4 million patients were included representing 10 million abx prescriptions
 - Alerts were removed regardless of reaction type and included all generations of cephalosporins
 - Significant increase in cephalosporin use from 18% to 27% at the intervention site
 - 1st generation cephalosporins represented 71%
 - IV cefazolin represented ~20%
 - No significant difference in secondary outcomes including anaphylaxis, new allergy treatment failures, all-cause mortality, hospital days and new infections
- A recent meta-analysis looking at the incidence of dual allergy to cefazolin and PCN and found a meta-analytical frequency of 0.7%⁸

Assessment

- Side chain similarity is the theoretical basis for cross reactivity reflected in our current policy allowing use of cefazolin and 2nd – 5th and next G cephalosporins in penicillin allergy.
 - Newer literature does not implicate cefoxitin as having a similar side chain to penicillin
- Cefazolin has a dissimilar side chain and recent population based data from Kaiser supports safe use in patients with penicillin allergy.

Recommendation:

P&P 43008 Modified to allow:	Exclusion	Necessary changes	Benefit
1. IV cefazolin and formulary 2nd-5th G cephalosporins in patients with a PCN allergy including anaphylaxis	1 st Gen PO cephalosporins, cephalexin and cefadroxil, due to same R1 side chain as ampicillin and amoxicillin, respectfully	<ul style="list-style-type: none">• Policy 43008 updated• Remove Cerner alerts for cefazolin in PCN allergy (pending, anticipated 06/2022)	Increased use of cefazolin for first line surgical prophylaxis, MSSA treatment, abx de-escalations
2. Penicillin administration in patients with IV cefazolin and/or formulary 2nd-5th G cephalosporin allergies	PCN administration in cephalexin, cefadroxil, cefaclor, cefprozil allergy due to shared R1 side chains	<ul style="list-style-type: none">• Policy 43008 updated• Remove Cerner alerts (pending, anticipated 06/2022)	Use of beta-lactam as first line agents Not currently addressed in Policy 43008

References

1. Chaudhry SB et al. Cephalosporins: A Focus on Side Chains and Beta-Lactam Cross-Reactivity. Chaudhry S.B. Pharmacy (Basel). 2019; 7: 103
2. Solensky R et al. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010 Oct;105(4):259-273.
3. Kim MH, Lee JM. Diagnosis and management of immediate hypersensitivity reactions to cephalosporins. Allergy Asthma Immunol Res. 2014 Nov;6(6):485-95
4. Zhao Z, Baldo BA, Rimmer J. beta-Lactam allergenic determinants: fine structural recognition of a cross-reacting determinant on benzylpenicillin and cephalothin. Clin Exp Allergy. 2002 Nov;32(11):1644-50.
5. Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. Pediatrics. 2005 Apr;115(4):1048-57.
6. Romano A et al. Cross-Reactivity and Tolerability of Cephalosporins in Patient with IgE-Mediated Hypersensitivity to Penicillins. J Allergy Clin Immunol Pract 2018; 6(5): 1662-72.
7. Macy E et al. Association Between Removal of a Warning Against Cephalosporin Use in Patients with Penicillin Allergy and Antibiotic Prescribing. JAMA Netw Open. 2021;4(4):e21836.
8. Sousa-Pinto B et al. Assessment of the Frequency of Dual Allergy to Penicillins and Cefazolin: A Systematic Review and Meta-analysis. JAMA Surg. 2021 Apr 1;156(4):e210021.