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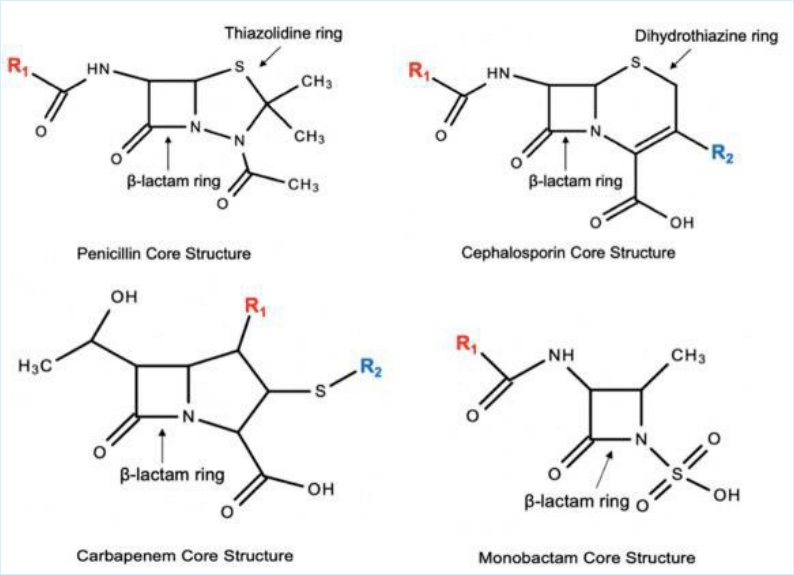
Penicillin Allergy & Cross-Reactivity

Introduction

1. Only 0.5% to 2% of patients with a documented penicillin allergy that are administered a penicillin will exhibit a hypersensitivity reaction, usually presenting as a rash or hives.
2. True IgE-mediated penicillin allergies that cause anaphylaxis are rare.
3. An IgE-mediated penicillin allergy can diminish over time, as 80% of patients become tolerant after a decade.
4. Patients with a documented penicillin allergy may be inappropriately exposed to alternative antibiotics, resulting in increased treatment failures, adverse effects, and antimicrobial resistance.
5. Penicillins, cephalosporins, and carbapenems all share a beta-lactam core structure, thus raising the potential for cross-reactivity among these agents.

Pharmacology

- The following drugs in each group ***may have cross-reactivity to each other due to similar side chains***
- Cross-reactivity between penicillins and cephalosporins is about **2%**
- Cefazolin is **NOT likely to cross react** with penicillin (side chains NOT similar)
- Cross-reactivity with monobactams (i.e. aztreonam) is **negligible**
- Cross-reactivity between penicillins and carbapenems is **<1%**



Group 1	Group 2	Group 3	Group 4
Penicillin Cefoxitin Cefuroxime	Amoxicillin Ampicillin Cefaclor Cephalexin Cefadroxil	Ceftriaxone Cefotaxime Cefuroxime Cefepime Cefpodoxime Ceftaroline	Aztreonam Ceftolazane Ceftazidime

Overview of Evidence			
Author	**Design**	**Intervention & Comparison**	**Outcome**
Why Cross-Reactivity?			
Nagakura, 1990 **Mayorga, 1995**	Animal study	-Studied antibodies formed when animals were immunized with protein-beta-lactam conjugates	-92% of the antibodies recognized an epitope in which the side chain was the main constituent **-The side chain is the most important determinant in penicillin immunogenicity**
Cephalosporins			
Goodman, 2001	Retrospective review (n=2933)	-Orthopedic patients with penicillin allergy receiving cefazolin prior to a procedure	• Only 1 patient may have had an allergic reaction to cefazolin • **Cross-reactivity rate with cefazolin was 0.33%**
Daulat, 2004	Retrospective review (n=606)	-Patients with penicillin allergy receiving cephalosporins -42% 1st gen., 21% 2nd gen., and 37% 3rd or 4th gen. cephalosporins	• Only 1 patient had an allergic reaction that was documented as worsening of underlying eczema after being placed on cefazolin • **Cross-reactivity was 0.17%**
Apter, 2006	Retrospective review (n=3920)	-Patients with a prescription for penicillin followed by a prescription for a cephalosporin -Identified allergic-like events within 30 days after each prescription	• Only 43 patients who experienced an allergic- like reaction after both penicillin and cephalosporin • **Cross-reactivity rate was 1.1%** • 70% of these patients **just had urticaria** • **The risk of anaphylaxis to cephalosporins was only 0.001%**
Romano, 2018	Prospective review (n=252)	Prospective study of 252 subjects with IgE-mediated hypersensitivity to penicillins - Serum specific IgE assays for cefaclor and skin tests for 10 cephalosporins -Oral challenges with cefuroxime axetil, ceftriaxone, cefaclor, and cefadroxil for subjects with negative skin tests	• 99 subjects (39.3%) had positive allergy tests for cephalosporins • 95 subjects (37.7%) were positive to aminocephalosporins and/or cefamandole, which share side chains with penicillins • All 244 subjects who underwent challenges with cefuroxime axetil and ceftriaxone tolerated them • 7 subjects reacted to cefaclor or cefadroxil

Carbapenems			
Romano, 2006	Prospective study (n=112)	-Skin tested to penicillins and then skin tested to imipenem -If skin test to imipenem was negative, then challenged with IM dose	• Only 1 patient of the penicillin skin-test positive patients had a positive skin test to imipenem • **Cross-reactivity rate was 0.9%** • None of the 110 patients with a negative imipenem skin test that underwent IM challenge had a reaction
Romano, 2007	Prospective study (n=104)	-Skin tested to penicillins and then skin tested to meropenem -If skin test to imipenem was negative, then challenged with IV dose	• Only 1 patient of the penicillin skin-test positive patients had a positive skin test to meropenem • **Cross-reactivity rate was 1%** • All 103 patients with a negative meropenem skin test tolerated the IV challenge
Atanaskovic-Markovic, 2008	Prospective study (n=108)	-Children with penicillin allergy were skin tested to penicillin and meropenem -If skin test to meropenem was negative, then challenged with IV dose	• Only 1 patient with a positive penicillin test reacted to the meropenem skin test • **Cross-reactivity rate was 0.9%** • All 107 patients with a negative meropenem skin test tolerated the IV challenge
Sánchez de Vicente, 2020	Prospective study (n=137)	Tolerance testing for cephalosporins and carbapenems in patients with confirmed penicillin allergy	• 0/46 patients showed positive skin tests for imipenem. • **0.79%** (1/137) patients showed a positive skin test for cefuroxime. • **0.79%** (1/137) patients showed a positive skin test for ceftriaxone.

Conclusions

1. True penicillin allergies are less common than reported, and anaphylaxis is uncommon.
2. Cross-reactivity among penicillins and cephalosporins is attributed to similarity in side chains.
3. Cephalosporin cross-reactivity with penicillins is much lower than reported in early studies partly due to contamination of study drugs with penicillin.
4. **Cross-reactivity between cephalosporins is about 2% and with carbapenems is <1%**

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