Meghan Jeffres, PharmD
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Beta-lactam Side Chains and Cross-reactivity Handout

Cross-reactivity between penicillins, cephalosporins, carbapenems, and monobactams is not a class effect. Contemporary data indicates the R1 sidechain on cephalosporins and monobactams and the R sidechain on penicillins are the antigenic component responsible for cross-reactivity.[1, 2] All carbapenems have dissimilar sidechains to other beta-lactams and are not cross-reactive.[3, 4] The table identifies penicillins and cephalosporins that share identical side chains and known cross-reactivity unrelated to sidechains between natural penicillins (penicillin, amoxicillin, ampicillin).

Cross-reactivity risk between penicillins and cephalosporins <u>with the same side chain</u>

- History of Type I hypersensitivity (immediate, anaphylaxis) = 40%
- History of Type IV hypersensitivity (delayed, dermatologic) = 20%

(+) Known cross-reactive (X) Same side chain	Penicillin	Amoxicillin	Ampicillin	Cephalexin	Cefadroxil	Cefazolin	Cefuroxime	Cefoxitin	Cefotaxime	Cefixime	Cefpodoxime	Ceftriaxone	Ceftazidime	Cefepime	Cefiderocol	Cefotolozane	Ceftarolin[e]	Cefotobiprole	Aztreonam
Penicillin		+	+	+															
Amoxicillin	+		+	+	X														
Ampicillin	+	+		X															
1st Generation Cephalosporins																			
Cephalexin	+	+	X																
Cefadroxil		X																	
Cefazolin																			
2nd Generation Cephalosporins																			
Cefuroxime																			
Cefoxitin																			
3rd Generation Cephalosporins																			
Cefotaxime											X	X		X					
Cefixime																			
Cefpodoxime									X			X		X					
Ceftriaxone									X		X			X					
Ceftazidime															X				X
Later Generation Cephalosporins																			

Cefepime									X		X	X						
Cefiderocol													X					X
Ceftolozane																		
Ceftaroline																	X	
Ceftobiprole																X		
Monobactam																		
Aztreonam													X		X			

Cephalosporin-penicillin cross-reactivity nuance

There are two important cephalosporin-penicillin sidechain pairs: cefadroxil-amoxicillin and cephalexin-ampicillin. There is little clinical data about the risk of cross-reactivity between these two pairs as well as between penicillin, cefadroxil, and cephalexin. One large database study found no increased risk of hypersensitivity reactions between ampicillin-cephalexin compared to a TMP/SMX control.[5] A more conservative approach is to avoid the use of cefadroxil and cephalexin due to known cross-reactivity between penicillin, amoxicillin, and ampicillin. The ideal approach is to perform an oral amoxicillin challenge prior to initiation of cefadroxil and cephalexin. When an oral amoxicillin challenge is not possible, use shared decision making which weighs the advantages of cheap high-bioavailable oral cephalosporins (cefadroxil, cephalexin) against the disadvantages of 2nd and 3rd generation cephalosporins and non-beta-lactams.[6]

Cefazolin does not share a sidechain with any penicillins or cephalosporins available in the US and can be used in patients with a history of beta-lactam allergy regardless of symptoms.[7]

There is no data about the risk of cross-reactivity between or among nafcillin, piperacillin, and cephalosporins. Use shared decision making and/or reach out to Antimicrobial Stewardship for assistance.

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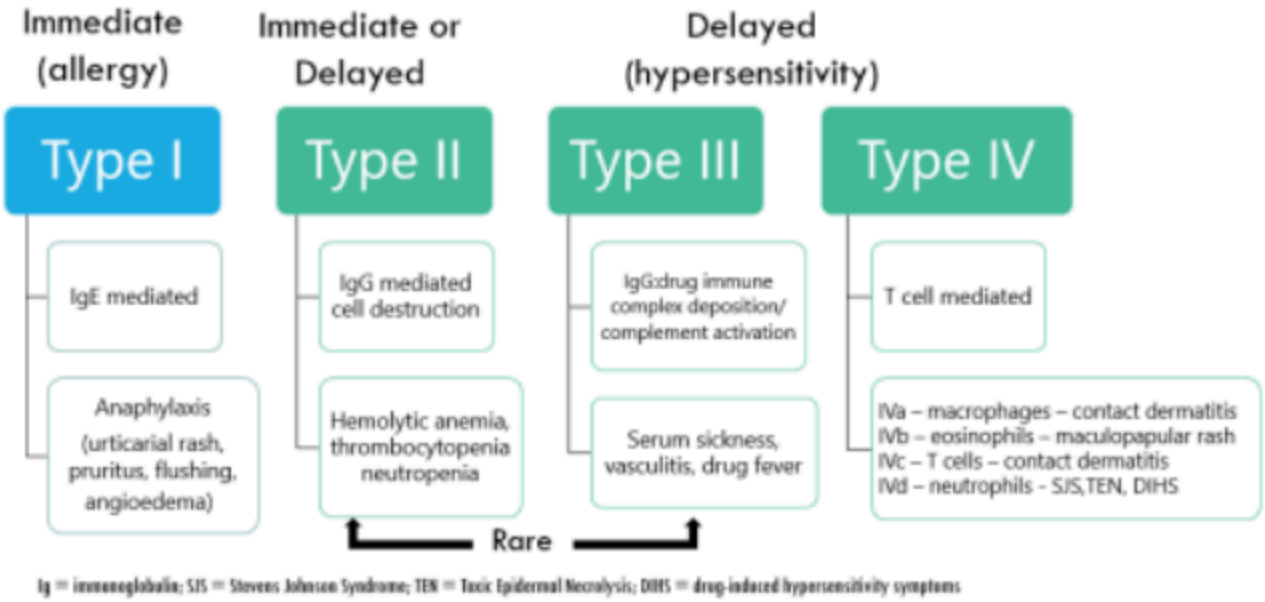
Penicillins and Cephalosporins Key Clinical Studies

252 patients with immediate (Type I) hypersensitive to a penicillin-based antibiotic underwent cephalosporin skin and ImmunoCAP testing. 99 (39%) also reacted to a cephalosporin. 95 (38%) reacted to cephalosporin with an identical sidechain to a penicillin antibiotic (cefaclor, cephalexin, cefadroxil, cefamandole). Only 4/252 (1.5%) patients reacted to cephalosporins that have dissimilar sidechains to penicillin-based antibiotics (ceftriaxone, cefuroxime, cefotaxime).[1]

214 patients with history of delayed (Type IV) hypersensitivity, including SJS/TEN, to penicillin underwent skin testing with six beta lactams, three with similar side chains to penicillins, and three with dissimilar side chains. Cross-reactivity was found in 40 (19%) of patients; all reactions were from the three cephalosporins with the same sidechains as penicillin derivatives. Cefaclor and cephalexin have the same sidechain as ampicillin and resulted in positive skin tests in 39 and 31 patients respectively. Cefadroxil has the same sidechain as amoxicillin and resulted in positive skin tests in 17 patients.[2]

Note: patient with hypersensitivity reactions to beta-lactams with dissimilar sidechains likely represent a second hypersensitivity, not cross-reactivity.

Coombs and Gell's hypersensitivity classification



Medical Liability Concerns[8]

Fear of litigation has been identified as a potential reason to avoid using beta-lactams in a patient with a penicillin allergy. Since 1959, 27 medical malpractice or negligence cases have been published in which a patient with a penicillin allergy received a beta-lactam and experienced an adverse reaction. Defendants (clinical providers) were found liable in 3 of 7 cases in which a penicillin-based antibiotic was prescribed to a patient with a known penicillin allergy. Defendants were not found liable in any cases in which a cephalosporin or
carbapenem was prescribed excluding 1 case in which physicians settled out of court. Judges have cited a lack of scientific evidence demonstrating cephalosporins or carbapenems are contraindicated for patients with a penicillin allergy.

References

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